Quantifying drivers of antibiotic resistance in humans: A systematic review

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Summary (150 words)

A horizon scan linking the quality/quantity of data reported on the drivers of antibiotic resistance (AR) in humans arising from the human, animal and environment reservoirs is needed to mitigate risks of AR. We adopted a systematic reviewing methodology using a "One Health" approach to survey the key drivers in humans.

565 studies from 2,819 title/abstracts were identified after two sets of reviewers selected studies from Embase, MEDLINE, and Scopus (2005-2018), ECDC, CDC, and WHO (One Health data). Quality assessment was carried out in line with Cochrane recommendations.

Prior antibiotic exposure, underlying disease, and invasive procedures were the key risk factors identified from the 88 risk factors retrieved. Studies primarily reported a 2 to 4-fold increased risk of AR due to these risks identified. Food/water transmission were frequently quantified from the animal/environment-reservoirs respectively.

Uniformly quantifying relationships between risk factors will help researchers better understand the cycle of AR in humans.

Introduction

Antibiotic resistance (AR) is a growing, multifaceted health concern, resulting in increased morbidity, mortality for patients, and financial costs for healthcare systems[1]. Antibiotic-resistant bacteria (ARB) are found in humans, diverse animal hosts and in the environment. Each of these contributes to the epidemiology of AR[2–5]. (See Panel A)

Reviews, meta-analyses and observational studies determining drivers of the emergence and transmission of AR have been published[2,3,6–8]. Antibiotic use and failure to apply effective infection prevention and control measures are well established as key drivers of AR[9,10]. However, given the recent international focus on reducing AR[11] and a greater attention to modelling the risk of the "One Health" impact on humans (Panel A)[4], there is a need for detailed knowledge of the reservoirs and emerging cross-reservoir risk factors of AR. In particular, we need to broaden our understanding of the natural selection and transmission patterns of ARB which currently threaten healthcare delivery, particularly for patients undergoing invasive procedures such as surgery or those receiving immunosuppressive therapies[1].

In an attempt to depict the links between the human, animal and environmental reservoirs of antimicrobial resistance (AMR), a systems map was published by the UK Department of Health (DH), as part of the UK's national AMR strategy[12]. However, these maps were created using expert opinion rather than literature sources and the links were not quantified[12]. There has been no systematic retrieval or quality assessment of evidence for the risk factors for AR in humans, nor the quantification of these risk factors among major bacterial species across the three reservoirs. A synthesis of evidence is urgently required to aid policy-level decision making, ensuring that strategies to minimise the burden of AR can be appropriately prioritised.

Therefore, the aim of this research was to conduct a survey of the evidence available on the quantified risk factors of AR in humans by systematically retrieving and reviewing this evidence and generating an overview of the quality and quantity of these studies. In addition, this data was used to create an up-to-date map quantifying the drivers identified as part of this horizon scan for AR to compliment and extend the UK AMR systems map[12].

Methods

Search strategy and selection criteria

The PRISMA protocol was followed to conduct this systematic review[13]. Quantified evidence on the risk factors from human, animal and environment, which result in AR in humans, were identified. EMBASE, MEDLINE(R) In-Process & Other Non-Indexed Citations, MEDLINE(R) were searched via Ovid, and Scopus was searched separately. Only full text articles published in English between 01.01.2005 - 14.02.2018 were included. Grey literature quantifying the most recent primary data on One health from the European Centre for Disease Prevention and Control (ECDC) and Centers for Disease Control and Prevention (CDC) and World Health Organisation (WHO) websites were searched. Additional meta-analyses studies on risk factors of AR in humans were also included from Pubmed (Section II in supplementary web appendix) to capture any missed risk factors not identified from the primary data search in Ovid and Scopus. Population, Intervention, Comparator, Outcome, and Study design (PICOS) criteria were utilised for inclusion/exclusion decisions. (Table S1). No studies were excluded based on the quality of the papers or the sample size. From the included studies, study characteristics and outcomes were extracted into a pre-specified Data Extraction Table (in Microsoft Excel© 2016) (Table S2).

Panel A: Study Terminology

- Antibiotic resistance is defined as bacteria with acquired or inherent resistance to at least 1 antibiotic.
- Community setting includes a setting outside of a healthcare environment such as households. The animal and environment reservoirs are included within this setting.
- Environmental reservoir includes non-meat related food (e.g. vegetables), soil or water related sources.
- Healthcare setting includes hospitals and long-term care facilities.
- Invasive procedures include procedures carried out at a healthcare setting, for example, use of indwelling devices such as catheterisation or intubation.
- Multidrug resistant bacteria are defined as bacteria with acquired resistance to at least 3 drugs from different classes of antibiotics[77].
- ESBL-Bacteria have been separately coded to MDR-B despite ESBL-B being a type of MDR-B since there has been a surge of international concern around these organism types, and a large number of papers were also identified for this group of organisms.
- One Health is defined as the inter-relationship between the human, animal and environmental reservoirs, and how these relationships impact AR in humans.
- 'Risk factor' is used as a proxy term for drivers of antibiotic resistance.

  "A risk factor is any attribute, characteristic or exposure of an individual that increases the likelihood of the individual:

  i) being colonised/infected by antibiotic-resistant bacteria, or

  ii) transmitting such types of bacteria to another individual or the surrounding environment"

169
170 **Study selection and quality assessment**
171 Four reviewers conducted the review and applied the PICOS criteria to select the relevant articles.
172 One reviewer (AC) assessed all title/abstracts (T/A) and full texts (FTs) for inclusion, a second
173 reviewer (MM) assessed 50% of all T/A and FTs, and a third (SEB) and fourth reviewer (NRN) assessed
174 25% each of the remaining T/A and FTs titles. In the event of a disagreement, a senior researcher
175 (JR), independent of the four reviewers, was consulted. After final study selection, duplicates were
176 removed by identification of the same Ovid ID alongside hand searching. Following the identification
177 of the FTs, one reviewer (AC) conducted the quality assessment of all papers and a second reviewer
178 (MM) independently checked 12 randomly selected articles. Quality was determined using the
179 Critical Appraisal Skills Programme (CASP) based on Cochrane guidelines[7,14–16], in which selection,
180 information and confounding bias were assessed. Reporting bias criteria were defined in line with
181 methodology utilised in a recently published meta-analysis on observational studies in AR[14].
182 (Supplementary Section III)
183 The full study protocol was prospectively registered with PROSPERO (CRD42016038450).
184

Panel B: Search strategy*

Microbial-drug-resistan$.tw. or ((microb$ or antimicrob$ or anti-microb$ or anti microb$) adj2 resist$).tw. or ((antibiot$ or anti-biot$ or anti biot$) adj2 resist$).tw. or Multidrug resistan$.tw. or multidrug-resistant bacteria.ti,ab. or exp Drug Resistance, Microbial/ or (superbug$ or super-bug$ or super bug$).tw. or Superinfection/ or (resistant adj2 infection$).ti,ab.

AND

(emergence or spread or outbreak* or prevalence or incidence or acquisition).tw. or exp cross infection/ or exp infectious disease transmission, patient-to-professional/ or exp infection control/ or (patient-to-patient adj2 transmission).tw. or exp infectious disease transmission, professional-to-patient/ or exp disease transmission, infectious/ or infectious disease transmission.tw. or disease transmission.tw. or ((transfer or transmission) adj2 resist$).ti,ab. Or contamination.tw. or ((bacterial pathogen* and coloni$) or Coloni?ation).tw. or (resist$ adj2 develop$).tw

AND

((cause or drive or driving or driver or predictor or determinant or determinants or mechanism) adj4 resist$).ti,ab. or exp risk factor/ or risk factor.ti,ab. or risk score.tw. or infection reduction.tw. or infection risk.tw. or risk assessment.tw. or risk benefit analysis.tw. or (antibiotic adj2 (use$ or usage or consum$ or prescri$)).tw. or (food chain or (water and (supply or quality)) or animal husbandry or food producing animal or food-producing animal).tw. or (poor adj2 hygiene).tw. or (poor and (infection control or infection-control)).tw.

AND

(risk ratio or relative risk or odds ratio or hazard ratio or statistical correlation or correlation coefficient or statistical analysis or multivariable analysis or regression).tw. or epidemiology studies.ti,ab. or exp odds ratio/ or exp epidemiologic studies/ or exp Statistics as Topic/ or exp Epidemiologic Study Characteristics as Topic/ or estimat$.tw. or quantif$.tw.

Limits: English language, full texts, 2005 onwards

Excludes: book or book series or chapter or conference abstract or editorial or erratum or letter or note

exp: Explosion terms (in Embase) /MESH terms (in Medline)

*Search strategy developed with medical librarian

Data analysis

Quantitative evidence which included statistically significant results and point estimates for the risk factors of AR from the human reservoir or AR prevalence levels from food or water sources as potential transmission routes into the human reservoir were extracted. Only statistically significant risk factor estimates based on p-values were extracted from the human reservoir studies. If there were discrepancies between what was stated as statistically significant and reported p-values, then these results were not extracted. For the multivariate sub-analysis, only complete results with significant p-values, complete confidence intervals and sample size were included. If odds ratios were reported as significant with confidence intervals that included 1, these results were excluded. In addition, these result discrepancies were captured under reporting bias during the quality assessment stage.

Due to limited quantified evidence from the animal and environment reservoirs, prevalence levels were extracted (e.g. Prevalence of resistant bacteria from retail meat or prevalence of resistant genes from water sources as proxies for indirect transmission routes into the humans reservoir). Following data extraction, all data was imported into R version 3.4.1 and analysed using the 'dplyr' package.

A meta-analysis was deemed inappropriate given the heterogeneity in terms of patient population, definition of outcomes and risk factors under study. Mean quality assessment scores were reported with their respective standard deviation (SD) on a range from 0-1. Due to cell structure differences, compared to Gram-positive bacteria, Gram-negative bacteria are more resistant to antibiotics, thus, the results of the review were often split based on this classification criterion.

The drivers of AR map and risk factor grouping

All risk factor estimates were coded based on their study-specific definitions, for example prior antibiotic use, with or without underlying disease (Table S4). Based on classification methods utilised in previous AR related meta-analyses[17–19] and risk factor framework studies in medical literature[20–22], the themes arising from these risk factors were split into the following risk domains: 1) Patient clinical history: Includes underlying disease or comorbidities ; 2) Demographics : age, gender, ethnicity; 3) Healthcare factors: includes various procedure related contact with hospital / intensive care unit / nursing home/ long-term care facility/ outpatient services or hospital environment related factors ; 4) Antibiotic use related factors: includes prior history of antibiotic use or impact of antibiotic use in animals on humans 5) Community-level factors: where risk factors were neither related to healthcare contact, nor due to the clinical condition of the patient. Cross-reservoir drivers such as meat related food transmission, occupational and domestic exposure to animals from the animal reservoir, or water and vegetable related food transmission from the environment reservoir were included within this community domain. Notably, these domains are not mutually exclusive, and the potential for causal relationships across and between these domains are discussed within the discussion section, as identifying such links between the domains was not within the scope of this review.

To be able to report on all the risk factors we had identified in the review (see Table S4 in the supplementary index for a full list of risk factors), creation of these domains was needed to enable description of the overall evidence on risk factors of AR impacting humans in a holistic way.

Results

In total 2,819 title and abstracts were screened. The PRISMA flow diagram (Figure 1) describes the selection process.

Figure 1: PRISMA flow diagram*

*Please refer to the PICOS exclusion criteria in supplementary appendix for further explanation (Table S1)

[Figure supplied in PDF to be inserted here.]

1,883 title/abstracts were excluded, following which 936 full text articles were reviewed, out of which 371 articles were ineligible for inclusion. In total, 565 full text articles were included for data extraction and quality assessment. Out of the 565 full text articles, 527 were primary studies and 38 were meta-analysis studies.

Study population and reservoirs

Overall

Out of the primary studies, a total of 469 studies (89%) were reporting on risk factors from within the human reservoir and 58 studies (11%) were reporting on cross reservoir risk factors on the relationship between the animal or environment and human reservoir (Figure 2). Four meta-analyses studies pooled quantified risk factors from the animal and human reservoir. No meta-analysis was identified for the overlap between environment and human reservoir.

The top three resistant bacteria under study were multidrug-resistant bacteria (excludes extended spectrum beta-lactamase-producing bacteria) (MDR-B: 20% (104 studies)), meticillin-resistant *Staphylococcus aureus* (MRSA: 19% (98 studies)), and antibiotic-resistant *Escherichia coli* (R-EC: 15% (78 studies)) (Table S5). Most (42% (16) meta-analysis studies quantified risk factors of MRSA. The full list of included articles and their study characteristics are reported in Table S2. Of the 469 human-only studies, 65% related to an adult population, and 8% did not explicitly specify age groups.

Cross reservoir

Antibiotic-resistant *Escherichia coli* (R-EC) was the most frequently studied organism (38% (22 studies)) among cross-reservoir drivers.

The potential transmission routes from the animal to human reservoir were either via food sources[25,27–46], or from animal contact[24,36,45–52]. In contrast, environment to human reservoir routes were water[39,46,53–59] and vegetable related sources[60]. The highest reported resistant isolates out of all the cross reservoir risk factors were from broiler meat which were ESBL-EC samples (43% (resistant isolates: 36,241) followed by meat from turkey which were R-EC samples (25% (1714 resistant isolates).

Study types and quantification techniques

The majority of studies (55% (312)) adopted a cohort design, while 26% (146) adopted a case-control methodology. A cross-sectional, prevalence or time-series study approach was used for 12% (65) (Figure SF1), and 7% (38) were meta-analyses. There were no meta-analyses that included links between human and environmental reservoirs. In the human reservoir, an odds ratio (OR) was frequently used to quantify the risk factors; incidence and prevalence rates were the common outcome measures in the other reservoirs (Figure SF2). The majority of studies were based in Organisation of Economic Cooperation and Development (OECD) countries (76% (404)), whilst 19% (99) were based in non-OECD countries, and 1% (3) were global. The meta-analyses studies primarily (92% (35) had a global scope.

Study quality

Quality assessment showed that overall there was a low risk of bias among the 527 observational studies (Table S2, Figure SF3). 56% (312) of the observational studies were reported well; failure to report study design (18% (96)) and baseline characteristics (13% (71)) were the commonest reasons for studies to score poorly (Panel 1: Figure SF3). However, around 30% of the studies were subject to confounding bias (34% (177)) and information bias (29% (155)) when it came to identification of exposure variables (Panel 2: Figure SF3). The meta-analyses studies were primarily of good quality according to the PRISMA assessment tool. (Mean: 0·90 (0·09))

Primary studies focusing on the human reservoir showed on average the highest quality score ratings (mean: 0·66 (SD: 0·18), indicating a lower risk of bias. In comparison, the other reservoirs had a higher risk of bias (mean 0·33-0·47 (SD: 0·16-0·17)) (Figure 2).

Figure 2: Reservoir specific number of studies, quality and top risk factors
[Figure supplied in PDF to be inserted here.]

Risk factors

The 527 primary studies were utilised to construct an AR drivers' map (Figure 3). Most studies quantify links between antibiotic use (56%), healthcare contact (53%) or patient clinical history (47%), and AR in humans. (Figure 3).

Fewer studies reported risk factors from the community factors (20%) and patient demographics (18%) domains.

The studies from the healthcare factors domain were on average of better quality (0·68 (0·18)) compared to studies reporting community factors (0·46 (0·18)). (Figure 4)

A detailed table with the five domains and their respective risk factors are presented in Table S4 along with the number of studies retrieved and their respective quality scores.

Figure 3: Percentage of studies quantifying the drivers of antibiotic resistance in humans N = 527 studies

Please note the bubble size represents the percentage of studies out of the total number of primary studies (n = 527) for both the risk domains and their individual risk factors.

For ease of presentation and clarity only the top 5 risk factors from the individual risk domains have been presented - these percentages may not add up to the total risk domain percentage. A singular study may report a variety of risk factors across all of these domains so there will be duplicate studies present in the domains. The distance between the bubbles are not indicative of anything.

[Figure supplied in PDF to be inserted here.]

Figure 4: Quality of studies quantifying the drivers of antibiotic resistance in humans
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Bubble size represents mean quality score

Sub-analysis of outcomes reported across the domains

The risk factors identified in the review were reported for various outcomes of AR in humans. Figure 5 describes the type of outcomes and number of studies extracted from each risk domain. AR-related infections were most frequently reported, followed by colonisation with ARB across all studies. Gram-negative bacteria were the most frequently estimated resistant bacteria across all outcomes with the exception of carriage of ARB, where Gram-positive bacteria predominated. In terms of risk domains driving the respective outcomes, healthcare contact was most frequently reported to result in AR-related infections (64% (113 studies)), whereas patient clinical history was most frequently reported to result in colonisation with ARB. Antibiotic use was reported to result in acquisition (57% (48 studies)), emergence (66% (40 studies) or carriage (55% (31 studies) of AR. In contrast, community-level factors were driving indirect routes arising from cross-reservoir transmission. (45 studies)

The quality of the studies reporting on infection (mean: 0·65 S.D:0·2) and colonization (mean: 0·63, S.D: 0·2) were better with lower risk of bias compared to the transmission related studies (mean: 0·45 S.D: 0·23).

Majority (39% (15 studies) of the meta-analyses studies quantified AR outcomes for infection, followed by colonisation (21% (8 studies).

Figure 5: Overview of the risk factor domains stratified by outcomes† of AR. Panel A: Total number of studies split based on type of outcome for AR across the five risk domains; Panel B: Total number of studies split based on type of outcome for AR and bacteria type

[Figure supplied in PDF to be inserted here.]

*Mixed includes estimates from resistant genes or studies reporting pooled results for Gram-positive and Gram-negative bacteria

Please note: 1) Studies reporting on resistant genes have not been presented in Panel B – this is the reason behind fewer studies in e.g. transmission outcome in Panel B compared to Panel A,

2) one study may report on both Gram-positive and Gram-negative bacteria types, this overlap is the reason behind e.g. higher infection studies in Panel B compared to Panel A

†Infection: ARB causing infection; Colonised: Colonised but not infected by ARB; Acquisition: Directly acquiring ARB (including infection) from another host or the surrounding environment; Emergence: Determinants, predictors, factors increasing prevalence of antibiotic resistance in humans; Carriage: Includes nasal / faecal / skin carriage; Indirect transmission: Indirect acquisition routes which facilitate the transfer of ARB from one host to another host (human to human / animal to human) or from environment to host (and vice versa). Prevalence of ARB from uncooked/cooked food sources as well as water sources have also been used as proxies for these routes; Other: includes combination of 'colonisation/infection/acquisition', 'transmission/carriage' or specified as a 'risk factor of resistant organism'

Note: Transmission, emergence or acquisition routes are often difficult to determine clinically, in particular from retrospective studies. These terms have been directly elicited from the studies giving rise to i) overlap between these outcomes and ii) heterogeneity across their study specific definitions.

Sub-analysis of odds ratio estimates reported from multivariate analysis results and meta-analyses

Up until this point the drivers of AR were expressed in terms of the quantity and quality of evidence extracted. To determine the strength of the evidence, a sub analysis was conducted of the odd ratio (OR) from independent risk factors reported from studies which conducted a multivariate analysis (does not include the meta-analyses results). Within this analysis, only studies reporting complete datasets (i.e. number of cases, OR with significant confidence intervals) were included.

(Table S6 provides the OR ranges elicited from this analysis along with the number of studies and their quality) Table 1 provides the percentage of studies reporting the specified OR ranges split for

the top two outcomes and for Gram-positive and Gram-negative bacteria. Risk of AR due to antibiotic use and community level factors had wide OR ranges, compared to the other domains. Table 1 displays the OR distribution, where the odds of ARB in humans was primarily reported to be between 2 to 4 fold higher due to the impact of the different risk domains. The distribution from the meta-analyses studies in Table 2 shows that odds of AR in humans are primarily reported to be between 2 to 3 fold higher given these risk domains. A larger number of studies reported odds of AR due to healthcare contact risk between 1 and 2. Whereas, the number studies reporting on odds for AR due to antibiotic use were spread between 2 and 4.

Table 1: Percentage of studies per domain reporting specified odds ratio ranges* from the multivariate analysis results

Overall	OR >1 - <2	OR ≥2 - <3	OR ≥3 - <4	OR ≥4 - <5	OR ≥5 - <6	OR ≥6 - <7	OR ≥7 - <8	OR ≥8 - <9	OR ≥9 - <10	OR ≥10 - <12	OR ≥12 - <14	OR ≥14 - <16	OR ≥16 - <18	OR ≥18 - <20	OR ≥20
Patient clinical history (n = 147)	16%	34%	22%	15%	7%	8%	8%	3%	5%	3%	3%	4%	2%	3%	5%
Health care contact (n = 184)	24%	35%	27%	20%	12%	7%	6%	4%	3%	5%	4%	2%	4%	1%	9%
Antibiotic use (n = 189)	15%	32%	20%	13%	16%	7%	10%	3%	4%	5%	7%	4%	1%	2%	8%
Community level factors (n = 34)	21%	29%	29%	12%	12%	9%	3%	9%	0%	3%	3%	3%	3%	6%	15%
Patient demographics (n = 54)	28%	37%	19%	11%	6%	2%	4%	0%	2%	2%	4%	4%	0%	0%	2%
Comparison of top two outcomes from the review															
Infection	OR >1 - <2	OR ≥2 - <3	OR ≥3 - <4	OR ≥4 - <5	OR ≥5 - <6	OR ≥6 - <7	OR ≥7 - <8	OR ≥8 - <9	OR ≥9 - <10	OR ≥10 - <12	OR ≥12 - <14	OR ≥14 - <16	OR ≥16 - <18	OR ≥18 - <20	OR ≥20
Patient clinical history (n = 53)	19%	36%	17%	15%	9%	6%	8%	4%	6%	4%	6%	0%	2%	0%	6%
Health care contact (n = 73)	26%	30%	27%	26%	12%	3%	5%	3%	5%	10%	4%	1%	3%	0%	8%
Antibiotic use (n = 69)	6%	32%	20%	13%	17%	7%	9%	1%	4%	6%	12%	4%	0%	0%	6%
Community level factors (n = 7)	14%	14%	29%	0%	0%	0%	14%	0%	0%	0%	0%	0%	0%	14%	14%
Patient demographics (n = 18)	33%	33%	22%	6%	6%	0%	0%	0%	0%	6%	0%	0%	0%	0%	6%
Colonisation	OR >1 - <2	OR ≥2 - <3	OR ≥3 - <4	OR ≥4 - <5	OR ≥5 - <6	OR ≥6 - <7	OR ≥7 - <8	OR ≥8 - <9	OR ≥9 - <10	OR ≥10 - <12	OR ≥12 - <14	OR ≥14 - <16	OR ≥16 - <18	OR ≥18 - <20	OR ≥20
Patient clinical history (n = 40)	15%	33%	30%	18%	8%	3%	10%	8%	10%	5%	0%	15%	0%	3%	8%
Health care contact (n = 39)	23%	36%	21%	15%	15%	15%	5%	3%	3%	3%	3%	0%	8%	0%	13%
Antibiotic use (n = 40)	23%	38%	20%	5%	15%	0%	15%	8%	0%	8%	3%	3%	3%	3%	10%
Community level factors (n = 12)	25%	25%	50%	17%	8%	25%	0%	8%	0%	8%	0%	8%	0%	8%	8%
Patient demographics (n = 16)	13%	44%	13%	13%	13%	6%	6%	0%	6%	0%	13%	6%	0%	0%	0%
Comparison of Gram-positive and Gram-negative bacteria type															
Gram-positive	OR >1 - <2	OR ≥2 - <3	OR ≥3 - <4	OR ≥4 - <5	OR ≥5 - <6	OR ≥6 - <7	OR ≥7 - <8	OR ≥8 - <9	OR ≥9 - <10	OR ≥10 - <12	OR ≥12 - <14	OR ≥14 - <16	OR ≥16 - <18	OR ≥18 - <20	OR ≥20

Patient clinical history (n = 50)	18%	36%	26%	12%	6%	10%	8%	4%	2%	6%	0%	6%	0%	0%	6%
Health care contact (n = 52)	27%	42%	25%	6%	12%	0%	4%	0%	4%	0%	4%	4%	2%	0%	10%
Antibiotic use (n = 42)	17%	26%	21%	17%	7%	7%	5%	5%	5%	5%	2%	7%	0%	0%	5%
Community level factors (n = 13)	23%	38%	31%	23%	8%	8%	0%	15%	0%	0%	0%	0%	0%	8%	15%
Patient demographics (n = 23)	35%	30%	17%	0%	4%	0%	4%	0%	4%	0%	0%	9%	0%	0%	4%
Gram-negative	OR >1 - <2	OR ≥2 - <3	OR ≥3 - <4	OR ≥4 - <5	OR ≥5 - <6	OR ≥6 - <7	OR ≥7 - <8	OR ≥8 - <9	OR ≥9 - <10	OR ≥10 - <12	OR ≥12 - <14	OR ≥14 - <16	OR ≥16 - <18	OR ≥18 - <20	OR ≥20
Patient clinical history (n = 88)	15%	27%	24%	15%	6%	8%	8%	2%	7%	2%	6%	3%	2%	3%	6%
Health care contact (n = 111)	22%	31%	24%	22%	14%	11%	8%	5%	4%	6%	5%	1%	5%	2%	8%
Antibiotic use (n = 130)	15%	31%	20%	12%	18%	7%	11%	3%	3%	5%	9%	2%	1%	2%	9%
Community level factors (n = 19)	16%	26%	26%	5%	11%	5%	5%	5%	0%	0%	5%	5%	5%	0%	16%
Patient demographics (n = 27)	19%	48%	19%	15%	0%	0%	4%	0%	0%	4%	7%	0%	0%	0%	0%

*Blue to red scale represents the highest to lowest reported odds ratio using the number of studies as the measure of frequency (Highest reported = 100% and least reported = 0%)
Please note: Since some studies would report multiple odds ratios for mulitple factors within each domain there are duplicate studies and the individual rows will add upto >100%.

Table 2: Percentage of studies per domain reporting specified odds ratio ranges from the meta-analyses studies*

Meta-analyses studies (n = 22)*	OR >1 - <2	OR ≥2 - <3	OR ≥3 - <4	OR ≥4 - <5	OR ≥5 - <6	OR ≥6 - <7	OR ≥7 - <8	OR ≥8 - <9	OR ≥9 - <10	OR ≥10 - <12	OR ≥12 - <14	OR ≥14 - <16
Patient clinical history (n = 11)	27%	73%	9%	9%	0%	18%	9%	9%	0%	0%	9%	9%
Health care contact (n = 12)	58%	50%	25%	25%	17%	0%	0%	0%	0%	0%	8%	0%
Antibiotic use (n = 15)	27%	53%	47%	40%	7%	7%	7%	7%	0%	7%	13%	0%
Patient demographics (n = 2)	50%	50%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

*Out of 38 meta-analyses studies, 22 reported Odds ratio which were included in this anaylses to maintain a measure of comparison across the primary and meta-analyses studies.
OR: Odds ratio, OR > 16 were not reported in any of the estimates extracted from the meta-analyses, No odds ratios reporting on community level factors were identified from the meta-analyses
Blue to red scale represents the highest to lowest reported odds ratio using the number of studies as the measure of frequency (Highest reported = 100% and least reported = 0%)
Please note: Since some studies would report multiple odds ratios for mulitple factors within each domain there are duplicate studies and the individual rows will add upto >100%.

Discussion

This review is aimed at providing an evidence-base for the drivers of AR across the human, animal and environment reservoirs. Understanding the underlying epidemiology of AR is an important step towards the formulation of interventions to control its' emergence and transmission in humans. The review found that the largest quantified drivers of AR evidence were from within the human reservoir, with little evidence supporting a direct relationship from the cross-reservoir drivers. Among this evidence, the impact of the animal reservoir on humans was the most frequently studied aspect. Minimal evidence exists to support the environment as a common transmission route to the human reservoir. Evidence for cross-reservoir drivers were primarily from cross-sectional and prevalence studies, where methodological limitations such as greater selection, misclassification and confounding bias reduced their reliability. Such types of bias are usually avoided within well-conducted, cohort and case control studies.

This review describes five risk factor domains of AR in humans. Based on the results from the top three risk factors, determined by the frequency and the quality of the quantified evidence, the review finds underlying disease, antibiotic use and invasive procedures in healthcare settings as the risk factors with the most supporting evidence. The majority of case-control and cohort studies collected data on patient characteristics in hospitals. This suggests the feasibility of retrospectively accessing hospital records to assess potential risk factors. In contrast, the risk factors from the community domain are less frequently included in case-control and cohort study protocols. This suggests that either it is less feasible to collect this data or investigators do not feel they merit inclusion when designing these studies

This review highlights three key gaps in our understanding of the drivers of AR in humans. Firstly, there is a lack of studies investigating causal relationships amongst the risk factor domains and reservoirs. Instead, well-established risk factors such as prior antibiotic exposure and invasive procedures during healthcare contact have been the emphasis of most studies investigating risk factors for AR in humans. The lack of evidence in other areas, for example of risks across cross reservoirs, may not necessarily be indicative of the lack of risk, and the numeric load of evidence should be interpreted with caution.

Secondly, local-level factors correlated with the increase of AR from hospital settings are underrepresented in literature. For example, the impact of scarce resource allocation on staff to patient ratio [61], infection control practices[62], the role of inter-staff transmission of pathogens, and patient isolation rates[63,64] cannot be determined from the current literature. At the time of the review, only one meta-analysis reported the impact of prior room occupation on increased risk of AR[65].

Thirdly, methodologically rigorous studies capturing community-level risk factors are limited. These include impact of environment-related transmission, primary care conditions (e.g. GP contact hours/availability)[66], impact of education, income, food source, household size, or influence of ethnicity on travel patterns and on health-related behaviour.

Based on these research gaps, the following suggestions for future research can be made. Inclusion of the risk factor domains framework from this review within standardised data collection protocols for AR risk factor studies would ensure inclusion of not only clinical characteristics but also community and hospital-specific characteristics to rule out their confounding effects. Repeated quantification and focus on established risks may in turn lead to more studies being conducted in these similar established risk areas rather in entirely novel areas. There is a need for in depth qualitative research to help justify exploration of underlying factors and raise the profile of certain understudied areas. Thus to further highlight local level risk factors, studies could incorporate qualitative techniques such as surveys and interviews[67] to support the quantified data from hospital patient records from the retrospective studies.

Given the highly variable outcomes, along with variable individual outcome definitions (e.g. carriage of or acquisition of resistant bacteria), identified from the data extraction in Figure 5, there is a need for clarity and uniformity of these definitions across the field of AR. This would serve to improve granularity and enhance understanding of the methods of transmission or emergence to, in turn, aid efficacy of interventions targeted towards AR in humans

Some limitations of this review should be noted. Firstly, the data extraction and quality assessment was conducted by one reviewer, which may have led to discrepancies in data collection and analysis. All measures have been taken by double checking of data extractions and conducting stress tests when coding the data to limit any discrepancies. The authors (of the studies which were included in this review) were not contacted to clarify the data extractions and should be considered a limitation of this review. The quality assessment was randomly checked by a second reviewer to minimise any bias.

Secondly, due to the recent surge of publications related to AR and the broad search terms which did not use drug-bug combinations as search strings, and the language restriction, this review will not have identified all risk factor studies across all drug-bug combinations and settings. However, the meta-analyses search in Pubmed which utilized the drug-bug combinations from the WHO's antibiotic priority list for the search terms should minimise the risk of missed risk factors

Thirdly, better quality and greater quantity of evidence was retrieved from studies specific to the human reservoir. The key risk domains: antibiotic use, healthcare contact and patient history, were studied to a greater extent possibly due to them being easier to study in terms of data availability from healthcare records and limited resources that are required to conduct retrospective analysis on such data. As a result, there is potential publication bias towards retrospective studies using hospital data to determine risk factors of AR in humans.

Last of all, the review included only studies that provided quantitative evidence on the drivers and risks in humans from within the human reservoir and across the other two reservoirs. Descriptive studies were not included in this analysis, meaning evidence of risk factors from such studies was not captured, and comparison between quantitative and descriptive evidence could not be conducted

In conclusion, this systematic review provides an essential reference document upon which to assess the current state of risk factor studies for AR in humans over the past 10 years. Essentially, this review provides an indication as to the relative importance of risk factors as well as where information is lacking.

The added value of this study is that it emphasises the need for researchers to use standardised data collection protocols for observational studies aiming to report on AR risk factors in humans to increase the clarity with which risk factors are being captured. A simple framework utilising risk factor domains established in this review could enable a better representation of the underlying local level risks of AR in humans by increasing the granularity amongst the established risk being captured to improve our understanding of the risks of AR in humans. This framework could also be amended to enable health policy makers and funding bodies to allocate research funding towards setting specific factors which may contribute to the risk of AR in humans and in turn effectively prioritise resource allocation decisions to tackle AR. Thus by promoting alternative research agendas targeted towards a better understanding of underlying risks our understanding of the risks of AR may be altered. We hope that research agendas would benefit by moving away from convenient easy to produce studies to more exploratory studies hypothesizing the potential importance of the understudied areas arising from the community as clearly demonstrated in this review. These understudied areas may lead to further important factors which impact AR in humans, which may change our understanding of the transmission dynamics of AR in humans. This overview could be utilised to prioritise resources in terms of intervention choice and intervention evaluation, as well as direction of further research needs highlighted under recent AMR related funding initiatives.[73–76].

Contributors

Anuja Chatterjee, Julie Robotham, Rifat Atun, Sara Boyd and Nichola Naylor were involved in the final study protocol development. Anuja Chatterjee carried out the literature search, independent review of all title abstracts and full texts, completed quality assessment, data analysis, result dissemination and manuscript write up. Maryam Modarai, Sara Boyd and Nichola Naylor were the three independent reviewers. Maryam Modarai checked at random the quality assessments conducted by Anuja Chatterjee. Julie Robotham and James Barlow were involved in the manuscript development and first draft. James Barlow, Nichola Naylor, Alison Holmes and Alan Johnson contributed to the final structure and content of the manuscript. The corresponding author and all co-authors contributed to the final version of the manuscript.

Declaration of Interests

All authors have completed the ICMJE uniform disclosure form and declare no competing interests relevant to the submitted work. SEB reports that outside of this work she receives research support from Roche Pharma, Allecra Therapeutics and Antabio. Outside of this work AHH has consulted for bioMérieux.

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