Cochrane Library

Cochrane Database of Systematic Reviews

Antibiotics for chronic pulmonary infection in children with a neurodisability (neurodevelopmental disorder) (Protocol)

Sanner JRF, Jain K, Williams J, Smyth AR, Hurley MN

Sanner JRF, Jain K, Williams J, Smyth AR, Hurley MN.
Antibiotics for chronic pulmonary infection in children with a neurodisability (neurodevelopmental disorder) (Protocol).
Cochrane Database of Systematic Reviews 2020, Issue 12. Art. No.: CD013813.
DOI: 10.1002/14651858.CD013813.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

Antibiotics for chronic pulmonary infection in children with a neurodisability (neurodevelopmental disorder)

Juliane RF Sanner[1], Kamini Jain[2], Jane Williams[1], Alan R Smyth[3], Matthew N Hurley[4]

[1]Department of Family Health, Nottingham University Hospitals NHS Trust, Nottingham, UK. [2]Leicester Children's Hospital, University Hospitals of Leicester NHS Trust, Leicester, UK. [3]Division of Child Health, Obstetrics & Gynaecology, School of Medicine, University of Nottingham, Nottingham, UK. [4]Paediatric Respiratory Medicine, Nottingham University Hospitals NHS Trust, Nottingham, UK

Contact address: Juliane RF Sanner, Juliane.Sanner@nottingham.ac.uk, juliane.sanner@nottingham.ac.uk.

Editorial group: Cochrane Airways Group.
Publication status and date: Edited (no change to conclusions), published in Issue 2, 2021.

Citation: Sanner JRF, Jain K, Williams J, Smyth AR, Hurley MN. Antibiotics for chronic pulmonary infection in children with a neurodisability (neurodevelopmental disorder) (Protocol). *Cochrane Database of Systematic Reviews* 2020, Issue 12. Art. No.: CD013813. DOI: 10.1002/14651858.CD013813.

ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the effectiveness and adverse effects of antibiotic treatment for chronic pulmonary infection in children and young people living with a neurodisability, including quality-of-life measures, effects on hospitalisation and healthcare contacts.

BACKGROUND

Description of the condition

Neurodisability in childhood is an umbrella term used to describe a group of individuals living with long-term conditions, who have similar health and educational needs (Morris 2013). It is often characterised due to a primarily neurological problem (e.g. cerebral palsy) or a neuromuscular problem (e.g. a muscular dystrophy).

Neurodisability has been defined as "a group of congenital or acquired long-term conditions that are attributed to impairment of the brain and/or neuromuscular system and create functional limitations. A specific diagnosis may not be identified. Conditions may vary over time, occur alone or in combination, and include a broad range of severity and complexity. The impact may include difficulties with movement, cognition, hearing and vision, communication, emotion, and behaviour" (Morris 2013). Whilst the conditions that can be classified under this umbrella term may be rare individually, grouped together, they are more common. Up to 8% of children in the UK live with any form of disability (Family Resources Survey 2016). Furthermore, it has been estimated that 3% to 4% of children in high-income countries are affected by intellectual and developmental disabilities (Emerson 2012).

For children and young people living with a neurodisability, respiratory complications are a major cause of morbidity and mortality. In 2018, the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) published a comprehensive review of cerebral palsy (CP) as an example of conditions causing neurodisability in those under 25 years of age in the UK (NCEPOD 2018). For this report, the cerebral palsies were chosen as the exemplar neurodisabling condition as they are most common cause of physical disability in childhood, affecting 3 per 1000 live births (NCEPOD 2018). In addition, the cerebral palsies comprise a wide spectrum of severity, and can frequently be associated with a range of co-existing impairments. The enquiry found that respiratory conditions made up a significant proportion of healthcare utilisation for children and young people living with CP. Respiratory problems were the most common cause of primary care attendance, emergency hospitalisation and admission to paediatric intensive care units. In addition, respiratory issues were recorded as the primary cause of death in 51% of children and young people with CP who died (NCEPOD 2018). Improving the treatment of respiratory problems is key to improving quality of life (QoL) and survival of such individuals.

While neurodisability may be due to a range of heterogeneous conditions, the mechanisms by which pulmonary (lung) complications result are often common to all, i.e. impaired airway clearance due to a weak or poorly co-ordinated cough and aspiration of orogastric secretions provoking inflammation. Clearance of the infected thickened secretions is more difficult and lung infection can result. Persistence of these factors can cause repeated or chronic pulmonary infections, resulting in parenchymal lung damage (Fitzgerald 2009; Hurley 2015). High antibiotic consumption in these children may predispose them to antimicrobial resistance (Chang 2015).

Apart from impact on the quality of life of the child or young person, there is often a significant impact on families and carers. In addition to direct healthcare-associated costs, there is a larger societal cost due to the potential loss of earnings of carers, in addition to the costs for potential special educational needs as well as additional factors. A study from England and Wales estimates that neurodevelopmental impairment during mid-childhood equates to an annual economic burden of approximately GBP 1990 million to the broader public services, as well as GBP 333 million to health and social services (Petrou 2013).

As mentioned above, children and young people living with a neurodisability represent a heterogenous group, with different needs. For the purpose of this systematic review and meta-analysis, we will divide children and young people into four broad categories. Whilst the cerebral palsies in themselves represent a broad spectrum of disease, these are considered to be "non-progressive" in origin and are used in the literature as a representative of conditions resulting in neurodisability; we will therefore assess these on their own. Neuromuscular disorders (such as Duchenne muscular dystrophy or spinal muscular atrophy) are well known to have pulmonary implications, often due to progressive respiratory muscle weakness; these will form a second group in our review. Neurodegenerative causes of neurodisability will form a third group, to include conditions such as Batten disease and some metabolic conditions. The final group will include all other causes of neurodisability (including acquired brain injury) and may include those children and young people without a specific diagnosis (including Syndromes Without a Name (SWAN)). Furthermore, only chronic respiratory infections will be included as defined in the methodology section.

Description of the intervention

Antibiotics are a class of medication that kill bacteria (bacteriocidal) or inhibit bacterial growth (bacteriostatic). Antibiotics can be administered by a variety of routes (treatment of pulmonary infection is commonly via oral, intravenous or nebulised routes) and these considerations can impact on the setting in which care is provided. The duration of antibiotic usage can be a few days in the case of acute infections, or long-term in the case of chronic infection. Multiple subclasses of antibiotics exist, including beta-lactams, tetracyclines, macrolides and aminoglycosides, amongst others. Usage of these agents in isolation or combination for pulmonary infections can be influenced by local prevalence, resistance patterns, patient factors and availability.

Despite widespread use, the consumption of antibiotics is accompanied by risk and adverse effects. Side effects of antibiotic usage are commonplace depending on the type of antibiotic used (Gleckman 2000). These side effects can range from relatively mild (e.g. diarrhoea in 2.2% to 18.9% of children and generalised rash in 1.4% to 6.5% of children (Hum 2019)) through to nephrotoxicity/hepatotoxicity and rare but potentially life-threatening events such as anaphylaxis (Cunha 2001). Antibiotic use also drives antibiotic resistance, both within patients and within communities.

How the intervention might work

The mechanism of antibiotic actions can broadly be divided into two categories: bacteriostatic antibiotics work by slowing the growth of bacteria and therefore rely on the host organism's defence mechanisms, whereas bacteriocidal antibiotics lead to or induce bacterial cell death (Kohanski 2010). In order to effectively treat bacterial infections, combinations of antibiotics from various classes may be used.

Why it is important to do this review

There are several uncertainties regarding the treatment of chronic pulmonary infection for children and young people living with a neurodisability. Currently, clinical decisions are often informed by extrapolating information from other conditions, such as cystic fibrosis or bronchiectasis. An awareness of respiratory complications in various causes of neurodisability exists, with multiple papers describing the problem, potential physiological causes and management considerations (Dohna-Schwake 2006; Kansra 2016; Proesmans 2016; Boel 2019). Whilst a recent systematic review has highlighted a limited to absent evidence base for the prevention and management of respiratory disease in children and young people living with CP (Blackmore 2019), this review will assess the evidence base across of wider range of conditions resulting in neurodisability.

Whilst timely prescription of antibiotics is important for the effective management of bacterial infections, antibiotic resistance is a growing problem and inappropriate use of antibiotics can result in increased antibiotic resistance. In 2015 alone, resistant bacteria resulted in an estimated 671,689 infections and 33,110 attributable deaths across all ages in the European Union and European Economic Area (Cassini 2019). With this in mind, a robust evidence base is required to guide clinicians in their decision making when prescribing antibiotics, to enable the targeted and effective treatment of bacterial infections whilst minimising risks to individuals and populations.

With respiratory complications being a significant cause of illness and mortality for children and young people living with a neurodisability, effective treatment to improve quality of life is required. When considering antibiotic treatment, the route of administration is a factor of particular importance as this can directly affect the burden of treatment on children and young people and their families/carers. This systematic review and meta-analysis will therefore be used to understand the evidence base for antibiotic treatment of chronic pulmonary infections in children and young people living with different types of neurodisability.

OBJECTIVES

To assess the effectiveness and adverse effects of antibiotic treatment for chronic pulmonary infection in children and young people living with a neurodisability, including quality-of-life measures, effects on hospitalisation and healthcare contacts.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) only. We will include trials with a cross-over design, but we will restrict the analysis to the first phase of the study only as a significant carry-over effect is expected (Elbourne 2002). We will include studies reported in full text, those published as an abstract only and unpublished data. We will include studies in all languages, where interpretation is possible.

Types of participants

We will include children and young people up to 18 years of age living with a neurodisability, who have been diagnosed with chronic pulmonary infection. There will be no restrictions on the care setting. For the purpose of this review, neurodisability will be defined according to the Delphi survey by Morris 2013. For the purpose of analysis, we will group the underlying conditions into the following categories:

- Cerebral palsy (as this is frequently used as a representative of conditions resulting in neurodisability);
- Neuromuscular causes (e.g. spinal muscular atrophy, Duchenne muscular dystrophy);
- Neurometabolic causes (e.g. Batten disease, Krabbe disease);
- Other complex neurodisability (including children and young people with conditions not falling under the other categories and including acquired brain injury).

Chronic pulmonary infection will be defined according to the trialist, but is likely to include one or more of the following:

- The presence of clinical features of pulmonary infection (such as a chronic wet cough or persistent need for airway clearance) for a minimum of six months;
- Positive microbiology (more than 50% of respiratory samples positive over 12 months);
- Radiological features in keeping with chronic respiratory infection (such as persistently abnormal chest X-rays on two or more occasions in 12 months or evidence of bronchiectasis on computerised tomography (CT)).

Where studies include a proportion of trial participants not meeting the inclusion criteria (e.g. participants aged 18 years or over) we will aim to only analyse those meeting our pre-defined criteria. If this is not obvious from the publication, we will contact the study authors for the data of those participants of interest only. If no response is received to a further reminder email, we will include the trial in the 'Summary of findings' table as well as the narrative synthesis if it is clear that more than 75% of trial participants meet our pre-defined inclusion criteria. However, we will not include the trial in a meta-analysis.

Types of interventions

We will include studies comparing antibiotics of any group, administered by any route (e.g. oral/intravenous/nebulised) with placebo or standard care (or both). We will analyse primarily based on the route of administration and secondarily by antibiotic group. We will include comparative effectiveness trials as well as studies assessing single antibiotics or combinations of antibiotics as the intervention or comparator (or both).

We will include the following co-interventions, provided they are not part of the randomised treatment:

- Standard care;
- Physiotherapy (including respiratory physiotherapy);
- Other antimicrobials (such as antifungals).

Types of outcome measures

We will analyse the following outcomes in the review, but we will not use them as a basis for including or excluding studies. We will consider outcome measures reported over the period of one year following randomisation and will extract data at three, six and 12 months where available.

Primary outcomes

1. Cumulative number of days of hospital admission secondary to respiratory causes per child or young person within one year;
2. Quality-of-life measures as validated patient-reported and/or parent/carer-reported outcomes (such as DISABKIDS-CP (Baars 2005), CP QOL Child (Waters 2006)) or CP QOL Teen (Davis 2013)
3. Average time to next pulmonary exacerbation (defined according to the trialist or by the provision of additional antibiotics) within one year

Secondary outcomes

1. Respiratory symptom scores (such as the Liverpool Respiratory Symptom Questionnaire - Neuro (Trinick 2015))
2. Requirement of new respiratory support (invasive or non-invasive ventilation including high-flow nasal cannula) within one year
3. Number of critical care admissions (including high-dependency units) within one year
4. Number of emergency medical visits (including emergency department visits and out-of-hours care) within one year
5. Adverse events and serious adverse events (including new development of antimicrobial resistance)
6. Survival

Search methods for identification of studies

Electronic searches

We will identify studies from searches of the following databases and trial registries:

- Cochrane Airways Trials Register (Cochrane Airways 2019), via the Cochrane Register of Studies, all years to date;
- Cochrane Acute Respiratory Infections Group Register of Trials (CARIGRT), all years to date;
- Cochrane Central Register of Controlled Trials (CENTRAL), via the Cochrane Register of Studies, all years to date;
- MEDLINE Ovid SP, 1946 to date;
- Embase Ovid SP, 1974 to date;
- Cumulative Index to Nursing and Allied Health Literature (CINAHL), 1937 to date;
- OpenGrey (www.opengrey.eu);
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov);
- World Health Organization International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch);
- International Standard Randomised Controlled Trials Number (ISRCTN) registry.

The proposed MEDLINE search strategy is listed in Appendix 1. This will be adapted for use in the other databases. The search strategy was developed by the Cochrane Airways Information Specialist in collaboration with the authors, and was peer-reviewed by another Cochrane Information Specialist using the PRESS checklist (McGowan 2016). Of note, the search strategy includes some older descriptive terms (such as mental retardation) that are not in use anymore. Whilst we do not advocate the use of these terms, it is necessary to utilise them to comprehensively identify older studies.

All databases and trials registries will be searched from their inception to the present, and there will be no restriction on language or type of publication. Handsearched conference abstracts and grey literature will be identified through the Cochrane Airways Trials Register and the CENTRAL database.

Searching other resources

We will check the reference lists of all primary studies for additional references. Furthermore, we will search Epistemonikos.org, a database of systematic reviews relevant for health decision-making, to identify relevant systematic reviews in order to handsearch the references of relevant systematic reviews. We will use Google Scholar for forward citation searches of all included studies.

We will search for errata or retractions from included studies published in full text on PubMed, and report the date this was done within the review.

Data collection and analysis

Selection of studies

We plan to use Cochrane's Screen4Me workflow to help assess the search results. Screen4Me comprises three components:

- known assessments (a service that matches records in the search results to records that have already been screened in Cochrane Crowd and been labelled as 'RCT' or as 'not an RCT');
- the RCT classifier (a machine learning model that distinguishes RCTs from non-RCTs); and
- Cochrane Crowd (Cochrane's citizen science platform where the Crowd help to identify and describe health evidence), if appropriate.

More detailed information about the Screen4Me components can be found in the following publications: McDonald 2017; Thomas 2017; Marshall 2018; Noel-Storr 2018.

Following this initial assessment, two out of three review authors (JS, KJ, MH) will screen the titles and abstracts of the remaining search results independently and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full-text study reports of all potentially eligible studies and two out of three review authors (JS, KJ, MH) will independently screen them for inclusion, recording the reasons for exclusion of ineligible studies. We will resolve any disagreement through discussion. We will identify and exclude duplicates and collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Moher 2009). We will use Covidence to help with the title and abstract screening, full-text screening, 'Risk of bias' assessment and data extraction stages of the systematic review. We will not include any new studies once the data extraction phase has started.

Data extraction and management

We will use a data collection form for study characteristics and outcome data, which has been piloted on at least one study in the review. Two out of three review authors (JS, KJ, MH) will independently extract the following study characteristics from included studies.

- Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, withdrawals and date of study
- Participants: number (N), mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria and exclusion criteria
- Interventions: intervention, comparison, concomitant medications and excluded medications
- Outcomes: primary and secondary outcomes specified and collected, and time points reported
- Notes: funding for studies and notable conflicts of interest of trial authors

We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We will resolve disagreements by consensus. One review author (JS) will transfer data into the Review Manager file (RevMan 2020). We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (MH or KJ) will spot-check study characteristics for accuracy against the study report.

Assessment of risk of bias in included studies

Two out of three review authors (JS, KJ, MH) will assess risk of bias independently for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020). We will resolve any disagreements by discussion. We will assess the risk of bias according to the following domains:

- Random sequence generation;
- Allocation concealment;
- Blinding of participants and personnel;
- Blinding of outcome assessment;
- Incomplete outcome data;
- Selective outcome reporting;
- Other bias (including, but not limited to, study funding and declaration of interest conflicts).

We will judge each potential source of bias as high, low or unclear and provide a quote from the study report together with a justification for our judgement in the 'Risk of Bias' table. We will summarise the 'Risk of bias' judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient-reported pain scale). Where risk of bias is initially unclear from the available data we will contact the trial's contact author via email to gain further information about the risk of bias. Two reminder emails will be sent if no reply is received to the initial email. If no response is received, the impact of this will be highlighted in the review. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of Bias' table. When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and justify any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data as odds ratios (ORs) and continuous data as the mean difference (MD) or standardised mean difference (SMD). If data from rating scales are combined in a meta-analysis, we will ensure they are entered with a consistent direction of effect (e.g. lower scores always indicate improvement). We will undertake meta-analyses only where this is meaningful; that is, if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense. We will describe skewed data narratively (for example, as medians and interquartile ranges for each group).

Where multiple trial arms are reported in a single study, we will include only the relevant arms. If two comparisons (e.g. drug A versus placebo and drug B versus placebo) are combined in the same meta-analysis, we will either combine the active arms or halve the control group to avoid double-counting.

If adjusted analyses are available (ANOVA or ANCOVA) we will use these as a preference in our meta-analyses. If both change-from-baseline and end-point scores are available for continuous data, we will use change-from-baseline unless there is low correlation between measurements in individuals. If a study reports outcomes at multiple time points, we will aim to extract data at one year.

We will use intention-to-treat (ITT) or 'full analysis set' analyses where they are reported (i.e. those where data have been imputed for participants who were randomly assigned but did not complete the study) instead of completer or per protocol analyses.

Unit of analysis issues

For dichotomous outcomes, we will use participants, rather than events, as the unit of analysis (i.e. number of children admitted to hospital, rather than number of admissions per child). However, if rate ratios are reported in a study, we will analyse them on this basis. We will only meta-analyse data from cluster-RCTs if the available data have been adjusted (or can be adjusted), to account for the clustering.

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as an abstract only). Where this is not possible, and the missing data are thought to introduce serious bias, we will take this into consideration in the GRADE rating for affected outcomes. We will use an imputation method if possible, as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020). Where this is not possible, we plan to perform a sensitivity analysis including only studies with complete data to assess the effect of missing data upon the final result.

Assessment of heterogeneity

We will use the I^2 statistic to measure heterogeneity among the studies in each analysis. If we identify substantial heterogeneity we will report it and explore the possible causes by prespecified

subgroup analysis. The thresholds for interpretation of the I^2 value will be according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

We will contact the authors of studies published as abstract only or registered clinical trials to ask for further information. Unpublished trials will be included in the analysis but unpublished status will be highlighted. In order to reduce the risk of outcome reporting bias we will compare the outcomes in protocols, where available, to the outcomes reported.

If we are able to pool more than 10 studies, we will create and examine a funnel plot to explore possible small-study and publication biases.

Data synthesis

We will use a random-effects model and will perform a sensitivity analysis using a fixed-effect model. Outcomes will be combined and calculated using the software Review Manager 5.4 (RevMan 2020) , in accordance with guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020). The Mantel-Haenszel method will be used for the fixed-effect model if tests of heterogeneity are not significant. If statistical heterogeneity is observed (i.e. I^2 value of 50% or greater or P value less than 0.1), the random-effects model will be chosen. If heterogeneity is substantial, meta-analyses will not be performed and instead a narrative, qualitative summary will be completed.

A systematic narrative synthesis will be provided with information presented in the text and tables to summarise and explain the characteristics and findings of the studies included. Narrative synthesis will explore the relationship and findings within and between studies.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses, if appropriate:

- Grading of cerebral palsy as defined by the Gross Motor Function Classification System (GMFCS): grading at GMFCS level 4 and 5 compared to levels 1, 2 and 3;
- Microbiological evidence of isolation of *Pseudomonas aeruginosa: c*omparing CYP who have ever had *Pseudomonas aeruginosa* confirmed on microbiological testing to those who have not;
- Diagnosis of bronchopulmonary dysplasia (BPD): Children and young people with a diagnosis of BPD compared to those without

We will use the following outcomes in subgroup analyses:

- Cumulative number of days of hospital admission secondary to respiratory causes per child or young person within one year;
- Quality-of-life measures as validated patient-reported and/or parent/carer-reported outcomes (such as DISABKIDS-CP (Baars 2005), CP QOL Child (Waters 2006)) or CP QOL Teen (Davis 2013);
- Average time to next pulmonary exacerbation (defined according to the trialist or by the provision of additional antibiotics) within one year;
- Number of critical care admissions (including high-dependency units) within one year;
- Adverse events and serious adverse events (including new development of antimicrobial resistance).

We will use the formal test for subgroup interactions in Review Manager (RevMan 2020).

Sensitivity analysis

In order to determine whether the results were affected by arbitrary decisions made in the protocol writing stage, we plan to carry out the following sensitivity analyses for the primary outcomes:

- Excluding trials at high risk of bias in any of the domains;
- Excluding trials with missing data.

We will also compare the results from a fixed-effect model with the random-effects model.

Summary of findings and assessment of the certainty of the evidence

We will create a 'Summary of findings' table using the following outcomes:

- Cumulative number of days of hospital admission secondary to respiratory causes per child or young person within 12 months;
- Quality-of-life measures as validated patient-reported and/or parent/carer-reported outcomes;
- Average time to next pulmonary exacerbation (defined according to the trialist or by the provision of additional antibiotics) within one year;
- Requirement of new respiratory support (invasive or non-invasive ventilation including high-flow nasal cannula) within one year;
- Number of critical care admissions (including high-dependency units) within one year;
- Number of emergency medical visits (including emergency department visits and out-of-hours care) within one year;
- Adverse events and serious adverse events (including new development of antimicrobial resistance)

We will use the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence as it relates to the studies that contribute data for the pre-specified outcomes. We will use the methods and recommendations described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020), using GRADEpro GDT software (GRADEpro GDT). We will justify all decisions to downgrade the quality of the evidence using footnotes and we will make comments to aid the reader's understanding of the review where necessary.

ACKNOWLEDGEMENTS

The Background and Methods sections of this protocol are based on a standard template used by Cochrane Airways. We are grateful to Liz Stovold, Information Specialist for Cochrane Airways, for her advice and help in the creation of the sample search strategy for this protocol.

The authors and Airways Editorial Team are grateful to the following peer reviewers for their time and comments:

Susan M Smith, Professor of Primary Care Medicine, Royal College of Surgeons, Ireland;

Paul McNamara, Professor in Child Health, University of Liverpool, UK;
Pauline Campbell, UK (consumer reviewer);
A. Marie Blackmore, Ability Centre and Telethon Kids Institute, Australia;
Candida Fenton, Information Specialist, Cochrane Dementia and Cognitive Improvement Group and Cochrane Vascular, UK.

This project was supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure funding to Cochrane Airways. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

REFERENCES

Additional references

Baars 2005

Baars RM, Atherton C, Koopman HM, Bullinger M, Power M, DISABKIDS group. The European DISABKIDS project: development of seven condition-specific modules to measure health related quality of life in children and adolescents. *Health and Quality of Life Outcomes* 2005;**3**:70. [DOI: 10.1186/1477-7525-3-70]

Blackmore 2019

Blackmore AM, Gibson N, Cooper MS, Langdon K, Moshovis L, Wilson AC. Interventions for management of respiratory disease in young people with cerebral palsy: A systematic review. *Child: Care, Health and Development* 2019;**45**(5):754-71.

Boel 2019

Boel L, Pernet K, Toussaint M, Ides K, Leemans G, Haan J, et al. Respiratory morbidity in children with cerebral palsy: an overview. *Developmental Medicine and Child Neurology* 2019;**61**(6):646-53.

Cassini 2019

Cassini A, Högberg LD, Plachouras D, Quattrocchi A, Hoxha A et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *The Lancet Infectious Diseases* 2019;**19**(1):56-66.

Chang 2015

Chang B, Nariai A, Sekizuka T, Akeda Y, Kuroda M, Oishi K, et al. Capsule switching and antimicrobial resistance acquired during repeated Streptococcus pneumoniae pneumonia episodes. *Journal of Clinical Microbiology* Oct 2015;**53**(10):3318-24. [DOI: 10.1128/JCM.01222-15]

Cochrane Airways 2019

Cochrane Airways Trials Register. airways.cochrane.org/trials-register (accessed 7 May 2019).

Covidence [Computer program]

Veritas Health Innovation Covidence. Melbourne, Australia: Veritas Health Innovation, accessed 25 October 2019. Available at www.covidence.org.

Cunha 2001

Cuhna BA. Antibiotic side effects. *Medical Clinics of North America* 2001;**85**:149-85.

Davis 2013

Davis E, Mackinnon A, Davern M, Boyd R, Bohanna I, Waters E, Graham HK, Reid S, Reddihough D. Description and psychometric properties of the CP QOL-Teen: A quality of life questionnaire for adolescents with cerebral palsy. *Research in Debelopmental Disabilities* Jan 2013;**34**(1):344-352. [DOI: https://doi.org/10.1016/j.ridd.2012.08.018]

Dohna-Schwake 2006

Dohna-Schwake C, Ragette R, Teschler H, Voit T, Mellies U. Predictors of severe chest infections in pediatric neuromuscular disorders. *Neuromuscular Disorders* 2006;**16**(5):325-8. [DOI: 10.1016/j.nmd.2006.02.003]

Elbourne 2002

Elbourne DR, Altman DG, Higgins JPT, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2002;**31**(1):140-9. [DOI: 10.1093/ije/31.1.140]

Emerson 2012

Emerson E. Deprivation, ethnicity and the prevalence of intellectual and developmental disabilities. *Journal of Epidemiology and Community Health* 2012;**66**(3):218-24. [DOI: 10.1136/jech.2010.111773]

Family Resources Survey 2016

Department for Work and Pensions, UK. Family resources survey: financial year 2016/17. www.gov.uk/government/statistics/family-resources-survey-financial-year-201617 (accessed prior to 29 November 2020).

Fitzgerald 2009

Fitzgerald DA, Follett J, Van Asperen PP. Assessing and managing lung disease and sleep disordered breathing in children with cerebral palsy. *Paediatric Respiratory Reviews* 2009;**10**(1):18-24.

Gleckman 2000

Gleckman RA, Czachor JS. Antibiotic side effects. *Seminars in Respiratory and Critical Care Medicine* 2000;**21**(1):61-70.

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime) GRADEpro GDT. Version accessed 25 October 2019. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015. Available at gradepro.org.

Higgins 2020

Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 6.1 (updated September 2020). Cochrane, 2020. Available from training.cochrane.org/handbook.

Hum 2019

Hum S, Shaikh K, Musa S, Shaikh N. Adverse events of antibiotics used to treat acute otitis media in children: a systematic meta-analysis. *The Journal of Pediatrics* 2019;**215**:139-143.e7. [DOI: 10.1016/j.jpeds.2019.08.043]

Hurley 2015

Hurley M, Vyas H. Respiratory problems in children with neurodisability. *Paediatrics and Child Health* 2015;**25**(10):463-6.

Kansra 2016

Kansra S, Ugonna K. Fifteen-minute consultation: approach to management of respiratory problems in children with neurodisability. *Archives of Disease in Childhood Education and Practice Edition* 2016;**101**(5):226-31.

Kohanski 2010

Kohanski MA, Dwyer DJ, Collins JJ. How antibiotics kill bacteria: from targets to networks. *Nature Reviews Microbiology* 2010;**8**(6):423-35.

Marshall 2018

Marshall IJ, Noel-Storr AH, Kuiper J, Thomas J, Wallace BC. Machine learning for identifying randomized controlled trials: an evaluation and practitioner's guide. *Research Synthesis Methods* 2018;**9**(4):602-14.

McDonald 2017

McDonald S, Noel-Storr AH, Thomas J. Harnessing the efficiencies of machine learning and Cochrane Crowd to identify randomised trials for individual Cochrane reviews. In: Global Evidence Summit; 2017 September 13-16; Cape Town, South Africa. 2017.

McGowan 2016

McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS peer review of electronic search strategies: 2015 guideline statement. *Journal of Clinical Epidemiology* 2016;**75**:40-6. [DOI: 10.1016/j.jclinepi.2016.01.021]

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman D. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine* 2009;**6**(7):e1000097. [DOI: 10.1371/journal.pmed.1000097]

Morris 2013

Morris C, Janssens A, Tomlinson R, Williams J, Logan S. Towards a definition of neurodisability: a Delphi survey. *Developmental Medicine and Child Neurology* 2013;**55**(12):1103-8. [DOI: 10.1111/dmcn.12218]

NCEPOD 2018

National Confidential Enquiry into Patient Outcome and Death. Each and every need - a review of the quality of care provided to patients aged 0-25 years old with chronic neurodisability, using the cerebral palsies as examples of chronic neurodisabling conditions. www.ncepod.org.uk/2018report1/downloads/EachAndEveryNeed_FullReport.pdf (accessed prior to 5 November 2019).

Noel-Storr 2018

Noel-Storr AH, Project Transform team. Cochrane Crowd: new ways of working together to produce health evidence. In: Evidence Live; 2018 June 18-20; Oxford, UK. 2018.

Petrou 2013

Petrou S, Johnson S, Wolke D, Marlow N. The association between neurodevelopmental disability and economic outcomes during mid-childhood. *Child: Care, Health and Development* 2013;**39**(3):345-57. [DOI: 10.1111/j.1365-2214.2012.01368.x]

Proesmans 2016

Proesmans M. Respiratory illness in children with disability: a serious problem? *Breathe* 2016;**12**(4):e97-e103.

RevMan 2020 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration Review Manager (RevMan). Version 5.4. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2020.

Thomas 2017

Thomas J, Noel-Storr AH, Marshall I, Wallace B, McDonald S, Mavergames C, et al. Living systematic review network. Living systematic reviews: 2. Combining human and machine effort. *Journal of Clinical Epidemiology* 2017;**91**:31-7.

Trinick 2015

Trinick RE, Bunni L, Thorburn K, Hackett AP, Dalzell M, McNamara PS. An observational study examining the relationship between respiratory symptoms, airway inflammation and bacteriology in children with severe neurodisability. *PloS one* 2015;**10**(4):e0124627. [DOI: 10.1371/journal.pone.0124627]

Waters 2006

Waters E, Davis E, Mackinnon A, Boyd R, Graham HK, Kai Lo S, et al. Psychometric properties of the quality of life questionnaire for children with CP. Developmental Medicine and Child Neurology 2006;**49**(1):49-55. [DOI: 10.1017/S0012162207000126.x]

APPENDICES

Appendix 1. Medline search strategy

Ovid MEDLINE(R) ALL <1946 to 15 November 2019>

#	Search terms	Results
1	exp Neurodevelopmental Disorders/	175867
2	Developmental Disabilities/	19504

(Continued)

3	exp Intellectual Disability/	94182
4	Child Development Disorders, Pervasive/	6528
5	exp Learning Disorders/	21774
6	exp Communication Disorders/	62246
7	Disabled Children/	6043
8	exp Muscular Diseases/	168883
9	exp Neuromuscular Diseases/	299040
10	Cerebral Palsy/	19929
11	exp Muscular Dystrophies/	25950
12	((neurodevelopment$ or development$) adj3 (delay$ or disorder$ or disabilit$ or impair$ or condition$)).tw.	80148
13	neurodisabilit$.tw.	242
14	neurological disabilit$.tw.	1837
15	(multiple adj3 disabilit$).tw.	1911
16	(neuromuscular$ adj3 (disease$ or disorder$ or disabilit$ or impair$ or condition$)).tw.	12393
17	myopath$.tw.	25774
18	cerebral palsy.tw.	21062
19	(muscular adj3 dystroph$).tw.	22955
20	handicap$.tw.	23232
21	(mental$ adj3 retard$).tw.	33033
22	or/1-21	745487
23	exp Respiratory Tract Infections/	349071
24	exp Respiratory Tract Diseases/	1306377
25	Sputum/	20919
26	Mucus/	9451
27	((respiratory or airway$ or pulmonary or chest$ or lung$) adj3 (problem$ or infection$ or condition$ or disease$ or disorder$)).tw.	250063
28	((respiratory or airway$ or pulmonary or chest$ or lung$) adj3 (morbidit$ or complication$)).tw.	24997

(Continued)

29	Pseudomonas aeruginosa/	41464
30	Pseudomonas.tw.	93875
31	(secretion$ or sputum or mucus).tw.	388983
32	(chronic$ adj3 infection$).tw.	42064
33	bronchiectasis.tw.	8839
34	exp Bronchiectasis/	9046
35	exp Pneumonia/	89378
36	pneumonia.tw.	109472
37	or/23-36	1912405
38	22 and 37	32756
39	exp Anti-Bacterial Agents/	710844
40	antibiotic$.tw.	319274
41	exp Macrolides/	107226
42	(macrolide$ or azithromycin or clarithromycin or erythromycin or roxithromycin or spiramycin).tw.	44853
43	(penicillin or amoxicillin or amoxycillin or ampicillin or benzylpenicillin or cloxacillin or dicloxacillin or flucloxacillin or piperacillin or ticarcillin or sulbactam).tw.	87503
44	(cephalosporin$ or cephalexin or cephaclor or cefaclor or cefepime or cefotaxime or cephamycin$ or cefotetan or cefoxitin or cefmetazole or cefpirome or cefpodoxime or ceftazidime or ceftriaxone or cephamandole or cephazolin).tw.	48139
45	(fluoroquinolone$ or ciprofloxacin or enoxacin or norfloxacin or ofloxacin or pefloxacin or fleroxacin or levofloxacin or moxifloxacin).tw.	48812
46	(tetracycline$ or doxycycline or methacycline or minocycline).tw.	50412
47	(amikacin or gentamicin or neomycin or netilmicin).tw.	39637
48	(clindamycin or lincomycin).tw.	12341
49	(chloramphenicol or amantadine or cotrimoxazole or trimethoprim).tw.	46388
50	(tobramycin$ or co-amoxiclav$ or Augmentin or cotrimoxazole or Sulfamethoxazole or trimethoprim or Spetra or Bactrim or Clavulin$).tw.	28899
51	colistin$.tw.	5826
52	or/39-51	938892

(Continued)

53	38 and 52	1191
54	(controlled clinical trial or randomised controlled trial).pt.	583238
55	(randomised or randomised).ab,ti.	594921
56	placebo.ab,ti.	208680
57	dt.fs.	2158069
58	randomly.ab,ti.	322916
59	trial.ab,ti.	567081
60	groups.ab,ti.	2003617
61	or/54-60	4645999
62	Animals/	6510996
63	Humans/	18119089
64	62 not (62 and 63)	4610798
65	61 not 64	4029911
66	53 and 65	658

WHAT'S NEW

Date	Event	Description
25 February 2021	Amended	Amended to correct unusual characters in original version.

HISTORY

Protocol first published: Issue 12, 2020

CONTRIBUTIONS OF AUTHORS

JS drafted the protocol. All authors critically reviewed the protocol prior to publication.

Contributions of editorial team

Chris Cates (Co-ordinating Editor) checked the planned methods, edited the protocol; advised on methodology; and approved the protocol prior to publication.

Kristin V Carson-Chahhoud (Contact Editor): edited the protocol; advised on content.

Emma Dennett (Managing Editor): co-ordinated the editorial process; advised on content; and edited the protocol.

Emma Jackson (Assistant Managing Editor): conducted peer review; and edited the references and protocol.

Elizabeth Stovold (Information Specialist): designed the search strategy; and arranged for peer review of the search strategy.

DECLARATIONS OF INTEREST

JS is an NIHR-funded Academic Clinical Fellow.

ARS declares relevant activities of membership of an advisory board member (Vertex) and lectures paid for by Teva. He has received a research grant from Vertex (outside the submitted work).

KJ, JW and MH declare no conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- Nottingham University Hospitals NHS Trust, UK

  Employer of JS, JW and MH
- University of Nottingham, UK

  Employer of AS
- University Hospitals of Leicester NHS Trust, UK

  Employer of KJ

External sources

- National Institute for Health Research, UK

  JS is undertaking this review as part of an NIHR funded Academic Clinical Fellowship