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Review Article

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Surveillance of the Impact of Antimicrobial Resistant Infections in Immunocompromised Children's Therapy: A Systematic Review

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Abstract

Background: *Antimicrobial resistance (AMR) is a global problem. For many reasons, resistant bacteria do not cease to emerge and re-emerge. The impact of AMR on patient therapy is still limited in literature, but there is still much to do, mainly in pediatric settings. It is vital to assess the necessity of observing the impact of such infections on the clinical care trends to which some kids may already be subject, strengthening, improving, and, where necessary, implementing new age policies and regulations that may help contain the spread of AMR.*

Method: *We performed a yearlong review of literature on antimicrobial resistance in paediatrics immunosuppressed patients until September 2022. We draw up a protocol to which we adhered rigorously, following the prescribed including and excluding criteria.*

Results: *From the 110 articles finally selected following the PRISMA workflow diagram, from which 29% of them were in the majority randomized controlled trials studies, the remaining selection ranged from case controls to cohort studies, systematic reviews, held before and after reports trials, matched case-control and placebo reports trials and few not reported research article types (15%).*

Conclusion: *The process yielded the confirmation that there is good evidence of the lethal effect of resistant microbiological infections in immunocompromised children in and out of hospitals. What needs to be added is practical evidence of such damage to the patient and the public health sector, which can be conquered through well-programmed cohort-based studies.*

Keywords: Antimicrobial Resistance, Surveillance, Immune Depression, Children, Antimicrobial Stewardship

1. Introduction

1.1. Rationale

According to the World Health Organization's annual reports on microbial resistance, antimicrobial resistance (AMR) is a global threat [1-5]. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) defines AMR in two ways: firstly, by the population of bacteria that exist before exposure to the antimicrobial agent, and secondly, by adverse clinical outcomes related to uncontrolled infection, if a patient receives that antimicrobial [6].

A microorganism is resistant if it has an acquired or a genetic mutational type of reluctance mechanism to the drug in question [7]. Clinical resistance, on the other hand, is defined by the level of antimicrobial activity associated with a high likelihood of therapeutic failure [8]. Pathogens like Pseudomonas Burkholderia sp, [9-11]. Shigella sp and other pan-resistant bacteria, Pandorea sp, among others gram-negative microorganisms, Staphylococci (MRSA), coagulase-negative Enterobacter sp, with variants of the strep groups, have been identified as highly dangerous among immunocompromised patients and immunocompromised pediatric patients [12-26]. Risk factors associated with bacterial resistance are diverse and often interconnected [27].

Exposure of a patient to certain drugs and therapies is likely to generate severe adverse consequences to infectious pathogens [20,28-30]. Wang et al, just like in the case of mixed infections (transfer of resistance mechanisms via bacterial phage), rending specific pathogens resistant to drugs they used to respond positively to Amin et al, Chu et al, Kwong et al, Pelton [31-35]. AMR develops when microorganisms (bacteria, fungi, viruses, or parasites) no longer respond to a drug it was previously sensitive [3,36,37]. The current affirmation means that standard treatments no longer work; infections are more complicated and impossible to control; the risk of spreading disease to others is higher than usual; illness and hospital stays are prolonged, with added economic and social costs [38-40].

The risk of death is increased in many cases, twice that of patients with infections caused by non- resistant bacteria [4,41]. The clinical breakpoint explains or qualifies the microorganism's change of resistance patterns throughout the years [35]. The exact type and amount of antibiotics used (also called Antimicrobial Use AMU) in paediatric wards is still difficult to estimate [42]. However, they are essential in treating most infections, meaning there is little to no choice in using or not using this treatment whenever necessary [43]. The actual worry lies in the need to slow down the ongoing trend of spreading of microbial resistance and reduce the impact on subject's health status [44,45].

The current opinion is that not addressing AMR's current and future problems with emphasis will result in severe health degradation [46-49]. This health degradation seems to be due to the fact that most currently commercialized antibiotics, used to fight against ongoing resistant infections trends, are those of the third-generation [50]. Third-generation antibiotics are often administrated only in hospital settings [30,51,52]. A result of the increase use of this drug may make them become less effective than first-generation's antibiotics, more expensive, and, unfortunately, often associated with severe side effects on the patient's status or therapy [1].

Reports indicate that AMR disproportionately affects high, low-income countries with a relatively higher infection rate and limited access to effective therapies and funds for appropriate bacterial investigation and reporting from one place to the other [40,53-55]. Therefore, developing protocols or optimizing the existing ones overall or in specific settings, in particular, is highly necessary [55-58]. The problem is so severe that it threatens the achievements of modern medicine, as a post-antibiotic era, in which common microbial infections and minor injuries will eventually cause death, is a genuine possibility. Therefore, a clinical surveillance system is necessary and monitored constantly. The main challenges in tackling antimicrobial resistance are social, ecological, intellectual, economic, and political [59]. Unfortunately, middle-income countries hardly follow up with surveillance programs, do not achieve good reporting, nor keep up with standard recommendations, such as reporting AMR with the type of sample of origin of the isolate, with accuracy [5,40,45,60].

In the routine microbiology laboratory, checking for antimicrobial resistance of bacteria to most antibiotics is a standard operating procedure [61,62]. It is said that microbiologist always report with sadness, resistance, but more especially when pediatric samples are involved [4]. Though resistant bacteria have become an ordinary matter in clinical setting, they can still be controlled to the best of practice and be prevented by good clinical exercise and optimal turn-around time [63-67].

Nevertheless, more must be done to provide public health services and hospitals with necessary information on the health, economic and social risks of dealing with resistant bacterial infections in any population, among children and immune-suppressed children [68]. Therefore, this systematic review is critical to raise awareness of this latent problem before it becomes even more severe and help implement and improve antimicrobial stewardship programs worldwide.

1.2. Objectives

To analyses and draw conclusions from peer-reviewed and published work on what has been said so far in literature on the impact of antibacterial resistance infections on immunosuppressed children. Provide necessary information on the patient's mortality and morbidity after bacteremia, therapy, and final output of the combined care condition. The study will also be interested in the patient's length of stay after bacterial identification, treatment, and therapy's outcome.

2. Methods

2.1. Eligibility Criteria

The study selected as part of this systematic review followed the PECO-based selection criteria. All relevant reports will be included unless there is clear evidence of an update of an older edition. This study will give preference to peer-reviewed articles. Only published manuscripts, conference abstracts, and outdated guidelines will be included. Studies will be excluded because of outcomes that are not in line with the current study objectives ("wrong outcome") and if the study of the impact of resistant infection on therapy is focused only on adult populations or cases.

2.2. Information Sources

A first attempt to search for literature for the current study was made on May 9th, 2022, on the following databases: PubMed, Embase, and Cochrane, Ovid's "Bambino Gesù" Pediatric Hospital's

library platform in Rome. Secondarily to these conventional search strategies, we did a comprehensive grey literature search with Google search engine and websites from the ministries of health, healthcare services of Italy and Cameroon, institutes of public health, European Centre for Disease Prevention and Control (ECDC), World Health Organization (WHO), scientific societies in the field (including the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the International Society for Infectious Diseases (ISID), the International Epidemiological Association (IEA), the European Society of Intensive Care Medicine (ESICM) and the European Respiratory Society (ERS)). For the search strategy, we used the following terms in English and local languages (French and Italian): 'Antimicrobial resistance' AND/OR 'Hospital-associated' OR 'Hospital-acquired' OR 'Nosocomial' AND 'Surveillance' AND 'epidemiology' OR 'prevalence' OR 'incidence.' In addition, the European Committee on Infection Control (EUCIC) websites of ESCM were consulted as an additional source to help us find specific publicly available documents that might have been missed with our search strategy. However, only data from publicly available sources were included in the review.

2.3. Search Strategy

This systematic review follows the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidance. However, it did not follow any registration into conventional systematic review registration sites.

The research team conducted an electronic systematic search using the PubMed, Cochrane, and Embase databases from October 2021 to September 2022. The search did not apply any restrictions to the year of publication. The participants' ages were limited to 18 years old. No limitations further limitations were applied to article types and language of publication. The search strategy in PubMed combined the subject headings and free-text keywords: ((((("hospital s" [All Fields] OR "hospitalization" [All Fields] OR "hospitalization" [MeSH Terms] OR "hospitalization" [All Fields] OR "hospitalizing" [All Fields] OR "hospitality" [All Fields] OR "hospitalizations" [All Fields] OR "hospitalized" [All Fields] OR "hospitalizations" [All Fields] OR "hospitalized" [All Fields] OR "hospitalize" [All Fields] OR "hospitalizing" [All Fields] OR "hospitals" [MeSH Terms] OR "hospitals" [All Fields] OR "hospital" [All Fields]) AND ("patient s" [All Fields] OR "patients" [MeSH Terms] OR "patients" [All Fields] OR "patient" [All Fields] OR "patients s" [All Fields])) OR (("oncologic" [All Fields] OR "oncological" [All Fields] OR "oncologically" [All Fields] OR "oncologics" [All Fields]) AND ("patients" [All Fields] OR "patients" [MeSH Terms] OR "patients" [All Fields] OR "patient" [All Fields] OR "patients" [All Fields])) OR (("oncologic" [All Fields] OR "oncological" [All Fields] OR "oncologically" [All Fields] OR "oncologics" [All Fields]) AND ("disease" [MeSH Terms] OR "disease" [All Fields] OR "diseases" [All Fields] OR "diseases" [All Fields] OR "diseased" [All Fields])) OR ("genetic diseases, inborn" [MeSH Terms] OR ("genetic" [All Fields] AND "diseases" [All Fields] AND "inborn" [All Fields]) OR "inborn genetic diseases" [All Fields] OR ("genetic" [All Fields] AND "diseases" [All Fields]) OR "genetic diseases" [All Fields]) OR ("genetic diseases, inborn" [MeSH Terms] OR ("genetic" [All Fields] AND "diseases" [All Fields] AND "inborn" [All Fields]) OR "inborn genetic diseases" [All Fields] OR ("genetic" [All Fields] AND "disorders" [All Fields]) OR "genetic disorders" [All Fields]) OR ("chronic disease" [MeSH Terms] OR ("chronic" [All Fields] AND "disease" [All Fields]) OR "chronic disease" [All Fields] OR ("chronic" [All Fields] AND "diseases" [All Fields]) OR "chronic diseases" [All Fields]) OR (("patients" [All Fields] OR "patients" [MeSH Terms] OR "patients" [All Fields] OR "patient" [All Fields] OR "patients" [All Fields]) AND ("chronic disease" [MeSH Terms] OR ("chronic" [All Fields] AND "disease" [All Fields]) OR "chronic disease" [All Fields] OR ("chronic" [All Fields] AND "diseases" [All Fields]) OR "chronic diseases" [All Fields])) OR "oncology patient" [All Fields]) AND "Drug Therapy" [MeSH Terms] AND "Treatment Outcome" [MeSH Terms] AND ("drug resistance, bacterial" [MeSH Terms] OR (("anti-infective agents" [Pharmacological Action] OR "anti-infective agents" [MeSH Terms] OR ("anti-infective" [All Fields] AND "agents" [All Fields]) OR "anti-infective agents" [All Fields] OR "antimicrobial" [All Fields] OR "antimicrobials" [All Fields] OR "antimicrobially" [All Fields]) AND ("resist" [All Fields] OR "resistance" [All Fields] OR "resistances" [All Fields] OR "resistant" [All Fields] OR "resistant's" [All Fields] OR "resisted" [All Fields] OR "resistance" [All Fields] OR "resistances" [All Fields] OR "resistant" [All Fields] OR "resistibility" [All Fields] OR "resisting" [All Fields] OR "resistive" [All Fields] OR "resistively" [All Fields] OR "resistivities" [All Fields] OR "resistivity" [All Fields] OR "resists" [All Fields]))))).

The following string was used in Embase, ('treatment outcome'/exp OR 'treatment outcome') AND ('antibiotic resistance'/exp OR 'antibiotic resistance') AND ('hospital patient'/exp OR 'hospital patient' OR 'oncology patient' OR (('oncology'/exp OR oncology) AND ('patient'/exp OR patient)) OR 'chronic disease'/exp OR 'chronic disease' OR 'genetic disorder'/exp OR 'genetic disorder' OR 'oncological disease' OR (oncological AND ('disease'/exp OR disease)) OR 'patients chronic diseases' OR (('patients'/exp OR patients) AND chronic AND ('diseases'/exp OR diseases))) AND ('drug therapy'/exp OR 'drug therapy') AND ([adolescent]/lim OR [child]/lim OR [infant]/lim OR [newborn]/lim). Before further search with a broader string #17 AND 'article'/it AND ([adolescent]/lim OR [child]/lim OR [fetus]/lim OR [infant]/lim OR [newborn]/lim OR [preschool]/lim OR [school]/lim) AND ('adverse device effect'/lnk OR 'adverse drug reaction'/lnk OR 'disease management'/lnk OR 'drug combination'/lnk OR 'drug concentration'/lnk OR 'drug interaction'/lnk OR 'drug resistance'/lnk OR 'drug toxicity'/lnk OR 'side effect'/lnk OR 'special situation for pharmacovigilance'/lnk OR 'therapy'/lnk OR 'unexpected outcome of drug treatment'/lnk) and in Cochrane 'antibiotic resistance'/exp/mj AND ([cochrane review]/lim OR [systematic review]/lim OR [meta-analysis]/lim OR [randomised controlled trial]/lim OR 'controlled clinical trial'/de) AND [article in press]/lim AND ([english]/lim OR [french]/lim OR [italian]/lim) AND ([embryo]/lim OR [fetus]/lim OR [newborn]/lim OR [infant]/lim OR [child]/lim OR [preschool]/lim OR [school]/lim OR [adolescent]/lim)

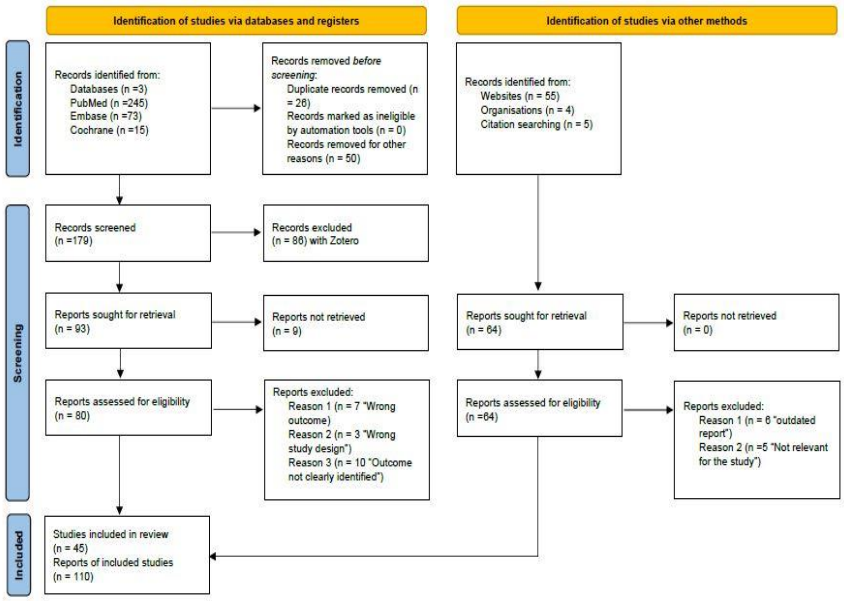
AND [humans]/lim AND [abstracts]/lim AND [clinical study]/lim AND ([embase]/lim OR [medline]/lim OR [pubmed-not-medline]/lim) AND [medline]/lim was the label used. Extended literature hunting in the CMI database: antimicrobial resistance children OR impact OR on OR therapy OR surveillance OR control OR management OR stewardship "immune depressed" was also made. The modified PECO inclusion/exclusion criteria (Table 1) served to screen titles/abstracts and complete texts.

Criteria	Inclusion	Exclusion
Population	All relevant reports will be included unless there is clear evidence of an update of an older edition. This study will give preference to peer-reviewed articles. Only published manuscripts, conference abstracts, and outdated guidelines will be included if necessary.	Studies will be excluded because of outcomes that are not in line with the current study objectives ("wrong outcome") and if the study of the impact of resistant infection on therapy is focused only on adult populations or cases.
Outcomes	They are associated with immune depression (a relative state of fragile health requiring constant or ongoing care). Impact on ongoing therapy at the time of infection	Health-related quality of life only Outcomes associated with the evaluation of the intervention only Reports on analytic methodologies
Study design	Case-control studies Cohort studies Cross-sectional studies Longitudinal studies Randomised control trials Modelling studies Economic evaluations Evaluations of intervention reporting the impact of exposure of fragile children to AMR	Letters Reviews not focusing on AMR in pediatrics Editorials Conference reports Case series reports Evaluations of interventions not reporting the impact of exposure

Table 1: Inclusion/Exclusion Criteria Applied

2.4. Data Selection and Collection Process

Reviewers (D:D and INW) screened the references (Titles and Abstracts) individually, and disagreements were resolved through discussion with mates investigating in the same field and consensus with co-authors. The primary reviewer used predominantly manual screening tools like Excel to select the qualifying articles, like in previous systematic reviews; titles and abstracts of the retrieved documents were initially assessed, and other documents non-related to the topic were excluded. For data from the grey literature, executive summaries, tables of contents, and available documents were screened. The full text of potentially eligible studies was obtained afterwards and assessed for relevance or duplication against predefined selection criteria. Searches were limited to English, Italian and French articles to avoid unreliable translations. Duplicates were removed with Zotero, and relevant information was grouped in a table summary upon final analysis (See PRISMA flow diagram for articles selection).



Flowchart: PRISMA 2020 Flow Diagram for New Systematic Reviews Which Included Searches of Databases, Registers and Other Sources [69].

Selected literature went through critical screens for relevancy to the population (Children), antibiotic resistance of investigation, pathogens involved in the study, type of resistance mechanism, and information on mortality and LoS.

2.5. Data Collection

Two (Danielle Domo and Ivo Ngundu Woogeng) reviewers independently examined the selected articles at the primary stage of the process. The PRISMA RoB 2 and ROBINS tools were used to assess the risks of bias in the selected literature.

Collected data (Table S1 – Appendix) included studies focusing on children, the average time of stay in the hospital of the patients, the average mortality and morbidity rate, and the impact of the resistant bacterial infection on the outcome of the patient, in association with the type of bacterial resistance, immunodepression and the AMR of question. Data on mortality rate was retrieved from the studies as much as possible, as a significant outcome of the burden of AMR, together with information on the hospital's length of stay (LoS) upon detection of the resistance; LoS is a significant contributing factor to hospital increased costs [39]. It is prudent to pay attention to the cost of hospitals' consumables, as they are always part of a budget. We did not request ethical approval for this work because the analyzed data was not directly related to individuals.

Author and year	Study design	Study Location	SP	Type of resistance	Pathogens	Type of antibiotics	Type of immunodepression	Mortality & LoS
Pugès, et al [15]	Case report	France	Peds	MDR	*Pandoraea sp.*			
Mariappan, et al [70]	Case report	Malaysia	Peds	MDR	Burkholderia pseudomallei G-		Cystic fibrosis	D
Perovic, et al [71]	Case report	South Africa, Johannesburg	Peds	MDR	*Pseudomonas spp.*			
Moodley, et al [72]	Case report	South Africa, Pretoria	Peds					
Pardy, et al [73]	Case report	UK	Peds	MDR	*Serratia marescens & S. aureus granulomatous disease (CGD)*		X-linked chronic granulomatous disease (CGD)	D
O'Sullivan, et al [11]	Case report	USA, Canada, and Australia	Peds	None - Reduced sensitivity	*B. pseudomallei*	agressive treatment regimen	Cystic fibrosis	D
Moriyama, et al [74]	Case report		Peds	MDR	P. aeruginosa		Severe aplastic anemia	

Higgins, et al [75]	Case report		Peds Fluoroquinolone	U. urealyticum	Azythromycin & doxycycline		Kidney transplant	
Wilson, et al [76]	Case report		Peds	MDR	Acute otitis media		D	
Johnson, et al [14]	Case report		Peds	MDR	Pandoraea		Cystic fibrosis	
Ashley, et al [63]	Case report		Peds	No resistance	Staph. Pseudintermedius	Methicillin	Anaplastic ependymoma	
Chu, et al [33]	Cohort study		Peds	P. aeruginosa; ESBL producers	Gram -negative	Empiric antibiotic therapy	Neaonates intensive care unit	D
Alhajri, et al [22]	Cohort study		Peds	MDR including ESBL	Enterobacter cloacae		ICU	
Pokhrel, et al [77]	Cross-sectional study	Nepal	Peds	First-line antibiotics like ampicilin	For pneumonia	Ampicillin + ceftriaxone + others	N/HC	D
Füller, et al [21]	Propective osservational cohort study	European	Peds	MRSA	Gram-positive & gram-negative (-50%; Klebsiella & Acinetobacter spp.) Candida spp. 7%			
Ford-Jones, et al [27]	Prospective, multi-site, cohort study	Canada	Peds		H. influenzae & M. catarrhalis, S. pneumoniae Acquired infection			
Mckinzie, et al [78]	Case report	USA	Peds	MRSA	Vancomycin		Cystic fibrosis	D
Suvada, et al [79]	Prospective multicenter study	Uganda	Peds	MDR	G- & G+	Multiple	Oncologic patients	I
Jackson, et al [80]	Prospective observational study		Peds	Pseudomonas spp.			Cystic fibrosis	
Singh, et al [81]	Prospective study		Peds	Third generation cephalosporins	>G-; Extended b-lactamases producers	Cefoperazone-sulbactam or carbapenems	Liver disease-related ascites	I
Dhingra, et al [82]	RCT	India	Peds	GPC and E. coli, Kliebsiella spp.; P. aeruginosa	Mix pathogen		Oncologic patients	D
Qiu, et al [83]	RCT	China	Peds	Multiple	K. Pneumoniae		Neonates	D
Huen, et al [84]	RCT		Peds	MDR	Gram-negative		Neurogenic bladder	D
Brad, et al [85]	RCT		Peds	Antibiotic associated diarrhea	Pseudomonas spp.	cephalosporins	Pseudomonas associated diarrhea	
Aguillera-Alanso, et al	RCT	Spain	Peds	Methicillin	S. pyogenes & S. pneumoniae		Hospitalized children	
Mithal, et al [86]	RCT		Peds	MDR	Gram-negative		Urinary tract infection	
Wang, et. al [31]	RCT prospective	Taiwan	Peds	MDR, VAP	MDR-VAP	VAP infection &		D
Vergison, et al [87]	RCT, prospective	Europe	Peds	MRSA	Gram-positive & gram-negative (-50%; Klebsiella & Acinetobacter spp.) Candida spp. 7%		Cystic fibrosis; toxic shock syndrome; skin and soft tissue infections	

Liebson et al.	RCT, prospective	Israel	Peds	Piperaciclin & Amikacin	CoNS bacteremia; Acinetobacter & K. Spp; Candida spp.	Oncologic patients		D
Yahaba, et al [88]	Retrospective cohort study	Japan	Peds	MDR	For Community acquired pneumonia (CAP)	B-lactams; tetracycline and quinolone	None	D
Sampaga, et al [89]	Retrospective study RCT	Peds	MDR				Hematological malignancies	
Dìez Dorado, et al [90]	Review	Madrid, Spain	Peds	MDR	*Non Salmonella typhi*	11 underlying immunedepression: malignancy; IgA-IgG2 deficit; chronic granulomatous disease; HIV; Systemic lupus erythematosus; liver disease; hypoxic hypoxic - ischemic encephalopathy		
Hirst, et al [91]	Systematic review		Peds	MDR			Cystic fibrosis	AO
Milczewska, et al [92]			Peds		*P. aeruginosa*	S: Colistin	N/HC	AO
Medoua-Benbalagh, et al [93]		Benin	Peds	ESBL- E	*K. pneumoniae; E. coli*		Oncologic patients	
Vinker-Shuster, et al [19]			Peds				Malignancies and haematopoietic steem cell transplant	
English, et al [94]			Peds	MDR	CA-MRSA	Clindamysin, Vancomycin		
Nielsen, et al [95]		Ghana	Peds	MDR	Non typhoidal salmonellae ; S. aureus; S. pneumoniae; Salmonella ser. & typhi			
Zajac-Spychala, et al			Peds	MDR	Mix pathogen	Haematopoeitic stem cell transplantation		D
Swanson, et al [96]			Peds	Penicillin-resistant	Aerococcus viridans		Sickle-cell anemia	
Hsu, et al [97]		Taiwan	Peds				Congenital anomalies	
Ye, et al [98]			Peds	MDR - A. baumannii	Gram-negative	Tigecycline		
Stiefel et al [99]			Peds				Oncologic patients	D
Tran, et al [100]			Peds	MDR	Mix pathogens		Children	D
Ruhayel, et al [23]			Peds		Viridans group streptococci (VGS)		Immunocompromised	

RCT: Randomised controlled trials; **Peds**: paediatrics; **MDR:** Multiple-drug resistance; **VAP**: Ventilator-associated pneumonia); **ESBL:** Extended spectrum b-lactamase (ESBL-E : ESBL- Enterobacteriaceae); **MRSA**: Methicillin-resistant Staphylococcus aureus; **CoNS bacteraemia:** Coagulase negative staphylococci bacteraemia; CA-MRSA: Community associated – MRSA; **G-**: Gram-negative bacteria; **G+**: Gram-positive bacteria; **Mix (G-; G+; Fungi; ecc) / pathogens: Mix** microbial stumps isolated and identified as causal agents of the patient's infection; >**G+**/ -: More numerous gram-negative / positive bacteria; **ICU**: Intensive care unit; **N/HC:** Neonates / hospitalized children. Micoplasmi: Infectious agent identified as a member of the mycoplasma group. Not clearly identified: the resistant agent not stated at all, suspects raised about the origin of the resistance being enhanced by primary therapy, drugs defects, unknown and /unidentified mutation, hospital contamination, misidentification of the infective agent, wrong therapy / diagnosis; **D:** Decreased mortality rate; **I:** Increased mortality rate; **AO**: reported death, not as increased nor decreased, but more "accidentally", since it was not part of the scope of the study in question.

Table S1: Summary Table of the Information Obtained from Screening Articles for Types of Resistant Pathogens, Microbial Resistance Types among Children, Immunederession Categories, and Length of Stay in Hospital and Mortality Rate

2.6. Data Analysis

We screened the selected studies according to the following criteria: study type, populations, pathogens, AMR, immunodepression, and reporting of the mortality and LoS in the hospital during therapy. The analysis compared the percentage of different categories and subcategories under revision to understand what happens in the pediatric world of immune-depressed children contracting resistant infections.

3. Results

About 350 unique titles and abstracts were retrieved from October 2021 to September 2022. Applying the selection process resulted in 110 studies being included in the final review, as appears on the PRISMA workflow diagram (Figure 1: PRISMA 2020 flow diagram for new systematic reviews, which had searches of databases, registers and other sources [69]). We further assessed all selected studies for bias following the PRISMA guidelines for

the writing-up of systematic reviews, using the RoB II analytic tool for all randomized controlled trials included in the review. The risk of bias assessment generated an overall positive analysis was low (Figure 1A).

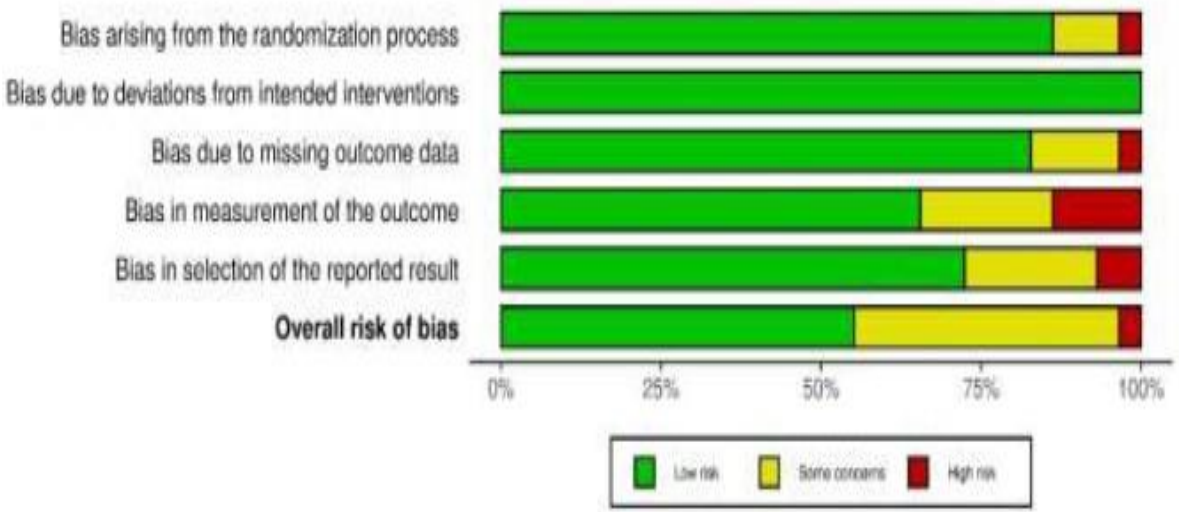


Figure 1A: Summary Plot of the Risk of Bias Assessment of Studies Identified as Randomized Controlled Trials (RCT)

Most of the induced bias arose from the scarcity of information on pediatric populations, mortality, and LoS in hospitals during events of AMR infections, as it appears on both the bar chart and the traffic light plot (Figure 1b).

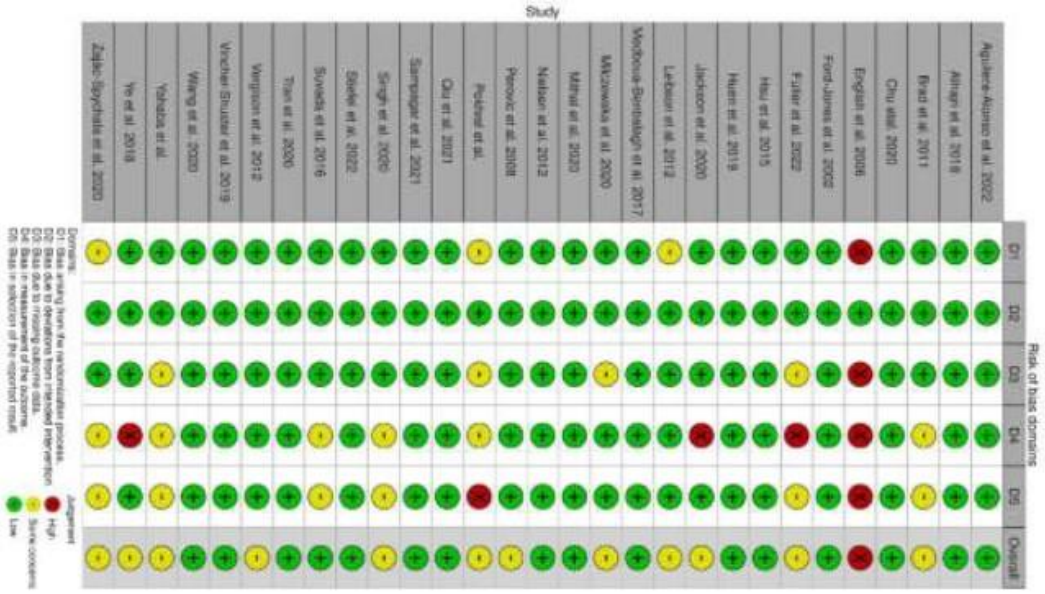


Figure 1B: Traffic Light Plot of the Five Main ROBINS Domains of Bias Assessment for RCT

We pooled articles for information relative to the current review scope: population, pathogens of concern in the study, type of resistance mechanisms of matter, type of immunodepression present among the people, and the mortality and morbidity rate eventually reported.

The following data helped construct the descriptive tables and figures (Pies distribution charts) mentioned in the results and discussion sessions from Microsoft Word and Excel 2019. From the 110 studies selected for the review, the more numerous types of studies, with 29 % of the total being randomized controlled trials (RCTs), as per Table 2 and Figure 2.

Studies	Number	Percentage
Case reports	18	16%
Cohort study	14	13%
Reviews	9	8%
Systematic reviews	15	14%
Randomized controlled trials	32	29%
Controlled before after	1	1%
Matched case-control &controlled-placebo	4	4%
Not clearly stated	17	15%
Total	110	100%

Table 2: Estimative Numbers and Percentages of Studies Per Category

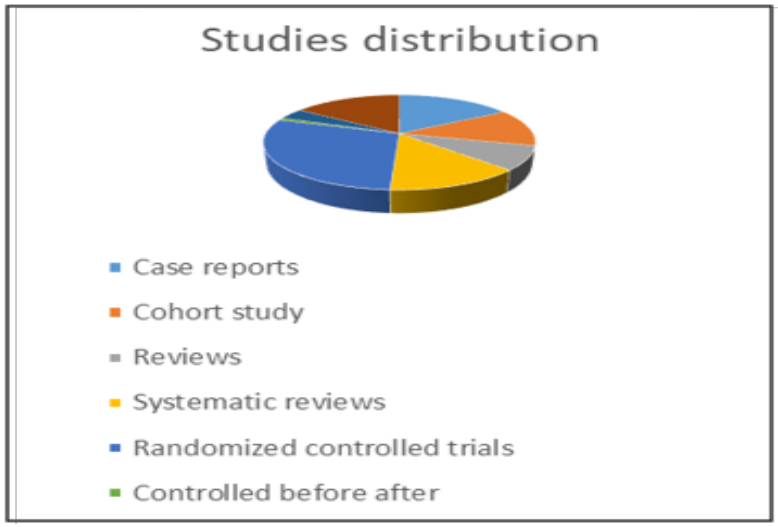


Figure 2: Distribution of the Percentage of the Number of Studies Per Category, as Per Table 2

Although it was successfully possible to analyses the articles from the types, some (17, thus 15%) could not be accurately identified. From table 3, forty-five studies, thus 41% of the same articles specifically included pediatric populations. About 50% of them, around 55 (Table 3), needed to have the study population type clearly defined, as represented in Figure 3.

Populations	Number	Percentage
Peds	45	41%
Mix (Pediatrics & Adults)	9	8%
Adults	1	0.01%
Not clearly defined	55	50%
Total	110	100%

Table 3: Estimative Population of Study Types, Per Studies. Peds: Pediatrics; Not clearly stated: The Study Needed to Provide the Reader with More Clarity on the Population's Composition

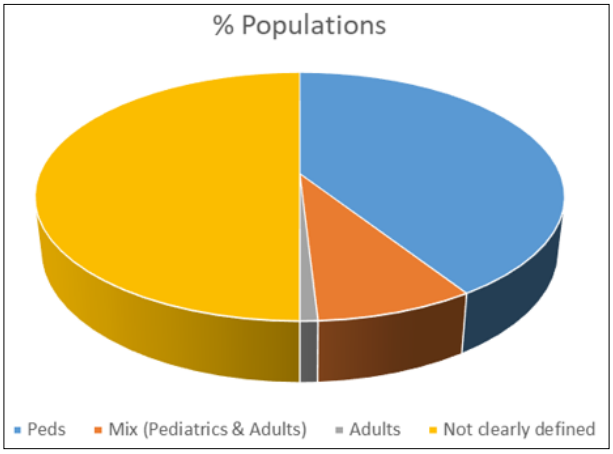


Figure 3: Distributions of Study Populations among Pre-Selected Articles, in Percentage, as Per Table 3

This distribution can be explained by the fact that most studies did instead report the pathogens of concern (Table 4), and the investigation resistance in the study's scope (Table 5).

Pathogens	N#	Percentage
G-	21	47%
G+	6	13%
Mix (G-; G+; Fungi; ecc)	10	22%
Micoplasmi	1	2%
Not identified (Therapy resistance- Oncology; drugs; ecc)	8	18%
Total	45	100%

Table 4: Estimated repartition of resistant bacteria per categories. G-: Gram-negative bacteria; G+: Gram-positive bacteria; Mix (G-; G+; Fungi; ecc): Mix microbial stumps isolated and identified as causal agents of the patient's dysfunction; Micoplasmi: Infectious agent identified as a member of the mycoplasma group. Not specified: The resistant agent was not stated at all, and suspects were raised about the origin of the resistance being enhanced by primary therapy, drug defects, unknown and /or unidentified mutation, hospital contamination, misidentification of the infective agent, and wrong therapy/diagnosis.

Resistance	N#	Percentage
Ampicillin	1	2%
Fluoroquinolones	1	2%
Penicillin	1	2%
ESBL	2	4%
MRSA	3	7%
MDR	23	51%
Third generationcephalosporins	1	2%
Reduced sensitivity tocolistin	1	2%
Chemoresistance	1	2%
Drug-associated diarrhoea	1	2%
Not clearly defined	10	22%
Total	45	100%

Table 5: Estimated repartition of resistance per studies screened. MRSA: Methicillin-resistant Staphylococcus aureus; ESBL: Extended-spectrum B-lactamase; MDR: Multiple drug resistance; Not clearly defined: the actual cause of the resistance was not confirmed/identified in the study

In fact, from the 45 pediatric studies, only 8, thus 18 % of them, did not state which type of pathogen was of concern in their studies (Figure 4), versus a relatively low number of 10 or 22%, on the other hand, which did not mention the type of resistance mechanisms (Figure 5).

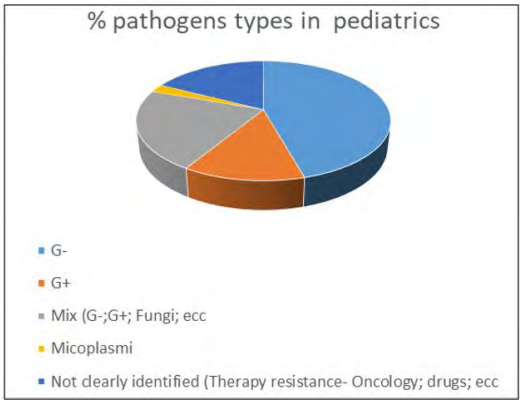


Figure 4: Distribution of the Percentage of Pathogen Types Encountered among Paediatrics, as Per Table 4

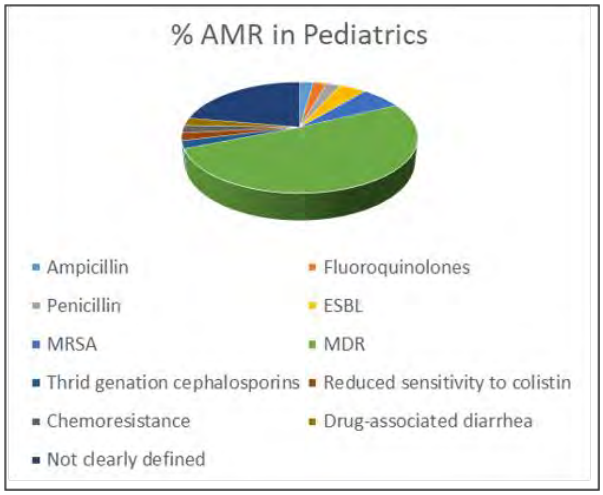


Figure 5: Distribution of the Percentages of Repartition of Resistances per Studies Screened, as Per Table 5

From these two figures (4 & 5), it is visible that current studies report harmful gram-negative pathogens as the most commonly reported or encountered among children compared to gram-positive organisms and others (mycoplasma, fungi and other microorganisms), followed by the infections caused by mixed pathogens. MDR is the most common type of resistance reported in studies (Figure 5), explained by the high number of infections caused by gram-negative bacteria and mixed pathogens (Table 4).

Broad-spectrum antibiotics are often used in these situations, which may become favorable for resistances, and why not, of multiple types. The current figure (Figure 5) shows how AMR reporting among paediatrics has been distributed worldwide. Few studies report single AMR (2%) to antibiotics like colistin, ampicillin, fluoroquinolones, penicillin, third-generation cephalosporins, and another rare phenomenon–related - resistance types, like chemoresistance or drug-associated diarrhoea. The number of MRSA seems to be low (7% alone), because the majority of the reviewed studies reported them under the MDR. The number of ESBL found in this population (4%) is insignificant, although public opinion sustains that this type of infection could be ordinary and lethal in children. The estimated distribution of the data mentioned above (Figure 5) is enough of a red flag to set the alarm on the necessity of better controlling the situation at a global level.

Further investigations on the types of immune depression encountered among the reported patients' populations describe many genetic diseases and acquired severe pathologies as the leading cause of immune suppression in children. Among studies focusing on paediatrics, only one reported on a case of immune depression associated with organ transplantation or hospitalization from ICU / Trauma units; 16% of studies on neonates, generally considered as fragile from birth till the sixth month of growth, or "hospitalized children" (HC), (Table 6), referring to those having six months onwards. Even in this case, 20% of the studies could not clearly state the type of disease associated with the specific study population (Figure 6).

Immunodepression	N#	Percentage
Neonates / Hospitalized children	7	16%
ICU / Trauma	1	2%
Genetic / Acquired pathologies	27	60%
Transplants	1	2%
Not clearly defined	9	20%
Total	45	100%

Table 6: Estimated Repartition of Immune-Depression Categories from the Screened Studies ICU: Intensive Care Unit

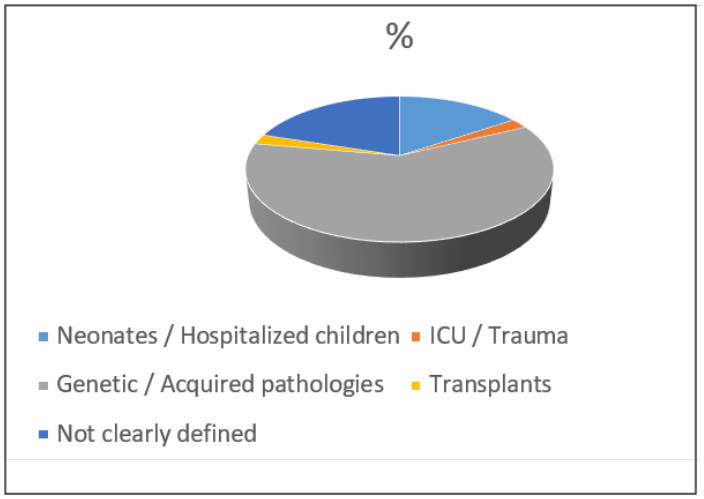


Figure 6: Distribution of the Percentages of the Repartition of Immune-Depression Categories that Emerged from the Screened Studies, as per Table 6

An attempt to evaluate the burden of AMR on the mortality and length of stay in hospital in the pediatric population from the studies mentioned above yielded the discovery that most research in the pediatric camp does not aim at investigating the duration in a hospital or the mortality rate among children, due to AMR. About 56% should have mentioned this information in the study (Table 7).

Mortality & LoS	N#	Percentage
Decreased to control/AMS	16	36%
Increased mortality & LoS	2	4%
Accidentally reportedoutcome	2	4%
Not reported	25	56%
Total	45	100%

Table 7: Estimated Repartition of Mortality and Length of Hospital Stay (LOS) from Selected Studies. AMS: Antimicrobial Stewardship. Not Reported: Some Studies Said Resistant Therapies or Microbial Agents without Focusing on Patients' Status

About 36% declared a decrease in death and duration of hospitalization after infections caused by AMR bacteria associated with AMS programs and other surveillance strategies against AMR infections; 2 of 45 studies report a noted increased mortality rate in the cause of the study due to the infections; and about the same number of studies purposely said current features, o as a deviated outcome (Figure 7).

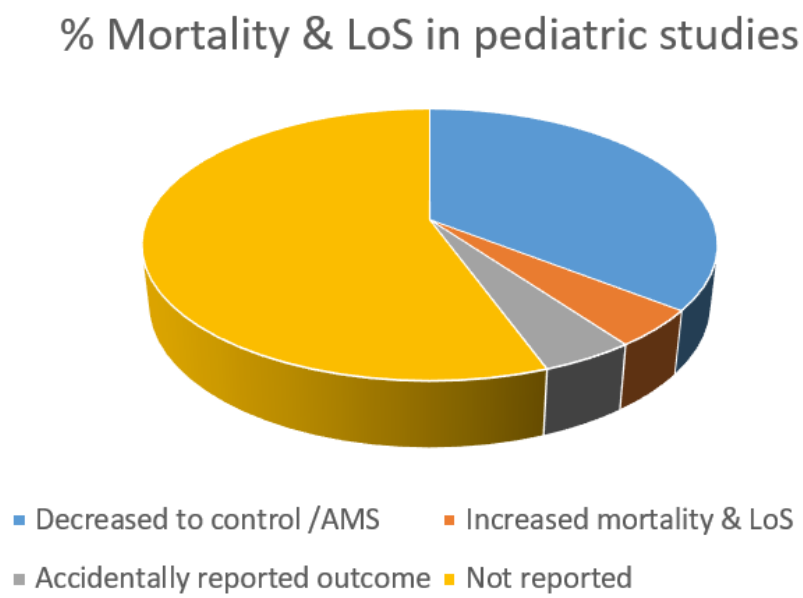


Figure 7: Distribution of the Percentages of the Repartition of Mortality and Length of Hospital Stay (LoS) from Selected Studies, as Per Table 7

4. Discussion

The present systematic review of studies aimed to search and present what in the peer-reviewed literature is the current knowledge of the impact resistant bacterial infections have on children in general, but on fragile kids, in particular. Then, based on the statistical results found, estimate the necessity to re-propose actions and undertake practical activities suggested by experts, like doing more research on the topic and providing as much data as possible at various levels [7,101,102]. Experts suggest overcoming the growth of AMR through observational studies (prospective and retrospective), randomized controlled trials, and case controls to raise public health concerns, participation, and exemplary implementation of antimicrobial stewardship programs (AMS) where necessary.

Reviewers found that studies address the burden of AMR, mainly when a particular case arises. The issue reported will further generate a specific interest in the particularities of the experience, like the patient category (sex, age, nationality, parents' economic status, health status) and hospital/community of concern. Therefore, some trials followed up, together with some cohort and case-control studies. Results presented in this review describe that out of about 350 studies, only a few focused on the impact of antimicrobial resistance in paediatrics (45 articles; Table 3). However, the quality of the studies was overall good, from the bar chart of risk of bias assessment of studies identified as RCT and other assessment tools used for further studies.

The variety of isolates of concern among children (Table 4) may indicate how urgent it is to protect fragile immunocompromised children from most pathogens, but more especially from gram-negative bacteria already known to be able to develop resistance against antibiotics. The list of antibiotics presented in Table 5 indicates how many drugs are in need among kids. It is already being emphasized that they are of few benefits to their health. However, their necessity is visible, especially in the amount of MDR infections. This study showed that most infected patients in this category are fragile children affected by genetic conditions or certain severe diseases acquired during their lives. These underlying conditions might explain why gram-negative pathogens easily threaten them [103,104]. These are often encountered in hospital standard wards and fewer in intensive care units, like trauma or ICUs, which are generally much more sterilized units [20,38].

Precise data on the mortality and morbidity rate of fragile pediatric patients after hospitalization is almost impossible, if not wholly absent from previous work [105]. A last review on a similar topic affirms that researchers agree that AMR increases mortality and length of hospital stay in about 50 % of the studies [79,105-110]. Researchers are convinced that there is an evident increase in mortality among this patient group (hospitalized children). Still, precise data are necessary to evaluate to which extent. To avoid inappropriate prescribing of antibiotics or administration, specific centers carefully adhere to collaboration programs for the control, management, and surveillance of antibiotics, which cultivate a cautious use of them and, therefore, lessen the insurgence of resistance [55-57,66,101,111].

Several of these centers report successful implementation of ASP in their facilities. When possible, they also publish work on successful therapies against resistant bacteria, which is very important for health care and public knowledge of the status of AMR in general [84,98,112-119]. The latter may explain why about 36% (Table 7) of the studies screened reported decreased mortality and LOS in hospitalized immune-depressed kids during their experimentation.

5. Conclusion

This study confirms the need for relevant information on AMR's impact on hospitalized immune-depressed children. This information will be helpful in understanding how to control the emergency of resistance in and out of hospital settings. These will also be very helpful in knowing how to handle the therapy of these patients, such as not to create more harm than to cure them and to control the cost associated with the treatments involved in the cure of these patients, with the extensive use of antibiotics in general and in particular, where possible and where necessary. Hospitals and laboratories engaged in stewardship programs should collaborate in continuation to share and promote successful therapies and experiences as there seem to be ways to bypass antimicrobial resistance, keeping an eye on the dosages and type of combination therapy to implement [120]. Further reviews are necessary to perform a meta-analysis of the estimated burden of AMR infections in paediatrics to confirm the theory in the literature. Awareness campaigns for vaccinations need to be promoted accordingly, whenever necessary, but more importantly, taught and prepared well in advance by well-trained local and international professionals to avoid consequential limitations to the programs [42,52,121-126]. Relevant suggestions for managing community immunocompromised patients should be considered and implemented where and when possible [127-131].

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