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Long-term noninvasive ventilation interventions in children: a scoping review protocol

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ABSTRACT

Introduction: Non-invasive ventilation (NIV) in children has become an increasingly common modality of breathing support where pressure support is delivered through a mask interface or less common through other non-invasive interfaces. At this time, NIV is considered a first line option for ventilatory support of chronic respiratory insufficiency associated with a range of respiratory and sleep disorders. Previous reviews on the effectiveness, complications and adherence to NIV treatment have lacked systematic methods. The aim of this scoping review is to provide an overview of the evidence for the use of long-term NIV in children. Using a scoping review methodology, the following research question will be addressed: "What is known about the benefits, complications and challenges of long-term home NIV in children?" **Methods and analysis:** We will use previously established scoping methodology. Ten electronic databases will be searched to identify studies in children using NIV for longer than 3 months outside an intensive care setting. Gray literature search will include conference proceedings, thesis, unpublished trials, reports from regulatory agencies and manufacturers. Two reviewers will independently screen titles and abstracts for inclusion, followed by full text screening of potentially relevant articles to determine final inclusion. Data synthesis will be performed at three levels: 1) an analysis of the number, publication type, publication year, and country of publication of the studies; 2) a summary of the study designs, outcomes measures used; 3) a thematic analysis of included studies by subgroups. **Ethics and dissemination**: This study will provide a wide and rigorous overview of the evidence on the use of long-term non-invasive ventilation in children and provide critical information for health care professionals and policy makers to better care for this group of children. We will disseminate our findings through

conference proceedings and publications, and evaluate the results for further systematic reviews and meta-analysis.

STRENGHTS AND LIMITATIONS OF THIS STUDY

- This is a novel review approach to define the full scope of literature available on the use of long-term non-invasive ventilation in children.
- In addition to methodological experts, key knowledge translation partners were engaged to support the design of the protocol.
- Subgroup for separate summary will be determined after review of the identified literature.
- As this is a scoping review, the quality of the evidence and risk of bias will not be evaluated.
- This review will be limited to English, French and Spanish.

BACKGROUND

The purpose of this scoping review is to provide a rigorous overview of the evidence for the use of long-term non-invasive ventilation (NIV) in children with respiratory and/or sleep disorders. NIV in children is an increasingly common modality of breathing support where a mask interface, rather than an endotracheal tube or tracheostomy, is used to connect to pressure support. Long-term use of NIV provides an option for children who require intermittent ventilatory support (i.e. for sleep only) or as part of palliative care. The use of NIV in children has expanded worldwide including developing countries, since its first reported use in the early 1990s, resulting in a decrease in the use of long-term invasive ventilation via tracheostomy.[1-

11] Factors contributing to the increased use of NIV likely include increased survival of children with complex medical conditions, a shift in the emphasis of health care from hospital to home based care, and technological advances in the masks and machines to support home use of NIV in children.

Today, NIV is considered a first line option of ventilatory support for chronic respiratory insufficiency associated with a range of respiratory and sleep disorders including chronic respiratory failure,[12-14] cystic fibrosis,[15-18] musculoskeletal weakness or chest wall restriction,[19-24] obstructive sleep apnea (OSA) and craniofacial malformations,[25-28] sleep disorders associated with neurological conditions and abnormalities in central respiratory drive.[29-32] Long-term NIV has been used successfully in infants, from the first weeks of life. It has been shown NIV can be used long-term across all age groups.[33-37] Safety and efficacy of NIV use in children have been documented for children with certain underlying conditions such as neuromuscular disease or OSA.[38-40] Adherence to NIV therapy is also an outcome of interest as there are considerable challenges in establishing and maintaining use of NIV in children.[41-46] Reported benefits of NIV use in children are broad and include outcomes related to acute illness,[47] chronic respiratory function,[18 23 48] sleep and daytime function,[28 49 50] behaviour and neurocognitive outcomes,[51] general health outcomes,[20] quality of life,[49 52] progression of underlying disease, and survival.[52 53] Funding for NIV and access to this technology are also important considerations.[54]

Previous reviews on long-term NIV use in children have lacked systematic methodology or NIV in children has been included in systematic reviews of broader topics.

From a preliminary search strategy using terms related to NIV and children, we identified 758 review articles of which 91 may have some information relevant to long-term NIV use in children. Of these, only eight previous reviews described a search strategy or systematic methodology.[55-62] Of note, none of the reviews had a specific focus of enquiry regarding long-term use of NIV in children but rather included NIV as one possible intervention for a particular pediatric population. Moreover, only four of these reviews had a specific section on NIV or included studies with NIV interventions. The aim of this scoping review is to provide a systematic overview of the existing evidence for the use of long-term NIV in children.

METHODS AND ANALYSIS

Study design: The methodology of this scoping review is based on the methodological frameworks developed by Bragge *et al*. and Arksey and O'Malley.[63 64] The results will be reported following the reporting guidelines of the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocols (PRISMA-P) 2015 statement".[65] This approach will enable a rational assessment of the evidence that is available on long-term NIV interventions in children and ensure a transparent and complete report of the same.

We gathered an advisory team of experts in systematic reviews, pediatric respirologists, sleep medicine specialists, pediatric nurse practitioners and industry representatives, to provide input on the search strategy as well as in the discussion of the results of the scoping review. In addition, children using long-term NIV and their caregivers have been included in the advisory

team with the aim of prioritising the outcomes identified in this scoping review from the patient and caregiver perspective as well as identifying important outcomes that have not been included in previous studies.

Eligibility criteria:

Types of Participants/ Population: Studies reporting results for children from newborn to age 18 years will be included. Studies that include both adults and children will be included if data for children is reported separately.

Types of Interventions: Eligible studies must contain information on NIV use defined as the administration of breathing support delivered through a non-invasive interface most commonly a nasal or face mask but also a mouth piece or abdominal belt. Types of breathing support includes (1) positive pressure support including continuous positive airway pressure (CPAP) or an inspiratory and expiratory airway pressure (bi-level), (2) negative pressure ventilation (NPV). Long-term use is defined as the use of NIV for at least three months outside an acute care environment. This may include, but not be limited to, use of NIV in community-based settings such as homes, a family or group home, or specialized non-acute hospital based units.

Type of outcomes: No restriction with regard to outcomes will be applied.

Types of Studies: Original studies published from 1990 onwards will be considered for inclusion including randomized and non-randomized clinical trials, controlled before- after, cross-

sectional studies, longitudinal observational studies, retrospective cohorts, qualitative and mixed methods research and case series with three or more cases; 1990 was determined as a starting date because the first study of long-term NIV use in children we identified was published in 1993.

Exclusion: Case reports, case series with less than three subjects, comments, editorials, letters and reviews will be excluded. Studies where NIV is used solely for the treatment of acute illness will be excluded. During the full text screening, only articles in English, French and Spanish will be included as the review authors are proficient in these languages.

Information sources: An information specialist working for the Alberta Research Centre for Health Evidence (ARCHE) at the University of Alberta collaborated with investigators to design a comprehensive and sensitive search strategy with terms for non-invasive ventilation and children from newborn to age 18 years. The search strategy (Table 1) was developed for Ovid Medline with a validated child search filter,[66] and will be translated into Ovid Embase, PubMed (last year only), CINAHL via EbscoHOST, and Wiley Cochrane Library (including the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews of Effects, the Health Technology Assessment Database, and the NHS Economic Evaluation Database). Database search results will be limited to human studies published after 1990. No language or study design restrictions will be applied.

Table 1 Search strategy developed for MEDLINE using OVID

Search terms
1. Continuous Positive Airway Pressure/
2. Noninvasive Ventilation/
3. Intermittent Positive-Pressure Breathing/
4. Ventilators, Negative-Pressure/
5. AVAPS.tw.
6. ((auto* or adaptive) adj2 (servoventilation or ventilation)).tw.
7. AutoSet*.tw.
8. ((bi level or bilevel) adj2 (airway* or air way* or assist* or breath* or positive pressure* or respirat* or ventilat* or support* or therap*)).tw.
9. BIPAP*.tw.
10. BPAP*.tw.
11. c flex.tw.
12. CNEP.tw.
13. (continuous negative adj2 pressure).tw.
14. (continuous positive airway* or continuous positive air way*).tw.
15. (continuous positive adj2 pressure).tw.
16. CPAP*.tw.
17. ((domicil* or home*) adj5 ventilat*).tw.
18. intermittent positive pressure breathing.tw.
19. IPPB*.tw.
20. ((long term or longterm) adj5 ventilat*).tw.
21. ((nasal* or mask*) adj2 (positive adj2 pressure)).tw.
22. ((nasal* or mask*) adj2 ventilat*).tw.
23. nCPAP*.tw.
24. ((negative pressure) adj2 (respirat* or ventilat*)).tw.
25. ((night* or nocturnal* or sleep*) adj5 ventilat*).tw.
26. NIPPV*.tw.
27. ((noninvasive adj5 ventilat*) or (non invasive adj5 ventilat*)).tw.
28. (noninvasive respiratory support* or non invasive respiratory support*).tw.
29. NPPV*.tw.
30. (positive pressure adj2 respirat*).tw.
31. REMstar*.tw.
32. (tank adj (respirat* or ventilat*)).tw.
33. VPAP*.tw.
34. or/1-33
35. Hypoventilation/pc, rh, th [Prevention & Control, Rehabilitation, Therapy]
36. Interactive Ventilatory Support/
37. Intermittent Positive-Pressure Ventilation/
38. Positive-Pressure Respiration/
39. Respiration, Artificial/
40. Respiratory Insufficiency/pc, rh, th [Prevention & Control, Rehabilitation, Therapy]
41. exp Sleep Apnea Syndromes/ pc, rh, th [Prevention & Control, Rehabilitation, Therapy]
42. Ventilators, Mechanical/
43. ((airway* or air way* or breath* or inspirat* or respirat* or ventilat*) and (positive adj2 pressure)).tw.
44. intermittent positive pressure.tw.
45. IPPV*.tw.
46. (mechanical adj (respirat* or ventilat*)).tw.
47. (positive adj2 pressure adj (assist* or support* or therap*)).tw.
48. positive airway pressure.tw.
49. pulmonary ventilator*.tw.
50. respiratory support*.tw.
51. or/35-50
52. (noninvasive or non invasive or spontaneous*).mp.

53. 51 and 52
54. 34 or 53
55. exp Adolescent/
56. exp Child/
57. exp Infant/
58. exp Minors/
59. exp Pediatrics/
60. exp Puberty/
61. exp Schools/
62. adoles*.mp.
63. (baby* or babies or infant* or infancy or neonat* or newborn* or postmatur* or prematur* or preterm*).mp.
64. (boy* or girl* or teen*).mp.
65. (child* or kid or kids or preschool* or school age* or schoolchild* or toddler*).mp.
66. (elementary school* or high school* or highschool* or kindergar* or nursery school* or primary school* or secondary school*).mp.
67. minors*.mp.
68. (paediatric* or peadiatric* or pediatric*).mp.
69. (prepubescen* or pubescen* or pubert*).mp.
70. or/55-69
71. 54 and 70
72. (case reports or comment or editorial or letter).pt.
73. 71 not 72
74. exp animals/ not humans.sh.
75. 73 not 74
76. limit 75 to yr="1990 -Current"
77. remove duplicates from 76

Reference lists of all studies selected for this scoping review will be scanned to identify further relevant studies not detected by the search strategy.

We will also search for gray literature (non-peer reviewed investigations) including conference proceedings, thesis and dissertations, unpublished trials, regulatory agencies and manufacturers reports. In consultation with the advisory team, a list of conference proceedings and annual meeting reports to review from January 2012 to December 2014 will be established. The information specialist will search websites of the conferences relevant to NIV such as the American Thoracic Society, the American College of Chest Physicians, the Canadian Thoracic Society, the European Respiratory Society, the American Academy of Sleep Medicine, the European Society of Sleep Research, the Australasian Sleep Association, and the American

Association of Neuromuscular and Electrodiagnostic Medicine. Investigators will search for publications of relevant proceeding abstracts or contact presenters to request study data. ClinicalTrials.gov and the World Health Organization's International Clinical Trials Registry Platform will also be searched for trials registered after 2012 on NIV and positive airway pressure. Investigators will search for publications of relevant trials or attempt to contact study coordinators to request unpublished data. Regulatory agencies will be searched for ventilator device approval documents, premarket notifications, recall notices and safety advisories. Government sources will include Health Canada's Medical Device Active License Listing (MDALL), the U.S. Food and Drug Administration (FDA) device website (Devices@FDA), the Australian Government's Department of Health and Ageing Therapeutic Goods Administration (TGA) Database of Adverse Event Notifications, the European Medicines Agencies, and the New Zealand Medicines and Medical Devices Safety Authority (Medsafe: Medical Devices). Device manufacturers may be contacted with requests for premarket trial data. ProQuest Theses & Dissertations will also be searched for theses submitted after 1990 on noninvasive ventilation in children.

The Ovid Medline search strategy and the list of information sources will be approved by the advisory team prior to running the searches.

Study records

Data management: Results of searches will be imported into an EndNote library, and duplicates will be removed. Two exact copies of the EndNote library will be created for independent screening by two reviewers.

Selection process: Two independent reviewers will screen titles and abstracts of retrieved articles for eligibility based on the inclusion criteria. . The full text will be retrieved for all potentially relevant articles; each will be evaluated independently for eligibility by two reviewers. Discrepancies will be resolved through discussion between the reviewers to establish the final list of studies to be included in the scoping review. Reasons for exclusion will be recorded at the full text review.

Data collection process: Data extraction will be completed by one reviewer using a pre-designed standardized form and entered into Microsoft Excel database (Microsoft, Redmond, Washington, USA). Data extraction will be verified by a second reviewer for a sample of 10% of the studies. The data extraction form is based on Bragge *et al*. data extraction database and modified for this project to ensure that appropriate and relevant data is obtained (Table 2).[56] When there is missing information, two attempts to contact the corresponding authors will be made to obtain additional data. To avoid double counting in the instance of the same data set published in more than one publication, only one article per data set will be retained.

Table 2 Data extraction form

Study characteristics	Extracted data
General information	Author last name Publication year Country of study Publication type: journal, abstract, dissertation, unpublished trial, report
Introduction	Aims of the study/ Study research question Study population: mean age and range, gender distribution, primary underlying condition, comorbidities
Design	Study design: - Quantitative: randomized controlled trial, non-randomized controlled trial, controlled before-after, observational, cross-sectional - Qualitative: case series, others, mixed methods Sample size Intervention, duration of intervention, co-interventions Description of the control group
Outcomes measures (whether self- reported or objective tools)*	Primary clinical outcomes Secondary outcomes and adverse outcomes Timing of assessment/ length of follow-up

* Units of measurements will be reported, as well as statistical analysis methods, and effect of the intervention and size.

Data synthesis: The identified evidence will be collated using a specific analytical framework in order to present a narrative account of the existing literature.

Once the information has been extracted, we will present a narrative account of findings in three different ways: 1) a basic numerical analysis of the number, publication type, publication

year, and country of publication of the studies included in the review. 2) A narrative description of the study design, aims, participant characteristics, sample size, intervention type, control group description, outcomes measures, and statistical methods. We will use this information to establish subcategorise of studies which may include grouping based on age (e.g. infants, children, and adolescents), intervention type (e.g. CPAP, bi-level, and NPV) and disease categories (e.g. OSA, neuromuscular disease). 3) A thematic analysis of included studies by subgroups if appropriate. The results will be presented based on the priorities established by our advisory team including input from children using NIV and their caregivers.

CONCLUSION

This scoping review will be the first, to our knowledge, to provide a systematic overview of the evidence on the use of long-term NIV in children. The findings from this review will provide stakeholders with a rigorous research base to support health care providers to improve clinical practice and policy makers to support resource needs for this complex group of children. We will disseminate our findings through conference proceedings and publications. The gathered data can be used to inform the development of guidelines for the care of children using long-term NIV and will identify gaps in knowledge to support future research endeavors. Based on the results, we will determine whether the application of other systematic review methodologies, such as meta-analysis or meta-synthesis, will be appropriate for any of the subgroups that we identify for future research.

CONTRUBUTORSHIP STATEMENT

MCC, RF, LH, and JM conceived the idea of this study and designed its methodology. MCC and RF wrote the protocol, developed the search strategy and performed a preliminary literature review. KW, CM, SK, EC, GB, CS, FA, RY, DO, VW, LH, and JM reviewed the protocol. All authors read and approved the final manuscript.

COMPETING INTERESTS

None

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DATA SHARING STATEMENT

The protocol of this scoping review and additional unpublished data on the preliminary search strategy and a summary of previous review articles on NIV in children are available by contacting the corresponding author.

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Long-term noninvasive ventilation therapies in children: a scoping review protocol

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Long-term noninvasive ventilation therapies in children: a scoping review protocol

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WORD COUNT: 2059

ABSTRACT

Introduction: Non-invasive ventilation (NIV) in children has become an increasingly common modality of breathing support where pressure support is delivered through a mask interface or less common through other non-invasive interfaces. At this time, NIV is considered a first line option for ventilatory support of chronic respiratory insufficiency associated with a range of respiratory and sleep disorders. Previous reviews on the effectiveness, complications and adherence to NIV treatment have lacked systematic methods. The purpose of this scoping review is to provide an overview of the evidence for the use of long-term NIV in children.

Methods and analysis: We will use previously established scoping methodology. Ten electronic databases will be searched to identify studies in children using non-invasive ventilation for longer than 3 months outside an intensive care setting. Gray literature search will include conference proceedings, thesis and dissertations, unpublished trials, reports from regulatory agencies and manufacturers. Two reviewers will independently screen titles and abstracts for inclusion, followed by full text screening of potentially relevant articles to determine final inclusion. Data synthesis will be performed at three levels: 1) an analysis of the number, publication type, publication year, and country of publication of the studies; 2) a summary of the study designs, outcomes measures used; 3) a thematic analysis of included studies by subgroups. **Ethics and dissemination**: This study will provide a wide and rigorous overview of the evidence on the use of long-term non-invasive ventilation in children and provide critical information for health care professionals and policy makers to better care for this group of children. We will disseminate our findings through conference proceedings and publications, and evaluate the results for further systematic reviews and meta-analysis.

STRENGHTS AND LIMITATIONS OF THIS STUDY

- This is a novel review approach to define the full scope of literature available on the use of long-term non-invasive ventilation in children.
- In addition to methodological experts, key knowledge translation partners were engaged to support the design of the protocol.
- Subgroup for separate summary will be determined after review of the identified literature.
- As this is a scoping review, the quality of the evidence and risk of bias will not be evaluated.
- This review will be limited to English, French, Spanish, Portuguese, Italian and Catalan.

BACKGROUND

The purpose of this scoping review is to provide a rigorous overview of the evidence for the use of long-term non-invasive ventilation (NIV) in children with respiratory and/or sleep disorders. NIV in children is an increasingly common modality of breathing support where a mask interface, rather than an endotracheal tube or tracheostomy, is used to connect to pressure support. Long-term use of NIV provides an option for children who require intermittent ventilatory support (i.e. for sleep only) or as part of palliative care. The use of NIV in children has expanded worldwide including developing countries, since its first reported use in the early 1990s, resulting in a decrease in the use of long-term invasive ventilation via tracheostomy.[1-11] Factors contributing to the increased use of NIV likely include increased survival of children with complex medical conditions, a shift in the emphasis of health care from hospital to home

based care, and technological advances in the masks and machines to support home use of NIV in children.

Today, NIV is considered a first line option of ventilatory support for chronic respiratory insufficiency associated with a range of respiratory and sleep disorders including chronic respiratory failure,[12-14] cystic fibrosis,[15-18] musculoskeletal weakness or chest wall restriction,[19-24] obstructive sleep apnea (OSA) and craniofacial malformations,[25-28] sleep disorders associated with neurological conditions and abnormalities in central respiratory drive.[29-32] Long-term NIV has been used successfully in infants, from the first weeks of life. It has been shown NIV can be used long-term across all age groups.[33-37] Safety and efficacy of NIV use in children have been documented for children with certain underlying conditions such as neuromuscular disease or OSA.[38-40] Adherence to NIV therapy is also an outcome of interest as there are considerable challenges in establishing and maintaining use of NIV in children.[41-46] Reported benefits of NIV use in children are broad and include outcomes related to acute illness,[47] chronic respiratory function,[18 23 48] sleep and daytime function,[28 49 50] behaviour and neurocognitive outcomes,[51] general health outcomes,[20] quality of life,[49 52] progression of underlying disease, and survival.[52 53] Funding for NIV and access to this technology are also important considerations.[54]

Previous reviews on long-term NIV use in children have lacked systematic methodology or NIV in children has been included in systematic reviews of broader topics. From a preliminary search strategy using terms related to NIV and children, we identified 758 review articles of

which 91 may have some information relevant to long-term NIV use in children. Of these, only eight previous reviews described a search strategy or systematic methodology.[55-62] Of note, none of the reviews had a specific focus of enquiry regarding long-term use of NIV in children but rather included NIV as one possible intervention for a particular pediatric population. Moreover, only four of these reviews had a specific section on NIV or included studies with NIV interventions. The aim of this scoping review is to define the body of literature relevant for the use of long-term NIV in children and provide a systematic overview of the existing evidence. Using this process, we will not only define the scope of existing data but also determine if there is sufficient literature relevant to subgroups that would be appropriate to apply systematic review or meta-analysis.

METHODS AND ANALYSIS

Study design: The methodology of this scoping review is based on the methodological frameworks developed by Bragge *et al*. and Arksey and O'Malley.[63 64] The results will be reported following the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocols (PRISMA-P) 2015 statement".[65] This approach will enable a rational assessment of the evidence that is available on long-term NIV interventions in children and ensure a transparent and complete report of the same.

We gathered an advisory team of experts in systematic reviews, pediatric respirologists, sleep medicine specialists, pediatric nurse practitioners and industry representatives, to provide input on the search strategy as well as in the discussion of the results of the scoping review. In addition, children using long-term NIV and their caregivers have been included in the advisory

team with the aim of prioritising the outcomes identified in this scoping review from the patient and caregiver perspective as well as identifying important outcomes that have not been included in previous studies.

Eligibility criteria:

Types of Participants/ Population: Studies reporting results for children from newborn to age 18 years will be included. Studies that include both adults and children will be included if data for children is reported separately.

Types of Interventions: Eligible studies must contain information on NIV use defined as the administration of breathing support delivered through a non-invasive interface most commonly a nasal or face mask but also a mouth piece or abdominal belt. Types of breathing support includes (1) positive pressure support including continuous positive airway pressure (CPAP) or an inspiratory and expiratory airway pressure (bi-level), (2) negative pressure ventilation (NPV). Similar to the definition we found in other review articles from the preliminary search review, we will define long-term use as the use of NIV for at least three months outside an acute care environment. This may include, but not be limited to, use of NIV in community-based settings such as homes, a family or group home, or specialized non-acute hospital based units. This definition is intended to include children with chronic conditions that require long-term NIV and are stable enough to receive ventilatory therapy at home or in a chronic care environment. Articles that describe long-term use of NIV with no time specification will be included if there is a clear intention of treating a chronic problem.

Type of outcomes: No restriction with regard to outcomes will be applied.

Types of Studies: Original studies published from 1990 onwards will be considered for inclusion including randomized and non-randomized clinical trials, controlled before- after, cross-sectional studies, longitudinal observational studies, retrospective cohorts, qualitative and mixed methods research and case series with three or more cases; 1990 was determined as a starting date because the first study of long-term NIV use in children we identified was published in 1993.

Exclusion: Case reports, case series with less than three subjects, comments, editorials, letters and reviews will be excluded. Studies where NIV is used solely for the treatment of acute illness will be excluded. During the full text screening, only articles in English, French, Spanish, Portuguese, Italian and Catalan will be included as the review authors are proficient in those languages.

Information sources: An information specialist working for the Alberta Research Centre for Health Evidence (ARCHE) at the University of Alberta collaborated with investigators to design a comprehensive and sensitive search strategy with terms for non-invasive ventilation and children from newborn to age 18 years. The search strategy (Table 1) was developed for Ovid Medline with a validated child search filter,[66] and will be translated into Ovid Embase, PubMed (last year only), CINAHL via EbscoHOST, and Wiley Cochrane Library (including the

Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews of Effects, the Health Technology Assessment Database, and the NHS Economic Evaluation Database). Database search results will be limited to human studies published after 1990. No language or study design restrictions will be applied.

Table 1 Search strategy developed for MEDLINE using OVID

Search terms
1. Continuous Positive Airway Pressure/
2. Noninvasive Ventilation/
3. Intermittent Positive-Pressure Breathing/
4. Ventilators, Negative-Pressure/
5. AVAPS.tw.
6. ((auto* or adaptive) adj2 (servoventilation or ventilation)).tw.
7. AutoSet*.tw.
8. ((bi level or bilevel) adj2 (airway* or air way* or assist* or breath* or positive pressure* or respirat* or ventilat* or support* or therap*)).tw.
9. BIPAP*.tw.
10. BPAP*.tw.
11. c flex.tw.
12. CNEP.tw.
13. (continuous negative adj2 pressure).tw.
14. (continuous positive airway* or continuous positive air way*).tw.
15. (continuous positive adj2 pressure).tw.
16. CPAP*.tw.
17. ((domicil* or home*) adj5 ventilat*).tw.
18. intermittent positive pressure breathing.tw.
19. IPPB*.tw.
20. ((long term or longterm) adj5 ventilat*).tw.
21. ((nasal* or mask*) adj2 (positive adj2 pressure)).tw.
22. ((nasal* or mask*) adj2 ventilat*).tw.
23. nCPAP*.tw.
24. ((negative pressure) adj2 (respirat* or ventilat*)).tw.
25. ((night* or nocturnal* or sleep*) adj5 ventilat*).tw.
26. NIPPV*.tw.
27. ((noninvasive adj5 ventilat*) or (non invasive adj5 ventilat*)).tw.
28. (noninvasive respiratory support* or non invasive respiratory support*).tw.
29. NPPV*.tw.
30. (positive pressure adj2 respirat*).tw.
31. REMstar*.tw.
32. (tank adj (respirat* or ventilat*)).tw.
33. VPAP*.tw.
34. or/1-33
35. Hypoventilation/pc, rh, th [Prevention & Control, Rehabilitation, Therapy]
36. Interactive Ventilatory Support/
37. Intermittent Positive-Pressure Ventilation/
38. Positive-Pressure Respiration/

39. Respiration, Artificial/
40. Respiratory Insufficiency/pc, rh, th [Prevention & Control, Rehabilitation, Therapy]
41. exp Sleep Apnea Syndromes/ pc, rh, th [Prevention & Control, Rehabilitation, Therapy]
42. Ventilators, Mechanical/
43. ((airway* or air way* or breath* or inspirat* or respirat* or ventilat*) and (positive adj2 pressure)).tw.
44. intermittent positive pressure.tw.
45. IPPV*.tw.
46. (mechanical adj (respirat* or ventilat*)).tw.
47. (positive adj2 pressure adj (assist* or support* or therap*)).tw.
48. positive airway pressure.tw.
49. pulmonary ventilator*.tw.
50. respiratory support*.tw.
51. or/35-50
52. (noninvasive or non invasive or spontaneous*).mp.
53. 51 and 52
54. 34 or 53
55. exp Adolescent/
56. exp Child/
57. exp Infant/
58. exp Minors/
59. exp Pediatrics/
60. exp Puberty/
61. exp Schools/
62. adoles*.mp.
63. (baby* or babies or infant* or infancy or neonat* or newborn* or postmatur* or prematur* or preterm*).mp.
64. (boy* or girl* or teen*).mp.
65. (child* or kid or kids or preschool* or school age* or schoolchild* or toddler*).mp.
66. (elementary school* or high school* or highschool* or kindergar* or nursery school* or primary school* or secondary school*).mp.
67. minors*.mp.
68. (paediatric* or peadiatric* or pediatric*).mp.
69. (prepubescen* or pubescen* or pubert*).mp.
70. or/55-69
71. 54 and 70
72. (case reports or comment or editorial or letter).pt.
73. 71 not 72
74. exp animals/ not humans.sh.
75. 73 not 74
76. limit 75 to yr="1990 -Current"
77. remove duplicates from 76

Reference lists of all studies selected for this scoping review will be scanned to identify further relevant studies not detected by the search strategy.

We will also search for gray literature (non-peer reviewed investigations) including conference proceedings, thesis and dissertations, unpublished trials, regulatory agencies and manufacturers reports. In consultation with the advisory team, a list of conference proceedings

and annual meeting reports to review from January 2012 to December 2014 will be established. The information specialist will search websites of the conferences relevant to NIV such as the American Thoracic Society, the American College of Chest Physicians, the Canadian Thoracic Society, the European Respiratory Society, the American Academy of Sleep Medicine, the European Society of Sleep Research, the Australasian Sleep Association, and the American Association of Neuromuscular and Electrodiagnostic Medicine. Investigators will search for publications of relevant proceeding abstracts or contact presenters to request study data if needed. ClinicalTrials.gov and the World Health Organization's International Clinical Trials Registry Platform will also be searched for trials registered after 2012 on NIV and positive airway pressure. Investigators will search for publications of relevant trials or attempt to contact study coordinators to request unpublished data. Regulatory agencies will be searched for ventilator device approval documents, premarket notifications, recall notices and safety advisories. Government sources will include Health Canada's Medical Device Active License Listing (MDALL), the U.S. Food and Drug Administration (FDA) device website (Devices@FDA), the Australian Government's Department of Health and Ageing Therapeutic Goods Administration (TGA) Database of Adverse Event Notifications, the European Medicines Agencies, and the New Zealand Medicines and Medical Devices Safety Authority (Medsafe: Medical Devices). Device manufacturers may be contacted with requests for premarket trial data. ProQuest Theses & Dissertations will also be searched for theses submitted after 1990 on noninvasive ventilation in children.

The Ovid Medline search strategy and the list of information sources will be approved by the advisory team prior to running the searches.

Study records

Data management: Results of searches will be imported into an EndNote library, and duplicates will be removed. Two exact copies of the EndNote library will be created for independent screening by two reviewers.

Selection process: Two independent reviewers will screen titles and abstracts of retrieved articles for eligibility based on the inclusion criteria. The full text will be retrieved for all potentially relevant articles; each will be evaluated independently for eligibility by two reviewers. Discrepancies will be resolved through discussion between the reviewers to establish the final list of studies to be included in the scoping review. Reasons for exclusion will be recorded at the full text review.

Data collection process: Data extraction will be completed by one reviewer using a pre-designed standardized form and entered into Microsoft Excel database (Microsoft, Redmond, Washington, USA). Data extraction will be verified by a second reviewer for a sample of 10% of the studies. The data extraction form is based on Bragge *et al*. data extraction database and modified for this project to ensure that appropriate and relevant data is obtained (Table 2).[56] When there is missing information, two attempts to contact the corresponding authors will be made to obtain additional data. To avoid double counting in the instance of the same data set published in more than one publication, only one article per data set will be retained.

Table 2 Data extraction form

Study characteristics	Extracted data
General information	First author last name Title Journal Publication year Country of study/Continent/Multi-national Publication type: journal, abstract, dissertation, unpublished trial, report
Introduction	Aims of the study Study research question Study population: number of subjects using NIV, mean age, age range, gender, primary underlying condition, comorbidities
Design	Study design: - Quantitative: randomized controlled trial, non-randomized controlled trial, controlled before-after, observational, cross-sectional - Qualitative: case series, ethnography, grounded theory, phenomenology, other, mixed methods Sample size Intervention type, NIV term used, interface type, duration of intervention, co-interventions Statistical analysis methods used Control group: number of control subjects, y/n, intervention in control group
Outcomes measures (whether self- reported or objective tools)*	Primary outcomes Secondary outcomes Adverse outcomes Duration of the follow-up
Authors conclusions	Positive, negative, neutral, indeterminate
Gaps and limitations identified by authors	

* Units of measurements will be reported.

Data synthesis: The identified evidence will be collated using a specific analytical framework in order to present a narrative account of the existing literature.

Once the information has been extracted, we will present a narrative account of findings in three different ways: 1) a basic numerical analysis of the number, publication type, publication year, and country of publication of the studies included in the review. 2) A narrative description of the study design, aims, participant characteristics, sample size, intervention type, control group description, outcomes measures, and statistical methods. We will use this information to establish subcategorise of studies which may include grouping based on age (e.g. infants, children, and adolescents), intervention type (e.g. CPAP, bi-level, and NPV) and disease categories (e.g. OSA, neuromuscular disease). 3) A thematic analysis of included studies by subgroups if appropriate. The results will be presented based on the priorities established by our advisory team including input from children using NIV and their caregivers.

Timeline: We anticipate finishing the search, screening, data extraction and synthesis within 6 months. A search update may be required if the timeline is longer than expected.

CONCLUSION

This scoping review will be the first, to our knowledge, to provide a systematic overview of the evidence on the use of long-term NIV in children. The findings from this review will provide stakeholders with a rigorous research base to support health care providers to improve clinical practice and policy makers to support resource needs for this complex group of children. We

will disseminate our findings through conference proceedings and publications. The gathered data can be used to inform the development of guidelines for the care of children using long-term NIV and will identify gaps in knowledge to support future research endeavors. Based on the results, we will determine whether the application of other systematic review methodologies, such as meta-analysis or meta-synthesis, will be appropriate for any of the subgroups that we identify for future research.

CONTRIBUTORSHIP STATEMENT

MCC, RF, LH, and JM conceived the idea of this study and designed its methodology. MCC and RF wrote the protocol, developed the search strategy and performed a preliminary literature review. KW, CM, SK, EC, GB, CS, FA, RY, DO, VW, LH, and JM reviewed the protocol. All authors read and approved the final manuscript.

COMPETING INTERESTS

None

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DATA SHARING STATEMENT

The protocol of this scoping review, the reference list of included articles, additional unpublished data from the preliminary search strategy and a summary of previous review articles on NIV in children are available by contacting the corresponding author.

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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