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Informed Consent, Risk Communication, and Patient Concerns in Antimicrobial Clinical Trials: A Systematic Review

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ABSTRACT

Objectives Randomized trials for the management of drug-resistant infections are challenging to conduct as target patient populations often lack decision-making capacity, and enrolment windows are typically short. Improving informed consent and risk communication in these trials is especially crucial for protecting patient interests and maximizing trial efficiency. This study aimed to understand informed consent, risk communication and patient concerns in antimicrobial clinical trials.

Design Systematic review.

Data Sources Searches were conducted in Embase, Medline, CINAHL, and Web of Science Core for peer-reviewed English articles that were published from January 2000 to April 2023.

Eligibility criteria Included articles were empirical studies or an expert opinion guidelines that sought experts', patients' or representatives' opinions on informed consent in the context of clinical trials involving antibiotic/anti-infective agents.

Data extraction and synthesis Abstract screening, full-text review, data extraction and evidence rating were performed by two independent reviewers. Extracted data were summarized and reported qualitatively based on common themes. A total of 2330 records were retrieved and 29 articles were included in the review.

Results Half of the articles involving medical experts and a third involving patients and representatives reported that full comprehension by patients and representatives was challenging or not achievable. Healthcare providers and consent takers were crucial for the quality of informed consent. The level of trust consent givers placed on healthcare providers had a critical influence on consent rate. Emotional distress was pervasive among patients/representatives.

Conclusion The findings indicate that strengthening consent takers' communication skills in providing emotional support to patients and their representatives may improve informed consent. More research is needed to understand informed consent in low- and middle-income and non-English speaking countries.

INTRODUCTION

Expensive and inefficient randomized trials for novel antibiotics and diagnostics are key factors contributing to the "valley of death" for research and innovation in this field. This leads to delay in regulatory approvals for these life-saving drugs and deters pharmaceutical companies from investing in antimicrobial drug discovery.[1] One contributing hurdle to inefficiency in these trials is low consent rates coupled with poor quality of informed consent.[2–5] Poor quality of informed consent can harm the public's trust in healthcare and medicine while slow recruitment can drive up the costs of trials and threaten their internal validity and generalizability. [6,7]

Informed consent involves "voluntary authorization, by a patient or research subject, with full comprehension of the risks involved" [8] and is one fundamental ethical requirement for human subject research. Risk and uncertainty exist when information is incomplete, and our knowledge of the negative outcomes, benefits, or other aspects of a medical treatment is limited during the informed consent procedure. [9–11] In most medical research, risk usually refers to the possibility of having undesirable outcomes such as adverse effects. Poor communication of the trial information is one main reason for the ineffective informed consent. [6]

Treatment strategy trials for multidrug-resistant infections hold unique challenges for informed consent. These challenges include strict enrolment criteria, limited timeframe for enrolment, and target patient populations not having decision-making capacity for consent due to underlying severe infections. Specifically, the window for recruitment and consent is often narrow as the antibiotics under evaluation need to be administered as quickly as possible to control infections.

These challenges are exacerbated by other pervasive reasons behind poor understanding of informed consent forms and low consent rates for other types of clinical

trials. Several studies found that information sheets, including templates provided by Institutional Research Boards (IRBs), are difficult to read,[12,13] have great variability or insufficient explanation when stating risk and/or benefit,[14,15] and might not encourage decisions that meet recommendations such as the International Patient Decision Aids Standards instrument.[4] The issue might be exacerbated by language and literacy barriers, especially those in low- to middle-income countries.[16] Secondly, doctor-patient communication is often inadequate in explaining complex concepts such as randomisation, placebo, and priority given to patient well-being.[2,17] While several strategies such as improving doctor-patient communication and relationships have been implemented to optimize recruitment in clinical trials, there is a lack of evidence-based strategy.[6] Despite the introduction of "good clinical practice" guidelines by the World Health Organization,[3,18] systematic reviews show that participants' understanding of clinical trials, especially risk and side effects, had no substantial improvement over the past two decades.

There is a need for evidence-based strategies which balance individual patient autonomy and broader societal justice derived from successfully completed clinical trials. The current review aimed to understand experts' suggestions for best practice for informed consent and patients' concerns around the risk and uncertainty in the context of antimicrobial trials. We sourced both empirical studies that address patients' perspectives and articles that present domain experts' views. The specific objectives are to ascertain: (1) experts' views and recommendations on risk communication; (2) patients' or representatives' concerns around risk and uncertainty when deciding for participation; (3) how communication of trial information and other factors could influence consent in the context of antimicrobial clinical trials.

METHODS

Search strategy

We conducted searches in the following databases: Embase via Elsevier, Medline via Elsevier, PsycINFO via Ovid, CINAHL via EBSCOhost, and Web of Science Core. The initial searches were conducted on 26 Dec 2022, and update searches were conducted on 26 Apr 2023. The search strategy aimed to locate peer-reviewed articles published in the English language from January 2000. The details about the searches and full-search strategies are found in the online supplementary material. All results were collated using both the SR-accelerator and EndNote.

Data selection

The inclusion criteria were: (1) in the context of clinical trials involving antibiotic/ anti-infective agents; (2) empirical studies (e.g., qualitative or quantitative), or an expert opinion guideline (experts defined in this review included health professionals, academics/ or researchers, research staff, and regulators); and (3) addressed one or more of the following topics: patients' willingness to participate in trials; risk and benefit considerations when participating in trials; content of informed consent; ethical issues relating to informed consent. The exclusion criteria were (1) studies that tested the efficacy or safety of a drug; (2) focused on antibiotic prescription in healthcare settings; or (3) emphasized on vaccines, HIV, or Tuberculosis as typically such patients are generally less acutely unwell or decision for treatment was less urgent.

The quality of evidence from each shortlisted study was rated by two reviewers (YS, JY) based on the modified Oxford Centre for Evidence-Based Medicine (OCEBM) levels of evidence. Level 1 referred to the highest level of quality (including RCTs with proper power) while Level 5 referred to the lowest level of evidence (including case reports, opinions)[19].

Data extraction

Data extracted included the country/countries where the study was conducted, the type of clinical trial, and the target patient population. Data extracted for empirical studies also included study sample details (sample size and sample characteristics), methods (survey, interview, focus groups), and results and themes relating to informed consent. Data extracted for experts' articles included opinions and statements in relation to consent. Initial data extraction was performed by two independent reviewers (any two of JY, AP, YS). The aggregated data were then reviewed and revised by all reviewers (JY, AP, YS). The extracted qualitative data were coded thematically and categorized based on common themes by YS and were revised by JY.

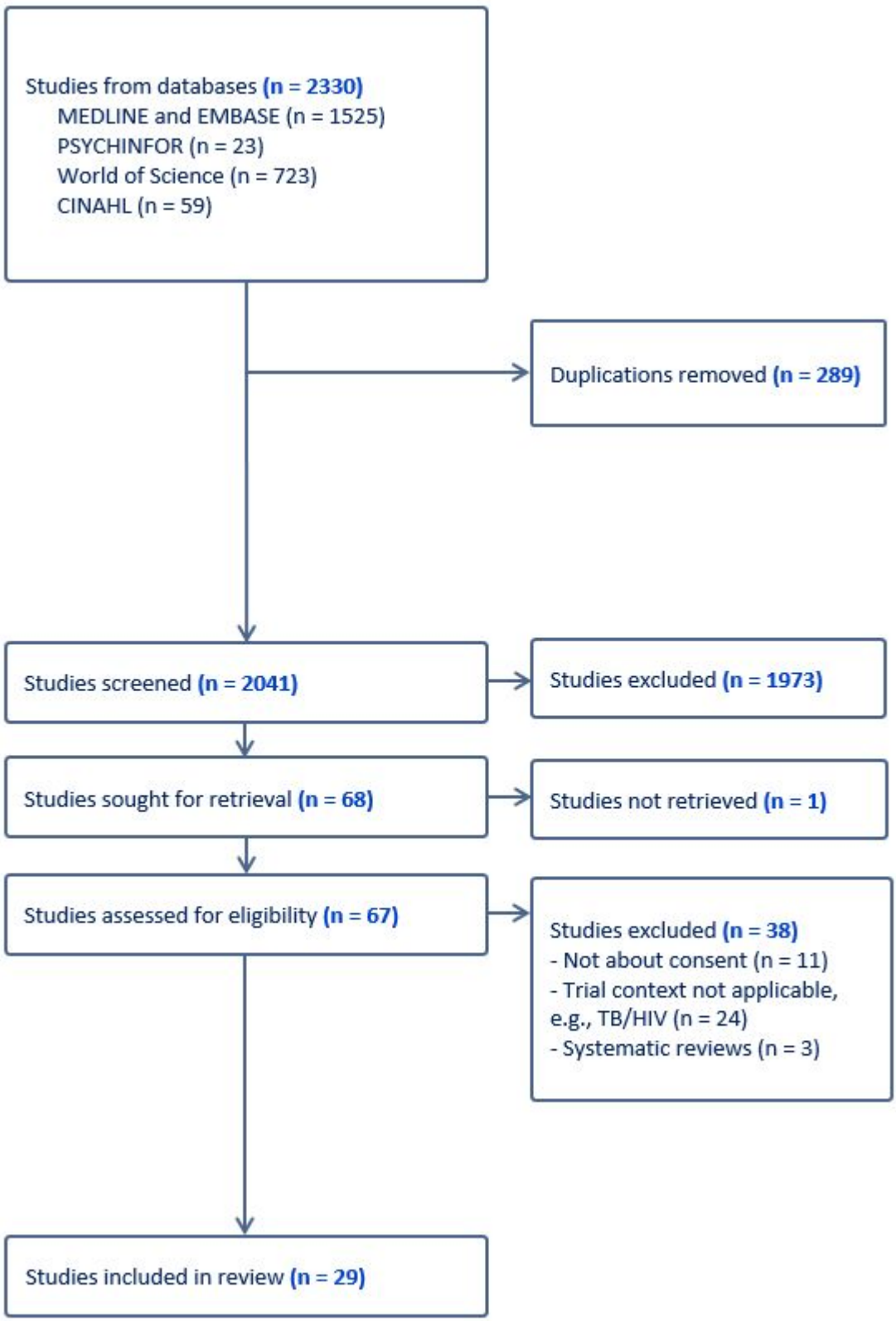

Figure 1. PRISMA flow chart of evidence selection

RESULTS

A total of 2041 unique records were screened and assessed by two independent reviewers. A total of 29 articles were selected for data extraction. These included 14 experts' opinions, 11 studies that focused on views of patients or representatives and 4 included both expert and patient responses (see Figure 1). Three, 1, 11, and 14 articles were of Oxford Centre for Evidence-Based Medicine levels 1, 3, 4, and 5 evidence, respectively.

Amongst the 18 articles based on experts' views (12 articles by individual experts and 6 articles summarizing aggregated experts' views), the vast majority of the experts were doctors or medical researchers in English-speaking high-income countries such as US, UK, Canada, and Australia (17/18, 94%) (Table 1). Three articles focused on informed consent for minors, two for pregnant women, one for older adults, and one for participants in developing countries. Among the 15 articles based on patients' and representatives' views, five focused on minors, two on pregnant women and one on older adults (see Table 2).

Achieving informed consent is challenging

A frequent concern among experts was that true informed consent with full comprehension by patients and representatives was challenging or not achievable[20–27] (Table 3). One reason was that because clinical trials are meant to establish evidence or explore uncertainties for the interventions they are testing, specific risks may not be clearly known at the time of research.[20,23,28–30] Other reasons included patients and representatives being unable to fully understand the research,[21,27,31] due to a lack of health literacy, complexity of research terms, and cultural and language barriers. While improving patients' understanding[24,25,32,33] was frequently recommended for improving informed consent, experts were also concerned that patients might have cognitive impairment or declined cognitive capacity in acute illness, who might be deemed to have decision-

making capacity but unable to fully comprehend the complexities of the proposed research.[22,23,25,31]

On the other hand, patients and representatives valued being well informed and receiving information about the research.[21,31,34–36] However, recurrent themes included the difficulty, lack of, or misunderstanding of research and the trial designs, especially randomizations and blinding.[35–39] Patients had an inaccurate understanding and underestimated the risk of the research.[37,38,40,41] Patients believed that there was minimal or even no risk involved in the research,[40] while overestimating the benefit or being over-optimistic about the treatment.[37]

Doctors and research staff are critical for the success and quality of consent

The experts generally agreed that doctors and research staff hold the responsibility to explain risk to patients.[20,23,29,33] However, doctors' and research staff's own preferences, understanding, and experiences might influence risk communication with patients and patients' consent.[21,31,39] Corneli[21] reported that the doctors and research staff might have misconceptions of terms like noninferiority, and their misunderstanding could negatively impact their risk communication to patients. Similarly, staff or doctors-related factors were the most commonly raised[35–40,42] by patients and representatives. Those factors included trust in doctors and research staff,[35,37,38,40,42] doctors' attitudes and opinions and how they frame risks during the communication,[35,37–40,42] and friendliness[36] and sympathy[35,38] from the staff. Furthermore, the need for counselling or discussion between patients and representatives and doctors and staff, including exploring alternative options[35,39] was both proposed by patients, representatives and experts.[20,23,24,39,43] Providing training to doctors and staff [25,32,39] was recommended for improving informed consent.

Table 1. Characteristics of Included Papers Synthesizing Expert views

Citation	Trial Related Context	Country of the trial/ context	Type	Expert Background	Level of Evidence
Savitz 2002[33]	Prophylactic antibiotics for neurosurgical procedure including clinical trials	US	Opinion	Doctor/Researcher	5
Jegede 2009[24]	Trovafloxacine for meningitis in child trial Target patient: Minors	Nigeria-Kano	Opinion	Researcher in sociology	5
Briggs 2015[20]	Phase IV clinical trials Target patient: Pregnant women	US	Opinion	Doctor/Researcher	5
Doig 2019[22]	The Closed or Open after Laparotomy (NCT03163095) Study (clinical trial for severe complicated intra-abdominal sepsis)	Canada	Opinion	Doctor/Researcher	5
Monach 2021[27]	Pragmatic trials for pneumonia	US	Opinion	Doctor/Researcher	5
Russell 2022[32]	Clinical trials for COVID-19 treatments and vaccines	International	Opinion	Doctor/Researcher	5
Parker 2021[43]	Pharmacogenetics to Avoid Loss of Hearing trial (ISRCTN13704894) Target patient: Minors Consent giver: Parents	UK	Opinion	Doctor/Researcher	5
van Iersel 2022[28]	Phase 1/2 clinical trials	-	Opinion	Pharmacological researchers	5
Green 2006[23]	-	UK	Opinion	Doctor/Researcher	5
Rogers 2020[29]	Evaluating Diuretics in Normal Care Study (ISRCTN46635087) Cluster randomised trials of hypertension prescribing policy Discussed consent mode: opt-in/out	UK	Opinion	Doctor/Researcher	5
Kirschner 2003[44]	Trials among stroke patients	US	Opinion	Doctor/Researcher	5

Menache 2003[26]	-	-	Opinion	Veterinarian	5
Knirsch 2016[25]	Clinical trials for Hospital-Acquired/Ventilator-Associated Bacterial Pneumonia	US	Meetings involving doctors and research staff in 2013	An expert team of various stakeholders including academic scientists, clinicians, regulators, trial monitors and coordinators, and patient and industry representatives	5
Sewell 2022[30]	Clinical trials for COVID-19 treatments and vaccines Target patient: Pregnant women	US	A public meeting involving doctors and research staff in 2021	Stakeholder categories including academia, industry, governmental agencies, and patient advocacy groups	5
Corneli 2018[34]	Noninferiority treatment trial for healthcare associated pneumonia Discussed consent mode: Advanced consent	US	Interviews and meetings involving health professionals, research staff and IRB members	10 IRB representatives; 7 investigators; 5 study coordinators	4
Corneli 2020[21]	Noninferiority treatment trial for healthcare associated pneumonia Discussed consent mode: Advanced consent	US	Interviews and meetings involving doctors, research staff and IRB members during 2017-2018	10 IRB representatives; 7 investigators; 5 study coordinators	4
Sherratt 2020[39]	CONservative TReatment of Appendicitis in Children a randomised controlled Trial (ISRCTN15830435) Target patient: Minors Consent giver: Parents	UK	Interviews with doctors during 2017-2018	35 health professionals (25 surgeons, 7 research nurses, 3 ward nurses)	4
Wood 2013[31]	Probiotics for Antibiotic Associated Diarrhoea study (ISRCTN 7954844) Target patient: Older adults in care homes Discussed consent mode: Advanced consent	UK	Interviews with doctors and staff in 2013/2014	19 care home staff; 10 GPs	4

Table 2. Characteristics of Included Papers Synthesizing Views of Patients and Representatives

Citation	Trial Related Context	Country of the context	Study Year	Method	Participant Characteristics	Level of evidence
Wood 2013[31]	Probiotics for Antibiotic Associated Diarrhoea study (ISRCTN 7954844) Target patient: older adults in care homes Consent mode: Advanced consent	UK	2013-2014	Interview	14 Residents in age cares 14 Relatives (4 partners, 10 children)	4
Kenyon 2006[38]	Overview of the Role of Antibiotics in Curtailing Labour and Early delivery - Antibiotics for Preterm, Prelabor Rupture of Membranes trial (ISRCTN53994660) Target patient: Pregnant women	UK	-	Interview	20 Patients	4
Tarrant 2015[40]	Overview of the Role of Antibiotics in Curtailing Labour and Early delivery - Antibiotics for Preterm, Prelabor Rupture of Membranes trial (ISRCTN53994660) Target patients: Pregnant women	UK	-	Interview	38 Patients (Age range: 28-59)	4
Corneli 2018[34]	Noninferiority treatment trial for healthcare associated pneumonia Discussed consent mode: Advanced consent	US	2016	Interview	18 Patients (22% male, Age range: 29-75, 10 had tertiary education) 12 caregivers (33% male; 4 had tertiary education)	4
Corneli 2020[21]	Noninferiority treatment trial for healthcare associated pneumonia Discussed consent mode: Advanced consent	US	2016-2017	Delphi method including semi-structured telephone interview and surveys	Interview study sample same as [34]	4

Sherratt 2020[39]	CONservative TReatment of Appendicitis in Children a randomised controlled Trial (ISRCTN15830435) Target patients: minors Consent giver: parents	UK	2017-2018	Interview	28 Families (15 with mothers only, 7 with father only, 6 with both parents; and 14 children completed interviews	4
Greenberg 2017[35]	Initial goal is antibacterial drug development pediatric trials; later expanded to any pediatric trials (including antibiotics) Target patient: minors Consent giver: parents	US	2015	Interview	24 Parents (19 consented trial participation, 5 declined trial participation)	4
Sureshkumar 2012[42]	Prevention of Recurrent Urinary Tract Infection in Children with Vesicoureteric Reflux and Normal Renal Tracts study (ACTRN12608000470392) Target patients: minors Consent giver: parents	Australia	-	Secondary data analysis mainly	1109 Parents (412 consented to clinical trial participation, 697 declined but gave reasons).	4
Songstad 2018[45]	The High Flow Nasal Cannulae as Primary Support in the Treatment of Early Respiratory Distress trial (ACTRN12613000303741) Target patients: minors Consent giver: parents Consent mode: prospective and retrospective consent	Australia	2013 (Era 1) 2014 (Era 2)	Secondary data analysis	220 Eligible babies in Era 1 (53% male, mean gestational age = 31.1 weeks) 209 Eligible babies in Era 2 (56% male, mean gestational age 31.1 weeks)	3
Criscione 2003[37]	Single site, double-masked, randomized, placebo-controlled trial to evaluate intravenous doxycycline for rheumatoid arthritis	US	-	Survey	30 Baseline patients (20% males, mean age = 44.9, median of 12.5 years of education) 26 Follow-up patients	4
Kyaw 2020[36]	Treatment of acute uncomplicated appendicitis comparing surgery to	Singapore	2017-2018	Survey	113 Patients' parents (Patients: 53.3% male, mean age = 9.7; parents: 33.6% Father, mean	4

	conservative management with antibiotics Target patient: minors Consent giver: parents				age = 44.2, 69.8% had tertiary education)	
Webster 2020[41]	Hypothetic randomized controlled antibiotic trials	UK	-	Experiment via online survey	1067 Participants (48.80% male, age range = 14.9% 65-75, 16.2% 55-64, 18.7% 45-54, 17.2% 35-44, 18.7% 25-34, 14.2% 16-24; 52.2% had tertiary education)	1
Lois 2023[46]	Comparison of Outcomes of antibiotic Drugs and Appendectomy trial (NCT02800785) (pragmatic, nonblinded, noninferiority, multicenter RCT comparing antibiotics and surgery for acute appendicitis)	US	2016-2020	Experiment	4627 patients (55% male, Age: 39% 18-29, 26% 30-39, 16% 40-49, 10% 50-59, 6% 60-69, 2% above 70; 3111 patients declined randomization)	1
Saadi 2023[47]	Hypothetic RCT antibiotic trials	UK	-	Experiment via online survey	443 participants (18.30% male, mean age = 25.5, 47% had had tertiary education)	1
Hickey 2010[48]	Oral ciprofloxacin with nebulised colistin vs intravenous anti-pseudomonal antibiotics for Pseudomonas aeruginosa infection Target patient: patients with cystic fibrosis	UK	2006	Survey	106 consumers (42% Male, 36% respondents were parents)	4

Table 3. Summary of Main Findings

Experts	Citations	Patients and representative	Citations
Informed consent and patient understanding			
True informed consent can be challenging		Patients and representative can have misunderstandings	
• Risk and uncertainty are the nature of the research; risks may not be clearly known at the time of research	[20,23,26,28–30]	• Lack the understanding, misunderstanding of risk; or believe in minimal to no risk; believe risks should have been known already	[37,38,40,41]
• Patients or representatives may not fully understand or misunderstand the research /risk; not pay attention or quickly forget the information	[21,24,27,31]	• Lack the understanding, misunderstanding of research design	[35–39]
• Patients may have impairment or do not have the capacity of decision-making	[22,23,25,31]	• Inaccurate/over-optimistic/overestimate of benefit	[37]
• Cultural and language barriers in developing countries may negatively impact comprehension	[24]		
• (Elderly) Participants may quickly forget the purpose of the study	[31]		
How much information should be given is not clear cut	[33]	Knowing information about the research and trial is important for patients and representatives	[21,34–36]
Improving patient understanding, and patient education are recommended	[24,25,32,33]		
Doctors/research staff are critical			
• Doctors/research staff have the responsibility to explain risks, including antimicrobial-resistant risk in antibiotic trials	[20,23,29,33]	Patients and representatives are influenced by:	
• Doctors/staff's own preference and understanding may result in biased explanation or wording when communicating with patients	[21,39]	• Doctors' attitudes and opinion, and how doctors frame risks	[35,36,38,39,42]
• Doctors/staff should provide counselling to patients; discussion with patients such as exploration of options	[20,23,24,33,39,43]	• Counselling and discussion with doctors and staff	[35,39]

• Coercive decisions during informed consent may happen	[23,24]	• Trust in/preferences of staff or doctors; believe that staff or doctors have their best interest	[35,37,38,40,42]
• Staff/doctor training, and improve communication/language of risk communication are recommended	[25,32,39]	• Friendliness and empathy of staff	[35,36,38]
• Senior/more experienced staff have better consent rate	[31]		
Information leaflets and consent forms			
• Staff indicated that representatives may want simple explanations and can be put off by the lengthy information sheet	[31]	• Participants may not interpret the information in consent forms as what is intended to be convened	[40]
• Consent forms should provide balanced information about alternatives	[21]	• Framing and format of consent form may influence risk perception when participants have sufficient time to read information but may not influence consent	[41,46,47]
		• Some patient information leaflets poorly inform people about risk	[41]
Enablers and barriers of consent			
Factors specific to trial properties and outcomes			
• Altruism	[28,30]	• Benefit other patients like them, and benefit science and research	[31,36–38,40,48]
• Risk-benefit considerations including long-term ones; uncertainty around the treatment	[27,28,32]	• Patient benefits from the treatment, hope	[31,35,37,38,40]
		• Safety/minimal risk, side effects and health risk to patients and/or their unborn child	[31,35,36,38,40,46]
• Logistics/time/convenience/ transport	[23,28,32]	• Logistics/time/convenience/ transport	[35,42,48]
• Financial incentives/barriers	[28]	• Reimbursement/incentives; Costs related to the treatment	[35,36,46]
• Social interaction with others during trial participation	[28]	• Disruption to social life	[35]

		• Interest	[31,46]
		• believe to have better medical care via trial participation	[37]
		• Concerned about blinding	[38]
		• Privacy and confidentiality	[46]
Other key factors/concerns			
• Trust in medicine	[24,32]	• Trust in regulation, system, or authorities	[35,36,38,40]
• Partnership, patients' knowledge, and contribution are acknowledged	[28]	• Trust in research	[36,40]
• Reliable information and source of information	[30,32]	• Family or friends' recommendations	[37]
		• Having preferences on treatment options	[36,42,46,48]
		• Autonomy	[36,46]
		• Having the right to withdraw	[34,36]
		• Socio-demographic factors	[36,42]
Consent Procedure			
Issues related to time			
• Time constraint in regular doctor consult session and variation in patient background	[27]	• Time pressure; limited processing of information, rely on common sense/heuristics	[38–40]
• Should allow sufficient time for patients to understand information and make decisions	[23,24]	• Some may make decisions with little consideration or straightway	[39,40]
		• Timing of approaching for recruitment is important	[35]
Health professionals and staff may be concerned about worrying families about treatment risks	[39]	Emotional distress, anxiety, fear, worry	[34–36,38–40,46]
Consent procedures especially complex ones take time and increase workload	[25,27,29,31,34]		
IRB complications and issues impose challenges	[25,27]		
Consent mode			
• Consider advanced consent and early enrolment	[25,31,34]	• No concerns over advanced consent and early enrolment	[31,34]

• Waiver or deferred consent	[22,27]	• Retrospective consent may increase consent rate	[45]
• The usual prior consent can be impractical or difficult, especially in urgent situations	[22,23,25,44]		
• The legally authorized representative should be communicated in any trial participation conversations	[25,34]		
• Opt-in/out recruitment	[27,29]		
• Use eConsent	[28]		
• Not all situations can omit consent process	[43]		

Consent forms

Several articles mentioned informed consent forms having either too much information, insufficient details for participants to understand the research, or being prone to misinterpretation by participants.[31,40,41,47] Three articles investigated the effect of the format and framing of information sheets on participants' perceptions or consent.[41,46,47] The framing of the side effects might influence risk perceptions when participants spent adequate time reading the information but did not appear to influence consent or perceived research credibility.[41]

Patients' concerns centred around risks and benefits to individual and wider population

Experts recognized a range of factors that influence patients' decision to provide informed consent, especially those relating to trial properties and outcomes such the study's risk and benefit,[27,28] altruism,[27,28] convenience (e.g. logistics, flexibility in time, etc.),[23,32] financial hurdles,[28] and social interaction with others and partnership (e.g. patients' expertise, trust and contribution are acknowledged) during the trial participation.[28] Similar factors were mentioned by patients and representatives, including health-related risk and outcomes,[31,35,36,38,40,46] perceived benefit to the patient's health condition and hope,[31,35,37,38,40] altruism (e.g. benefiting science and medical research, and other patients),[31,36–38,40,48] logistics and opportunity cost,[35,42] incentives and cost incurred due to complications,[36,46] and disruption to social lives.[35] Patients and representatives were also motivated by interest[31,46] and the belief that they might receive better care[37] through trial participation.

Both experts and patients also indicated trust as an important factor, including patients' trust in medicine,[24,32] the system and government regulation,[35,36,38,40] and science and medical research.[36,40] Patients' rights to withdrawal, autonomy, and having

had a decision or preference of a specific treatment option were also frequently mentioned.[36,42,46,48]

Consent procedures can be time-constrained and distressing

Experts expressed that the consent taking procedures, especially complex ones, can be laborious and increase the workload of healthcare professionals.[25,27,29,31,34] While experts recommended allowing more time for consent givers to make decision,[23,24,39] time-related issues such as time pressure were experienced by both experts and consent givers.[38–40] Recruiting doctors might face the challenge of time constraints during the usual doctor consultation.[27] Meanwhile, consent givers reported that they relied on common sense and heuristics during decision-making[40] and might have little consideration during the process.[39,40]

It was also observed that negative emotions, especially emotional distress, during the decision process among patients and representatives were reported in almost all the primary research studies.[34–40] Anxiety, fear, and worry were the common emotions expressed or shown by patients and representatives. Relating to the consent takers factors above, patients appreciate empathy from recruiting staff.[35,38]

Alternatives to conventional consenting process

Experts expressed concern that conventional informed consent after infection onset can be impractical.[22,23,25,44] Some experts suggested the implementation of advanced consent and early enrolment (consent and enrolment before a patient becomes eligible for a study) prior to infection onset.[25,31,34] Patients and relatives also expressed no major concerns about early recruitment/enrolment or advanced consent.[31,34]

DISCUSSION

The key findings in our review were that achieving true informed consent can be challenging. Doctors and research staff were suggested to be the most essential in the

informed consent and risk communication process. Trust in doctors and staff, medical research, the healthcare and regulatory systems were key influences during consent givers' decision-making. Lastly, there was pervasive emotional distress among patients and representatives during the consent procedure.

The finding that true informed consent might not be achieved, either due to the lack of understanding or the lack of capacity from patients and representatives, aligned with previous systematic reviews that consent givers' misunderstanding of clinical trials was one of the main issues in informed consent.[3,18] Given that clinical research is difficult to explain, patients' trust in doctors and research becomes critical for informed consent. The role of trust in patient decisions is also discussed in the previous literature.[2,49] Believing that doctors and staff have their best interests, and that safety is ensured via strict regulation reassures consent givers that any risks or negative consequences will be managed and minimized. However, trust could also be a double-edged blade, especially when consent givers do not have an accurate understanding of the research. Doctors and research staff may consciously or unconsciously express their own preferences and biases when communicating with consent givers and sometimes may even have misconceptions about the research. These in turn influence consent givers' understanding and decisions. Consent givers might also overly rely on trust rather than engaging in understanding the research. The experience of adverse effects that were not expected by patients due to misunderstanding can result in substantial damage to their trust in medicine.[24,40]

Furthermore, we observed that consent givers, including patients and family members, expressed anxiety, fear, worry, and feeling overwhelmed during the decision process. This is in line with the observation by a previous study that found that anxiety associated with these high-stakes interventions may impact patients' ability to understand the documents and make informed decisions about participation in the trial.[13] Anxiety and fear

can bias risk and benefit perceptions, thus influencing informed decision.[50,51] Managing consent givers' negative emotions and showing empathy and sensitivity from staff can be important during the informed consent procedure.

Our review did not find evidence that informed consent forms played a crucial role in consent in antimicrobial clinical trials. In fact, many participants might spend little time reading the information sheets in hypothetical clinical trials.[46] Consent givers in real trial settings might feel having little time to process information, thus may largely rely on heuristics.[52–54] Although it has been recommended that sufficient time should be allowed for consent givers to understand the information and make decisions,[23,24,39] time constraints can still be challenging, especially in trials with narrow recruitment window. An alternative solution is advanced consent and early enrolment (i.e., before patients become eligible) to address issues including patients having limited decision time or lack of decision capacity, which were found acceptable by both experts, and patients and their representatives.

We found a lack of research for informed consent in antimicrobial resistance trials in low- to middle-income countries. This contrasts with a review by the United States Food and Drug Administration, which included 42 phase 3 antibiotic trials that showed just 16.7% of participants were from the United States.[55] A recent systematic review found that the consent rate in low- to middle-income countries was significantly higher than in high-income countries.[56] However, the quality of the informed consent might be questionable as language and cultural barriers in developing countries might exacerbate the comprehension issues in informed consent.[57–60] Participants' consent in developing countries might also be influenced by unique factors such as social influence,[53] free medical care, and opportunities to gain knowledge and skills during the trial participation.[58,59] It is critical to understand informed consent from participants in low- to middle-income countries.

Two limitations of this review should be noted. First, we included articles which predominantly focused on bacterial infections. However, our findings may be extrapolated to other medical conditions and clinical trials which are time-sensitive. Second, we focused on risk and uncertainty communication during informed consent. Future research may have broader investigations on other factors that may influence informed consent.

In conclusion, our review found that difficulty in achieving full informed consent and adequate comprehension among patients and representatives, exacerbated by a narrow consent window, are major challenges in antimicrobial trials. Table 4 summarizes the main recommendations for improving informed consent and consent rate. Improving professionality, communication skills, and empathy amongst doctors and staff may improve consent quality, reduce negative emotions associated with the consent procedure and promote trust building. The current review also highlights the knowledge gap in developing countries and non-English speaking population and call for more research in under-researched populations.

Table 4. Recommendations for improving informed consent and consent rate

Challenges	**Recommendations**
Risk (mis)communication	1. Provide training to recruiting doctors and consent takers to improve communication of trial information and better manage patients' and representatives' expectations of risk
Emotional distress of patients and representatives	2. Provide training to recruiting doctors and consent takers to improve interpersonal skills to (1) be more sensitive to patients' circumstances and approach patients and representatives at an appropriate time. (2) be more empathetic and manage negative emotions of patients and representatives.
Refusals due to trial-related barriers	3. Involve patients and representatives in study design including informed consent process. 4. Identify local cultural barriers of consent among patients and representatives; address the manageable barriers (e.g., logistics, cost, social isolation etc) accordingly.
Refusals due to misperception of clinical trials	5. Public engagement to increase awareness and trust in clinical trials.

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Competing interest. The authors report no competing interest.

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Preregistration. This study was preregistered at https://osf.io/fu49y/. We report Oxford Centre for Evidence-Based Medicine levels of evidence as quality appraisal ratings in this manuscript instead of JBI/CASP as preregistered due to the significant heterogeneity in the articles included in the review.

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Supplement 1

Search Strategies (26 April 2023)

Published since 2010	
Embase (including embase and medline): (risk* OR uncertain* OR 'risk'/exp OR 'uncertainty'/exp OR 'side effect'/exp OR 'adverse event'/exp OR 'harm*':ab,ti) AND ('information sheet*':ab,ti OR 'information leaflet*':ab,ti OR 'information form*':ab,ti OR consent*:ab,ti OR 'informed':ab,ti OR 'informed consent'/exp) AND trial*:ab,ti AND (antibiotic*:ab,ti OR antibacterial*:ab,ti OR antiviral*:ab,ti OR antiinfective*:ab,ti OR 'anti biotic*':ab,ti OR 'anti bacterial*':ab,ti OR 'anti viral*':ab,ti OR 'anti infective*':ab,ti OR antimicrobi*:ab,ti OR antifung*:ab,ti OR antiparasit*:ab,ti OR 'antiinfective agent'/exp) AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [english]/lim AND [2010-2023]/py	
CINAHL **Limiters** - Published Date: 20100101-20231231; Exclude Pre-CINAHL; Exclude MEDLINE records; Language: English; Peer Reviewed ((TI ('information sheet*' OR 'information leaflet*' OR 'information form*' OR consent* OR informed) OR AB ('information sheet*' OR 'information leaflet*' OR 'information form*' OR consent* OR informed) OR (MM "Consent (Research)"))) AND ((TI trial* OR AB trial*)) AND (TX (risk* OR uncertain*) OR TI ('side effect*' OR 'side reaction*' OR 'adverse effect*' OR 'adverse event*' OR 'adverse reaction*' OR harm*) OR AB('side effect*' OR 'side reaction*' OR 'adverse effect*' OR 'adverse event*' OR 'adverse reaction*' OR harm*) OR (MM "Uncertainty") OR (MH "Adverse Drug Event+") OR (MM "Medication Side Effects (Saba CCC)")) AND ((TI (antibiotic* OR antibacterial* OR antiviral* OR antiinfective* OR anti-biotic* OR anti-bacterial* OR anti-viral* OR anti-infective* OR antimicrobi* OR antifung* OR antiparasit*) OR AB (antibiotic* OR antibacterial* OR antiviral* OR antiinfective* OR anti-biotic* OR anti-bacterial* OR anti-viral* OR anti-infective* OR antimicrobi* OR antifung* OR antiparasit*) OR (MH "Antiinfective Agents+")))	
PsychInfor (OVID)	
1	(antibiotic* or antibacterial* or antiviral* or antiinfective* or anti-biotic* or anti-bacterial* or anti-viral* or anti-infective* or antimicrobi* or antifung* or antiparasit*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]
2	(harm* or 'adverse effect*' or 'adverse event*' or 'adverse reaction*').mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]
3	exp "side effects (drug)"/ or exp "side effects (treatment)"/ or exp Uncertainty/
4	(risk* or uncertain*).af.
5	2 or 3 or 4
6	('information sheet*' or 'information leaflet*' or 'information form*' or consent* or informed).ab,ti.
7	exp Informed Consent/
8	6 or 7

9	trial*.ab,ti.
10	1 and 5 and 8 and 9
11	limit 10 to (peer reviewed journal and english language and yr="2010 - Current")

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2: TS=(antibiotic* OR antibacterial* OR antiviral* OR antiinfective* OR anti-biotic* OR anti-bacterial* OR anti-viral* OR anti-infective* OR antimicrobi* OR antifung* OR antiparasit*)

3: TI=(trial*) or AB=(trial*)

4: ALL=(risk* OR uncertain*) OR TS=("side effect*" OR "adverse effect*" OR "adverse reaction*"OR "adverse event*" OR harm*)

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PsychInfor (OVID)

1	(antibiotic* or antibacterial* or antiviral* or antiinfective* or anti-biotic* or anti-bacterial* or anti-viral* or anti-infective* or antimicrobi* or antifung* or antiparasit*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]
2	(harm* or 'adverse effect*' or 'adverse event*' or 'adverse reaction*').mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]
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Web of Science Core (2000-2009)

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3: TI=(trial*) or AB=(trial*)

4: ALL=(risk* OR uncertain*) OR TS=("side effect*" OR "adverse effect*" OR "adverse reaction*"OR "adverse event*" OR harm*)

5: #4 AND #3 AND #2 AND #1 and Review Article or Article (Document Types) and English (Languages)

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Informed Consent and Risk Communication Challenges in Antimicrobial Clinical Trials: A Scoping Review

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Primary Subject Heading:	Ethics
Secondary Subject Heading:	Infectious diseases
Keywords:	Clinical Trial, MEDICAL ETHICS, Patient Participation, Systematic Review

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Informed Consent and Risk Communication Challenges in Antimicrobial Clinical Trials: A Scoping Review

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ABSTRACT

Objectives Randomized trials for the management of drug-resistant infections are challenging to conduct as target patient populations often lack decision-making capacity, and enrolment windows are typically short. Improving informed consent and risk communication in these trials is especially crucial for protecting patient interests and maximizing trial efficiency. This study aimed to understand challenges in risk communication and informed consent in antimicrobial clinical trials.

Design Scoping review.

Data Sources Searches were conducted in Embase, Medline, CINAHL, and Web of Science Core for peer-reviewed English articles that were published from January 2000 to April 2023.

Eligibility criteria Included articles were empirical studies or expert opinions that sought experts', patients' or representatives' opinions on informed consent in the context of clinical trials involving antibiotic/anti-infective agents.

Data extraction and synthesis Abstract screening, full-text review, data extraction and evidence rating were performed by two independent reviewers. Extracted data were summarized and reported qualitatively based on common themes. A total of 2330 records were retrieved, and 29 articles were included in the review.

Results Half of the articles involving medical experts and a third involving patients and representatives reported that full comprehension by patients and representatives was challenging or not achievable. Healthcare providers and consent takers were crucial for the quality of informed consent. The level of trust consent givers placed on healthcare providers had a critical influence on consent rate. Emotional distress was pervasive among patients/representatives.

Conclusion The findings indicate that strengthening consent takers' communication skills in providing emotional support to patients and their representatives may improve informed consent. More research is needed to understand informed consent in low- and middle-income and non-English speaking countries.

Strengths and limitations of this study

- This study includes views from experts and patients or representatives on informed consent.
- This study advances the understanding of challenges in informed consent in antimicrobial trials.
- The main limitation is that this study predominantly focuses on bacterial infections thus has limited generalisability to other types of trials.

INTRODUCTION

Expensive and inefficient randomized trials for novel antibiotics and diagnostics are key factors contributing to the "valley of death" for research and innovation in this field [1]. This leads to delay in regulatory approvals for these life-saving drugs and deters pharmaceutical companies from investing in antimicrobial drug discovery.[2,3] One contributing hurdle to inefficiency in these trials is low consent rates coupled with poor quality of informed consent.[4–7] Poor quality of informed consent can harm the public's trust in healthcare and medicine. Slow recruitment in clinical trials threatens internal validity by increasing the risk of confounding factors, differential attrition, and operational drift, while it compromises generalizability by potentially altering the target population, reducing temporal relevance, and introducing selection bias. [8,9]

Informed consent involves "voluntary authorization, by a patient or research subject, with full comprehension of the risks involved" [10] and is one fundamental ethical requirement for human subject research. Risk and uncertainty exist when information is incomplete, and our knowledge of the negative outcomes, benefits, or other aspects of a medical treatment is limited during the informed consent procedure. [11–13] In most medical research, risk usually refers to the possibility of having undesirable outcomes such as adverse effects. Poor communication of the trial information is one main reason for the ineffective informed consent. [8]

Treatment strategy trials for multidrug-resistant infections hold unique challenges for informed consent. These challenges include strict enrolment criteria, limited timeframe for enrolment, and target patient populations not having decision-making capacity for consent due to underlying severe infections. Specifically, the window for recruitment and consent is often narrow as the antibiotics under evaluation need to be administered as quickly as possible to control infections.

These challenges are exacerbated by other pervasive reasons behind poor understanding of informed consent forms and low consent rates for other types of clinical trials. Several studies found that information sheets, including templates provided by Institutional Research Boards (IRBs), are difficult to read,[14,15] have great variability or insufficient explanation when stating risks and/or benefits,[16,17] and might not encourage decisions that meet recommendations such as the International Patient Decision Aids Standards instrument.[6] The issue might be exacerbated by language and literacy barriers, especially those in low- to middle-income countries.[18] Secondly, doctor-patient communication is often inadequate in explaining complex concepts such as randomisation, placebo, and priority given to patient well-being.[4,19] While several strategies such as improving doctor-patient communication and relationships have been implemented to optimize recruitment in clinical trials, there is a lack of evidence-based strategy.[8] Despite the introduction of "good clinical practice" guidelines by the World Health Organization,[5,20] systematic reviews show that participants' understanding of clinical trials, especially risk and side effects, had no substantial improvement over the past two decades.

There is a need for evidence-based strategies which balance individual patient autonomy and broader societal justice derived from successfully completed clinical trials. The current review aimed to understand challenges in informed consent in the context of antimicrobial trials, by focusing on issues around risk communication, including patients' concerns around the risk and uncertainty from experts' and consent givers' perspectives. We sourced both empirical studies that address patients' perspectives and articles that present domain experts' views. The specific objectives are to ascertain: (1) experts' views and recommendations on risk communication; (2) patients' or representatives' concerns around risk and uncertainty when deciding for participation; (3) how communication of trial

information and other factors could influence consent in the context of antimicrobial clinical trials.

METHODS

Search strategy

We conducted searches in the following databases: Embase via Elsevier, Medline via Elsevier, PsycINFO via Ovid, CINAHL via EBSCOhost, and Web of Science Core. The initial searches were conducted on 26 Dec 2022, and update searches were conducted on 26 Apr 2023. The search strategy aimed to locate peer-reviewed articles published in the English language from January 2000 for relevance and recency considerations in relation to treatment approaches and regulatory aspects. The details about the searches and full-search strategies are found in the online supplementary material. All results were collated using both the SR-accelerator [21] and EndNote.

Data selection

The inclusion criteria were: (1) in the context of clinical trials involving antibiotic/ anti-infective agents; (2) empirical studies (e.g., qualitative or quantitative), or an expert opinion guideline (experts defined in this review included health professionals, academics or researchers, research staff, and regulators); and (3) addressed one or more of the following topics: patients' willingness to participate in trials; risk and benefit considerations when participating in trials; content of informed consent; ethical issues relating to informed consent. The exclusion criteria were (1) studies that tested the efficacy or safety of a drug; (2) focused on antibiotic prescription in healthcare settings; or (3) articles that emphasized on cases (e.g., vaccines, parasites, HIV, or Tuberculosis) that have more unique treatment approaches and regulatory considerations, and patients are typically less acutely unwell or decision for treatment was less urgent. Title and abstract screening and full-text screening were performed by two reviewers (YS, AP). Discrepancies in selecting final included studies

were resolved by consensus or a third reviewer (YM). Data selection was performed using SR-accelerator and COVIDENCE [22].

The quality of evidence from each shortlisted study was rated by two reviewers (YS, JY) based on the modified Oxford Centre for Evidence-Based Medicine (OCEBM) levels of evidence. Level 1 referred to the highest level of quality (including RCTs with proper power) while Level 5 referred to the lowest level of evidence (including case reports, opinions)[23].

Data extraction

Data extracted included the country/countries where the study was conducted, the type of clinical trial, and the target patient population. Data extracted for empirical studies also included study sample details (sample size and sample characteristics), methods (survey, interview, focus groups), and results and themes relating to informed consent. Data extracted for experts' articles included opinions and statements in relation to consent. Initial data extraction was performed by two independent reviewers (any two of JY, AP, YS). The aggregated data were then reviewed and revised by all reviewers (JY, AP, YS). The extracted qualitative data were synthesized in a narrative format and categorized based on common themes by YS and were revised by JY. All authors reviewed the final themes.

Patient and Public Involvement

None.

RESULTS

A total of 2041 unique records were screened and assessed by two independent reviewers. A total of 29 articles were selected for data extraction. These included 14 experts' opinions, 11 studies that focused on views of patients or representatives and 4 included both expert and patient responses (see Figure 1). Three, 1, 11, and 14 articles were of Oxford Centre for Evidence-Based Medicine levels 1, 3, 4, and 5 evidence, respectively.

Amongst the 18 articles based on experts' views (12 articles by individual experts and 6 articles summarizing aggregated experts' views), the vast majority of the experts were doctors or medical researchers in English-speaking high-income countries such as US, UK, Canada, and Australia (17/18, 94%) (Table 1). Three articles focused on informed consent for minors, two for pregnant women, one for older adults, and one for participants in developing countries. Among the 15 articles based on patients' and representatives' views, five focused on minors, two on pregnant women and one on older adults (see Table 2).

Achieving informed consent is challenging

A frequent concern among experts was that true informed consent with full comprehension by patients and representatives was challenging or not achievable [24–31] (Table 3). One reason was that because clinical trials are meant to establish evidence or explore uncertainties for the interventions they are testing, specific risks may not be clearly known at the time of research.[24,27,32–34] Other reasons included patients and representatives being unable to fully understand the research,[25,31,35] due to a lack of health literacy, complexity of research terms, and cultural and language barriers. While improving patients' understanding[28,29,36,37] was frequently recommended for improving informed consent, experts were also concerned that patients might have cognitive impairment or declined cognitive capacity in acute illness, who might be deemed to have decision-making capacity but unable to fully comprehend the complexities of the proposed research.[26,27,29,35]

On the other hand, patients and representatives valued being well informed and receiving information about the research.[25,35,38–40] However, recurrent themes included the difficulty, lack of, or misunderstanding of research and trial designs, especially randomizations and blinding.[39–43] Patients had an inaccurate understanding and underestimated the risk of the research.[41,42,44,45] Patients believed that there was minimal

or even no risk involved in the research,[44] while overestimating the benefit or being over-optimistic about the treatment.[41]

Doctors and research staff are critical for the success and quality of consent

The experts generally agreed that doctors and research staff hold the responsibility to explain risks to patients.[24,27,33,37] However, doctors' and research staff's own preferences, understanding, and experiences might influence risk communication with patients and patients' consent.[25,35,43] Corneli[25] reported that the doctors and research staff might have misconceptions of terms like noninferiority, and their misunderstanding could negatively impact their risk communication to patients. Similarly, staff or doctors-related factors were the most commonly raised [39–44,46] by patients and representatives. Those factors included trust in doctors and research staff,[39,41,42,44,46] doctors' attitudes and opinions and how they frame risks during the communication,[39,41–44,46] and friendliness[40] and sympathy[39,42] from the staff. Furthermore, the need for counselling or discussion between patients and representatives and doctors and staff, including exploring alternative options[39,43] was both proposed by patients, representatives and experts.[24,27,28,43,47] Providing training to doctors and staff [29,36,43] was recommended for improving informed consent.

Table 1. Characteristics of Included Papers Synthesizing Expert views

Citation	Trial Related Context	Country of the trial/ context	Type	Expert Background	Level of Evidence
Savitz 2002[37]	Prophylactic antibiotics for neurosurgical procedure including clinical trials	US	Opinion	Doctor/Researcher	5
Jegede 2009[28]	Trovafloxacine for meningitis in child trial Target patient: Minors	Nigeria-Kano	Opinion	Researcher in sociology	5
Briggs 2015[24]	Phase IV clinical trials Target patient: Pregnant women	US	Opinion	Doctor/Researcher	5
Doig 2019[26]	The Closed or Open after Laparotomy (NCT03163095) Study (clinical trial for severe complicated intra-abdominal sepsis)	Canada	Opinion	Doctor/Researcher	5
Monach 2021[31]	Pragmatic trials for pneumonia	US	Opinion	Doctor/Researcher	5
Russell 2022[36]	Clinical trials for COVID-19 treatments and vaccines	International	Opinion	Doctor/Researcher	5
Parker 2021[47]	Pharmacogenetics to Avoid Loss of Hearing trial (ISRCTN13704894) Target patient: Minors Consent giver: Parents	UK	Opinion	Doctor/Researcher	5
van Iersel 2022[32]	Phase 1/2 clinical trials	-	Opinion	Pharmacological researchers	5
Green 2006[27]	-	UK	Opinion	Doctor/Researcher	5
Rogers 2020[33]	Evaluating Diuretics in Normal Care Study (ISRCTN46635087) Cluster randomised trials of hypertension prescribing policy Discussed consent mode: opt-in/out	UK	Opinion	Doctor/Researcher	5
Kirschner 2003[48]	Trials among stroke patients	US	Opinion	Doctor/Researcher	5

Menache 2003[30]	-	-	Opinion	Veterinarian	5
Knirsch 2016[29]	Clinical trials for Hospital-Acquired/Ventilator-Associated Bacterial Pneumonia	US	Meetings involving doctors and research staff in 2013	An expert team of various stakeholders including academic scientists, clinicians, regulators, trial monitors and coordinators, and patient and industry representatives	5
Sewell 2022[34]	Clinical trials for COVID-19 treatments and vaccines Target patient: Pregnant women	US	A public meeting involving doctors and research staff in 2021	Stakeholder categories including academia, industry, governmental agencies, and patient advocacy groups	5
Corneli 2018[38]	Noninferiority treatment trial for healthcare associated pneumonia Discussed consent mode: Advanced consent	US	Interviews and meetings involving health professionals, research staff and IRB members	10 IRB representatives; 7 investigators; 5 study coordinators	4
Corneli 2020[25]	Noninferiority treatment trial for healthcare associated pneumonia Discussed consent mode: Advanced consent	US	Interviews and meetings involving doctors, research staff and IRB members during 2017-2018	10 IRB representatives; 7 investigators; 5 study coordinators	4
Sherratt 2020[43]	CONservative TReatment of Appendicitis in Children a randomised controlled Trial (ISRCTN15830435) Target patient: Minors Consent giver: Parents	UK	Interviews with doctors during 2017-2018	35 health professionals (25 surgeons, 7 research nurses, 3 ward nurses)	4
Wood 2013[35]	Probiotics for Antibiotic Associated Diarrhoea study (ISRCTN 7954844) Target patient: Older adults in care homes Discussed consent mode: Advanced consent	UK	Interviews with doctors and staff in 2013/2014	19 care home staff; 10 GPs	4

Table 2. Characteristics of Included Papers Synthesizing Views of Patients and Representatives

Citation	Trial Related Context	Country of the context	Study Year	Method	Participants Characteristics	Level of evidence
Wood 2013[35]	Probiotics for Antibiotic Associated Diarrhoea study (ISRCTN 7954844) Target patient: older adults in care homes Consent mode: Advanced consent	UK	2013-2014	Interview	14 Residents in age cares 14 Relatives (4 partners, 10 children)	4
Kenyon 2006[42]	Overview of the Role of Antibiotics in Curtailing Labour and Early delivery - Antibiotics for Preterm, Prelabor Rupture of Membranes trial (ISRCTN53994660) Target patient: Pregnant women	UK	-	Interview	20 Patients	4
Tarrant 2015[44]	Overview of the Role of Antibiotics in Curtailing Labour and Early delivery - Antibiotics for Preterm, Prelabor Rupture of Membranes trial (ISRCTN53994660) Target patients: Pregnant women	UK	-	Interview	38 Patients (Age range: 28-59)	4
Corneli 2018[38]	Noninferiority treatment trial for healthcare associated pneumonia Discussed consent mode: Advanced consent	US	2016	Interview	18 Patients (22% male, Age range: 29-75, 10 had tertiary education) 12 caregivers (33% male; 4 had tertiary education)	4
Corneli 2020[25]	Noninferiority treatment trial for healthcare associated pneumonia Discussed consent mode: Advanced consent	US	2016-2017	Delphi method including semi-structured telephone interview and surveys	Interview study sample same as [38]	4

Sherratt 2020[43]	CONservative TReatment of Appendicitis in Children a randomised controlled Trial (ISRCTN15830435) Target patients: minors Consent giver: parents	UK	2017-2018	Interview	28 Families (15 with mothers only, 7 with father only, 6 with both parents; and 14 children completed interviews	4
Greenberg 2017[39]	Initial goal is antibacterial drug development pediatric trials; later expanded to any pediatric trials (including antibiotics) Target patient: minors Consent giver: parents	US	2015	Interview	24 Parents (19 consented trial participation, 5 declined trial participation)	4
Sureshkumar 2012[46]	Prevention of Recurrent Urinary Tract Infection in Children with Vesicoureteric Reflux and Normal Renal Tracts study (ACTRN12608000470392) Target patients: minors Consent giver: parents	Australia	-	Secondary data analysis mainly	1109 Parents (412 consented to clinical trial participation, 697 declined but gave reasons).	4
Songstad 2018[49]	The High Flow Nasal Cannulae as Primary Support in the Treatment of Early Respiratory Distress trial (ACTRN12613000303741) Target patients: minors Consent giver: parents Consent mode: prospective and retrospective consent	Australia	2013 (Era 1) 2014 (Era 2)	Secondary data analysis	220 Eligible babies in Era 1 (53% male, mean gestational age = 31.1 weeks) 209 Eligible babies in Era 2 (56% male, mean gestational age 31.1 weeks)	3
Criscione 2003[41]	Single site, double-masked, randomized, placebo-controlled trial to evaluate intravenous doxycycline for rheumatoid arthritis	US	-	Survey	30 Baseline patients (20% males, mean age = 44.9, median of 12.5 years of education) 26 Follow-up patients	4
Kyaw 2020[40]	Treatment of acute uncomplicated appendicitis comparing surgery to	Singapore	2017-2018	Survey	113 Patients' parents (Patients: 53.3% male, mean age = 9.7; parents: 33.6% Father, mean	4

	conservative management with antibiotics Target patient: minors Consent giver: parents				age = 44.2, 69.8% had tertiary education)	
Webster 2020[45]	Hypothetic randomized controlled antibiotic trials	UK	-	Experiment via online survey	1067 Participants (48.80% male, age range = 14.9% 65-75, 16.2% 55-64, 18.7% 45-54, 17.2% 35-44, 18.7% 25-34, 14.2% 16-24; 52.2% had tertiary education)	1
Lois 2023[50]	Comparison of Outcomes of antibiotic Drugs and Appendectomy trial (NCT02800785) (pragmatic, nonblinded, noninferiority, multicenter RCT comparing antibiotics and surgery for acute appendicitis)	US	2016-2020	Experiment	4627 patients (55% male, Age: 39% 18-29, 26% 30-39, 16% 40-49, 10% 50-59, 6% 60-69, 2% age 70; 3111 patients declined randomization)	1
Saadi 2023[51]	Hypothetic RCT antibiotic trials	UK	-	Experiment via online survey	443 participants (18.30% male, mean age = 25.5, 47% had had tertiary education)	1
Hickey 2010[52]	Oral ciprofloxacin with nebulised colistin vs intravenous anti-pseudomonal antibiotics for Pseudomonas aeruginosa infection Target patient: patients with cystic fibrosis	UK	2006	Survey	106 consumers (42% Male, 36% respondents were parents)	4

Table 3. Summary of Main Findings

Experts	Citations	Patients and representative	Citations
Informed consent and patient understanding			
True informed consent can be challenging		Patients and representative can have misunderstandings	
• Risk and uncertainty are the nature of the research; risks may not be clearly known at the time of research	[24,27,30,32–34]	• Lack the understanding; misunderstanding of risk; or believe in minimal to no risk; believe risks should have been known already	[41,42,44,45]
• Patients or representatives may not fully understand or misunderstand the research /risk; not pay attention or quickly forget the information	[25,28,31,35]	• Lack the understanding; misunderstanding of research design	[39–43]
• Patients may have impairment or do not have the capacity of decision-making	[26,27,29,35]	• Inaccurate/over-optimistic/overestimate of benefit	[41]
• Cultural and language barriers in developing countries may negatively impact comprehension	[28]		
• (Elderly) Participants may quickly forget the purpose of the study	[35]		
How much information should be given is not clear cut	[37]	Knowing information about the research and trial is important for patients and representatives	[25,38–40]
Improving patient understanding, and patient education are recommended	[28,29,36,37]		
Doctors/research staff are critical			
• Doctors/research staff have the responsibility to explain risks, including antimicrobial-resistant risk in antibiotic trials	[24,27,33,37]	Patients and representatives are influenced by:	
• Doctors/staff's own preference and understanding may result in biased explanation or wording when communicating with patients	[25,43]	• Doctors' attitudes and opinion, and how doctors frame risks	[39,40,42,43,46]
• Doctors/staff should provide counselling to patients; discussion with patients such as exploration of options	[24,27,28,37,43,47]	• Counselling and discussion with doctors and staff	[39,43]

• Coercive decisions during informed consent may happen	[27,28]	• Trust in/preferences of staff or doctors; believe that staff or doctors have their best interest	[39,41,42,44,46]
• Staff/doctor training, and improve communication/language of risk communication are recommended	[29,36,43]	• Friendliness and empathy of staff	[39,40,42]
• Senior/more experienced staff have better consent rate	[35]		
Information leaflets and consent forms			
• Staff indicated that representatives may want simple explanations and can be put off by the lengthy information sheet	[35]	• Participants may not interpret the information in consent forms as what is intended to be convened	[44]
• Consent forms should provide balanced information about alternatives	[25]	• Framing and format of consent form may influence risk perception when participants have sufficient time to read information but may not influence consent	[45,50,51]
		• Some patient information leaflets poorly inform people about risk	[45]
Patients' considerations in consenting			
Factors specific to trial properties and outcomes			
• Altruism	[32,34]	• Benefit other patients like them, and benefit science and research	[35,40–42,44,52]
• Risk-benefit considerations including long-term ones; uncertainty around the treatment	[31,32,36]	• Patient benefits from the treatment, hope	[35,39,41,42,44]
		• Safety/minimal risk, side effects and health risk to patients and/or their unborn child	[35,39,40,42,44,50]
• Logistics/time/convenience/ transport	[27,32,36]	• Logistics/time/convenience/transport	[39,46,52]
• Financial incentives/barriers	[32]	• Reimbursement/incentives; Costs related to the treatment	[39,40,50]
• Social interaction with others during trial participation	[32]	• Disruption to social life	[39]

		• Interest	[35,50]
		• Believe to have better medical care via trial participation	[41]
		• Concerned about blinding	[42]
		• Privacy and confidentiality	[50]
Other key factors/concerns			
• Trust in medicine	[28,36]	• Trust in regulation, system, or authorities	[39,40,42,44]
• Partnership, patients' knowledge, and contribution are acknowledged	[32]	• Trust in research and researchers (e.g., researchers will aim for more benefits and less risks for patients)	[40,44]
• Reliable information and source of information	[34,36]	• Family or friends' recommendations	[41]
		• Having preferences on treatment options	[40,46,50,52]
		• Autonomy	[40,50]
		• Having the right to withdraw	[38,40]
		• Socio-demographic factors (e.g., education, age of patients, language spoken at home)	[40,46]
Consent Procedure			
Issues related to time			
• Time constraint in regular doctor consult session and variation in patient background	[31]	• Time pressure; limited processing of information, rely on common sense/heuristics	[42–44]
• Should allow sufficient time for patients to understand information and make decisions	[27,28]	• Some may make decisions with little consideration or straightway	[43,44]
		• Timing of approaching for recruitment is important	[39]
Health professionals and staff may be concerned about worrying families about treatment risks	[43]	Emotional distress, anxiety, fear, worry	[38–40,42–44,50]
Consent procedures especially complex ones take time and increase workload	[29,31,33,35,38]		
IRB complications and issues impose challenges	[29,31]		
Consent mode			

• Consider advanced consent and early enrolment	[29,35,38]	• No concerns over advanced consent and early enrolment	[35,38]
• Waiver or deferred consent	[26,31]	• Retrospective consent may increase consent rate	[49]
• The usual prior consent can be impractical or difficult, especially in urgent situations	[26,27,29,48]		
• The legally authorized representative should be communicated in any trial participation conversations	[29,38]		
• Opt-in/out recruitment	[31,33]		
• Use eConsent	[32]		
• Not all situations can omit consent process	[47]		

Consent forms

Several articles mentioned informed consent forms having either too much information, insufficient details for participants to understand the research, or being prone to misinterpretation by participants.[35,44,45,51] Three articles investigated the effect of the format and framing of information sheets on participants' perceptions or consent.[45,50,51] The framing of the side effects might influence risk perceptions when participants spent adequate time reading the information but did not appear to influence consent or perceived research credibility.[45]

Patients' concerns centred around risks and benefits to individual and wider population

Experts recognized a range of factors that influence patients' decision to provide informed consent, especially those relating to trial properties and outcomes such the study's risk and benefit,[31,32] altruism,[31,32] convenience (e.g. logistics, flexibility in time, etc.),[27,36] financial hurdles,[32] and social interaction with others and partnership (e.g. patients' expertise, trust and contribution are acknowledged) during the trial participation.[32] Similar factors were mentioned by patients and representatives, including health-related risk and outcomes,[35,39,40,42,44,50] perceived benefit to the patient's health condition and hope,[35,39,41,42,44] altruism (e.g. benefiting science and medical research, and other patients),[35,40–42,44,52] logistics and opportunity cost,[39,46] incentives and cost incurred due to complications,[40,50] and disruption to social lives.[39] Patients and representatives were also motivated by their interest in the study [35,50] and the belief that they might receive better care[41] through trial participation.

Both experts and patients also indicated trust as an important factor, including patients' trust in medicine,[28,36] the system and government regulation,[39,40,42,44] and science and medical research.[40,44] Patients' rights to withdrawal, autonomy (e.g., being

able to make a choice or act based on their will), and having had a decision or preference of a specific treatment option were also frequently mentioned.[40,46,50,52]

Consent procedures can be time-constrained and distressing

Experts expressed that the consent taking procedures, especially complex ones, can be laborious and increase the workload of healthcare professionals.[29,31,33,35,38] While experts recommended allowing more time for consent givers to make decision,[27,28,43] time-related issues such as time pressure were experienced by both experts and consent givers.[42–44] Recruiting doctors might face the challenge of time constraints during the usual doctor consultation.[31] Meanwhile, consent givers reported that they relied on common sense and heuristics during decision-making, [44] and might have little consideration during the process.[43,44]

It was also observed that negative emotions, especially emotional distress, during the decision process among patients and representatives were reported in almost all the primary research studies.[38–44] Anxiety, fear, and worry were the common emotions expressed or shown by patients and representatives. Relating to the consent takers factors above, patients appreciate empathy from recruiting staff.[39,42]

Alternatives to conventional consenting process

Experts expressed concern that conventional informed consent after infection onset can be impractical.[26,27,29,48] Some experts suggested the implementation of advanced consent and early enrolment (consent and enrolment before a patient becomes eligible for a study) prior to infection onset.[29,35,38] Patients and relatives also expressed no major concerns about early recruitment/enrolment or advanced consent.[35,38]

DISCUSSION

The current review explored challenges in informed consent by focusing on risk communication, including patients' concerns about risk and uncertainty, in the context of

antimicrobial trials. One key finding in our review was that achieving true informed consent can be challenging. Doctors and research staff were suggested to be the most essential in the informed consent and risk communication process. Trust in doctors and staff, medical research, the healthcare and regulatory systems were key influences during consent givers' decision-making. Lastly, there was pervasive emotional distress among patients and representatives during the consent procedure.

The finding that true informed consent might not be achieved, either due to the lack of understanding or the lack of capacity from patients and representatives, aligned with previous systematic reviews that consent givers' misunderstanding of clinical trials was one of the main issues in informed consent.[5,20] Given that clinical research is difficult to explain, patients' trust in doctors and research becomes critical for informed consent. The role of trust in patient decisions is also discussed in the previous literature.[4,53] Believing that doctors and staff have their best interests, and that safety is ensured via strict regulation reassures consent givers that any risks or negative consequences will be managed and minimized. However, trust could also be a double-edged blade, especially when consent givers do not have an accurate understanding of the research. Doctors and research staff may consciously or unconsciously express their own preferences and biases when communicating with consent givers and sometimes may even have misconceptions about the research. These in turn influence consent givers' understanding and decisions. Consent givers might also overly rely on trust rather than engaging in understanding the research. The experience of adverse effects that were not expected by patients due to misunderstanding can result in substantial damage to their trust in medicine.[28,44]

Furthermore, we observed that consent givers, including patients and family members, expressed anxiety, fear, worry, and feeling overwhelmed during the decision process. This is in line with the observation by a previous study that found that anxiety

associated with these high-stakes interventions may impact patients' ability to understand the documents and make informed decisions about participation in the trial.[15] Anxiety and fear can bias risk and benefit perceptions, thus influencing informed decision.[54,55] Managing consent givers' negative emotions and showing empathy and sensitivity by staff can be important during the informed consent procedure.

Our review did not find evidence that informed consent forms played a crucial role in consent in antimicrobial clinical trials. In fact, many participants might spend little time reading the information sheets in hypothetical clinical trials.[50] Consent givers in real trial settings might feel having little time to process the given information, and thus may largely rely on heuristics.[56–58] Although it has been recommended that sufficient time should be allowed for consent givers to understand the information and make decisions,[27,28,43] time constraints can still be challenging, especially in trials with narrow recruitment windows. An alternative solution is allowing advanced consent and early enrolment (i.e., before patients become eligible), to address issues including patients having limited decision time or lack of decision capacity, which were found acceptable by both experts, and patients or their representatives.

We found a lack of research for informed consent in antimicrobial resistance trials in low- to middle-income countries. This contrasts with a review by the United States Food and Drug Administration, which included 42 phase 3 antibiotic trials that showed just 16.7% of participants were from the United States.[59] A recent systematic review found that the consent rate in low- to middle-income countries was significantly higher than in high-income countries.[60] However, the quality of the informed consent might be questionable as language and cultural barriers in developing countries might exacerbate the comprehension issues in informed consent.[61–64] Participants' consent in developing countries might also be influenced by unique factors such as social influence,[61] free medical care, and

opportunities to gain knowledge and skills during the trial participation.[62,63] Meanwhile, significant disparities exist where middle and lower-middle income countries have limited access to healthcare including antibodies. [65] Risks and benefits of trials and participants' motivations to consent in middle and lower-middle income countries encompass a unique set of ethical challenges.[66] It is critical to understand informed consent from participants in low- to middle-income countries.

Several limitations of this review should be noted. First, we included articles which predominantly focused on bacterial infections. However, our findings may be extrapolated to other medical conditions and clinical trials which are time-sensitive. Second, we focused on risk and uncertainty communication during informed consent. Future research may have broader investigations on other factors that may influence informed consent. Furthermore, challenges in recruitment and issues of trial validity go beyond those in risk communication, comprehension and acceptance of trial participation. The extent to which a trial is inclusive in reaching patients from diverse backgrounds also influences the trial recruitment and generalizability of the trial results. Inclusiveness and diversity have been increasingly emphasized by both scientific communities and regulatory bodies. [67] Future research should have a more in-depth understanding of the interplay between consent, inclusiveness and diversity in trial conduct.

Finally, the articles in the current review are exclusive academic articles and have been more focused on issues relating to consent givers. Successful recruitment, effective risk communications and high-quality conduct of trials can depend on investigators' ability to conduct trials and the availability of the research staff to invest in the time to facilitate consent. Future research should also include challenges relating to trial investigators and regulators (e.g., Institutional Review Boards) and review literature beyond traditional academic publications.

In conclusion, our review found that difficulty in achieving full informed consent and adequate comprehension among patients and representatives, exacerbated by a narrow consent window, are major challenges in antimicrobial trials. Improving professionality, communication skills, and empathy amongst doctors and staff may improve consent quality, reduce negative emotions associated with the consent procedure and promote trust building. Table 4 summarizes the main recommendations for improving informed consent and consent rate based on the current review. Meanwhile, more research and empirical evidence are needed to develop a more systematic and effective guidance for those recommendations. The current review also highlights the knowledge gap in developing countries and non-English speaking population and call for more research in under-researched populations.

Table 4. Recommendations for improving informed consent and consent rate

Challenges	Recommendations
Risk (mis)communication	1. Provide training to recruiting doctors and consent takers to improve communication of trial information and better manage patients' and representatives' expectations of risk
Emotional distress of patients and representatives	2. Provide training to recruiting doctors and consent takers to improve interpersonal skills to (1) be more sensitive to patients' circumstances and approach patients and representatives at an appropriate time. (2) be more empathetic and manage negative emotions of patients and representatives.
Refusals due to trial-related barriers	3. Involve patients and representatives in study design including informed consent process. 4. Identify local cultural barriers of consent among patients and representatives; address the manageable barriers (e.g., logistics, cost, social isolation, etc.) accordingly.
Refusals due to misperception of clinical trials	5. Public engagement to increase awareness and trust in clinical trials.

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Data availability. The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Competing interest. The authors report no competing interest.

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Preregistration. This study was preregistered at https://osf.io/fu49y/. We report Oxford Centre for Evidence-Based Medicine levels of evidence as quality appraisal ratings in this manuscript instead of JBI/CASP as preregistered due to the significant heterogeneity in the articles included in the review.

Ethics Approval. Not Applicable. This study does not involve human participants.

Contributorship Statement. YS, YM and DP conceptualised and designed the study. YS, JY and AP contributed to data collection. YS wrote the original draft and acted as guarantor. All authors contributed to interpretation, and reviewed, edited, and approved the final version of the manuscript.

Figure 1. PRISMA flow chart of evidence selection

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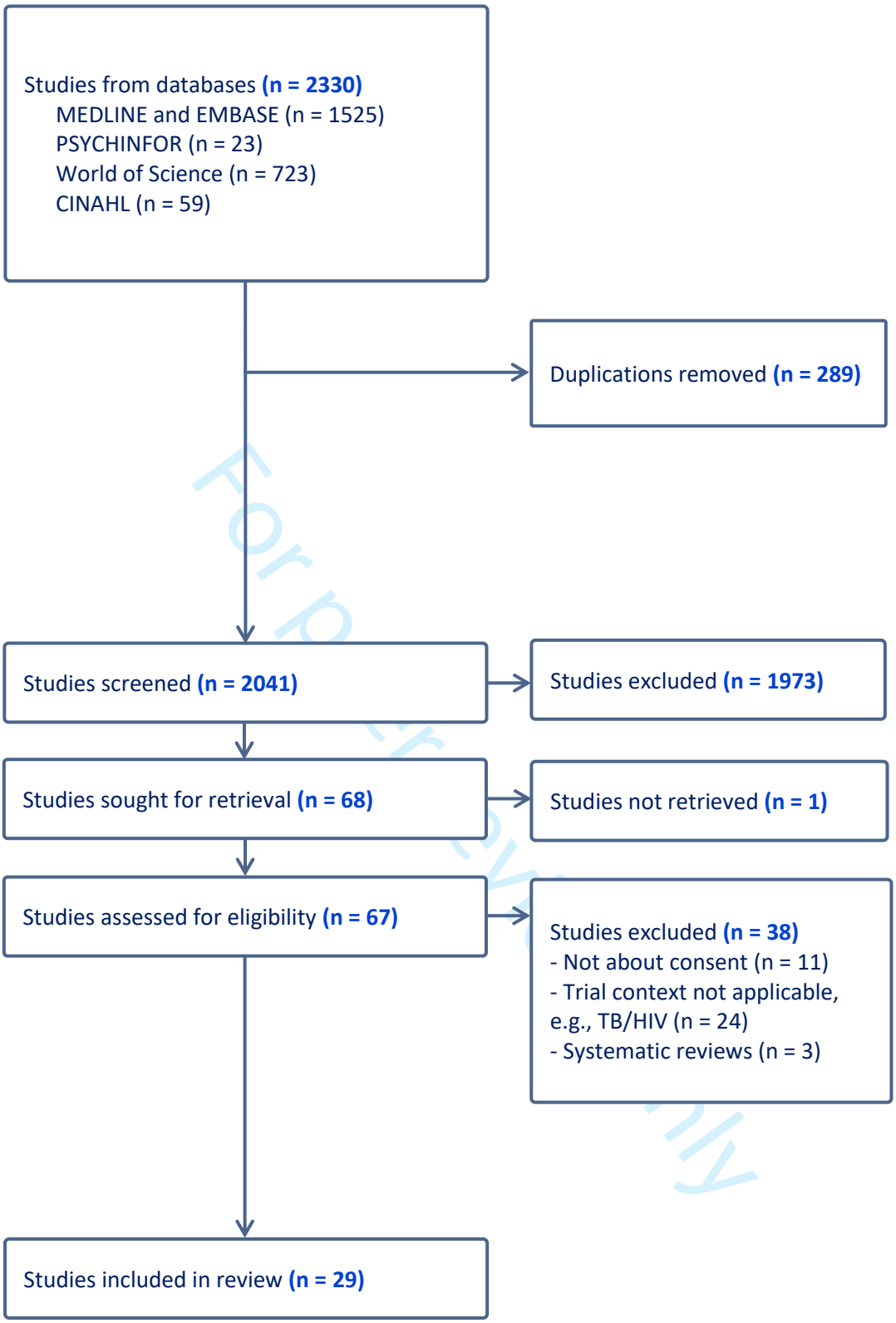

Supplement 1

Search Strategies (26 April 2023)

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((TI ('information sheet*' OR 'information leaflet*' OR 'information form*' OR consent* OR informed) OR AB ('information sheet*' OR 'information leaflet*' OR 'information form*' OR consent* OR informed) OR (MM "Consent (Research)"))) AND ((TI trial* OR AB trial*)) AND (TX (risk* OR uncertain*) OR TI ('side effect*' OR 'side reaction*' OR 'adverse effect*' OR 'adverse event*' OR 'adverse reaction*' OR harm*) OR AB('side effect*' OR 'side reaction*' OR 'adverse effect*' OR 'adverse event*' OR 'adverse reaction*' OR harm*) OR (MM "Uncertainty") OR (MH "Adverse Drug Event+") OR (MM "Medication Side Effects (Saba CCC)")) AND ((TI (antibiotic* OR antibacterial* OR antiviral* OR antiinfective* OR anti-biotic* OR anti-bacterial* OR anti-viral* OR anti-infective* OR antimicrobi* OR antifung* OR antiparasit*) OR AB (antibiotic* OR antibacterial* OR antiviral* OR antiinfective* OR anti-biotic* OR anti-bacterial* OR anti-viral* OR anti-infective* OR antimicrobi* OR antifung* OR antiparasit*) OR (MH "Antiinfective Agents+")))

PsychInfor (OVID)

1	(antibiotic* or antibacterial* or antiviral* or antiinfective* or anti-biotic* or anti-bacterial* or anti-viral* or anti-infective* or antimicrobi* or antifung* or antiparasit*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]
2	(harm* or 'adverse effect*' or 'adverse event*' or 'adverse reaction*').mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]
3	exp "side effects (drug)"/ or exp "side effects (treatment)"/ or exp Uncertainty/
4	(risk* or uncertain*).af.
5	2 or 3 or 4
6	('information sheet*' or 'information leaflet*' or 'information form*' or consent* or informed).ab,ti.
7	exp Informed Consent/
8	6 or 7
9	trial*.ab,ti.
10	1 and 5 and 8 and 9
11	limit 10 to (peer reviewed journal and english language and yr="2010 -Current")

Web of Science Core (since 2010)

1: TI=('information sheet*' OR 'information leaflet*' OR 'information form*' OR consent* OR

informed) OR AB=('information sheet*' OR 'information leaflet*' OR 'information form*' OR consent* OR informed) 2: TS=(antibiotic* OR antibacterial* OR antiviral* OR antiinfective* OR anti-biotic* OR anti-bacterial* OR anti-viral* OR anti-infective* OR antimicrobi* OR antifung* OR antiparasit*) 3: TI=(trial*) or AB=(trial*) 4: ALL=(risk* OR uncertain*) OR TS=("side effect*" OR "adverse effect*" OR "adverse reaction*"OR "adverse event*" OR harm*) 5: #4 AND #3 AND #2 AND #1 and Review Article or Article (Document Types) and English (Languages)

3

Published 2000- 2009
Embase (including embase and medline): (risk* OR uncertain* OR 'risk'/exp OR 'uncertainty'/exp OR 'side effect'/exp OR 'adverse event'/exp OR 'harm*':ab,ti) AND ('information sheet*':ab,ti OR 'information leaflet*':ab,ti OR 'information form*':ab,ti OR consent*:ab,ti OR 'informed':ab,ti OR 'informed consent'/exp) AND trial*:ab,ti AND (antibiotic*:ab,ti OR antibacterial*:ab,ti OR antiviral*:ab,ti OR antiinfective*:ab,ti OR 'anti biotic*':ab,ti OR 'anti bacterial*':ab,ti OR 'anti viral*':ab,ti OR 'anti infective*':ab,ti OR antimicrobi*:ab,ti OR antifung*:ab,ti OR antiparasit*:ab,ti OR 'antiinfective agent'/exp) AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [english]/lim AND [2000-2009]/py
CINAHL **Limiters** - Published Date: 20000101-20091231; Exclude Pre-CINAHL; Exclude MEDLINE records; Language: English; Peer Reviewed ((TI ('information sheet*' OR 'information leaflet*' OR 'information form*' OR consent* OR informed) OR AB ('information sheet*' OR 'information leaflet*' OR 'information form*' OR consent* OR informed) OR (MM "Consent (Research)"))) AND ((TI trial* OR AB trial*)) AND (TX (risk* OR uncertain*) OR TI ('side effect*' OR 'side reaction*' OR 'adverse effect*' OR 'adverse event*' OR 'adverse reaction*' OR harm*) OR AB('side effect*' OR 'side reaction*' OR 'adverse effect*' OR 'adverse event*' OR 'adverse reaction*' OR harm*) OR (MM "Uncertainty") OR (MH "Adverse Drug Event+") OR (MM "Medication Side Effects (Saba CCC)")) AND ((TI (antibiotic* OR antibacterial* OR antiviral* OR antiinfective* OR anti-biotic* OR anti-bacterial* OR anti-viral* OR anti-infective* OR antimicrobi* OR antifung* OR antiparasit*) OR AB (antibiotic* OR antibacterial* OR antiviral* OR antiinfective* OR anti-biotic* OR anti-bacterial* OR anti-viral* OR anti-infective* OR antimicrobi* OR antifung* OR antiparasit*) OR (MH "Antiinfective Agents+")))
PsychInfor (OVID)
1 (antibiotic* or antibacterial* or antiviral* or antiinfective* or anti-biotic* or anti-bacterial* or anti-viral* or anti-infective* or antimicrobi* or antifung* or antiparasit*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]
2 (harm* or 'adverse effect*' or 'adverse event*' or 'adverse reaction*').mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word]
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4 (risk* or uncertain*).af.
5 2 or 3 or 4
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7 exp Informed Consent/

8	6 or 7
9	trial*.ab,ti.
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5: #4 AND #3 AND #2 AND #1 and Review Article or Article (Document Types) and English (Languages)