JHPHS
Journal of Hospital Pharmacy and Health Services

Original Paper **Open Access**

Effectiveness and safety of ceftazidime-avibactam and ceftolozane-tazobactam in the pediatric population: Systematic review and meta-analysis protocol

Thaís Aguiar GOUVÊA[1], Paula PIMENTA-DE-SOUZA[1], Alice RAMOS-SILVA[1], Fernando FERNANDEZ-LLIMOS[2], Elisangela Costa LIMA[1]

[1]Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brasil; [2]Universidade do Porto, Porto, Portugal.

Corresponding author: Gouvêa TA, thaisaguiar93@gmail.com

Submitted: 04-08-2025 Resubmitted: 27-10-2025 Accepted: 31-10-2025

Double blind peer review

Abstract

Objectives: This protocol describes a systematic review with meta-analysis and evidence gap map to evaluate the efficacy, effectiveness, and safety of the antibiotic combinations ceftazidime-avibactam and ceftolozane-tazobactam in hospitalized children and adolescents with infections caused by multidrug-resistant organisms (MDROs). Pediatric patients are especially vulnerable to adverse outcomes due to limited pharmacological data, off-label drug use, and increasing antimicrobial resistance. **Methods:** The review is registered on PROSPERO (CRD420251025715) and follows *Cochrane Collaboration*. Eligible studies include randomized controlled trials, observational studies (cohort and case-control and case reports), involving children aged 0–18 years with complicated intra-abdominal infections, urinary tract infections, hospital-acquired or ventilator-associated pneumonia, or bacteremia. Comparators will include other intravenous antibiotics with similar indications. Searches will be conducted in MEDLINE, Embase, CENTRAL, LILACS, Scopus, Web of Science, Epistemonikos, and Scielo, with no language or date restrictions. Two reviewers will independently perform screening, data extraction, and risk-of-bias assessment using RoB 2, ROBINS-I, JBI, as appropriate. The quality of the studies included will be assessed according to GRADE. Meta-analyses will be performed using a random-effects model. Heterogeneity will be assessed through the I^2 statistics. In addition to the random-effects meta-analysis, an evidence gap map will be developed using RStudio. The visual matrix will cross interventions with outcomes, where colored bubbles will represent study designs and density of evidence. **Expected Results:** Identify the scope, quality, and gaps in the current literature regarding these antimicrobial combinations in pediatric populations. The visual mapping will support decision-making and help prioritize areas for future research.

Keywords: ceftazidime, avibactam, tazobactam, pediatrics, drug resistance, microbial.

Efetividade, eficácia e segurança de ceftazidima-avibactam e ceftolozano-tazobactam na população pediátrica: protocolo de revisão sistemática com metanálise

Resumo

Objetivo: Este protocolo descreve uma revisão sistemática com metanálise e construção de mapa de lacunas de evidência, com o objetivo de avaliar a eficácia, efetividade e segurança das combinações antibióticas ceftazidima-avibactam e ceftolozano-tazobactam em crianças e adolescentes hospitalizados com infecções causadas por microrganismos multirresistentes (MDRs). A população pediátrica é especialmente vulnerável devido à escassez de dados farmacológicos, uso *off-label* e crescente resistência antimicrobiana. **Métodos:** A revisão está registrada na plataforma PROSPERO (CRD420251025715) e seguirá as diretrizes da *Cochrane Collaboration*. Serão incluídos ensaios clínicos randomizados, estudos observacionais (coorte, caso-controle, série e relatos de caso), envolvendo crianças de 0 a 18 anos com infecções intra-abdominais complicadas, urinárias complicadas, pneumonia hospitalar (com ou sem ventilação mecânica) ou bacteremia. Os comparadores serão antibióticos intravenosos com indicações similares. A busca será realizada nas bases MEDLINE, Embase, CENTRAL, LILACS, Scopus, Web of Science, Epistemonikos e Scielo, sem restrição de idioma ou data. Dois revisores independentes conduzirão a seleção, extração e avaliação de viés com as ferramentas RoB 2, ROBINS-I, JBI. A qualidade dos estudos incluídos será realizada conforme o GRADE. A metanálise usará modelo de efeitos aleatórios. Heterogeneidade será avaliada por estatística I^2. Será também elaborado um mapa de lacunas de evidência. O gráfico será gerado no RStudio, cruzando intervenções com desfechos e codificando os tipos de estudo por cor e densidade de evidência. **Resultados esperados:** Espera-se identificar a quantidade, qualidade e distribuição das evidências disponíveis, além de destacar lacunas críticas no conhecimento para subsidiar decisões clínicas e orientar pesquisas futuras.

Palavras-chave: ceftazidima, avibactam, tazobactam, pediatria, resistência a medicamentos.

JHPHS
Journal of Hospital Pharmacy and Health Services

Introduction

Evidence-based clinical practice has been consolidated as a cornerstone for safe and effective therapeutic decision-making, especially in challenging contexts such as pediatric therapeutics[1,2]. The scarcity of studies in this population, combined with pharmacological complexity, often results in the off-label use of medications, which increases the risk of adverse events and may compromise patient safety[2-4].

In the pediatric hospital setting, these risks are amplified by children's physiological vulnerability and the complexity of the therapies employed[4]. This scenario becomes even more critical in light of the growing threat of antimicrobial resistance (AMR), which jeopardizes the effectiveness of conventional antimicrobials[5]. As a response, the progressive use of last-line antimicrobials has been observed in hospitalized children and adolescents, often without robust scientific support[6].

Among the leading agents of severe infections in pediatrics are *Klebsiella pneumoniae*, *Escherichia coli*, and *Pseudomonas aeruginosa*, which frequently produce β-lactamases and are associated with multidrug resistance, presenting high morbidity and mortality rates[6]. In such cases, combinations such as ceftazidime–avibactam (C/A) and ceftolozane–tazobactam (C/T) have emerged as promising therapeutic alternatives. Both were approved for pediatric use by the U.S. Food and Drug Administration (FDA) in 2019, the European Medicines Agency (EMA) in 2020, and the Brazilian Health Regulatory Agency (ANVISA) in 2021, according to the official information from these regulatory agencies, highlighting that they are relatively recent options compared to other antimicrobials.

It is important to clarify that these agents are not used exclusively off-label in pediatrics. Ceftazidime–avibactam is indicated for patients aged 3 months and older, while ceftolozane–tazobactam is approved for all pediatric age groups, according to ANVISA's electronic drug label (2021) and the approvals granted by the FDA (2019) and EMA (2020).

Off-label use may occur, however, in situations where the clinical indication or infection site is not covered in the product label. Examples include the treatment of primary bloodstream infections or certain cases of osteomyelitis and meningitis—conditions for which no specific approval exists for C/A or C/T, despite reports of their use in clinical practice[7,8].

Hospitalized pediatric patients, particularly those in intensive care units (ICUs), are at increased risk of infection by multidrug-resistant organisms (MDROs) due to immunological immaturity, prolonged use of empirical antibiotics, and exposure to invasive procedures[5]. The scarcity of robust clinical data on the use of C/A and C/T in this population hampers the development of safe and up-to-date clinical protocols[9,10].

Beyond assessing the efficacy and effectiveness of these therapies, it is crucial to identify gaps in the scientific literature, considering the limited production of clinical evidence focused on the pediatric population[1,2]. In this context, evidence maps represent an innovative methodological tool for organizing and synthesizing available knowledge, identifying priority research areas, and supporting clinical decision-making[11]. Unlike traditional systematic reviews, this approach provides a panoramic overview of the distribution, quality, and types of available studies[11,12], making it particularly useful for neglected populations such as children.

Therefore, this article describes the methodological structure of a systematic review protocol integrated with the development of an evidence gap map, registered in the PROSPERO platform, aimed at analyzing the use of C/A and C/T in hospitalized children and adolescents with MDRO infections.

Methods

Registration and affiliation

The protocol was registered in the PROSPERO database under number CRD420251025715. The review will be conducted by the team from the Laboratory of Pharmacoepidemiology and Clinical Pharmacy (Laffclin) at the Federal University of Rio de Janeiro, with support from the Laboratory of Pharmacology of the Faculty of Pharmacy at the University of Porto. The development of the protocol was based on recommendations from the Cochrane Collaboration[12], the Campbell Collaboration[13], and was reported according to the PRISMA-P guidelines[14].

Research question

The research question was formulated using the PICOS acronym: In hospitalized children and adolescents with severe infections caused by multidrug-resistant microorganisms (P), is treatment with ceftazidime–avibactam (C/A) or ceftolozane–tazobactam (C/T) (I), compared with other intravenous antimicrobials (C), associated with differences in mortality, clinical cure, microbiological cure, and adverse events (O), considering experimental and observational studies (S)?

Eligibility criteria

Study selection for the systematic review was guided by the PICOS criteria (Population, Intervention, Comparison, Outcomes, and Study Design), including publications in English, Portuguese, and Spanish, with no date restrictions, in order to identify the most comprehensive and relevant literature, as shown in Table 1.

Search strategy

Searches will be conducted in the PubMed/MEDLINE, Cochrane CENTRAL, LILACS, Scopus, Web of Science, Epistemonikos, and SciELO databases. Controlled descriptors (MeSH/DeCS) combined with Boolean operators will be used, with no date restriction, but limited to English, Portuguese, and Spanish. Complete strategies are provided in Table 2. Searches in gray literature and manual review of reference lists of included studies will not be performed, due to the high specificity of the target population and the objective of focusing on clinically robust evidence. According to the literature, the impact of including these sources is minimal[15]. This decision aims to prioritize indexed sources, reduce the risk of selection bias, and enhance reproducibility.

JHPHS
Journal of Hospital Pharmacy and Health Services

Table 1. Eligibility Criteria of the Studies

Criterion	Description
Population	Hospitalized children and adolescents (0 to 18 years) with complicated intra-abdominal infections, complicated urinary tract infections, hospital-acquired pneumonia (with or without mechanical ventilation), or bacteremia.
Interventions	Ceftazidime–avibactam and ceftolozane–tazobactam administered intravenously.
Comparators	Intravenous antibiotics with similar indications.
Outcomes	30-day mortality (primary), clinical cure, microbiological cure, and adverse events (secondary).
Study Types	Randomized clinical trials and observational studies (cohort, case-control, and case reports).

Table 2. Databases and Search Strategies Used

Database	Search Strategy
Pubmed	(((“avibactam”[TIAB] OR “avibactam”[NM]) AND (“ceftazidime”[MH] OR “ceftazidime”[TIAB]) OR “avibactam, ceftazidime drug combination”[NM]) OR ((“tazobactam”[MH] OR “tazobactam”[TIAB]) AND (“ceftolozane”[NM] OR “ceftolozane”[TIAB]) OR “ceftolozane, tazobactam drug combination”[NM])) AND (“child”[MH] OR “child”[TIAB] OR “children”[TIAB] OR “pediatric*”[TIAB] OR “pediatrics”[MH] OR “neonates”[TIAB] OR “Infant, Newborn”[MH])
Scopus	TITLE-ABS ((("avibactam" AND "ceftazidime") OR ("tazobactam" AND "ceftolozane")) AND ("child" OR "children" OR "pediatric*" OR "neonate*" OR "Infant, Newborn"))
Central	(("avibactam, ceftazidime drug combination" OR "ceftazidime/avibactam" OR "ceftazidime-avibactam" OR "avibactam-ceftazidime") AND (Children OR Pediatrics OR Neonate OR Infant OR Child)) ((“ceftolozane, tazobactam drug combination” OR “ceftolozane/tazobactam” OR “ceftolozane-tazobactam” OR “tazobactam-ceftolozane” OR “ceftolozane”) AND (Children OR Pediatrics OR Neonate OR Infant OR Child))
Epistemonikos	(title:(((((("avibactam" AND "ceftazidime") OR ("tazobactam" AND "ceftolozane")) AND ("child" OR "children" OR "pediatric*" OR "neonate*" OR "Infant, Newborn")))) OR abstract:(((((("avibactam" AND "ceftazidime") OR ("tazobactam" AND "ceftolozane")) AND ("child" OR "children" OR "pediatric*" OR "neonate*" OR "Infant, Newborn")))))
Lilacs	((((("avibactam" AND "ceftazidime") OR ("tazobactam" AND "ceftolozane")) AND ("child" OR "children" OR "pediatric*" OR "neonate*" OR "Infant, Newborn"))) OR ((((“avibactam” AND “ceftazidime”) OR (“tazobactam” AND “ceftolozane”)) AND (“niño*” OR “pediatrico*” OR “neonato*” “recien nacido”))) OR ((((“avibactam” AND “ceftazidima”) OR (“tazobactam” AND “ceftolozane”)) AND (“menino*” OR “pediatric*” OR “neonato*” OR “criança*”)))
Web of Science	TS=((((("avibactam" AND "ceftazidime") OR ("tazobactam" AND "ceftolozane")) AND ("child" OR "children" OR "pediatric*" OR "neonate*" OR "Infant, Newborn")))
Scielo	((("avibactam"[TIAB] OR "avibactam"[NM]) AND ("ceftazidime"[MH] OR "ceftazidime"[TIAB]) OR “avibactam, ceftazidime drug combination”[NM]) OR (("tazobactam"[MH] OR "tazobactam"[TIAB]) AND ("ceftolozane"[NM] OR "ceftolozane"[TIAB]) OR “ceftolozane, tazobactam drug combination”[NM])) AND ("child"[MH] OR "child"[TIAB] OR "children"[TIAB] OR "pediatric*"[TIAB] OR "pediatrics"[MH] OR “neonates”[TIAB] OR "Infant, Newborn”[MH])

Inclusion and exclusion criteria

The review will include randomized clinical trials and observational studies (cohort, case-control, case series, and case reports) that evaluate hospitalized pediatric patients (0 to 18 years old) treated with C/A or C/T, affected by at least one of the following infections: complicated intra-abdominal infections, complicated urinary tract infections, hospital-acquired or ventilator-associated pneumonia, or bacteremia. Studies must report at least one of the following outcomes: 30-day mortality (primary), clinical cure, microbiological cure, or adverse events (secondary).

Studies published in non-Roman characters, review articles, letters, and commentaries will be excluded. Additionally, the review will exclude studies involving children undergoing renal replacement therapy; pediatric patients with tuberculosis; those with oncological conditions or neutropenia; and patients with nephropathy or hepatopathy.

Selection and data extraction process

EndNote will be used for deduplication, and an Excel spreadsheet will be used to organize the study screening process. Before screening, two independent reviewers will perform a concordance assessment, estimated using the Kappa coefficient. After reaching a satisfactory value (>0.7), they will screen titles and abstracts, followed by full-text evaluation of eligible articles. Disagreements will be resolved by consensus or, if discordance persists, by a third reviewer.

Data extraction will also be performed independently in pairs, monitored by a third reviewer, using a standardized spreadsheet. Before extraction, reviewers will undergo a pilot test by extracting information from two articles to assess the adequacy of the extraction form. After the pilot test, the following information will be extracted into the standardized form: (i) general characteristics (authors, year, country, study

design); (ii) population characteristics (age, sex, weight, infection site); (iii) interventions (C/A or C/T, dose, treatment duration, administration frequency); (iv) comparators (antimicrobials used, dose, duration); (v) outcomes assessed (mortality, clinical cure, microbiological cure, adverse events); (vi) methodological information relevant for quality assessment.

Methodological quality assessment

The methodological quality of the included studies will be systematically assessed by pairs of independent reviewers using tools specific to each study design. For randomized clinical trials, the RoB 2.0 tool (Cochrane Risk of Bias Tool for Randomized Trials) will be applied[16]. For cohort studies, quality assessment will be performed using the ROBINS-I tool (Risk Of Bias In Non-randomized Studies of Interventions)[17]. For case-control studies and case series/reports, the corresponding JBI checklists will be used: the *Checklist for Case Control Studies*[18] and the *Critical Appraisal Checklist for Case Reports*[19], as presented in Table 3. In addition, the overall quality of evidence for each outcome will be classified according to the GRADE methodology (Grading of Recommendations, Assessment, Development and Evaluations), enabling the identification of the robustness and reliability of the findings.

Statistical analysis

Statistical analysis will be conducted comprehensively, incorporating effect measures and meta-analytic techniques. For dichotomous outcomes, odds ratios (ORs) with 95% confidence intervals (CIs) will be used to estimate the magnitude and precision of treatment effects.

Meta-analyses will be performed using random-effects models, given the expected clinical and methodological heterogeneity across studies. Heterogeneity will be assessed using Cochran's Q test and the I^2 statistic, with values above 50% indicating moderate to high heterogeneity.

Sensitivity analyses will be conducted to test the robustness of the results, including the exclusion of studies with high risk of bias and comparisons between fixed-effects and random-effects models.

When appropriate, meta-regressions will be conducted to explore the impact of study-level variables on the observed effects, such as mean age of participants, drug dose, and presence of comorbidities. Subgroup analyses will also be performed based on infection type, age group, therapeutic regimen, and study design.

Furthermore, for studies without a comparator group (such as case series), single-arm meta-analyses will be performed, pooling proportions of clinical outcomes of interest (e.g., cure rate, adverse events) with Freeman–Tukey or logit transformations when necessary to stabilize variance.

Results will be presented as pooled proportions with 95% CIs under random-effects models. When meta-analysis is not feasible due to heterogeneity or insufficient number of studies, findings will be synthesized narratively or descriptively, following criteria of consistency and clinical relevance.

Evidence gap mapping

After extraction of the studies included in the systematic review, a map will be developed to identify evidence gaps related to the research question. The map will be presented as a bubble plot, created using the *ggplot2* package within the RStudio interface[20,21]. The goal is to visually display an intervention-versus-outcome matrix, with existing studies placed at each intersection and classified by study design, represented with different colors, according to the methodology described by the German Institute for Development Evaluation (DEval) in its Evidence Gap Maps guidelines. This approach will enable a graphical visualization of the distribution of scientific knowledge on the topic. The development of the evidence gap map will be based on the following steps:

I. Search Strategy and Inclusion and Exclusion Criteria:

The same strategy, databases, and criteria defined for the systematic review will be used.

II. Coding and Categorization:

A table will be created with rows representing the interventions (Ceftazidime/Avibactam and Ceftolozane/Tazobactam) and columns representing the outcomes. It is proposed that study designs and types of infections treated will also be assessed.

III. Risk of Bias and Evidence Quality Assessment:

The included studies will be evaluated for risk of bias using tools appropriate for each study design (e.g., ROB-2 for randomized clinical trials and ROBINS-I for observational studies). In addition, the overall quality of evidence for each outcome will be graded according to the GRADE methodology (Grading of Recommendations, Assessment, Development and Evaluations), enabling identification of the robustness and reliability of the findings.

IV. Visualization:

The x-axis will represent the outcome and the y-axis will represent the intervention (drug used). At each intersection, bubbles of different colors will indicate the study designs identified, and the size of each bubble will represent the density of studies for each outcome. Bubbles will also be annotated with information on the level of evidence (GRADE) and risk of bias, allowing a more comprehensive interpretation of the scientific landscape.

Table 3. Methodological Quality Assessment Instruments by Study Type

Study Type	Methodological Quality Assessment Tool
Randomized clinical trials	RoB 2.0 (Cochrane Risk of Bias Tool for Randomized Trials)
Cohort studies	ROBINS-I (Risk Of Bias In Non-randomised Studies of Interventions)
Case–control studies	JBI Checklist for Case Control Studies
Case series and case reports	JBI Critical Appraisal Checklist for Case Reports

Final Considerations

This systematic review with meta-analysis, integrated with the development of an evidence gap map, is expected to contribute to the consolidation of scientific knowledge on the safety, efficacy, and effectiveness of the ceftazidime/avibactam and ceftolozane/tazobactam combinations in hospitalized children and adolescents with severe infections. The investigation will be conducted with rigorous methodology, in accordance with the Cochrane Handbook, and results will be presented following the PRISMA statement, in order to support clinical decision-making, promote the rational use of these antimicrobials in pediatric settings, and inform evidence-based therapeutic guidelines.

The construction of an evidence map will not only identify areas with greater scientific robustness but also reveal critical knowledge gaps, guiding the development of future research—particularly clinical trials and real-world studies with robust designs. Moreover, the findings may provide technical support for health technology assessment processes and contribute to public policy formulation related to the management of severe infections in pediatric populations, such as guiding decisions on clinical protocols and resource allocation in strategies to combat antimicrobial resistance.

Funding

This work was supported by the Carlos Chagas Filho Foundation for Research Support of the State of Rio de Janeiro (Faperj) (grant no. E-26/201.373/2022).

Contributors

TG, AR, EC, and FFL contributed to the conception of the research question. TG, PP, AR, FFL, and EC contributed to the development of search strategies, eligibility criteria, and data synthesis methodology. TG, PP, AR, FFL, and EC contributed to the development of the protocol and approved the final version. All authors will contribute to study screening and selection, data extraction and analysis, and to reading and approving the final manuscript.

Conflict of Interest Statement

The authors declare no conflicts of interest related to this work.

Artificial intelligence (AI) systems

ChatGPT (OpenAI) was used to assist in linguistic revision of the manuscript. All generated suggestions were carefully evaluated.

References

1. Lehane E, Leahy-Warren P, O'Riordan C, *et al.* Evidence-based practice education for healthcare professions: an expert view. BMJ Evid Based Med. 2019;24(3):103-108. doi:10.1136/bmjebm-2018-111019
2. Meng M, Zhou Q, Lei W, *et al.* Recommendations on Off-Label Drug Use in Pediatric Guidelines. Front Pharmacol. 2022;13:892574. doi:10.3389/fphar.2022.892574
3. Tang L, Zhao K, Hou N. Off-label use of antimicrobials among hospitalized children: a retrospective study of 3,406 patients. Front Microbiol. 2023;14:1173042. doi:10.3389/fmicb.2023.1173042
4. Romandini A, Pani A, Schenardi PA, *et al*. Antibiotic Resistance in Pediatric Infections: Global Emerging Threats, Predicting the Near Future. Antibiotics. 2021;10(4):393. doi:10.3390/antibiotics10040393
5. Fanelli U, Chiné V, Pappalardo M, *et al.* Improving the Quality of Hospital Antibiotic Use: Impact on Multidrug-Resistant Bacterial Infections in Children. Front Pharmacol. 2020;11:745. doi:10.3389/fphar.2020.00745
6. Rodriguez BA, Girotto JE, Nicolau DP. Ceftazidime/avibactam and ceftolozane/tazobactam: novel therapy for multidrug-resistant gram-negative infections in children. Curr Pediatr Rev. 2018;14(2):97-109. doi:10.2174/1573396314666181127124112
7. Tamma PD, Aitken SL, Bonomo RA, *et al*. Infectious Diseases Society of America Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and Pseudomonas aeruginosa with Difficult-to-Treat Resistance (DTR-P. aeruginosa). Clin Infect Dis. 2021;72(7):e169-e183. doi:10.1093/cid/ciaa1478
8. Olney KB, Thomas JK, Johnson WM. Review of novel β-lactams and β-lactam/β-lactamase inhibitor combinations with implications for pediatric use. Pharmacotherapy. 2023;43(7):713-731. doi:10.1002/phar.2782
9. Labé P, Husain M, Parize P, *et al.* Evaluation of Ceftazidime-avibactam and Ceftolozane-tazobactam Prescriptions in a Tertiary Hospital for Children in France: An Observational Study, 2017-2022. Pediatr Infect Dis J. 2025;44(7):630-636. doi:10.1097/INF.0000000000004768
10. Perruccio K, D'Amico MR, Baretta V, *et al*. Ceftolozane/Tazobactam and Ceftazidime/Avibactam: An Italian Multi-center Retrospective Analysis of Safety and Efficacy in Children With Hematologic Malignancies and Multi-drug Resistant Gram-negative Bacteria Infections. Pediatr Infect Dis J. 2022;41(12):994-996. doi:10.1097/INF.0000000000003716
11. Miake-Lye IM, Hempel S, Shanman R, *et al*. What is an evidence map? A systematic review of published evidence maps and their definitions, methods, and products. Syst Rev. 2016;5:28. doi:10.1186/s13643-016-0204-x

12. Higgins JPT, Thomas J, Chandler J, *et al*. Cochrane Handbook for Systematic Reviews of Interventions, version 6.5. Chichester : Cochrane; 2024.

13. Campbell F, Tricco AC, Munn Z, *et al.* Mapping reviews, scoping reviews, and evidence and gap maps (EGMs): the same but different—the "Big Picture" review family. Syst Rev. 2023;12:45. doi:10.1186/s13643-023-02178-5

14. Page MJ, McKenzie JE, Bossuyt PM, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi:10.1136/bmj.n71

15. Hartling L, Featherstone R, Nuspl M, *et al*. Grey literature in systematic reviews: a cross-sectional study of the contribution of non-English reports, unpublished studies and dissertations to the results of meta-analyses in child-relevant reviews. BMC Med Res Methodol. 2017;17(1):64. doi:10.1186/s12874-017-0347-z.

16. Sterne JAC, Savović J, Page MJ, *et al.* RoB 2: a revised tool for assessing risk of bias in randomized trials. BMJ. 2019;366:l4898. doi:10.1136/bmj.l4898

17. Sterne JAC, Hernán MA, Reeves BC, *et al.* ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919. doi:10.1136/bmj.i4919

18. Joanna Briggs Institute. Checklist for Case Control Studies. Adelaide: JBI; 2020.

19. Joanna Briggs Institute. Critical Appraisal Checklist for Case Reports. Adelaide: JBI; 2020

20. Basu A. A tutorial on how to write evidence gap maps. Qeios. 2021; PPR622210. doi:10.32388/A58M1M

21. Wickham H. ggplot2: Elegant Graphics for Data Analysis. Cham. Bern: Springer;2016. doi:10.1007/978-3-319-24277-4