Advancing Methods for Overviews of Reviews of Healthcare Interventions

by

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Abstract

Background

Overviews of reviews of healthcare interventions (overviews) compile information from multiple systematic reviews (SRs) to provide a single synthesis of relevant evidence for health-care decision-making. Their increasing popularity, combined with a lack of evidence-based guidance for their conduct and reporting, creates a knowledge gap that must be addressed. The objective of this thesis was to examine methods for conducting and reporting overviews.

Methods

This thesis consisted of three studies and one protocol. First, a scoping review was conducted to identify and summarize all existing methodological guidance for conducting overviews of healthcare interventions. Then, the results of the scoping review were used to inform the development of two methods studies to provide empirical evidence on outstanding issues related to conducting overviews. One study was a multiple case study that explored the impact of different inclusion decisions on the comprehensiveness and results of overviews. The other was a descriptive study that examined issues related to using A MeaSurement Tool to Assess systematic Reviews (AMSTAR) to assess methodological quality of SRs included in overviews. Lastly, a study protocol outlined a project plan to develop a reporting guideline for overviews.

Results

First, the scoping review found limited guidance, and a number of challenges, for conducting several steps of the overview process, such as including non-Cochrane SRs in overviews and conducting quality assessments. Second, the multiple case study found that different inclusion decisions led to different amounts of outcome data loss and change across overviews, and

presented an evidence-based decision tool to help researchers make inclusion decisions in overviews. Third, the descriptive study found that AMSTAR can be used successfully in overviews, and that using AMSTAR scores as an exclusion criterion may not introduce bias into the overview process. Lastly, a study protocol described methods for the development of PRIOR (Preferred Reporting Items for Overviews of Reviews), an evidence-based and consensus-based reporting guideline for overviews.

Conclusions

While gaps in guidance still exist, these thesis projects play an important role in advancing methods for conducting and reporting overviews of reviews of healthcare interventions. Strengthening overview methods can help ensure a rigorous and valid evidence base for knowledge translation and dissemination.

Preface

This doctoral thesis is an original work by Michelle Pollock. Some of the publications referenced in this thesis were published by the student under the name "Michelle Foisy".

A version of Chapter 2 has been published as: "Pollock M, Fernandes RM, Becker LA, Featherstone R, Hartling L. What guidance is available for researchers conducting overviews of reviews of healthcare interventions? a scoping review and qualitative metasummary. Systematic Reviews. 2016;5:190". It appears in a special collection titled "Overviews of systematic reviews: development and evaluation of methods". MP conceived of, designed, coordinated, and conducted all aspects of the study. RMF and LAB participated in interpretation of results. RF participated in reference tracking, database searching, and web searching. LH conceived of the study and participated in its design and conduct. MP drafted the manuscript, and all authors provided feedback and approved the final manuscript. The copyright agreement is in Appendix 1A.

Chapter 3 of this thesis has been formatted for submission to "Systematic Reviews" as: "Pollock M, Fernandes RM, Newton AS, Scott SD, Hartling L. The impact of different inclusion decisions on the comprehensiveness and results of overviews of reviews of healthcare interventions". MP and LH conceived of the study. MP, RMF, SDS, and LH designed the study. MP, RMF, and LH conducted the study. MP, RMF, ASN, and LH interpreted the results of the study. MP drafted the manuscript, and all authors provided feedback and approved the final manuscript.

A version of Chapter 4 has been published as: "Pollock M, Fernandes RM, Hartling L. Evaluation of AMSTAR to assess the methodological quality of systematic reviews in overviews

of reviews of healthcare interventions. BMC Medical Research Methodology. 2017;17:48". MP and LH conceived of, designed, coordinated, and conducted all aspects of the study. RMF participated in interpretation of results. MP drafted the manuscript, and all authors provided feedback and approved the final manuscript. The copyright agreement is in Appendix 1A.

Chapter 5 of this thesis has been formatted for submission to "Systematic Reviews" as: "Preferred Reporting Items for Overviews of Reviews (PRIOR): a protocol for development of a reporting guideline for overviews of reviews of healthcare interventions". MP and LH conceived of and designed the study. MP drafted the protocol, and LH provided feedback and approved the final protocol.

Dedication

I dedicate this thesis to my father

Gaétan Foisy (1961-2013)

and my stepfather

Richard Wright (1961-2015).

To my husband, Iain Pollock,

my mother, Sonya Morin,

and my parents-in-law:

Thank you.

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Chapter 2: I wish to thank Megan Nuspl for assistance with searching and screening, and Sanja Schreiber and the Norwegian Knowledge Centre for the Health Services for assistance with German and Norwegian translations. I also thank all overview authors and Managing Editors of Cochrane Review Groups and Fields who responded to requests for guidance documents, and all authors of the guidance documents included in this review who kindly shared their unpublished documents and/or responded to requests for additional information.

Chapters 3 and 4: I wish to thank the following individuals for assistance with searching, screening, inclusion, and/or AMSTAR assessments: Annabritt Chisholm, Andrea Milne, Melanie

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Chapter 5: I wish to thank Amanda Newton, Andrea Tricco, and Monika Kastner for providing valuable insights into the methodological considerations involved in conducting a Delphi exercise.

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List of Abbreviations

AC1	Alternative chance-correlated coefficient
AMSTAR	A MeaSurement Tool to Assess systematic Reviews
CCA	Corrected covered area
CCRG	Cochrane Consumers and Communication Review Group
CDSR	Cochrane Database of Systematic Reviews
CHF	Cochrane Child Health Field
CI	Confidence interval
CM	Cochrane Musculoskeletal Review Group
CMIMG	Cochrane Comparing Multiple Interventions Methods Group
Cochrane	The Cochrane Collaboration
Cochrane Handbook	*Cochrane Handbook for Systematic Reviews of Interventions*
CPHG	Cochrane Public Health Group
CS	Cochrane Stroke Group
DARE	Database of Abstracts of Reviews of Effects
DCC	Dutch Cochrane Centre
DukeU	Duke University
EMBASE	Excerpta Medica dataBASE
EPOC	Cochrane Effective Practice and Organization of Care Review Group
EPPI	Evidence for Policy and Practice Information and Co-ordinating Centre
EQUATOR	Enhancing QUAlity and Transparency Of health Research
GRADE	Grading of Recommendations Assessment, Development and Evaluation
JBI	Joanna Briggs Institute Umbrella Reviews Methodology Group
LBI	Ludwig Boltzmann Institute for Health Technology Assessment

NOKC	Norwegian Knowledge Centre for the Health Services
Overview	Overview of reviews
PRIOR	Preferred Reporting Items for Overviews of Reviews
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analysis
PXU	Pontifical Xavierian University
SD	Standard deviation
SR	Systematic review
TCD	Trinity College Dublin
UBirm	University of Birmingham
UDun	University of Dundee
WHU	Witten/Herdecke University
WJNR	Western Journal of Nursing Research

Chapter 1

Introduction

1.1. SUMMARY OF THE PROBLEM TO BE ADDRESSED

Overviews of reviews of healthcare interventions (overviews) are an emerging method of knowledge synthesis in the medical health sciences. Overviews compile information from multiple systematic reviews (SRs) to provide a single synthesis of evidence for health-care decision-making [1]. Given their objective to synthesize extensive SR data in an accessible, user-friendly format, overviews have been gaining momentum as a valuable product to facilitate the uptake and application of knowledge by clinical and policy decision-makers. Thus, the number of published overviews has been steadily increasing in recent years [2, 3].

Despite the increasing popularity of overviews, there is limited guidance available for researchers conducting and reporting overviews. Furthermore, since the unit of searching, inclusion, and data analysis is the SR, overview authors face unique methodological and reporting challenges for which there are no obvious solutions. As a result, current practice when conducting and reporting overviews is driven largely by personal experience and trial-and-error rather than empirical evidence [4], and published overviews show considerable variation in their methods and reporting [2, 3]. The increasing popularity of overviews, combined with a lack of evidence-based guidance for their conduct and reporting, creates a knowledge gap that must be addressed. Thus, this doctoral thesis aimed to provide empirical evidence on methods that researchers can use when conducting and reporting overviews. Advancing methods for overviews can help ensure that they are conducted and reported in a rigorous fashion to yield valid and reliable results.

1.2. EMERGENCE AND EVOLUTION OF OVERVIEWS AS A VALUABLE RESEARCH DESIGN IN THE MEDICAL HEALTH SCIENCES

Archie Cochrane, an influential physician and epidemiologist, first recognized the need to synthesize medical research evidence in 1972 when he wrote that "it is surely a great criticism of [the medical] profession that we have not organized a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomized controlled trials" [5]. This set the stage for the publication of the first SRs in medicine in 1989 [5, 6]. Now, systematic reviews are often considered a cornerstone of knowledge translation that provide the highest level of evidence when making health-care decisions [7]. They aim to answer a specific research question by using explicit and reproducible methods to rigorously and systematically identify, select, appraise, and synthesize all relevant primary studies [8]. By synthesizing all available data, SRs attempt to facilitate clinical and policy decision-making by exploring and resolving discrepancies among primary studies that may have different or even contradictory results.

The number of published SRs has been steadily increasing. For example, The Cochrane Collaboration (Cochrane), an international organization that produces high-quality SRs of healthcare interventions [9], has published almost 8,000 SRs in the Cochrane Database of Systematic Reviews (CDSR) [10]. The number of SRs indexed in Medline, another popular health sciences database, has increased from 7 per day in 2004 [11] to 22 per day in 2014 [12]. Though SRs are a valuable resource for health-care decision-making, the sheer amount of SRs that exist can lead to information overload for health-care decision-makers who have limited time, resources, and ability to manage large amounts of information [13].

In recent years, overviews of reviews have been gaining momentum as a novel and innovative solution to help manage this information overload. The first overview in the medical health sciences was published in 1998 [3, 14], and since then the number of published overviews and overview protocols has been steadily increasing (Figure 1.1). Overviews use explicit and systematic methods to search for, identify, extract data from, and analyze the results of multiple SRs that examine a set of related interventions, conditions, populations, or outcomes [1]. Overviews in medicine often examine questions related to the prevention or treatment of various clinical conditions (i.e., questions about healthcare interventions). They often include multiple SRs of different interventions for the same condition or population, though they can also investigate other types of research questions (Table 1.1). A variety of terms are currently used to refer to this study design (Table 1.2). In keeping with the terminology used by Cochrane, this thesis will use the term "overviews of reviews" (abbreviated "overviews").

Overviews may be preferred by health-care decision-makers because they synthesize all SR evidence in one single document. Child-relevant SRs in the CDSR include a median of eight primary studies and 980 participants, and often focus on specific population subgroups, single interventions or comparisons, or select outcomes [15]. However, overviews produced by Cochrane Child Health include a median of five SRs, and they typically address broader research questions that cover a more extensive body of evidence [16]. For example, in 2010 eleven SRs in the CDSR addressed the following interventions for treating bronchiolitis: antibiotics [17], bronchodilators [18], chest physiotherapy [19], epinephrine [20], extrathoracic pressure [21], glucocorticoids [22], heliox [23], hypertonic saline [24], immunoglobulin [25], inhaled corticosteroids [26], and oxygen therapy [27]. To determine which treatments were effective in inpatient, outpatient, and intensive care populations, our research group conducted an overview

that synthesized evidence from 93 primary studies and 8,556 participants across these eleven SRs [28]. Completed overviews can be used in two main ways to facilitate the uptake and application of knowledge by decision-makers. They can be used to disseminate knowledge directly to end-users such as healthcare providers, patients, caregivers, researchers, grant funders, and government and healthcare policy representatives. Alternatively, they can be used to inform the development of knowledge translation tools such as patient decision aids, clinical practice guidelines, and policy briefs [29].

1.3. HIGH-LEVEL SUMMARY OF METHODS FOR CONDUCTING AND REPORTING OVERVIEWS

Despite the increasing popularity of overviews, methods for the conduct and reporting of overviews are still in their infancy. Overview methods evolved from SR methods for which there are well-established standards of conduct to ensure rigour, validity, and reliability of results [30]. However, since the unit of searching, inclusion, and data extraction is the SR (rather than the primary study), methods for conducting overviews must necessarily differ from those used to conduct SRs. Accordingly, some stages of the overview process must be modified or added to address methodological issues unique to overviews. When conducting an overview, researchers generally aim to: define the research question; develop inclusion criteria for SRs; search for SRs; select SRs for inclusion; collect and present data on descriptive characteristics of included SRs (and their primary studies); assess methodological quality of included SRs (and their primary studies); collect, analyze, and present outcome data; and assess the certainty of evidence of outcome data [1]. These steps must then be reported in a manner that is clear, detailed, complete, and transparent.

Though conducting and reporting the above-listed steps may seem straightforward in theory, overview authors often face unique methodological challenges for which there are no obvious solutions or clear guidance. These challenges stem from several converging factors. First, managing the two levels of information in overviews (from SRs, and from their included primary studies) adds an additional level of complexity. Second, because SRs are syntheses of pre-existing data, overview authors are limited by the methods and reporting of the included SRs. Lastly, including SRs published outside of the CDSR (i.e., "non-Cochrane SRs") raises unique challenges due to the increased potential for topic overlap across multiple similar SRs [31] and the greater variation in methods and reporting of non-Cochrane SRs [12, 32-34]. In recent years, overview authors have recognized the need for comprehensive, up-to-date guidance that accounts for these unique features of overviews [2, 3, 35]. To help meet this need, this thesis: located and summarized existing methods guidance for overviews; explored potential solutions to outstanding methodological issues in overviews; and established a project plan for a reporting guideline for overviews.

1.4. RESEARCH QUESTION AND OBJECTIVES

This doctoral thesis aimed to answer the following research question: "What methods can researchers use to conduct and report overviews of reviews of healthcare interventions?" To answer the above research question, this thesis had three main objectives:

1) To identify and summarize existing methods guidance for conducting overviews;
2) To provide empirical evidence on issues related to conducting overviews; and
3) To establish a project plan to develop a reporting guideline for overviews.

Four research projects, described below, were conducted to fulfill these objectives.

1.5. THE FOUR RESEARCH PROJECTS

This is a paper-based thesis. Chapter 2 contains a scoping review that was designed to fulfill Objective 1. Chapters 3 and 4 contain two empirical methods studies that were designed to fulfill Objective 2. Chapter 5 contains a protocol for development of a reporting guideline for overviews that was designed to fulfill Objective 3. The relationships between the doctoral research question, three objectives, and four research projects are depicted in Figure 1.2. The following sections describe these relationships in detail.

1.5.1. Chapter 2 (scoping review)

Because overviews are relatively new, though increasingly popular [2, 3], there has been no systematic and comprehensive effort to identify and map all existing methods guidance for their conduct. Thus, a logical first step for this doctoral thesis was to compile and summarize all existing guidance for conducting overviews. To do so, we conducted a scoping review, which is presented in Chapter 2 to fulfill Objective 1. While the published scoping review is a useful scientific output in and of itself, we also used the results to update the chapter on overview methods in the *Cochrane Handbook for Systematic Reviews of Interventions* (currently under review), and to prioritize empirical methods studies evaluating methods for conducting overviews. These two outputs are discussed later in this thesis as relevant.

Chapter 2 of this thesis has been published as: "Pollock M, Fernandes RM, Becker LA, Featherstone R, Hartling L. What guidance is available for researchers conducting overviews of reviews of healthcare interventions? A scoping review and qualitative metasummary. Systematic

Reviews. 2016;5:190". It appears in a special collection titled "Overviews of systematic reviews: development and evaluation of methods". The copyright agreement is in Appendix 1A.

1.5.2. Link between Chapter 2 (scoping review) and Chapters 3 and 4 (empirical methods studies)

Ultimately, it is important to provide methodological guidance based on empirical evidence for those stages of the overview process where methods guidance is conflicting or missing and where outstanding challenges remain. Thus, we used the results of the scoping review (Chapter 2) to inform the development of two empirical methods studies. The two studies are presented in Chapters 3 and 4 to fulfill Objective 2.

We used the same convenience sample of overviews for both methods studies. For an overview to be included in the sample, it had to meet four criteria:

1) Fulfil the four key characteristics of overviews (Table 1.3);
2) Examine the efficacy or effectiveness of multiple interventions for the prevention or treatment of a clinical condition;
3) Investigate a clinical condition related to pediatric health; and
4) Be conducted between 2010 and 2016 by researchers at the Alberta Research Centre for Health Evidence.

Sixteen overviews fulfilled these inclusion criteria, and a convenience sample of seven overviews was selected for inclusion into the two methods studies (Appendix 1B).

The first methods study (Chapter 3) was a multiple case study that assessed how different decisions surrounding the inclusion and exclusion of SRs in overviews affected the comprehensiveness and results of overviews. The results were then used to develop a decision

tool to help researchers make inclusion decisions in overviews. Chapter 3 of this thesis has been formatted for submission to "Systematic Reviews ".

The second methods study (Chapter 4) was a descriptive study that examined methodological considerations involved in using A MeaSurement Tool to Assess systematic Reviews (AMSTAR) [36-38] to assess the methodological quality of SRs in overviews. Chapter 4 has been published as: "Pollock M, Fernandes RM, Hartling L. Evaluation of AMSTAR to assess the methodological quality of systematic reviews in overviews of reviews of healthcare interventions. BMC Medical Research Methodology. 2017;17:48".

1.5.3. Link between Chapter 2 (scoping review) and Chapter 5 (reporting guideline protocol)

When we developed the project plan for the scoping review conducted in Chapter 2, we had originally intended to include guidance for reporting, as well as conducting, overviews. However, we located limited guidance for reporting overviews [1, 2, 39-41]. Instead of summarizing this paucity of evidence, we instead opted to develop a protocol for a multi-year project to produce an evidence-based and consensus-based reporting guideline for overviews. This protocol is presented in Chapter 5 to fulfill Objective 3. It has been formatted for submission to "Systematic Reviews".

1.6. SUMMARY

Overviews provide a novel and innovate solution to help manage the sheer amount of health data that exist. Investing in strengthening this methodology has the potential to increase the uptake and application of knowledge by clinical and policy decision-makers. This, in turn,

can help address crucial health issues and improve health outcomes in diverse populations. Together, these four projects provide much-needed guidance for researchers conducting overviews and help identify gaps and next steps for future research.

1.7. REFERENCES

1. Becker LA, Oxman AD. Chapter 22: overviews of reviews. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.1.0). The Cochrane Collaboration; 2011. http://www.handbook.cochrane.org.
2. Hartling L, Chisholm A, Thomson D, Dryden DM. A descriptive analysis of overviews of reviews published between 2000 and 2011. PLoS One. 2012;7(11):e49667.
3. Pieper D, Buechter R, Jerinic P, Eikermann M. Overviews of reviews often have limited rigor: a systematic review. J Clin Epidemiol. 2012;65(12):1267-73.
4. Smith V, Devane D, Begley CM, Clarke M. Methodology in conducting a systematic review of systematic reviews of healthcare interventions. BMC Med Res Methodol. 2011;11(1):15.
5. Chalmers I, Hedges LV, Cooper H. A brief history of research synthesis. Eval Health Prof. 2002;25(1):12-37.
6. Chalmers I, Enkin M, Keirse MJNC. Effective care in pregnancy and childbirth. Oxford: Oxford University Press; 1989.
7. Evans D. Hierarchy of evidence: a framework for ranking evidence evaluating healthcare interventions. J Clin Nurs. 2003;12(1):77-84.
8. Green S, Higgins JPT, Alderson P, Clarke M, Mulrow CD, Oxman AD. Chapter 1: introduction. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews

of interventions (version 5.1.0). The Cochrane Collaboration; 2011. http://www.handbook.cochrane.org.

9. Cochrane. About us. http://www.cochrane.org/about-us (n.d.). Accessed 01 Sept 2017.
10. Cochrane. Cochrane in numbers: April-June 2017. http://www.cochrane.org/news/cochrane-numbers-april-june-2017 (2017). Accessed 01 Sept 2017.
11. Moher D, Tetzlaff J, Tricco AC, Sampson M, Altman DG. Epidemiology and reporting characteristics of systematic reviews. PLoS Med. 2007;4(3):e78.
12. Page MJ, Shamseer L, Altman DG, Tetzlaff J, Sampson M, Tricco AC, *et al*. Epidemiology and reporting characteristics of systematic reviews of biomedical research: a cross-sectional study. PLoS Med. 2016;13(5):e1002028.
13. Bastian H, Glasziou P, Chalmers I. Seventy-five trials and eleven systematic reviews a day: how will we ever keep up? PLoS Med. 2010;7(9):e1000326.
14. Bero LA, Grilli R, Grimshaw JM, Harvey E, Oxman AD, Thomson MA. Closing the gap between research and practice: an overview of systematic reviews of interventions to promote the implementation of research findings. The Cochrane Effective Practice and Organization of Care Review Group. BMJ. 1998;317(7156):465-8.
15. Crick K, Thomson D, Fernandes RM, Nuspl M, Eurich DT, Rowe BH, *et al*. Descriptive analysis of cochrane child-relevant systematic reviews: an update and comparison between 2009 and 2013. BMC Pediatr. 2017;17(1):155.
16. Thomson D, Foisy M, Oleszczuk M, Wingert A, Chisholm A, Hartling L. Overview of reviews in child health: evidence synthesis and the knowledge base for a specific population. Evid Based Child Health. 2013;8(1):3-10.

17. Spurling GKP, Fonseka K, Doust J, Del Mar C. Antibiotics for bronchiolitis in children. Cochrane Database Syst Rev. 2007;1:CD005189.
18. Gadomski A, Brower M. Bronchodilators for bronchiolitis. Cochrane Database Syst Rev. 2010;12:CD001266.
19. Perrotta C, Ortiz Z, Figuls M. Chest physiotherapy for acute bronchiolitis in paediatric patients between 0 and 24 months old. Cochrane Database Syst Rev. 2007;1:CD004873.
20. Hartling L, Bialy LM, Vandermeer B, Tjosvold L, Johnson DW, Plint AC, *et al*. Epinephrine for bronchiolitis. Cochrane Database Syst Rev. 2011;6:CD003123.
21. Shah PS, Ohlsson A, Shah JP. Continuous negative extrathoracic pressure or continuous positive airway pressure for acute hypoxemic respiratory failure in children. Cochrane Database Syst Rev. 2008;1:CD003699.
22. Fernandes R, Bialy L, Vandermeer B, Tjosvold L, Plint A, Patel H, *et al*. Glucocorticoids for acute viral bronchiolitis in infants and young children. Cochrane Database Syst Rev. 2010;10:CD004878.
23. Liet JM, Ducruet T, Gupta V, Cambonie G. Heliox inhalation therapy for bronchiolitis in infants. Cochrane Database Syst Rev. 2010;4:CD006915.
24. Zhang L, Mendoza-Sassi RA, Wainwright C, Klassen TP. Nebulized hypertonic saline solution for acute bronchiolitis in infants. Cochrane Database Syst Rev. 2008;4:CD006458.
25. Fuller HL, Del Mar C. Immunoglobulin treatment for respiratory syncytial virus infection. Cochrane Database Syst Rev. 2006;4:CD004883.
26. Blom DJM, Ermers M, Bont L, van Woensel JBM, van Aalderen WMC. Inhaled corticosteroids during acute bronchiolitis in the prevention of post-bronchiolitic wheezing. Cochrane Database Syst Rev. 2007;1:CD004881.

27. Rojas-Reyes MX, Granados RC, Charry-Anzola LP. Oxygen therapy for lower respiratory tract infections in children between 3 months and 15 years of age. Cochrane Database Syst Rev. 2009;1:CD005975.
28. Bialy L, Foisy M, Smith M, Fernandes RM. The Cochrane Library and the treatment of bronchiolitis in children: an overview of reviews. Evid Based Child Health. 2011;6(1):258-75.
29. Grimshaw J. A knowledge synthesis chapter. In: A guide to knowledge synthesis. Canadian Institutes of Health Research; 2010. http://www.cihr-irsc.gc.ca/e/41382.html. Accessed 01 Sept 2017.
30. Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.1.0). The Cochrane Collaboration; 2011. http://www.handbook.cochrane.org.
31. Pieper D, Antoine SL, Mathes T, Neugebauer EA, Eikermann M. Systematic review finds overlapping reviews were not mentioned in every other overview. J Clin Epidemiol. 2014;67(4):368-75.
32. Fleming PS, Seehra J, Polychronopoulou A, Fedorowicz Z, Pandis N. Cochrane and non-Cochrane systematic reviews in leading orthodontic journals: a quality paradigm? Eur J Orthod. 2013;35(2):244-8.
33. MacDonald SL, Canfield SE, Fesperman SF, Dahm P. Assessment of the methodological quality of systematic reviews published in the urological literature from 1998 to 2008. J Urol. 2010;184(2):648-53.
34. Moseley AM, Elkins MR, Herbert RD, Maher CG, Sherrington C. Cochrane reviews used more rigorous methods than non-Cochrane reviews: survey of systematic reviews in physiotherapy. J Clin Epidemiol. 2009;62(10):1021-30.

35. Foisy M, Dryden DM, Fernandes RM, Hartling L, Thomson D. Advancing methods for overviews of reviews: a discussion of challenges and potential solutions. Abstracts of the 22nd Cochrane Colloquium; 21-26 Sept 2014; Hyderabad, India: John Wiley & Sons; 2014.
36. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, *et al*. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 2007;7:10.
37. Shea BJ, Bouter LM, Peterson J, Boers M, Andersson N, Ortiz Z, *et al*. External validation of a measurement tool to assess systematic reviews (AMSTAR). PLoS One. 2007;2(12):e1350.
38. Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J, *et al*. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol. 2009;62(10):1013-20.
39. Li L, Tian J, Tian H, Sun R, Liu Y, Yang K. Quality and transparency of overviews of systematic reviews. J Evid Based Med. 2012;5(3):166-73.
40. Singh JP. Development of the Metareview Assessment of Reporting Quality (MARQ) checklist. Rev Fac Med. 2012;60(4):325-32.
41. Wagner S, White M, Schultz I, Iverson R, Hsu V, McGuire L, *et al*. Assessing a systematic review of systematic reviews: developing a criteria. Abstracts of the Canadian Association for Research on Work and Health Conference; 01-02 Jun 2012; Vancouver, Canada.

Table 1.1. Types of questions about healthcare interventions that overviews can examine.

1) Different interventions for the same condition or population
2) The same intervention for different conditions or populations
3) Adverse effects of an intervention for one or more conditions or populations
4) The same intervention for the same condition or population, where different outcomes or time points are addressed in different systematic reviews

Modified from Becker & Oxman [1].

Table 1.2. Terms used to describe "overviews of reviews" from overviews published in the medical literature between 2000 and 2011.[a]

Analysis of systematic reviews	Review of systematic reviews
Guideline based on systematic review evidence	Summary of Cochrane reviews
Meta-review	Summary of systematic reviews
Overview	Synopsis of Cochrane systematic reviews
Overview of Cochrane and non-Cochrane reviews	Systematic meta-review
Overview of Cochrane reviews	Systematic review
Overview of Cochrane systematic reviews	Systematic review of reviews
Overview of reviews	Systematic review of systematic reviews
Overview of systematic reviews	Systematic umbrella review
Review	Umbrella review

Modified from Hartling *et al.* [2].

[a] The five most commonly used terms are "overviews of reviews" (27%), "overviews of systematic reviews" (13%), "umbrella reviews" (11%), "reviews of systematic reviews" (8%), and "overviews of Cochrane systematic reviews" (5%).

Table 1.3. Key characteristics of overviews.

Overviews should:
1) Contain a clearly stated objective designed to answer at least one research question.
2) Intend to search for and include only systematic reviews (with or without meta-analyses).
3) Use formalized methods to identify multiple systematic reviews that meet their inclusion criteria [and assess the methodological quality of these systematic reviews[a]].
4) Intend to collect, analyze, and present the descriptive characteristics of their included systematic reviews (and their primary studies) and the quantitative outcome data contained within the systematic reviews.

Modified from Becker & Oxman [1] and Hartling *et al.* [2]. Documents were considered to be 'systematic reviews' if they contained a clear objective statement, used formalized methods to search for and identify primary studies that met their inclusion criteria, and presented descriptive characteristics and quantitative outcome data from those primary studies.

[a] Overviews did not have to meet this criterion to be included in the study sample for the two empirical methods studies (Chapters 3 and 4).

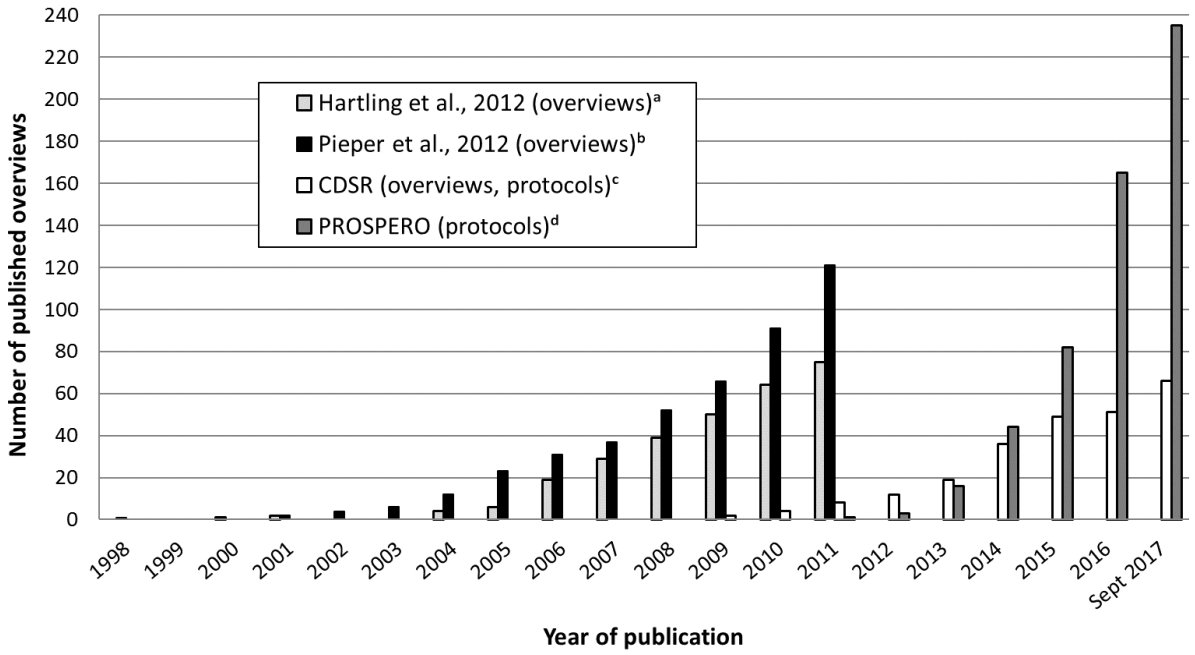


Figure 1.1. Number of overviews and overview protocols published by year, between 1998 and September 2017. [a] Data come from Hartling *et al.* [2]; [b] Data come from Pieper *et al.* [3]; [c] CDSR (Cochrane Database of Systematic Reviews) was searched using the term "overview" restricted to the title, abstract, and keywords (September 01, 2017); [d] PROSPERO (International prospective register of systematic reviews) was searched using the terms "overview of reviews", "overview of systematic reviews", "umbrella review", "review of systematic reviews", and "overview of Cochrane systematic reviews" restricted to the title of ongoing, completed, and published non-Cochrane protocols (September 01, 2017).

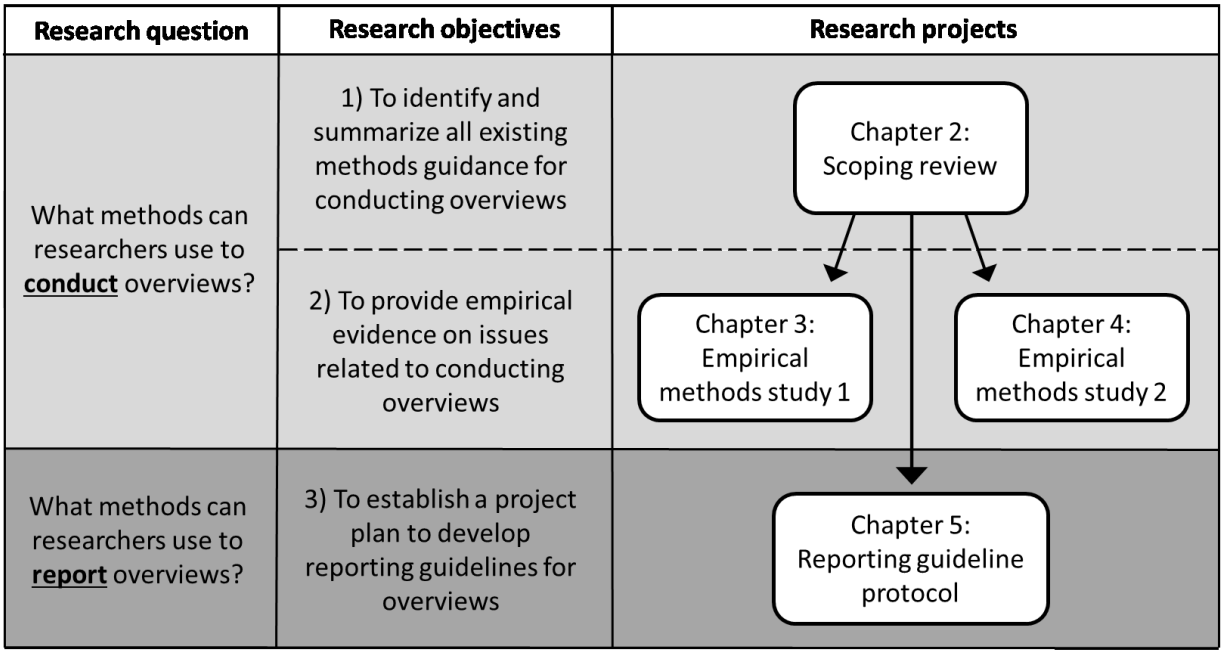


Figure 1.2. Relationship between doctoral research question, objectives, and projects.

Chapter 2

What guidance is available for researchers conducting overviews of reviews of healthcare interventions? A scoping review and qualitative metasummary

A version of this chapter has been published as: "Pollock M, Fernandes RM, Becker LA, Featherstone R, Hartling L. What guidance is available for researchers conducting overviews of reviews of healthcare interventions? A scoping review and qualitative metasummary. Systematic Reviews. 2016;5:190". It appears in a special collection titled "Overviews of systematic reviews: development and evaluation of methods". The copyright agreement is in Appendix 1A.

2.1. ABSTRACT

Background

Overviews of reviews (overviews) compile data from multiple systematic reviews (SRs) to provide a single synthesis of relevant evidence for decision-making. Despite their increasing popularity, there is limited methodological guidance available for researchers wishing to conduct overviews. The objective of this scoping review was to identify and collate all published and unpublished documents containing guidance for conducting overviews examining the efficacy, effectiveness and/or safety of healthcare interventions. Our aims were to: provide a map of existing guidance documents; identify similarities, differences, and gaps in the guidance contained within these documents; and identify common challenges involved in conducting overviews.

Methods

We conducted an iterative and extensive search to ensure breadth and comprehensiveness of coverage. The search involved reference tracking, database and web searches (Medline, EMBASE, DARE, Scopus, Cochrane Methods Studies Database, Google Scholar), handsearching of websites and conference proceedings, and contacting overview producers. Relevant guidance statements and challenges encountered were extracted, edited, grouped, abstracted, and presented using a qualitative metasummary approach.

Results

We identified 52 guidance documents produced by 19 research groups. Relatively consistent guidance was available for the first stages of the overview process (deciding when and why to conduct an overview, specifying the scope, and searching for and applying inclusion criteria to SRs). In contrast, there was limited or conflicting guidance for the latter stages of the overview process (quality assessment of SRs and their primary studies, collecting and analyzing data, and assessing certainty of evidence), and many of the challenges identified also related to these stages. An additional, overarching challenge identified was that overviews are limited by the methods, reporting, and coverage of their included SRs.

Conclusions

This compilation of methodological guidance for conducting overviews of healthcare interventions will facilitate the production of future overviews and can help authors address key challenges they are likely to encounter. The results of this project have been used to identify areas where future methodological research is required to generate empirical evidence for overview methods. Additionally, these results have been used to update the chapter on overviews in the next edition of the *Cochrane Handbook for Systematic Reviews of Interventions*.

2.2. BACKGROUND

Systematic reviews (SRs) combine the results of multiple similar primary studies to answer a specific research question [1]. With the dramatic increase in the number of published SRs [2], overviews of reviews (overviews) have emerged as a logical solution to help manage this information overload. The purpose of overviews is to integrate information from multiple related SRs to provide a comprehensive synthesis of all SR evidence related to a specific research question [3]. They are designed to be accessible, user-friendly documents that are typically broader in scope than any individual SR. Overviews are often conducted to address questions related to the efficacy, effectiveness and/or safety of healthcare interventions—for example, examining multiple interventions for the prevention or treatment of a specific health condition [3]. Table 2.1 describes key characteristics of overviews.

Given their objective to synthesize extensive data in a user-friendly format, overviews have been gaining momentum as a valuable knowledge synthesis product to facilitate the uptake and application of knowledge by decision-makers. Thus, the number of published overviews has been steadily increasing in recent years [4-6]. This increase is at least partially due to the pioneering efforts of The Cochrane Collaboration, an international organization widely recognized as producing high-quality SRs of health evidence [7]. In 2004, the Comparing Multiple Interventions Methods Group (originally called the Umbrella Reviews Methods Group) was established to develop general guidance for conducting overviews [8]. This preliminary guidance was first published as a chapter in the *Cochrane Handbook for Systematic Reviews of Interventions (Cochrane Handbook)* in 2008 [3], and the first overview was published in the Cochrane Database of Systematic Reviews (CDSR) in 2009 [9]. Today, Cochrane authors can publish overviews in the CDSR with a label that allows readers to distinguish them from

standard SRs. Other research groups and organizations around the world have also adopted this research design as a valuable knowledge synthesis product [10, 11].

Overview methods evolved from SR methods for which there are well-established standards of conduct to ensure rigor, validity, and reliability of results [12]. Overviews therefore aim to use explicit, reproducible, and systematic methods to search for, identify, and extract outcome data from SRs. However, since the unit of searching, inclusion, and data extraction is the SR, overview authors often encounter unique methodological challenges for which there are no obvious solutions or clear guidance. As a result, current practice when conducting overviews is driven largely by personal experience and trial and error, and published overviews show considerable variation in their methods and reporting [4-6]. In recent years, a number of overview authors have recognized the methodological challenges inherent in conducting overviews and expressed a need for comprehensive, up-to-date guidance for overviews [4, 5, 13].

The purpose of this scoping review was to identify and summarize all documents containing methodological guidance for conducting overviews examining the efficacy, effectiveness and/or safety of healthcare interventions. The aims were to: 1) locate, access, compile, and create a map of documents that provide explicit methodological guidance for conducting overviews; 2) identify and describe areas where guidance for conducting overviews is clear and consistent, as well as areas where guidance is conflicting or missing; and 3) document common challenges involved in conducting overviews and determine whether existing guidance can help researchers overcome these challenges. We then used the results of this scoping review to update the chapter on overview methods appearing in the next edition of the *Cochrane Handbook* (currently under review).

2.3. METHODS

This scoping review adhered to the methods established by Arksey & O'Malley [14] and expanded upon by Levac [15].

2.3.1. Eligibility criteria

To be included in the scoping review, documents had to meet one of two criteria: 1) *provide explicit guidance for conducting overviews of healthcare interventions*, defined as any guidance related to either the context or the process of conducting an overview, or 2) *describe an author team's experience conducting one or more overviews of healthcare interventions*. When selecting documents for inclusion, we used the definition of overviews provided in Table 2.1. We included guidance that applied to overviews examining the efficacy, effectiveness and/or safety of healthcare interventions, and excluded guidance that applied to other types of overviews (e.g., diagnostic test accuracy, prognostic, and qualitative overviews). We included documents produced in any language, year, or format.

2.3.2. Search methods for identification of documents

Our scoping review aimed to identify and include a wide range of document types, including unpublished documents such as internal documents, training manuals, and conference proceedings. We therefore conducted an iterative and extensive search to ensure breadth and comprehensiveness of coverage [14-17]. The search was conducted between January and March 2014 and involved reference tracking, database and web searches, handsearching of websites and conference proceedings, and contacting producers of overviews.

Our iterative reference tracking ("snowballing") search [16, 17] was conducted by a research librarian (RF). The reference tracking search used a total of 30 target articles about overviews that were identified by the study authors prior to the start of the search and as the search progressed. For each target article, we searched for "citing" references using Google Scholar, "cited" references using Scopus and reference lists, and "similar articles" using PubMed. Database and web searches were conducted to supplement and enhance our reference tracking search (RF). We first updated the database searches reported in Hartling 2012 [4]. This involved searching Medline (via Ovid), EMBASE (via Ovid), DARE (via Cochrane Library), and Scopus, for articles published between January 2010 and December 2013. We then augmented this search with two additional databases (Medline via Web of Science, and Cochrane Methods Studies Database via Ovid) and one additional web search engine (Google Scholar). Relevant articles identified by the database and web searches were fed back into the reference tracking search and used as target articles to help locate additional relevant articles.

A number of additional sources were searched in an attempt to locate all unpublished and internal guidance documents (MP, RF). We handsearched the websites of 26 organizations that we knew had published at least one overview, and the conference proceedings (2000-2013) of three conferences: the International Cochrane Colloquium, Health Technology Assessment International, and the Canadian Agency for Drugs and Technologies in Health Symposium. Additionally, we contacted overview producers to ask if they had followed any specific guidance when conducting their overview(s): this involved contacting 20 Managing Editors of Cochrane Review Groups and Fields who oversaw the preparation of a combined 64 overviews published in the CDSR and *"Evidence-Based Child Health: A Cochrane Review Journal"*, and 110 authors who published a combined 148 overviews in journals other than the CDSR (lists of overviews

obtained from [4] and [5]). We had satisfactory response rates (57% for authors of conference proceedings, 96% for Managing Editors of Cochrane Review Groups and Fields, and 55% for overview authors).

We updated select components of the search in November 2015. To ensure we continued to capture relevant documents published after our search dates, we used article alerts from Medline (via Web of Science) and Google Scholar to monitor new articles between January 2014 and November 2015. Additionally, we searched conference proceedings for 2014 and 2015, and contacted an additional five Managing Editors of Cochrane Review Groups who oversaw the preparation of five overviews published in the CDSR in 2014 and 2015.

Finally, we handsearched the reference lists of the 52 guidance documents included in this scoping review. Due to the variability in terminology used to refer to overviews [4], we searched for and included terms such as "overview", "overview of reviews", "overview of systematic reviews", "umbrella review", "systematic review of systematic reviews", and "metareview", among others. See Appendix 2A for complete search strategies.

2.3.3. Selection of documents

All titles and abstracts were independently screened by one reviewer (MP) and one research assistant (MN) . We kept those documents that were not overviews but that met the broad definition of "being about overviews" or "discussing some aspect of overviews". We then retrieved the full text of all potentially relevant titles and abstracts. Full-text articles were assessed for inclusion by two independent reviewers (MP, LH) using the previously described eligibility criteria, with discrepancies resolved through discussion.

2.3.4. Data extraction and analysis

Relevant text contained within each included document was extracted and analyzed using a qualitative metasummary approach, which is an iterative, quantitatively oriented method of data analysis that involves aggregating textual data to identify and expose patterns of findings across groups of related documents [18, 19]. This involved extracting, editing, grouping, abstracting, and presenting findings (this work was completed using Microsoft Word and Excel). All data collection and analysis was conducted by one reviewer (MP) and checked for accuracy by a second reviewer (LH), with disagreements resolved through discussion. The qualitative metasummary process is described below.

First, we clearly specified the text eligible and not eligible for extraction using the criteria presented in Appendix 2B [18]. For documents that *provided explicit guidance for conducting overviews of healthcare interventions*, we extracted text that provided guidance on how to conduct any part of an overview and text that described challenges involved when conducting overviews. For documents that *described an author team's experience conducting one or more overviews of healthcare interventions*, we extracted only text that described challenges author teams encountered. We then separated guidance statements and challenges from all other text in the documents, and edited the guidance and challenges to ensure that they were presented in a way that was accessible to readers while preserving their underlying content and meaning [18]. Guidance statements and challenges were then separated from each other and grouped, abstracted, and presented in parallel.

For both guidance statements and challenges, we used a two-stage approach to group similar findings together. First, we grouped all documents produced by the same research group to avoid giving extra weight to statements that were included in multiple documents produced by

the same research group [18]. Within each of these groupings, we further edited the findings to eliminate redundancies and duplicate text while leaving the meaning of the statements unchanged. Second, we grouped statements across research groups by stage of the overview process to ensure that all statements related to the same stage of the overview process appeared in the same place [18]. The stages of the overview process included: deciding when and why to conduct an overview, specifying the scope, searching for and including SRs, quality assessment of SRs and their primary studies, collecting and analyzing data, grading certainty of evidence, and drawing conclusions. These stages were identified iteratively: they were selected in advance using the stages presented in the *Cochrane Handbook*) [12], and modified as needed to accommodate the specific guidance and challenges identified.

We then abstracted findings to summarize the content of each group of topically related guidance statements and challenges [18, 19]. For each stage of the overview process, we reworked our lists of guidance statements and challenges until we developed a new list of abstracted statements that captured the overall meaning of the original statements. This was done by eliminating redundancies, refining statements to ensure they were inclusive of the ideas presented by each research group, preserving ambiguity and contradictions, and ensuring clarity and accessibility.

Lastly, we provided a narrative summary of the abstracted guidance statements followed by a narrative summary of the abstracted challenges. For guidance statements only, we also calculated frequency and intensity effect sizes. These were used to extract more meaning from the narrative summaries by numerically describing the magnitude of the abstracted findings [18, 19]. Frequency effect sizes described the amount of guidance on each topic area, and were calculated by dividing the number of research groups contributing guidance on a topic area by

the total number of research groups. Intensity effect sizes described the amount of guidance contributed by each research group, and were calculated by dividing the number of topic areas addressed by each research group by the total number of topic areas.

2.4. RESULTS

2.4.1. Results of the search

The literature search retrieved 2,418 unique references. 176 references were identified as potentially eligible, and the full-text articles were assessed for inclusion. Of these, 124 documents were excluded (list available upon request). Fifty-two documents produced by 19 research groups were included; these documents are listed in Appendix 2C and are labeled "A1", "A2", ..., "A52" in the text below. Figure 2.1 contains a flow diagram of documents through the review process. As anticipated, published articles that could be located through database searching comprised a minority (29%) of included documents; the majority (71%) were unpublished documents identified through other searching methods.

2.4.2. Summary of included guidance documents

Table 2.2 summarizes the characteristics of the included guidance documents and presents abbreviations for research groups that will be used throughout the remainder of the results.

Of the 52 included documents, 41 *provided explicit methodological guidance for conducting overviews of healthcare interventions* (Appendix 2C, references A1-A41). These documents were produced between 2008-2015 by twelve research groups (range: 1-18 documents per group). The three most common types of documents were oral presentations

(37%), journal articles (24%), and internal documents (22%). Four research groups (CHF, CMIMG, CPHG, EPOC) contributing 28 documents (68%) had primary affiliations associated with The Cochrane Collaboration. Eleven documents *described an author team's experience conducting one or more overviews of healthcare interventions* (Appendix 2C, references A42-A52). These documents (5 posters, 4 journal articles, 2 oral presentations) were produced between 2004-2015 by nine research groups (range: 1-2 documents per group). Six research groups (CCRG, CHF, CM, CS, DDC, EPOC) contributing eight documents (73%) had primary affiliations associated with The Cochrane Collaboration. We first summarize the existing guidance for conducting overviews, with frequency and intensity effect sizes. We then summarize the challenges identified.

2.4.3. Guidance for conducting overviews

The guidance contained within the 41 documents that *provided explicit methodological guidance* fell into two broad categories: guidance related to the context for conducting overviews and guidance related to the process of conducting overviews. These categories could be further subdivided into 15 topic areas. The existing methods guidance for each topic area is summarized below; terms in italics are defined in Table 2.3.

2.4.3.1. Guidance related to the context for conducting overviews

Choosing between conducting an overview and a SR. Two groups provided guidance on this topic (CMIMG, EPPI). The CMIMG stated that authors should conduct an overview only when they intend to search for and extract data from SRs as opposed to primary studies (A16). Authors should conduct a SR when they intend to: search for or extract data from primary

studies, conduct a *network meta-analysis*, or rank order interventions (A16). When choosing between both study designs, the scope of the research question should be taken into account (A12). See reference A23 for additional guidance on choosing between both study designs (CMIMG). EPPI-Centre stated that authors may consider conducting an overview when a broad research question co-occurs with a short time frame and limited resources (A30).

What questions about healthcare interventions can be answered using the overview format? One group (CMIMG) provided guidance on this topic, though six additional groups (CHF: A2; DukeU: A29; JBI: A34; NOKC: A36; TCD: A37; UBirm: A38) referenced this guidance in their own documents. The CMIMG stated that overviews can summarize evidence from multiple SRs about "different interventions for the same condition; the same intervention for different conditions; the same intervention for the same condition where different outcomes are addressed in different SRs; or adverse effects of interventions" (A16).

Questions to consider before deciding to conduct an overview. Six groups (CHF, CMIMG, EPPI, JBI, TCD, WJNR) stated that the overview format must be suitable for the proposed research question. Questions to consider include: is the topic clinically relevant (CHF: A8); is the field too new or changing too rapidly to preclude the utility of an overview (EPPI: A30); are there enough relevant SRs on major interventions and/or disorders of interest (e.g., are SRs up-to-date and clinically and methodologically homogeneous) (CHF: A8; CMIMG: A16; WJNR: A39); have important organizational factors been considered (e.g., author team, time frame, and funding) (CHF: A8; CMIMG: A14; JBI: A34; TCD: A37); and does it make methodological sense to include all SRs in the same overview (e.g., has the *transitivity assumption* been met) (CHF: A3; CMIMG: A24)? The CHF states that proper planning is

important, and that authors should "beware of the common misperception that overviews are easy and straightforward" (A3).

Author team composition and roles. Four groups (CHF, CMIMG, JBI, WJNR) stated that a complete multidisciplinary author team is needed that ideally includes a project coordinator (CHF: A4), clinician or content expert (CHF: A9), researcher with methodological expertise (CHF: A9; CMIMG: A20; JBI: A34; WJNR: A39), statistician (as needed) (CHF: A9; CMIMG: A20) and information specialist (as needed) (CHF: A9). Additional members may also be required, and roles should correspond to each member's area of expertise (CHF: A9). See reference A9 for additional detail on team member roles (CHF).

Target audience. Eight groups (CHF, CMIMG, DukeU, EPOC, EPPI, TCD, WHU, WJNR) stated that the target audience for overviews is health-care decision-makers including clinicians (CHF: A10; CMIMG: A16; EPOC: A27; TCD: A37; WHU: A41; WJNR: A39), researchers (DukeU: A29; EPOC: A27; WJNR: A39), informed patients/consumers (CHF: A10; CMIMG: A16; WHU: A41), and policy-makers/commissioning agents (CHF: A10; CMIMG: A16; EPOC: A27; EPPI: A30; WHU: A41; WJNR: A39).

2.4.3.2. Guidance related to the process for conducting overviews

Specifying the scope. Ten groups provided guidance on this topic (CHF, CMIMG, CPHG, DukeU, EPOC, EPPI, JBI, NOKC, TCD, WJNR). They stated that authors should clearly specify and describe the clinical characteristics (e.g., populations, interventions, comparators, and outcomes) and study design information (e.g., SRs) of interest for the overview (CHF: A8; CMIMG: A16; CPHG: A28; EPOC: A27; JBI: A34; NOKC: A36; TCD: A37; WJNR: A39). Reference A9 contains additional detail about specifying outcomes of interest (CHF).

Additionally, authors may wish to restrict their scope based on clinical or methodological characteristics (CHF: A6; CMIMG: A16; DukeU: A29; EPOC: A27; EPPI: A30; JBI: A33; NOKC: A36; TCD: A37).

Searching for SRs. Eleven groups provided guidance on this topic (CHF, CMIMG, CPHG, DukeU, EPOC, EPPI, JBI, NOKC, TCD, WHU, WJNR). They stated that authors should search the CDSR to locate Cochrane SRs (CHF: A8; CMIMG: A16; EPPI: A30; JBI: A34; TCD: A37). To locate *non-Cochrane SRs*, authors should search additional databases (e.g., Medline, EMBASE) and SR registries (e.g., Epistemonikos) (CHF: A8; CMIMG: A26; CPHG: A28; DukeU: A29; EPOC: A27; EPPI: A30; JBI: A34; TCD: A37; WJNR: A39), and contact experts or conduct handsearching of sources relevant to the topic (JBI: A34; TCD: A37). Overview authors may choose to use SR-specific search terms and/or validated SR search filters (CHF: A8; DukeU: A29; EPOC: A27; JBI: A34; TCD: A37). They may also restrict their search by date, language, and/or publication status, if appropriate (CPHG: A28; DukeU: A29; EPOC: A27; JBI: A34; TCD: A37). Conflicting guidance was provided regarding whether or not overview authors should search for and include primary studies that are not contained within any included SR (CHF: A2; CMIMG: A16; CPHG: A28; DukeU: A29; EPPI: A30; NOKC: A36; WHU: A41). Different ways of searching for primary studies were described; for example, see reference A41 (WHU).

Selecting SRs for inclusion. Six groups (CHF, CMIMG, DukeU, EPOC, NOKC, TCD) indicated that authors should select SRs for inclusion using pre-defined inclusion criteria. The scopes of the SRs and overview may sometimes differ (DukeU: A29; NOKC: A36); in these cases, authors must assess the primary studies contained within each SR for inclusion, and they should only include the subset of primary studies that meet the overview's inclusion criteria

(CHF: A8; CMIMG: A16). Two groups (EPOC: A27; TCD: A37) recommended that documents be assessed for inclusion by two independent reviewers with consensus.

Should an overview include non-Cochrane SRs? Nine groups provided guidance on this topic (CHF, CMIMG, DukeU, EPOC, EPPI, JBI, NOKC, TCD, WHU). Two groups affiliated with The Cochrane Collaboration (CHF: A8; CMIMG: A16) stated that authors of Cochrane overviews should include only Cochrane SRs, if possible, but they also stated that including *non-Cochrane SRs* has both advantages (e.g., greater topic coverage) and disadvantages (e.g., increases complexity of the overview). The groups provided conflicting guidance regarding whether or not overview authors should use SR quality as an inclusion criterion for *non-Cochrane SRs* (and if so, what procedure to follow and which tool to use) (CHF: A8; DukeU: A29; EPOC: A27; EPPI: A30; JBI: A34; NOKC: A36; TCD: A37; WHU: A40). There was uncertainty and conflicting guidance on the methods that should be used to manage *overlapping SRs* in overviews (e.g., should authors include only one SR per topic area, or should they include all relevant SRs regardless of overlap?) (CHF: A8; CMIMG: A26 ; DukeU: A29; EPPI: A30; TCD: A37; WHU: A41). See reference A40 (WHU) for ways to assess and report overlap in overviews, and references A8 (CHF) and A29 (DukeU), for ways to potentially manage overlap in overviews.

Assessing quality of included SRs. All twelve groups stated that quality assessment of SRs is important and should be done. Conflicting guidance was provided regarding the tool that should be used. A MeaSurement Tool to Assess systematic Reviews (AMSTAR) [20] was mentioned most often, by seven research groups (CHF: A8; CMIMG: A16; DukeU: A29; EPOC: A27; JBI: A33; TCD: A37; WJNR: A39); the other groups mentioned a variety of older or less commonly known tools. Six groups recommended dual independent quality assessments with

consensus (CMIMG: A16; DukeU: A29; EPOC: A27; JBI: A34; NOKC: A36; TCD: A37). No guidance was provided describing the specific methods that should be used to assess SR quality (e.g., whether and how to modify the quality assessment tool for use in overviews).

Collecting and presenting data on descriptive characteristics of included SRs (and their primary studies). Six groups (CHF, CMIMG, EPOC, JBI, TCD, WJNR) provided guidance on this topic. They stated that authors should extract information about the objectives, inclusion criteria, and methods of each included SR (CHF: A8; CMIMG: A16; EPOC: A27; JBI: A33; TCD: A37; WJNR: A39). Authors should also extract information about the primary studies included in each SR (CHF: A8; EPOC: A27; JBI: A33; TCD: A37; WJNR: A39).

Collecting and presenting data on quality of primary studies contained within included SRs. Seven groups provided conflicting guidance regarding how overview authors should collect and present data on primary study quality; methods proposed included extracting and reporting the quality assessments conducted within each SR, or referring back to each primary study to conduct quality assessments (CHF: A8; CMIMG: A16; DukeU: A29; EPPI: A30; JBI: A34; NOKC: A36; WJNR: A39). Four groups explicitly recommended the former method over the latter, if possible (CHF: A8; CMIMG: A16; JBI: A34; NOKC: A36). No guidance was provided regarding the logistical concerns likely to be encountered (e.g., use of different quality assessment tools in different SRs).

Collecting, analyzing, and presenting outcome data. Seven groups provided guidance on this topic and described quantitative and narrative methods of presenting data (CHF, CMIMG, DukeU, EPOC, EPPI, JBI, UBirm). Three groups (CHF: A8; DukeU: A29; UBirm: A38) stated that outcome data could be extracted from SRs and analyzed or presented in a different way than the analyses contained within the SRs (e.g., using meta-analysis or other complex methods). Two

groups (CMIMG: A16; JBI: A33) stated that outcome data could simply be presented in the overview as they were presented in SRs. Two groups (EPOC: A27; EPPI: A30) acknowledged both approaches without recommending one over the other. Research groups advised that the most appropriate method of data analysis may depend upon the overview's research question and the amount of clinical, methodological and/or statistical heterogeneity in the SRs (CHF: A9; CMIMG: A12; EPPI: A30). Three groups recommended dual independent data extraction with consensus (EPOC: A27; JBI: A33; UBirm: A38). Research groups provided limited guidance regarding the logistical concerns likely to be encountered when analyzing outcome data. For example, there is uncertainty regarding how to analyze data from *overlapping SRs* (though at a minimum, authors should acknowledge the overlap and potential for bias) (CHF: A9; CMIMG: A26; EPPI: A30; JBI: A33; also see WHU: A40).

Assessing certainty of evidence. Six groups stated that it is important to assess the *certainty of evidence* of outcome data, for example using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool (CHF: A8; CMIMG: A16; EPPI: A30; JBI: A34; NOKC: A36; TCD: A37) [21]. However, only two groups provided guidance regarding how to assess quality of outcome data in overviews; they stated that authors could either extract quality assessments from included SRs, or conduct quality assessments themselves at the overview level (CHF: A8; CMIMG: A16). CMIMG recommended that two reviewers independently assess *certainty of evidence* with a process for consensus (A16). No other guidance was provided regarding the logistical concerns likely to be encountered when conducting quality assessments (e.g., what if not all SRs assessed *certainty of evidence*?).

Interpreting outcome data and drawing conclusions. Three groups (CMIMG, EPPI, WHU) provided guidance on this topic. They stated that authors must ensure that the conclusions

they make are warranted based on the quality of the primary studies and SRs and the methods used to analyze data (CMIMG: A16; EPPI: A30). Authors should avoid making informal *indirect comparisons* across different interventions because the *transitivity assumption* will likely be problematic (CMIMG: A24). Authors should also state whether more research is likely to change the results of the overview (based on *certainty of evidence*, if assessed) (WHU: A41).

2.4.3.3. Frequency and intensity effect sizes

The research groups that contributed the most guidance to this scoping review, as measured using intensity effect sizes (Table 2.4), were as follows: CMIMG (15/15 topics), CHF (13/15 topics), and EPPI and JBI (11/15 topics each). The topic areas that the most research groups discussed, as measured using frequency effect sizes, were as follows: "assessing quality of SRs" (12/12 groups), "searching for SRs" (11/12 groups), and "specifying the scope" (10/12 groups). Topics that the least number of research groups discussed were: "choosing between conducting an overview and a SR" (2/12 groups), "interpreting outcome data and drawing conclusions" (3/12 groups), and "author team composition and roles" (4/12 groups each).

2.4.4. Challenges identified when conducting overviews

All nineteen research groups contributing explicit guidance and/or author experiences identified at least one challenge involved when conducting overviews of healthcare interventions. These challenges are summarized in Table 2.5. Nine research groups also described limitations inherent to the overview format itself (CHF, CMIMG, CPHG, DukeU, EPOC, EPPI, JBI, WHU, WJNR). Specifically, they stated that overviews can be complex and resource intensive (CHF: A43; EPOC: A46; EPPI: A30; WHU: A40); susceptible to bias (CMIMG: A17; CPHG: A28; DukeU: A29; EPPI: A30; JBI: A34; WHU: A40); and dependent

on (and limited by) the scope, inclusion criteria, methods, reporting, and coverage of their included SRs (CHF: A9; CPHG: A28; DukeU: A29; EPOC: A45; EPPI: A30; JBI: A34; WHU: A41; WJNR: A39). Few of the challenges identified when conducting overviews were adequately addressed by the methodological guidance previously summarized.

2.5. DISCUSSION

This scoping review found relatively consistent and comprehensive guidance for the first stages of the overview process, from choosing to conduct an overview through to selecting SRs for inclusion. Guidance for the latter stages was often conflicting and/or missing, and a number of outstanding challenges were identified. These latter stages included: deciding whether to include SRs published outside of the CDSR, assessing quality of SRs and their primary studies, collecting and analyzing data, and assessing certainty of evidence of outcome data.

The shift from consistent to conflicting and/or missing guidance that occurs after the inclusion stage may be due to several factors. First, this is the point at which methods for overviews take on an additional level of complexity. Within an overview there are two levels for assessing and reporting SR/study characteristics, quality/risk of bias, and outcome data (i.e., for both the SRs and their included primary studies). Existing methodological guidance does not yet adequately address how these stages of the overview process should occur relative to these two levels of information. Second, SRs are syntheses of pre-existing data, and we found that overviews are limited by the methods and reporting of their included SRs. Data may be missing, inadequately reported, or reported differently across included SRs, and it is currently unclear whether overview authors should rely solely on the SRs as they were conducted and presented, or whether and to what extent authors should refer back to the primary studies for additional

information. Lastly, including SRs published outside of the CDSR can increase the complexity of the latter stages of the overview process due to greater variation in the methods and reporting of non-Cochrane SRs [22, 23] and the potential for topic overlap across multiple similar SRs [24]. Limited guidance was available regarding the specific methods authors can use to address and manage these issues in overviews.

To circumvent some of the challenges authors are likely to encounter during the latter stages of the overview process, authors should first ensure that the overview format is appropriate for their question of interest. The CMIMG in particular provided comprehensive guidance regarding the context for conducting an overview (i.e., when and why to conduct an overview); however, prior to this study, much of the guidance appeared only in the form of internal documents and conference proceedings that were difficult for authors to access. Authors should also prepare a detailed protocol for their overview. Often overview authors describe their scope and inclusion criteria, but provide less detail about methods to be used for quality assessments and data extraction and analysis. As well as reducing bias and promoting rigor and transparency of methods [11, 25], a protocol would allow overview authors to become familiar with the challenges they are likely to encounter and develop *a priori* decision rules to appropriately address those challenges. The guidance and challenges described in this paper will be useful for authors to consider when developing their protocols.

As is common when using a qualitative metasummary approach [18], an important insight emerged when we analyzed our data across topic areas; namely, that overviews are often conducted for one of two main purposes. The first purpose is to present and describe the complete body of SR evidence on a clearly defined topic [26, 27]. The second purpose is to address a research question that differs from the question(s) in the underlying SRs and that often

relates to a subset of the questions in the SRs (e.g., subpopulations, or subsets of interventions or outcomes) [28, 29]. Distinguishing between these two purposes, and recognizing that different methods may be used for each, can help resolve some discrepancies and challenges likely to be encountered during the latter stages of the overview process. For example, if the purpose is to answer a different research question from those posed in the SRs, authors may wish to re-extract and re-analyze outcome data (e.g., using meta-analysis) from a set of non-overlapping SRs. However, if the purpose is to describe the complete body of SR evidence on a topic, authors may find it more appropriate to include all relevant SRs regardless of topic overlap and then present these results as they appeared in the SRs. Empirical evidence will be needed to determine whether these approaches affect the results or introduce bias at the overview level.

Ultimately, methodological guidance is required for those stages of the overview process where guidance is conflicting and/or missing, and where outstanding challenges remain. This future guidance should be based on empirical evidence generated from well-conducted studies that evaluate methods for conducting overviews. While outside of the scope of the present paper, we identified several relevant methods studies (recently published, and in progress) when conducting this scoping review. These methods studies examined: implications of including multiple SRs published on the same topic area [24]; issues related to quality assessment of SRs [30-32]; different methods for presenting outcome data [33]; methods for assessing certainty of evidence using GRADE [34, 35]; and reporting conflicts of interest in overviews [36]. One additional study (in progress) was identified that will aim to summarize all empirical studies [37]. Developing future methodological guidance for overviews based on the results of empirical studies will help ensure that guidance is based on sound evidence as opposed to personal experience or trial and error.

The current scoping review aimed to identify and collate all documents containing methodological guidance for conducting overviews of healthcare interventions. Due to the variety of publication formats and the difficulty in locating and accessing some of these documents, it is possible we may have missed relevant guidance documents. To maximize retrieval, our search utilized multiple complimentary methods in addition to database searching. We had satisfactory response rates (ranging from 55-96%) when locating and obtaining the full text of unpublished documents, and we were able to translate and extract data from all relevant non-English documents identified. We then used a rigorous process for identifying, extracting, and analyzing guidance statements and challenges from these documents. Importantly, we were interested in methods guidance and challenges for overviews examining the efficacy, effectiveness and/or safety of healthcare interventions, and have excluded guidance and challenges specific to overviews that may address broader or different clinical questions. Guidance for conducting these other types of overviews is also needed, but is outside the scope of the current project. It is important to note that the guidance and challenges summarized here were written by research groups with different organizational processes that likely produce overviews with differing purposes, scopes, target audiences, and/or resource requirements. Researchers should identify the purpose, scope, target audience, and resource requirements of their overview at the outset and determine how well the guidance and challenges presented here apply to their specific situation. Lastly, the guidance included in this scoping review came from documents that explicitly *intended* to provide methods guidance to readers: the methods presented here do not come from the actual methods used in published overviews. However, discussions with overview authors [13] and critical appraisal of published overviews [4, 5, 38,

39] indicates that the guidance and challenges in this scoping review are congruent with overview authors' experiences.

2.6. CONCLUSIONS

This scoping review provides a systematic summary of existing methodological guidance for conducting overviews examining the efficacy, effectiveness and/or safety of healthcare interventions. It highlights the stages of the overview process where guidance is consistent, conflicting, or missing, and it also provides a summary of the challenges involved in conducting overviews. This scoping review will serve as a useful resource for authors wishing to conduct overviews, as well as researchers wishing to conduct empirical research on overview methods. It is also a necessary first step to developing a cohesive methods guidance document that addresses relevant issues and areas of uncertainty when conducting overviews of healthcare interventions. Accordingly, the results of this scoping review were used to update the chapter on overview methods in the *Cochrane Handbook* (currently under review). There has been a dramatic rise in the production of SRs and overviews in recent years. These syntheses are an important vehicle to increase the uptake and application of knowledge by clinical and policy decision-makers, and they can help address crucial health issues and ultimately improve health outcomes in diverse populations. Investing in strengthening the methods guidance for conducting overviews can help ensure a rigorous and valid evidence base for knowledge translation and dissemination.

2.7. REFERENCES

1. Green S, Higgins JPT, Alderson P, Clarke M, Mulrow CD, Oxman AD. Chapter 1: introduction. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews

of interventions (version 5.1.0). The Cochrane Collaboration; 2011. http://www.handbook.cochrane.org.

2. Bastian H, Glasziou P, Chalmers I. Seventy-five trials and eleven systematic reviews a day: how will we ever keep up? PLoS Med. 2010;7(9):e1000326.
3. Becker LA, Oxman AD. Chapter 22: overviews of reviews. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.1.0). The Cochrane Collaboration; 2011. http://www.handbook.cochrane.org.
4. Hartling L, Chisholm A, Thomson D, Dryden DM. A descriptive analysis of overviews of reviews published between 2000 and 2011. PLoS One. 2012;7(11):e49667.
5. Pieper D, Buechter R, Jerinic P, Eikermann M. Overviews of reviews often have limited rigor: a systematic review. J Clin Epidemiol. 2012;65(12):1267-73.
6. Li L, Tian J, Tian H, Sun R, Liu Y, Yang K. Quality and transparency of overviews of systematic reviews. J Evid Based Med. 2012;5(3):166-73.
7. Cochrane: About us. http://www.cochrane.org/about-us (n.d.). Accessed 01 Sept 2017.
8. Cochrane Comparing Multiple Interventions Methods Group: About us. http://www.methods.cochrane.org/cmi/about-us (2015). Accessed 01 Sept 2017.
9. Singh JA, Christensen R, Wells GA, Suarez-Almazor ME, Buchbinder R, Lopez-Olivo MA, *et al*. Biologics for rheumatoid arthritis: an overview of Cochrane reviews. Cochrane Database Syst Rev. 2009;4:CD007848.
10. Aromataris E, Fernandez R, Godfrey C, Holly C, Khalil H, Tungpunkom P, editors. The Joanna Briggs Institute reviewers' manual 2014: methodology for JBI umbrella reviews. University of Adelaide: Joanna Briggs Institute; 2014.

11. Grimshaw J. A knowledge synthesis chapter. In: A guide to knowledge synthesis. Canadian Institutes of Health Research. 2010. http://www.cihr-irsc.gc.ca/e/41382.html. Accessed 01 Sept 2017.
12. Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.1.0). The Cochrane Collaboration; 2011. http://www.handbook.cochrane.org.
13. Foisy M, Dryden DM, Fernandes RM, Hartling L, Thomson D. Advancing methods for overviews of reviews: a discussion of challenges and potential solutions. Abstracts of the 22nd Cochrane Colloquium, 21-26 Sept 2014. Hyderabad, India: John Wiley & Sons; 2014.
14. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol. 2005;8(1):19-32.
15. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. Implement Sci. 2010;5:69.
16. Horsley T, Dingwall O, Sampson M. Checking reference lists to find additional studies for systematic reviews. Cochrane Database Syst Rev. 2011;8:MR000026.
17. Greenhalgh T, Peacock R. Effectiveness and efficiency of search methods in systematic reviews of complex evidence: audit of primary sources. BMJ. 2005;331(7524):1064-5.
18. Sandelowski M, Barroso J. Chapter 6: synthesizing qualitative research findings: qualitative metasummary. In: Sandelowski M, Barroso J, editors. Handbook for synthesizing qualitative research. New York: Springer Publishing Company; 2006. p. 151-97.
19. Sandelowski M, Barroso J. Creating metasummaries of qualitative findings. Nurs Res. 2003;52(4):226-33.

20. Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J, *et al*. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol. 2009;62(10):1013-20.
21. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, *et al*. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-6.
22. Moher D, Tetzlaff J, Tricco AC, Sampson M, Altman DG. Epidemiology and reporting characteristics of systematic reviews. PLoS Med. 2007;4(3):e78.
23. Moseley AM, Elkins MR, Herbert RD, Maher CG, Sherrington C. Cochrane reviews used more rigorous methods than non-Cochrane reviews: survey of systematic reviews in physiotherapy. J Clin Epidemiol. 2009;62(10):1021-30.
24. Foisy M, Dryden DM, Fernandes RM, Hartling L. Multiple systematic reviews published on the same topic area: an analysis of systematic reviews that overlap in content. Abstracts of the 22nd Cochrane Colloquium, 21-26 Sept 2014. Hyderabad, India: John Wiley & Sons; 2014.
25. Green S, Higgins JPT. Chapter 2: preparing a Cochrane review. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.1.0). The Cochrane Collaboration; 2011. http://www.handbook.cochrane.org.
26. Worswick J, Wayne SC, Bennett R, Fiander M, Mayhew A, Weir MC, *et al*. Improving quality of care for persons with diabetes: an overview of systematic reviews - what does the evidence tell us? Syst Rev. 2013;2:26.

27. Farquhar C, Rishworth JR, Brown J, Nelen WL, Marjoribanks J. Assisted reproductive technology: an overview of Cochrane reviews. Cochrane Database Syst Rev. 2015;7:CD010537.
28. Foisy M, Boyle RJ, Chalmers JR, Simpson EL, Williams HC. The prevention of eczema in infants and children: an overview of Cochrane and non-Cochrane reviews. Evid Based Child Health. 2011;6(5):1322-39.
29. Cates CJ, Wieland LS, Oleszczuk M, Kew KM. Safety of regular formoterol or salmeterol in adults with asthma: an overview of Cochrane reviews. Cochrane Database Syst Rev. 2014;2:CD010314.
30. Pieper D, Mathes T, Eikermann M. Impact of choice of quality appraisal tool for systematic reviews in overviews. J Evid Based Med. 2014;7(2):72-8.
31. Foisy M, Hartling L. Challenges and considerations involved in using AMSTAR in overviews of reviews. Abstracts of the 22nd Cochrane Colloquium, 21-26 Sept 2014. Hyderabad, India: John Wiley & Sons; 2014.
32. Jia P, Chen J, Zhang L, Zhao P, Zhang M. Challenges and considerations in assessing the reporting quality of systematic reviews in overviews using PRISMA. Abstracts of the 23rd Cochrane Colloquium, 03-07 Oct 2015. Vienna, Austria: John Wiley & Sons; 2015.
33. Crick K, Wingert A, Williams K, Fernandes RM, Thomson D, Hartling L. An evaluation of harvest plots to display results of meta-analyses in overviews of reviews: a cross-sectional study. BMC Med Res Methodol. 2015;15:91.
34. Pollock A, Farmer SE, Brady MC, Langhorne P, Mead GE, Mehrholz J, *et al*. An algorithm was developed to assign GRADE levels of evidence to comparisons within systematic reviews. J Clin Epidemiol. 2015;70:106-10.

35. Foisy M, Fernandes RM, Dryden DM, Hartling L. Grading the quality of evidence in existing systematic reviews: challenges and considerations. Abstracts of the 22nd Cochrane Colloquium, 21-26 Sept 2014. Hyderabad, India: John Wiley & Sons; 2014.
36. Buchter RB, Pieper D. Most overviews of Cochrane reviews neglected potential biases from dual authorship. J Clin Epidemiol. 2016;77:91-4.
37. Lunny C, Brennan SE, McDonald S, McKenzie JE. Evidence map of studies evaluating methods for conducting, interpreting and reporting overviews of systematic reviews of interventions: rationale and design. Syst Rev. 2016;5:4.
38. Thomson D, Foisy M, Oleszczuk M, Wingert A, Chisholm A, Hartling L. Overview of reviews in child health: evidence synthesis and the knowledge base for a specific population. Evid Based Child Health. 2013;8(1):3-10.
39. Cochrane. Special collection: Cochrane overviews. http://www.cochranelibrary.com/app/content/special-collections/article/?doi=10.1002/(ISSN)14651858(CAT)na(VI)SC000036 (2014). Accessed 01 Sept 2017.

Table 2.1. Key characteristics of overviews.

Overviews should:
1) Contain a clearly stated objective designed to answer at least one research question.
2) Intend to search for and include only systematic reviews (with or without meta-analyses).
3) Use formalized methods to identify multiple systematic reviews that meet their inclusion criteria and assess the methodological quality of these systematic reviews.
4) Intend to collect, analyze, and present the descriptive characteristics of their included systematic reviews (and their primary studies) and the quantitative outcome data contained within the systematic reviews.

Modified from Becker & Oxman [3] and Hartling *et al.* [4]. Documents were considered to be 'systematic reviews' if they contained a clear objective statement, used formalized methods to search for and identify primary studies that met their inclusion criteria, and presented descriptive characteristics and quantitative outcome data from those primary studies.

Table 2.2. Characteristics of included guidance documents (52 documents produced by 19 research groups).

	Documents that contain explicit methodological guidance for conducting overviews (41 documents produced by 12 research groups)			**Documents that describe an author team's experience conducting one or more published overviews (11 documents produced by 9 research groups)**		
Research group	**Number of documents (Appendix 2C references)**	**Years documents were produced**	**Document formats**	**Number of documents (Appendix 2C references)**	**Years documents were produced**	**Document formats**
Cochrane Child Health Field (CHF)	11[a] (A1-A11)	2010-2015	6 oral presentations, 2 internal documents, 2 posters, 1 journal article	2 (A42, A43)	2011, 2013	1 journal article, 1 poster
Cochrane Comparing Multiple Interventions Methods Group (CMIMG)	18[a] (A1, A6, A7, A12-A26)	2008-2015	10 oral presentations, 5 internal documents, 1 journal article, 1 book chapter, 1 website	--	--	--
Cochrane Consumers and Communication Review Group (CCRG)	--	--	--	1 (A44)	2009	1 journal article
Cochrane Effective Practice and Organization of Care Review Group (EPOC)	1 (A27)	2011	1 oral presentation	2 (A45, A46)	2011, 2015	1 oral presentation, 1 poster
Cochrane Musculoskeletal Review Group (CM)	--	--	--	1 (A47)	2010	1 poster
Cochrane Public Health Group (CPHG)	1 (A28)	2014	1 journal article	--	--	--
Cochrane Stroke Group (CS)	--	--	--	1 (A48)	2015	1 oral presentation

Duke University (DukeU)	1 (A29)	2012	1 journal article	--	--	--
Dutch Cochrane Centre (DCC)	--	--	--	1 (A49)	2009	1 poster
Evidence for Policy and Practice Information and Co-ordinating Centre (EPPI)	2 (A30, A31)	2015	1 journal article, 1 oral presentation	--	--	--
Joanna Briggs Institute Umbrella Reviews Methodology Group (JBI)	4 (A32-A35)	2013-2015	2 internal documents, 1 journal article, 1 book chapter	--	--	--
Ludwig Boltzmann Institute for Health Technology Assessment (LBI)	--	--	--	1 (A50)	2015	1 journal article
Norwegian Knowledge Centre for the Health Services (NOKC)	1 (A36)	2013	1 book chapter	--	--	--
Pontifical Xavierian University (PXU)	--	--	--	1 (A51)	2011	1 poster
Trinity College Dublin (TCD)	1 (A37)	2011	1 journal article	--	--	--
University of Birmingham (UBirm)	1 (A38)	2012	1 journal article	--	--	--
University of Dundee (UDun)	--	--	--	1 (A52)	2004	1 journal article
Western Journal of Nursing Research (WJNR)	1 (A39)	2014	1 editorial	--	--	--
Witten/Herdecke University (WHU)	2 (A40, A41)	2014	2 journal articles	--	--	--

[a] Three documents are counted twice because they were produced by authors affiliated with both of these groups (Appendix 2C, references A1, A6, and A7). For these three documents, guidance presented by DT, LH, and MF was extracted into the CHF category, and guidance presented by DC, LAB, and RMF was extracted into the CMIMG category.

Table 2.3. Definitions.

Indirect comparison: "A comparison of two interventions via one or more common comparators. For example, the combination of intervention effects from AC and intervention effects from BC studies may (in some situations) be used to learn about the intervention effect AB." (http://methods.cochrane.org/cmi/node/61)
Network meta-analysis: "An analysis that synthesizes information over a network of comparisons to assess the comparative effects of more than two alternative interventions for the same condition. A network meta-analysis synthesizes direct and indirect evidence over the entire network, so that estimates of intervention effect are based on all available evidence for that comparison. This evidence may be direct evidence, indirect evidence or mixed evidence. Typical outputs of a network meta-analysis are a) relative intervention effects for all comparisons; and b) a ranking of the interventions." (http://methods.cochrane.org/cmi/node/61)
Non-Cochrane systematic reviews: Systematic reviews published outside of the Cochrane Database of Systematic Reviews.
Overlapping systematic reviews: Two or more systematic reviews examining the same intervention for the same disorder. Overlapping systematic reviews will often contain one or more of the same primary studies, which may lead to including the same study's outcome data in an overview two or more times.
Certainty of evidence: The confidence we have in the outcome effect estimates, often assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool.
Transitivity assumption: "The situation in which an intervention effect measured using an indirect comparison is valid and equivalent to the intervention effect measured using a direct comparison. Specifically, the transitivity assumption states that (the benefit of A over B) is equal to (the benefit of A over C) plus (the benefit of C over B). Equivalently, this may be written as (the benefit of A over C) minus (the benefit of B over C). In practice, transitivity requires similarity; that is that the sets of studies used to obtain the indirect comparison are sufficiently similar in characteristics that moderate the intervention effect. Transitivity can be thought of as a network meta-analysis extension of the idea of homogeneity in a standard meta-analysis." (http://methods.cochrane.org/cmi/node/61)

Table 2.4. Map of methodological guidance for conducting overviews.

Topic area	CHF	CMIMG	CPHG	DukeU	EPOC	EPPI	JBI	NOKC	TCD	UBirm	WHU	WJNR	Frequency effect size
Guidance related to the context for conducting overviews (i.e., when and why should you conduct an overview?)													
Choosing between conducting an overview and a SR		✓				✓							**2/12**
What questions about healthcare interventions can be answered using the overview format?	✓	✓		✓			✓	✓	✓	✓			**7/12**
Questions to consider before deciding to conduct an overview	✓	✓				✓	✓		✓			✓	**6/12**
Author team composition and roles	✓	✓					✓					✓	**4/12**
Target audience	✓	✓		✓	✓	✓			✓		✓	✓	**8/12**
Guidance related to the process of conducting overviews (i.e., how do you conduct an overview?)													
Specifying the scope	✓	✓	✓	✓	✓	✓	✓	✓	✓			✓	**10/12**
Searching for SRs	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	**11/12**
Selecting SRs for inclusion	✓	✓		✓	✓			✓	✓				**6/12**
Should an overview include non-Cochrane SRs?	✓	✓		✓	✓	✓	✓	✓	✓		✓		**9/12**

Assessing quality of included SRs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	**12/12**
Collecting and presenting data on descriptive characteristics of included SRs (and their primary studies)	✓	✓			✓		✓		✓			✓	**6/12**
Collecting and presenting data on quality of primary studies contained within included SRs	✓	✓		✓		✓	✓	✓				✓	**7/12**
Collecting, analyzing, and presenting outcome data	✓	✓		✓	✓	✓	✓			✓			**7/12**
Assessing certainty of evidence	✓	✓				✓	✓	✓	✓				**6/12**
Interpreting outcome data and drawing conclusions		✓				✓					✓		**3/12**
Intensity effect size	**13/15**	**15/15**	**3/15**	**9/15**	**8/15**	**11/15**	**11/15**	**8/15**	**10/15**	**3/15**	**5/15**	**8/15**	

Table 2.5. Common challenges involved in conducting overviews.

Topic area	Number of groups contributing challenges (/19)	Summary of challenges identified
Challenges related to the context for conducting overviews (i.e., when and why should you conduct an overview?)		
Choosing between conducting an overview and a SR	1 (CMIMG)	*Network meta-analyses* are very difficult to conduct in overviews and should likely not be conducted within overviews. It may be difficult to determine whether it is more appropriate to conduct an overview, or a systematic review with or without *network meta-analysis*.
What types of questions about healthcare interventions can be answered using the overview format?	2 (CCRG, CM)	Methods used to conduct overviews may vary according to the type of question (e.g., scope, clinical characteristics) being posed in the overview.
Questions to consider before deciding to conduct an overview	5 (CHF, CMIMG, DCC, JBI, UDun)	Should authors conduct an overview if there are not enough relevant SRs (e.g., if SRs do not address all important interventions)?
Author team composition and roles	2 (CHF, CMIMG)	Overview authors often have limited time. What skills are required for authors wishing to conduct overviews?
Target audience of the overview	0	No challenges identified.
Challenges related to the process of conducting overviews (i.e., how do you conduct an overview?)		
Specifying the scope	4 (EPPI, LBI, UBirm, UDun)	Defining the scope, and selecting and prioritizing outcomes, can be difficult. The scope of the overview may have almost complete overlap, or very limited overlap, with the scope of the relevant SRs.
Searching for SRs	5 (CHF, CPHG, EPOC, LBI, UBirm)	Search strategies can be complex. It is unclear whether government reports that include both primary studies and SRs should be included in an overview. It is unclear whether and how overview authors should search for primary studies that are not contained within any included SR.

Selecting SRs for inclusion	8 (CHF, CMIMG, DukeU, EPPI, JBI, UBirm, UDun, WHU)	It is unclear whether lower-quality SRs or older SRs should be included or excluded. Decisions surrounding inclusion and exclusion can affect the efficiency, utility, and breadth of the overview.
Should an overview include non-Cochrane SRs?	9 (CHF, CMIMG, CPHG, DukeU, EPOC, EPPI, TCD, WHU, WJNR)	Including *non-Cochrane SRs* can be difficult and will increase the complexity of the overview process. *Non-Cochrane SRs* can be of low methodological quality and may be poorly reported. Additionally, some Cochrane and *non-Cochrane SRs* will have overlap in their clinical questions, inclusion criteria, and/or included primary studies, and may have discordant results and/or conclusions. *Overlapping SRs* can be problematic, and there are potential challenges involved in assessing the amount of overlap in included SRs. Additionally, methods for choosing between *overlapping SRs* have not yet been developed; for example, it is unclear whether authors should include only one SR per topic area (and if so, which one?), or if they should include all SRs regardless of overlap (and if so, how will overlap be managed?). Authors including *non-Cochrane SRs* also have to clearly define what counts as a SR.
Assessing quality of included SRs	9 (CCRG, CHF, CMIMG, CPHG, EPOC, EPPI, PXU, UBirm, UDun)	Assessing quality of SRs can be difficult and time-consuming. Many different tools could be used to assess SR quality, and some tools designed to assess quality (e.g., AMSTAR) may also assess reporting. There is also uncertainty surrounding how to interpret and apply the results of quality assessments in the context of overviews.
Collecting and presenting data on descriptive characteristics of included SRs (and their primary studies)	11 (CCRG, CHF, CM, CMIMG, DCC, DukeU, EPOC, JBI, LBI, UDun, NOKC)	Data may be missing, inadequately reported, or reported differently across included SRs, and it is unclear what to do when reporting is incomplete (e.g., should the data be extracted from primary studies?). Additionally, data extraction errors in SRs could lead to errors in the overview.
Collecting and presenting data on quality of primary studies contained within included SRs	7 (CCRG, CHF, CM, DCC, EPOC, EPPI, UDun)	Collecting and presenting quality of primary studies can be difficult and time-intensive. Information about the quality of primary studies included in SRs may be missing, inadequately reported, or reported differently across included SRs. For example, different SRs may use different tools to assess quality of primary studies.

Collecting, analyzing, and presenting outcome data	15 (CCRG, CHF, CM, CMIMG, DCC, DukeU, EPOC, EPPI, JBI, LBI, NOKC, UBirm, UDun, WJNR, WHU)	Collecting, analyzing and presenting outcome data can be difficult, especially when the scope, methods, or results of the included SRs are heterogeneous. Outcome data may be missing, inadequately reported, or reported inconsistently across included SRs, and it is unclear what to do in these situations (e.g., should the data be extracted from primary studies instead?). It is also unclear how best to summarize and report outcome data that come from *overlapping* (and potentially discordant) *SRs*. It may not always be possible or appropriate to conduct meta-analyses in overviews or to directly compare results across different SRs. Similarly, *network meta-analyses* are often not appropriate in overviews. Additionally, overviews may not accurately capture information about adverse effects or cost-effectiveness of interventions, and data extraction errors in SRs could lead to errors in the overview.
Assessing certainty of evidence of outcome data	9 (CCRG, CHF, CM, CPHG, DCC, EPOC, PXU, UDun, WHU)	It may not be possible to simply extract existing GRADE assessments from SRs. However, it may be challenging to conduct (or re-do) GRADE assessments at the overview level, using data from SRs. For example: data needed to assess *certainty of evidence* in SRs may be missing, inadequately reported, and/or reported differently across included SRs; the "study quality" domain may be assessed differently across similar SRs (e.g., different tools used, same tool used but different assessments obtained, only summary assessments reported); and the "consistency" and "precision" domains may be affected if different methodological decisions are made in similar SRs (e.g., pooling versus not pooling data). Additionally, achieving consensus may be difficult. The GRADE tool may need to be modified for use in overviews.
Interpreting outcome data and drawing conclusions	6 (CHF, CMIMG, DukeU, EPOC, LBI, WJNR)	Interpreting outcome data and drawing conclusions can be difficult. There is uncertainty surrounding how to interpret outcome data in overviews. It can be difficult to form a coherent judgment when multiple different comparisons from multiple SRs are included in the same overview, and/or when *overlapping SRs* report discordant results. It can also be difficult to determine implications for research. Additionally, there is concern that the methods used to conduct overviews might affect the conclusions reached.

CDSR: Cochrane Database of Systematic Reviews; DARE: Database of Abstracts of Reviews of Effectiveness; EMBASE: Excerpta Medica dataBASE; GRADE: Grading of Recommendations Assessment, Development and Evaluation; PICO: populations, interventions, comparators and outcomes; SR: systematic review.

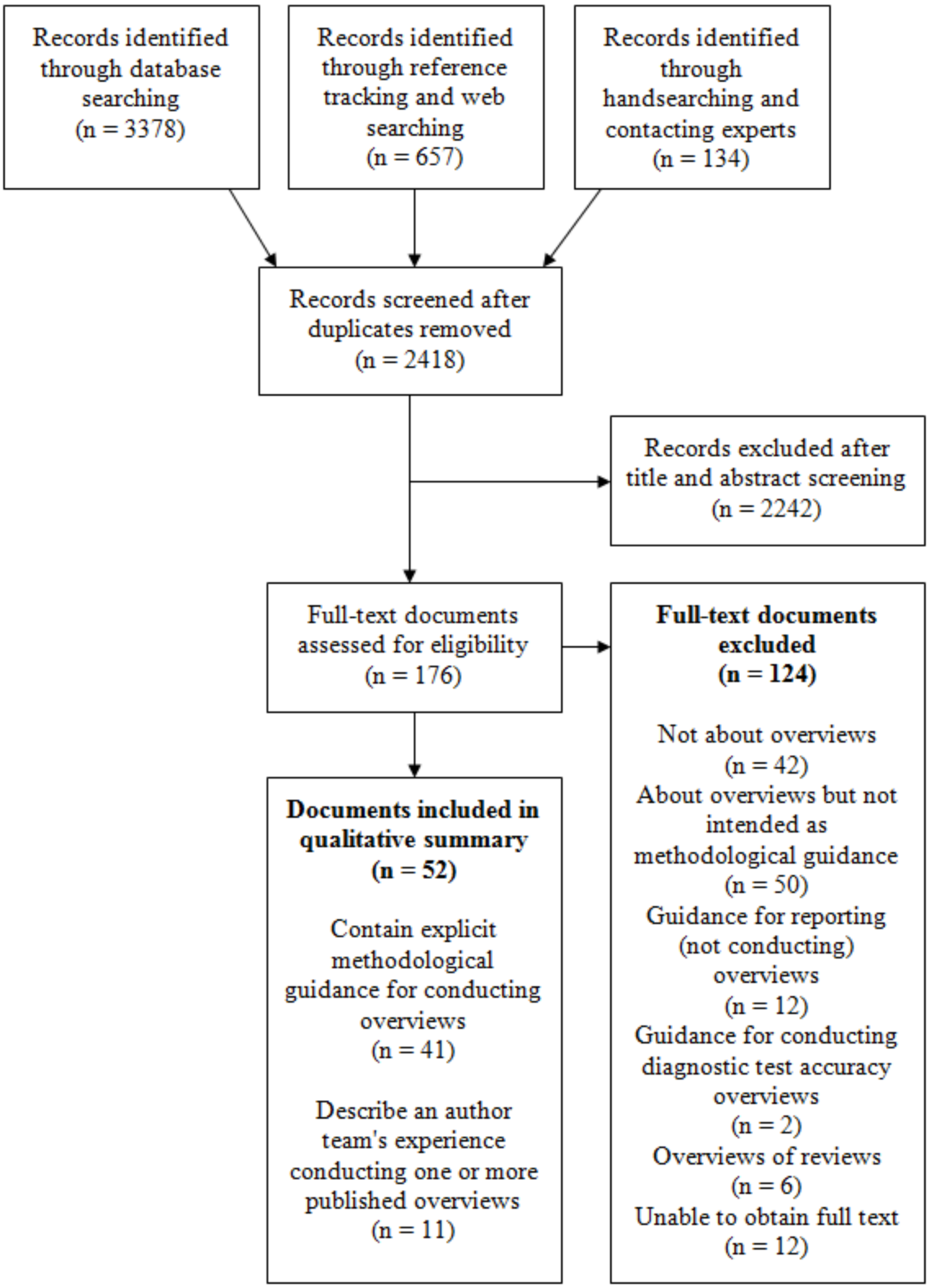


Figure 2.1. Flow diagram of documents through the scoping review.

Chapter 3

The impact of different inclusion decisions on the comprehensiveness and results of overviews of reviews of healthcare interventions

This chapter has been formatted for submission to "Systematic Reviews". The authors are: Pollock M, Fernandes RM, Newton AS, Scott SD, Hartling L.

3.1. ABSTRACT

Background

Overviews of reviews (overviews) compile information from multiple systematic reviews (SRs) to provide a single synthesis of relevant evidence for decision-making. Overviews may identify multiple SRs that examine the same intervention for the same condition and include some, but not necessarily all, of the same primary studies. There is currently limited guidance on whether and how to include overlapping SRs in overviews. Our objectives were to: assess how different inclusion decisions in overviews affect the comprehensiveness and results of overviews of healthcare interventions, and develop an evidence-based decision tool to help overview authors make inclusion decisions.

Methods

We used five inclusion decisions to conduct overviews across seven topic areas, resulting in 35 overviews. The inclusion decisions were: (1) include all Cochrane and non-Cochrane SRs; (2) include only Cochrane SRs; and include all non-overlapping SRs, and for groups of overlapping SRs, include (3) the Cochrane SR, (4) the most recent SR (by publication or search date), or (5)

the highest quality SR (assessed using AMSTAR). We assessed the amount of outcome data loss and change observed in the overviews as a result of these inclusion decisions.

Results

Including only Cochrane SRs, instead of all SRs, often, but not always, led to the loss or change of outcome data (median: 31% of outcomes lost/changed; range: 0-100%). Including all Cochrane SRs and non-overlapping SRs allowed some outcome data to be recaptured, but only for overviews where the Cochrane SRs did not examine all relevant intervention comparisons of interest (median: 42% of lost/changed outcomes recaptured; range: 28-86%). Including non-overlapping SRs and selecting the Cochrane SR for groups of overlapping SRs (instead of the most recent or highest quality SRs) minimized the amount of outcome data lost or changed.

Conclusions

Overlapping SRs present a methodological challenge for overview authors. This study demonstrates that different inclusion decisions affect the comprehensiveness and results of overviews in different ways, depending in part on whether or not Cochrane SRs examine all intervention comparisons relevant to the overview. Study results were used to develop an evidence-based decision tool that provides practical guidance for overview authors and warrants further evaluation.

3.2. BACKGROUND

Systematic reviews (SRs) of healthcare interventions aim to assess an intervention's efficacy or effectiveness by using explicit and reproducible methods to combine the results of all relevant primary studies [1]. By synthesizing all available data, SRs attempt to explore and ultimately resolve discrepancies among primary studies that may have different, and sometimes

contradictory, results of an intervention's effect. However, as the number of published SRs steadily increases [2], it is becoming increasingly common to find multiple SRs that address the same, or very similar, clinical questions [3]. These overlapping SRs may include many, but not necessarily all, of the same primary studies, due to differences in methods used for inclusion criteria, search strategies, study selection, and data extraction and analysis [3].

Researchers conducting overviews of reviews of healthcare interventions (overviews) often encounter overlapping SRs. Overviews use explicit and systematic methods to compile data from multiple, related SRs to provide a single synthesis of evidence for healthcare decision-making [4]. They are typically broader in scope than any individual SR, and often examine the efficacy or effectiveness of multiple interventions for preventing or treating a specific clinical condition [4]. Overview authors can encounter overlapping SRs when they decide to include both SRs published in and outside of the Cochrane Database of Systematic Reviews ("Cochrane SRs" and "non-Cochrane SRs"). This is because Cochrane attempts to avoid duplication of effort by publishing only one SR on healthcare interventions for a specific condition or illness, whereas multiple non-Cochrane SRs can exist to address the same, or very similar, clinical questions. Researchers that choose to include overlapping SRs in overviews will encounter important methodological considerations [5-8]. Overview authors should properly assess the amount of overlap in the primary studies contained within the overview's included SRs. If overlap exists, and the outcome data from some primary studies contribute more than once to the analyses, bias can be introduced into the overview as disproportionate weight has been given to some of the data [5]. Researchers may also find it difficult to appropriately extract and analyze outcome data from overlapping SRs if the conduct, quality, and/or reporting differs between SRs [6]. Further, if overlapping SRs included in the overview have discordant results and/or conclusions,

researchers need to decide how they will synthesize and discuss these differences [6]. Despite these methodological considerations, only half of the overviews that contain overlapping SRs currently acknowledge and discuss the overlap [5].

To date, researchers have used several approaches to manage overlapping SRs in overviews [6, 7]. Some researchers have included all relevant Cochrane and non-Cochrane SRs, and avoided overlap by extracting outcome data for each primary study only once (regardless of how many SRs contained that study's data) [9, 10]. Others have avoided overlap by restricting the overview to synthesizing only Cochrane SRs [4, 11], while others have included Cochrane and non-Cochrane SRs and avoided overlap by using specific criteria to prioritize SR inclusion when confronted with multiple, overlapping SRs (e.g., only include the Cochrane, most recent, or highest-quality SR) [9]. Currently, there is no empirical evidence on the impact of these different inclusion decisions, and no guidance for how to choose one method of inclusion over another [6, 7].

The purpose of this study was to provide empirical evidence examining the inclusion of overlapping SRs in overviews of reviews of healthcare interventions. Specifically, we aimed to: (1) assess how different decisions surrounding the inclusion and exclusion of overlapping SRs in overviews affect the comprehensiveness and results of overviews, and (2) develop an evidence-based decision tool to help overview authors make inclusion decisions in overviews.

3.3. METHODS

3.3.1. Study procedures

This was a multiple case study [12]. Each "case" was an overview of reviews conducted by the Alberta Research Centre for Health Evidence between 2010 to 2016 that examined a

question related to the efficacy or effectiveness of multiple healthcare interventions for preventing or treating a clinical condition related to pediatric health. Seven cases [13-19] were included in the study based on convenience sampling [20]: acute asthma [13], acute otitis media [14], bronchiolitis [15], croup [16], eczema [17], gastroenteritis [18], and procedural sedation [19]. The inclusion criteria (populations, interventions, comparators, outcome measures, and study designs) for each case are provided in Appendix 3A. For feasibility, we used clinical judgement to restrict the inclusion criteria of four cases, compared to the inclusion criteria used in the published overviews (see footnotes in Appendix 3A). We then conducted each of the seven overview cases using five different inclusion decisions (described in detail below). This resulted in 35 overviews of healthcare interventions. We assessed the impact of the different inclusion decisions on the comprehensiveness and results of the overviews, both within and across overview cases.

3.3.2. Conducting the overviews

For each overview, all published, English-language Cochrane and non-Cochrane SRs that met the overview's inclusion criteria were identified from its reference list. All seven overviews included Cochrane SRs; four also included non-Cochrane SRs. For the three overviews that did not include non-Cochrane SRs [14-16], we conducted additional literature searches to locate and include non-Cochrane SRs that met the overview's inclusion criteria. An information specialist conducted the literature searches using the inclusion criteria and search dates from each overview (AM). The search strategies for all overview topics are available in published overviews and upon request. Screening non-Cochrane SRs for inclusion was conducted independently by two reviewers, with discrepancies resolved by consensus or third party

adjudication (AC, AM, DO, JS, MM, MO). At the end of the literature identification stage, each of the seven cases consisted of a published overview along with all published English-language Cochrane and non-Cochrane SRs that met that overview's inclusion criteria. Two reviewers independently assessed the methodological quality of each SR in each overview using A MeaSurement Tool to Assess systematic Reviews (AMSTAR) [21-23], with discrepancies resolved via consensus or third party adjudication (MP, LH, AC, AM, IS, MO, SS). AMSTAR scores (/11) were summarized using means and standard deviations.

The seven overview cases were conducted sequentially, according to five different inclusion scenarios, for a total of 35 overviews. The five inclusion scenarios were chosen because they are commonly cited in the literature as potentially appropriate ways to manage overlapping SRs in overviews [6, 7, 9]. The inclusion scenarios guided decisions about which SRs and outcome data to include in each overview, as follows:

- **Full inclusion scenario: All eligible outcome data were extracted from all eligible Cochrane and non-Cochrane SRs.** We ensured accuracy of effect estimates by making sure that each primary study's outcome data were extracted only once (regardless of how many SRs contained that study's data). This involved extracting data from the Cochrane SR (if present), followed sequentially by the most recent and/or highest quality SRs that most closely matched the overview's scope for each intervention comparison.
- **Restricted scenario 1: All eligible outcome data were extracted from all Cochrane SRs.**
- **Restricted scenarios 2 to 4: All eligible outcome data were extracted from all non-overlapping SRs, and in the case of groups of overlapping SRs, we included**

outcome data from: the Cochrane SR (restricted scenario 2), most recent SR (restricted scenario 3), or the highest quality SR (restricted scenario 4). For restricted scenario 2, if there was no Cochrane SR within a group of overlapping SRs, no outcome data were extracted. For restricted scenario 3, the most recent SR was defined as the SR with the most recent year of publication (for Cochrane SRs, we used the "year last assessed as up-to-date"). If two SRs were tied for "most recent", we included the one with the most recent search date. For restricted scenario 4, the highest quality SR was defined as the SR with the highest AMSTAR score (/11). If two SRs were tied for "highest quality", we simply noted this in the results files and did not extract data.

Matrices showing which comparisons and SRs were included in the overviews are provided in Appendix 3B. Because many SRs examined multiple interventions and comparators, we assessed overlap within SRs for each individual comparison.

Data extraction and analysis for the 35 overviews adhered to standard methods [4]. The following data were extracted for each of the 35 overviews: 1) descriptive characteristics of the SRs (e.g., Cochrane or non-Cochrane, first author, year of publication, populations, and included comparisons); 2) descriptive characteristics of the included primary studies contained within the SRs (e.g., first author, year of publication, study design, and sample size, for studies that matched the relevant overview's inclusion criteria); and 3) outcome data. We extracted outcome data from all relevant primary studies for all primary, secondary, adverse effects, and supplemental outcome measures, as specified in the corresponding overviews (Appendix 3A). When raw outcome data were reported in SRs, numerical data were extracted from SRs and re-analyzed in Review Manager 5.3 (The Cochrane Collaboration, Copenhagen, Denmark), using

standard meta-analysis techniques [24]. Outcome data were expressed using the measures of effect used in the corresponding overviews (risk ratios, odds ratios, and/or risk differences for dichotomous outcomes, and mean differences and/or standardized mean differences for continuous outcomes), with 95% confidence intervals. We conducted all analyses using random effects modeling and the Mantel-Haenszel method (dichotomous data) or inverse variance method (continuous data). When meta-analyzed data were reported in SRs but raw study data were not provided, or when only narrative data were provided, the data were extracted and reported based on statistical significance or the SR authors' description as "significant in favour of intervention", "not significant", or "significant in favour of comparator". For additional methodological decisions unique to each case, we adhered to the decision rules contained within the "Methods" section of the published overviews (though for feasibility, we did not conduct any subgroup or sensitivity analyses). Outcome data from the SRs contained within the procedural sedation overview case were not extracted, because data for the comparator groups were often not available.

We classified all outcome data using published criteria as "favourable" ($p \leq 0.05$ in favour of the intervention, or finding described as "significant"), "neutral" ($p > 0.05$, or finding described as "not different between groups") or "unfavourable" ($p \leq 0.05$ in favour of the comparator, or finding described as "favouring non-intervention comparator") [25, 26]. We classified outcome data as "unknown" when the effect estimate was not estimable (due to no events in either group) or when the "full inclusion scenario" contained discordant outcome data from multiple overlapping SRs. One reviewer (MP) extracted and analyzed data. Two additional reviewers (RMF, LH) oversaw this process and provided clinical and methodological input as

needed. When conducting the overviews, we also noted and narratively described challenges we encountered related to inclusion of overlapping SRs in overviews.

3.3.3. Data analysis

Data analysis consisted of both within-case analyses and cross-case syntheses [12, 27]. For each of the seven overview topics, we used three complimentary methods to visualize and describe the "full inclusion scenario": 1) we reported characteristics of the included SRs and their primary studies; 2) we generated a citation matrix [5] to show which SRs (columns) included which primary studies (rows), with sample sizes of primary studies reported in relevant cells; and 3) we used the citation matrix to calculate the "corrected covered area" (CCA) [5] to assess the extent of primary study overlap between the SRs included in the overview. The CCA represents "the area [of the citation matrix] that is covered after eliminating the inclusion of all primary studies the first time they are counted" [5]. The formula is, CCA = $\frac{N-r}{rc-r}$, where N = total number of included primary studies (number of non-empty cells); r = total number of unique primary studies (number of rows); and c = total number of SRs (number of columns). The amount of overlap could range from 0-100, and was categorized using published criteria as "slight" (0-5), "moderate" (6-10), "high" (11-15) or "very high" (>15). Detailed instructions for creating citation matrices and calculating the CCA can be found in Pieper 2014 [5].

For each of the six overview topics for which outcome data were extracted, we systematically compared "restricted scenarios 1 to 4" to the full inclusion scenario and documented the extent of data loss and change. We calculated the number and percentage of SRs, intervention comparisons, primary studies, and subjects that were lost in each restricted scenario. For the overviews' outcome data, we compared the result classifications obtained in

each of the four restricted scenarios to those obtained in the full scenario. Each outcome was described as "no change" (the result classification remained the same in both the restricted and full scenarios), "change" (the result classification differed in the restricted compared to the full scenario), or "data lost" (all data for that outcome were lost in the restricted scenario). We then calculated the number and percentage of primary, secondary, adverse effect, and supplemental outcomes that were lost and changed in each restricted scenario. These data were organized into a case-ordered descriptive matrix to permit within-case and cross-case analyses [12, 27].

As is standard with a multiple case study, we aimed to demonstrate replication logic across cases [12]. We summarized the effects of the five inclusion decisions on the comprehensiveness and results of each overview, examined the patterns and themes that emerged across overviews, identified groups of similar and contrasting overviews, and narratively described these different groups of overviews [12, 27]. We then reconfigured the inclusion decisions and study results into an ordered decision model [27]; the resulting evidence-based decision tool can help overview authors consider the potential implications of different inclusion decisions in overviews.

3.4. RESULTS

The seven overviews included in this study contained 6-19 SRs (range: 0-7 Cochrane SRs, and 2-13 non-Cochrane SRs, per overview). The SRs had a median publication year of 2008 (range: 1989-2013) and a mean AMSTAR score of 7.0/11 (SD: 2.8). Compared to the non-Cochrane SRs included in the overviews, the Cochrane SRs were more recent (2010 *vs.* 2007) and of higher quality (9.6 *vs.* 5.7). Across the overviews, 43% of the included primary studies appeared in multiple SRs (range: 30-55% per overview topic), and 53% and 77% were included

in Cochrane and non-Cochrane SRs, respectively. Across the overviews, the study overlap between the SRs ranged from slight (CCA: 3.3) to high (CCA: 14.9). The characteristics of the SRs included in the seven overviews are presented in Table 3.1. To maintain consistency with subsequent results tables, this table is organized using the categorization scheme described in the next paragraph.

3.4.1. Inclusion decisions

When analyzing study results, we identified two distinct groups of overviews: overviews for which Cochrane SRs did, and did not, examine all relevant intervention comparisons. All overviews within each group showed similar patterns of outcome data loss and change, which differed from those observed in the overviews belonging to the other group. All study results are presented according to this grouping. The impact of the different inclusion decisions on the comprehensiveness and results of overviews is displayed in Table 3.2, summarized in Table 3.3, and described below.

3.4.1.1. Overviews for which Cochrane SRs examined all relevant intervention comparisons (bronchiolitis, croup, gastroenteritis)

For the bronchiolitis and gastroenteritis overviews, though all non-Cochrane SRs overlapped with Cochrane SRs, the non-Cochrane SRs sometimes contributed additional primary studies, outcomes, and/or time points that were not included in the Cochrane SRs. Thus, when restricting to Cochrane SRs only (restricted scenario 1), these additional non-Cochrane data, which contributed to 13% (bronchiolitis) and 31% (gastroenteritis) of all outcomes, were lost. When reintroducing all non-overlapping SRs to the Cochrane SRs (restricted scenario 2), these

outcome data remained lost. For the croup overview, the non-Cochrane SRs did not contribute any unique outcome data not already contained within the Cochrane SRs, so data loss was 0%. For all three overviews, the outcome data in restricted scenarios 1 and 2 were the same, because there were no non-overlapping, non-Cochrane SRs.

For the bronchiolitis and croup overviews, the Cochrane SRs (restricted scenario 2) were always the most recent SRs (restricted scenario 3) and the highest quality SRs (restricted scenario 4), making restricted scenarios 1-4 the same in terms of comprehensiveness and results. For the gastroenteritis overview, the Cochrane SRs were always the highest quality SRs (restricted scenario 4), making restricted scenarios 1, 2 and 4 the same. Including Cochrane SRs (restricted scenarios 1, 2 and 4) compared to the most recent SRs (restricted scenario 3) led to less data loss and change.

3.4.1.2. Overviews for which Cochrane SRs did not examine all relevant intervention comparisons (acute asthma, acute otitis media, eczema, procedural sedation)

For the acute asthma, eczema, and acute otitis media overviews, when restricting to Cochrane SRs only (restricted scenario 1), the non-Cochrane outcome data, which contributed to 28% (acute asthma), 54% (acute otitis media) and 67% (eczema) of all outcomes, were lost. When reintroducing all non-overlapping SRs to the Cochrane SRs (restricted scenario 2), all non-Cochrane data for unique intervention comparisons were re-captured. In restricted scenario 2, data remained lost or changed for 4% (acute asthma) and 39% (acute otitis media, eczema) of outcomes. Thus, the outcome data in restricted scenario 2 were always more comprehensive than those in restricted scenario 1, and data were recaptured for 86% (acute asthma), 28% (acute otitis media), and 42% (eczema) of lost or changed outcomes. We were unable to extract outcome data

for the procedural sedation overview because data for the comparator groups were often unavailable. However, no Cochrane SRs were included in this overview. Thus, in restricted scenario 1, all outcome data would have been lost.

For the acute asthma, acute otitis media, and eczema overviews, including Cochrane SRs (restricted scenario 2) compared to the most recent SRs (restricted scenario 3) led to less or the same amount of data loss and change. For the acute asthma overview, the Cochrane SRs (restricted scenario 2) were always the highest quality SRs (restricted scenario 4), making restricted scenarios 2 and 4 the same in terms of comprehensiveness and results. For the eczema and acute otitis media overviews, we were unable to calculate the amount of data loss and change for restricted scenario 4, because SRs were sometimes "tied" for highest quality. Notably, it was always a Cochrane SR and a most recent SR that were tied for highest quality (Appendix 3B). For the procedural sedation overview, it is unclear what would have happened in restricted scenarios 2-4.

3.4.2. Challenges encountered

We noted additional relevant challenges when conducting the seven overviews and analyzing their outcome data. The challenges related to: identifying overlapping SRs (two challenges); making inclusion decisions when faced with overlapping SRs (seven challenges); and extracting and analyzing outcome data from overlapping SRs (three challenges). These challenges, along with potential implications and examples, are presented and discussed in Table 3.4.

3.4.3. Decision tool

We used the above-described study results (effects of inclusion decisions, and challenges encountered) to develop an evidence-based decision tool to help researchers consider the potential implications of different inclusion decisions in overviews. The decision tool is presented and described in Figure 3.1. It contains the following four decision points:

- Decision point 1: Do Cochrane SRs likely examine all relevant intervention comparisons?
- Decision points 2 and 3: Do the included SRs overlap?
- Decision point 4: Are researchers prepared and able to avoid double-counting outcome data from overlapping SRs, by ensuring that each primary study's outcome data are extracted from overlapping SRs only once?

3.5. DISCUSSION

The current study involved conducting each of seven overviews using five different sets of inclusion criteria, to provide empirical evidence examining the inclusion of overlapping SRs in overviews and to support the development of an evidence-based decision tool. This study found that different inclusion decisions led to different amounts of outcome data loss and change across overviews, and that extracting outcome data from overlapping SRs in overviews often posed challenges. These findings were used to develop an evidence-based decision tool for making inclusion decisions in overviews.

After examining the different inclusion scenarios across overview topics, we found that including only Cochrane SRs, compared to all Cochrane and non-Cochrane SRs, often, but not always, led to a loss of outcome data. The data loss always occurred for one of two reasons. First, when overviews had Cochrane SRs that examined all relevant intervention comparisons, all

data loss occurred because the overlapping non-Cochrane SRs contributed additional primary studies, outcomes, and/or time points for existing intervention comparisons. It is unclear whether these additional outcome data are of clinical importance. On the one hand, these outcome data are lost. In the current study, this led to the complete loss of some outcomes, and changes in the statistical significance of some outcomes. On the other hand, some of these lost outcome data came from primary studies in non-Cochrane SRs that were identified by, but excluded from, the Cochrane SRs, for being outside their scope or having methodological deficiencies. If researchers agree with the inclusion decisions made in the Cochrane SRs, it may not be appropriate to include this subset of excluded primary studies in the overview, especially if these studies are of lower quality or do not increase the certainty of evidence (i.e., GRADE). Second, when overviews had Cochrane SRs that did *not* examine all relevant intervention comparisons, data loss also occurred because the non-Cochrane SRs contributed outcome data for unique intervention comparisons not examined in any Cochrane SR. These additional data fall within the scope of the overview and are likely of clinical importance, since restricting to only Cochrane SRs would exclude relevant intervention comparisons from the overview. However, reintroducing all non-overlapping SRs to the Cochrane SRs allowed non-Cochrane data for all of the non-overlapping intervention comparisons to be recaptured.

By examining the different inclusion scenarios we also found that selecting the Cochrane SR for groups of overlapping SRs, as opposed to the most recent or highest quality SR, maximized the amount of outcome data included in the overview. Across overview topics, the Cochrane SRs were sometimes the most recent SRs, and were always or often the highest quality SRs. Thus, researchers may often end up selecting Cochrane SRs for inclusion in overviews regardless of which inclusion criteria are used. Further, including Cochrane SRs, even when

there are more recent or higher quality non-Cochrane SRs available, may result in more outcome data included in the overview. To capture outcome data for groups of overlapping SRs that do not contain a Cochrane SR, researchers may choose to include one of the non-Cochrane SRs. In these cases, our results suggest that selecting the highest quality, as opposed to the most recent, non-Cochrane SR may minimize data loss.

When conducting the overviews, we observed that there were often practical challenges associated with inclusion of overlapping SRs. Though researchers conducting overviews often refer to the issue of "overlapping SRs" [5-7], we found that within SRs, overlap can also occur at the level of the included primary studies, intervention comparisons, and outcome data. Thus, the issue of "overlap" may be more complex than previously envisioned. As most SRs examined more than one intervention and comparator, this study assessed overlap at the level of the intervention comparison. Further, we often encountered issues when extracting and analyzing outcome data, especially when multiple SRs contained the same or similar outcome data and when non-Cochrane SRs were poorly conducted and/or reported. Researchers should be aware of these potential challenges when including overlapping SRs in overviews.

Using the evidence-based decision tool to make inclusion decisions in overviews (see Figure 3.1) can help promote transparency and rigour, and decrease bias. Four conditions should be met prior to using the decision tool. First, the overview should examine multiple interventions for preventing or treating a health condition, though future testing and real-life application of the tool can help determine whether it can be used with other types of overviews [4]. Second, the overview format should be more appropriate than the SR format to answer the research question [6]. Third, researchers should intend to search for and include only SRs in the overview [4, 6]. Fourth, researchers should be prepared and able to avoid double-counting outcome data from

overlapping SRs, either by not including overlapping SRs in the overview or by ensuring that each primary study's outcome data are extracted from overlapping SRs only once [5-7]. The layout of the decision tool is also based on two practical considerations. First, we acknowledge that researchers may decide to prioritize Cochrane SRs for inclusion in overviews due to both their higher methodological rigour (on average) [28], and the additional time, skills, resources, and challenges associated with searching for, including, and extracting data from non-Cochrane SRs [4, 6]. The tool's layout ensures that researchers consider the potential implications of this inclusion decision upfront, in the context of their specific overview question. Second, we anticipate that some questions in the decision tool may be difficult to answer. To address this, we identified two points in the tool where researchers may wish to gather more information to help inform their decision. This decision tool can provide practical guidance and support for overview authors by helping them consider questions that can affect the nature and extent of outcome data included and not included in overviews, as well as the impact, advantages, disadvantages, and potential trade-offs of making different inclusion decisions in overviews. We welcome further discussion, testing, and refinement of the proposed tool.

Our study findings should be considered in light of two methodological considerations. First, this study operated under the simplified assumption that within each overview, all outcome data, intervention comparisons, primary studies, and SRs were equally relevant. This is because judgements about "relevance" would have been difficult to incorporate into the analysis in an objective and systematic way. Thus, we weighted all outcome data equally, and did not comment on the clinical relevance of the specific data that were lost or changed. For similar reasons, we were unable to account for potential differences in reporting of SRs (specifically selective outcome reporting) that may have affected the comprehensiveness and results of the overview

cases. Second, though we extracted, analyzed, and presented data for a number of potentially relevant variables of interest, we focused our results on the variable that helped explain the different patterns of outcome data loss (i.e., the number of intervention comparisons included in Cochrane and non-Cochrane SRs) [12]. We opted not to discuss the other variables in detail, as they did not contribute to the overall pattern of findings in a cohesive or consistent way. For example, we hypothesized that differences in amounts of primary study overlap may lead to systematic differences in comprehensiveness and results of overviews across various inclusion scenarios, but found that this was not the case.

As is standard with a multiple case study, we aimed to establish generalizability of our findings by demonstrating replication logic across cases [12]. We described individual cases, looked for patterns across cases, identified similar and contrasting cases, and described groups of similar cases together. Our main study findings remained stable across overviews with a range of characteristics. For example, the overviews: included different numbers of SRs (6-19) with various publication dates (1989-2013) and quality scores (1-11 out of 11); had "slight" to "high" primary study overlap between SRs; and had non-Cochrane SRs that contributed 0-100% of outcome data. Achieving replication across multiple cases with different characteristics helps establish robustness of the findings and suggests that the patterns observed within and across cases are coherent, systematically related, and unified [12]. This strengthens the generalizability of the patterns of knowledge gained from the study [12]. Thus, though we used a convenience sample of seven overviews that posed unique clinical questions within the bounds of certain pre-defined limits, the patterns of data loss (as opposed to the specific amounts of data loss) may generalize to a range of overviews examining healthcare interventions. However, findings should

not be generalized to overviews that address broader or different clinical questions (e.g., qualitative, diagnostic test accuracy, or prognostic overviews).

The inclusion decisions examined in this study and reflected in the decision tool are commonly cited in the literature as practical ways to manage overlapping SRs in overviews while avoiding issues related to double-counting outcome data [6, 7, 11]. However, researchers may sometimes make different inclusion decisions motivated by reasons other than considerations about overlapping SRs. For example, researchers that suspect that Cochrane SRs are comprehensive may still opt to search for and potentially include non-Cochrane SRs in the overview, while those that suspect that Cochrane SRs are *not* comprehensive may opt to include only Cochrane SRs and discuss this as a study limitation. Other researchers who are unable to avoid double-counting outcome data may still opt to include all Cochrane and non-Cochrane SRs and discuss this as a study limitation. Yet other researchers may use results of quality assessments as an exclusion criterion. They may also manage groups of overlapping SRs by choosing to include the "most comprehensive SRs" or the "most relevant SRs" (though these subjective assessments may be operationalized in different ways depending on the overview topic, and thus were not examined in the current methods study). Though outside the scope of the current study, research investigating the implications of these other inclusion decisions in overviews is also needed.

3.6. CONCLUSIONS

There is currently limited guidance available for researchers conducting overviews of healthcare interventions. For example, there are challenges and uncertainty regarding the methods that should be used to manage overlapping SRs in overviews. The current study helps

address this gap in guidance by contributing empirical evidence examining the impact of different inclusion decisions on the comprehensiveness and results of overviews. Our results highlight practical challenges related to inclusion of overlapping SRs in overviews, and show that different inclusion decisions affect the comprehensiveness and results of overviews in different ways. The results were used to develop an evidence-based decision tool to help researchers make transparent and well-informed inclusion decisions in overviews. This tool provides practical guidance for overview authors and warrants further evaluation.

3.7. REFERENCES

1. Green S, Higgins JPT, Alderson P, Clarke M, Mulrow CD, Oxman AD. Chapter 1: introduction. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.1.0). The Cochrane Collaboration; 2011. http://www.handbook.cochrane.org.
2. Bastian H, Glasziou P, Chalmers I. Seventy-five trials and eleven systematic reviews a day: how will we ever keep up? PLoS Med. 2010;7(9):e1000326.
3. Jadad AR, Cook DJ, Browman GP. A guide to interpreting discordant systematic reviews. Can Med Assoc J. 1997;156(10):1411-6.
4. Becker LA, Oxman AD. Chapter 22: overviews of reviews. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.1.0). The Cochrane Collaboration; 2011. http://www.handbook.cochrane.org.
5. Pieper D, Antoine SL, Mathes T, Neugebauer EA, Eikermann M. Systematic review finds overlapping reviews were not mentioned in every other overview. J Clin Epidemiol. 2014;67(4):368-75.

6. Pollock M, Fernandes RM, Becker LA, Featherstone R, Hartling L. What guidance is available for researchers conducting overviews of reviews of healthcare interventions? A scoping review and qualitative metasummary. Syst Rev. 2016;5:190.
7. Ballard M, Montgomery P. Risk of bias in overviews of reviews: a scoping review of methodological guidance and four-item checklist. Res Synth Methods. 2017;8(1):92-108.
8. Pollock A, Campbell P, Brunton G, Hunt H, Estcourt L. Selecting and implementing overview methods: implications from five exemplar overviews. Syst Rev. 2017;6:145.
9. Cooper H, Koenka AC. The overview of reviews: unique challenges and opportunities when research syntheses are the principal elements of new integrative scholarship. Am Psychol. 2012;67(6):446-62.
10. Caird J, Sutcliffe K, Kwan I, Dickson K, Thomas J. Mediating policy-relevant evidence at speed: are systematic reviews of systematic reviews a useful approach? Evid Policy. 2015;11(1):81-97.
11. Thomson D, Foisy M, Oleszczuk M, Wingert A, Chisholm A, Hartling L. Overview of reviews in child health: evidence synthesis and the knowledge base for a specific population. Evid Based Child Health. 2013;8(1):3-10.
12. Yin RK. Case study research: design and methods. 5th ed. Thousand Oaks: SAGE Publications; 2013.
13. Pollock M, Sinha I, Hartling L, Rowe BH, Schrieber S, Fernandes RM. Inhaled short-acting bronchodilators for managing emergency childhood asthma: an overview of reviews. Allergy. 2017;72(2):183-200.
14. Oleszczuk M, Fernandes RM, Thomson D, Shaikh N. The Cochrane Library and acute otitis media in children: an overview of reviews. Evid Based Child Health. 2012;7(2):393-402.

15. Bialy L, Foisy M, Smith M, Fernandes RM. The Cochrane Library and the treatment of bronchiolitis in children: an overview of reviews. Evid Based Child Health. 2011;6(1):258-75.
16. Bjornson C, Russell K, Foisy M, Johnson DW. The Cochrane Library and the treatment of croup in children: an overview of reviews. Evid Based Child Health. 2010;5(4):1555-65.
17. Foisy M, Boyle RJ, Chalmers JR, Simpson EL, Williams HC. The prevention of eczema in infants and children: an overview of Cochrane and non-Cochrane reviews. Evid Based Child Health. 2011;6(5):1322-39.
18. Freedman SP, Ali S, Oleszczuk M, Gouin S, Hartling L. Treatment of acute gastroenteritis in children: an overview of systematic reviews of interventions commonly used in developed countries. Evid Based Child Health. 2013;8(4):1123-37.
19. Hartling L, Milne A, Foisy M, Lang E, Sinclair D, Klassen TP, *et al*. What works and what's safe in pediatric emergency procedural sedation: an overview of reviews. Acad Emerg Med. 2016;23(5):519-30.
20. Etikan I, Musa SA, Alkassim RS. Comparison of convenience sampling and purposive sampling. Am J Theor Appl Stat. 2016;5(1):1-4.
21. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, *et al*. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 2007;7:10.
22. Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J, *et al*. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol. 2009;62(10):1013-20.

23. Shea BJ, Bouter LM, Peterson J, Boers M, Andersson N, Ortiz Z, *et al*. External validation of a measurement tool to assess systematic reviews (AMSTAR). PLoS One. 2007;2(12):e1350.
24. Deeks J J, T. HJP, Altman DG. Chapter 9: analysing data and undertaking meta-analyses. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.1.0). The Cochrane Collaboration; 2011. http://www.handbook.cochrane.org.
25. Tricco AC, Tetzlaff J, Pham B, Brehaut J, Moher D. Non-Cochrane vs. Cochrane reviews were twice as likely to have positive conclusion statements: cross-sectional study. J Clin Epidemiol. 2009;62(4):380-6.
26. Lai NM, Teng CL, Lee ML. Interpreting systematic reviews: are we ready to make our own conclusions? A cross-sectional study. BMC Med. 2011;9:30.
27. Miles MB, Huberman AM, Saldana J. Qualitative data analysis: a methods sourcebook. 3rd ed. Thousand Oaks: SAGE Publications; 2014.
28. Page MJ, Shamseer L, Altman DG, Tetzlaff J, Sampson M, Tricco AC, *et al*. Epidemiology and reporting characteristics of systematic reviews of biomedical research: a cross-sectional study. PLoS Med. 2016;13(5):e1002028.

Table 3.1. Characteristics of the systematic reviews included in each overview.

Overview topic and SR category	Number of included SRs	Years of publication of SRs, median (range)[a]	AMSTAR score, mean (standard deviation)	Total number of included primary studies	Unique primary studies, *n* and % included in at least one SR[b]	Primary study overlap between SRs ("CCA")[c]
OVERVIEWS FOR WHICH COCHRANE SRs EXAMINED ALL RELEVANT INTERVENTION COMPARISONS						
Bronchiolitis	**7**	**2009 (1996-2010)**	**8.1 (3.0)**	**55**	**29**	**High (14.9)**
Cochrane	4	2010 (2009-2010)	10.5 (0.6)	33	26 (90%)	
Non-Cochrane	3	1997 (1996-2004)	5.0 (1.0)	22	13 (45%)	
Croup	**6**	**2008 (1989-2010)**	**8.3 (3.0)**	**69**	**53**	**Moderate (6.0)**
Cochrane	4	2010 (2006-2010)	9.5 (1.9)	51	50 (94%)	
Non-Cochrane	2	1995 (1989-2000)	6.0 (4.2)	18	18 (34%)	
Gastroenteritis	**15**	**2007 (2001-2012)**	**7.7 (1.8)**	**228**	**114**	**High (13.3)**
Cochrane	3	2010 (2006-2010)	10.7 (0.6)	88	88 (77%)	
Non-Cochrane	12	2007 (2001-2012)	6.9 (1.1)	140	82 (72%)	
OVERVIEWS FOR WHICH COCHRANE SRs DID NOT EXAMINE ALL RELEVANT INTERVENTION COMPARISONS						
Acute asthma	**13**	**2011 (1997-2013)**	**7.8 (2.0)**	**82**	**56**	**Slight (3.9)**
Cochrane	7	2011 (2002-2013)	8.4 (1.8)	48	45 (80%)	
Non-Cochrane	6	2006 (1997-2013)	7.0 (2.0)	34	34 (61%)	
Acute otitis media	**15**	**2009 (1994-2011)**	**8.1 (2.6)**	**260**	**135**	**Moderate (6.6)**
Cochrane	6	2009 (2007-2011)	10.2 (0.8)	87	84 (62%)	
Non-Cochrane	9	2006 (1994-2010)	6.7 (2.5)	173	107 (79%)	
Eczema	**19**	**2007 (2003-2011)**	**6.6 (2.9)**	**198**	**136**	**Slight (2.5)**
Cochrane	6	2007 (2006-2011)	9.3 (1.8)	29	29 (21%)	
Non-Cochrane	13	2008 (2003-2010)	5.4 (2.4)	169	130 (96%)	
Procedural sedation	**13**	**2009 (2004-2013)**	**3.7 (1.8)**	**180**	**85**	**Moderate (9.3)**
Cochrane	0	NA	NA	NA	NA	
Non-Cochrane	13	2009 (2004-2013)	3.7 (1.8)	180	85 (100%)	
ALL OVERVIEWS						
Total	**88**	**2008 (1989-2013)**	**7.0 (2.8)**	**1,072**	**608**	**NA**
Cochrane	30	2010 (2002-2013)	9.6 (1.6)	336	322 (53%)	
Non-Cochrane	58	2007 (1989-2013)	5.7 (2.3)	736	469 (77%)	

CCA: corrected covered area; NA: not applicable; SR: systematic review.

[a] For Cochrane SRs we used the year last assessed as up-to-date; [b] Each primary study was counted only once, regardless of how many SRs included that study. [c] Categorized using published criteria as “slight” (0-5), “moderate” (6-10), “high” (11-15) or “very high” (>15).

Table 3.2. Impact of the full and restricted inclusion scenarios on the comprehensiveness and results of overviews.

Overviews and inclusion scenarios[a]	Number of included SRs (% data loss)	Number of intervention comparisons (% data loss)	Number of primary studies included (% data loss)	Number of subjects included (% data loss)	Number of outcomes (L: % outcomes lost; C: % outcomes changed)				
					Primary	Secondary	Adverse effects	Supplemental	Overall
OVERVIEWS FOR WHICH COCHRANE SRs EXAMINED ALL RELEVANT INTERVENTION COMPARISONS									
Bronchiolitis									
Full scenario	7 (0%)	8 (0%)	29 (0%)	3,526 (0%)	13 (0%)	15 (0%)	20 (0%)	--	48 (0%)
Restricted scenario 1	4 (43%)	8 (0%)	26 (10%)	3,294 (7%)	L: 1 (8%) C: 0 (0%)	L: 2 (13%) C: 1 (7%)[c]	L: 2 (10%) C: 0 (0%)	--	L+C: 6 (13%)
Restricted scenario 2	Same as restricted scenario 1								
Restricted scenario 3	Same as restricted scenario 1								
Restricted scenario 4	Same as restricted scenario 1								
Croup									
Full scenario	6 (0%)	16 (0%)	53 (0%)	5,181 (0%)	31 (0%)	19 (0%)	0 (0%)	--	50 (0%)
Restricted scenario 1	4 (33%)	16 (0%)	50 (6%)	4,717 (9%)	L: 0 (0%) C: 0 (0%)	L: 0 (0%) C: 0 (0%)	L: 0 (0%) C: 0 (0%)	--	L+C: 0 (0%)
Restricted scenario 2	Same as restricted scenario 1								
Restricted scenario 3	Same as restricted scenario 1								
Restricted scenario 4	Same as restricted scenario 1								
Gastroenteritis									
Full scenario	15 (0%)	9 (0%)	114 (0%)	14,801 (0%)	6 (0%)	7 (0%)	22 (0%)	--	35 (0%)
Restricted scenario 1	3 (80%)	9 (0%)	88 (23%)	11,147 (25%)	L: 0 (0%) C: 1 (17%)[d]	L: 1 (14%) C: 1 (14%)[c]	L: 5 (23%) C: 3 (14%)[c]	--	L+C: 11 (31%)
Restricted scenario 2	Same as restricted scenario 1								
Restricted scenario 3	3 (80%)	9 (0%)	46 (60%)	6,070 (59%)	L: 0 (0%) C: 1 (17%)[d]	L: 0 (0%) C: 2 (29%)[c]	L: 6 (27%) C: 3 (14%)[c]	--	L+C: 12 (34%)

Restricted scenario 4	Same as restricted scenario 1								
OVERVIEWS FOR WHICH COCHRANE SRs DID NOT EXAMINE ALL RELEVANT INTERVENTION COMPARISONS									
Acute asthma									
Full scenario	13 (0%)	11 (0%)	56 (0%)	5,527 (0%)	12 (0%)	29 (0%)	19 (0%)	16 (0%)	76 (0%)
Restricted scenario 1	7 (46%)	9 (18%)	45 (20%)	4,521 (18%)	L: 2 (17%) C: 1 (8%)[b]	L: 10 (35%) C: 0 (0%)	L: 5 (26%) C: 1 (5%)[c]	L: 2 (13%) C: 0 (0%)	L+C: 21 (28%)
Restricted scenario 2	9 (30.8%)	11 (0%)	50 (11%)	5,023 (9%)	L: 0 (0%) C: 1 (8%)[b]	L: 1 C: 0 (0%)	L: 0 (0%) C: 1 (5%)[c]	L: 0 (0%) C: 0 (0%)	L+C: 3 (4%)
Restricted scenario 3	9 (30.8%)	11 (0%)	49 (13%)	5,006 (9%)	L: 0 (0%) C: 1 (8%)[b]	L: 1 C: 0 (0%)	L: 6 (32%) C: 1 (5%)[c]	L: 0 (0%) C: 0 (0%)	L+C: 9 (12%)
Restricted scenario 4	Same as restricted scenario 2								
Acute otitis media									
Full scenario	15 (0%)	18 (0%)	135 (0%)	28,323 (0%)	6 (0%)	22 (0%)	13 (0%)	--	41 (0%)
Restricted scenario 1	6 (60%)	10 (44%)	84 (62%)	21,907 (32%)	L: 0 (0%) C: 0 (0%)	L: 14 (64%) C: 1 (5%)[c]	L: 4 (31%) C: 3 (23%)[cd]	--	L+C: 22 (54%)
Restricted scenario 2	8 (47%)	15 (17%)	117 (13%)	26261 (7%)	L: 0 (0%) C: 0 (0%)	L: 9 (41%) C: 1 (5%)[c]	L: 3 (23%) C: 3 (23%)[cd]	--	L+C: 16 (39%)
Restricted scenario 3	5 (67%)	18 (0%)	106 (21%)	23,122 (18%)	L: 2 (33%) C: 0 (0%)	L: 6 (27%) C: 3 (14%)[bc]	L: 2 (15%) C: 3 (23%)[cd]	--	L+C: 16 (39%)
Restricted scenario 4	Unable to calculate[e]								
Eczema									
Full scenario	19 (0%)	27 (0%)	136 (0%)	794,014 (0%)	27 (0%)	--	25 (0%)	--	52 (0%)
Restricted scenario 1	6 (68%)	7 (75%)	29 (79%)	11,418 (99%)	L: 20 (74%) C: 2 (7%)[bc]	--	L: 13 (52%) C: 0 (0%)	--	L+C: 35 (67%)
Restricted scenario 2	11 (42%)	22 (19%)	115 (17%)	697,014 (15%)	L: 5 (19%) C: 2 (7%)[bc]	--	L: 13 (52%) C: 0 (0%)	--	L+C: 20 (39%)
Restricted scenario 3	12 (42%)	27 (0%)	133 (15%)	792,721 (4%)	L: 0 (0%) C: 3 (11%)[bcd]	--	L: 22 (88%) C: 0 (0%)	--	L+C: 25 (48%)
Restricted scenario 4	Unable to calculate[e]								

Procedural sedation									
Full scenario	13	--	85	149,088	--	--	--	--	--
Restricted scenario 1	0 (100%)	--	0 (100%)	0 (100%)	--	--	--	--	--
Restricted scenario 2	--	--	--	--	--	--	--	--	--
Restricted scenario 3	--	--	--	--	--	--	--	--	--
Restricted scenario 4	--	--	--	--	--	--	--	--	--

[a] Full scenario: Include all Cochrane and non-Cochrane SRs; Restricted scenario 1: Include only Cochrane SRs; Restricted scenarios 2-4: Include all non-overlapping SRs, and in the case of overlapping SRs include the Cochrane SR (restricted scenario 2), the most recent SR (restricted scenario 3), or the highest quality SR (restricted scenario 4); [b] Result assessment changed from "Favourable" or "Unfavourable" to "Neutral"; [c] Result assessment changed from "Unknown" to something else; [d] Result assessment changed from "Neutral" to "Favourable" or "Unfavourable"; [e] Two systematic reviews were tied for "highest quality".

Table 3.3. Summary table: Amount of data loss and change when comparing different inclusion scenarios.

	Restricted scenario 1 *vs.* full scenario[a]	**Restricted scenario 2 *vs.* 1[a]**	**Restricted scenario 2 *vs.* 3[a]**	**Restricted scenario 2 *vs.* 4[a]**	**Restricted scenario 3 *vs.* 4[a]**
OVERVIEWS FOR WHICH COCHRANE SRS EXAMINED ALL RELEVANT INTERVENTION COMPARISONS					
Bronchiolitis	More	Same	Same	Same	Same
Croup	Same	Same	Same	Same	Same
Gastroenteritis	More	Same	Less	Same	More
OVERVIEWS FOR WHICH COCHRANE SRS DID NOT EXAMINE ALL RELEVANT INTERVENTION COMPARISONS					
Acute asthma	More	Less	Less	Same	More
Acute otitis media	More	Less	Similar[b]	Unknown[c]	Unknown[c]
Eczema	More	Less	Less	Unknown[c]	Unknown[c]
Procedural sedation	More	Unknown[c]	Unknown[c]	Unknown[c]	Unknown[c]

[a] Full scenario: Include all Cochrane and non-Cochrane SRs; Restricted scenario 1: Include only Cochrane SRs; Restricted scenarios 2-4: Include all non-overlapping SRs, and in the case of overlapping SRs include the Cochrane SR (restricted scenario 2), the most recent SR (restricted scenario 3), or the highest quality SR (restricted scenario 4); [b] Overall amount of data loss and change was the same, but breakdown differed across outcomes; [c] Unable to calculate amount of data loss and change.

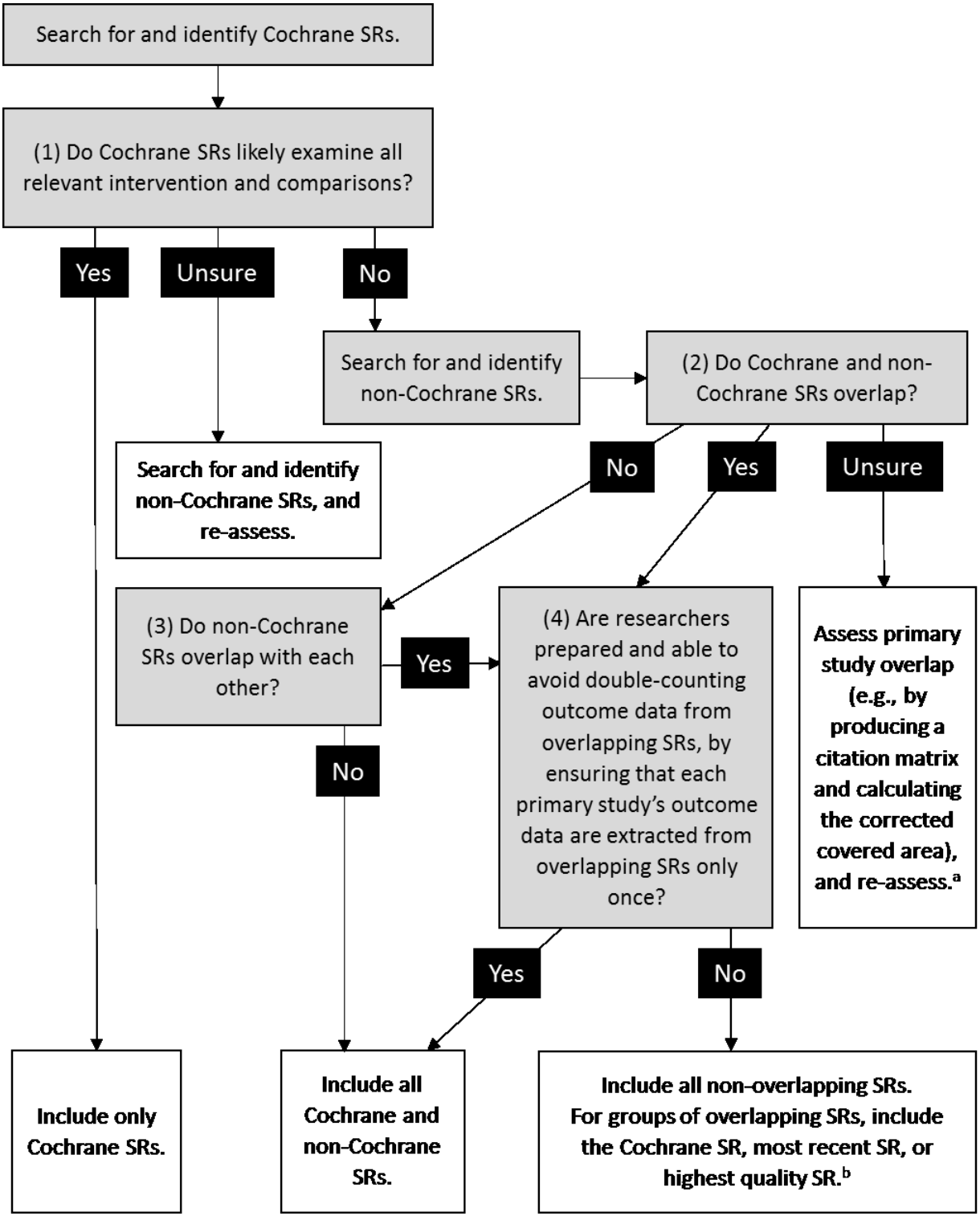
Table 3.4. Challenges encountered when including overlapping systematic reviews in overviews.

Challenge	Implication	Example
Challenges related to identifying overlapping SRs		
Some non-Cochrane SRs were quite broad and examined all relevant interventions for the condition of interest (3/7 overviews affected).	Overview authors may need to closely examine the results of the SRs to identify all intervention comparisons included within these SRs.	One SR in the acute otitis media overview examined "the comparative effectiveness of [all] different treatment options for treating uncomplicated acute otitis media" and contributed outcome data to ten relevant intervention comparisons.
SRs sometimes referenced only one of several duplicate publications. Across SRs, this made duplicate publications hard to identify since they looked like independent publications (2/7 overviews affected).	When looking for overlap among primary studies included in SRs, overview authors should look closely for multiple publications of the same primary study.	In the eczema overview, one Cochrane SR included a primary study published by Kramer (2000), and one non-Cochrane SR included a primary study published by Kramer (2002). Examining the "list of excluded references" in the Cochrane SR revealed that these two references were duplicate publications of the same primary study.
Challenges related to including all Cochrane and non-Cochrane SRs (full inclusion scenario)		
Some overlapping primary studies included in non-Cochrane SRs were identified by, but excluded from, the Cochrane SRs for being outside the scope or for having methodological deficiencies (6/7 overviews affected).	If researchers agree with the inclusion decisions made in the Cochrane SRs, it may not be appropriate to include this subset of excluded primary studies in the overview.	One non-Cochrane SR in the acute asthma overview included a primary study by Fuglsang (1986). A Cochrane SR on the same topic excluded this study due to methodological deficiencies (cross-over design inappropriate for acute asthma).
Challenges related to including only Cochrane SRs (restricted scenario 1)		
Input from a clinical expert was often required to determine whether the Cochrane SRs comprehensively examined all relevant intervention comparisons (6/7 overviews affected).	Clinical experts should be prepared and able to help make methodological decisions related to inclusion of SRs in overviews.	A clinical expert determined that the Cochrane SRs identified for the croup and acute otitis media overviews likely were comprehensive, and were not comprehensive, respectively.
Multiple Cochrane SRs sometimes contributed outcome data to the same comparison (i.e., Cochrane SRs sometimes overlapped) (2/7 overviews affected).	Including Cochrane SRs in overviews may not always eliminate issues related to overlapping SRs. Additional decision rules may be needed to address this situation.	Two Cochrane SRs on epinephrine for treatment of bronchiolitis, and glucocorticoids for treatment of bronchiolitis, each included outcome data for the comparison "epinephrine and glucocorticoid vs. placebo".

Challenges related to including all non-overlapping SRs, and in the case of overlapping SRs, the Cochrane, most recent, or highest quality SR (restricted scenarios 2-4)		
Not all groups of overlapping SRs included a Cochrane SR (2/7 overviews affected).	Additional decision rules may be needed to capture data from groups of overlapping SRs that do not include a Cochrane SR.	In the eczema overview, two overlapping non-Cochrane SRs (but no Cochrane SRs) provided outcome data on "pet exposure *vs.* no pet exposure at home".
Overlapping SRs were sometimes "tied" for most recent year of publication or for highest quality (3/7 overviews affected).	Additional decision rules may be needed to differentiate between SRs with similar publication dates or quality scores.	Because the two most recent overlapping SRs in the acute otitis media overview were both published in 2010, we instead examined the search dates to determine which to include in the overview.
Search dates were not comprehensively or consistently reported in all SRs (6/7 overviews affected).	Using search dates to choose between overlapping SRs published in the same year may not always be possible or straightforward.	When looking at search dates of SRs, the following issues were encountered: exact search dates not reported; month of search not reported; and different search dates reported for different databases.
Conducting quality assessments could be challenging and time-intensive (7/7 overviews affected).	Using methodological quality as an inclusion criteria to choose between groups of overlapping SRs may be more complex than using other decision rules.	For all overview topics, we found that conducting quality assessments was always more time and resource intensive than simply assessing the Cochrane status or year of publication of the SRs.
Challenges related to extracting and analyzing outcome data from overlapping SRs		
Overlapping SRs sometimes presented the same or similar outcome data in different ways (6/7 overviews affected).	Researchers must decide how best to extract data from overlapping SRs when the same or similar outcome data are reported differently across SRs.	Different SRs sometimes: reported different numerators or denominators for the same outcomes; used different types of analysis or statistical methods to analyze the same outcomes; or measured similar outcomes using different definitions, instruments, scales, or time-points.
Overlapping SRs sometimes had discordant results for the same outcome (5/7 overviews affected).	Including outcome data from all overlapping SRs may not result in a coherent overall analysis within a single outcome. Reconciling the discordance may require in-depth exploration of the methods and results of the different SRs.	Two SRs in the gastroenteritis overview examined "length of hospital stay" for "oral rehydration therapy *vs.* intravenous therapy". One SR contained meta-analyzed data that significantly favoured the intervention. The other SR contained narrative data that was not significant.

When including non-Cochrane SRs, data extraction was sometimes difficult due to deficiencies in conduct and reporting of SRs (6/7 overviews affected).	Non-Cochrane SRs with gross deficiencies in conduct and/or reporting may be difficult to include in overviews.	For Cochrane SR, study-level outcome data were always available in well-reported narrative summaries or meta-analyses, but this was not always the case for non-Cochrane SRs.

A


Search for and identify Cochrane SRs.
(1) Do Cochrane SRs likely examine all relevant intervention and comparisons?
Yes
Unsure
No
Search for and identify non-Cochrane SRs.
(2) Do Cochrane and non-Cochrane SRs overlap?
Search for and identify non-Cochrane SRs, and re-assess.
No
Yes
Unsure
(3) Do non-Cochrane SRs overlap with each other?
Yes
(4) Are researchers prepared and able to avoid double-counting outcome data from overlapping SRs, by ensuring that each primary study's outcome data are extracted from overlapping SRs only once?
Assess primary study overlap (e.g., by producing a citation matrix and calculating the corrected covered area), and re-assess.[a]
No
Yes
No
Include only Cochrane SRs.
Include all Cochrane and non-Cochrane SRs.
Include all non-overlapping SRs. For groups of overlapping SRs, include the Cochrane SR, most recent SR, or highest quality SR.[b]

B

Decision point 1: Do Cochrane SRs likely examine all relevant intervention comparisons? If yes, researchers may choose to include only Cochrane SRs in the overview. An advantage (and potential disadvantage) of this inclusion decision is that researchers are likely (but not guaranteed) to avoid issues related to overlapping SRs. A disadvantage (and potential advantage) is that there will likely (but not always) be some data loss from non-Cochrane SRs for overlapping intervention comparisons. The current study found that input from a clinical expert may be required to assess whether the Cochrane SRs comprehensively examined all relevant intervention comparisons. Researchers who are not comfortable answering this question based on the Cochrane SRs alone may opt to search for and identify non-Cochrane SRs, and re-assess.

Decision points 2 and 3: Do the included SRs overlap? If researchers suspect that the Cochrane SRs are not comprehensive, the second and third decision points ask them to search for and identify non-Cochrane SRs, and determine whether the included SRs overlap. If they do not overlap, researchers can include all Cochrane and non-Cochrane SRs without concern for issues related to double-counting outcome data. If researchers are unsure whether or to what extent the SRs overlap, they can produce a citation matrix and calculate the corrected covered area, and re-assess.

Decision point 4: Are researchers prepared and able to avoid double-counting outcome data from overlapping SRs, by ensuring that each primary study's outcome data are extracted from overlapping SRs only once? When the included SRs overlap, researchers may opt to include all Cochrane and non-Cochrane SRs if they are prepared and able to avoid issues related to identifying overlapping SRs and extracting and analyzing their outcome data (see Table 3.4). An advantage of this inclusion decision is that it is the only way to ensure that all data from all SRs are included in the overview. Disadvantages are that: the non-Cochrane SRs may be older and of lower quality; primary studies contained within non-Cochrane SRs may have been identified by (but excluded from) the Cochrane SRs; and unique challenges exist when extracting and analyzing outcome data from overlapping SRs. If researchers cannot avoid double-counting outcome data from overlapping SRs, they may opt to balance comprehensiveness and complexity by including all non-overlapping SRs; for groups of overlapping SRs, they may opt to include the Cochrane, most recent, or highest quality SR. Using specific criteria to prioritize SR inclusion when confronted with multiple, overlapping SRs can allow researchers to capitalize on the advantages of the previous two inclusion scenarios by avoiding potential issues related to double-counting outcome data while maximizing the amount of data included in the overview. For groups of overlapping SRs, including Cochrane SRs compared to the most recent or highest quality SRs may most effectively minimize both data loss and methodological issues. Researchers may face several challenges if including the most recent or highest quality SRs for groups of overlapping SRs; for example, some SRs may be "tied" for most recent or highest quality, recency of SRs may be operationalized in different ways, data on recency may not be reported in all SRs, and conducting quality assessments may be challenging and time-intensive. However, if including the Cochrane SRs for groups of overlapping SRs, researchers should be aware that multiple Cochrane SRs may contribute outcome data to the same comparison (i.e., Cochrane SRs may sometimes overlap), and not all groups of overlapping SRs may include a Cochrane SR.

Figure 3.1. Decision tool to help researchers make inclusion decisions in overviews (a) and details on application of the decision tool (b). [a] Detailed instructions for assessing primary study overlap can be found in Pieper 2014 [5]; [b] For groups of overlapping SRs, researchers may also choose to include the most relevant SRs or the most comprehensive SRs (though these inclusion decisions were not examined in the current methods study).

Chapter 4

Evaluation of AMSTAR to assess the methodological quality of systematic reviews in overviews of reviews of healthcare interventions

A version of this chapter has been published as: "Pollock M, Fernandes RM, Hartling L. Evaluation of AMSTAR to assess the methodological quality of systematic reviews in overviews of reviews of healthcare interventions. BMC Medical Research Methodology. 2017;17:48". The copyright agreement is in Appendix 1A.

4.1. ABSTRACT

Background

Overviews of reviews (overviews) compile information from multiple systematic reviews (SRs) to provide a single synthesis of relevant evidence for decision-making. It is recommended that authors assess and report the methodological quality of SRs in overviews—for example, using A MeaSurement Tool to Assess systematic Reviews (AMSTAR). Currently, there is variation in whether and how overview authors assess and report SR quality, and limited guidance is available. Our objectives were to: examine methodological considerations involved in using AMSTAR to assess the quality of Cochrane and non-Cochrane SRs in overviews of healthcare interventions; identify challenges (and develop potential decision rules) when using AMSTAR in overviews; and examine the potential impact of considering methodological quality when making inclusion decisions in overviews.

Methods

We selected seven overviews of healthcare interventions and included all SRs meeting each overview's inclusion criteria. For each SR, two reviewers independently conducted AMSTAR assessments with consensus and discussed challenges encountered. We also examined the correlation between AMSTAR assessments and SR results/conclusions.

Results

95 SRs were included (30 Cochrane, 65 non-Cochrane). Mean AMSTAR assessments (9.6/11 *vs.* 5.5/11; $p < 0.001$) and inter-rater reliability (agreement coefficient 1: 0.84 *vs.* 0.69; "almost perfect" vs. "substantial" using the Landis & Koch criteria) were higher for Cochrane compared to non-Cochrane SRs. Four challenges were identified when applying AMSTAR in overviews: the scope of the SRs and overviews often differed; SRs examining similar topics sometimes made different methodological decisions; reporting of non-Cochrane SRs was sometimes poor; and some non-Cochrane SRs included other SRs as well as primary studies. Decision rules were developed to address each challenge. We found no evidence that AMSTAR assessments were correlated with SR results/conclusions.

Conclusions

Results indicate that the AMSTAR tool can be used successfully in overviews that include Cochrane and non-Cochrane SRs, though decision rules may be useful to circumvent common challenges. Findings support existing recommendations that quality assessments of SRs in overviews be conducted independently, in duplicate, with a process for consensus. Results also suggest that using methodological quality to guide inclusion decisions (e.g., to exclude poorly conducted and reported SRs) may not introduce bias into the overview process.

4.2. BACKGROUND

Systematic reviews (SRs) aim to answer a specific clinical question by identifying, selecting, appraising and synthesizing all relevant primary studies using explicit and well-defined methods [1]. The number of published SRs is constantly increasing [2]. To help manage this information overload, overviews of reviews (overviews) have emerged as an increasingly popular knowledge synthesis product. Overviews use explicit and systematic methods to integrate information from multiple related SRs to provide a comprehensive synthesis of all SR evidence related to a specific clinical question [3]. As a result, overviews are broader in scope than any individual SR, and often examine evidence from multiple SRs to assess the efficacy or effectiveness of multiple interventions for preventing or treating one specific clinical condition. Overviews can include both SRs published in and outside of the Cochrane Database of Systematic Reviews (CDSR; referred to as "Cochrane SRs" and "non-Cochrane SRs", respectively). An estimated 48-86% of published overviews include both Cochrane and non-Cochrane SRs, while the remaining overviews include Cochrane SRs only [4-6].

There is consensus in the research community that researchers conducting overviews of healthcare interventions ought to assess and report the methodological quality of the SRs included in their overview [7]. These assessments should ideally be conducted by two independent reviewers, with a process for consensus, and reported transparently [3]. However, researchers conducting overviews have indicated that assessing methodological quality of SRs may be difficult and time-consuming [7]. Studies have indicated that only 37-64% of published overviews assess and report the methodological quality of their included SRs, and among these overviews, there is variation in the methods used [4-6]. This variation is not surprising, as to date there is limited guidance regarding the specific methods that should be used to assess SR quality.

Quality assessments of SRs are important in overviews for two main reasons. First, quality assessments should be used by overview authors when making conclusions in overviews (e.g., to help contextualize the evidence by providing insight into whether and to what extent SR methods may have affected the comprehensiveness and results of overviews). However, it is not known whether and how existing quality assessment criteria need to be modified for use in overviews [7]. Assessing the quality of SRs in the context of overviews may pose unique challenges, and decision rules may be helpful to promote consistent assessments both within and across overview topics. Second, results of quality assessments may help inform inclusion decisions [7]. This may be especially relevant when including non-Cochrane SRs in overviews. On average, non-Cochrane SRs have lower methodological rigor than Cochrane SRs, and the methods and reporting of non-Cochrane SRs can vary widely [8-10]. Researchers conducting overviews have indicated that including lower-quality SRs in overviews can increase the complexity of the overview process because data may be missing, poorly reported, or inconsistently reported in the SRs, and it is unclear what to do in these situations (e.g., should overview authors refer back to the relevant primary studies, or attempt to use the poorly conducted and/or reported SRs?) [7]. However, existing methodological guidance on this topic is conflicting. One potential solution proposed by researchers [7] and employed by overview authors [11-18] is to use the results of methodological quality assessments to identify and exclude SRs with gross deficiencies in conduct and/or reporting that would make the SRs difficult to include and use in overviews. However, using results of quality assessments to inform inclusion decisions may introduce bias if the results and conclusions of these SRs differ systematically from other well-conducted and reported SRs.

A MeaSurement Tool to Assess systematic Reviews (AMSTAR) is the most frequently mentioned tool for assessing SR quality in overviews [7]. AMSTAR consists of eleven questions designed to assess the appropriateness of the methods used at different stages of the SR process, and it has been shown to be reliable, valid, and easy to use when assessing the quality of published SRs [19-21]. The objectives of the present study were: 1) to examine methodological considerations involved in using the AMSTAR tool to assess the quality of Cochrane and non-Cochrane SRs in overviews of healthcare interventions, 2) to identify challenges involved when using AMSTAR in overviews and to develop potential decision rules to overcome these challenges, and 3) to examine the potential impact of considering methodological quality when making inclusion decisions in overviews. To achieve these objectives, we examined AMSTAR assessments, inter-rater reliability of AMSTAR, the association between AMSTAR assessments and inter-rater reliability, and the association between AMSTAR assessments and results and conclusions of SRs, for Cochrane and non-Cochrane SRs.

4.3. METHODS

4.3.1. Sample selection

This descriptive study used a convenience sample of seven overviews of healthcare interventions that were selected from overviews conducted by the Alberta Research Centre for Health Evidence between 2010 to 2016. These overviews examined questions related to the efficacy or effectiveness of multiple interventions for preventing or treating clinical conditions related to pediatric health [22-28]. For each overview topic, all published English-language Cochrane and non-Cochrane SRs that met the overview's inclusion criteria were identified from the reference list of the published overview and included in the study sample. All seven

overviews included Cochrane SRs, and four also included non-Cochrane SRs. For the three overviews that did not include non-Cochrane SRs [23-25], we conducted additional literature searches to locate and include relevant non-Cochrane SRs. The literature searches were conducted by an information specialist using the inclusion criteria and search dates from each overview. Screening and inclusion were conducted independently by two reviewers, with discrepancies resolved by consensus or third party adjudication. For feasibility, we restricted the scope of one overview topic by population (outpatients only) [24]. Search strategies for all overview topics are available in published overviews and upon request.

4.3.2. AMSTAR assessments

Two reviewers used the AMSTAR tool to independently assess the methodological quality of each SR included in the sample. Each of the eleven questions in the AMSTAR tool was answered "yes", "no", "can't answer", or "unable to assess", and discrepancies between reviewers for individual AMSTAR questions were resolved via consensus or third party adjudication. In accordance with other empirical studies assessing measurement properties of AMSTAR [20, 21, 29-32], all items scoring "yes" received one point, and points were summed to a maximum of eleven for each SR.

When conducting AMSTAR assessments, reviewers also independently documented any challenges or issues that arose when assessing AMSTAR in the context of the overview of interest, including which question(s) of the AMSTAR tool were impacted by each challenge and potential reasons why each challenge posed difficulties. Reviewers also independently developed decision rules that could be used to address the challenges identified. Challenges and decision

rules were discussed between reviewers until agreement was reached and were then summarized narratively.

4.3.3. Result and conclusion statement assessments

The following data about the results and conclusions of each included SR were extracted: the outcome data for the first outcome listed in the corresponding overview (see Table 4.1); and the authors' conclusion regarding that outcome, as stated in the abstract, discussion and/or conclusion section of each SR. For SRs that did not contain results data for the overview's first-listed outcome, data were extracted for the overview's second or third-listed outcome, if available. For SRs that included more than one comparison, the outcome data and conclusion statement for the comparison that was listed first in the relevant overview were extracted (as a proxy for the most clinically relevant comparison). Outcome data from the SRs contained within the procedural sedation overview were not extracted, because data for the comparator group were often not available.

Results and conclusions from each SR were classified based on published criteria [33, 34]. Results were classified as "favourable" ($p \leq 0.10$ in favour of the intervention, or finding described as 'significant'), "neutral" ($p > 0.10$, or finding described as 'not different between groups'), or "unfavourable" ($p \leq 0.10$ in favour of the comparator, or finding described as 'favouring non-intervention comparator'). Conclusions were classified as "positive-strong" (authors stated that there was clear evidence of effectiveness, and no further research was required), "positive-weak" (authors stated that there seemed to be evidence of effectiveness, but more research was required to confirm the findings), "neutral" (authors stated that there was no or insufficient evidence about whether the intervention was effective or not, and more research

was required to reach a conclusion), "negative-weak" (authors stated that there seemed to be evidence against use of the intervention, but more research was required to confirm the findings), or "negative-strong" (authors stated that there was clear evidence against use of the intervention, and no further research was required). One reviewer extracted and classified results data, and a second reviewer verified the classifications. Two reviewers independently extracted and classified conclusion statements, and discrepancies were resolved by consensus.

4.3.4. Data analysis

Overall AMSTAR assessments were summarized using means and standard deviations (SD), and independent samples t-tests were used to compare Cochrane and non-Cochrane SRs. Medians and ranges were also examined. The number and percentage of positive responses per AMSTAR question were calculated, and chi square tests were used to compare Cochrane and non-Cochrane SRs. For descriptive purposes, AMSTAR assessments were divided into categories and described using established criteria (AMSTAR assessments of 0-3, 4-7, and 8-11) [17, 35, 36].

Overall inter-rater reliability for AMSTAR overall assessments, and per AMSTAR question, was calculated using the alternative chance-corrected agreement coefficient (AC1) statistic, with 95% confidence intervals (CIs) [37, 38]. The AC1 statistic was used in place of the kappa statistic in order to overcome the limitation of the "kappa paradox", which occurs when high agreement between reviewers results in low kappa scores [39, 40]. Interpretation of the AC1 statistic is similar to the kappa statistic: AC1 ranges from -1.00 (perfect disagreement) to 1.00 (perfect agreement), with a value of zero indicating reliability equivalent to chance. Accordingly, inter-rater reliability was classified using criteria established by Landis & Koch: "less than

chance" (< 0.00), "slight" (0.00–0.20), "fair" (0.21–0.40), "moderate" (0.41–0.60), "substantial" (0.61–0.80), and "almost perfect" (0.81–0.99) [41, 42]. An additional level of classification, "perfect" (1.00), was also added. In addition, overall percent agreement, and percent agreement per AMSTAR question, was also calculated, with 95% CIs; chi square tests were used to compare Cochrane and non-Cochrane SRs per AMSTAR question.

Pearson correlation coefficients were used to correlate AMSTAR assessments and inter-rater reliability for Cochrane and non-Cochrane SRs. The strength of the resulting correlations was described using established criteria as "negligible" (0.00–0.30), "low" (0.30–0.50), "moderate" (0.50–0.70), "high" (0.70–0.90), or "very high" (0.90–1.00) [43]. For non-Cochrane SRs, a post-hoc regression analysis using a quadratic model was also examined (with AMSTAR assessments as the independent variable). The relationships were then depicted graphically.

The distributions of result and conclusion assessments were summarized using the number and percentage of SRs obtaining each classification. Mann-Whitney U-tests were used to examine differences in the breakdown of result and conclusion assessments for Cochrane compared to non-Cochrane SRs, and Spearman correlation coefficients were used to correlate AMSTAR assessments with result and conclusion assessments.

A narrative summary of challenges involved in using AMSTAR in overviews was also provided, and potential solutions were described. AgreeStat 2015.5 was used to calculate AC1 statistics (Advanced Analytics LLC., Gaitherburg, MD, USA). SPSS version 23 was used to analyze numerical data (SPSS Inc., Chicago, IL, USA).

4.4. RESULTS

4.4.1. Study sample

The study sample included 95 SRs—30 Cochrane SRs and 65 non-Cochrane SRs—across seven overview topics (Table 4.1). A list of included SRs, along with their AMSTAR assessments, can be found in Appendix 4A. The mean AMSTAR assessment (/11) for the 95 SRs was 6.8 (SD: 2.9), with ratings ranging from 1 to 11. The mean AMSTAR assessment was 9.6 (SD: 1.6) for Cochrane SRs and 5.5 (SD: 2.4) for non-Cochrane SRs. AMSTAR assessments were significantly higher for Cochrane compared to non-Cochrane SRs by a mean of 4.1 points (95% CI: 3.2, 5.1; $p < 0.001$). This pattern of results was consistent across all overview topics (with the exception of the procedural sedation topic, which had no Cochrane SRs), with mean AMSTAR assessments ranging from 1.4 points to 5.5 points higher per topic area for Cochrane compared to non-Cochrane SRs (Appendix 4B, first table). Eighty-seven percent of the Cochrane SRs had AMSTAR assessments of eight or more, compared to 22% of non-Cochrane SRs. On the other hand, 22% of the non-Cochrane SRs had AMSTAR assessments of three or less, compared to 0% of Cochrane SRs (Figure 4.1a). Although AMSTAR assessments were not normally distributed, mean and median assessments were very similar, and median AMSTAR assessments were higher for Cochrane compared to non-Cochrane SRs both overall and per topic area (Appendix 4B, first table).

On average, Cochrane SRs received more positive responses for each of the eleven questions of the AMSTAR tool than the non-Cochrane SRs. This difference was statistically significant for eight questions (Q1-Q7, Q11; $p \leq 0.045$). For Cochrane SRs, all eleven AMSTAR questions received positive responses more than 50% of the time (range: 53-100% positive responses per question), compared to 5/11 questions for non-Cochrane SRs (range: 14-88% positive responses per question) (Table 4.2, first column).

4.4.2. Inter-rater reliability

The mean inter-rater reliability between reviewers for the 95 included SRs, as classified using the Landis & Koch levels of classification [41], was "substantial" (AC1: 0.74; 95% CI: 0.70, 0.79), with inter-rater reliability per SR ranging from "slight" (AC1: 0.09) to "perfect" (AC1: 1.00). The mean inter-rater reliability was one level higher for Cochrane compared to non-Cochrane SRs: "almost perfect" for Cochrane SRs (AC1: 0.84; 95% CI: 0.77, 0.91) compared to "substantial" for non-Cochrane SRs (AC1: 0.69; 95% CI: 0.64, 0.75) (Figure 4.1b). For the six overview topics that included both Cochrane and non-Cochrane SRs, mean inter-rater reliability ranged from 0.05-0.45 points higher per topic area for Cochrane compared to non-Cochrane SRs, and was at least one level higher for Cochrane SRs for two of the six overview topics (Appendix 4B, first table). The same pattern of results was observed when examining percentage agreement; namely, agreement was higher for Cochrane compared to non-Cochrane SRs both overall, and per topic area (Appendix 4B, first table).

Inter-rater reliability for the eleven individual questions of the AMSTAR tool ranged from "substantial" (Q2, Q8, Q10, Q11) to "perfect" (Q5, Q6) for the Cochrane SRs, and from "moderate" (Q8) to "almost perfect" (Q6) for the non-Cochrane SRs. Inter-rater reliability was at least one level higher for Cochrane compared to non-Cochrane SRs for 8/11 questions (Q1, Q3-Q9) (Table 2, second column). A similar pattern was observed when examining percentage agreement between reviewers: Cochrane compared to non-Cochrane SRs had higher agreement for 9/11 questions (Q1, Q3-Q9, Q11), and this difference was significant for 3/11 questions (Q3, Q5, Q7) (Appendix 4B, second table).

4.4.3. Challenges involved when using AMSTAR in overviews, and potential decision rules

Four main challenges were identified when assessing AMSTAR in the context of overviews. These four challenges primarily affected the AMSTAR questions concerned with quality assessments and data extraction and analysis (i.e., Q5-Q10). Each challenge is described below, along with the decision rule (and rationale) that was developed to help address each challenge (Table 4.3).

First, many non-Cochrane SRs provided limited detail when reporting the characteristics and evaluating the quality of their included primary studies. This often made it difficult to determine whether certain AMSTAR criteria were met, and it was unclear whether deficiencies in SRs were related to methodological quality or reporting. Overview authors rely upon the information reported in the included SRs when conducting their overview; therefore, we recommend awarding points only if the amount and quality of information reported in the SR is sufficient for use at the overview level.

Second, some SRs that examined the same interventions for the same disorder analyzed outcome data in different ways and/or reached different conclusions. It was difficult to determine whether SR methods were appropriate when different SRs used different methodologies, and we were uncertain whether multiple similar SRs should be compared against each other when conducting AMSTAR assessments. In these instances, it may not be possible to objectively determine which conclusions or methods of analysis are most appropriate or valid; therefore, we recommend awarding points only if SR authors provide appropriate justification for why they chose a certain method of analysis and/or why they reached a certain conclusion.

Third, many SRs were broader in scope than the clinical question posed in the overview, meaning that not all primary studies included in the SRs were subsequently included in the overview. Reviewers were unsure whether to assess the quality of the SRs in their entirety or

whether to assess the quality of only those components of the SRs that were relevant to the overview topic. However, attempting to isolate only the components of interest in SRs was unnecessarily difficult and time-consuming, and we agreed that it was important to capture information about the conduct of the SRs as a whole. Therefore, we recommend that overview authors assess the quality of the overall SRs, without trying to "piece apart" only those components that are relevant to the overview topic.

Lastly, difficulties were encountered when assessing the quality of non-Cochrane SRs that included both primary studies and other SRs. It was unclear whether and how to assess the quality of the SRs that were embedded within the original SRs, and we were uncertain whether the AMSTAR assessments of the original SRs should be affected by the quality of the embedded SRs. When conducting AMSTAR assessments, we found that it was often not possible, nor desirable, to integrate the quality of the embedded SRs into the AMSTAR assessments of the original SRs. Therefore, when SRs include both primary studies and other embedded SRs, we recommend that overview authors treat each embedded SR as an independent publication by retrieving and assessing the full text of that SR for inclusion into the overview. The AMSTAR assessments for the overview can then proceed as usual by assessing the quality of each included SR separately.

4.4.4. Association between AMSTAR assessments and inter-rater reliability

For Cochrane SRs, there was a significant positive linear correlation of "moderate" strength between AMSTAR assessments and inter-rater reliability (AC1), $r(29) = 0.62$, $p < 0.001$. Thus, inter-rater reliability increased as quality of Cochrane SRs increased. There was no evidence of a linear correlation between AMSTAR assessments and inter-rater reliability for

non-Cochrane SRs ($p = 0.38$). However, visual examination of the scatterplot (Figure 4.2) suggested a quadratic (curvilinear) relationship, with higher inter-rater reliability for non-Cochrane SRs that received both lower and higher assessments and lower inter-rater reliability for non-Cochrane SRs that received moderate assessments. Therefore, a quadratic model was examined. Though not statistically significant ($p = 0.09$), results suggest that inter-rater reliability may be lower for non-Cochrane SRs with moderate AMSTAR assessments and higher for non-Cochrane SRs with lower and higher ratings (Figure 4.2).

4.4.5. Association between AMSTAR assessments and results and conclusions of systematic reviews

There was no significant difference in the distribution of the results assessments for Cochrane compared to non-Cochrane SRs ($p = 0.14$) (Table 4.4). There was also no significant evidence of correlation between AMSTAR assessments and the direction of effect for the main result of each SR when looking at all SRs combined ($p = 0.53$), Cochrane SRs only ($p = 0.30$), or non-Cochrane SRs only ($p = 0.72$).

The data indicated a significant difference in the distribution of the conclusion assessments for Cochrane compared to non-Cochrane SRs ($p = 0.035$). Specifically, Cochrane SRs reported significantly more "negative" conclusions, whereas non-Cochrane SRs reported significantly more "positive" conclusions (Table 4.4). Despite these group differences, AMSTAR assessments were not correlated with the direction and strength of effect for the main conclusion of each SR when looking at all SRs combined ($p = 0.17$), Cochrane SRs only ($p = 0.68$), or non-Cochrane SRs only ($p = 0.80$).

4.5. DISCUSSION

The current study used a convenience sample of 95 SRs included across seven overview topics to provide empirical evidence on issues surrounding quality assessments of SRs in overviews. This study found that AMSTAR assessments and inter-rater reliability were higher for Cochrane compared to non-Cochrane SRs; these results were consistent within each overview topic and for many of the individual questions of the AMSTAR tool. Minor challenges were encountered when assessing quality of SRs in the context of overviews, but decision rules were developed and recommendations for overview authors were provided. Results also suggested that inter-rater reliability of Cochrane and non-Cochrane SRs may be lower for SRs with moderate AMSTAR assessments and higher for SRs that were assessed as strong or weak. Consistent with a previous study [33], we found that the conclusions, but not the results, of Cochrane and non-Cochrane SRs differed systematically, indicating that different author groups weighed outcomes differently when coming to an overall conclusion or interpreted similar outcome data in different ways. However, we found no evidence that AMSTAR assessments were correlated with results or conclusions of SRs.

Taken together, the results of the current study suggest that AMSTAR is a useful tool for assessing the quality of Cochrane and non-Cochrane SRs in overviews. Authors should be aware of some minor challenges they may face when applying AMSTAR in overviews. Specifically, there may be deficiencies in the reporting of some SRs; SRs examining similar topics may sometimes make different methodological decisions; the scope of some SRs may differ from, or be broader than, the scope of the overview; and some non-Cochrane SRs may include other SRs as well as primary studies. We recommend that overview authors use *a priori* decision rules, such as those presented in Table 4.4, to circumvent these challenges and help ensure consistent

judgments across reviewers. In addition, Cochrane currently recommends that quality assessments of SRs in overviews be conducted independently, in duplicate, with a process for consensus [3], and the results of this study provide empirical evidence to support this recommendation. Specifically, Cochrane SRs showed some variation in AMSTAR assessments and inter-rater reliability, and non-Cochrane SRs had lower AMSTAR assessments and inter-rater reliability combined with higher variation for both of these variables. To promote transparency, we also recommend that overview authors provide breakdowns of individual AMSTAR questions for all included SRs.

The current study found that the AMSTAR tool can be used with high inter-rater reliability to successfully identify SRs with lower quality assessments that may be difficult to use in overviews due to gross deficiencies in conduct and reporting. This study also found that AMSTAR assessments were not correlated with results or conclusions of SRs. The lack of correlation may be due to a common criticism of AMSTAR—namely, that AMSTAR may actually assess quality of reporting as well as (or instead of) methodological quality [44-46]. Quality of reporting may not necessarily be associated with SR results and conclusions. However, reporting is closely tied to usability of SRs in overviews, since overview authors cannot effectively use SRs in overviews if the data are missing, inadequately reported, or reported inconsistently [7]. The results of this study suggest that overview authors may consider using AMSTAR assessments to guide inclusion decisions (e.g., to identify and exclude poorly conducted and/or reported SRs that may be difficult to use in overviews). Using the AMSTAR tool to inform inclusion decisions may not introduce bias into the overview process since the results and conclusions of SRs assessed as weak and strong did not differ systematically. However, overview authors should use their judgment when deciding whether or not to use

results of AMSTAR assessments to guide inclusion decisions. Factors to consider include the quality of the overall body of SR evidence and the purpose of the overview. For example, overview authors may not need to include poorly conducted and reported SRs when there are adequately conducted SRs that address all main interventions and outcomes of interest. In contrast, they may choose to retain poorly conducted and reported SRs when the overall body of SR evidence is generally poor or when the purpose of the overview is to describe the complete body of SR evidence on a topic. Though overall AMSTAR assessments may obscure effects of individual questions [47], SRs that score poorly across most AMSTAR domains likely have multiple serious limitations that subsequently make them difficult to include and use in overviews. To promote transparency, overview authors should establish *a priori* decision rules indicating whether and how quality assessments will be used to inform inclusion decisions; authors should also clearly indicate in their overview which SRs (if any) were excluded based on results of quality assessments or specific methodological deficiencies.

This study identified areas where authors can enhance the conduct and/or reporting of their Cochrane and non-Cochrane SRs. Previous research shows that Cochrane SRs generally have higher methodological rigour than non-Cochrane SRs [8-10], and the results of the current study extend this finding to SRs included in a sample of overviews. Non-Cochrane SRs showed room for improvement for all but two AMSTAR domains (Q6: study characteristics; Q9: methods to combine studies). However, not all Cochrane SRs received high assessments (13% were rated between 4-7 on AMSTAR), and two AMSTAR domains (Q10: publication bias; Q11: conflicts of interest) showed considerable room for improvement. This study also found that inter-rater reliability varied in conjunction with both AMSTAR assessments and type of SR (Cochrane, non-Cochrane). Inter-rater reliability was lower for SRs that obtained moderate

AMSTAR assessments (as opposed to very weak or strong assessments); it was also lower for non-Cochrane SRs both overall and for many of the individual AMSTAR domains (e.g., Q3: search strategy; Q7: scientific quality; Q8: formulating conclusions). This may be because discrete "yes/no" judgments become more difficult when quality and/or reporting is mediocre, or when only some criteria for multi-part questions are addressed in the SR. The variable reporting of non-Cochrane SRs, combined with limits on manuscript length, may also contribute to difficulties conducting AMSTAR assessments. Adhering to accepted standards of conduct and reporting, such as the methods guidance contained within the *Cochrane Handbook for Systematic Reviews of Interventions* [48] and the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) reporting guidelines [49], can help ensure adequate quality and reporting of SRs (and may also increase the inter-rater reliability of quality assessments for SRs). This could, in turn, make SRs easier to assess, include, and use in overviews.

The current study used a convenience sample of overview topics that met specific inclusion criteria and shared certain characteristics (e.g., all overviews were conducted by our research group and examined interventions for disorders related to pediatric health). Though the researchers conducting this study were authors of all included overviews, they were only authors of three of the 95 included SRs, and duplicate independent quality assessments were conducted to mitigate the potential for reviewer bias. It is possible that the overview topics selected for this study may have influenced the results to some extent; however, to increase the generalizability of the knowledge gained from this study, overviews were selected that examined a range of populations (e.g., infants, children, adolescents), interventions (e.g., pharmacological, non-pharmacological), comparators (e.g., placebo, active comparators), research questions (e.g.,

prevention, treatment), and topic areas (e.g., acute respiratory infections, gastrointestinal diseases, skin disorders). In addition, we found that the AMSTAR assessments obtained for the SRs in our sample of seven overviews fell within the range of scores observed in a broader sample of overviews (all relevant overviews identified by [4] and [5] and contained within issue 12, 2016 of the CDSR). Our inter-rater reliability assessments were also similar to published data on agreement for AMSTAR [50]. Thus, the results of the current study, and subsequent recommendations for quality assessment of SRs in overviews, may generalize to a range of overviews examining healthcare interventions. However, results and recommendations should not be generalized to overviews that address broader or different clinical questions (e.g., diagnostic test accuracy, prognostic, or qualitative overviews).

It should be noted that there is debate surrounding whether or not overall AMSTAR scores should be calculated. The developers of AMSTAR addressed this concern by ensuring (through statistical analysis) that the component questions do not overlap and by validating the overall score against an external standard. Thus, they concluded that the overall score is meaningful [21]. However, overall quality scores assume that all questions are equal (which can be difficult to justify) [50, 51], summing individual items may artificially increase the precision of the assessment, and studies have shown that incorporating overall quality of primary studies into meta-analyses can alter effect estimates in SRs [52, 53]. Despite the uncertainty regarding use of summary scores, there is a precedent for calculating and reporting overall AMSTAR assessments both in empirical studies assessing measurement properties of AMSTAR [20, 21, 29-32, 54-56] and in overviews of healthcare interventions [16, 18, 35, 36, 57-71], and incorporating overall quality of SRs into results of overviews has not been found to alter overview results [72]. Other potential limitations of AMSTAR may include difficulty

meaningfully differentiating between several of the response options ("no", "not applicable", and "can't answer") and difficulty answering multi-part questions when only some criteria are met [44, 45]. There are also no questions in the AMSTAR tool examining whether appropriate methods were used in SRs to assess the quality of a body of evidence or to conduct subgroup and/or sensitivity analyses [44, 45], and in the context of overviews AMSTAR cannot capture potentially important differences in comprehensiveness and recency of searches across SRs. As previously mentioned, the AMSTAR tool may also assess aspects related to quality of reporting as opposed to methodological quality [44-46]. Despite these potential limitations, the results of this study demonstrate that reviewers can conduct AMSTAR assessments with adequate inter-rater reliability, using decision rules to help overcome some of the above-listed challenges.

In addition to AMSTAR, other quality assessment tools exist. AMSTAR 2 is currently being developed in response to feedback from users of the original AMSTAR tool [73], and the ROBIS tool was recently published to assess issues related to the risk of bias (as opposed to the methodological quality) of SRs [74]. Methodological research examining the reliability, validity, and feasibility of AMSTAR 2 and ROBIS in overviews would be valuable. In addition, research comparing AMSTAR, AMSTAR 2 and ROBIS on important outcomes (e.g., quality assessments, inter-rater reliability, and time to complete assessments) and across important comparisons (e.g., Cochrane vs. non-Cochrane SRs, SRs with meta-analyses vs. narrative summaries, and publication year of SRs) may provide insight into the trade-offs involved in selecting one tool over another for use in overviews.

4.6. CONCLUSIONS

There is currently limited guidance available for researchers conducting overviews of healthcare interventions. This gap in guidance is most pronounced when examining methods for conducting the latter stages of the overview process (e.g., quality assessments and data extraction and analysis). The current study plays a role in addressing this gap in guidance. It contributes empirical evidence and recommendations regarding the use of the AMSTAR tool to assess the methodological quality of SRs in overviews. Based on the results of this study, we show that AMSTAR can be used successfully to assess the methodological quality of both Cochrane and non-Cochrane SRs included in overviews of healthcare interventions. When using AMSTAR in overviews, individual assessments should be reported for each of the eleven questions of the AMSTAR tool. Results of quality assessments of SRs can then be used alongside quality assessments of primary studies and outcome data to help contextualize the results and conclusions of overviews.

4.7. REFERENCES

1. Green S, Higgins JPT, Alderson P, Clarke M, Mulrow CD, Oxman AD. Chapter 1: Introduction. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.1.0). The Cochrane Collaboration; 2011. http://www.handbook.cochrane.org.
2. Bastian H, Glasziou P, Chalmers I. Seventy-five trials and eleven systematic reviews a day: how will we ever keep up? PLoS Med. 2010;7(9):e1000326.
3. Becker LA, Oxman AD. Chapter 22: overviews of reviews. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.1.0). The Cochrane Collaboration; 2011. http://www.handbook.cochrane.org.

4. Hartling L, Chisholm A, Thomson D, Dryden DM. A descriptive analysis of overviews of reviews published between 2000 and 2011. PLoS One. 2012;7(11):e49667.
5. Pieper D, Buechter R, Jerinic P, Eikermann M. Overviews of reviews often have limited rigor: a systematic review. J Clin Epidemiol. 2012;65(12):1267-73.
6. Li L, Tian J, Tian H, Sun R, Liu Y, Yang K. Quality and transparency of overviews of systematic reviews. J Evid Based Med. 2012;5(3):166-73.
7. Pollock M, Fernandes RM, Becker LA, Featherstone R, Hartling L. What guidance is available for researchers conducting overviews of reviews of healthcare interventions? A scoping review and qualitative metasummary. Syst Rev. 2016;5:190.
8. Page MJ, Shamseer L, Altman DG, Tetzlaff J, Sampson M, Tricco AC, *et al*. Epidemiology and reporting characteristics of systematic reviews of biomedical research: a cross-sectional study. PLoS Med. 2016;13(5):e1002028.
9. Fleming PS, Seehra J, Polychronopoulou A, Fedorowicz Z, Pandis N. Cochrane and non-Cochrane systematic reviews in leading orthodontic journals: a quality paradigm? Eur J Orthod. 2013;35(2):244-8.
10. MacDonald SL, Canfield SE, Fesperman SF, Dahm P. Assessment of the methodological quality of systematic reviews published in the urological literature from 1998 to 2008. J Urol. 2010;184(2):648-53.
11. Bennett K, Manassis K, Duda S, Bagnell A, Bernstein GA, Garland EJ, *et al*. Preventing child and adolescent anxiety disorders: overview of systematic reviews. Depress Anxiety. 2015;32(12):909-18.

12. Bennett K, Rhodes AE, Duda S, Cheung AH, Manassis K, Links P, *et al*. A youth suicide prevention plan for Canada: a systematic review of reviews. Can J Psychiatry. 2015;60(6):245-57.
13. Fishta A, Backe EM. Psychosocial stress at work and cardiovascular diseases: an overview of systematic reviews. Int Arch Occup Environ Health. 2015;88(8):997-1014.
14. Misfeldt R, Linder J, Lait J, Hepp S, Armitage G, Jackson K, *et al*. Incentives for improving human resource outcomes in health care: overview of reviews. J Health Serv Res Policy. 2014;19(1):52-61.
15. Patnode CD, Henderson JT, Thompson JH, Senger CA, Fortmann SP, Whitlock EP. Behavioral counseling and pharmacotherapy interventions for tobacco cessation in adults, including pregnant women: a review of reviews for the U.S. Preventive Services Task Force. Rockville: Agency for Healthcare Research and Quality, 2015.
16. Remes O, Brayne C, van der Linde R, Lafortune L. A systematic review of reviews on the prevalence of anxiety disorders in adult populations. Brain Behav. 2016;6(7):e00497.
17. Ryan R, Santesso N, Lowe D, Hill S, Grimshaw J, Prictor M, *et al*. Interventions to improve safe and effective medicines use by consumers: an overview of systematic reviews. Cochrane Database Syst Rev. 2014;4:CD007768.
18. Worswick J, Wayne SC, Bennett R, Fiander M, Mayhew A, Weir MC, *et al*. Improving quality of care for persons with diabetes: an overview of systematic reviews - what does the evidence tell us? Syst Rev. 2013;2:26.
19. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, *et al*. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 2007;7:10.

20. Shea BJ, Bouter LM, Peterson J, Boers M, Andersson N, Ortiz Z, *et al*. External validation of a measurement tool to assess systematic reviews (AMSTAR). PLoS One. 2007;2(12):e1350.
21. Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J, *et al*. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol. 2009;62(10):1013-20.
22. Pollock M, Sinha I, Hartling L, Rowe BH, Schrieber S, Fernandes RM. Inhaled short-acting bronchodilators for managing emergency childhood asthma: an overview of reviews. Allergy. 2017;72(2):183-200 [Electronic publication: 05 Oct 2016].
23. Oleszczuk M, Fernandes RM, Thomson D, Shaikh N. The Cochrane Library and acute otitis media in children: an overview of reviews. Evid Based Child Health. 2012;7(2):393-402.
24. Bialy L, Foisy M, Smith M, Fernandes RM. The Cochrane Library and the treatment of bronchiolitis in children: an overview of reviews. Evid Based Child Health. 2011;6(1):258-75.
25. Bjornson C, Russell K, Foisy M, Johnson DW. The Cochrane Library and the treatment of croup in children: an overview of reviews. Evid Based Child Health. 2010;5(4):1555-65.
26. Foisy M, Boyle RJ, Chalmers JR, Simpson EL, Williams HC. The prevention of eczema in infants and children: an overview of Cochrane and non-Cochrane reviews. Evid Based Child Health. 2011;6(5):1322-39.
27. Freedman SP, Ali S, Oleszczuk M, Gouin S, Hartling L. Treatment of acute gastroenteritis in children: an overview of systematic reviews of interventions commonly used in developed countries. Evid Based Child Health. 2013;8(4):1123-37.

28. Hartling L, Milne A, Foisy M, Lang E, Sinclair D, Klassen TP, *et al*. What works and what's safe in pediatric emergency procedural sedation: an overview of reviews. Acad Emerg Med. 2016;23(5):519-30.
29. Kang D, Wu Y, Hu D, Hong Q, Wang J, Zhang X. Reliability and external validity of AMSTAR in assessing quality of TCM systematic reviews. Evid Based Compliment Alternat Med. 2012;2012:732195.
30. Melchiors AC, Correr CJ, Venson R, Pontarolo R. An analysis of quality of systematic reviews on pharmacist health interventions. Int J Clin Pharm. 2012;34(1):32-42.
31. Passon AM, Drabik A, Sawicki PT. Quality scores do not predict discrepant statistical significances among meta-analyses on different targets of glycemic control in type 2 diabetes. J Clin Epidemiol. 2013;66(12):1356-66.
32. Weed DL, Althuis MD, Mink PJ. Quality of reviews on sugar-sweetened beverages and health outcomes: a systematic review. Am J Clin Nutr. 2011;94(5):1340-7.
33. Tricco AC, Tetzlaff J, Pham B, Brehaut J, Moher D. Non-Cochrane vs. Cochrane reviews were twice as likely to have positive conclusion statements: cross-sectional study. J Clin Epidemiol. 2009;62(4):380-6.
34. Lai NM, Teng CL, Lee ML. Interpreting systematic reviews: are we ready to make our own conclusions? A cross-sectional study. BMC Med. 2011;9:30.
35. Flodgren G, Eccles MP, Shepperd S, Scott A, Parmelli E, Beyer FR. An overview of reviews evaluating the effectiveness of financial incentives in changing healthcare professional behaviours and patient outcomes. Cochrane Database Syst Rev. 2011;7:CD009255.
36. Payne C, Wiffen PJ, Martin S. Interventions for fatigue and weight loss in adults with advanced progressive illness. Cochrane Database Syst Rev. 2012;1:CD008427.

37. Gwet KL. Handbook of inter-rater reliability: the definitive guide to measuring the extent of agreement among raters. 2nd ed. Gaithersburg: Advanced Analytics, LLC; 2010.
38. Gwet KL. Computing inter-rater reliability and its variance in the presence of high agreement. Br J Math Stat Psychol. 2008;61(Pt 1):29-48.
39. Feinstein AR, Cicchetti DV. High agreement but low kappa: I. The problems of two paradoxes. J Clin Epidemiol. 1990;43(6):543-9.
40. Viera AJ, Garrett JM. Understanding interobserver agreement: the kappa statistic. Fam Med. 2005;37(5):360-3.
41. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33(1):159-74.
42. Berkman ND, Lohr KN, Morgan LC, Kuo TM, Morton SC. Interrater reliability of grading strength of evidence varies with the complexity of the evidence in systematic reviews. J Clin Epidemiol. 2013;66(10):1105-17.
43. Hinkle DE, Wiersma W, Jurs SG. Applied statistics for the behavioral sciences. 5th ed. Boston: Houghton Mifflin; 2002.
44. Burda BU, Holmer HK, Norris SL. Limitations of A Measurement Tool to Assess Systematic Reviews (AMSTAR) and suggestions for improvement. Syst Rev. 2016;5:58.
45. Wegewitz U, Weikert B, Fishta A, Jacobs A, Pieper D. Resuming the discussion of AMSTAR: what can (should) be made better? BMC Med Res Methodol. 2016;16:111.
46. Faggion CM. Critical appraisal of AMSTAR: challenges, limitations, and potential solutions from the perspective of an assessor. BMC Med Res Methodol. 2015;15:63.
47. Juni P, Altman DG, Egger M. Systematic reviews in health care: assessing the quality of controlled clinical trials. BMJ. 2001;323(7303):42-6.

48. Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.1.0). The Cochrane Collaboration; 2011. http://www.handbook.cochrane.org.
49. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
50. Pieper D, Buechter RB, Li L, Prediger B, Eikermann M. Systematic review found AMSTAR, but not R(evised)-AMSTAR, to have good measurement properties. J Clin Epidemiol. 2014; 68(5):574-83.
51. Higgins JPT, Altman DG, Sterne JAC. Chapter 8: assessing risk of bias in included studies. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.1.0). The Cochrane Collaboration; 2011. http://www.handbook. cochrane.org.
52. Juni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. JAMA. 1999;282(11):1054-60.
53. Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, *et al*. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? Lancet. 1998;352(9128):609-13.
54. Faggion CM, Schmitter M. Using the best available evidence to support clinical decisions in implant dentistry. Int J Oral Maxillofac Implants. 2010;25(5):960-9.
55. Popovich I, Windsor B, Jordan V, Showell M, Shea B, Farquhar CM. Methodological quality of systematic reviews in subfertility: a comparison of two different approaches. PLoS One. 2012;7(12):e50403.
56. Tunis AS, McInnes MD, Hanna R, Esmail K. Association of study quality with completeness of reporting: have completeness of reporting and quality of systematic reviews and meta-

analyses in major radiology journal changed since publication of the PRISMA statement? Radiology. 2013;269(2):413-26.

57. Andersen JH, Fallentin N, Thomsen JF, Mikkelsen S. Risk factors for neck and upper extremity disorders among computers users and the effect of interventions: an overview of systematic reviews. PLoS One. 2011;6(5):e19691.
58. Berkhof M, van Rijssen HJ, Schellart AJ, Anema JR, van der Beek AJ. Effective training strategies for teaching communication skills to physicians: an overview of systematic reviews. Patient Educ Couns. 2011;84(2):152-62.
59. Brouwers MC, Garcia K, Makarski J, Daraz L. The landscape of knowledge translation interventions in cancer control: what do we know and where to next? A review of systematic reviews. Implement Sci. 2011;6:130.
60. Cates CJ, Oleszczuk M, Stovold E, Wieland LS. Safety of regular formoterol or salmeterol in children with asthma: an overview of Cochrane reviews. Cochrane Database Syst Rev. 2012;10:CD010005.
61. Cates CJ, Wieland LS, Oleszczuk M, Kew KM. Safety of regular formoterol or salmeterol in adults with asthma: an overview of Cochrane reviews. Cochrane Database Syst Rev. 2014;2:CD010314.
62. Jones L, Othman M, Dowswell T, Alfirevic Z, Gates S, Newburn M, *et al*. Pain management for women in labour: an overview of systematic reviews. Cochrane Database Syst Rev. 2012;3:CD009234.
63. Kumar A, Galeb S, Djulbegovic B. Treatment of patients with multiple myeloma: an overview of systematic reviews. Acta Haematol. 2011;125(1-2):8-22.

64. Leucht S, Hierl S, Kissling W, Dold M, Davis JM. Putting the efficacy of psychiatric and general medicine medication into perspective: review of meta-analyses. Br J Psychiatry. 2012;200(2):97-106.

65. List T, Axelsson S. Management of TMD: evidence from systematic reviews and meta-analyses. J Oral Rehabil. 2010;37(6):430-51.

66. Mikton C, Butchart A. Child maltreatment prevention: a systematic review of reviews. Bull World Health Organ. 2009;87(5):353-61.

67. O'Connell NE, Wand BM, McAuley J, Marston L, Moseley GL. Interventions for treating pain and disability in adults with complex regional pain syndrome. Cochrane Database Syst Rev. 2013;4:CD009416.

68. Oestergaard S, Moldrup C. Improving outcomes for patients with depression by enhancing antidepressant therapy with non-pharmacological interventions: a systematic review of reviews. Public Health. 2011;125(6):357-67.

69. Welsh EJ, Evans DJ, Fowler SJ, Spencer S. Interventions for bronchiectasis: an overview of Cochrane systematic reviews. Cochrane Database Syst Rev. 2015;7:CD010337.

70. Wu L, Norman G, Dumville JC, O'Meara S, Bell-Syer SE. Dressings for treating foot ulcers in people with diabetes: an overview of systematic reviews. Cochrane Database Syst Rev. 2015;7:CD010471.

71. Zwicker JG, Mayson TA. Effectiveness of treadmill training in children with motor impairments: an overview of systematic reviews. Pediatr Phys Ther. 2010;22(4):361-77.

72. Pieper D, Mathes T, Eikermann M. Impact of choice of quality appraisal tool for systematic reviews in overviews. J Evid Based Med. 2014;7(2):72-8.

73. Shea B, Henry D. Development of AMSTAR 2. Abstracts of the 24th Cochrane Colloquium, 23-27 Oct 2016. Seoul, Korea: John Wiley & Sons; 2016.
74. Whiting P, Savovic J, Higgins JP, Caldwell DM, Reeves BC, Shea B, *et al*. ROBIS: a new tool to assess risk of bias in systematic reviews was developed. J Clin Epidemiol. 2016;69:225-34.
75. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, *et al*. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Controlled Clin Trials. 1996;17(1):1-12.

Table 4.1. Overview topics and their included systematic reviews.

Overview topic	Author, Year (reference)	First outcome listed in overview	Number of included systematic reviews		
			Cochrane	Non-Cochrane	Total
Acute asthma	Pollock, 2017 [22]	Hospital admission	7	6	**13**
Acute otitis media	Oleszczuk, 2012 [23]	Pain early in therapy	6	10	**16**
Bronchiolitis	Bialy, 2011 [24]	Hospital admission	4	3	**7**
Croup	Bjornson, 2010 [25]	Clinical score	4	2	**6**
Eczema	Foisy, 2011 [26]	Incidence of eczema	6	19	**25**
Gastroenteritis	Freedman, 2013 [27]	Hospital admission	3	12	**15**
Procedural sedation	Hartling, 2016 [28]	Adverse effects[a]	0	13	**13**
Total			**30**	**65**	**95**

[a] We were unable to extract primary outcome data from the systematic reviews included within the procedural sedation overview because data for the comparator group were often not available.

Table 4.2. Positive responses and inter-rater reliability per AMSTAR question, for Cochrane and non-Cochrane systematic reviews.

AMSTAR question	Positive responses *n* (%)			Inter-rater reliability AC1 (95% confidence interval)		
	Cochrane (*n* = 30)	Non-Cochrane (*n* = 65)	Difference between groups (*p*-value for chi square test)	Cochrane (*n* = 30)	Non-Cochrane (*n* = 65)	Difference between groups (Landis & Koch criteria) [41]
1. Was an "*a priori*" design provided?	29 (96.7%)[a]	10 (15.4%)	< 0.001[b]	0.93 (0.82, 1.00)	0.78 (0.63, 0.92)	"Almost perfect" vs. "substantial"[c]
2. Was there duplicate study selection and data extraction?	24 (80.0%)	21 (32.3%)	< 0.001[b]	0.65 (0.36, 0.93)	0.75 (0.59, 0.91)	"Substantial" vs. "substantial"
3. Was a comprehensive literature search performed?	30 (100.0%)	42 (64.6%)	< 0.001[b]	0.96 (0.89, 1.00)	0.64 (0.44, 0.83)	"Almost perfect" vs. "substantial"[c]
4. Did the authors search for reports regardless of their publication type?	27 (90.0%)	23 (35.4%)	< 0.001[b]	0.85 (0.68, 1.00)	0.72 (0.55, 0.89)	"Almost perfect" vs. "substantial"[c]
5. Was a list of studies (included and excluded) provided?	30 (100.0%)	24 (36.9%)	< 0.001[b]	1.00 (1.00, 1.00)	0.65 (0.47, 0.84)	"Perfect" vs. "substantial"[c]
6. Were the characteristics of the included studies provided?	30 (100.0%)	57 (87.7%)	0.045[b]	1.00 (1.00, 1.00)	0.91 (0.82, 0.99)	"Perfect" vs. "almost perfect"[c]
7. Was the scientific quality of the included studies assessed and documented?	29 (96.7%)	39 (60.0%)	< 0.001[b]	0.97 (0.89, 1.00)	0.62 (0.43, 0.82)	"Almost perfect" vs. "substantial"[c]
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	26 (86.7%)	47 (72.3%)	0.12	0.79 (0.59, 0.99)	0.60 (0.40, 0.80)	"Substantial" vs. "moderate"[c]
9. Were the methods used to combine the findings of studies appropriate?	28 (93.3%)	55 (84.6%)	0.23	0.84 (0.66, 1.00)	0.69 (0.52, 0.87)	"Almost perfect" vs. "substantial"[c]
10. Was the likelihood of publication bias assessed?	16 (53.3%)	30 (46.2%)	0.52	0.67 (0.39, 0.95)	0.71 (0.53, 0.88)	"Substantial" vs. "substantial"
11. Was the conflict of interest stated?	19 (63.3%)	9 (13.9%)	< 0.001[b]	0.75 (0.51, 1.00)	0.65 (0.46, 0.84)	"Substantial" vs. "substantial"

[a] One Cochrane systematic review did not have a protocol for reasons explained in the "Notes" section of the manuscript (Kramer MS, Kakuma R. Optimal duration of exclusive breastfeeding. Cochrane Database Syst Rev. 2002;1:CD003517); [b] Significant in favour of Cochrane systematic reviews; [c] Inter-rater reliability for Cochrane systematic reviews was at least one level higher.

Table 4.3. Description of challenges identified when using AMSTAR in overviews, with corresponding recommendations.

Challenge	Domain(s) affected	Explanation	Decision rule	Rationale
Many non-Cochrane SRs provided limited detail when reporting the characteristics and quality of their included primary studies.	Q6: Were the characteristics of the included studies provided? Q7: Was the scientific quality of the included studies assessed and documented?	Q6: Some SRs presented only aggregate study characteristics; others provided insufficient detail about the populations, interventions, comparators, outcome assessments, and/or study settings. Q7: Non-Cochrane SRs used various quality assessment tools including the Cochrane Risk of Bias tool [51], the Jadad tool [75], and additional lesser-known tools. The Risk of Bias tool was often applied inconsistently across SRs, with different SRs assessing and reporting different domains.	Award point(s) only if the amount and quality of information reported in the SR is sufficient for use at the overview level.	Overview authors rely upon the primary study information as it is reported in the included SRs, and overview quality may be compromised due to inadequate reporting of SRs.
Some SRs that examined the same interventions for the same disorder analyzed outcome data differently and/or came to different conclusions.	Q8: Was the scientific quality of the included studies used appropriately in formulating conclusions? Q9: Were the methods used to combine the findings of studies appropriate?	There were several instances where one SR conducted meta-analyses while another SR examining the same intervention for the same disorder presented narrative summaries only. In several instances, these SRs also reached different conclusions.	Award point(s) if authors provide appropriate justification for why they chose their method of data analysis and/or how they came to a particular conclusion.	It may not be possible to objectively determine whether the conclusions or methods of analysis of one SR were more appropriate or valid than those in another, similar SR. It is more objective to examine the authors' justification for whichever decisions were made.

Some SRs were broader in scope than the overview's clinical question, meaning that some primary studies included in the SRs were excluded from the overview.	Q5: Was a list of studies (included and excluded) provided? Q6, Q7, Q8, Q9: See above. Q10: Was the likelihood of publication bias assessed?	For both Cochrane and non-Cochrane SRs, there were many instances where the scope of the SRs were broader than those of the corresponding overviews. For example, an overview that is restricted to children only will aim to exclude adult data from primary studies contained within relevant SRs.	Assess quality of the SRs overall; do not try to "piece apart" the SRs to assess only those parts that are relevant.	It is important to capture information about the conduct of the SR as a whole; attempting to isolate only the primary studies of interest is unnecessarily difficult.
Some non-Cochrane SRs, such as those produced for government or research organizations, searched for and included other SRs as well as primary studies. It was difficult to assess the quality of the 'original' SRs when they also included other 'embedded' SRs.	Q5, Q6, Q7, Q8, Q9, Q10: See above.	The 'original' non-Cochrane SRs often did not provide sufficient information about their 'embedded' SRs (or the studies contained within the embedded SRs). This scenario also raises a number of questions for which there are no adequate answers. For example, would the original SR be awarded a point for Q5 if it did not contain a list of the primary studies included in each of its embedded SRs?	Assess the 'embedded' SRs for inclusion into the overview. If any of them meet the inclusion criteria, obtain and refer to the full-text of these SRs and treat them as independent publications (in place of using the descriptions provided in the 'original' SR).	It is likely not possible, nor desirable, to integrate the 'embedded' SRs with the primary studies included in the 'original' SR.

Table 4.4. Distribution of result and conclusion assessments for Cochrane and non-Cochrane systematic reviews.

Result and conclusion assessments	Distribution of responses, *n* (%)		Difference between groups (*p*-value for Mann-Whitney U-test)
	Cochrane systematic reviews (*n* = 28[a])	Non-Cochrane systematic reviews (*n* = 43[a])	
Results			
Unfavourable	4 (14.3%)	0 (0.0%)	
Neutral	14 (50.0%)	23 (53.5%)	0.14
Favourable	10 (35.7%)	20 (46.5%)	
Conclusions			
Negative-Strong	6 (21.4%)	1 (2.3%)	
Negative-Weak	6 (21.4%)	7 (16.3%)	
Neutral	3 (10.7%)	7 (16.3%)	0.035[b]
Positive-Weak	7 (25.0%)	13 (30.2%)	
Positive-Strong	6 (21.4%)	15 (34.9%)	

[a] Twenty-four systematic reviews (2 Cochrane, 22 non-Cochrane) were excluded from this analysis because they did not contain relevant outcome data; [b] Conclusions of Cochrane systematic reviews were more likely to be "negative" and conclusions of non-Cochrane systematic reviews were more likely to be "positive".

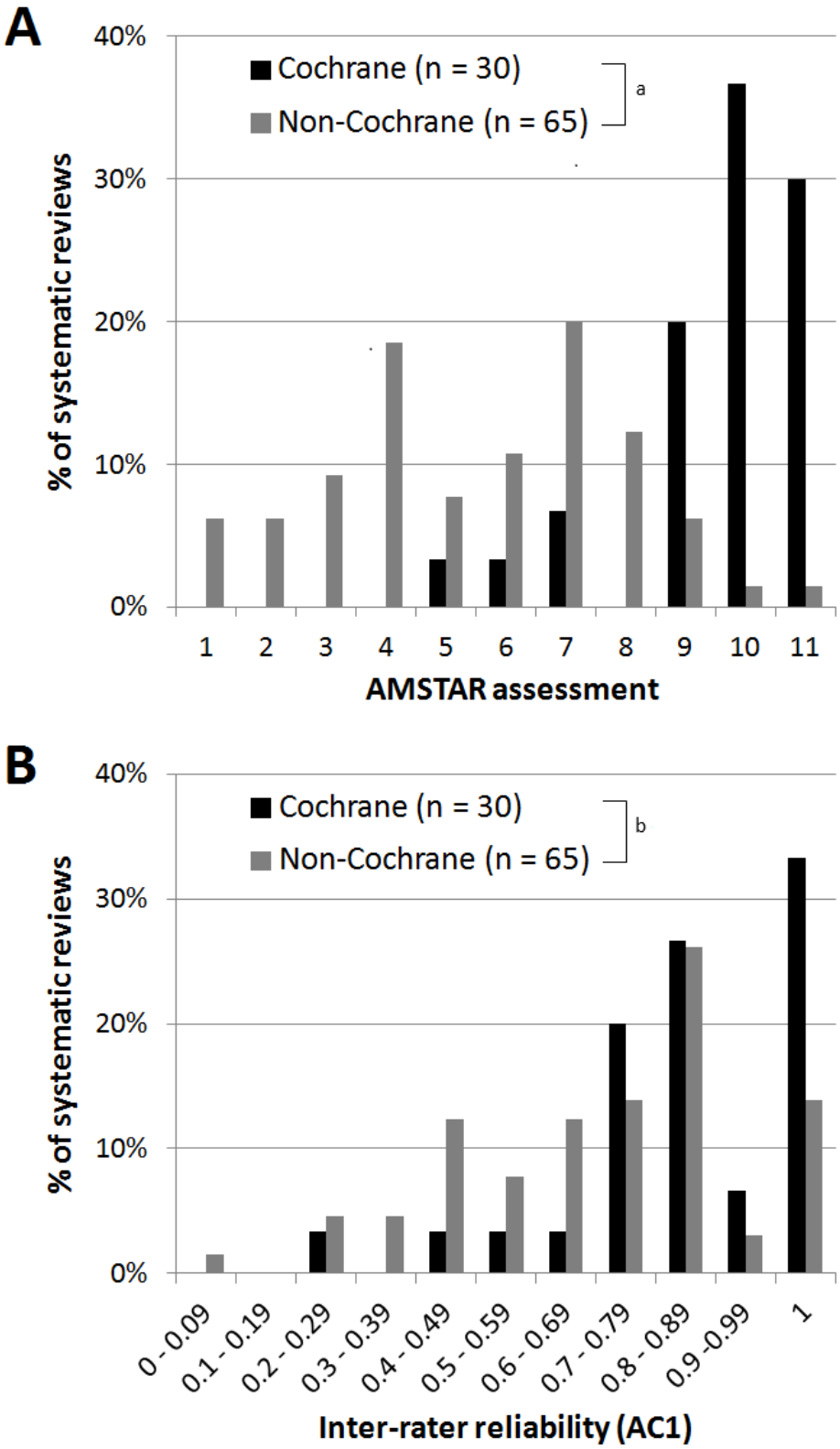


Figure 4.1. AMSTAR assessments (a), and inter-rater reliability (b), for Cochrane and non-Cochrane systematic reviews. [a] $p < 0.001$ in favour of Cochrane systematic reviews (independent samples t-test); [b] Mean inter-rater reliability was one level higher for Cochrane compared to non-Cochrane SRs ("almost perfect" vs. "substantial").

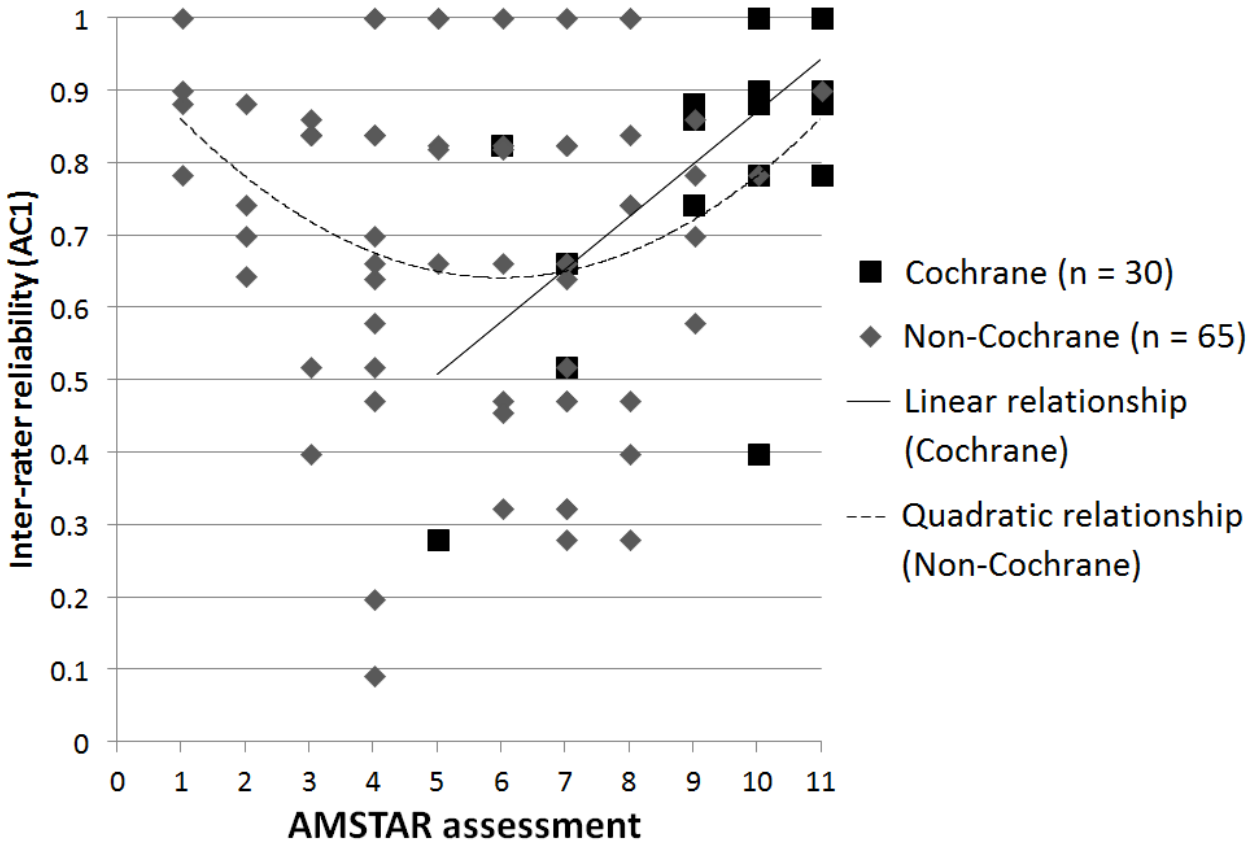


Figure 4.2. Relationship between AMSTAR assessments and inter-rater reliability, for Cochrane and non-Cochrane systematic reviews. Linear relationship (Cochrane): $p < 0.001$; Quadratic relationship (non-Cochrane): $p = 0.09$.

Chapter 5

Preferred Reporting Items for Overviews of Reviews (PRIOR): a protocol for development of a reporting guideline for overviews of reviews of healthcare interventions

This chapter has been formatted for submission to "Systematic Reviews". The author list will be finalized prior to submission.

5.1. ABSTRACT

Background

Overviews of reviews (overviews) compile information from multiple systematic reviews to provide a single synthesis of relevant evidence for healthcare decision-making. Despite their increasing popularity, there are currently no systematically developed reporting guidelines for overviews. This is problematic because reporting of published overviews varies considerably and is often substandard. Our objective is to use explicit, systematic, and transparent methods to develop an evidence-based and consensus-based reporting guideline for overviews of reviews of healthcare interventions (PRIOR: Preferred Reporting Items for Overviews of Reviews).

Methods

We will develop the PRIOR reporting guideline in four stages, using established methods for developing reporting guidelines in health research. First, we will establish an international and multidisciplinary expert advisory board that will oversee the conduct of the project and provide methodological support. Second, we will use the results of comprehensive literature reviews to develop a list of prospective checklist items for the reporting guideline. Third, we will use a modified Delphi exercise to achieve expert consensus on the list of items to be included in the

PRIOR reporting guideline. We will identify and recruit up to 30 international experts to complete three iterations of a survey: the first two rounds will occur online, and the third round will occur during an in-person consensus meeting that will use a nominal group technique. Fourth, we will produce and publish the PRIOR reporting guideline.

Discussion

A systematically developed reporting guideline for overviews could help improve the accuracy, completeness, and transparency of overviews. This, in turn, could help maximize the value and impact of overviews by allowing more efficient interpretation and use of their research findings.

5.2. BACKGROUND

Overviews of reviews of healthcare interventions (overviews) use explicit and systematic methods to search for, identify, extract data from, and analyze the results of multiple related SRs. Their aim is to provide a single synthesis of SR evidence to answer different types of questions related to the efficacy, effectiveness and/or safety of healthcare interventions for preventing or treating various clinical conditions (Table 5.1) [1]. Because overviews have been gaining momentum as an increasingly popular knowledge synthesis product [2, 3], methods for conducting overviews have evolved in recent years. For example, we recently published a scoping review summarizing existing guidance for conducting overviews of healthcare interventions [4], and we used the results to update the chapter on overview methods in the *Cochrane Handbook for Systematic Reviews of Interventions (Cochrane Handbook*; currently under review). Despite advances in methods for conducting overviews, the reporting of overviews varies considerably and is often substandard (Table 5.2) [2, 3].

Though we are aware of several relevant documents that narratively describe (based on personal experience and principles of "good practice") issues related to reporting overviews [1, 2, 5-8], we are not aware of any systematically developed evidence-based and consensus-based reporting guidelines for overviews. A reporting guideline is defined as "a checklist, flow diagram, or explicit text to guide authors in reporting a specific type of research, developed using explicit methodology" [9]. A reporting guideline for overviews could help authors report their methods and results in a clear, detailed, complete, and transparent way [9, 10]. This, in turn, could help end users better assess the reliability, validity, and applicability of overview results when making healthcare decisions [9, 12].

Our objective is to develop an evidence-based and consensus-based reporting guideline for overviews (PRIOR: Preferred Reporting Items for Overviews of Reviews) using explicit, systematic, and transparent methods. This guideline will consist of a "minimum essential set of items that should be reported" in overviews [9]. The PRIOR guideline will focus on overviews that examine the efficacy, effectiveness, and/or safety of healthcare interventions and that present narrative summaries and/or meta-analyses of quantitative outcome data. The target audience of the PRIOR reporting guideline will be overview authors, peer reviewers, journal editors, and healthcare decision-makers. We have registered our intent to develop the PRIOR reporting guideline for overviews on the Enhancing QUAlity and Transparency Of health Research (EQUATOR) Network website (http://www.equator-network.org/library/reporting-guidelines-under-development/#72).

5.3. METHODS

This study will follow the key steps recommended by the EQUATOR Network for developing reporting guidelines in health research [9], which were used to successfully develop reporting guidelines for other similar knowledge syntheses such as SRs [13] and network meta-analyses [14]. We will develop the reporting guideline in four stages: 1) project launch, 2) literature review, 3) modified Delphi exercise, and 4) development of the guidance statement. These stages are illustrated in Figure 5.1 and described below. We will obtain ethics approval from the University of Alberta Health Research Ethics Board prior to beginning this study.

5.3.1. Project launch

We will establish an international and multidisciplinary expert advisory board consisting of 3-6 individuals, including methodologists, journal editors, and decision-makers with expertise in evidence-based medicine, knowledge synthesis, and development of reporting guidelines for SRs (i.e., PRISMA and its extensions). To establish the advisory board, we will identify individuals for each of the above-stated roles, prioritize individuals within each list, and approach individuals sequentially. The advisory board will be consulted regularly throughout the guideline development process. They will be asked to: recommend relevant documents for the literature review; nominate participants for the Delphi exercise; review the checklist items for inclusion in the first round of the Delphi exercise; provide feedback after each round of the Delphi exercise (e.g., interpret results of the previous round, approve content for the next round); help plan and co-facilitate the in-person consensus meeting; contribute to the production of the final reporting guideline; and assist with dissemination and knowledge translation activities.

5.3.2. Literature review

To support the development of the PRIOR reporting guideline, we will conduct a methodological SR examining the quality of reporting of a sample of overviews of healthcare interventions published from 2012 to 2016 [15]. We will also search for and summarize methodological documents related to conducting and reporting overviews (e.g., documents that provide guidance for reporting overviews and other knowledge syntheses, documents that summarize methods used to conduct overviews, and empirical studies that evaluate methods for conducting overviews). To identify relevant methodological documents, we will use and expand upon the search strategies contained within the scoping review by Pollock *et al.* 2016 [4] and the methodological SR by Pieper *et al.* 2017 [15]. Our searches will consist of: database searches (MEDLINE via Ovid, EMBASE via Ovid, DARE via Cochrane Library, Scopus, MEDLINE via Web of Science, and Cochrane Methods Studies Database via Ovid); web searches (Google Scholar); reference tracking [16, 17]; monitoring article alerts; handsearching websites, conference proceedings, and personal files; contacting producers of overviews; and asking experts (e.g., advisory board members, Delphi participants) for relevant articles. Two independent reviewers will assess titles and abstracts, and all potentially relevant full-text articles, for inclusion, with discrepancies resolved by consensus or third party adjudication. Results of the literature review will be used to develop a list of checklist items that a panel of experts will assess for inclusion in the PRIOR reporting guideline.

5.3.3. Modified Delphi exercise

A panel of experts will participate in a modified Delphi exercise to achieve consensus on the list of items to be included in the PRIOR reporting guideline [9]. Experts will complete three iterations of a survey, using structured feedback between rounds to help transform individual opinion into group consensus [18-20]. Three survey rounds are likely to result in convergence of opinions between participants [18, 19]. The first two rounds will occur online via self-administered survey; the third round will occur during an in-person consensus meeting that will use a nominal group technique (i.e., a formal consensus technique where experts systematically review, discuss, and re-rate outstanding items) to achieve final consensus [18, 21]. Before the study, we will pilot test the survey's usability, clarity, and face validity by sending it to five individuals familiar with overview methods but uninvolved in the current project. Their feedback will be used to revise the survey format and checklist items as needed.

5.3.3.1. Participant recruitment

We will use a purposive sampling technique [20] to identify and recruit a panel of up to 30 experts [9] with extensive experience coordinating, conducting, reviewing, disseminating, and/or using overviews of healthcare interventions (e.g., editors, authors, peer reviewers, and end-users of published overviews). We will aim to recruit international participants who have diverse roles (e.g., researchers, healthcare professionals, patients, journal editors, policy-makers, funding agency representatives, etc.) and are employed in a range of settings (e.g., universities, hospitals, government, non-profit organizations, for-profit organizations, etc.). Experts will be invited via personalized email that will describe the PRIOR guideline development project and explain the objective, process, and timelines of the Delphi exercise. Informed consent will be obtained when participants agree to a consent statement at the start of the first online survey.

5.3.3.2. Round one: Online survey

The expert panel will be asked to use a self-administered online survey to rate, on a four-point Likert scale, the extent to which they agree with the inclusion of each checklist item in the PRIOR reporting guideline (1 = strongly disagree, 2 = somewhat disagree, 3 = somewhat agree, 4 = strongly agree) [22]. Participants may also choose to answer "I don't know" and provide an explanation [23]. For each item, a free text box will be provided for general comments (e.g., justification for their decision, proposed wording changes). Items will be presented in an order that reflects the progression of reporting in overviews (e.g., title, abstract, background, methods, results, discussion, other). At the end of the survey, two free text boxes will be provided for experts to suggest additional checklist items, and relevant methods papers. The Dillman principles for constructing respondent-friendly web surveys will be used to design the survey and its component items [23, 24].

Round one of the Delphi process will remain open for a minimum of three weeks, during which reminder emails will be sent prior to the closing date, as needed. The survey will be completed quasi-anonymously (i.e., the core project team, but not the other study participants, will know the identities and responses of the participants [20]), using a versatile online platform hosted and supported in Canada (e.g., Qualtrics, SimpleSurvey). We will collate and summarize survey results. Consensus will be defined using *a priori* criteria as ≥ 80% agreement for inclusion in (i.e., score of 3-4), or exclusion from (i.e., score of 1-2), the reporting guideline [25], based on the total number of responses obtained per question.

5.3.3.3. Round two: Online survey

In the second online survey, participants will view and/or re-rate the checklist items presented in the first survey [18, 19]. The content, structure and process will be similar to that of the first survey, with two differences. First, checklist items may be re-worded and/or re-formatted (e.g., items may be split or combined) based on the free text comments collected in round one [add citation]. Second, structured feedback will be embedded into each checklist item; this feedback will consist of each participants' previous rating, summary ratings from the group (e.g., medians, interquartile ranges, frequency distributions), and all anonymous free text comments [18, 19]. Checklist items will be presented in the same order as round one. The items that reached consensus (≥ 80%) in round one will be presented for information purposes only (i.e. no more voting will occur, though participants may respond to free-text comments). The items that did not reach consensus in round one will be re-rated by the expert panel. Experts will be asked to determine whether and how they wish to modify their original answers in light of the group responses and comments; they may also respond to free text comments if desired. At the end of the survey, we will ask the expert panel to rate and provide comments for each new checklist item generated by participants in round one. We will collate and summarize survey results, with consensus defined as previously described (≥ 80%).

5.3.3.4. Round three: In-person consensus meeting

The expert panel will convene at a one-day, in-person consensus meeting, where a nominal group technique and third round of real-time voting will be used to systematically discuss and resolve outstanding disagreements [9, 18, 21]. If needed, experts may participate remotely using interactive software that allows for real-time screen sharing, audio discussion, and user comments (e.g., Adobe Connect, GoToMeeting). Participants unable to attend in-person

or remotely will be asked to provide written feedback on the meeting summary. Moderators with expertise in overview methods and previous experience conducting consensus meeting for reporting guidelines will facilitate the meeting. We will audio record the meeting and take meeting minutes. The objective of the meeting will be to obtain final consensus on the list of items to be included in the PRIOR reporting guideline.

Prior to the meeting, each member of the expert panel will receive a copy of their second-round survey results. We will begin the consensus meeting by briefly summarizing the items reaching consensus for inclusion in, and exclusion from, the reporting guideline. No further voting will occur for these items, but outstanding free-text comments will be presented and resolved as needed. The bulk of the consensus meeting will use a nominal group technique to obtain consensus on those checklist items still lacking consensus [18, 21]. Each item will be reviewed sequentially, using a three-step process. First, facilitators will present the group survey results, all free text comments, and all relevant methodological literature related to each item. This can help structure the interaction, provide a common starting point for participants, and promote evidence-based discussions about guideline content [18]. Second, the expert panel will discuss, debate, and aim to resolve discrepancies in a structured large-group discussion [18, 21]. Third, a third round of voting will take place. The expert panel will be asked to re-rate the extent to which they agree with the inclusion of each checklist item. The content, structure and process of the survey will be similar to the online surveys, with two changes (the "I don't know" option will no longer be available, and no free-text comments will be solicited). Participants will complete the survey anonymously using a secure, online, live voting platform (e.g., Sli.do) that they will access using their personal electronic devices, with consensus defined as previously described (≥ 80%). Aggregate survey results will be automatically compiled by the software and

presented to the group at the end of the survey. If outstanding checklist items remain following the third survey, we will ask participants to divide themselves into one small group per checklist item. Each small group will engage in unmoderated discussion to achieve final consensus, with rationale, for each outstanding item. Post-meeting discussions may continue over email or teleconference to achieve consensus, if needed.

The consensus meeting will conclude by discussing the strategy for producing, publishing, and disseminating the final guideline. We will discuss: inclusion of a flow diagram; development of an accompanying explanation and elaboration document; considerations for authorship; who will be involved in which activities; and publication and knowledge translation strategies [9].

5.3.4. Development of the guidance statement

A small writing group will iteratively draft the final version of the PRIOR guidance document based on the final consensus of the expert panel. The writing group will consist of the core project team, with an open invitation issued to the advisory board members and expert panel members. We will aim to provide clear, concise, and unambiguous wording for each PRIOR checklist item. The reporting guideline will be circulated amongst all advisory board members and expert panel members to obtain final input and approval prior to publication.

5.4. DISCUSSION

Despite the growing number of published overviews and the commonly-observed deficiencies in reporting of overviews [2, 3], there are currently no systematically developed reporting guidelines for overviews of healthcare interventions. This protocol will help address this gap in guidance by using a four-stage process to develop the PRIOR reporting guideline, an

evidence-based and consensus-based reporting guideline for overviews of healthcare interventions. Once completed, we will submit the PRIOR reporting guideline for publication to an appropriate peer-reviewed journal (we may also seek co-publication in multiple journals, if appropriate). The guideline will also be published on the EQUATOR website and the Cochrane Comparing Multiple Interventions Methods Group (CMIMG) website. We will aim to present the guideline at conferences and workshops, disseminate the guideline via email lists, and solicit journal editors to actively endorse the guideline. In addition, we will also aim to incorporate the PRIOR reporting guideline into the next version of the *Cochrane Handbook*'s chapter on overview methods.

The PRIOR reporting guideline will be developed using a modified Delphi process, which is commonly used to develop reporting guidelines in the health sciences [9, 13, 14]. There are established benefits to using a modified Delphi process−for example, the online surveys provide a time- and cost-effective way to obtain preliminary consensus, while the more intensive consensus meeting with nominal group technique allows for face-to-face, in-depth discussion of outstanding issues [18]. Using an explicit, controlled, and scientifically credible process to achieve consensus amongst a group of experts can help to leverage the benefits of individual expertise and group decision-making, while simultaneously minimizing the biases associated with informal decision-making [18]. This can enhance credibility of the guideline development process and help to ensure widespread acceptance and uptake of the reporting guideline. However, the PRIOR reporting guideline will only capture current expertise based on the existing state of knowledge, and we expect that requirements for reporting overviews will evolve over time as overview methods evolve. Thus, the aim of the PRIOR reporting guideline will not

be to provide a definitive or unchanging list of reporting requirements, but rather to capture current expertise and knowledge upon which future research can build.

Once completed, the PRIOR reporting guideline can help overview authors improve the accuracy, completeness, and transparency of reporting. It can also provide a framework for peer reviewers, journal editors, and healthcare decision-makers to critically appraise submitted or published overviews. Strengthening the reporting of overviews can help healthcare decision-makers better evaluate the reliability, validity and applicability of overview results. This, in turn, can maximize the impact of overviews by allowing more accurate interpretation and use of their research findings.

5.5. REFERENCES

1. Becker LA, Oxman AD. Chapter 22: overviews of reviews. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.1.0). The Cochrane Collaboration; 2011. http://www.handbook.cochrane.org.
2. Hartling L, Chisholm A, Thomson D, Dryden DM. A descriptive analysis of overviews of reviews published between 2000 and 2011. PLoS One. 2012;7(11):e49667.
3. Pieper D, Buechter R, Jerinic P, Eikermann M. Overviews of reviews often have limited rigor: a systematic review. J Clin Epidemiol. 2012;65(12):1267-73.
4. Pollock M, Fernandes RM, Becker LA, Featherstone R, Hartling L. What guidance is available for researchers conducting overviews of reviews of healthcare interventions? A scoping review and qualitative metasummary. Syst Rev. 2016;5:190.
5. Onishi A, Furukawa TA. Chapter 13: state-of-the-art reporting. In: Biondi-Zoccai G, editor. Umbrella reviews: evidence synthesis with overviews of reviews and meta-epidemiologic studies. Cham: Springer International Publishing; 2016. p. 189-202.

6. Li L, Tian J, Tian H, Sun R, Liu Y, Yang K. Quality and transparency of overviews of systematic reviews. J Evid Based Med. 2012;5(3):166-73.
7. Singh JP. Development of the Metareview Assessment of Reporting Quality (MARQ) checklist. Rev Fac Med. 2012;60(4):325-32.
8. Wagner S, White M, Schultz I, Iverson R, Hsu V, McGuire L, *et al.* Assessing a systematic review of systematic reviews: developing a criteria. Abstracts of the Canadian Association for Research on Work and Health Conference, 01-02 Jun 2012. Vancouver, Canada.
9. Moher D, Schulz KF, Simera I, Altman DG. Guidance for developers of health research reporting guidelines. PLoS Med. 2010;7(2):e1000217.
10. Plint AC, Moher D, Morrison A, Schulz K, Altman DG, Hill C, *et al*. Does the CONSORT checklist improve the quality of reports of randomised controlled trials? A systematic review. Med J Aust. 2006;185(5):263-7.
11. Smidt N, Rutjes AW, van der Windt DA, Ostelo RW, Bossuyt PM, Reitsma JB, *et al*. The quality of diagnostic accuracy studies since the STARD statement: has it improved? Neurology. 2006;67(5):792-7.
12. Simera I, Moher D, Hoey J, Schulz KF, Altman DG. The EQUATOR Network and reporting guidelines: helping to achieve high standards in reporting health research studies. Maturitas. 2009;63(1):4-6.
13. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
14. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, *et al*. The PRISMA extension statement for reporting of systematic reviews incorporating network

meta-analyses of health care interventions: checklist and explanations. Ann Intern Med. 2015;162(11):777-84.

15. Pieper D, Pollock M, Fernandes RM, Buchter RB, Hartling L. Epidemiology and reporting characteristics of overviews of reviews of healthcare interventions published 2012-2016: protocol for a systematic review. Syst Rev. 2017;6(1):73.
16. Horsley T, Dingwall O, Sampson M. Checking reference lists to find additional studies for systematic reviews. Cochrane Database Syst Rev. 2011;8:MR000026.
17. Greenhalgh T, Peacock R. Effectiveness and efficiency of search methods in systematic reviews of complex evidence: audit of primary sources. BMJ. 2005;331(7524):1064-5.
18. Murphy MK, Black NA, Lamping DL, McKee CM, Sanderson CF, Askham J, *et al*. Consensus development methods, and their use in clinical guideline development. Health Technol Assess. 1998;2(3):1-88.
19. Hsu C, Sandford BA. The Delphi technique: making sense of consensus. Pract Assess Res Eval. 2007;12(10):1-8.
20. Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. J Adv Nurs. 2000;32(4):1008-15.
21. Jones J, Hunter D. Consensus methods for medical and health services research. BMJ. 1995;311(7001):376-80.
22. Streiner DL, Norman GR. Health measurement scales: a practical guide to their development and use. 4th ed. New York: Oxford University Press; 2008.
23. Dillman DA, Smyth JD, Melani Christian L. Internet, mail, and mixed-mode surveys: the tailored design method. 3rd ed. New Jersey: John Wiley & Sons; 2009.

24. Dillman DA, Tortora RD, Bowker D. Principles for constructing web surveys. SESRC Technical Report 98-50. 1998.

25. Diamond IR, Grant RC, Feldman BM, Pencharz PB, Ling SC, Moore AM, *et al*. Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. J Clin Epidemiol. 2014;67(4):401-9.

Table 5.1. Types of questions about healthcare interventions that overviews can examine.

1) Different interventions for the same condition or population.
2) The same intervention for different conditions or populations.
3) Adverse effects of an intervention for one or more conditions or populations.
4) The same intervention for the same condition or population, where different outcomes or time points are addressed in different systematic reviews.

Modified from Becker & Oxman [1].

Table 5.2. Percentage of overviews (published up to 2011[a]) reporting on key aspects of methods and results.

Reporting item	Percentage of overviews reporting each item (%)
Objectives [2]	99%
Inclusion criteria [2]	87%
Outcomes of interest [2]	36%
Databases and search dates [2, 3]	61-78%
Search strategies and key words [2]	77%
Description of methods used for screening and inclusion [2]	49%
Description of methods used for data extraction [2]	60%
Description of methods for addressing overlapping SRs in overviews [3]	5%
List of included SRs [2]	91%
List of excluded SRs [2]	27%
Description of included SRs (participants, interventions, outcomes) [2]	79%
Methodological quality of included SRs [2, 3]	37-64%
Methodological quality of primary studies contained within included SRs [2]	39%
Certainty of evidence of outcome data [2]	19%
Publication bias [2]	24%
Source of funding [2, 3]	42-57%

Data from Hartling *et al.* (n = 75 overviews) [2] and Pieper *et al.* (n = 126 overviews) [3].
[a] Five overviews from the sample contained in Pieper *et al.* were published in January or February 2012.

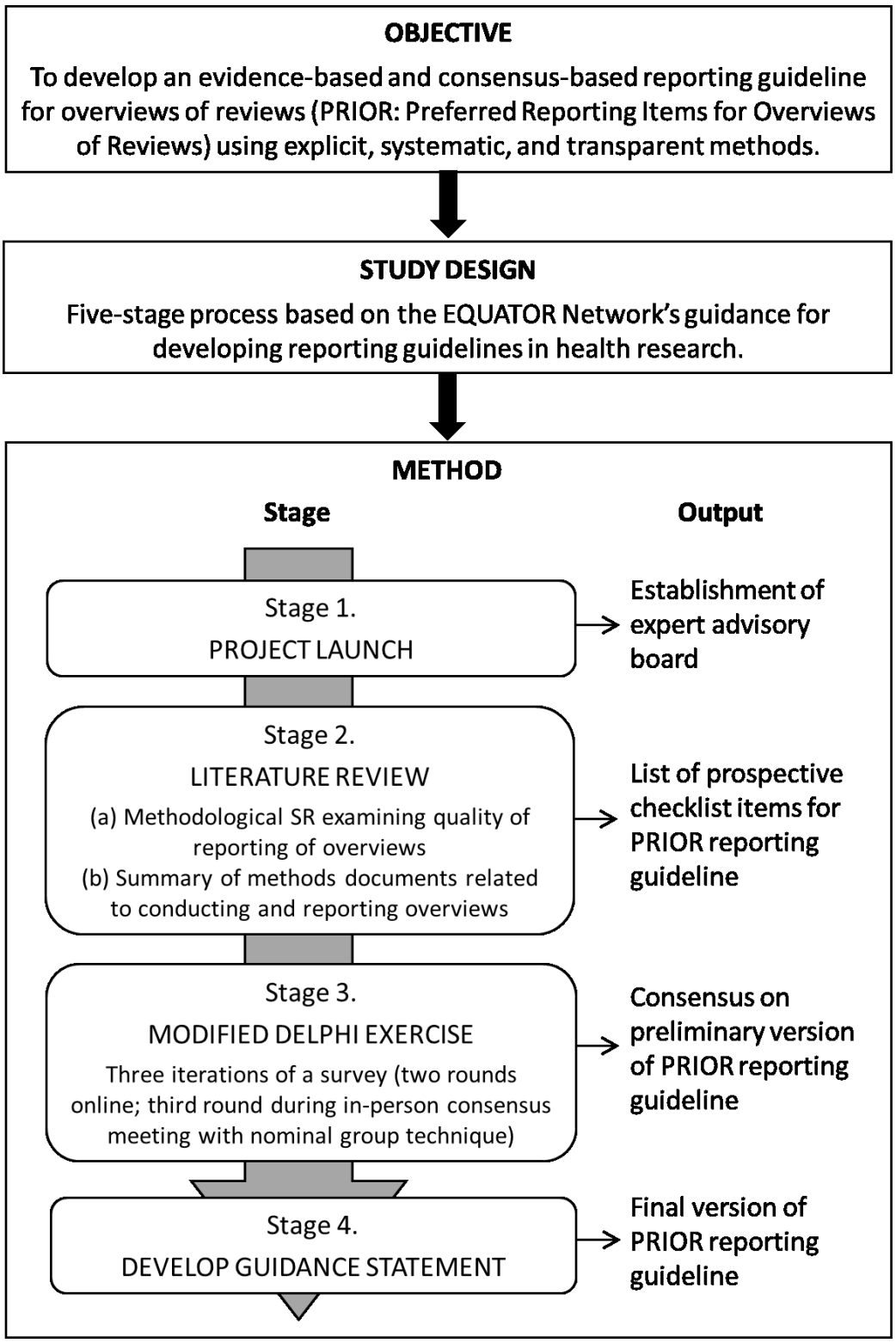


Figure 5.1. Study protocol.

Chapter 6

Discussion

6.1. SUMMARY OF FINDINGS

This thesis examined methods researchers can use to conduct and report overviews of reviews of healthcare interventions. A scoping review provided a timely and useful summary of all existing methods guidance for conducting overviews. Two methods studies then provided empirical evidence on two issues for which methods guidance was limited: a multiple case study examined inclusion of overlapping SRs in overviews, and a descriptive study examined use of the AMSTAR tool to assess quality of SRs in overviews. A project plan was also established to develop a reporting guideline for overviews. While remaining gaps in guidance still exist, these thesis projects play an important role in advancing methods for conducting and reporting overviews. Results of the first three studies examining methods for conducting overviews are discussed below.

6.1.1. Existing methods guidance for conducting overviews

Overall, there was relatively consistent and comprehensive guidance for the first stages of the overview process: deciding when and why to conduct an overview, specifying the scope, searching the literature, and applying inclusion criteria. Once researchers have decided that the overview format is appropriate, methods for conducting the preliminary stages of overviews largely mirror the well-established methods used in SRs (with minor, but often straightforward, deviations, detailed in the scoping review). There was conflicting or missing guidance, and a number of outstanding challenges, for the latter stages of the overview process: deciding whether to include SRs published outside of the Cochrane Database of Systematic Reviews, conducting

quality assessments of SRs and their primary studies, collecting and presenting outcome data, and assessing certainty of evidence of outcome data. For these stages, overview methods diverged from standard SR methods and took on an additional level of complexity. Unfortunately, few of the challenges related to these stages were adequately addressed by existing guidance.

The year after the scoping review was published, a complimentary yet distinct knowledge synthesis study was published by an independent group [1]. Both studies provide converging summaries of methods guidance for overviews. Our scoping review provides concise summaries of existing guidance across all stages of the overview process (i.e., we focus on breadth over depth); the other synthesis explores in detail a smaller number of stages with conflicting guidance (i.e., they focus on depth over breadth). Both studies also use differing yet complimentary methods to obtain guidance on when and why to conduct an overview. Our scoping review summarizes all existing guidance on this topic, most of which came from internal documents and conference proceedings that were difficult to locate; the other synthesis uses their study results to propose circumstances where it may or may not be appropriate to conduct an overview. Despite select differences in both studies' objectives, inclusion criteria, and approaches to data analysis and synthesis, their findings are largely complimentary. While the results of both studies will serve as useful resources for overview authors, researchers conducting the latter stages of overviews for which guidance is lacking would also benefit from empirically-supported methods guidance derived from studies evaluating overview methods. The results of two such studies are discussed below.

6.1.2. Impact of different inclusion decisions in overviews

This methods study provided empirical evidence on the impact, advantages, disadvantages, and potential trade-offs involved when making different inclusion decisions in overviews. The findings suggested that there is no straightforward, "one size fits all" approach to inclusion of SRs in overviews. Different overviews required different inclusion decisions depending on the overview's topic area, target audience, purpose, methodology, and logistical concerns. These different decisions affected the comprehensiveness and results of overviews in different ways, depending in part on the characteristics of the overview's relevant SRs; further, there were practical challenges associated with inclusion of overlapping SRs in overviews. The study findings were used to develop a decision tool to provide evidence-informed decision support for overview authors. The decision tool provides practical guidance and support for researchers conducting overviews by helping them consider questions that can affect the nature and extent of outcome data included and not included in overviews, as well as the impact, advantages, disadvantages, and potential trade-offs of making different inclusion decisions in overviews. Considering these issues upfront may also help researchers appropriately contextualize their overview findings in light of the potential completeness of the overview's evidence base.

6.1.3. Use of the AMSTAR tool to assess methodological quality of systematic reviews in overviews

Overall, the empirical evidence presented in this methods study supported the successful use of AMSTAR as a quality assessment tool for SRs in overviews, despite the presence of limited, minor, easily resolved challenges that occurred when applying the tool. Systematic differences in inter-rater reliability between SRs with different characteristics supported the

practice of dual independent quality assessments with consensus. The lack of relationship between AMSTAR scores and SR results and conclusions suggested that AMSTAR may assess reporting as opposed to methodological quality, and that using AMSTAR scores as an exclusion criterion in overviews may not introduce bias into the overview. These evidence-informed recommendations provide practical guidance for researchers regarding the methodological considerations involved in using AMSTAR to inform inclusion decisions and assess quality of SRs in overviews.

6.2. FUTURE RESEARCH

6.2.1. Methods for conducting overviews

The scoping review of existing methods guidance will serve as a useful resource for researchers conducting overviews and researchers conducting empirical studies evaluating overview methods. However, as more researchers start to formally evaluate the performance of overview methods [2-5], it will also be valuable to conduct a complementary knowledge synthesis study to summarize these methods studies. To meet this need, an independent group has published a protocol describing the rationale and design of a study that will systematically search for, identify, extract data from, and summarize empirical studies evaluating overview methods [6]. While our scoping review of existing guidance documents highlights stages of the overview process with consistent, conflicting, and missing guidance, an evidence map of studies evaluating the performance of these methods will also highlight specific methods that are supported by adequate or limited empirical evidence.

The multiple case study contributed evidence-based guidance that can help researchers make inclusion decisions in overviews. The resulting decision tool will require further

evaluation, testing, and refinement. This process will likely involve an iterative cycle of assessment and feedback based on researchers' use of the tool in real-world conditions, while conducting overviews examining a range of different questions. We encourage researchers to publish methods studies or commentaries describing the usability, strengths, and limitations of the tool in the context of their specific overview(s), and to suggest modifications or additions as appropriate.

Since conducting our descriptive study assessing the use of the AMSTAR tool in overviews, new quality assessment (AMSTAR 2) and risk of bias (ROBIS) tools have been developed [7, 8]. These three assessment tools have not yet been systematically compared to each other. Thus, members of our research team have developed a protocol to assess the reliability, practicability and external validity of the three tools. This study will build upon the results of the AMSTAR study by providing useful insight into the trade-offs and implications of selecting one tool over another to assess quality or risk of bias of SRs in overviews.

Lastly, additional methods research is required for other stages of the overview process that are currently characterized by conflicting guidance, outstanding challenges, and a lack of empirical research to inform their conduct. Two important stages of the overview process for which methods guidance and empirical research are largely lacking are: extracting and analyzing outcome data, and assessing certainty of evidence of outcome data. In addition, there are several other stages of the overview process for which select gaps in guidance still remain, despite the presence of some consistent and comprehensive guidance. Thus, there remains an identified need for future empirical methods studies that can help provide guidance, resolve discrepancies, and clarify challenges for researchers conducting overviews.

6.2.2. Methods for reporting overviews

As described in the PRIOR reporting guideline protocol, a crucial first step to developing a reporting guideline for overviews involves seeking evidence on the quality of reporting of recently published overviews. To do this, our research team is currently conducting a methodological SR examining the quality of reporting of a sample of overviews of healthcare interventions published from 2012 to 2016 [9]. This study involves comprehensively searching for and systematically identifying all published overviews; extracting and reporting the epidemiological, descriptive, and reporting characteristics of a random sample of 100 overviews; and comparing this sample's characteristics to those of two previously described samples of overviews published up to 2011 ([10, 11]). The results of this project can help identify whether and how reporting of overviews has changed over time, and areas where further improvement is needed. Results of this project will also help justify the need for, and assist with the development of, the PRIOR reporting guideline.

6.2.3. Beyond overviews of healthcare interventions

This thesis examined methods for overviews of healthcare interventions, since these are the most common types of overviews conducted both within and outside of Cochrane [11, 12]. However, researchers may also conduct overviews that examine questions related to risk factors, diagnosis, prognosis, epidemiology, economic evaluations, health technology assessments, or questions requiring a qualitative approach [11, 13]. Methods and reporting guidance for these other types of overviews are needed, as there is currently little to no guidance available. A useful starting point may be to explore whether and to what extent guidance for conducting and reporting overviews of healthcare interventions is transferable to these other types of overviews.

Researchers could use guidance for conducting and reporting overviews of healthcare interventions as a reference, compare the considerations for overviews of healthcare interventions with those for other types of overviews, suggest appropriate modifications for other types of overviews, provide examples from published overviews to exemplify these modifications, and test the proposed approaches in empirical methods studies. In this way, researchers could capitalize on existing methods guidance while also accounting for methodological features unique to other types of overviews.

6.3. STRENGTHS AND LIMITATIONS

This thesis consists of four studies with differing, yet complimentary, objectives and methodologies. All studies in this thesis were designed and conducted based on an identified need, and built incrementally upon each other. The scoping review of existing methods guidance was conducted in response to overview authors expressing a need for comprehensive, up-to-date guidance for overviews [10, 11, 14]. The empirical methods studies and reporting guideline protocol were informed by the results of the scoping review, which identified stages of the overview process in need of evidence-informed methods guidance and failed to identify sufficient guidance for reporting overviews. This thesis employed multiple methods where the four component studies had different study designs, sources of data, and approaches to data analysis. Tailoring the methodologies to each study's objective allowed us to capture the breadth of existing methods guidance while also exploring in depth areas in need of further guidance.

The studies in this thesis reflect an approach to conducting overviews typically associated with Cochrane [15]. As Cochrane overviews often synthesize evidence from Cochrane SRs of healthcare interventions, they often operate under specific assumptions (e.g., they often examine

questions about healthcare interventions, consider restricting inclusion to only Cochrane SRs, avoid double-counting outcome data, and re-extract and re-analyze outcome data from SRs). The studies in this thesis likely reflect these assumptions, for three reasons. First, when conducting the scoping review, we identified our preliminary list of overview stages from the guidance presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (*Cochrane Handbook)*. Second, over two thirds of the guidance documents in the scoping review came from researchers affiliated with Cochrane. Third, the convenience sample of seven overviews included in the methods studies were conducted by Cochrane researchers that operated under the assumptions described above. Thus, the results of this thesis may be most applicable to researchers conducting Cochrane overviews. Researchers conducting non-Cochrane overviews that differ in purpose, scope, and assumptions, should consider at the outset the extent to which these thesis results are generalizable to their specific situation.

6.4. KNOWLEDGE TRANSLATION AND DISSEMINATION

Together, the first three thesis projects examining methods for conducting overviews represent a necessary first step to developing a cohesive guidance document for researchers conducting overviews. Accordingly, our research team used the results of these projects, particularly the results of the scoping review, as a starting point to update the *Cochrane Handbook's* chapter on overview methods. The original chapter, published in 2008, described basic formatting requirements for Cochrane overviews that included only Cochrane SRs [15]. The updated chapter, which is currently under review, contains a wealth of new methods guidance for conducting Cochrane overviews that can include both Cochrane and non-Cochrane SRs. It begins with an expanded definition of overviews, a new section on when to conduct an

overview, and a new disclaimer highlighting issues related to informal indirect comparisons. The bulk of the chapter then provides detailed descriptions of all existing methods guidance. We discuss stages with consistent and comprehensive guidance in more depth than the scoping review permitted, and summarize the results of the empirical methods studies as relevant. For stages with conflicting or missing guidance, we present a range of potential methodological approaches and their implications. Thus, publication of the chapter update will provide an opportunity for widespread translation of these thesis findings. Lastly, the fourth and final thesis project, the study protocol, sets the stage for the development of PRIOR, an evidence-based and consensus-based reporting guideline for overviews.

The publication of the chapter update and future reporting guideline will represent valuable contributions to the field of overview methods by helping to provide empirically based, scientifically sound, and widely accessible guidance for conducting and reporting overviews. The chapter update can help researchers conduct high-quality overviews that are methodologically rigorous, while the future reporting guideline can help improve the accuracy, completeness, and transparency of reporting. Both products are expected to have an international reach. In particular, the chapter update will be published by Cochrane, a leading international organization that produces high-quality SRs of healthcare interventions. Notably, as methods for conducting overviews continue to evolve over time, it will be important to periodically update the chapter to ensure that it incorporates the newest research and contains up-to-date guidance.

6.5. CONCLUSIONS

The four studies presented in this thesis help advance methods for overviews of reviews of healthcare interventions by exploring the methods researchers can use to conduct and report

overviews. Specifically, these studies summarize existing guidance for conducting overviews, provide empirical evidence on issues related to conducting overviews, and present a project plan to develop a reporting guideline for overviews. These studies contribute to the growing evidence base and provide solid directions for future research in this field.

The Canadian Institutes of Health Research Strategic Plan aims to "mobilize health knowledge for transformation and impact [by] embracing the data revolution" [16]. Overviews provide an innovative solution to help manage the sheer amount of health data that exist. Continued investment in strengthening this methodology has the potential to increase the uptake and application of knowledge by clinical and policy decision-makers. This, in turn, can help address important health issues and improve health outcomes in diverse populations.

6.6. REFERENCES

1. Ballard M, Montgomery P. Risk of bias in overviews of reviews: a scoping review of methodological guidance and four-item checklist. Res Synth Methods. 2017;8(1):92-108.
2. Buchter RB, Pieper D. Most overviews of Cochrane reviews neglected potential biases from dual authorship. J Clin Epidemiol. 2016;77:91-4.
3. Crick K, Wingert A, Williams K, Fernandes RM, Thomson D, Hartling L. An evaluation of harvest plots to display results of meta-analyses in overviews of reviews: a cross-sectional study. BMC Med Res Methodol. 2015;15:91.
4. Pieper D, Mathes T, Eikermann M. Impact of choice of quality appraisal tool for systematic reviews in overviews. J Evid Based Med. 2014;7(2):72-8.

5. Pollock A, Farmer SE, Brady MC, Langhorne P, Mead GE, Mehrholz J, *et al*. An algorithm was developed to assign GRADE levels of evidence to comparisons within systematic reviews. J Clin Epidemiol. 2015;70:106-10.
6. Lunny C, Brennan SE, McDonald S, McKenzie JE. Evidence map of studies evaluating methods for conducting, interpreting and reporting overviews of systematic reviews of interventions: rationale and design. Syst Rev. 2016;5:4.
7. Shea B, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, *et al.* AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008.
8. Whiting P, Savovic J, Higgins JP, Caldwell DM, Reeves BC, Shea B, *et al*. ROBIS: a new tool to assess risk of bias in systematic reviews was developed. J Clin Epidemiol. 2016;69:225-34.
9. Pieper D, Pollock M, Fernandes RM, Buchter RB, Hartling L. Epidemiology and reporting characteristics of overviews of reviews of healthcare interventions published 2012-2016: protocol for a systematic review. Syst Rev. 2017;6(1):73.
10. Hartling L, Chisholm A, Thomson D, Dryden DM. A descriptive analysis of overviews of reviews published between 2000 and 2011. PLoS One. 2012;7(11):e49667.
11. Pieper D, Buechter R, Jerinic P, Eikermann M. Overviews of reviews often have limited rigor: a systematic review. J Clin Epidemiol. 2012;65(12):1267-73.
12. Cochrane. Special collection: Cochrane overviews. http://www.cochranelibrary.com/app/content/special-collections/article/?doi=10.1002/(ISSN)14651858(CAT)na(VI)SC000036 (2014). Accessed 01 Sept 2017.

13. Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. Int J Evid Based Healthc. 2015;13(3):132-40.
14. Foisy M, Dryden DM, Fernandes RM, Hartling L, Thomson D. Advancing methods for overviews of reviews: a discussion of challenges and potential solutions. Abstracts of the 22nd Cochrane Colloquium; 21-26 Sept 2014; Hyderabad, India: John Wiley & Sons; 2014.
15. Becker LA, Oxman AD. Chapter 22: overviews of reviews. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.1.0). The Cochrane Collaboration; 2011. http://www.handbook.cochrane.org.
16. Canadian Institutes of Health Research. Health research roadmap II: capturing innovation to produce better health and health care for Canadians. Strategic plan 2014-15 – 2018-19. http://cihr-irsc.gc.ca/e/48964.html (2015). Accessed 01 Sept 2017.

References

Chapter 1: Introduction

1. Becker LA, Oxman AD. Chapter 22: overviews of reviews. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.1.0). The Cochrane Collaboration; 2011. http://www.handbook.cochrane.org.
2. Hartling L, Chisholm A, Thomson D, Dryden DM. A descriptive analysis of overviews of reviews published between 2000 and 2011. PLoS One. 2012;7(11):e49667.
3. Pieper D, Buechter R, Jerinic P, Eikermann M. Overviews of reviews often have limited rigor: a systematic review. J Clin Epidemiol. 2012;65(12):1267-73.
4. Smith V, Devane D, Begley CM, Clarke M. Methodology in conducting a systematic review of systematic reviews of healthcare interventions. BMC Med Res Methodol. 2011;11(1):15.
5. Chalmers I, Hedges LV, Cooper H. A brief history of research synthesis. Eval Health Prof. 2002;25(1):12-37.
6. Chalmers I, Enkin M, Keirse MJNC. Effective care in pregnancy and childbirth. Oxford: Oxford University Press; 1989.
7. Evans D. Hierarchy of evidence: a framework for ranking evidence evaluating healthcare interventions. J Clin Nurs. 2003;12(1):77-84.
8. Green S, Higgins JPT, Alderson P, Clarke M, Mulrow CD, Oxman AD. Chapter 1: introduction. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.1.0). The Cochrane Collaboration; 2011. http://www.handbook.cochrane.org.
9. Cochrane. About us. http://www.cochrane.org/about-us (n.d.). Accessed 01 Sept 2017.

10. Cochrane. Cochrane in numbers: April-June 2017. http://www.cochrane.org/news/cochrane-numbers-april-june-2017 (2017). Accessed 01 Sept 2017.
11. Moher D, Tetzlaff J, Tricco AC, Sampson M, Altman DG. Epidemiology and reporting characteristics of systematic reviews. PLoS Med. 2007;4(3):e78.
12. Page MJ, Shamseer L, Altman DG, Tetzlaff J, Sampson M, Tricco AC, *et al*. Epidemiology and reporting characteristics of systematic reviews of biomedical research: a cross-sectional study. PLoS Med. 2016;13(5):e1002028.
13. Bastian H, Glasziou P, Chalmers I. Seventy-five trials and eleven systematic reviews a day: how will we ever keep up? PLoS Med. 2010;7(9):e1000326.
14. Bero LA, Grilli R, Grimshaw JM, Harvey E, Oxman AD, Thomson MA. Closing the gap between research and practice: an overview of systematic reviews of interventions to promote the implementation of research findings. The Cochrane Effective Practice and Organization of Care Review Group. BMJ. 1998;317(7156):465-8.
15. Crick K, Thomson D, Fernandes RM, Nuspl M, Eurich DT, Rowe BH, *et al*. Descriptive analysis of cochrane child-relevant systematic reviews: an update and comparison between 2009 and 2013. BMC Pediatr. 2017;17(1):155.
16. Thomson D, Foisy M, Oleszczuk M, Wingert A, Chisholm A, Hartling L. Overview of reviews in child health: evidence synthesis and the knowledge base for a specific population. Evid Based Child Health. 2013;8(1):3-10.
17. Spurling GKP, Fonseka K, Doust J, Del Mar C. Antibiotics for bronchiolitis in children. Cochrane Database Syst Rev. 2007;1:CD005189.
18. Gadomski A, Brower M. Bronchodilators for bronchiolitis. Cochrane Database Syst Rev. 2010;12:CD001266.

19. Perrotta C, Ortiz Z, Figuls M. Chest physiotherapy for acute bronchiolitis in paediatric patients between 0 and 24 months old. Cochrane Database Syst Rev. 2007;1:CD004873.
20. Hartling L, Bialy LM, Vandermeer B, Tjosvold L, Johnson DW, Plint AC, *et al*. Epinephrine for bronchiolitis. Cochrane Database Syst Rev. 2011;6:CD003123.
21. Shah PS, Ohlsson A, Shah JP. Continuous negative extrathoracic pressure or continuous positive airway pressure for acute hypoxemic respiratory failure in children. Cochrane Database Syst Rev. 2008;1:CD003699.
22. Fernandes R, Bialy L, Vandermeer B, Tjosvold L, Plint A, Patel H, *et al*. Glucocorticoids for acute viral bronchiolitis in infants and young children. Cochrane Database Syst Rev. 2010;10:CD004878.
23. Liet JM, Ducruet T, Gupta V, Cambonie G. Heliox inhalation therapy for bronchiolitis in infants. Cochrane Database Syst Rev. 2010;4:CD006915.
24. Zhang L, Mendoza-Sassi RA, Wainwright C, Klassen TP. Nebulized hypertonic saline solution for acute bronchiolitis in infants. Cochrane Database Syst Rev. 2008;4:CD006458.
25. Fuller HL, Del Mar C. Immunoglobulin treatment for respiratory syncytial virus infection. Cochrane Database Syst Rev. 2006;4:CD004883.
26. Blom DJM, Ermers M, Bont L, van Woensel JBM, van Aalderen WMC. Inhaled corticosteroids during acute bronchiolitis in the prevention of post-bronchiolitic wheezing. Cochrane Database Syst Rev. 2007;1:CD004881.
27. Rojas-Reyes MX, Granados RC, Charry-Anzola LP. Oxygen therapy for lower respiratory tract infections in children between 3 months and 15 years of age. Cochrane Database Syst Rev. 2009;1:CD005975.

28. Bialy L, Foisy M, Smith M, Fernandes RM. The Cochrane Library and the treatment of bronchiolitis in children: an overview of reviews. Evid Based Child Health. 2011;6(1):258-75.
29. Grimshaw J. A knowledge synthesis chapter. In: A guide to knowledge synthesis. Canadian Institutes of Health Research; 2010. http://www.cihr-irsc.gc.ca/e/41382.html. Accessed 01 Sept 2017.
30. Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.1.0). The Cochrane Collaboration; 2011. http://www.handbook.cochrane.org.
31. Pieper D, Antoine SL, Mathes T, Neugebauer EA, Eikermann M. Systematic review finds overlapping reviews were not mentioned in every other overview. J Clin Epidemiol. 2014;67(4):368-75.
32. Fleming PS, Seehra J, Polychronopoulou A, Fedorowicz Z, Pandis N. Cochrane and non-Cochrane systematic reviews in leading orthodontic journals: a quality paradigm? Eur J Orthod. 2013;35(2):244-8.
33. MacDonald SL, Canfield SE, Fesperman SF, Dahm P. Assessment of the methodological quality of systematic reviews published in the urological literature from 1998 to 2008. J Urol. 2010;184(2):648-53.
34. Moseley AM, Elkins MR, Herbert RD, Maher CG, Sherrington C. Cochrane reviews used more rigorous methods than non-Cochrane reviews: survey of systematic reviews in physiotherapy. J Clin Epidemiol. 2009;62(10):1021-30.
35. Foisy M, Dryden DM, Fernandes RM, Hartling L, Thomson D. Advancing methods for overviews of reviews: a discussion of challenges and potential solutions. Abstracts of the 22nd Cochrane Colloquium; 21-26 Sept 2014; Hyderabad, India: John Wiley & Sons; 2014.

36. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, *et al*. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 2007;7:10.
37. Shea BJ, Bouter LM, Peterson J, Boers M, Andersson N, Ortiz Z, *et al*. External validation of a measurement tool to assess systematic reviews (AMSTAR). PLoS One. 2007;2(12):e1350.
38. Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J, *et al*. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol. 2009;62(10):1013-20.
39. Li L, Tian J, Tian H, Sun R, Liu Y, Yang K. Quality and transparency of overviews of systematic reviews. J Evid Based Med. 2012;5(3):166-73.
40. Singh JP. Development of the Metareview Assessment of Reporting Quality (MARQ) checklist. Rev Fac Med. 2012;60(4):325-32.
41. Wagner S, White M, Schultz I, Iverson R, Hsu V, McGuire L, *et al*. Assessing a systematic review of systematic reviews: developing a criteria. Abstracts of the Canadian Association for Research on Work and Health Conference; 01-02 Jun 2012; Vancouver, Canada.

Chapter 2: What guidance is available for researchers conducting overviews of reviews of healthcare interventions? A scoping review and qualitative metasummary

1. Green S, Higgins JPT, Alderson P, Clarke M, Mulrow CD, Oxman AD. Chapter 1: introduction. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.1.0). The Cochrane Collaboration; 2011. http://www.handbook.cochrane.org.

2. Bastian H, Glasziou P, Chalmers I. Seventy-five trials and eleven systematic reviews a day: how will we ever keep up? PLoS Med. 2010;7(9):e1000326.
3. Becker LA, Oxman AD. Chapter 22: overviews of reviews. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.1.0). The Cochrane Collaboration; 2011. http://www.handbook.cochrane.org.
4. Hartling L, Chisholm A, Thomson D, Dryden DM. A descriptive analysis of overviews of reviews published between 2000 and 2011. PLoS One. 2012;7(11):e49667.
5. Pieper D, Buechter R, Jerinic P, Eikermann M. Overviews of reviews often have limited rigor: a systematic review. J Clin Epidemiol. 2012;65(12):1267-73.
6. Li L, Tian J, Tian H, Sun R, Liu Y, Yang K. Quality and transparency of overviews of systematic reviews. J Evid Based Med. 2012;5(3):166-73.
7. Cochrane: About us. http://www.cochrane.org/about-us (n.d.). Accessed 01 Sept 2017.
8. Cochrane Comparing Multiple Interventions Methods Group: About us. http://www.methods.cochrane.org/cmi/about-us (2015). Accessed 01 Sept 2017.
9. Singh JA, Christensen R, Wells GA, Suarez-Almazor ME, Buchbinder R, Lopez-Olivo MA, *et al*. Biologics for rheumatoid arthritis: an overview of Cochrane reviews. Cochrane Database Syst Rev. 2009;4:CD007848.
10. Aromataris E, Fernandez R, Godfrey C, Holly C, Khalil H, Tungpunkom P, editors. The Joanna Briggs Institute reviewers' manual 2014: methodology for JBI umbrella reviews. University of Adelaide: Joanna Briggs Institute; 2014.
11. Grimshaw J. A knowledge synthesis chapter. In: A guide to knowledge synthesis. Canadian Institutes of Health Research. 2010. http://www.cihr-irsc.gc.ca/e/41382.html. Accessed 01 Sept 2017.

12. Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.1.0). The Cochrane Collaboration; 2011. http://www.handbook.cochrane.org.
13. Foisy M, Dryden DM, Fernandes RM, Hartling L, Thomson D. Advancing methods for overviews of reviews: a discussion of challenges and potential solutions. Abstracts of the 22nd Cochrane Colloquium, 21-26 Sept 2014. Hyderabad, India: John Wiley & Sons; 2014.
14. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol. 2005;8(1):19-32.
15. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. Implement Sci. 2010;5:69.
16. Horsley T, Dingwall O, Sampson M. Checking reference lists to find additional studies for systematic reviews. Cochrane Database Syst Rev. 2011;8:MR000026.
17. Greenhalgh T, Peacock R. Effectiveness and efficiency of search methods in systematic reviews of complex evidence: audit of primary sources. BMJ. 2005;331(7524):1064-5.
18. Sandelowski M, Barroso J. Chapter 6: synthesizing qualitative research findings: qualitative metasummary. In: Sandelowski M, Barroso J, editors. Handbook for synthesizing qualitative research. New York: Springer Publishing Company; 2006. p. 151-97.
19. Sandelowski M, Barroso J. Creating metasummaries of qualitative findings. Nurs Res. 2003;52(4):226-33.
20. Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J, *et al*. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol. 2009;62(10):1013-20.

21. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, *et al*. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-6.
22. Moher D, Tetzlaff J, Tricco AC, Sampson M, Altman DG. Epidemiology and reporting characteristics of systematic reviews. PLoS Med. 2007;4(3):e78.
23. Moseley AM, Elkins MR, Herbert RD, Maher CG, Sherrington C. Cochrane reviews used more rigorous methods than non-Cochrane reviews: survey of systematic reviews in physiotherapy. J Clin Epidemiol. 2009;62(10):1021-30.
24. Foisy M, Dryden DM, Fernandes RM, Hartling L. Multiple systematic reviews published on the same topic area: an analysis of systematic reviews that overlap in content. Abstracts of the 22nd Cochrane Colloquium, 21-26 Sept 2014. Hyderabad, India: John Wiley & Sons; 2014.
25. Green S, Higgins JPT. Chapter 2: preparing a Cochrane review. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.1.0). The Cochrane Collaboration; 2011. http://www.handbook.cochrane.org.
26. Worswick J, Wayne SC, Bennett R, Fiander M, Mayhew A, Weir MC, *et al*. Improving quality of care for persons with diabetes: an overview of systematic reviews - what does the evidence tell us? Syst Rev. 2013;2:26.
27. Farquhar C, Rishworth JR, Brown J, Nelen WL, Marjoribanks J. Assisted reproductive technology: an overview of Cochrane reviews. Cochrane Database Syst Rev. 2015;7:CD010537.

28. Foisy M, Boyle RJ, Chalmers JR, Simpson EL, Williams HC. The prevention of eczema in infants and children: an overview of Cochrane and non-Cochrane reviews. Evid Based Child Health. 2011;6(5):1322-39.
29. Cates CJ, Wieland LS, Oleszczuk M, Kew KM. Safety of regular formoterol or salmeterol in adults with asthma: an overview of Cochrane reviews. Cochrane Database Syst Rev. 2014;2:CD010314.
30. Pieper D, Mathes T, Eikermann M. Impact of choice of quality appraisal tool for systematic reviews in overviews. J Evid Based Med. 2014;7(2):72-8.
31. Foisy M, Hartling L. Challenges and considerations involved in using AMSTAR in overviews of reviews. Abstracts of the 22nd Cochrane Colloquium, 21-26 Sept 2014. Hyderabad, India: John Wiley & Sons; 2014.
32. Jia P, Chen J, Zhang L, Zhao P, Zhang M. Challenges and considerations in assessing the reporting quality of systematic reviews in overviews using PRISMA. Abstracts of the 23rd Cochrane Colloquium, 03-07 Oct 2015. Vienna, Austria: John Wiley & Sons; 2015.
33. Crick K, Wingert A, Williams K, Fernandes RM, Thomson D, Hartling L. An evaluation of harvest plots to display results of meta-analyses in overviews of reviews: a cross-sectional study. BMC Med Res Methodol. 2015;15:91.
34. Pollock A, Farmer SE, Brady MC, Langhorne P, Mead GE, Mehrholz J, *et al*. An algorithm was developed to assign GRADE levels of evidence to comparisons within systematic reviews. J Clin Epidemiol. 2015;70:106-10.
35. Foisy M, Fernandes RM, Dryden DM, Hartling L. Grading the quality of evidence in existing systematic reviews: challenges and considerations. Abstracts of the 22nd Cochrane Colloquium, 21-26 Sept 2014. Hyderabad, India: John Wiley & Sons; 2014.

36. Buchter RB, Pieper D. Most overviews of Cochrane reviews neglected potential biases from dual authorship. J Clin Epidemiol. 2016;77:91-4.
37. Lunny C, Brennan SE, McDonald S, McKenzie JE. Evidence map of studies evaluating methods for conducting, interpreting and reporting overviews of systematic reviews of interventions: rationale and design. Syst Rev. 2016;5:4.
38. Thomson D, Foisy M, Oleszczuk M, Wingert A, Chisholm A, Hartling L. Overview of reviews in child health: evidence synthesis and the knowledge base for a specific population. Evid Based Child Health. 2013;8(1):3-10.
39. Cochrane. Special collection: Cochrane overviews. http://www.cochranelibrary.com/app/content/special-collections/article/?doi=10.1002/(ISSN)14651858(CAT)na(VI)SC000036 (2014). Accessed 01 Sept 2017.

Chapter 3: The impact of different inclusion decisions on the comprehensiveness and results of overviews of reviews of healthcare interventions

1. Green S, Higgins JPT, Alderson P, Clarke M, Mulrow CD, Oxman AD. Chapter 1: introduction. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.1.0). The Cochrane Collaboration; 2011. http://www.handbook.cochrane.org.
2. Bastian H, Glasziou P, Chalmers I. Seventy-five trials and eleven systematic reviews a day: how will we ever keep up? PLoS Med. 2010;7(9):e1000326.
3. Jadad AR, Cook DJ, Browman GP. A guide to interpreting discordant systematic reviews. Can Med Assoc J. 1997;156(10):1411-6.

4. Becker LA, Oxman AD. Chapter 22: overviews of reviews. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.1.0). The Cochrane Collaboration; 2011. http://www.handbook.cochrane.org.
5. Pieper D, Antoine SL, Mathes T, Neugebauer EA, Eikermann M. Systematic review finds overlapping reviews were not mentioned in every other overview. J Clin Epidemiol. 2014;67(4):368-75.
6. Pollock M, Fernandes RM, Becker LA, Featherstone R, Hartling L. What guidance is available for researchers conducting overviews of reviews of healthcare interventions? A scoping review and qualitative metasummary. Syst Rev. 2016;5:190.
7. Ballard M, Montgomery P. Risk of bias in overviews of reviews: a scoping review of methodological guidance and four-item checklist. Res Synth Methods. 2017;8(1):92-108.
8. Pollock A, Campbell P, Brunton G, Hunt H, Estcourt L. Selecting and implementing overview methods: implications from five exemplar overviews. Syst Rev. 2017;6:145.
9. Cooper H, Koenka AC. The overview of reviews: unique challenges and opportunities when research syntheses are the principal elements of new integrative scholarship. Am Psychol. 2012;67(6):446-62.
10. Caird J, Sutcliffe K, Kwan I, Dickson K, Thomas J. Mediating policy-relevant evidence at speed: are systematic reviews of systematic reviews a useful approach? Evid Policy. 2015;11(1):81-97.
11. Thomson D, Foisy M, Oleszczuk M, Wingert A, Chisholm A, Hartling L. Overview of reviews in child health: evidence synthesis and the knowledge base for a specific population. Evid Based Child Health. 2013;8(1):3-10.

12. Yin RK. Case study research: design and methods. 5th ed. Thousand Oaks: SAGE Publications; 2013.
13. Pollock M, Sinha I, Hartling L, Rowe BH, Schrieber S, Fernandes RM. Inhaled short-acting bronchodilators for managing emergency childhood asthma: an overview of reviews. Allergy. 2017;72(2):183-200.
14. Oleszczuk M, Fernandes RM, Thomson D, Shaikh N. The Cochrane Library and acute otitis media in children: an overview of reviews. Evid Based Child Health. 2012;7(2):393-402.
15. Bialy L, Foisy M, Smith M, Fernandes RM. The Cochrane Library and the treatment of bronchiolitis in children: an overview of reviews. Evid Based Child Health. 2011;6(1):258-75.
16. Bjornson C, Russell K, Foisy M, Johnson DW. The Cochrane Library and the treatment of croup in children: an overview of reviews. Evid Based Child Health. 2010;5(4):1555-65.
17. Foisy M, Boyle RJ, Chalmers JR, Simpson EL, Williams HC. The prevention of eczema in infants and children: an overview of Cochrane and non-Cochrane reviews. Evid Based Child Health. 2011;6(5):1322-39.
18. Freedman SP, Ali S, Oleszczuk M, Gouin S, Hartling L. Treatment of acute gastroenteritis in children: an overview of systematic reviews of interventions commonly used in developed countries. Evid Based Child Health. 2013;8(4):1123-37.
19. Hartling L, Milne A, Foisy M, Lang E, Sinclair D, Klassen TP, *et al*. What works and what's safe in pediatric emergency procedural sedation: an overview of reviews. Acad Emerg Med. 2016;23(5):519-30.
20. Etikan I, Musa SA, Alkassim RS. Comparison of convenience sampling and purposive sampling. Am J Theor Appl Stat. 2016;5(1):1-4.

21. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, *et al*. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 2007;7:10.
22. Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J, *et al*. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol. 2009;62(10):1013-20.
23. Shea BJ, Bouter LM, Peterson J, Boers M, Andersson N, Ortiz Z, *et al*. External validation of a measurement tool to assess systematic reviews (AMSTAR). PLoS One. 2007;2(12):e1350.
24. Deeks J J, T. HJP, Altman DG. Chapter 9: analysing data and undertaking meta-analyses. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.1.0). The Cochrane Collaboration; 2011. http://www.handbook.cochrane.org.
25. Tricco AC, Tetzlaff J, Pham B, Brehaut J, Moher D. Non-Cochrane vs. Cochrane reviews were twice as likely to have positive conclusion statements: cross-sectional study. J Clin Epidemiol. 2009;62(4):380-6.
26. Lai NM, Teng CL, Lee ML. Interpreting systematic reviews: are we ready to make our own conclusions? A cross-sectional study. BMC Med. 2011;9:30.
27. Miles MB, Huberman AM, Saldana J. Qualitative data analysis: a methods sourcebook. 3rd ed. Thousand Oaks: SAGE Publications; 2014.
28. Page MJ, Shamseer L, Altman DG, Tetzlaff J, Sampson M, Tricco AC, *et al*. Epidemiology and reporting characteristics of systematic reviews of biomedical research: a cross-sectional study. PLoS Med. 2016;13(5):e1002028.

Chapter 4: Evaluation of AMSTAR to assess the methodological quality of systematic reviews in overviews of reviews of healthcare interventions

1. Green S, Higgins JPT, Alderson P, Clarke M, Mulrow CD, Oxman AD. Chapter 1: Introduction. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.1.0). The Cochrane Collaboration; 2011. http://www.handbook.cochrane.org.
2. Bastian H, Glasziou P, Chalmers I. Seventy-five trials and eleven systematic reviews a day: how will we ever keep up? PLoS Med. 2010;7(9):e1000326.
3. Becker LA, Oxman AD. Chapter 22: overviews of reviews. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.1.0). The Cochrane Collaboration; 2011. http://www.handbook.cochrane.org.
4. Hartling L, Chisholm A, Thomson D, Dryden DM. A descriptive analysis of overviews of reviews published between 2000 and 2011. PLoS One. 2012;7(11):e49667.
5. Pieper D, Buechter R, Jerinic P, Eikermann M. Overviews of reviews often have limited rigor: a systematic review. J Clin Epidemiol. 2012;65(12):1267-73.
6. Li L, Tian J, Tian H, Sun R, Liu Y, Yang K. Quality and transparency of overviews of systematic reviews. J Evid Based Med. 2012;5(3):166-73.
7. Pollock M, Fernandes RM, Becker LA, Featherstone R, Hartling L. What guidance is available for researchers conducting overviews of reviews of healthcare interventions? A scoping review and qualitative metasummary. Syst Rev. 2016;5:190.
8. Page MJ, Shamseer L, Altman DG, Tetzlaff J, Sampson M, Tricco AC, *et al*. Epidemiology and reporting characteristics of systematic reviews of biomedical research: a cross-sectional study. PLoS Med. 2016;13(5):e1002028.

9. Fleming PS, Seehra J, Polychronopoulou A, Fedorowicz Z, Pandis N. Cochrane and non-Cochrane systematic reviews in leading orthodontic journals: a quality paradigm? Eur J Orthod. 2013;35(2):244-8.
10. MacDonald SL, Canfield SE, Fesperman SF, Dahm P. Assessment of the methodological quality of systematic reviews published in the urological literature from 1998 to 2008. J Urol. 2010;184(2):648-53.
11. Bennett K, Manassis K, Duda S, Bagnell A, Bernstein GA, Garland EJ, *et al*. Preventing child and adolescent anxiety disorders: overview of systematic reviews. Depress Anxiety. 2015;32(12):909-18.
12. Bennett K, Rhodes AE, Duda S, Cheung AH, Manassis K, Links P, *et al*. A youth suicide prevention plan for Canada: a systematic review of reviews. Can J Psychiatry. 2015;60(6):245-57.
13. Fishta A, Backe EM. Psychosocial stress at work and cardiovascular diseases: an overview of systematic reviews. Int Arch Occup Environ Health. 2015;88(8):997-1014.
14. Misfeldt R, Linder J, Lait J, Hepp S, Armitage G, Jackson K, *et al*. Incentives for improving human resource outcomes in health care: overview of reviews. J Health Serv Res Policy. 2014;19(1):52-61.
15. Patnode CD, Henderson JT, Thompson JH, Senger CA, Fortmann SP, Whitlock EP. Behavioral counseling and pharmacotherapy interventions for tobacco cessation in adults, including pregnant women: a review of reviews for the U.S. Preventive Services Task Force. Rockville: Agency for Healthcare Research and Quality, 2015.
16. Remes O, Brayne C, van der Linde R, Lafortune L. A systematic review of reviews on the prevalence of anxiety disorders in adult populations. Brain Behav. 2016;6(7):e00497.

17. Ryan R, Santesso N, Lowe D, Hill S, Grimshaw J, Prictor M, *et al*. Interventions to improve safe and effective medicines use by consumers: an overview of systematic reviews. Cochrane Database Syst Rev. 2014;4:CD007768.
18. Worswick J, Wayne SC, Bennett R, Fiander M, Mayhew A, Weir MC, *et al*. Improving quality of care for persons with diabetes: an overview of systematic reviews - what does the evidence tell us? Syst Rev. 2013;2:26.
19. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, *et al*. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 2007;7:10.
20. Shea BJ, Bouter LM, Peterson J, Boers M, Andersson N, Ortiz Z, *et al*. External validation of a measurement tool to assess systematic reviews (AMSTAR). PLoS One. 2007;2(12):e1350.
21. Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J, *et al*. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol. 2009;62(10):1013-20.
22. Pollock M, Sinha I, Hartling L, Rowe BH, Schrieber S, Fernandes RM. Inhaled short-acting bronchodilators for managing emergency childhood asthma: an overview of reviews. Allergy. 2017;72(2):183-200 [Electronic publication: 05 Oct 2016].
23. Oleszczuk M, Fernandes RM, Thomson D, Shaikh N. The Cochrane Library and acute otitis media in children: an overview of reviews. Evid Based Child Health. 2012;7(2):393-402.
24. Bialy L, Foisy M, Smith M, Fernandes RM. The Cochrane Library and the treatment of bronchiolitis in children: an overview of reviews. Evid Based Child Health. 2011;6(1):258-75.

25. Bjornson C, Russell K, Foisy M, Johnson DW. The Cochrane Library and the treatment of croup in children: an overview of reviews. Evid Based Child Health. 2010;5(4):1555-65.
26. Foisy M, Boyle RJ, Chalmers JR, Simpson EL, Williams HC. The prevention of eczema in infants and children: an overview of Cochrane and non-Cochrane reviews. Evid Based Child Health. 2011;6(5):1322-39.
27. Freedman SP, Ali S, Oleszczuk M, Gouin S, Hartling L. Treatment of acute gastroenteritis in children: an overview of systematic reviews of interventions commonly used in developed countries. Evid Based Child Health. 2013;8(4):1123-37.
28. Hartling L, Milne A, Foisy M, Lang E, Sinclair D, Klassen TP, *et al*. What works and what's safe in pediatric emergency procedural sedation: an overview of reviews. Acad Emerg Med. 2016;23(5):519-30.
29. Kang D, Wu Y, Hu D, Hong Q, Wang J, Zhang X. Reliability and external validity of AMSTAR in assessing quality of TCM systematic reviews. Evid Based Compliment Alternat Med. 2012;2012:732195.
30. Melchiors AC, Correr CJ, Venson R, Pontarolo R. An analysis of quality of systematic reviews on pharmacist health interventions. Int J Clin Pharm. 2012;34(1):32-42.
31. Passon AM, Drabik A, Sawicki PT. Quality scores do not predict discrepant statistical significances among meta-analyses on different targets of glycemic control in type 2 diabetes. J Clin Epidemiol. 2013;66(12):1356-66.
32. Weed DL, Althuis MD, Mink PJ. Quality of reviews on sugar-sweetened beverages and health outcomes: a systematic review. Am J Clin Nutr. 2011;94(5):1340-7.

33. Tricco AC, Tetzlaff J, Pham B, Brehaut J, Moher D. Non-Cochrane vs. Cochrane reviews were twice as likely to have positive conclusion statements: cross-sectional study. J Clin Epidemiol. 2009;62(4):380-6.
34. Lai NM, Teng CL, Lee ML. Interpreting systematic reviews: are we ready to make our own conclusions? A cross-sectional study. BMC Med. 2011;9:30.
35. Flodgren G, Eccles MP, Shepperd S, Scott A, Parmelli E, Beyer FR. An overview of reviews evaluating the effectiveness of financial incentives in changing healthcare professional behaviours and patient outcomes. Cochrane Database Syst Rev. 2011;7:CD009255.
36. Payne C, Wiffen PJ, Martin S. Interventions for fatigue and weight loss in adults with advanced progressive illness. Cochrane Database Syst Rev. 2012;1:CD008427.
37. Gwet KL. Handbook of inter-rater reliability: the definitive guide to measuring the extent of agreement among raters. 2nd ed. Gaithersburg: Advanced Analytics, LLC; 2010.
38. Gwet KL. Computing inter-rater reliability and its variance in the presence of high agreement. Br J Math Stat Psychol. 2008;61(Pt 1):29-48.
39. Feinstein AR, Cicchetti DV. High agreement but low kappa: I. The problems of two paradoxes. J Clin Epidemiol. 1990;43(6):543-9.
40. Viera AJ, Garrett JM. Understanding interobserver agreement: the kappa statistic. Fam Med. 2005;37(5):360-3.
41. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33(1):159-74.
42. Berkman ND, Lohr KN, Morgan LC, Kuo TM, Morton SC. Interrater reliability of grading strength of evidence varies with the complexity of the evidence in systematic reviews. J Clin Epidemiol. 2013;66(10):1105-17.

43. Hinkle DE, Wiersma W, Jurs SG. Applied statistics for the behavioral sciences. 5th ed. Boston: Houghton Mifflin; 2002.
44. Burda BU, Holmer HK, Norris SL. Limitations of A Measurement Tool to Assess Systematic Reviews (AMSTAR) and suggestions for improvement. Syst Rev. 2016;5:58.
45. Wegewitz U, Weikert B, Fishta A, Jacobs A, Pieper D. Resuming the discussion of AMSTAR: what can (should) be made better? BMC Med Res Methodol. 2016;16:111.
46. Faggion CM. Critical appraisal of AMSTAR: challenges, limitations, and potential solutions from the perspective of an assessor. BMC Med Res Methodol. 2015;15:63.
47. Juni P, Altman DG, Egger M. Systematic reviews in health care: assessing the quality of controlled clinical trials. BMJ. 2001;323(7303):42-6.
48. Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.1.0). The Cochrane Collaboration; 2011. http://www.handbook.cochrane.org.
49. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
50. Pieper D, Buechter RB, Li L, Prediger B, Eikermann M. Systematic review found AMSTAR, but not R(evised)-AMSTAR, to have good measurement properties. J Clin Epidemiol. 2014; 68(5):574-83.
51. Higgins JPT, Altman DG, Sterne JAC. Chapter 8: assessing risk of bias in included studies. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.1.0). The Cochrane Collaboration; 2011. http://www.handbook. cochrane.org.
52. Juni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. JAMA. 1999;282(11):1054-60.

53. Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, *et al*. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? Lancet. 1998;352(9128):609-13.

54. Faggion CM, Schmitter M. Using the best available evidence to support clinical decisions in implant dentistry. Int J Oral Maxillofac Implants. 2010;25(5):960-9.

55. Popovich I, Windsor B, Jordan V, Showell M, Shea B, Farquhar CM. Methodological quality of systematic reviews in subfertility: a comparison of two different approaches. PLoS One. 2012;7(12):e50403.

56. Tunis AS, McInnes MD, Hanna R, Esmail K. Association of study quality with completeness of reporting: have completeness of reporting and quality of systematic reviews and meta-analyses in major radiology journal changed since publication of the PRISMA statement? Radiology. 2013;269(2):413-26.

57. Andersen JH, Fallentin N, Thomsen JF, Mikkelsen S. Risk factors for neck and upper extremity disorders among computers users and the effect of interventions: an overview of systematic reviews. PLoS One. 2011;6(5):e19691.

58. Berkhof M, van Rijssen HJ, Schellart AJ, Anema JR, van der Beek AJ. Effective training strategies for teaching communication skills to physicians: an overview of systematic reviews. Patient Educ Couns. 2011;84(2):152-62.

59. Brouwers MC, Garcia K, Makarski J, Daraz L. The landscape of knowledge translation interventions in cancer control: what do we know and where to next? A review of systematic reviews. Implement Sci. 2011;6:130.

60. Cates CJ, Oleszczuk M, Stovold E, Wieland LS. Safety of regular formoterol or salmeterol in children with asthma: an overview of Cochrane reviews. Cochrane Database Syst Rev. 2012;10:CD010005.

61. Cates CJ, Wieland LS, Oleszczuk M, Kew KM. Safety of regular formoterol or salmeterol in adults with asthma: an overview of Cochrane reviews. Cochrane Database Syst Rev. 2014;2:CD010314.

62. Jones L, Othman M, Dowswell T, Alfirevic Z, Gates S, Newburn M, *et al*. Pain management for women in labour: an overview of systematic reviews. Cochrane Database Syst Rev. 2012;3:CD009234.

63. Kumar A, Galeb S, Djulbegovic B. Treatment of patients with multiple myeloma: an overview of systematic reviews. Acta Haematol. 2011;125(1-2):8-22.

64. Leucht S, Hierl S, Kissling W, Dold M, Davis JM. Putting the efficacy of psychiatric and general medicine medication into perspective: review of meta-analyses. Br J Psychiatry. 2012;200(2):97-106.

65. List T, Axelsson S. Management of TMD: evidence from systematic reviews and meta-analyses. J Oral Rehabil. 2010;37(6):430-51.

66. Mikton C, Butchart A. Child maltreatment prevention: a systematic review of reviews. Bull World Health Organ. 2009;87(5):353-61.

67. O'Connell NE, Wand BM, McAuley J, Marston L, Moseley GL. Interventions for treating pain and disability in adults with complex regional pain syndrome. Cochrane Database Syst Rev. 2013;4:CD009416.

68. Oestergaard S, Moldrup C. Improving outcomes for patients with depression by enhancing antidepressant therapy with non-pharmacological interventions: a systematic review of reviews. Public Health. 2011;125(6):357-67.
69. Welsh EJ, Evans DJ, Fowler SJ, Spencer S. Interventions for bronchiectasis: an overview of Cochrane systematic reviews. Cochrane Database Syst Rev. 2015;7:CD010337.
70. Wu L, Norman G, Dumville JC, O'Meara S, Bell-Syer SE. Dressings for treating foot ulcers in people with diabetes: an overview of systematic reviews. Cochrane Database Syst Rev. 2015;7:CD010471.
71. Zwicker JG, Mayson TA. Effectiveness of treadmill training in children with motor impairments: an overview of systematic reviews. Pediatr Phys Ther. 2010;22(4):361-77.
72. Pieper D, Mathes T, Eikermann M. Impact of choice of quality appraisal tool for systematic reviews in overviews. J Evid Based Med. 2014;7(2):72-8.
73. Shea B, Henry D. Development of AMSTAR 2. Abstracts of the 24th Cochrane Colloquium, 23-27 Oct 2016. Seoul, Korea: John Wiley & Sons; 2016.
74. Whiting P, Savovic J, Higgins JP, Caldwell DM, Reeves BC, Shea B, *et al*. ROBIS: a new tool to assess risk of bias in systematic reviews was developed. J Clin Epidemiol. 2016;69:225-34.
75. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, *et al*. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Controlled Clin Trials. 1996;17(1):1-12.

Chapter 5: Preferred Reporting Items for Overviews of Reviews (PRIOR): a protocol for development of a reporting guideline for overviews of reviews of healthcare interventions

1. Becker LA, Oxman AD. Chapter 22: overviews of reviews. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.1.0). The Cochrane Collaboration; 2011. http://www.handbook.cochrane.org.
2. Hartling L, Chisholm A, Thomson D, Dryden DM. A descriptive analysis of overviews of reviews published between 2000 and 2011. PLoS One. 2012;7(11):e49667.
3. Pieper D, Buechter R, Jerinic P, Eikermann M. Overviews of reviews often have limited rigor: a systematic review. J Clin Epidemiol. 2012;65(12):1267-73.
4. Pollock M, Fernandes RM, Becker LA, Featherstone R, Hartling L. What guidance is available for researchers conducting overviews of reviews of healthcare interventions? A scoping review and qualitative metasummary. Syst Rev. 2016;5:190.
5. Onishi A, Furukawa TA. Chapter 13: state-of-the-art reporting. In: Biondi-Zoccai G, editor. Umbrella reviews: evidence synthesis with overviews of reviews and meta-epidemiologic studies. Cham: Springer International Publishing; 2016. p. 189-202.
6. Li L, Tian J, Tian H, Sun R, Liu Y, Yang K. Quality and transparency of overviews of systematic reviews. J Evid Based Med. 2012;5(3):166-73.
7. Singh JP. Development of the Metareview Assessment of Reporting Quality (MARQ) checklist. Rev Fac Med. 2012;60(4):325-32.
8. Wagner S, White M, Schultz I, Iverson R, Hsu V, McGuire L, *et al.* Assessing a systematic review of systematic reviews: developing a criteria. Abstracts of the Canadian Association for Research on Work and Health Conference, 01-02 Jun 2012. Vancouver, Canada.
9. Moher D, Schulz KF, Simera I, Altman DG. Guidance for developers of health research reporting guidelines. PLoS Med. 2010;7(2):e1000217.

10. Plint AC, Moher D, Morrison A, Schulz K, Altman DG, Hill C, *et al*. Does the CONSORT checklist improve the quality of reports of randomised controlled trials? A systematic review. Med J Aust. 2006;185(5):263-7.
11. Smidt N, Rutjes AW, van der Windt DA, Ostelo RW, Bossuyt PM, Reitsma JB, *et al*. The quality of diagnostic accuracy studies since the STARD statement: has it improved? Neurology. 2006;67(5):792-7.
12. Simera I, Moher D, Hoey J, Schulz KF, Altman DG. The EQUATOR Network and reporting guidelines: helping to achieve high standards in reporting health research studies. Maturitas. 2009;63(1):4-6.
13. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
14. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, *et al*. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med. 2015;162(11):777-84.
15. Pieper D, Pollock M, Fernandes RM, Buchter RB, Hartling L. Epidemiology and reporting characteristics of overviews of reviews of healthcare interventions published 2012-2016: protocol for a systematic review. Syst Rev. 2017;6(1):73.
16. Horsley T, Dingwall O, Sampson M. Checking reference lists to find additional studies for systematic reviews. Cochrane Database Syst Rev. 2011;8:MR000026.
17. Greenhalgh T, Peacock R. Effectiveness and efficiency of search methods in systematic reviews of complex evidence: audit of primary sources. BMJ. 2005;331(7524):1064-5.

18. Murphy MK, Black NA, Lamping DL, McKee CM, Sanderson CF, Askham J, *et al*. Consensus development methods, and their use in clinical guideline development. Health Technol Assess. 1998;2(3):1-88.
19. Hsu C, Sandford BA. The Delphi technique: making sense of consensus. Pract Assess Res Eval. 2007;12(10):1-8.
20. Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. J Adv Nurs. 2000;32(4):1008-15.
21. Jones J, Hunter D. Consensus methods for medical and health services research. BMJ. 1995;311(7001):376-80.
22. Streiner DL, Norman GR. Health measurement scales: a practical guide to their development and use. 4th ed. New York: Oxford University Press; 2008.
23. Dillman DA, Smyth JD, Melani Christian L. Internet, mail, and mixed-mode surveys: the tailored design method. 3rd ed. New Jersey: John Wiley & Sons; 2009.
24. Dillman DA, Tortora RD, Bowker D. Principles for constructing web surveys. SESRC Technical Report 98-50. 1998.
25. Diamond IR, Grant RC, Feldman BM, Pencharz PB, Ling SC, Moore AM, *et al*. Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. J Clin Epidemiol. 2014;67(4):401-9.

Chapter 6: Discussion

1. Ballard M, Montgomery P. Risk of bias in overviews of reviews: a scoping review of methodological guidance and four-item checklist. Res Synth Methods. 2017;8(1):92-108.

2. Buchter RB, Pieper D. Most overviews of Cochrane reviews neglected potential biases from dual authorship. J Clin Epidemiol. 2016;77:91-4.
3. Crick K, Wingert A, Williams K, Fernandes RM, Thomson D, Hartling L. An evaluation of harvest plots to display results of meta-analyses in overviews of reviews: a cross-sectional study. BMC Med Res Methodol. 2015;15:91.
4. Pieper D, Mathes T, Eikermann M. Impact of choice of quality appraisal tool for systematic reviews in overviews. J Evid Based Med. 2014;7(2):72-8.
5. Pollock A, Farmer SE, Brady MC, Langhorne P, Mead GE, Mehrholz J, *et al*. An algorithm was developed to assign GRADE levels of evidence to comparisons within systematic reviews. J Clin Epidemiol. 2015;70:106-10.
6. Lunny C, Brennan SE, McDonald S, McKenzie JE. Evidence map of studies evaluating methods for conducting, interpreting and reporting overviews of systematic reviews of interventions: rationale and design. Syst Rev. 2016;5:4.
7. Shea B, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, *et al.* AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008.
8. Whiting P, Savovic J, Higgins JP, Caldwell DM, Reeves BC, Shea B, *et al*. ROBIS: a new tool to assess risk of bias in systematic reviews was developed. J Clin Epidemiol. 2016;69:225-34.
9. Pieper D, Pollock M, Fernandes RM, Buchter RB, Hartling L. Epidemiology and reporting characteristics of overviews of reviews of healthcare interventions published 2012-2016: protocol for a systematic review. Syst Rev. 2017;6(1):73.

10. Hartling L, Chisholm A, Thomson D, Dryden DM. A descriptive analysis of overviews of reviews published between 2000 and 2011. PLoS One. 2012;7(11):e49667.
11. Pieper D, Buechter R, Jerinic P, Eikermann M. Overviews of reviews often have limited rigor: a systematic review. J Clin Epidemiol. 2012;65(12):1267-73.
12. Cochrane. Special collection: Cochrane overviews. http://www.cochranelibrary.com/app/content/special-collections/article/?doi=10.1002/(ISSN)14651858(CAT)na(VI)SC000036 (2014). Accessed 01 Sept 2017.
13. Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. Int J Evid Based Healthc. 2015;13(3):132-40.
14. Foisy M, Dryden DM, Fernandes RM, Hartling L, Thomson D. Advancing methods for overviews of reviews: a discussion of challenges and potential solutions. Abstracts of the 22nd Cochrane Colloquium; 21-26 Sept 2014; Hyderabad, India: John Wiley & Sons; 2014.
15. Becker LA, Oxman AD. Chapter 22: overviews of reviews. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.1.0). The Cochrane Collaboration; 2011. http://www.handbook.cochrane.org.
16. Canadian Institutes of Health Research. Health research roadmap II: capturing innovation to produce better health and health care for Canadians. Strategic plan 2014-15 – 2018-19. http://cihr-irsc.gc.ca/e/48964.html (2015). Accessed 01 Sept 2017.

Appendices

Chapter 1: Introduction

Appendix 1A. BioMed Central copyright and license agreement.

Appendix 1B. Overviews selected for inclusion into the two empirical methods studies.

Chapter 2: What guidance is available for researchers conducting overviews of reviews of healthcare interventions? A scoping review and qualitative metasummary

Appendix 2A. Complete search strategies.

Appendix 2B. Text extracted and not extracted from included documents.

Appendix 2C. Included documents.

Chapter 3: The impact of different inclusion decisions on the comprehensiveness and results of overviews of reviews of healthcare interventions

Appendix 3A. Inclusion criteria used in each overview, stratified by overview topic.

Appendix 3B. Comparisons and systematic reviews included in different inclusion scenarios, for each overview topic.

Chapter 4: Evaluation of AMSTAR to assess the methodological quality of systematic reviews in overviews of reviews of healthcare interventions

Appendix 4A. List of included systematic reviews, along with their AMSTAR assessments.

Appendix 4B. Additional results data.

Chapter 5: Preferred Reporting Items for Overviews of Reviews (PRIOR): a protocol for development of reporting guidelines for overviews of reviews of healthcare interventions

No appendices.

Chapter 6: Discussion

No appendices.

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Appendix 1B. Overviews selected for inclusion into the two empirical methods studies.

Acute asthma (included in study sample)
Pollock M, Sinha I, Hartling L, Rowe BH, Schreiber S, Fernandes RM. Inhaled short-acting bronchodilators for managing emergency childhood: an overview of reviews. Allergy. 2017; 72(2):183-200. (Electronic publication: 05 Oct 2016)

Acute otitis media (included in study sample)
Oleszczuk M, Fernandes RM, Thomson D, Shaikh N. The Cochrane Library and acute otitis media in children: an overview of reviews. Evid Based Child Health. 2012; 7(2):393-402.

Anxiety disorders
Manassis K, Russell K, Newton AS. The Cochrane Library and the treatment of childhood and adolescent anxiety disorders: an overview of reviews. Evid Based Child Health. 2010; 5(2):541-54.

Attention deficit hyperactivity disorder
Foisy M, Williams K. The Cochrane Library and non-pharmacological treatments for attention deficit hyperactivity disorder in children and adolescents: An overview of reviews. Evid Based Child Health. 2011; 6(2):283-97.

Bicycle helmet use
Russell K, Foisy M, Parkin P, Macpherson A. The promotion of bicycle helmet use in children and youth: An overview of reviews. Evid Based Child Health. 2011; 6(6):1780-9.

Bronchiolitis (included in study sample)
Bialy L, Foisy M, Smith M, Fernandes RM. The Cochrane Library and the treatment of bronchiolitis in infants: An overview of reviews. Evid Based Child Health. 2011; 6(1):258-75.

Bronchopulmonary dysplasia
Harrold J, Ali S, Oleszczuk M, Lacaze-Masmonteil T, Hartling L. Corticosteroids for the prevention of bronchopulmonary dysplasia in preterm infants: an overview of Cochrane reviews. Evid Based Child Health. 2013; 8(6):2063-75.

Chronic abdominal pain
Foisy M, Ali S, Geist R, Weinstein M, Michail S, Thakkar K. The Cochrane Library and the treatment of chronic abdominal pain in children and adolescents: An overview of reviews. Evid Based Child Health. 2011; 6(4):1027-43.

Chronic cough
Russell K, Chang AB, Foisy M, Thomson D, Williams K. The Cochrane Library and the treatment of chronic cough in children: An overview of reviews. Evid Based Child Health. 2010; 5(3):1196-205.

Croup (included in study sample)

Bjornson C, Russell K, Foisy M, Johnson DW. The Cochrane Library and the treatment of croup in children: An overview of reviews. Evid Based Child Health. 2010; 5(4):1555-65.

Eczema (included in study sample)
Foisy M, Boyle RJ, Chalmers JR, Simpson EL, Williams HC. The prevention of eczema in infants and children: An overview of Cochrane and non-Cochrane reviews. Evid Based Child Health. 2011; 6(5):1322-39.

Gastroenteritis (included in study sample)
Freedman SB, Ali S, Oleszczuk M, Gouin S, Hartling L. Treatment of acute gastroenteritis in children: an overview of systematic reviews of interventions commonly used in developed countries. Evid Based Child Health. 2013; 8(4): 1123-37.

Patent ductus arteriosus
Harrold J, Lacaze-Masmonteil T, Hartling L, Oleszczuk M. The Cochrane Library and treatment of patent ductus arteriosus: an overview of reviews. Evid Based Child Health. 2012; 7(4):1185-95.

Procedural pain
Curtis S, Wingert A, Ali S. The Cochrane Library and procedural pain in children: an overview of reviews. Evid Based Child Health. 2012; 7(5):1363-99.

Procedural sedation (included in study sample)
Hartling L, Milne A, Foisy M, Lang E, Sinclair D, Klassen TP, Evered L. What works and what's safe in pediatric emergency procedural sedation: an overview of reviews. Acad Emerg Med. 2016;23(5):519-30.

Sore throat
Foisy M, Martin B, Domino F, Becker LA. The Cochrane Library and the treatment of sore throat in children and adolescents: An overview of reviews. Evid Based Child Health. 2011; 6(3):810-23.

Appendix 2A. Complete search strategies.

1. Reference Tracking

Start Date: 21 January 2014

End Date: 14 March 2014

Procedure[a]: For each target article, we searched for "citing" references (Google Scholar), "cited" references (Scopus, reference lists), and "similar articles" (PubMed).

Target Articles (30):

1. Agency for Quality and Accreditation in Health Care Croatia. The Croatian guideline for health technology assessment process and reporting. 1st ed. Zagreb: XXX; 2011.

2. Becker L, Caldwell D, Higgins J, Li T, Salanti G, Schmid C. Comparing multiple interventions in Cochrane reviews. In: Comparing multiple interventions in Cochrane reviews. Cochrane Comparing Multiple Interventions Methods Group. 2013. http://www.Cmim.cochrane.org/comparing-multiple-interventions-cochrane-reviews [Follow link saying "A background paper explaining the rationale"]. Accessed 01 Sept 2017.

3. Becker LA, Oxman AD. Chapter 22: overviews of reviews. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.1.0). The Cochrane Collaboration; 2011. http://www.handbook.cochrane.org. [Originally published in 2008].

4. Caldwell DM, Welton NJ, Ades AE. Mixed treatment comparison analysis provides internally coherent treatment effect estimates based on overviews of reviews and can reveal inconsistency. J Clin Epidemiol. 2010;63(8):875-82.

5. Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care. York: University of York; 2009.

6. Cleemput I, Van Den Bruel A, Kohn L, Vlayen J, Vinck I, Thiry N, *et al*. Search for evidence & critical appraisal: health technology assessment (HTA) (version 2007-1.1). Brussels: Belgian Health Care Knowledge Centre; 2007.

7. Conn VS, Coon Sells TG. WJNR welcomes umbrella reviews. West J Nurs Res. 2014;36(2):147-51.

8. Cooper H, Koenka AC. The overview of reviews: unique challenges and opportunities when research syntheses are the principal elements of new integrative scholarship. Am Psychol. 2012;67(6):446-62.

9. Delgado-Rodriguez M. Systematic reviews of meta-analyses: applications and limitations. J Epidemiol Commun H. 2006;60:90-2.

10. Elliott L, Crombie IK, Irvine L, Cantrell J, Taylor J. The effectiveness of public health nursing: the problems and solutions in carrying out a review of systematic reviews. J Adv Nurs. 2004;45(2):117-25.

11. Froschl B, Brunner-Ziegler S, Conrads-Frank A, Eisenmann A, Gartlehner G, Grillich L, *et al*. Methodenhandbuch fur health technology assessment (vorab-version 1.2012) [Methods manual for health technology assessment (pre-version 1.2012)]. Vienna: Health Austria GmbH; 2012.

12. Hartling L, Vandermeer B, Fernandes RM. Systematic reviews, overviews of reviews and comparative effectiveness reviews: a discussion of approaches to knowledge synthesis. Evid Based Child Health. 2014;9(2):486-94.

13. Hartling L, Chisholm A, Thomson D, Dryden DM. A descriptive analysis of overviews of reviews published between 2000 and 2011. PLoS One. 2012;7(11):e49667.

14. Hartling L, Vandermeer B, Moher D, Caldwell D, Dryden D. Optimizing evidence synthesis for informed decision-making. Canadian Institutes of Health Research Operating Grant. 2011.

15. Healthcare Improvement Scotland. Standard operating procedure for production of evidence notes. 2012.

16. Hemming K, Bowater RJ, Lilford RJ. Pooling systematic reviews of systematic reviews: a Bayesian panoramic meta-analysis. Stat Med. 2012;31(3):201-16.

17. Ludwig Boltzmann Gesellschaft Institute for Health Technology Assessment. (Internes) Manual ablaufe und methoden (teil 2) [(Internal) Manual of processes and methods (part 2)]. Vienna: Ludwig Boltzmann Gesellschaft GmbH; 2007.

18. Institute for Quality and Efficiency in Health Care. Allgemeine methoden (version 4.0) [General methods (version 4.0)]. Cologne; 2011.

19. Ioannidis JPA. Integration of evidence from multiple meta-analyses: a primer on umbrella reviews, treatment networks and multiple treatments meta-analyses. Can Med Assoc J. 2009;181(8):488-93.

20. Li L, Tian J, Tian H, Sun R, Liu Y, Yang K. Quality and transparency of overviews of systematic reviews. J Evid Based Med. 2012;5(3):166-73.

21. National Institute for Health and Clinical Excellence. Methods for the development of NICE public health guidance. 3rd ed. 2012.

22. Pertl D, Froschl B, Rosian-Schikuta I, Sturzlinger H, Freiberger I. Prozesshandbuch für health technology assessment (Bundesinstitut fur Qualita im Gesundheitswesen) [Process

manual for health technology assessment (Federal Institute for Quality in Health Care)]. Vienna: Health Austria GmbH; 2010.

23. Pieper D, Antoine SL, Mathes T, Neugebauer EA, Eikermann M. Systematic review finds overlapping reviews were not mentioned in every other overview. J Clin Epidemiol. 2014;67(4):368-75.

24. Pieper D, Buchter RB, Antoine SL, Eikermann M. Overviews - status quo, potentiale und ausblick [Overviews - status quo, potentials and perspectives]. Z Evid Fortbild Qual Gesundhwes. 2013;107:592-6.

25. Pieper D, Antoine SL, Morfeld JC, Mathes T, Eikermann M. Methodological approaches in conducting overviews: current state in HTA agencies. Res Synth Methods. 2013;5(3):187-99.

26. Pieper D, Buechter R, Jerinic P, Eikermann M. Overviews of reviews often have limited rigor: a systematic review. J Clin Epidemiol. 2012;65(12):1267-73.

27. Ryan RE, Kaufman CA, Hill SJ. Building blocks for meta-synthesis: data integration tables for summarising, mapping, and synthesising evidence on interventions for communicating with health consumers. BMC Med Res Methodol. 2009;9:16.

28. Smith V, Devane D, Begley CM, Clarke M. Methodology in conducting a systematic review of systematic reviews of healthcare interventions. BMC Med Res Methodol. 2011;11(1):15.

29. Thomson D, Foisy M, Oleszczuk M, Wingert A, Chisholm A, Hartling L. Overview of reviews in child health: evidence synthesis and the knowledge base for a specific population. Evid Based Child Health. 2013;8(1):3-10.

30. Thomson D, Russell K, Becker LA, Klassen T, Hartling L. The evolution of a new publication type: steps and challenges of producing overviews of reviews. Res Synth Meth. 2010;1(3-4):198-211.

[a] Procedure modified from: Horsley T, Dingwall O, Sampson M. Checking reference lists to find additional studies for systematic reviews. Cochrane Database Syst Rev. 2011;8:MR000026. Greenhalgh T, Peacock R. Effectiveness and efficiency of search methods in systematic reviews of complex evidence: audit of primary sources. BMJ. 2005;331(7524):1064-5.

2. Database and Web Searches

Database: Medline via Ovid (1946 to Present)

Search Date: 17 January 2014

Search Results:

1. ((overview adj3 reviews) or (overview adj2 review*)).tw.
2. (umbrella adj5 review*).tw.

3. (systematic adj3 overview*).tw.
4. (overview adj2 cochrane adj2 reviews).tw.
5. (systematic adj1 reviews).ti.
6. ((appraisal or analysis or results) adj2 systematic adj review*).tw.
7. (meta-synthesis or (meta adj synthesis)).tw.
8. (meta-review or (meta adj review)).tw.
9. or/1-8 (3561)
10. limit 9 to (english language and humans and yr="2010 - 2013") (994)

Database: EMBASE via Ovid (1996 to 2014 Week 03)

Search Date: 17 January 2014

Search Results:

1. ((overview adj3 reviews) or (overview adj2 review*)).tw.
2. (umbrella adj5 review*).tw.
3. (systematic adj3 overview*).tw.
4. (overview adj2 cochrane adj2 reviews).tw.
5. (systematic adj1 reviews).ti.
6. ((appraisal or analysis or results) adj2 systematic adj review*).tw.
7. (meta-synthesis or (meta adj synthesis)).tw.
8. (meta-review or (meta adj review)).tw.
9. or/1-8 (4335)
10. limit 9 to (english language and humans and yr="2010 - 2013") (1468)

Database: Database of Abstracts of Reviews of Effects (DARE) via Cochrane Library (Issue 4 of 4, October 2013)

Search Date: 17 January 2014

Search Results:

1. (overview near/3 reviews) or (overview near/2 review*)
2. (umbrella near/5 review*)
3. (systematic near/3 overview*)
4. (overview near/2 cochrane near/2 reviews)
5. ((appraisal or analysis or results) near/2 systematic near/1 review)
6. (meta-synthesis or (meta next synthesis))
7. (meta-review or (meta next review))
8. #1 or #2 or #3 or #4 or #5 or #6 or #7 (1604)
9. Limit #8 to “Other Reviews” (288)
10. Limit #9 to “2010-2013” (112)

Database: Scopus

Search Date: 17 January 2014

Search Results:

TITLE((overview PRE/3 reviews) OR (umbrella PRE/2 review*) OR (systematic PRE/2 overviews) OR (overview PRE/2 cochrane PRE/1 reviews) OR meta-review) OR ABS((overview PRE/3 reviews) OR (umbrella PRE/2 review*) OR (systematic PRE/2 overviews) OR (overview PRE/2 cochrane PRE/1 reviews) OR meta-review) AND LANGUAGE(english) AND (LIMIT-TO(PUBYEAR, 2010) OR LIMIT-TO(PUBYEAR, 2011) OR LIMIT-TO(PUBYEAR, 2012) OR LIMIT-TO(PUBYEAR, 2013)) AND (LIMIT-TO(EXACTKEYWORD, "Human") OR LIMIT-TO(EXACTKEYWORD, "Humans")) (324)

Database: Medline via Web of Science[b]

Search Date: 21 January 2014 (search strategy, except for date restriction, was then turned into an article alert; alerts were monitored as part of the update search up to 09 November 2015)

Search Results:

(1.) TI="analys* of systematic reviews"
(2.) TI="guideline* based on systematic review*"
(3.) TI="overview* of Cochrane and non-Cochrane reviews"
(4.) TI="overview* of Cochrane reviews"
(5.) TI="overview* of Cochrane systematic reviews"
(6.) TI="overview* of review*"
(7.) TI="overview* of systematic reviews"
(8.) TI="review* of meta-analyses"
(9.) TI="review* of reviews"
(10.) TI="review* of systematic reviews"
(11.) TI="summar* of Cochrane"
(12.) TI="summar* of systematic reviews"
(13.) TI="synops* of Cochrane systematic reviews"
(14.) TI="systematic review* of meta-analyses"
(15.) TI="systematic review* of reviews"
(16.) TI ="systematic review* of systematic reviews"
(17.) #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 (266)
(18.) #17 Indexes=MEDLINE Timespan=2010-2013 (158)

[b] Medline via Web of Science was searched in addition to Medline via Ovid because the interface allows stop words (e.g., of, on, etc.).

Database: Cochrane Methods Studies Database via Cochrane Library

Search Date: 17 January 2014

Search Results:

1. "overview* of cochrane reviews":ti,ab,kw
2. "overview* of reviews":ti,ab,kw
3. "overview* of systematic reviews":ti,ab,kw

4. "review* of meta-analyses":ti,ab,kw
5. "review* of reviews":ti,ab,kw
6. "review* of systematic reviews":ti,ab,kw
7. "summar* of systematic reviews":ti,ab,kw
8. "systematic review* of reviews":ti,ab,kw
9. "systematic review* of systematic reviews":ti,ab,kw
10. "analys* of systematic reviews":ti,ab,kw
11. “umbrella review*”:ti,ab,kw
12. “systematic overview*”:ti,ab,kw
13. meta-synthes*:ti,ab,kw
14. meta-review*:ti,ab,kw
15. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 from 2010 to 2014 (189)
Limit #15 to Methods Studies (85)

Website: Google Scholar

Search Date: 17 March 2014 (search strategy was then turned into an article alert; alerts were monitored as part of the update search up to 09 November 2015)

Results:

(”review of reviews”|”overview of systematic reviews”|”review of systematic reviews”|”systematic review of reviews”|”overview of reviews”|”umbrella review”|”systematic overview”) (200)[c]

[c] The first 20 pages of results were reviewed.

3. Handsearching Websites and Conference Proceedings

Search Date (Websites): 17 March 2014

Websites Searched (26):

Website	**URL**
Alberta Heritage Foundation for Medical Research	http://www.aihealthsolutions.ca/
Canadian Agency for Drugs and Technologies in Health	http://www.cadth.ca/
Canadian Institutes of Health Research	http://www.cihr-irsc.gc.ca/e/193.html
Centro Cochrane do Brasil	http://www.centrocochranedobrasil.org.br/cms/
Cochrane Child Health Field	http://www.childhealth.cochrane.org/
Cochrane Comparing Multiple Interventions Methods Group	http://www.cmim.cochrane.org/
Cochrane Consumers and Communications Group	http://www.cccrg.cochrane.org/
Cochrane Effective Practice and Organization of Care	http://www.epoc.cochrane.org/
Cochrane Hepato-Biliary Group	http://www.hbg.cochrane.org/

Cochrane Incontinence Group	http://www.incontinence.cochrane.org/
Cochrane Musculoskeletal Group	http://www.musculoskeletal.cochrane.org/
Cochrane Schizophrenia Group	http://www.szg.cochrane.org/
Comprehensive Cancer Centre South, The Netherlands	http://www.eindhovencancerregistry.nl/page.php?id=3527&nav_id=97
Department of Violence and Injury Prevention and Disability, World Health Organization	http://www.who.int/violence_injury_prevention/en/
Finnish Office for Health Technology Assessment and National Research and Development Centre for Welfare and Health	http://www.thl.fi/en_US/web/en
Health Protection Scotland	http://www.hps.scot.nhs.uk/
Iberoamerican Cochrane Group	http://www.es.cochrane.org/es
Institute for Clinical Effectiveness and Health Policy, Argentina	http://www.iecs.org.ar/index.php
Joanna Briggs Institute	http://www.joannabriggs.org/
McMaster University Health Systems Evidence.	http://www.healthsystemsevidence.org
Netherlands Institute for Health Services Research	http://www.nivel.nl/en
Norwegian Knowledge Centre for the Health Services	http://www.kunnskapssenteret.no/home
South African Cochrane Centre	http://www.mrc.ac.za/cochrane/
Netherlands Institute of Mental Health and Addiction	http://www.trimbos.org/
UK Cochrane Centre	http://www.ukcc.cochrane.org/about-uk-cochrane-centre
Workers' Compensation Board Evidence Based Practice Group, Workers' Compensation Board of BC	http://www.worksafebc.com/health_care_providers/related_information/evidence_based_medicine/default.asp

Search Date (Conference Proceedings): 03 March 2014 (Conference Years: 2000-2013)

Search Date for Update Search: 09 November 2015 (Conference Years: 2014-2015)

Conference Proceedings Searched (3):

Conference Name	**URL**
International Cochrane Colloquium	http://www.abstracts.cochrane.org
Health Technology Assessment (HTA) International[d]	http://www.htai.org/meetings/annual-meetings/past-annual-meetings.html
Canadian Agency for Drugs and Technologies in Health (CADTH) Symposium[e]	https://www.cadth.ca/cadth-symposium-archives (also used general web searches)

[d] HTA International could only be searched between 2007-2015; [e] CADTH Symposium could only be searched between 2005-2015.

4. Contacting Producers of Overviews

Date Contacted: April 15, 2014

Date Contacted for Update Search: 09 November 2015

Results:

Type of overview producer	Number contacted (number contacted for update search)
Managing Editors of Cochrane Review Groups and Fields	20 (5)
Authors of published overviews[f]	110 (0)

[f] Lists of authors were obtained from: Hartling L, Chisholm A, Thomson D, Dryden DM. A descriptive analysis of overviews of reviews published between 2000 and 2011. PLoS One. 2012;7(11):e49667. Pieper D, Buechter R, Jerinic P, Eikermann M. Overviews of reviews often have limited rigor: a systematic review. J Clin Epidemiol. 2012;65(12):1267-73.

Appendix 2B. Text extracted and not extracted from included documents.

Type of guidance document	Text targeted for extraction	Text not eligible for extraction
Provides explicit methodological guidance for conducting overviews of healthcare interventions.	Any text that *provides guidance or advice* to help overview authors conduct any part of an overview of healthcare interventions. This includes guidance related to the *context* for conducting overviews (i.e., when and why should researchers conduct an overview?) and guidance related to the *process* of conducting overviews (i.e., how should researchers conduct an overview?).	1) Guidance or advice on how to conduct *other types of overviews* (e.g., diagnostic test accuracy, prognostic, and qualitative overviews). 2) *Examples from published overviews* showing how the guidance can be put into practice. 3) Statements explaining the *rationale* behind, or the *importance* of, the guidance. 4) Descriptions of guidance that originate from *other guidance documents* already included in this scoping review. 5) Guidance statements relating to *organizational structures and/or processes* of overview-producing organizations (e.g., The Cochrane Collaboration). 6) Guidance or advice on how to *report, peer review, or critically appraise* any part of an overview.
	Any text that *describes challenges involved* when conducting an overview of healthcare interventions, regardless of whether or not specific guidance or advice is provided on how to address the challenge.	1) Descriptions of challenges specific to conducting other types of overviews (e.g., diagnostic test accuracy, prognostic, and qualitative overviews). 2) *Content from published overviews* showing examples of the challenge encountered. 3) Explanations describing *why* the challenge was encountered or *how* the challenge was resolved. 4) Descriptions of challenges that originate from *other documents* already included in this scoping review. 5) Text that describes challenges author teams encountered when *reporting, peer reviewing, or critically appraising* any part of an overview.
Describes an author team's experience conducting one or more overviews of healthcare interventions.	Any text that *describes challenges author teams encountered* when conducting an overview of healthcare interventions, regardless of whether or not specific guidance or advice is provided on how to address the challenge.	See above.

Appendix 2C. Included documents.

Documents that contain explicit methodological guidance for conducting overviews (41 documents produced by 12 research groups)

A1. Becker LA, Thomson D, Caldwell D. Addressing multiple treatments: i - Cochrane overviews. Abstracts of the Joint Colloquium of The Cochrane and Campbell Collaborations, 18-22 Oct 2010. Keystone, USA: John Wiley & Sons; 2010. [Available online: http://www.cmim.cochrane.org/keystone-2010. Accessed 01 Sept 2017.]

A2. Foisy M. An introduction to overviews of reviews (umbrella reviews). Northern Alberta Health Libraries Association Leading Edge Symposium, 26 Nov 2014. Edmonton, Canada.

A3. Foisy M, Thomson D, Dryden DM, Fernandes RM, Hartling L. Conducting overviews of reviews: lessons learned since 2006. Abstracts of the 22nd Cochrane Colloquium, 21-26 Sept 2014. Hyderabad, India: John Wiley & Sons; 2014.

A4. Foisy M, Thomson D, Dryden DM, Hartling L. Overviews of reviews: a new publication type and an emerging method of knowledge synthesis. Connecting Through Research Pediatric Research Day, 30 May 2014. Edmonton, Canada.

A5. Foisy M, Thomson D, Dryden DM, Hartling L. Overviews of reviews: a new publication type and an emerging method of knowledge synthesis. Women and Children's Health Research Institute Research Day, 12 Nov 2014. Edmonton, Canada.

A6. Hartling L, Fernandes R, Becker L, Foisy M. Comparing multiple treatments: an introduction to overviews of reviews. Abstracts of the 23rd Cochrane Colloquium, 03-07 Oct 2015. Vienna, Austria: John Wiley & Sons; 2015.

A7. Thomson D, Becker LA, Foisy M. A primer to Cochrane overviews of reviews. Cochrane Canada Live Webinars, 06 Jun 2011. https://www.youtube.com/watch?v=HzSPAvpWpl8 (2011). Accessed 01 Sept 2017.

A8. Thomson D, Foisy M, Hartling L. Overviews of reviews: what they are, what they aren't and how and when to do one. Cochrane Canada Live Webinars, 05 Dec 2013. http://www.youtube.com/watch?v=kj4aA2wPIRs (2013). Accessed 01 Sept 2017.

A9. Thomson D, Russell K, Becker LA, Klassen T, Hartling L. The evolution of a new publication type: steps and challenges of producing overviews of reviews. Res Synth Meth. 2010;1(3-4):198-211.

A10. Cochrane Child Health. Getting started on an overview of reviews. n.d. [Unpublished.]

A11. Cochrane Child Health. Notes on the process of preparing an umbrella review for Evidence-Based Child Health. n.d. [Unpublished.]

A12. Becker L, Caldwell D. Comparing multiple treatments: overviews versus intervention reviews. Abstracts of the 19th Cochrane Colloquium, 19-22 Oct 2011. Madrid, Spain: John Wiley & Sons; 2011. [Available online: http://www.cmim.cochrane.org/workshops-19th-cochrane-colloquium-october-2011. Follow link for workshop 1 slides. Accessed 01 Sept 2017.]

A13. Becker L, Caldwell D, Higgins J, Li T, Salanti G, Schmid C. Comparing multiple interventions in Cochrane reviews. In: Comparing multiple interventions in Cochrane reviews. Cochrane Comparing Multiple Interventions Methods Group. 2013. http://www.cmim.cochrane.org/comparing-multiple-interventions-cochrane-reviews [Follow link saying "A background paper explaining the rationale"]. Accessed 01 Sept 2017.

A14. Becker LA, Caldwell D, Salanti G, Li T. Editorial considerations for reviews that compare multiple interventions. In: Editorial considerations for reviews that compare multiple interventions. Cochrane Comparing Multiple Interventions Methods Group. 2013. http://www.cmimg.cochrane.org/editorial-considerations-reviews-compare-multiple-interventions [Follow links for slides]. Accessed 01 Sept 2017.

A15. Becker LA, Li T, Caldwell D. Comparing multiple treatments 1: overview or intervention review? Abstracts of the 20th Cochrane Colloquium, 30 Sept-03 Oct 2012. Auckland, New Zealand: John Wiley & Sons; 2012. [Available online: http://www.cmim.cochrane.org/20th-cochrane-colloquium-auckland-2012. Follow link saying "Click here for slides from this workshop" for workshop 1 slides. Accessed 01 Sept 2017.]

A16. Becker LA, Oxman AD. Chapter 22: overviews of reviews. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.1.0). The Cochrane Collaboration; 2011. http://www.handbook.cochrane.org. [Originally published in 2008.]

A17. Caldwell DM, Welton NJ, Ades AE. Mixed treatment comparison analysis provides internally coherent treatment effect estimates based on overviews of reviews and can reveal inconsistency. J Clin Epidemiol. 2010;63(8):875-82.

A18. Li T. Comparing multiple treatments: overview or intervention review? Abstracts of the 21st Cochrane Colloquium, 19-23 Sept 2013. Quebec City, Canada: John Wiley & Sons; 2013. [Available online: http://www.cmim.cochrane.org/quebec-2013. Follow link for workshop 1 slides. Accessed 01 Sept 2017.]

A19. Li T, Becker LA. Comparing multiple treatments 1: intervention review or overview? Abstracts of the 22nd Cochrane Colloquium, 21-26 Sept 2014. Hyderabad, India: John Wiley & Sons; 2014.

A20. Salanti G, Becker LA, Caldwell D, Higgins J, Li T, Schmid C. Evolution of Cochrane intervention reviews and overviews of reviews to better accommodate comparisons among multiple interventions. In: Evolution of Cochrane intervention reviews and overviews of reviews to better accommodate comparisons among multiple interventions. Cochrane

Comparing Multiple Interventions Methods Group. 2011. http://www.cmim.cochrane.org/Milan-report [Follow link saying "To download a copy of the full report in PDF format click here]. Accessed 01 Sept 2017.

A21. Agency for Healthcare Research and Quality Evidence-based Practice Centre Program Working Group 3: integrating bodies of evidence: systematic reviews and individual studies. Interview transcript: Lorne Becker. 2014. [Unpublished.]

A22. Cochrane Comparing Multiple Interventions Methods Group. Comparing Multiple Interventions Methods Group meeting minutes. In: Paris meeting - comparing multiple interventions in Cochrane reviews. Cochrane Comparing Multiple Interventions Methods Group. 2012. http://www.cmim.cochrane.org/Paris-2012 [Follow link saying "Minutes of the meeting"]. Accessed 01 Sept 2017.

A23. Cochrane Comparing Multiple Interventions Methods Group. Editorial decision tree for overviews. In: Comparing multiple interventions in Cochrane reviews. Cochrane Comparing Multiple Interventions Methods Group. 2013. http://www.cmim.cochrane.org/comparing-multiple-interventions-cochrane-reviews [Follow link saying "An editorial decision tree"]. Accessed 01 Sept 2017.

A24. Cochrane Comparing Multiple Interventions Methods Group. Methods innovation fund - stream 1. http://www.cmim.cochrane.org/methods-innovation-fund-stream-1 (2013). Accessed 01 Sept 2017.

A25. Cochrane Comparing Multiple Interventions Methods Group. Multiple intervention reviews: reflections from CoEds discussions this week. In: Paris meeting - comparing multiple interventions in Cochrane reviews. Cochrane Comparing Multiple Interventions Methods Group. 2012. http://www.cmim.cochrane.org/Paris-2012 [Follow link saying "Powerpoint summary of CoEds discussion"]. Accessed 01 Sept 2017.

A26. Cochrane Comparing Multiple Interventions Methods Group. Review type and methodological considerations - background paper for the first part of the Paris CMIMG discussion. In: Paris meeting - comparing multiple interventions in Cochrane reviews. Cochrane Comparing Multiple Interventions Methods Group. 2012. http://www.cmim.cochrane.org/Paris-2012 [Follow link saying "Background paper"]. Accessed 01 Sept 2017.

A27. Worswick J, Wayne SC. Methodology of meta-synthesis: overviews of systematic reviews. Canadian Agency for Drugs and Technology in Health Symposium, 03-05 Apr 2011. Vancouver, Canada.

A28. Baker PR, Costello JT, Dobbins M, Waters EB. The benefits and challenges of conducting an overview of systematic reviews in public health: a focus on physical activity. J Public Health (Oxf). 2014;36(3):517-21.

A29. Cooper H, Koenka AC. The overview of reviews: unique challenges and opportunities when research syntheses are the principal elements of new integrative scholarship. Am Psychol. 2012;67(6):446-62.

A30. Caird J, Sutcliffe K, Kwan I, Dickson K, Thomas J. Mediating policy-relevant evidence at speed: are systematic reviews of systematic reviews a useful approach? Evid Policy. 2015;11(1):81-97.

A31. Thomas J. What should we expect from overviews? 23rd Cochrane Colloquium, Overviews of Systematic Reviews Post-Colloquium Symposium, 08 Oct 2015. Vienna, Austria.

A32. Aromataris E, Fernandez R, Godfrey C, Holly C, Khalil H, Tungpunkom P. Methodology for JBI umbrella reviews. 2013. [Unpublished.]

A33. Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. Int J Evid Based Healthc. 2015;13(3):132-40.

A34. Aromataris E, Fernandez R, Godfrey C, Holly C, Khalil H, Tungpunkom P, editors. The Joanna Briggs Institute reviewers' manual 2014: methodology for JBI umbrella reviews. University of Adelaide: Joanna Briggs Institute; 2014.

A35. Joanna Briggs Institute Umbrella Review Methods Group. Umbrella review - systematic review methods group progress report. 2013. [Unpublished.]

A36. Norwegian Knowledge Centre for the Health Services. 2: Vare ulike produkter [2: Our various products]. In: Slik oppsummerer vi forskning: handbok for Nasjonalt kunnskapssenter for helsetjenesten (reviderte utg 3.2) [How we summarize research: handbook for Norwegian Knowledge Centre for the Health Services (revised edition 3.2)]. Oslo: Norwegian Centre for the Health Services; 2013.

A37. Smith V, Devane D, Begley CM, Clarke M. Methodology in conducting a systematic review of systematic reviews of healthcare interventions. BMC Med Res Methodol. 2011;11(1):15.

A38. Hemming K, Bowater RJ, Lilford RJ. Pooling systematic reviews of systematic reviews: a Bayesian panoramic meta-analysis. Stat Med. 2012;31(3):201-16.

A39. Conn VS, Coon Sells TG. WJNR welcomes umbrella reviews. West J Nurs Res. 2014;36(2):147-51.

A40. Pieper D, Antoine SL, Mathes T, Neugebauer EA, Eikermann M. Systematic review finds overlapping reviews were not mentioned in every other overview. J Clin Epidemiol. 2014;67(4):368-75.

A41. Pieper D, Antoine SL, Neugebauer EA, Eikermann M. Up-to-dateness of reviews is often neglected in overviews: a systematic review. J Clin Epidemiol. 2014;67(4):1302-8.

Documents that describe an author team's experience conducting one or more published overviews (11 documents produced by 9 research groups)

A42. Foisy M, Becker LA, Chalmers JR, Boyle RJ, Simpson EL, Williams HC. Mixing with the 'unclean': including non-Cochrane reviews alongside Cochrane reviews in overviews of reviews. Abstracts of the 19th Cochrane Colloquium, 19-22 Oct 2011. Madrid, Spain: John Wiley & Sons; 2011.

A43. Thomson D, Foisy M, Oleszczuk M, Wingert A, Chisholm A, Hartling L. Overview of reviews in child health: evidence synthesis and the knowledge base for a specific population. Evid Based Child Health. 2013;8(1):3-10.

A44. Ryan RE, Kaufman CA, Hill SJ. Building blocks for meta-synthesis: data integration tables for summarising, mapping, and synthesising evidence on interventions for communicating with health consumers. BMC Med Res Methodol. 2009;9:16.

A45. Flodgren GS, Shepperd S, Eccles, M. Challenges facing reviewers preparing overviews of reviews. Abstracts of the 19th Cochrane Colloquium, 19-22 Oct 2011. Madrid, Spain: John Wiley & Sons; 2011.

A46. Pantoja T, Opiyo N, Ciaponni A, Herrera C, Lewin S, Oxman A, *et al*. Strategies for improving health systems in low-income countries: lessons learnt from four overviews of systematic reviews of health systems interventions. Abstracts of the 23rd Cochrane Colloquium, 03-07 Oct 2015. Vienna, Austria: John Wiley & Sons; 2015.

A47. Tanjong Ghogomu E, Maxwell L, Singh J, Christensen R, Wells G, Buchbinder R, *et al*. Overcoming methodological challenges associated with network meta-analysis: the experience of the Musculoskeletal Group. Abstracts of the 19th Cochrane Colloquium, 19-22 Oct 2011. Madrid, Spain: John Wiley & Sons; 2011.

A48. Pollock A, Farmer SE, Brady MC, Langhorne P, Mead GE, Mehrholz J, *et al*. Completing the first Cochrane overview of stroke reviews: experiences of the Cochrane Stroke Group. Abstracts of the 23rd Cochrane Colloquium, 03-07 Oct 2015. Vienna, Austria: John Wiley & Sons; 2015.

A49. Kramer SFL, Langendam M, Elbers R, Scholten R, Hooft L. Preparing an overview of reviews: lessons learned. Abstracts of the 17th Cochrane Colloquium, 11-14 Oct 2009. Singapore, Singapore: John Wiley & Sons; 2009.

A50. Piso B, Semlitsch T, Reinsperger I, Breuer J, Kaminski-Hartenthaler A, Kien C, *et al*. Praxiserfahrungen mit overviews of reviews - wertvolle entscheidungsunterstützung oder wissenschaftliche fingerübung? [Practical experience with overviews of reviews - valuable

decision aid or academic exercise?]. Z Evid Fortbild Qual Gesundhwes. 2015;109(4-5):300-8.

A51. Rojas ML, Lozano J, Sola I, Bonfill X. Incorporating the GRADE approach in overviews of systematic reviews: an example from an overview in neonatal respiratory care. Abstracts of the 19th Cochrane Colloquium, 19-22 Oct 2011. Madrid, Spain: John Wiley & Sons; 2011.

A52. Elliott L, Crombie IK, Irvine L, Cantrell J, Taylor J. The effectiveness of public health nursing: the problems and solutions in carrying out a review of systematic reviews. J Adv Nurs. 2004;45(2):117-25.

Appendix 3A. Inclusion criteria used in each overview, stratified by overview topic.

Population	Intervention	Comparator	Outcome measures[a]	Study design
Acute asthma				
Children aged 0-18 years treated in the ED or equivalent for acute exacerbation of asthma or recurrent wheeze.	Any inhaled short-acting bronchodilator. All doses and frequencies of administration were included.	All comparators.	Primary outcomes: Hospital admission, ED LOS, ICU admission. Secondary outcomes: Clinical severity scores, vital signs (respiratory rate, heart rate, oxygen saturation). Adverse effects: Nausea, vomiting, tremor, other general or specific outcomes deemed undesirable. Supplemental outcomes: PEF, FEV_1.	SRs of RCTs
Acute otitis media				
Children aged 0-18 years with acute otitis media.	All pharmacological interventions.[b]	All pharmacological comparators.[b]	Primary outcome: Pain early in the course of therapy. Secondary outcomes: Treatment failure (persistence of acute otitis media signs and symptoms) at the end of therapy, recurrence. Adverse effects: Any.	SRs of RCTs
Bronchiolitis				
Outpatient children with bronchiolitis.[c]	All interventions.	All comparators.	Primary outcomes: Hospitalization rate on day one, within seven days, at any other time points. Secondary outcomes: ED LOS, clinical severity score at 60 and 120 minutes. Adverse effects: Any.	SRs of RCTs
Croup				
Children with croup.	Glucocorticoids, inhaled epinephrine, humidified air or heliox.	Glucocorticoids, inhaled epinephrine, humidified air or heliox.	Primary outcome: Severity of respiratory distress (clinical croup score, clinical improvement). Secondary outcomes: Hospital admissions, length of stay, re-admissions, risk of intubation.	SRs of RCTs

Eczema				
Children aged 0-18 years at high-risk, and not selected for risk, of developing eczema.	All interventions.[d]	All comparators.[d]	Primary outcome: Incidence of eczema or atopic eczema.[e] Adverse effects: Any	SRs of RCTs and observational studies
Gastroenteritis				
Children aged 0-18 years with acute gastroenteritis.	ORT, anti-emetics and probiotics.[f]	All comparators.[f]	Primary outcome: Rate of hospital admission. Secondary outcomes: Hospital LOS, rate of return visits, administration of IV therapy (due to failure of ORT). Adverse effects: Any, including dysnatremia (for comparisons involving IV therapy)	SRs of RCTs
Procedural sedation				
Children aged 1 month to 21 years requiring procedure-related sedation in the ED or similar setting.	All doses and routes of administration for: propofol (with or without opioid), ketamine, ketamine/propofol combined, nitrous oxide, and midazolam.	All comparators.	Primary outcome: Adverse effects (any side effect, adverse effect, or adverse event). Secondary outcomes: Serious interventions for an adverse effect, efficacy (successful completion of the procedure, level/depth of sedation), length of sedation, ED LOS.	SRs of RCTs and observational studies

ED: emergency department; FEV_1: forced expiratory volume in one second; ICU: intensive care unit; IgE: immunoglobulin E; IV: intravenous; LOS: length of stay; ORT: oral rehydration therapy; PEF: peak expiratory flow; RCT: randomized controlled trial; SR: systematic review.

[a] For overviews that did not specify primary outcomes (acute otitis media, bronchiolitis, croup, gastroenteritis), we considered the efficacy outcome listed first in the overview to be the primary outcome and all other efficacy outcomes to be secondary outcomes.

[b] We excluded comparisons involving bromidoprim (which is not commonly used), and comparisons examined in only one primary study.

[c] The original overview included outpatients, inpatients, and ICU patients.

[d] Except for comparisons examined in only one primary study.
[e] The original overview also included “atopy/IgE sensitization”, “eczema severity”, “time to development of eczema”, “quality of life”, and “healthcare utilization” as secondary outcomes.
[f] We excluded comparisons involving pyrilamine-pentobarbital, promethazine, and trimethobenzamide (which are not commonly used).

Appendix 3B. Comparisons and systematic reviews included in different inclusion scenarios, for each overview topic.

Table 1. Acute asthma.

Comparison	Systematic reviews	Full scenario: Include all Cochrane and non-Cochrane SRs	Restricted scenario 1: Include only Cochrane SRs	Include all non-overlapping SRs, and for each group of overlapping SRs include the…		
				Restricted scenario 2: Cochrane SR	Restricted scenario 3: Most recent SR	Restricted scenario 4: Highest quality SR
Younger children[a]: SABA *vs.* placebo	Chavasse Ⓒ	✓	✓	✓	✓	✓
Younger children: SABA and SAAC *vs.* SABA alone	Everard Ⓒ	✓	✓	✓	✓	✓
Younger children: SABA delivered by MDI with spacer or VHC *vs.* nebuliser	Cates ⒸⓇⓆ	✓	✓	✓	✓	✓
	Castro-Rodriguez	✓				
Older children[b]: SABA *vs.* SAAC	Teoh Ⓒ	✓	✓	✓	✓	✓
Older children: SABA *vs.* adrenaline	Rodrigo 2006	✓		✓	✓	✓
Older children: SABA *vs.* SABA	Jat	✓		✓	✓	✓
Older children: SABA and SAAC *vs.* SABA alone	Griffiths ⒸⓇⓆ	✓	✓	✓	✓	✓
	Rodrigo 2005	✓				
Older children: SABA and SAAC *vs.* SAAC alone	Teoh Ⓒ	✓	✓	✓	✓	✓
Older children: SABA and MgSO4 *vs.* SABA alone	Powell ⒸⓆ	✓	✓	✓		✓
	Shan Ⓡ	✓			✓	
Older children: SABA delivered by MDI with spacer or VHC *vs.* nebuliser	Cates ⒸⓇⓆ	✓	✓	✓	✓	✓
	Amirav	✓				
Older children: SABA delivered by continuous *vs.* intermittent nebulisation	Camargo Ⓒ	✓	✓	✓	✓	✓

Ⓒ: Cochrane SR; Ⓡ: Most recent SR; Ⓠ: Highest quality SR; MDI: metered dose inhaler; $MgSO_4$: magnesium sulfate; SAAC: short-acting anticholinergic; SABA: short-acting beta agonist; SR: systematic review; VHC: valved holding chamber.
[a] 0-3 years of age; [b] 3-18 years of age.

Table 2. Acute otitis media.

Comparison	Systematic reviews	Full scenario: Include all Cochrane and non-Cochrane SRs	Restricted scenario 1: Include only Cochrane SRs	Include all non-overlapping SRs, and for each group of overlapping SRs include the…		
				Restricted scenario 2: Cochrane SR	Restricted scenario 3: Most recent SR	Restricted scenario 4: Highest quality SR
Any antibiotic *vs.* placebo	Sanders Ⓒ	✓	✓	✓		
	Damoiseaux	✓				
	Del Mar	✓				
	Rosenfeld	✓				
	Rovers	✓				
	Shekelle ⓇⓆ	✓			✓	✓
	Vouloumanou	✓				
Short-course antibiotic (single dose azythromycin) *vs.* long-course antibiotic	Korzyskyj ⒸⓆ	✓	✓	✓		✓
	Courter	✓				
	Gulani	✓				
	Shekelle ⓇⓆ	✓			✓	✓
Short-course antibiotic (3-5 days azythromycin) *vs.* long-course antibiotic	Korzyskyj ⒸⓆ	✓	✓	✓		✓
	Courter	✓				
	Gulani	✓				
	Ioannidis	✓				
	Shekelle ⓇⓆ	✓			✓	✓
Short-course antibiotic (intramuscular ceftriaxone) *vs.* long-course antibiotic	Korzyskyj ⒸⓆ	✓	✓	✓		✓
	Gulani	✓				
	Shekelle ⓇⓆ	✓			✓	✓
Any other short-course antibiotic (> 48 hours) *vs.* long-course antibiotic	Korzyskyj ⒸⓆ	✓	✓	✓		✓
	Gulani	✓				
	Shekelle ⓇⓆ	✓			✓	✓

Amoxicillin with(out) clavulanate administered once or twice *vs.* three times daily	Thanaviratananich Ⓒ	✓	✓	✓		
	Shekelle ⓇⓆ	✓			✓	✓
Amoxicillin with(out) clavulanate *vs.* macrolide	Courter	✓				
	Shekelle ⓇⓆ	✓			✓	✓
Amoxicillin with(out) clavulanate *vs.* cephalosporin	Rosenfeld	✓				
	Shekelle ⓇⓆ	✓			✓	✓
Aminopenicillin *vs.* penicillin with(out) sulfisoxazole	Rosenfeld	✓		✓	✓	✓
Aminopenicillin *vs.* trimethoprim-sulfamethoxazole	Rosenfeld	✓		✓	✓	✓
Aminopenicillin *vs.* erythromycin	Rosenfeld	✓		✓	✓	✓
Erythromycin with sulfisoxazole *vs.* cephalosporin	Rosenfeld	✓		✓	✓	✓
Cefaclor vs. other cephalosporin	Rosenfeld	✓				
	Shekelle ⓇⓆ	✓			✓	✓
Cefdinir administered once *vs.* twice daily	Shekelle	✓		✓	✓	✓
Delayed *vs.* immediate antibiotic	Sanders Ⓒ	✓	✓	✓		
	Spurling Ⓒ	✓	✓	✓		
	Rovers	✓				
	Shekelle ⓇⓆ	✓			✓	✓
	Vouloumanou	✓				
Delayed *vs.* no antibiotic	Spurling Ⓒ	✓	✓	✓	✓	✓
Decongestant and/or antihistamine *vs.* none	Coleman Ⓒ	✓	✓	✓	✓	✓
Topical analgesia *vs.* placebo	Foxlee Ⓒ	✓	✓	✓	✓	✓

Ⓒ: Cochrane SR; Ⓡ: Most recent SR; Ⓠ: Highest quality SR; SR: systematic review.

Table 3. Bronchiolitis.

Comparison	Systematic reviews	Full scenario: Include all Cochrane and non-Cochrane SRs	Restricted scenario 1: Include only Cochrane SRs	Include all non-overlapping SRs, and for each group of overlapping SRs include the…		
				Restricted scenario 2: Cochrane SR	Restricted scenario 3: Most recent SR	Restricted scenario 4: Highest quality SR
Glucocorticoid *vs.* placebo	Fernandes ⒸⓇⓆ	✓	✓	✓	✓	✓
	King	✓				
Epinephrine *vs.* placebo	Hartling Ⓒ	✓	✓	✓	✓	✓
Epinephrine and glucocorticoid *vs.* placebo	Fernandes Ⓒ	✓	✓	✓		
	Hartling ⒸⓇⓆ	✓	✓	✓	✓	✓
Epinephrine *vs.* bronchodilator	Hartling ⒸⓇⓆ	✓	✓	✓	✓	✓
	King	✓				
Glucocorticoid *vs.* epinephrine	Fernandes Ⓒ	✓	✓	✓		
	Hartling ⒸⓇⓆ	✓	✓	✓	✓	✓
Glucocorticoid and bronchodilator *vs.* placebo	Fernandes Ⓒ	✓	✓	✓	✓	✓
Bronchodilator *vs.* placebo	Gadomski ⒸⓇⓆ	✓	✓	✓	✓	✓
	Flores	✓				
	Kellner	✓				
	King	✓				
3% hypertonic saline *vs.* 0.9% saline	Zhang 2008 Ⓒ	✓	✓	✓	✓	✓

Ⓒ: Cochrane SR; Ⓡ: Most recent SR; Ⓠ: Highest quality SR; SR: systematic review.

Table 4. Croup.

Comparison	**Systematic reviews**	**Full scenario: Include all Cochrane and non-Cochrane SRs**	**Restricted scenario 1: Include only Cochrane SRs**	**Include all non-overlapping SRs, and for each group of overlapping SRs include the…**		
				Restricted scenario 2: <u>Cochrane</u> SR	**Restricted scenario 3: <u>Most recent</u> SR**	**Restricted scenario 4: <u>Highest quality</u> SR**
Glucocorticoid *vs.* placebo	Russell ©®Ⓠ	✓	✓	✓	✓	✓
	Griffin	✓				
	Kairys	✓				
Dexamethasone *vs.* budenoside	Russell ©®Ⓠ	✓	✓	✓	✓	✓
	Griffin	✓				
Dexamethasone and budenoside *vs.* dexamethasone	Russell ©®Ⓠ	✓	✓	✓	✓	✓
	Griffin	✓				
Dexamethasone and budenoside *vs.* budenoside	Russell ©	✓	✓	✓	✓	✓
Dexamethasone *vs.* betamethasone	Russell ©	✓	✓	✓	✓	✓
Dexamethasone vs. prednisolone	Russell ©	✓	✓	✓	✓	✓
Oral dexamethasone *vs.* intramuscular dexamethasone	Russell ©	✓	✓	✓	✓	✓
Dexamethasone (0.30 mg/kg) *vs.* dexamethasone (0.15 mg/kg)	Russell ©	✓	✓	✓	✓	✓
Dexamethasone (0.60 mg/kg) *vs.* dexamethasone (0.30 mg/kg)	Russell ©	✓	✓	✓	✓	✓
Dexamethasone (0.60 mg/kg) *vs.* dexamethasone (0.15 mg/kg)	Russell ©	✓	✓	✓	✓	✓
Glucocorticoid *vs.* epinephrine	Russell ©	✓	✓	✓	✓	✓
Epinephrine *vs.* placebo	Bjornson ©	✓	✓	✓	✓	✓
Racemic epinephrine *vs.* L-epinephrine	Bjornson ©	✓	✓	✓	✓	✓

Epinephrine with IPPB *vs.* epinephrine without IPPB	Bjornson Ⓒ	✓	✓	✓	✓	✓
Humidified air *vs.* no treatment	Moore Ⓒ	✓	✓	✓	✓	✓
Heliox *vs.* 30% oxygen	Vorweck Ⓒ	✓	✓	✓	✓	✓

Ⓒ: Cochrane SR; Ⓡ: Most recent SR; Ⓠ: Highest quality SR; IPPB: intermittent positive pressure breathing; SR: systematic review.

Table 5. Eczema.

Comparison	Systematic reviews	Full scenario: Include all Cochrane and non-Cochrane SRs	Restricted scenario 1: Include only Cochrane SRs	Include all non-overlapping SRs, and for each group of overlapping SRs include the…		
				Restricted scenario 2: Cochrane SR	Restricted scenario 3: Most recent SR	Restricted scenario 4: Highest quality SR
EBF for at least 6 months *vs.* introduction of solids at 3-6 months	Kramer 2002 Ⓒ	✓	✓	✓		
	Schneider Chafen ⓇⓆ	✓			✓	✓
	Tarini	✓				
EBF for at least 3 months *vs.* partial breastfeeding	Yang	✓		✓	✓	✓
EBF for at least 3 months *vs.* cow's milk formula	Hanifin	✓				
	Hoare Ⓠ	✓				✓
	Yang Ⓡ	✓			✓	
EBF for at least 3 months *vs.* soy formula	Hanifin Ⓡ	✓			✓	
	Hoare Ⓠ	✓				✓
Hydrolysed formula *vs.* cow's milk formula	Osborn 2006a ⒸⓆ	✓	✓	✓		✓
	Alexander	✓				
	Hanifin	✓				
	Hoare	✓				
	Schneider Chafen	✓				
	Szajewska ⓇⓆ	✓			✓	✓
Extensively hydrolysed formula *vs.* partially hydrolysed formula	Osborn 2006a ⒸⓆ	✓	✓	✓		✓
	Hill	✓				
	Hoare	✓				
	Szajewska ⓇⓆ	✓			✓	✓
Soy formula *vs.* cow's milk formula	Osborn 2006b ⒸⓇⓆ	✓	✓	✓	✓	✓
	Hanifin	✓				
	Hoare	✓				

Soy formula *vs.* hydrolysed formula	Hill ®	✓			✓	
	Hoare Ⓠ	✓				✓
Amino acid-based formula *vs.* hydrolysed formula	Hill	✓		✓	✓	✓
Amino acid-based formula *vs.* soy formula	Hill	✓		✓	✓	✓
Maternal antigen avoidance *vs.* standard diet	Kramer 2006 ⒸⓇⓆ	✓	✓	✓	✓	✓
	Hoare	✓				
	Schneider Chafen	✓				
Omega 3 fatty-acid supplementation *vs.* placebo	Anandan Ⓠ	✓				✓
	Kremmyda ®	✓			✓	
Omega 6 fatty-acid supplementation *vs.* placebo	Anandan	✓		✓	✓	✓
High maternal fish intake *vs.* low or no maternal fish intake	Kremmyda	✓		✓	✓	✓
High infant fish intake *vs.* low or no infant fish intake	Kremmyda	✓		✓	✓	✓
Prebiotic *vs.* no prebiotic	Osborn 2007a Ⓒ	✓	✓	✓	✓	✓
Probiotic *vs.* no probiotic	Osborn 2007b ⒸⓆ	✓	✓	✓		✓
	Flohr	✓				
	Hanifin	✓				
	Lee	✓				
	Schneider Chafen ®	✓			✓	
Daycare *vs.* no daycare	Flohr	✓		✓	✓	✓
Living on a farm *vs.* not living on a farm	Flohr	✓		✓	✓	✓
Pet exposure at home *vs.* no pet exposure at home	Flohr Ⓠ	✓				✓
	Langan ®	✓			✓	
Endotoxin exposure *vs.* no endotoxin exposure	Flohr	✓		✓	✓	✓

Childhood infection *vs.* no childhood infection	Flohr	✓		✓	✓	✓
Endoparasites *vs.* no endoparasites	Flohr	✓		✓	✓	✓
Tuberculin response *vs.* no tuberculin response	Flohr	✓		✓	✓	✓
BCG vaccination *vs.* no BCG vaccination	Flohr	✓		✓	✓	✓
Childhood vaccination *vs.* no childhood vaccination	Flohr	✓		✓	✓	✓
Childhood antibiotics *vs.* no childhood antibiotics	Flohr	✓		✓	✓	✓

Ⓒ: Cochrane SR; Ⓡ: Most recent SR; Ⓠ: Highest quality BCG: Bacille Calmette-Guerin; EBF: exclusive breastfeeding; SR: systematic review.

[a] Osborn 2006a was included instead of Szajewska because it was more comprehensive (Osborn 2006a examined all hydrolysed formulas, whereas Szajewska examined only partially hydrolysed formulas).

Table 6. Gastroenteritis.

Comparison	Systematic reviews	Full scenario: Include all Cochrane and non-Cochrane SRs	Restricted scenario 1: Include only Cochrane SRs	Include all non-overlapping SRs, and for each group of overlapping SRs include the…		
				Restricted scenario 2: Cochrane SR	Restricted scenario 3: Most recent SR	Restricted scenario 4: Highest quality SR
ORT *vs.* IV therapy	Hartling ⒸⓇⓆ	✓	✓	✓	✓	✓
	Fonseca	✓				
Oral ondansetron *vs.* placebo	Fedorowicz ⒸⓇⓆ	✓	✓	✓	✓	✓
	DeCamp	✓				
	Szajewska 2007a	✓				
IV ondansetron *vs.* placebo	Fedorowicz ⒸⓇⓆ	✓	✓	✓	✓	✓
	DeCamp	✓				
	Szajewska 2007a	✓				
IV ondansetron *vs.* dexamethasone	Fedorowicz Ⓒ	✓	✓	✓	✓	✓
IV ondansetron *vs.* metoclopramide	Fedorowicz Ⓒ	✓	✓	✓	✓	✓
Dimenhydrinate *vs.* placebo	Fedorowicz Ⓒ	✓	✓	✓	✓	✓
Dexamethasone *vs.* placebo	Fedorowicz ⒸⓇⓆ	✓	✓	✓	✓	✓
	DeCamp	✓				
Metoclopramine *vs.* placebo	Fedorowicz ⒸⓇⓆ	✓	✓	✓	✓	✓
	DeCamp	✓				
Probiotics *vs.* placebo	Allen ⒸⓆ	✓	✓	✓		✓
	Chmielewska	✓				
	Dinleyici Ⓡ	✓				
	Huang	✓				
	McFarland	✓				
	Salari Ⓡ	✓			✓[a]	
	Szajewska 2001	✓				
	Szajewska 2007b	✓				

	Szajewska 2007c	✓				
	Van Neil	✓				

Ⓒ: Cochrane SR; Ⓡ: Most recent SR; Ⓠ: Highest quality SR; IV: intravenous; ORT: oral rehydration therapy; SR: systematic review.
[a] Salari was included instead of Dinleyici because it was more comprehensive (Salari examined all probiotics, whereas Dinleyici examined only one specific strain of probiotic).

Appendix 4A. List of included systematic reviews, along with their AMSTAR assessments.

First author, year [reference]	Topic area	Type of SR	AMSTAR assessments											
			Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Total
Camargo 2003 [1]	Acute asthma	Cochrane	✓	✓	✓	✓	✓	✓	✓		✓	✓		9
Cates 2013 [2]	Acute asthma	Cochrane	✓		✓	✓	✓	✓	✓	✓	✓	✓		9
Chavasse 2002 [3]	Acute asthma	Cochrane	✓		✓		✓	✓	✓					5
Everard 2005 [4]	Acute asthma	Cochrane	✓		✓		✓	✓	✓	✓	✓			7
Griffiths 2013 [5]	Acute asthma	Cochrane	✓		✓	✓	✓	✓	✓	✓	✓	✓		9
Powell 2012 [6]	Acute asthma	Cochrane	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	10
Teoh 2012 [7]	Acute asthma	Cochrane	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		10
Amirav 1997 [8]	Acute asthma	Non-Cochrane					✓	✓		✓	✓			4
Castro-Rodriguez 2004 [9]	Acute asthma	Non-Cochrane			✓	✓	✓	✓	✓	✓	✓	✓		8
Jat 2013 [10]	Acute asthma	Non-Cochrane	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	10
Rodrigo 2005 [11]	Acute asthma	Non-Cochrane			✓	✓		✓	✓	✓	✓	✓		7
Rodrigo 2006 [12]	Acute asthma	Non-Cochrane			✓	✓		✓	✓	✓	✓	✓		7
Shan 2013 [13]	Acute asthma	Non-Cochrane			✓			✓	✓	✓	✓	✓		6
Coleman 2008 [14]	Acute otitis media	Cochrane	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	11
Foxlee 2006 [15]	Acute otitis media	Cochrane	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	10
Kozyrskyj 2010 [16]	Acute otitis media	Cochrane	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	11
Sanders 2004 [17]	Acute otitis media	Cochrane	✓	✓	✓	✓	✓	✓	✓		✓		✓	9
Spurling 2007 [18]	Acute otitis media	Cochrane	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	10
Thanaviratananich 2008 [19]	Acute otitis media	Cochrane	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	10
Courter 2010 [20]	Acute otitis media	Non-Cochrane		✓	✓		✓	✓	✓	✓	✓	✓		8
Damoiseaux 1998 [21]	Acute otitis media	Non-Cochrane			✓	✓		✓		✓				4
Del Mar 1997 [22]	Acute otitis media	Non-Cochrane			✓			✓	✓		✓		✓	5
Gulani 2009 [23]	Acute otitis media	Non-Cochrane			✓	✓	✓	✓	✓	✓	✓	✓	✓	9
Ioannidis 2001 [24]	Acute otitis media	Non-Cochrane			✓		✓	✓	✓	✓	✓	✓	✓	8
Rahlfs 1996 [25]	Acute otitis media	Non-Cochrane						✓						1
Rosenfeld 1994 [26]	Acute otitis media	Non-Cochrane	✓	✓					✓	✓				4

Rovers 2006 [27]	Acute otitis media	Non-Cochrane					✓	✓			✓	✓	✓	5
Shekelle 2010 [28]	Acute otitis media	Non-Cochrane	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	11
Vouloumanou 2009 [29]	Acute otitis media	Non-Cochrane			✓			✓	✓	✓	✓		✓	6
Fernandes 2010 [30]	Bronchiolitis	Cochrane	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	11
Gadomski 2010 [31]	Bronchiolitis	Cochrane	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		10
Hartling 2011 [32]	Bronchiolitis	Cochrane	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	11
Zhang 2008 [33]	Bronchiolitis	Cochrane	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		10
Flores 1997 [34]	Bronchiolitis	Non-Cochrane				✓		✓	✓	✓	✓			5
Kellner 1996 [35]	Bronchiolitis	Non-Cochrane		✓	✓	✓	✓	✓	✓					6
King 2004 [36]	Bronchiolitis	Non-Cochrane			✓	✓					✓	✓		4
Bjornson 2011 [37]	Croup	Cochrane	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	11
Moore 2006 [38]	Croup	Cochrane	✓	✓	✓	✓	✓	✓			✓			7
Russell 2011 [39]	Croup	Cochrane	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	11
Vorweck 2010 [40]	Croup	Cochrane	✓	✓	✓	✓	✓	✓	✓	✓	✓			9
Griffin 2000 [41]	Croup	Non-Cochrane		✓	✓	✓	✓	✓	✓	✓	✓	✓		9
Kairys 1989 [42]	Croup	Non-Cochrane						✓	✓		✓	✓		4
Kramer 2002 [43]	Eczema	Cochrane			✓	✓	✓	✓	✓	✓				6
Kramer 2006 [44]	Eczema	Cochrane	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	11
Osborn 2006a [45]	Eczema	Cochrane	✓	✓	✓		✓	✓	✓	✓	✓		✓	9
Osborn 2006b [46]	Eczema	Cochrane	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	10
Osborn 2007a [47]	Eczema	Cochrane	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	10
Osborn 2007b [48]	Eczema	Cochrane	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	10
Alexander 2010 [49]	Eczema	Non-Cochrane			✓			✓		✓	✓	✓		5
Anandan 2009 [50]	Eczema	Non-Cochrane	✓	✓	✓	✓		✓	✓	✓	✓	✓		9
Dangour 2010 [51]	Eczema	Non-Cochrane	✓	✓	✓		✓	✓		✓	✓	✓		8
Ernst 2002 [52]	Eczema	Non-Cochrane			✓									1
Flohr 2005 [53]	Eczema	Non-Cochrane				✓		✓		✓	✓	✓		5
Gdalevich 2001 [54]	Eczema	Non-Cochrane		✓				✓	✓	✓	✓	✓		6
Hanifin 2003 [55]	Eczema	Non-Cochrane			✓			✓	✓					3
Hill 2007 [56]	Eczema	Non-Cochrane				✓	✓	✓	✓	✓	✓			6

Hoare 2000 [57]	Eczema	Non-Cochrane		✓	✓	✓	✓	✓	✓	✓	✓			8
Ip 2007 [58]	Eczema	Non-Cochrane			✓		✓	✓	✓	✓	✓		✓	7
Kremmyda 2009 [59]	Eczema	Non-Cochrane						✓						1
Langan 2007 [60]	Eczema	Non-Cochrane						✓		✓	✓	✓		4
Lee 2008 [61]	Eczema	Non-Cochrane			✓			✓	✓		✓			4
Muche-Borowski 2009 [62]	Eczema	Non-Cochrane			✓					✓				2
Oddy 2009 [63]	Eczema	Non-Cochrane					✓			✓				2
Schneider Chafen 2010 [64]	Eczema	Non-Cochrane	✓		✓		✓	✓	✓	✓	✓			7
Szajewska 2010 [65]	Eczema	Non-Cochrane		✓	✓	✓	✓	✓	✓	✓	✓	✓		9
Tarini 2006 [66]	Eczema	Non-Cochrane			✓			✓		✓				3
Yang 2009 [67]	Eczema	Non-Cochrane		✓	✓			✓		✓	✓	✓		6
Allen 2010 [68]	Gastroenteritis	Cochrane	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	11
Fedorowicz 2011 [69]	Gastroenteritis	Cochrane	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	10
Hartling 2006 [70]	Gastroenteritis	Cochrane	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	11
Chmielewska 2008 [71]	Gastroenteritis	Non-Cochrane		✓			✓	✓	✓	✓	✓	✓		7
DeCamp 2008 [72]	Gastroenteritis	Non-Cochrane		✓		✓		✓	✓	✓	✓	✓		7
Dinleyici 2012 [73]	Gastroenteritis	Non-Cochrane			✓	✓		✓		✓	✓	✓		6
Fonseca 2004 [74]	Gastroenteritis	Non-Cochrane		✓	✓	✓	✓	✓	✓		✓			7
Huang 2002 [75]	Gastroenteritis	Non-Cochrane			✓	✓	✓	✓	✓	✓	✓	✓		8
McFarland 2006 [76]	Gastroenteritis	Non-Cochrane	✓		✓	✓		✓	✓		✓	✓		7
Salari 2012 [77]	Gastroenteritis	Non-Cochrane							✓	✓	✓	✓		4
Szajewska 2001 [78]	Gastroenteritis	Non-Cochrane	✓	✓	✓		✓	✓	✓		✓			7
Szajewska 2007a [79]	Gastroenteritis	Non-Cochrane		✓	✓			✓	✓	✓	✓	✓		7
Szajewska 2007b [80]	Gastroenteritis	Non-Cochrane		✓	✓		✓	✓	✓	✓	✓	✓		8
Szajewska 2007c [81]	Gastroenteritis	Non-Cochrane		✓	✓		✓	✓	✓	✓	✓	✓		8
Van Neil 2002 [82]	Gastroenteritis	Non-Cochrane		✓	✓	✓	✓	✓			✓	✓		7
Deasy 2010 [83]	Procedural sedation	Non-Cochrane			✓			✓		✓	✓			4
Faddy 2005 [84]	Procedural sedation	Non-Cochrane						✓	✓	✓	✓			4
Green 2009 [85]	Procedural sedation	Non-Cochrane	✓					✓		✓	✓			4
Howes 2004 [86]	Procedural sedation	Non-Cochrane			✓			✓		✓	✓			4

Jameson 2011 [87]	Procedural sedation	Non-Cochrane						✓			✓			2
Lamond 2010 [88]	Procedural sedation	Non-Cochrane						✓	✓		✓			3
Leroy 2010 [89]	Procedural sedation	Non-Cochrane			✓					✓	✓			3
Mace 2004 [90]	Procedural sedation	Non-Cochrane						✓	✓	✓	✓			4
Migita 2005 [91]	Procedural sedation	Non-Cochrane		✓	✓	✓	✓	✓		✓	✓			7
Mistry 2005 [92]	Procedural sedation	Non-Cochrane						✓			✓			2
National Clinical Guideline Center 2010 [93]	Procedural sedation	Non-Cochrane	✓		✓			✓	✓	✓	✓		✓	7
Pedersen 2013 [94]	Procedural sedation	Non-Cochrane									✓			1
Symington 2006 [95]	Procedural sedation	Non-Cochrane						✓		✓	✓			3

References

1. Camargo Jr C, Spooner C, Rowe B. Continuous versus intermittent beta-agonists for acute asthma. Cochrane Database Syst Rev. 2003;4:CD001115.

2. Cates C, Welsh E, Rowe B. Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma. Cochrane Database Syst Rev. 2013;9:CD000052.

3. Chavasse R, Seddon P, Bara A, McKean M. Short acting beta2-agonists for recurrent wheeze in children under two years of age. Cochrane Database Syst Rev. 2002;2:CD002873.

4. Everard M, Bara A, Kurian M, N'Diaye T, Ducharme F, Mayowe V. Anticholinergic drugs forwheeze in children under the age of two years. Cochrane Database Syst Rev. 2005;3:CD001279.

5. Griffiths B, Ducharme F. Combined inhaled anticholinergics and short-acting beta2-agonists for initial treatment of acute asthma in children. Cochrane Database Syst Rev. 2013;8:CD000060.

6. Powell C, Dwan K, Milan S, Beasley R, Hughes R, Knopp-Sihota J, *et al*. Inhaled magnesium sulfate in the treatment of acute asthma. Cochrane Database Syst Rev. 2012;12:CD003898.

7. Teoh L, Cates C, Hurwitz M, Acworth J, van Asperen P, Chang A. Anticholinergic therapy for acute asthma in children. Cochrane Database Syst Rev. 2012;4:CD003797.

8. Amirav I, Newhouse M. Metered-dose inhaler accessory devices in acute asthma: efficacy and comparison with nebulizers: a literature review. Arch Pediatr Adolesc Med. 1997;151(9):876-82.

9. Castro-Rodriguez JA, Rodrigo GJ. Beta-agonists through metered-dose inhaler with valved holding chamber versus nebulizer for acute exacerbation of wheezing or asthma in children under 5 years of age: a systematic review with meta-analysis. J Pediatr. 2004;145(2):172-7.

10. Jat KR, Khairwa A. Levalbuterol versus albuterol for acute asthma: a systematic review and meta-analysis. Pulm Pharmacol Ther. 2013;26:239-48.

11. Rodrigo GJ, Castro-Rodriguez JA. Anticholinergics in the treatment of children and adults with acute asthma: a systematic review with meta-analysis. Thorax. 2005;60(9):740-6.

12. Rodrigo GJ, Nannini LJ. Comparison between nebulized adrenaline and beta2 agonists for the treatment of acute asthma. A meta-analysis of randomized trials. Am J Emerg Med. 2006;24(2):217-22.

13. Shan Z, Rong Y, Yang W, Wang D, Yao P, Xie J, *et al*. Intravenous and nebulized magnesium sulfate for treating acute asthma in adults and children: a systematic review and meta-analysis. Respir Med. 2013;107(3):321-30.

14. Coleman C, Moore M. Decongestants and antihistamines for acute otitis media in children. Cochrane Database Syst Rev. 2008;3:CD001727.

15. Foxlee R, Johansson A, Wejfalk J, Dooley L, Del Mar C. Topical analgesia for acute otitis media. Cochrane Database Syst Rev. 2006;3:CD005657.

16. Kozyrskyj A, Klassen T, Moffatt M, Harvey K. Short-course antibiotics for acute otitis media. Cochrane Database Syst Rev. 2010;9:CD001095.

17. Sanders S, Glasziou P, Del Mar C, Rovers M. Antibiotics for acute otitis media in children. Cochrane Database Syst Rev. 2004;1:CD000219.

18. Spurling G, Del Mar C, Dooley L, Foxlee R. Delayed antibiotics for respiratory infections. Cochrane Database Syst Rev. 2007;3:CD004417.

19. Thanaviratananich S, Laopaiboon M, Vatanasapt P. Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media. Cochrane Database Syst Rev. 2008;4:CD004975.

20. Courter JD, Baker WL, Nowak KS, Smogowicz LA, Desjardins LL, Coleman CI, *et al*. Increased clinical failures when treating acute otitis media with macrolides: a meta-analysis. Ann Pharmacother. 2010;44(3):471-8.

21. Damoiseaux R, van Balen F, Hoes A, de Melker R. Antibiotic treatment of acute otitis media in children under two years of age: evidence based? Br J Gen Pract. 1998;48(437):1861-4.

22. Del Mar C, Glasziou P, Hayem M. Are antibiotics indicated as initial treatment for children with acute otitis media? A meta-analysis. BMJ. 1997;314(7093):1526-9.

23. Gulani A, Sachdev H. Effectiveness of shortened course (≤ 3 days) of antibiotics for treatment of acute otitis media in children: a systematic review of randomized controlled efficacy trials. Geneva: World Health Organization, 2009.

24. Ioannidis J, Contopoulos-Ioannidis D, Chew P, Lau J. Meta-analysis of randomized controlled trials on the comparative efficacy and safety of azithromycin against other antibiotics for upper respiratory tract infections. J Antimicrob Chemother. 2001;48(5):677-89.

25. Rahlfs V, Macciocchi A, Monti T. Brodimoprim in upper respiratory tract infections. Clin Drug Invest. 1996;11(2):65-76.

26. Rosenfeld R, Vertrees J, Carr J, Cipolle R, Uden D, Giebink G, *et al*. Clinical efficacy of antimicrobial drugs for acute otitis media: metaanalysis of 5400 children from thirty-three randomized trials. J Pediatr. 1994;124(3):355-67.

27. Rovers MM, Glasziou P, Appelman CL, Burke P, McCormick DP, Damoiseaux RA, *et al*. Antibiotics for acute otitis media: a meta-analysis with individual patient data. Lancet. 2006;368(9545):1429-35.

28. Shekelle P, Takata G, Newberry S, Coker T, Limbos M, Chan L, *et al*. Management of acute otitis media: update. Rockville: Agency for Healthcare Research and Quality, RAND Evidence-Based Practice Center, 2010. Report No.: 11-E004.

29. Vouloumanou EK, Karageorgopoulos DE, Kazantzi MS, Kapaskelis AM, Falagas ME. Antibiotics versus placebo or watchful waiting for acute otitis media: a meta-analysis of randomized controlled trials. J Antimicrob Chemother. 2009;64(1):16-24.

30. Fernandes R, Bialy L, Vandermeer B, Tjosvold L, Plint A, Patel H, *et al*. Glucocorticoids for acute viral bronchiolitis in infants and young children. Cochrane Database Syst Rev. 2010;10:CD004878.

31. Gadomski A, Brower M. Bronchodilators for bronchiolitis. Cochrane Database Syst Rev. 2010;12:CD001266.

32. Hartling L, Bialy L, Vandermeer B, Tjosvold L, Johnson D, Plint A, *et al*. Epinephrine for bronchiolitis. Cochrane Database Syst Rev. 2011;6:CD003123.

33. Zhang L, Mendoza-Sassi R, Wainwright C, Klassen T. Nebulized hypertonic saline solution for acute bronchiolitis in infants. Cochrane Database Syst Rev. 2008;4:CD006458.

34. Flores G, Horwitz RI. Efficacy of beta 2-agonists in bronchiolitis: a reappraisal and meta-analysis. Pediatrics. 1997;100(2):233-9.

35. Kellner J, Ohlsson A, Gadomski A, Wang E. Efficacy of bronchodilator therapy in bronchiolitis. A meta-analysis. Arch Pediatr Adolesc Med. 1996;150(11):1166-72.

36. King V, Viswanathan M, Bordley W, Jackman A, Sutton S, Lohr K, *et al*. Pharmacologic treatment of bronchiolitis in infants and children: a systematic review. Arch Pediatr Adolesc Med. 2004;158(2):127-37.

37. Bjornson C, Russell K, Vandermeer B, Durec T, Klassen T, Johnson D. Nebulized epinephrine for croup in children. Cochrane Database Syst Rev. 2011;2:CD006619.

38. Moore M, Little P. Humidified air inhalation for treating croup. Cochrane Database Syst Rev. 2006;3:CD002870.

39. Russell K, Liang Y, O'Gorman K, Johnson D, Klassen T. Glucocorticoids for croup. Cochrane Database Syst Rev. 2011;1:CD001955.

40. Vorwerk C, Coats T. Heliox for croup in children. Cochrane Database Syst Rev. 2010;2:CD006822.

41. Griffin S, Ellis S, Fitzgerald-Barron A, Rose J, Egger M. Nebulised steroid in the treatment of croup: a systematic review of randomised controlled trials. Br J Gen Pract. 2000;50:135-41.

42. Kairys S, Marsh Olmstead E, O'Connor GT. Steroid treatment of laryngotracheitis: a meta-analysis of the evidence form randomized trials. Pediatrics. 1989;83(5):683-93.

43. Kramer MS, Kakuma R. Optimal duration of exclusive breastfeeding. Cochrane Database Syst Rev. 2002;1:CD003517.

44. Kramer MS, Kakuma R. Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. Cochrane Database Syst Rev. 2006;3:CD000133.

45. Osborn DA, Sinn JK. Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants. Cochrane Database Syst Rev. 2006;4:CD003664.

46. Osborn DA, Sinn JK. Soy formula for prevention of allergy and food intolerance in infants. Cochrane Database Syst Rev. 2006;4:CD003741.

47. Osborn DA, Sinn JK. Prebiotics in infants for prevention of allergic disease and food hypersensitivity. Cochrane Database Syst Rev. 2007;4:CD006474.

48. Osborn DA, Sinn JK. Probiotics in infants for prevention of allergic disease and food hypersensitivity. Cochrane Database Syst Rev. 2007;4:CD006475.

49. Alexander DD, Cabana MD. Partially hydrolyzed 100% whey protein infant formula and reduced risk of atopic dermatitis: a meta-analysis. J Pediatr Gastroenterol Nutr. 2010;50(4):422-30.

50. Anandan C, Nurmatov U, Sheikh A. Omega 3 and 6 oils for primary prevention of allergic disease: systematic review and meta-analysis. Allergy. 2009;64(6):840-8.

51. Dangour AD, Lock K, Hayter A, Aikenhead A, Allen E, Uauy R. Nutrition-related health effects of organic foods: a systematic review. Am J Clin Nutr. 2010;92(1):203-10.

52. Ernst E, Pittler MH, Stevinson C. Complementary/alternative medicine in dermatology: evidence-assessed efficacy of two diseases and two treatments. Am J Clin Dermatol. 2002;3(5):341-8.

53. Flohr C, Pascoe D, Williams HC. Atopic dermatitis and the 'hygiene hypothesis': too clean to be true? Br J Dermatol. 2005;152(2):202-16.

54. Gdalevich M, Mimouni D, David M, Mimouni M. Breast-feeding and the onset of atopic dermatitis in childhood: a systematic review and meta-analysis of prospective studies. J Am Acad Dermatol. 2001;45(4):520-7.

55. Hanifin JM, Van Voorhees AS, Cooper KD, Ho VC, Kang S, Krafchik BR, *et al*. Guidelines of care for atopic dermatitis. American Academy of Dermatology, 2003.

56. Hill DJ, Murch SH, Rafferty K, Wallis P, Green CJ. The efficacy of amino acid-based formulas in relieving the symptoms of cow's milk allergy: a systematic review. Clin Exp Allergy. 2007;37(6):808-22.

57. Hoare C, Li Wan Po A, Williams H. Systematic review of treatments for atopic eczema. Health Technol Assess. 2000;4(37).

58. Ip S, Chung M, Raman G, Chew P, Magula N, DeVine D, *et al*. Breastfeeding and maternal and infant health outcomes in developed countries. Rockville: Agency for Healthcare Research and Quality, Tufts-New England Medical Center Evidence-Based Practice Center, 2007. Report No.: 07-E007.

59. Kremmyda LS, Vlachava M, Noakes PS, Diaper ND, Miles EA, Calder PC. Atopy risk in infants and children in relation to early exposure to fish, oily fish, or long-chain omega-3 fatty acids: a systematic review. Clin Rev Allergy Immunol. 2009 (pre-publication);41(1):36-66.

60. Langan SM, Flohr C, Williams HC. The role of furry pets in eczema: a systematic review. Arch Dermatol. 2007;143(12):1570-7.

61. Lee J, Seto D, Bielory L. Meta-analysis of clinical trials of probiotics for prevention and treatment of pediatric atopic dermatitis. J Allergy Clin Immunol. 2008;121(1):116-21.

62. Muche-Borowski C, Kopp M, Reese I, Sitter H, Werfel T, Schafer T. Allergy prevention. Dtsch Arztebl Int. 2009;106(39):625-31.

63. Oddy WH. The long-term effects of breastfeeding on asthma and atopic disease. Adv Exp Med Biol. 2009;639:237-51.

64. Schneider Chafen JJ, Newberry S, Riedl M, Bravata DM, Maglione MA, Booth M, *et al*. Prevalence, natural history, diagnosis, and treatment of food allergy: a systematic review of the evidence. Santa Monica, CA: National Institute on Allergy and Infectious Diseases, RAND Corporation, 2010. Report No.: WR-757-1.

65. Szajewska H, Horvath A. Meta-analysis of the evidence for a partially hydrolyzed 100% whey formula for the prevention of allergic diseases. Curr Med Res Opin. 2010;26(2):423-37.

66. Tarini BA, Carroll AE, Sox CM, Christakis DA. Systematic review of the relationship between early introduction of solid foods to infants and the development of allergic disease. Arch Pediatr Adolesc Med. 2006;160(5):502-7.

67. Yang YW, Tsai CL, Lu CY. Exclusive breastfeeding and incident atopic dermatitis in childhood: a systematic review and meta-analysis of prospective cohort studies. Br J Dermatol. 2009;161(2):373-83.

68. Allen S, Martinez E, Gregorio G, Dans L. Probiotics for treating acute infectious diarrhoea. Cochrane Database Syst Rev. 2010;11:CD003048.

69. Fedorowicz Z, Jagannath V, Carter B. Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents. Cochrane Database Syst Rev. 2011;9:CD005506.

70. Hartling L, Bellemare S, Wiebe N, Russell K, Klassen T, Craig W. Oral versus intravenous rehydration for treating dehydration due to gastroenteritis in children. Cochrane Database Syst Rev. 2006;3:CD004390.

71. Chmielewska A, Ruszczynski M, Szajewska H. Lactobacillus reuteri strain ATCC 55730 for the treatment of acute infectious diarrhoea in children: a meta-analysis of randomized controlled trials. Pediatria Wspolczesna. 2008;10(1):32-6.

72. DeCamp L, Byerley J, Doshi N, Steiner M. Use of antiemetic agents in acute gastroenteritis: a systematic review and meta-analysis. Arch Pediatr Adolesc Med. 2008;162(9):858-65.

73. Dinleyici E, Eren M, Ozen M, Yargic Z, Vandenplas Y. Effectiveness and safety of Saccharomyces boulardii for acute infectious diarrhea. Expert Opin Biol Ther. 2012;12(4):395-410.

74. Fonseca B, Holdgate A, Craig J. Enteral vs intravenous rehydration therapy for children with gastroenteritis: a meta-analysis of randomized controlled trials. Arch Pediatr Adolesc Med. 2004;158(5):483-90.

75. Huang J, Bousvaros A, Lee J, Diaz A, Davidson E. Efficacy of probiotic use in acute diarrhea in children: a meta-analysis. Dig Dis Sci. 2002;47(11):2625-34.

76. McFarland LV, Elmer GW, McFarland M. Meta-analysis of probiotics for the prevention and treatment of acute pediatric diarrhea. Int J Probiotics Prebiotics. 2006;1(1):63-76.

77. Salari P, Nikfar S, Abdollahi M. A meta-analysis and systematic review on the effect of probiotics in acute diarrhea. Inflamm Allergy Drug Targets. 2012;11(1):3-14.

78. Szajewska H, Mrukowicz J. Probiotics in the treatment and prevention of acute infectious diarrhea in infants and children: a systematic review of published randomized, double-blind, placebo-controlled trials. J Pediatr Gastroenterol Nutr. 2001;33:S17-25.

79. Szajewska H, Gieruszczak-Bialek D, Dylag M. Meta-analysis: ondansetron for vomiting in acute gastroenteritis in children. Aliment Pharmacol Ther. 2007;25(4):393-400.

80. Szajewska H, Skorka A, Dylag M. Meta-analysis: Saccharomyces boulardii for treating acute diarrhoea in children. Aliment Pharmacol Ther. 2007;25(3):257-64.

81. Szajewska H, Skorka A, Ruszczynski M, Gieruszczak-Bialek D. Meta-analysis: Lactobacillus GG for treating acute diarrhoea in children. Aliment Pharmacol Ther. 2007;25(8):871-81.

82. Van Niel CW, Feudtner C, Garrison MM, Christakis DA. Lactobacillus therapy for acute infectious diarrhea in children: a meta-analysis. Pediatrics. 2002;109(4):678-84.

83. Deasy C, Babl FE. Intravenous vs intramuscular ketamine for pediatric procedural sedation by emergency medicine specialists: a review. Paediatr Anaesth. 2010;20(9):787-96.

84. Faddy SC, Garlick SR. A systematic review of the safety of analgesia with 50% nitrous oxide: can lay responders use analgesic gases in the prehospital setting? Emerg Med J. 2005;22(12):901-8.

85. Green SM, Roback MG, Krauss B, Brown L, McGlone RG, Agrawal D, *et al*. Predictors of airway and respiratory adverse events with ketamine sedation in the emergency department: an individual-patient data meta-analysis of 8,282 children. Ann Emerg Med. 2009;54(2):158-68.

86. Howes MC. Ketamine for paediatric sedation/analgesia in the emergency department. Emerg Med J. 2004;21(3):275-80.

87. Jameson E. Question 3 Ketamine or midazolam: does it matter which? Arch Dis Child. 2011;96(1):106-8.

88. Lamond DW. Review article: Safety profile of propofol for paediatric procedural sedation in the emergency department. Emerg Med Australas. 2010;22(4):265-86.

89. Leroy PL, Schipper DM, Knape HJ. Professional skills and competence for safe and effective procedural sedation in children: recommendations based on a systematic review of the literature. Int J Pediatr. 2010;2010:934298.

90. Mace SE, Barata IA, Cravero JP, Dalsey WC, Godwin SA, Kennedy RM, *et al*. Clinical policy: Evidence-based approach to pharmacologic agents used in pediatric sedation and analgesia in the emergency department. Ann Emerg Med. 2004;44(4):342-77.

91. Migita R, Klein E, Garrison M. Sedation and analgesia for pediatric fracture reduction in the emergency department: a systematic review. Arch Pediatr Adolesc Med. 2006;160(1):46-51.

92. Mistry R, Nahata M. Ketamine for conscious sedation in pediatric emergency care. Pharmacotherapy. 2005;25(8):1104-11.

93. National Clinical Guideline Centre. Sedation in children and young people: sedation for diagnostic and therapeutic procedures in children and young people. London, UK: National Institute for Health and Clinical Excellence, 2010. Report No.: 112.

94. Pedersen R, Bayat A, Steen N, Jacobsson M. Nitrous oxide provides safe and effective analgesia for minor paediatric procedures - a systematic review. Dan Med J. 2013;60(6):A4627.

95. Symington L, Thakore S. A review of the use of propofol for procedural sedation in the emergency department. Emerg Med J. 2006;23(2):89-93.

Appendix 4B. Additional results data.

Table 1. Characteristics of included systematic reviews, by topic area.

	Number of included reviews	Years of publication (median, range)	AMSTAR assessments (mean, standard deviation)	AMSTAR assessments (median, range)	Inter-rater reliability (AC1, 95% confidence interval[a])	Percentage agreement (%, 95% confidence interval[a])
Acute asthma	**13**	**2006 (1997-2013)**	**7.8 (2.0)**	**8.0 (4.0-10.0)**	**0.74 (0.59, 0.88)**	**84.6 (77.4, 91.8)**
Cochrane	7	2012 (2002-2013)	8.4 (1.8)	9.0 (5.0-10.0)	0.76 (0.51, 1.00)	85.7 (73.0, 98.4)
Non-Cochrane	6	2006 (1997-2013)	7.0 (2.0)	7.0 (4.0-10.0)	0.71 (0.49, 0.93)	83.3 (72.2, 94.5)
Acute otitis media	**16**	**2006 (1994-2010)**	**7.6 (3.1)**	**8.5 (1.0-11.0)**	**0.93 (0.88, 0.98)**	**95.5 (92.4, 98.5)**
Cochrane	6	2008 (2004-2010)	10.2 (0.8)	10.0 (9.0-11.0)	0.98 (0.92, 1.00)	98.5 (94.6, 100.0)
Non-Cochrane	10	2004 (1994-2010)	6.1 (2.9)	5.5 (1.0-11.0)	0.90 (0.83, 0.97)	93.6 (89.2, 98.0)
Bronchiolitis	**7**	**2008 (1996-2011)**	**8.1 (3.0)**	**10.0 (4.0-11.0)**	**0.69 (0.43, 0.94)**	**80.5 (66.4, 94.6)**
Cochrane	4	2010 (2008-2011)	10.5 (0.6)	10.5 (10.0-11.0)	0.74 (0.37, 1.00)	81.8 (61.4, 100.0)
Non-Cochrane	3	1997 (1996-2004)	5.0 (1.0)	5.0 (4.0-6.0)	0.61 (-0.28, 1.00)	78.8 (26.6, 100.0)
Croup	**6**	**2008 (1989-2012)**	**8.3 (3.0)**	**9.0 (3.0-11.0)**	**0.76 (0.64, 0.88)**	**83.3 (76.2, 90.5)**
Cochrane	4	2011 (2006-2012)	9.5 (1.9)	10.0 (7.0-11.0)	0.78 (0.63, 0.92)	84.1 (76.9, 91.3)
Non-Cochrane	2	1995 (1989-2000)	6.0 (4.2)	6.0 (3.0-9.0)	0.72 (-1.00, 1.00)	81.8 (0.00, 100.0)
Eczema	**25**	**2007 (2000-2010)**	**6.1 (3.0)**	**6.0 (1.0-11.0)**	**0.76 (0.68, 0.84)**	**85.8 (81.6, 90.0)**
Cochrane	6	2006 (2002-2007)	9.3 (1.8)	10.0 (6.0-11.0)	0.85 (0.76, 0.95)	89.4 (82.2, 96.6)
Non-Cochrane	19	2008 (2000-2010)	5.1 (2.6)	5.0 (1.0-9.0)	0.73 (0.63, 0.83)	84.7 (0.79, 0.90)
Gastroenteritis	**15**	**2007 (2001-2012)**	**7.7 (1.8)**	**7.0 (4.0-11.0)**	**0.61 (0.46, 0.76)**	**78.2 (70.6, 85.8)**
Cochrane	3	2010 (2006-2011)	10.7 (0.6)	11.0 (10.0-11.0)	0.97 (0.82, 1.00)	97.0 (83.9, 100.0)
Non-Cochrane	12	2007 (2001-2012)	6.9 (1.1)	7.0 (4.0-8.0)	0.52 (0.38, 0.66)	73.5 (66.8, 80.2)
Procedural sedation	**13**	**2009 (2004-2013)**	**3.7 (1.8)**	**4.0 (1.0-7.0)**	**0.65 (0.53, 0.78)**	**79.7 (72.9, 86.5)**
Cochrane	0	NA	NA	NA	NA	NA
Non-Cochrane	13	2009 (2004-2013)	3.7 (1.8)	4.0 (1.0-7.0)	0.65 (0.53, 0.78)	79.7 (72.9, 86.5)
Total	**95**	**2007 (1989-2013)**	**6.8 (2.9)**	**7.0 (1.0-11.0)**	**0.74 (0.70, 0.79)**	**84.7 (82.3, 87.1)**
Cochrane	30	2009 (2002-2013)	9.6 (1.6)	10.0 (5.0-11.0)	0.84 (0.77, 0.91)	89.4 (85.5, 93.3)
Non-Cochrane	65	2007 (1989-2013)	5.5 (2.4)	6.0 (1.0-11.0)	0.69 (0.64, 0.75)	82.5 (79.5, 85.5)

[a] 95% confidence intervals were capped at -1.00 and 1.00 for inter-rater reliability and 0.00 and 100.0 for percent agreement.

Table 2. Percentage agreement per AMSTAR question, for Cochrane and non-Cochrane systematic reviews.

AMSTAR question	Number of agreements N (%)		
	Cochrane (n = 30)	Non-Cochrane (n = 65)	Difference between groups (p-value for chi square test)
1. Was an "*a priori*" design provided?	28 (93.3%)	54 (83.1%)	0.18
2. Was there duplicate study selection and data extraction?	20 (66.7%)	56 (86.2%)	0.027[a]
3. Was a comprehensive literature search performed?	29 (96.7%)	52 (80.0%)	0.033[b]
4. Did the authors search for reports regardless of their publication type?	26 (86.7%)	55 (84.6%)	0.79
5. Was a list of studies (included and excluded) provided?	30 (100.0%)	53 (81.5%)	0.012[b]
6. Were the characteristics of the included studies provided?	30 (100.0%)	60 (92.3%)	0.12
7. Was the scientific quality of the included studies assessed and documented?	29 (96.7%)	52 (80.0%)	0.033[b]
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	26 (86.7%)	51 (78.5%)	0.34
9. Were the methods used to combine the findings of studies appropriate?	26 (86.7%)	52 (80.0%)	0.43
10. Was the likelihood of publication bias assessed?	25 (83.3%)	55 (84.6%)	0.87
11. Was the conflict of interest stated?	26 (86.7%)	50 (76.9%)	0.27

[a] Significant in favour of non-Cochrane systematic reviews; [b] Significant in favour of Cochrane systematic reviews.