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Should empiric antibiotic therapy be withheld when etiology of preterm birth is non-infectious? A protocol for a systematic review.

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Title: Should empiric antibiotic therapy be withheld when etiology of preterm birth is non-infectious? A protocol for a systematic review.

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Registration

"In accordance with the guidelines, our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 11 January 2016 and was last updated on 13 April, 2017 (registration number CRD 42016029707)."

Abstract

Introduction

Preterm birth (PTB) at less than 37 weeks of gestation is the leading cause of perinatal morbidity and mortality in developed countries. The traditional approach has been based on the assumption that PTB is primarily a result of intrauterine infection, which triggers preterm labour and puts the newborn at risk of early onset sepsis (EOS). However, we are currently experiencing a rise in iatrogenic prematurity that results from maternal and foetal diseases unrelated to infection. We have designed a systematic review to assess whether chemoprophylaxis should be withheld when the etiology of preterm birth is non-infectious.

Methods and Analysis

Our study will focus on studies evaluating EOS in preterm infants. An information specialist will search for eligible studies in Medline, (Ovid interface, 1948 and onwards), Embase (Ovid interface, 1980 onwards) and the Cochrane Central Register of Controlled Trials (Wiley interface, current issue). Additionally we will search databases and registers including records of on-going research, conference proceedings and thesis (Clinical trials, WHO International Clinical Trials Registry Platform). Two authors will independently extract data from eligible studies and assess risk of bias. For continuous outcomes, which follow discrete distribution, mean difference will be calculated. Dichotomous data will be presented using risk ratios, while count data will be expressed using rate ratios. Time-to-event outcomes will be reported as hazard ratios. All estimates will be presented together with 95% CI. Studies comparable with respect to methodology and reporting the same outcomes will be combined in a meta-analysis.

Ethics and dissemination

Our systematic review does not require approval from the research and ethics board. We will use the findings of this study to prepare a future multicenter randomized-control trial in order to establish safe and adequate antibiotics policies for extreme, severe, or moderately preterm infants, based on the indication for or etiology of PTB.

Protocol registration number Prospero CRD 42016029707

Study strengths: First systematic review to evaluate the use of empiric antibiotics in preterm babies born for non-infectious reasons. Results will be used to verify current guidelines and hospital policies.

Study limitations: Heterogeneity of study settings and design may influence results.

Acknowledgements

We would like to thank Dr Dayre McNally from the Department of Pediatrics, Children's Hospital of Eastern Ontario and Nassr Nama from the Faculty of Medicine, University of Ottawa for providing us with CrowdScreenSR.

Introduction

Preterm birth at less than 37 weeks of gestation is the leading cause of perinatal morbidity and mortality in developed countries. Despite on-going improvement in perinatal care, the frequency of preterm delivery remains high (11.4 % in the US and 5-9% in Europe and other developed countries).

The traditional approach has been based on the assumption that preterm birth is primarily a result of intrauterine infection, which triggers preterm labour and puts the newborn at risk of EOS. Hence, to treat EOS, all preterm infants should receive empirical antibiotics, until negative culture results exclude infection. Furthermore, antenatal antibiotics are often started with onset of preterm labour, making postnatal cultures less reliable and leading to a prolonged course of antibiotics, even in the face of negative blood cultures[2, 3].

Furthermore, we are currently experiencing a rise in iatrogenic prematurity, which is mainly a result of maternal or foetal diseases unrelated to infection (assisted fertilisation and multiple gestation, preeclampsia, intrauterine growth restriction - IUGR). There are limited data establishing the risk of EOS in this group of preterm infants, and even less understanding about potential adverse effects of early exposure to antibiotics on neonatal and longer-term outcomes. We suspect that there are many preterm infants delivered for maternal or foetal medical indications who are at low risk of EOS, and with unknown relative risk versus benefit of chemoprophylaxis within the first 48 hours of life.

Given the health risks associated with unnecessary antibiotic therapy and limited data for establishing risk factors for EOS, increasing rates of iatrogenic prematurity may lead to a rise in potential adverse effects and poor outcome in this age group. Understanding the consequences of chemoprophylaxis in most preterm infants (<32 weeks of gestation) born for non-infectious

reasons is critical to ensuring physicians and policy makers make informed decisions as to when and if such therapy should be implemented. This is particularly important in light of growing evidence that futile antibiotic therapy leads to alterations in and reduces diversity of the newborn microbiome, increased risk of necrotizing enterocolitis (NEC), poor neurological outcomes or death[5-7].

Available guidelines regarding treatment of suspected or possible early onset sepsis (EOS) refer to term newborns, or late preterm infants. There are no clear guidelines for risk assessment of EOS in (<28 weeks) and very preterm (28-<32 weeks) infants [2 3]. To our best knowledge there is no systemic review published regarding the use of antibiotics in preterm infants born secondary to non-infectious reasons.

OBJECTIVES

The aim of this systematic review is to evaluate the effectiveness and harms of antibiotic prophylaxis for early onset sepsis (EOS) in the management of preterm infants ≤32 weeks of gestation born for reasons unrelated to infection.

METHODS

Types of studies

We will consider primary studies with the following designs:

- Prospective or retrospective cohorts (including cohorts obtained from RCTs), nested case-control, case-cohort studies, or administrated database/registries.
- All types of prediction model studies, i.e., model development studies with/without validation, model validation studies, model re-development or updating studies.

Review articles, cross-sectional and case-control designs and models predicting composite outcomes case reports, Case series, will be excluded.

Study settings

Studies conducted in worldwide.

Types of interventions

The study will focus on infectious and non-infectious etiology of preterm birth, and evaluate short, medium and long exposure to antibiotics. Infectious etiology of preterm birth will be defined by maternal symptoms of *chorioamnionitis* as outlined by the American College of Obstetrics and Gynaecology (ACOG) such as maternal fever > 38°C and two of the following foetal tachycardia (>160/'), maternal tachycardia >80/', uterine tenderness, maternal leukocytosis > $15x10^6$, foul smelling discharge[8]. Non-infectious reasons will include causes such as foetal IUGR, fetal distress, maternal pre-eclampsia, (hemolysis, elevated liver enzymes, low platelet count), and placental abruption. Antibiotic exposure will be defined as short (≤72h), medium (>72h to ≤7days) or longer-term (>7days) empiric therapy.

Types of outcome measures

Primary outcomes

- Early onset sepsis,
- Late onset sepsis,
- Necrotizing enterocolitis,

Secondary outcomes

- Length of hospital stay,
- Neonatal death,
- Poor neurodevelopmental outcomes

Search methods for identification of studies.

Both qualitative and quantitative studies will be sought. No study design, or date limits will be imposed on the search, although only studies in English will be included. A health sciences librarian, with expertise in systematic review searching, will create the specific search strategies. The MEDLINE strategy will be developed with input from the project team. A draft MEDLINE search strategy is included in Appendix 1. After the MEDLINE strategy is finalized, it will be adapted to the syntax and subject headings of the other databases.

The search will be updated toward the end of the review, after being validated to ensure that the MEDLINE strategy retrieves a high proportion of eligible studies found through any means but indexed in MEDLINE.

Electronic searches.

Literature search strategies will be developed using medical subject headings (MeSH) and text words related to early onset sepsis, late onset sepsis and prematurity. Large databases, such as Medline, (Ovid interface, 1948 and onwards), Embase will be searched (Ovid interface, 1980 onwards) and the Cochrane Central Register of Controlled Trials (Wiley interface, current issue). We will try to minimize the possible bias by implementing a broad search strategy. Additionally we will search databases and registers including records of on-going research, conference proceedings and thesis (Clinical trials, WHO International Clinical Trials Registry Platform). All studies in English will be included.

Studies will be located by using a combination of approaches;

a. Searching electronic databases
b. Visually scanning reference lists from relevant studies
c. Contacting authors, experts
d. Searching relevant Internet resources
e. Citation searching

Data collection and analyses

Selection of studies

Literature search results will be uploaded to CrowdscreenSR, a website for crowdsourcing systematic reviews, which enables cooperation between reviewers during the study selection process. The selection process will be piloted by applying the inclusion criteria to a sample of papers in order to check if we can reliably interpret the findings. All papers will be assessed independently by two researches (JSS and JR). After duplicates are removed, retrieved records will be screened at two levels. Level 1 screening will be based on titles and abstract. One reviewer will include relevant records but exclusion will be based on consensual decision of two

reviewers. Two reviewers will independently assess eligibility after perusal of the full text of the record at Level 2 of screening. Reviewers will not be blinded to journal titles or the study authors or institutions. The above will be assessed against the predetermined inclusion criteria. Disagreements will be resolved by consensus or third party adjudication.

Data extraction

To reduce bias and improve validity and reliability an electronic standardized data extraction form (ESDEF) will be used (please see online supplementary appendix 2). The ESDEF will combine of key study characteristics (methods, participants, and outcomes). It will be piloted prior to use on at least five randomly identified studies form the list of included studies. Data extraction will be preformed by two researches (JSS and JR). A record of errors or amendments to data extractions will be kept for future reference.

Assessment of risk of bias in included studies

Two reviewers will assess risk of bias independently using *CHARMS checklist* to assess study validity [10]. We will use *Quality In Prognosis Studies* (QUIPS) to evaluate study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, statistical analysis and reporting[11]. To assess the quality of experimental studies the Cochrane's Collaboration's tool will be used[12].

Measures of treatment effect and data synthesis

For continuous outcomes, which follow discrete distribution, mean difference will be calculated. Dichotomous data will be presented using relative risk, while count data will be expressed using rate ratios. Time-to-event outcomes will be reported as hazard ratios. All estimates will be presented together with 95% confidence intervals.

Studies comparable with respect to methodology and reporting the same outcomes will be combined in a meta-analysis. Between-study heterogeneity will be examined using the χ^2 test and the I^2 statistics. Fixed-effect meta-analysis will be permitted only when p value of χ^2 test >0.1 and I^2 <40% indicating that the between-studies differences are not statistically significant and observed heterogeneity might not be important[12 13]. Random-effect meta-analysis will be carried out using either DerSimonian & Laird or inverse variance methods of weight assignment for either continuous data or all remaining outcomes[13]. Fixed-effect meta-analysis will be conducted using the algorithm proposed by Mantel and Haenszel as well as the inverse variance method for cardinal and all other types of outcomes, respectively[14]. Significance of the overall effect will be tested with two-tailed Z-test assuming $p < 0.05$ as the level of significance.

Qualitative synthesis with either narrative description or tabular representation will be presented when studies could not be quantitatively combined due to inacceptable heterogeneity of missing data precluding meta-analysis.

All statistical analyses will be conducted using dedicated software. Preferably R statistical software with 'metafor' package will be used for all calculations and generation of corresponding plots, but the use of other recognized programs cannot be excluded [15].

Dealing with missing data

The data will be analysed on an intention-to-treat principle. In case of missing data, which preclude inclusion of the outcome into quantitative accumulation, we will attempt to contact the corresponding author in order to obtain required information. Unavailable data will not be

imputed, since this could increase uncertainty of the final results, therefore only available data will be quantitatively accumulated. The extent and implications of missing data will be recorded.

Assessment of heterogeneity and sensitivity analysis

Between-study heterogeneity will be examined using the χ^2 test and the I^2 statistics, as described above. When between-trials variability reaches statistical significance (p value for heterogeneity < 0.1), attempts to explain heterogeneity will be undertaken using sensitivity analyses with either subgroup meta-analysis or meta-regression. Factors or continuous measures that may potentially influence the results will be analysed as covariates. For subgroup meta-analysis, identified studies will be stratified according to following explanatory variables: study quality, race (black vs non-black) or region (developing vs developed). Between-subgroup effects will be assessed using test for interaction as proposed by Borenstein et al. with $p < 0.05$ indicating statistically significant impact of the covariate on observed effect size[16]. The contribution of continuous covariates (i.e.: mean maternal age, mean gestational age at delivery, percent of black infants, mean birth weight, mean Apgar score) to between-study heterogeneity will be explored with random-effect meta-regression provided that at least ten studies will be available for each explanatory variable[12].

Assessment of publication biases

For meta-analyses with at least 10 studies the risk of publication bias will be examined by visual inspection of funnel plots and statistically assessed with the use of both Egger's and Begg's tests with $p < 0.05$ considered statistically significant.

DISCUSSION

By conducting this systematic review we plan to establish whether preterm infants born at <32 weeks of gestation due to non-infectious reasons should receive prophylactic antibiotic therapy. We will use the findings of this systematic review to prepare a future multicenter randomized-control study in order to establish safe and adequate antibiotics policies for extreme, severe, or moderately preterm infants. Furthermore, we will provide up-to-date evidence of the harms and benefits of chemoprophylaxis in the most premature group of newborns. Additionally we plan to discuss how our findings may be applied in future guidelines and hospital policies.

Ethics and dissemination.

We did not submit for ethical approval, as the study does not include individuals. All significant modifications in the protocol will be reported to PROSPERO. The full protocol will be widely available due to open access. We plan to submit our findings to international peer-reviewed journals (paediatric, infectious, epidemiology). Abstracts will be submitted to local and international conferences.

The Systematic Review will be used to prepare a multicenter prospective trial with the aim of evaluating the safety of using a more targeted antibiotics approach in low risk preterm infants, including a delay in antibiotic initiation until laboratory tests results and blood culture results are available.

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Authors' contributions

Dr's Joanna Seliga-Siwecka, Mohammed Ansari, Justyna Romanska conceptualized and designed the study; drafted the initial manuscript, and approved the final manuscript as submitted.

Dr Judy Aschner critically reviewed the manuscript, and approved the final manuscript as submitted.

Dr Margaret Sampson developed the electronic search strategies, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Funding and competing interests statement

- This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors'.
- All authors have no competing interests to declare.

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	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			1
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	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	13
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	n/a
Support:			
Sources	5a	Indicate sources of financial or other support for the review	n/a
Sponsor	5b	Provide name for the review funder and/or sponsor	n/a
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	n/a
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
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	7
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	8
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	8-9

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8-9
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)	8-10
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	8-10
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	8-10
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8
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	10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	10-12
	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)	12
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	n/a

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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Abstract

Introduction

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Methods and Analysis

Our study will focus on studies evaluating EOS in preterm infants. An information specialist will search for eligible studies in Medline, (Ovid interface, 1948 and onwards), Embase (Ovid interface, 1980 onwards) and the Cochrane Central Register of Controlled Trials (Wiley interface, current issue). We will search databases and registries including records of on-going research, conference proceedings and thesis (Clinical trials, WHO International Clinical Trials Registry Platform). Two authors will independently extract data from eligible studies and assess risk of bias. For continuous outcomes, which follow discrete distribution, mean difference will be calculated. Dichotomous data will be presented using risk ratios, while count data will be expressed using rate ratios. Time-to-event outcomes will be reported as hazard ratios. All estimates will be presented together with 95% CI. Studies comparable with respect to methodology and reporting the same outcomes will be combined in a meta-analysis.

Ethics and dissemination

Our systematic review does not require approval from the research and ethics board. We will use the findings to prepare a future multicenter randomized-control trial in order to establish safe and adequate antibiotics policies for extreme, severe, or moderately preterm infants, based on the etiology of PTB.

Protocol registration number Prospero CRD 42016029707

Study strengths:

- First systematic review to evaluate the use of empiric antibiotics in preterm babies born for non-infectious reasons.
- Results will be used to verify current guidelines and hospital policies.

Study limitations:

- Heterogeneity of study settings, design and missing data may influence results.

Acknowledgements

We would like to thank Dr Dayre McNally from the Department of Pediatrics, Children's Hospital of Eastern Ontario and Nassr Nama from the Faculty of Medicine, University of Ottawa for providing us with CrowdScreenSR (InsightScope).

INTRODUCTION

Preterm birth at less than 37 weeks of gestation is the leading cause of perinatal morbidity and mortality in developed countries. Despite on-going improvements in perinatal care, the frequency of preterm delivery remains high (11.4 % in the United States and 5-9% in Europe and other developed countries).

The traditional approach has been based on the assumption that preterm birth is primarily a result of intrauterine infection, which triggers preterm labour and puts the newborn at risk of early onset sepsis (EOS). Hence, to treat EOS, all preterm infants should receive empirical antibiotics, until negative culture results exclude infection.

However, we are currently experiencing a rise in the rate of prematurity, which is mainly a result of maternal or fetal diseases unrelated to infection (assisted fertilisation and multiple gestation, preeclampsia, intrauterine growth restriction - IUGR). There are limited data establishing the risk of EOS in this group of preterm infants, contrary to growing evidence of adverse effects of early exposure to antibiotics on neonatal outcome. Negative consequences of chemoprophylaxis, especially in culture negative premature infants include reduced diversity of the newborn microbiome, increased risk of late onset sepsis (LOS), necrotizing enterocolitis (NEC), poor neurological outcomes or death [1-3]. This all may lead to prolonged length of hospital, along with increased health-care costs. We suspect that there is a group of infants who are at low risk of EOS, and with unknown relative risk versus benefit of chemoprophylaxis within the first 48 hours of life.

Given the above facts, it is critical to provide physicians with up-to-date guidelines regarding implementation of antibiotic therapy in preterm infants, depending on their risk for EOS.

Unfortunately, available policies regarding treatment of suspected or possible EOS refer to term newborns, or late preterm infants. There are no clear guidelines for risk assessment of EOS in extreme (<28 weeks) and very preterm (28-<32 weeks) infants [4 5]. To our best knowledge there is no systemic review published regarding the use of antibiotics in preterm infants born secondary to non-infectious reasons.

OBJECTIVES

The first aim of this systematic review is to investigate whether infectious/non-infectious etiology of preterm birth lead to different adverse neonatal outcome. Secondly, we plan to assess whether there are differences in comparative effectiveness/harms of empiric antibiotic therapy for the two etiologies.

- Q1. Are there any risk prediction models for early onset sepsis (EOS), late onset sepsis (LOS), necrotizing enterocolitis (NEC), length of hospital stay (LOHS), neonatal death or poor neurodevelopmental outcomes developed exclusively for preterm birth ≤ 32 weeks of gestation? If yes, was infectious/non-infectious etiology of preterm birth evaluated as a predictor in the model(s)? If yes, is infectious/non-infectious etiology an independent predictor for one or more of these adverse outcomes?
- Q2. When non-infectious indications of preterm birth ≤32weeks of gestation are compared with infectious indications, what is the relative risk (or odds/hazards) of EOS, neonatal death, LOS, LOHS, NEC and poor neurodevelopmental outcomes?
- Q3. For births ≤32 weeks gestation, what is the comparative effectiveness and harm of no, short (≤72h), medium (>72h to ≤7days) or longer-term (>7days) empiric antibiotic

therapy for infectious and non-infectious -etiologies of preterm birth? Are there important differences in comparative effectiveness between the two etiologies?

METHODS AND ANALYSES

Types of studies

We will consider primary studies with the following designs:

- Prospective or retrospective cohorts (including cohorts obtained from RCTs), nested case-control, case-cohort studies, or administrated database/registries.
- All types of prediction model studies, i.e., model development studies with/without validation, model validation studies, model re-development or updating studies.

Review articles, cross-sectional and case-control designs and models predicting composite outcomes case reports, case series, will be excluded.

Study settings

Studies conducted worldwide. We plan to conduct separate analysis for developed and developing nations.

Types of interventions

The study will focus on infectious and non-infectious etiology of preterm birth, and evaluate short, medium and long exposure to antibiotics. Infectious etiology of preterm birth will be defined by maternal symptoms of *chorioamnionitis* as outlined by the American College of Obstetrics and Gynaecology (ACOG) such as maternal fever ≥38°C and two of the following fetal tachycardia (>160/'), maternal tachycardia >80/', uterine tenderness, maternal leukocytosis > $15x10^6$, foul smelling discharge[6]. Histological evidence of *chorioamnionitis* is present >70% of women who become febrile after an epidural (a common procedure during labour). Despite the lack of other symptoms, these cases will also be considered at risk of EOS together

with preterm premature rupture of membranes (pPROM), preterm labour and maternal colonisation with group B streptococcus [4]. Non-infectious reasons will include causes such as IUGR, fetal distress, maternal preeclampsia (hemolysis, elevated liver enzymes, low platelet count) and placental abruption. Antibiotic exposure will be defined as short (≤72h), medium (>72h to ≤7days) or longer-term (>7days) empiric therapy.

Types of outcome measures

Primary outcomes

- Early onset sepsis defined as positive blood or cerebral spinal fluid within the first 48-72 hours of life[4].
- Late onset sepsis defined as positive blood or cerebral spinal fluid after 72 hours of life[7].
- Necrotizing enterocolitis according to Bell's criteria[8].

Secondary outcomes

- Length of hospital stay.
- Neonatal death.
- Poor neurodevelopmental outcomes.

Data extraction items will include funding, geographic region of study, study characteristics (e.g. sample size, duration of follow-up and funding); population characteristics and eligibility criteria; intervention characteristics (e.g. type of antibiotics, dose, frequency, duration); exposure definitions, measurement tool and cut-offs; number randomized into each group and number analyzed; number exposed and unexposed; missing data and reasons for missing data; outcome definition, time-point, measurement tool employed, cut-offs, and metric; statistical analysis and

adjustments; and items necessary to assess risk of bias. For question 1, other data extraction items reported in the CHARMS checklist for risk prediction models will also be extracted [9].

One reviewer will extract data. Another reviewer will verify outcomes data independently. Discrepancies will be cross-checked against the full-text of the record and, where applicable, data entries will be corrected.

A table presenting review eligibility criteria is presented in appendix 1.

Search methods for identification of studies.

Both qualitative and quantitative studies will be sought. No language, study design, or date limits will be imposed on the search. A preliminary Medline search revealed that approximately 15% of the records are studies published in languages other than English. The search will not be limited to English, however studies in languages other than English will be excluded during screening as described below. A health sciences librarian, with expertise in systematic review searching, will create the specific search strategies. The MEDLINE strategy will be developed with input from the project team. A draft MEDLINE search strategy is included in appendix 2. After the MEDLINE strategy is finalized, it will be adapted to the syntax and subject headings of the other databases.

The search will be updated toward the end of the review, after being validated to ensure that the MEDLINE strategy retrieves a high proportion of eligible studies found through any means but indexed in MEDLINE.

Electronic searches.

Literature search strategies will be developed using medical subject headings (MeSH) and text words related to early onset sepsis, late onset sepsis and prematurity. Large databases, such as

Medline, (Ovid interface, 1948 and onwards), Embase will be searched (Ovid interface, 1980 onwards) and the Cochrane Central Register of Controlled Trials (Wiley interface, current issue). We will try to minimize the possible bias by implementing a broad search strategy. Additionally we will search databases and registers including records of on-going research, conference proceedings and thesis (Clinical trials, WHO International Clinical Trials Registry Platform). No language restrictions will be placed on the search although only reports written in English will be included in the review. In order to assess how many eligible non-English studies were excluded based on language of publication alone, titles and abstracts of all retrieved records will be screened at the first level. Any studies written in languages other than English but otherwise eligible will be excluded and given the exclusion reason "not English" so that the impact of the language exclusion can be formally assessed. Records in languages other than English that are ineligible for other reasons will be excluded for those reasons, not for language of publication.

Studies will be located by using a combination of approaches;

a. Searching electronic databases
b. Visually scanning reference lists from relevant studies
c. Contacting authors, experts
d. Searching relevant Internet resources
e. Citation searching

Data collection and analyses

Selection of studies

Literature search results will be uploaded to CrowdscreenSR (InsightScope), a website for crowdsourcing systematic reviews, which enables cooperation between reviewers during the study selection process. The selection process will be piloted by applying the inclusion criteria to a sample of papers in order to check if we can reliably interpret the findings. All papers will be assessed independently by two researches (JSS and JR). After duplicates are removed, retrieved records will be screened at two levels. Level 1 screening will be based on titles and abstract. One reviewer will include relevant records but exclusion will be based on consensual decision of two reviewers. Two reviewers will independently assess eligibility after perusal of the full text of the record at Level 2 of screening. Reviewers will not be blinded to journal titles or the study authors or institutions. The above will be assessed against the predetermined inclusion criteria. Disagreements will be resolved by consensus or third-party adjudication.

Data extraction

To reduce bias and improve validity and reliability an electronic standardized data extraction form (ESDEF) will be used (please see online supplementary appendix 3). The ESDEF will combine key study characteristics (methods, participants, and outcomes). It will be piloted prior to use on at least five randomly identified studies from the list of included studies. Data extraction will be performed by two researches (JSS and JR). A record of errors or amendments to data extractions will be kept for future reference.

Assessment of risk of bias in included studies

Risk of bias assessment is an assessment of the internal validity of studies. Two reviewers will assess risk of bias independently. Disagreements will be resolved by consensus or third-party adjudication. Risk of bias assessment will be undertaken for all biasing domains. Domain specific judgments will be categorised as high, moderate, low or unclear. Overall risk of bias of a

study will be judged across domains as high, moderate or low. A domain rating of high risk of bias will automatically lead to high overall risk of bias judgment. When no domain specific assessment of the risk of bias was rated as high, the overall risk of bias study will not be judged as high. Risk of bias assessments will be outcome specific.

For questions 1, we will use the *CHARMS checklist* to assess study validity [9]. For question 2, *Quality In Prognosis Studies* (QUIPS) tool that covers six domains, namely, study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting will be used [10]. When evidence for Question 3 originates in randomized controlled trials, the *Cochrane risk of bias tool* will be employed. Assessment of risk of bias of non-randomized studies addressing question 3 will be based on our generic assessment of selection bias (including attrition bias or missing data), confounding (including time-varying changes in treatment/confounders), information bias and bias due to use of co-interventions [11].

Publication bias will be investigated for the body of evidence from randomized controlled trials if the following criteria are met [12]:

- ≥ 10 studies contributing data for an outcome
- studies of unequal sizes
- no substantial clinical and methodological differences between smaller and larger studies
- quantitative results accompanied with measures of dispersion

Applicability

Study applicability or generalizability characterization will be made by two reviewers and categorised as major concerns, minor concerns or no concern with corresponding rationales

documented. Determinants of applicability will be population characteristics, study environmental settings, intervention dose/frequency/timing, definition of outcomes and exposure and their measurement techniques, adequacy of follow-up and background standards of care.

Measures of treatment effect

A qualitative synthesis of relevant literature will be undertaken informed by overall study risk of bias judgments to answer Question 1. Question 1 investigates whether infectious/non-infectious aetiology of birth ≤32 weeks would remain a significant predictor of a number of adverse neonatal and longer-term health outcomes in risk prediction models including other candidate predictors. The question does not inquire about the magnitude of calibration, discrimination or classification statistics as measures of model performance. Hence, no quantitative data pooling of these statistical estimates will be conducted. We will, however, report the range of these statistics reported in studies at low risk of bias with transportable (i.e. generalizable) models.

For Question 2, data will be pooled quantitatively for each outcome unless between-study heterogeneity (i.e. I squared > 50%) can be explained by study level clinical or methodological covariates. Statistical heterogeneity between studies will be quantified with I-squared statistics and the P value from the chi-squared test ($P \leq 0.10$ instead will be used to determine statistical significance). Between study heterogeneity will be explored with key clinical and methodological covariates. Methodological covariates may be items such as study design, study risk of bias and funding. Clinical covariates might be variables such as the severity of preterm birth, Apgar score, antibiotic therapy protocol, mode of delivery, and specific laboratory testing protocols. Heterogeneity would be investigated in subgroup analyses or meta-regression. Data will be pooled using random effects generic inverse variance or Mantel–Haenszel method because group sizes are likely to be different in data contributing observational studies. Other

random effects model (e.g. Peto odds or inverse variance method) may be used as recommended by previously published guidance [13]. The software used will be reported when we publish study findings. When both are reported, adjusted estimates of association will be preferentially selected over crude estimates in meta-analyses. Sensitivity analyses by study risk of bias will be undertaken as required. Evidence originating in studies that used prophylactic/empiric maternal or neonatal antibiotic therapy will be synthesized separately from those that did not. Pooled data will be reported as odds ratio, hazards ratio, relative risk or mean difference. *Post hoc* subgroup analyses may be undertaken if warranted by the data.

Approach to meta-analysis for evidence pertaining to Question 3 will be similar to the approach described for Question 2. Randomized controlled trial data will not be combined with non-randomized studies. Sparse data will not be meta-analyzed but described narratively. Studies with zero events in both arms will be excluded from meta-analysis.

Data synthesis

For continuous outcomes, which follow discrete distribution, mean difference will be calculated. Dichotomous data will be presented using relative risk, while count data will be expressed using rate ratios. Time-to-event outcomes will be reported as hazard ratios. All estimates will be presented together with 95% confidence intervals.

Studies comparable with respect to methodology and reporting the same outcomes will be combined in a meta-analysis. Between-study heterogeneity will be examined using the χ^2 test and the I^2 statistics. Fixed-effect meta-analysis will be permitted only when p value of χ^2 test >0.1 and I^2 <40% indicating that the between-studies differences are not statistically significant and observed heterogeneity might not be important[11 14]. Random-effect meta-analysis will be carried out using either DerSimonian & Laird or inverse variance methods of weight assignment

for either continuous data or all remaining outcomes[14]. Fixed-effect meta-analysis will be conducted using the algorithm proposed by Mantel and Haenszel as well as the inverse variance method for cardinal and all other types of outcomes, respectively[15]. Significance of the overall effect will be tested with two-tailed Z-test assuming $p < 0.05$ as the level of significance.

Qualitative synthesis with either narrative description or tabular representation will be presented when studies could not be quantitatively combined due to inacceptable heterogeneity of missing data precluding meta-analysis.

All statistical analyses will be conducted using dedicated software. Preferably R statistical software with 'metafor' package will be used for all calculations and generation of corresponding plots, but the use of other recognized programs cannot be excluded [16].

Assessment of Certainty of Evidence

For each outcome, when prognostic or effect estimates are not very wide and can be conclusively interpreted, we will grade the certainty of evidence as per the published GRADE approach [17] [18]. For example, if for Question 3, short duration of empiric antibiotic therapy versus long-term therapy yields wide confidence interval for the outcome necrotizing enterocolitis such that one can exclude the possibility that short duration may be harmful, equivalent or superior to long-term compared with long-term therapy, then results are inconclusive and as such grading of the certainty of evidence will not be attempted for this outcome.

Dealing with missing data

The data will be analysed on an intention-to-treat principle. In case of missing data, which preclude inclusion of the outcome into quantitative accumulation, we will attempt to contact the

corresponding author in order to obtain required information. The extent and implications of missing data will be reported.

Assessment of heterogeneity and sensitivity analysis

Between-study heterogeneity will be examined using the χ^2 test and the I^2 statistics, as described above. When between-trials variability reaches statistical significance (p value for heterogeneity < 0.1), attempts to explain heterogeneity will be undertaken using sensitivity analyses with either subgroup meta-analysis or meta-regression. Factors or continuous measures that may potentially influence the results will be analysed as covariates. For subgroup meta-analysis, identified studies will be stratified according to following explanatory variables: study quality, race (black vs non-black) or region (developing vs developed). Between-subgroup effects will be assessed using test for interaction as proposed by Borenstein et al. with $p < 0.05$ indicating statistically significant impact of the covariate on observed effect size[19]. The contribution of continuous covariates (i.e.: mean maternal age, mean gestational age at delivery, percent of black infants, mean birth weight, mean Apgar score) to between-study heterogeneity will be explored with random-effect meta-regression provided that at least ten studies will be available for each explanatory variable[11].

Assessment of publication biases

For meta-analyses with at least 10 studies the risk of publication bias will be examined by visual inspection of funnel plots and statistically assessed with the use of both Egger's and Begg's tests with $p < 0.05$ considered statistically significant.

DISCUSSION

By conducting this systematic review we plan to establish whether preterm infants born at ≤ 32 weeks of gestation due to non-infectious reasons should receive prophylactic antibiotic therapy. We will use the findings of this systematic review to prepare a future multicenter randomized-control study in order to establish safe and adequate antibiotics policies for extreme, severe, or moderately preterm infants. Furthermore, we will provide up-to-date evidence of the harms and benefits of chemoprophylaxis in the most premature group of newborns. Additionally we plan to discuss how our findings may be applied in future guidelines and hospital policies.

ETHICS AND DISSEMINATION

We did not submit for ethical approval, as the study does not include individuals. All significant modifications in the protocol will be reported to PROSPERO. The full protocol will be widely available due to open access. We plan to submit our findings to international peer-reviewed journals (paediatric, infectious, epidemiology). Abstracts will be submitted to local and international conferences.

The Systematic Review will be used to prepare a multicenter prospective trial with the aim of evaluating the safety of using a more targeted antibiotics approach in low risk preterm infants, including a delay in antibiotic initiation until laboratory tests results and blood culture results are available.

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Authors' contributions

Dr's Joanna Seliga-Siwecka, Mohammed Ansari, Justyna Romanska conceptualized and designed the study; drafted the initial manuscript, and approved the final manuscript as submitted.

Dr Judy Aschner critically reviewed the manuscript, and approved the final manuscript as submitted.

Dr Margaret Sampson developed the electronic search strategies, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Funding and competing interests statement

- This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors'.
- All authors have no competing interests to declare.

Appendix 1- Table 1. Review eligibility criteria

Question	Criteria	Population	Intervention/ Exposure	Comparator	Outcome*	Study design	Timing
1	Inclusion	Newborns ≤ 32 weeks GA	Infectious/non-infectious etiology of preterm birth	Other candidate variables	Early onset sepsis, late onset sepsis, necrotizing enterocolitis, length of hospital stay, neonatal death, poor neurodevelopment outcomes	Prospective or retrospective cohort (including cohorts obtained from RCTs), nested case-control, case-cohort studies, or admin database/registries All types of prediction model studies, i.e., model development studies with/without validation, model validation studies, model re-development or updating studies	Prognostication at birth Follow-up adequate for outcome of interest
	Exclusion	Non-English language literature, cross-sectional and case-control designs and models predicting composite outcomes					
2	Inclusion	As above	As above	Infectious indications for preterm birth	As above	As above, but not risk prediction models	Follow-up adequate for outcome of interest
	Exclusion	Non-English language literature, cross-sectional and case-control designs					
3	Inclusion	Newborns ≤ 32 weeks GA due to: Infectious indication (only) Non-infectious indication (only)	Short (≤72h), medium (>72h to ≤7days) or longer-term (>7days) empiric antibiotic therapy	No empiric antibiotic therapy or alternative duration of therapy	All of the above and total major or serious adverse events	Independent intervention-control comparative experimental or observational study	Follow-up adequate for outcome of interest
	Exclusion	Non-English language literature and cross-sectional studies					

* Outcomes will not be considered as eligibility criterion during screening. GA= gestational age; RCTs= randomized controlled trials; h= hours

Appendix 2 – Electronic search strategies

MEDLINE
1. Cesarean section/
2. Labor, induced/
3. Obstetric Labor, Premature/
4. (induc* or cesar*).mp.
5. or/1-4
6. exp Premature Birth/
7. exp Infant, Premature/
8. (pre-term or preterm or prematur*).mp.
9. or/6-8
10. exp Anti-Bacterial Agents/
11. exp Chemoprevention/
12. prophyla*.mp.
13. exp Sepsis/
14. (septic* or sepsis).tw.
15. or/10-14
16. 5 and 9 and 15
17. limit 16 to animals
18. limit 16 to humans
19. 16 not (17 not 18)
20. remove duplicates from 19

Embase
1. cesarean section/
2. exp labor induction/
3. ((induc* adj2 lab*) or cesar*).mp.
4. or/1-3
5. prematurity/
6. (pre-term or preterm or prematur*).mp.
7. or/5-6
8. exp antiinfective agent/
9. prophylaxis/ or exp antibiotic prophylaxis/ or exp chemoprophylaxis/ or exp infection prevention/
10. prophyla*.mp.
11. exp sepsis/
12. (septic* or sepsis).tw.
13. or/8-9,11-12
14. 4 and 7 and 13
15. limit 14 to human

16. limit 14 to animals
17. 14 not (16 not 15)
18. limit 17 to embase

CENTRAL
1. ((induc* adj2 lab*) or cesar*).mp.
2. (pre-term or preterm or prematur*).tw.
3. 1 and 2
4. (Antibiot* or anti-bacterial or antibacter*).tw.
5. (Anti-infect* or antiinfect*).tw.
6. (prophyla* or chemoprev*).tw.
7. (septic* or sepsis).tw.
8. or/4-7
9. 3 and 8

Appendix 3 Electronic data extraction sheet

General information		
Researcher		
Date of data extraction		
Record number		
Author		
Article title		
Citation		
Type of publication	journal article	conference abstract
Country of origin		
Source of funding		

Study characteristics	
Aim/objectives of the study	
Study design	
Study inclusion and exclusion criteria	
Recruitment procedures used (e.g. details of randomization, blinding)	
Unit of allocation	

Participant characteristics	
Age	
Gender	
Ethnicity	
Socio-economic status	
Disease characteristics	
Co-morbidities	

Intervention and setting	
Settings in which antibiotics where delivered (Level !, II, III care).	
Dose, route of administration, number of cycles	
Description of co-interventions	

Outcome data/results*	
Unit of assessment/analysis	
Statistical techniques used	
Whether reported	
Definition used in study	
Measurement tool or method used	
Unit of measurement (if appropriate)	
Length of follow-up, number and/or times of follow-up measurements	

*For each specified outcome

	Study group	**Control group**
Number of participants		
Number of participants included in analysis		
Number of withdrawals, exclusions, lost to follow-up		
Summary outcome data		
Dichotomous: number of events,		
Dichotomous: number of participants,		
Continuous: mean		
Continuous: standard deviation		

Type of analysis used in study (e.g. intention to treat, per protocol)	
Results of study analysis	
Dichotomous: odds ratio, risk ratio and confidence intervals, p-value	
Continuous: mean difference, confidence intervals	

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	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			1
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	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	13
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	n/a
Support:			
Sources	5a	Indicate sources of financial or other support for the review	n/a
Sponsor	5b	Provide name for the review funder and/or sponsor	n/a
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	n/a
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
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	7
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	8
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	8-9

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8-9
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)	8-10
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	8-10
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	8-10
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8
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	10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	10-12
	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)	12
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	n/a

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Should empiric antibiotic therapy be withheld when etiology of preterm birth is non-infectious? A protocol for a systematic review.

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Complete List of Authors:	Seliga-Siwecka, Joanna; Warszawski Uniwersytet Medyczny, Neonatology and Neonatal Intensive Care Ansari, Mohammed; School of Epidemiology, Public Health and Preventive Medicine, Faculty of Medicine, University of Ottawa Aschner, Judy; Albert Einstein College of Medicine and The Children's Hospital at Montefiore, Pediatrics Sampson, Margaret; Children's Hospital of Eastern Ontario Research Institute Romańska , Justyna; Warszawski Uniwersytet Medyczny, Neonatology and Neonatal Intensive Care
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Infectious diseases, Evidence based practice
Keywords:	Neonatal intensive & critical care < INTENSIVE & CRITICAL CARE, NEONATOLOGY, MICROBIOLOGY

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Title: Should empiric antibiotic therapy be withheld when etiology of preterm birth is non-infectious? A protocol for a systematic review.

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Word count: 2900

Registration

"In accordance with the guidelines, our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 11 January 2016 and was last updated on 13 April, 2017 (registration number CRD 42016029707)."

Abstract

Introduction

Preterm birth (PTB) at <37 weeks of gestation is the leading cause of perinatal morbidity and mortality in developed countries. The traditional approach has been based on the assumption that PTB is primarily a result of intrauterine infection, which triggers preterm labour and puts the newborn at risk of early onset sepsis (EOS). We are currently experiencing a rise in prematurity that results from maternal and fetal diseases unrelated to infection. We have designed a systematic review to assess whether chemoprophylaxis should be withheld when the etiology of preterm birth is non-infectious.

Methods and Analysis

Our study will focus on studies evaluating EOS in preterm infants. An information specialist will search for eligible studies in Medline, (Ovid interface, 1948 and onwards), Embase (Ovid interface, 1980 onwards) and the Cochrane Central Register of Controlled Trials (Wiley interface, current issue). Searches will be restricted to the last 30 years .We will search databases and registries including records of on-going research, conference proceedings and thesis (Clinical trials, WHO International Clinical Trials Registry Platform). Two authors will independently extract data from eligible studies and assess risk of bias. For continuous outcomes, which follow discrete distribution, mean difference will be calculated. Dichotomous data will be presented using risk ratios, while count data will be expressed using rate ratios. Time-to-event outcomes will be reported as hazard ratios. All estimates will be presented together with 95% CI. Studies comparable with respect to methodology and reporting the same outcomes will be combined in a meta-analysis.

Ethics and dissemination

Our systematic review does not require approval from the research and ethics board. We will use the findings to prepare a future multicenter randomized-control trial in order to establish safe and adequate antibiotics policies for extreme, severe, or moderately preterm infants, based on the etiology of PTB.

Protocol registration number Prospero CRD 42016029707

Study strengths:

- First systematic review to evaluate the use of empiric antibiotics in preterm babies born for non-infectious reasons.

Study limitations:

- Heterogeneity of study settings, design and missing data may influence results.

Acknowledgements

We would like to thank Dr Dayre McNally from the Department of Pediatrics, Children's Hospital of Eastern Ontario and Nassr Nama from the Faculty of Medicine, University of Ottawa for providing us with CrowdScreenSR (InsightScope).

INTRODUCTION

Preterm birth at less than 37 weeks of gestation is the leading cause of perinatal morbidity and mortality in developed countries. Despite on-going improvements in perinatal care, the frequency of preterm delivery remains high (11.4 % in the United States and 5-9% in Europe and other developed countries).

The traditional approach has been based on the assumption that preterm birth is primarily a result of intrauterine infection, which triggers preterm labour and puts the newborn at risk of early onset sepsis (EOS). Hence, to treat EOS, all preterm infants should receive empiric antibiotics, until negative culture results exclude infection. However, we are currently experiencing a rise in the rate of prematurity, which is mainly a result of maternal or fetal conditions unrelated to infection (assisted reproductive technologies and multiple gestation, preeclampsia, maternal obesity and diabetes, intrauterine growth restriction (IUGR)). While there are limited data establishing the risk of EOS in this group of preterm infants, there is growing evidence of adverse effects of early exposure to antibiotics on neonatal outcomes; reduced diversity of the newborn microbiome, increased risk of late onset sepsis (LOS), necrotizing enterocolitis (NEC), poor neurological outcomes and death [1-3]. Additional adverse consequences include impaired maternal-newborn bonding, delayed breastfeeding, increased risk of IV infiltrates, aminoglycoside toxicity and ototoxicity and prolonged length of hospital stay which increases health-care costs. We propose that there is a group of infants who are at low risk of EOS, and for these infants, relative risk versus benefit of chemoprophylaxis within the first 48 hours of life is unknown.

Moreover, it is critical to provide physicians with up-to-date guidelines regarding implementation of antibiotic therapy in preterm infants, stratified by risk of EOS. No clear

guidelines exist for preterm infants <32 weeks [4 5], nor are there published systemic review on the use of antibiotics in preterm infants born for reasons that are associated with a low likelihood of infection.

OBJECTIVES

The first aim of this systematic review is to investigate whether infectious versus non-infectious etiologies of preterm birth lead to different adverse neonatal outcomes. Secondly, we plan to assess whether there are differences in comparative effectiveness/harms of empiric antibiotic therapy for the two etiologies.

- Q1. Are there any risk prediction models for early onset sepsis (EOS), late onset sepsis (LOS), necrotizing enterocolitis (NEC), length of hospital stay (LOHS), neonatal death or poor neurodevelopmental outcomes developed exclusively for preterm births ≤ 32 weeks of gestation? If yes, was infectious/non-infectious etiology of preterm birth evaluated as a predictor in the model(s)? If yes, is infectious/non-infectious etiology an independent predictor for one or more of these adverse outcomes?
- Q2. When non-infectious indications of preterm birth ≤32weeks of gestation are compared with infectious indications, what is the relative risk (or odds/hazards) of EOS, neonatal death, LOS, LOHS, NEC and poor neurodevelopmental outcomes?
- Q3. For births ≤32 weeks gestation, what is the comparative effectiveness and harm of no, short (≤72h), medium (>72h to ≤7days) or longer-term (>7days) empiric antibiotic therapy for infectious and non-infectious etiologies of preterm birth? Are there important differences in comparative effectiveness between the two etiologies?

METHODS AND ANALYSES

Types of studies

We will consider primary studies with the following designs:

- Prospective or retrospective cohorts (including cohorts obtained from RCTs), nested case-control, case-cohort studies, or administrated database/registries.
- All types of prediction model studies, i.e., model development studies with/without validation, model validation studies, model re-development or updating studies.

Review articles, cross-sectional and case-control designs and models predicting composite outcomes, case reports and case series, will be excluded.

Study settings

Studies conducted worldwide. We plan to conduct separate analyses for developed and developing nations.

Types of interventions

The study will focus on infectious and non-infectious etiologies of preterm birth, and evaluate short, medium and long exposure to antibiotics. Infectious etiology of preterm birth will be defined by maternal symptoms of *chorioamnionitis* as outlined by the American College of Obstetrics and Gynaecology (ACOG) such as maternal fever ≥38°C and two of the following: fetal tachycardia (>160/'), maternal tachycardia >80/', uterine tenderness, maternal leukocytosis > $15x10^6$, foul smelling discharge[6]. Histological evidence of *chorioamnionitis* is present in >70% of women who become febrile after an epidural (a common procedure during labour). Despite the lack of other symptoms, these cases will also be considered at risk of EOS together

with preterm premature rupture of membranes (pPROM), preterm labour and maternal colonisation with group B streptococcus [4]. Non-infectious reasons will include causes such as IUGR, fetal distress, maternal preeclampsia (hemolysis, elevated liver enzymes, low platelet count) and placental abruption. Antibiotic exposure will be defined as short (≤72h), medium (>72h to ≤7days) or longer-term (>7days) empiric therapy.

Types of outcome measures

Primary outcomes

- Early onset sepsis defined as positive blood or cerebral spinal fluid within the first 48-72 hours of life[4].
- Late onset sepsis defined as positive blood or cerebral spinal fluid after 72 hours of life[7].
- Necrotizing enterocolitis according to Bell's criteria[8].

Secondary outcomes

- Length of hospital stay.
- Neonatal death.
- Poor neurodevelopmental outcomes.

Data extraction items will include funding, geographic region of study, study characteristics (e.g. sample size, duration of follow-up and funding); population characteristics and eligibility criteria; intervention characteristics (e.g. type of antibiotics, dose, frequency, duration); exposure definitions, measurement tool and cut-offs; number randomized into each group and number analyzed; number exposed and unexposed; missing data and reasons for missing data; outcome definition, time-point, measurement tool employed, cut-offs, and metric; statistical analysis and

adjustments; and items necessary to assess risk of bias. For question 1, other data extraction items reported in the CHARMS checklist for risk prediction models will also be extracted [9].

One reviewer will extract data. Another reviewer will verify outcomes data independently. Discrepancies will be cross-checked against the full-text of the record and, where applicable, data entries will be corrected.

A table presenting review eligibility criteria is presented in appendix 1.

Search methods for identification of studies.

Studies will be identified through searches of bibliographic databases and trial registries, cited and citing references, contacting experts and general Internet searching. Database search strategies will be developed by a librarian experienced in systematic review searching. The MEDLINE strategy will be developed first, with input from the research team. The search will then be adapted for the other databases. Medline, Embase and Cochrane Central Register of Controlled Trials will be searched using the Ovid platform. ClincialTrials.gov and WHO International Clinical Trials Registry Platform will be searched to identify in progress or completed but not yet published trials. Searches will be restricted to the last 30 years but no study design or language restrictions will be imposed. As preliminary searches suggest that approximately 15% of the records are published in a language other than English, studies in languages other than English will be excluded during screening as described below. The search will be updated toward the end of the review, after being validated to ensure that the MEDLINE strategy retrieves a high proportion of eligible studies found through any means but indexed in MEDLINE. A draft MEDLINE search strategy is included in Appendix 2.

Data collection and analyses

Selection of studies

Records identified through searching will be imported into Reference Manager were duplicate records will be removed, Remaining records will be uploaded to CrowdscreenSR (InsightScope), a website for crowdsourcing systematic reviews, which enables cooperation between reviewers during the study selection process. The selection process will be piloted by applying the inclusion criteria to a sample of publications to ensure inter-rated reliability. After that, all publications will be assessed independently by two researchers (JSS and JR) at two levels. First, titles and abstracts will be assessed, requiring consensus of two reviewers to exclude a record. Then, full text articles. Two reviewers assess the full text to determine final eligibility.. Disagreements will be resolved by consensus or third-party adjudication.

Data extraction

An electronic data extraction form will be used to extract key study characteristics (methods, participants and outcomes) (appendix 3). Data extraction will be piloted with five randomly selected eligible studies. Data extraction will be performed by two researchers (JSS and JR). Data corrections or amendments will be logged.

Assessment of risk of bias in included studies

Risk of bias assessment is an assessment of the internal validity of studies. Two reviewers will assess risk of bias independently for each outcome of interest. Disagreements will be resolved by consensus or third-party adjudication.

For question 1, we will use the *CHARMS checklist* to assess study validity [9]. For question 2, the *Quality In Prognosis Studies* (QUIPS) tool that covers six domains, namely, study

participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting will be used [10]. When evidence for Question 3 originates in randomized controlled trials, the *Cochrane risk of bias tool* will be employed. Assessment of risk of bias of non-randomized studies addressing question 3 will be based on our generic assessment of selection bias (including attrition bias or missing data), confounding (including time-varying changes in treatment/confounders), information bias and bias due to use of co-interventions [11]. Risk of bias assessment will be undertaken for all biasing domains, and each will be judged as high, moderate, low or unclear risk of bias. Overall risk of bias of a study will be judged across domains as high, moderate or low. A domain rating of high risk of bias will automatically lead to a judgment of high overall risk of bias. When no domain-specific assessment of the risk of bias was rated as high, the study's overall risk of bias will not be judged as high.

Publication bias will be investigated for the body of evidence from randomized controlled trials if the following criteria are met [12]:

- ≥ 10 studies contributing data for an outcome
- studies of unequal sizes
- no substantial clinical and methodological differences between smaller and larger studies
- quantitative results accompanied by measures of dispersion

Applicability

Characterization of study applicability or generalizability will be made by two reviewers and categorised as major concerns, minor concerns or no concern with corresponding rationales documented. Determinants of applicability incorporate population characteristics, study

environmental settings, intervention dose/frequency/timing, definition of outcomes and exposures and their measurement techniques, adequacy of follow-up and background standards of care.

Measures of treatment effect

Question 1 investigates whether infectious and non-infectious aetiologies of birth ≤32 weeks would remain a significant predictor of a number of adverse neonatal and longer-term health outcomes in risk prediction models including other candidate predictors. This will be answered through a descriptive synthesis of relevant literature, informed by judgments of overall study risk of bias. No quantitative data pooling of these statistical estimates will be conducted. We will report the parameters of models from studies assessed as low risk of bias and generalizable models.

For Question 2, the decision to conduct a meta-analysis will be based on an assessment of between study heterogeneity, measured by the I-squared statistic. Between-study heterogeneity (i.e. I squared > 50%) can be explained by study level clinical or methodological covariates. Statistical heterogeneity between studies will be quantified with I-squared statistics and the P value from the chi-squared test ($P \leq 0.10$) will be used to determine statistical significance. As well as statistically heterogeneity, clinical and methodological heterogeneity will be explored with methodological covariates including study design, study risk of bias and funding and clinical covariates such as the severity of preterm birth, Apgar scores, antibiotic therapy protocol, mode of delivery, and specific laboratory testing protocols. Such heterogeneity would be investigated in subgroup analyses or meta-regression. Where meta-analysis is warranted, data will be pooled using random effects generic inverse variance or Mantel–Haenszel method because group sizes are likely to be different in contributing observational studies. Other random

effects models (e.g. Peto odds or inverse variance method) may be used as recommended by previously published guidance [13]. Adjusted estimates of association will be preferentially selected over crude estimates in meta-analyses. Pooled data will be reported as odds ratio, hazards ratio, relative risk or mean difference. Sensitivity analyses by study risk of bias will be undertaken as required. Evidence originating in studies that used prophylactic/empiric maternal or neonatal antibiotic therapy will be synthesized separately from those that did not. *Post hoc* subgroup analyses may be undertaken if warranted by the data.

Approach to meta-analysis for evidence pertaining to Question 3 will be similar to the approach described for Question 2. Randomized controlled trial data will not be combined with non-randomized studies. Sparse data will not be included in the meta-analysis but rather described narratively. Studies with zero events in both arms will be excluded from the meta-analysis.

Data synthesis

For continuous outcomes, which follow discrete distribution, mean difference will be calculated. Dichotomous data will be presented using relative risk, while count data will be expressed using rate ratios. Time-to-event outcomes will be reported as hazard ratios. All estimates will be presented together with 95% confidence intervals.

Studies comparable with respect to methodology and reporting the same outcomes will be combined in a meta-analysis. Between-study heterogeneity will be examined using the χ^2 test and the I^2 statistics. Fixed-effect meta-analysis will be permitted only when p value of χ^2 test >0.1 and I^2 <40% indicating that the between-studies differences are not statistically significant and observed heterogeneity might not be important[11 14]. Random-effect meta-analysis will be carried out using either DerSimonian & Laird or inverse variance methods of weight assignment for either continuous data or all remaining outcomes[14]. Fixed-effect meta-analysis will be

conducted using the algorithm proposed by Mantel and Haenszel as well as the inverse variance method for cardinal and all other types of outcomes, respectively[15]. Significance of the overall effect will be tested with two-tailed Z-test assuming $p < 0.05$ as the level of significance.

Qualitative synthesis with either narrative description or tabular representation will be presented when studies could not be quantitatively combined due to inacceptable heterogeneity of missing data precluding meta-analysis.

All statistical analyses will be conducted using dedicated software. R statistical software with 'metafor' package will preferentially be used for all calculations and generation of corresponding plots, but the use of other statistical programs cannot be excluded [16].

Assessment of Certainty of Evidence

For each outcome, when prognostic or effect estimates are not very wide and can be conclusively interpreted, we will grade the certainty of evidence as per the published GRADE approach [17] [18]. For example, if for Question 3, short duration of empiric antibiotic therapy versus long-term therapy yields wide confidence interval for the outcome necrotizing enterocolitis, such that one cannot exclude the possibility that short duration may be harmful, equivalent or superior to long-term, then results are inconclusive and, as such, grading of the certainty of evidence will not be attempted for this outcome.

Dealing with missing data

The data will be analysed on an intention-to-treat principle. In case of missing data, which preclude inclusion of the outcome into quantitative accumulation, we will attempt to contact the corresponding author in order to obtain required information. The extent and implications of missing data will be reported.

Assessment of heterogeneity and sensitivity analysis

Between-study heterogeneity will be examined using the χ^2 test and the I^2 statistics, as described above. When between-trials variability reaches statistical significance (p value for heterogeneity < 0.1), attempts to explain heterogeneity will be undertaken using sensitivity analyses with either subgroup meta-analysis or meta-regression. Factors or continuous measures that may potentially influence the results will be analysed as covariates. For subgroup meta-analysis, identified studies will be stratified according to the following explanatory variables: study quality, race (Black vs non-Black), ethnicity (Hispanic versus non-Hispanic) or region (developing vs developed). Between-subgroup effects will be assessed using the test for interaction as proposed by Borenstein et al. with $p < 0.05$ indicating statistically significant impact of the covariate on observed effect size[19]. The contribution of continuous covariates (i.e.: mean maternal age, mean gestational age at delivery, percent of Black infants, mean birth weight, mean Apgar score) to between-study heterogeneity will be explored with random-effect meta-regression provided that at least ten studies will be available for each explanatory variable[11].

Assessment of publication biases

For meta-analyses with at least 10 studies the risk of publication bias will be examined by visual inspection of funnel plots and statistically assessed with the use of both Egger's and Begg's tests with $p < 0.05$ considered statistically significant.

DISCUSSION

By conducting this systematic review, we plan to establish whether preterm infants born at ≤ 32 weeks of gestation due to non-infectious reasons should receive prophylactic antibiotic therapy. We will use the findings of this systematic review to prepare a future multicenter randomized-control study in order to establish safe and adequate antibiotics policies for extreme, severe, or moderately preterm infants. Furthermore, we will provide up-to-date evidence of the harms and benefits of chemoprophylaxis in the most premature group of newborns. Additionally, we plan to discuss how our findings may be applied in future guidelines and hospital policies.

ETHICS AND DISSEMINATION

We did not submit for ethical approval, as the study does not include individuals. All significant modifications in the protocol will be reported to PROSPERO. The full protocol will be widely available due to open access. We plan to submit our findings to international peer-reviewed journals (paediatric, infectious, epidemiology). Abstracts will be submitted to local and international conferences.

The Systematic Review will be used to prepare a multicenter prospective trial with the aim of evaluating the safety of using a more targeted antibiotic approach in low risk preterm infants, including a delay in antibiotic initiation until laboratory tests results and blood culture results are available.

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Authors' contributions

Dr's Joanna Seliga-Siwecka, Mohammed Ansari, Justyna Romanska conceptualized and designed the study; drafted the initial manuscript, and approved the final manuscript as submitted.

Dr Judy Aschner critically reviewed the manuscript, and approved the final manuscript as submitted.

Dr Margaret Sampson developed the electronic search strategies, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Funding and competing interests statement

- This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors'.
- All authors have no competing interests to declare.

Appendix 1- Table 1. Review eligibility criteria

Question	Criteria	Population	Intervention/ Exposure	Comparator	Outcome*	Study design	Timing
1	Inclusion	Newborns ≤ 32 weeks GA	Infectious/non-infectious etiology of preterm birth	Other candidate variables	Early onset sepsis, late onset sepsis, necrotizing enterocolitis, length of hospital stay, neonatal death, poor neurodevelopment outcomes	Prospective or retrospective cohort (including cohorts obtained from RCTs), nested case-control, case-cohort studies, or admin database/registries All types of prediction model studies, i.e., model development studies with/without validation, model validation studies, model re-development or updating studies	Prognostication at birth Follow-up adequate for outcome of interest
	Exclusion	Non-English language literature, cross-sectional and case-control designs and models predicting composite outcomes					
2	Inclusion	As above	As above	Infectious indications for preterm birth	As above	As above, but not risk prediction models	Follow-up adequate for outcome of interest
	Exclusion	Non-English language literature, cross-sectional and case-control designs					
3	Inclusion	Newborns ≤ 32 weeks GA due to: Infectious indication (only) Non-infectious indication (only)	Short (≤72h), medium (>72h to ≤7days) or longer-term (>7days) empiric antibiotic therapy	No empiric antibiotic therapy or alternative duration of therapy	All of the above and total major or serious adverse events	Independent intervention-control comparative experimental or observational study	Follow-up adequate for outcome of interest
	Exclusion	Non-English language literature and cross-sectional studies					

* Outcomes will not be considered as eligibility criterion during screening. GA= gestational age; RCTs= randomized controlled trials; h= hours

Appendix 2 – Electronic search strategies

MEDLINE
1. Cesarean section/
2. Labor, induced/
3. Obstetric Labor, Premature/
4. (induc* or cesar*).mp.
5. or/1-4
6. exp Premature Birth/
7. exp Infant, Premature/
8. (pre-term or preterm or prematur*).mp.
9. or/6-8
10. exp Anti-Bacterial Agents/
11. exp Chemoprevention/
12. prophyla*.mp.
13. exp Sepsis/
14. (septic* or sepsis).tw.
15. or/10-14
16. 5 and 9 and 15
17. limit 16 to animals
18. limit 16 to humans
19. 16 not (17 not 18)
20. remove duplicates from 19

Embase
1. cesarean section/
2. exp labor induction/
3. ((induc* adj2 lab*) or cesar*).mp.
4. or/1-3
5. prematurity/
6. (pre-term or preterm or prematur*).mp.
7. or/5-6
8. exp antiinfective agent/
9. prophylaxis/ or exp antibiotic prophylaxis/ or exp chemoprophylaxis/ or exp infection prevention/
10. prophyla*.mp.
11. exp sepsis/
12. (septic* or sepsis).tw.
13. or/8-9,11-12
14. 4 and 7 and 13
15. limit 14 to human

16. limit 14 to animals
17. 14 not (16 not 15)
18. limit 17 to embase

CENTRAL
1. ((induc* adj2 lab*) or cesar*).mp.
2. (pre-term or preterm or prematur*).tw.
3. 1 and 2
4. (Antibiot* or anti-bacterial or antibacter*).tw.
5. (Anti-infect* or antiinfect*).tw.
6. (prophyla* or chemoprev*).tw.
7. (septic* or sepsis).tw.
8. or/4-7
9. 3 and 8

Appendix 3 Electronic data extraction sheet

General information		
Researcher		
Date of data extraction		
Record number		
Author		
Article title		
Citation		
Type of publication	journal article	conference abstract
Country of origin		
Source of funding		

Study characteristics	
Aim/objectives of the study	
Study design	
Study inclusion and exclusion criteria	
Recruitment procedures used (e.g. details of randomization, blinding)	
Unit of allocation	

Participant characteristics	
Age	
Gender	
Ethnicity	
Socio-economic status	
Disease characteristics	
Co-morbidities	

Intervention and setting	
Settings in which antibiotics where delivered (Level !, II, III care).	
Dose, route of administration, number of cycles	
Description of co-interventions	

Outcome data/results*	
Unit of assessment/analysis	
Statistical techniques used	
Whether reported	
Definition used in study	
Measurement tool or method used	
Unit of measurement (if appropriate)	
Length of follow-up, number and/or times of follow-up measurements	

*For each specified outcome

	Study group	**Control group**
Number of participants		
Number of participants included in analysis		
Number of withdrawals, exclusions, lost to follow-up		
Summary outcome data		
Dichotomous: number of events,		
Dichotomous: number of participants,		
Continuous: mean		
Continuous: standard deviation		

Type of analysis used in study (e.g. intention to treat, per protocol)	
Results of study analysis	
Dichotomous: odds ratio, risk ratio and confidence intervals, p-value	
Continuous: mean difference, confidence intervals	

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	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			1
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	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	13
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	n/a
Support:			
Sources	5a	Indicate sources of financial or other support for the review	n/a
Sponsor	5b	Provide name for the review funder and/or sponsor	n/a
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	n/a
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
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	7
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	8
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	8-9

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8-9
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)	8-10
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	8-10
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	8-10
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8
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	10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	10-12
	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)	12
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	n/a

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Should empiric antibiotic therapy be withheld when etiology of preterm birth is non-infectious? A protocol for a systematic review.

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Title: Should empiric antibiotic therapy be withheld when etiology of preterm birth is non-infectious? A protocol for a systematic review.

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Registration

"In accordance with the guidelines, our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 11 January 2016 and was last updated on 13 April, 2017 (registration number CRD 42016029707)."

Abstract

Introduction

Preterm birth (PTB) at <37 weeks of gestation is the leading cause of perinatal morbidity and mortality in developed countries. The traditional approach has been based on the assumption that PTB is primarily a result of intrauterine infection, which triggers preterm labour and puts the newborn at risk of early onset sepsis (EOS). We are currently experiencing a rise in prematurity that results from maternal and fetal diseases unrelated to infection. We have designed a systematic review to assess whether chemoprophylaxis should be withheld when the etiology of preterm birth is non-infectious.

Methods and Analysis

Our study will focus on studies evaluating EOS in preterm infants. We will conduct a comprehensive search of literature available up to 28 February 2018. An information specialist will search for eligible studies in Medline, (Ovid interface, 1948 and onwards), Embase (Ovid interface, 1980 onwards) and the Cochrane Central Register of Controlled Trials (Wiley interface, current issue) We will search databases and registries including records of on-going research, conference proceedings and thesis (Clinical trials, WHO International Clinical Trials Registry Platform). Two authors will independently extract data from eligible studies and assess risk of bias. For continuous outcomes, which follow discrete distribution, mean difference will be calculated. Dichotomous data will be presented using risk ratios, while count data will be expressed using rate ratios. Time-to-event outcomes will be reported as hazard ratios. All estimates will be presented together with 95% CI. Studies comparable with respect to methodology and reporting the same outcomes will be combined in a meta-analysis.

Ethics and dissemination

Our systematic review does not require approval from the research and ethics board. We will use the findings to prepare a future multicenter randomized-control trial in order to establish safe and adequate antibiotics policies for preterm infants, based on the etiology of PTB.

Protocol registration number Prospero CRD 42016029707

Study strengths:

- First systematic review to evaluate the use of empiric antibiotics in preterm babies born for non-infectious reasons.

Study limitations:

- Heterogeneity of study settings, design and missing data may influence results.

Acknowledgements

We would like to thank Dr Dayre McNally from the Department of Pediatrics, Children's Hospital of Eastern Ontario and Nassr Nama from the Faculty of Medicine, University of Ottawa for providing us with CrowdScreenSR (InsightScope).

INTRODUCTION

Preterm birth at less than 37 weeks of gestation is the leading cause of perinatal morbidity and mortality in developed countries. Despite on-going improvements in perinatal care, the frequency of preterm delivery remains high (11.4 % in the United States and 5-9% in Europe and other developed countries).

The traditional approach has been based on the assumption that preterm birth is primarily a result of intrauterine infection, which triggers preterm labour and puts the newborn at risk of early onset sepsis (EOS). Hence, to treat EOS, all preterm infants should receive empiric antibiotics, until negative culture results exclude infection. However, we are currently experiencing a rise in the rate of prematurity, which is mainly a result of maternal or fetal conditions unrelated to infection (assisted reproductive technologies and multiple gestation, preeclampsia, maternal obesity and diabetes, intrauterine growth restriction (IUGR)). While there are limited data establishing the risk of EOS in this group of preterm infants, there is growing evidence of adverse effects of early exposure to antibiotics on neonatal outcomes; reduced diversity of the newborn microbiome, increased risk of late onset sepsis (LOS), necrotizing enterocolitis (NEC), poor neurological outcomes and death [1-3]. Additional adverse consequences include impaired maternal-newborn bonding, delayed breastfeeding, increased risk of IV infiltrates, aminoglycoside toxicity and ototoxicity and prolonged length of hospital stay which increases health-care costs. We propose that there is a group of infants who are at low risk of EOS, and for these infants, relative risk versus benefit of chemoprophylaxis within the first 48 hours of life is unknown.

Moreover, it is critical to provide physicians with up-to-date guidelines regarding implementation of antibiotic therapy in preterm infants, stratified by risk of EOS. No clear

guidelines exist for preterm infants <32 weeks [4 5], nor are there published systemic review on the use of antibiotics in preterm infants born for reasons that are associated with a low likelihood of infection.

OBJECTIVES

The first aim of this systematic review is to investigate whether infectious versus non-infectious etiologies of preterm birth lead to different adverse neonatal outcomes. Secondly, we plan to assess whether there are differences in comparative effectiveness/harms of empiric antibiotic therapy for the two etiologies.

- Q1. Are there any risk prediction models for early onset sepsis (EOS), late onset sepsis (LOS), necrotizing enterocolitis (NEC), length of hospital stay (LOHS), neonatal death or poor neurodevelopmental outcomes developed exclusively for preterm births ≤ 32 weeks of gestation? If yes, was infectious/non-infectious etiology of preterm birth evaluated as a predictor in the model(s)? If yes, is infectious/non-infectious etiology an independent predictor for one or more of these adverse outcomes?
- Q2. When non-infectious indications of preterm birth ≤32weeks of gestation are compared with infectious indications, what is the relative risk (or odds/hazards) of EOS, neonatal death, LOS, LOHS, NEC and poor neurodevelopmental outcomes?
- Q3. For births ≤32 weeks gestation, what is the comparative effectiveness and harm of no, short (≤72h), medium (>72h to ≤7days) or longer-term (>7days) empiric antibiotic therapy for infectious and non-infectious etiologies of preterm birth? Are there important differences in comparative effectiveness between the two etiologies?

METHODS AND ANALYSES

Types of studies

We will consider primary studies with the following designs:

- Prospective or retrospective cohorts (including cohorts obtained from RCTs), nested case-control, case-cohort studies, or administrated database/registries.
- All types of prediction model studies, i.e., model development studies with/without validation, model validation studies, model re-development or updating studies.

Review articles, cross-sectional and case-control designs and models predicting composite outcomes, case reports and case series, will be excluded.

Study settings

Studies conducted worldwide. We plan to conduct separate analyses for developed and developing nations.

Types of interventions

The study will focus on infectious and non-infectious etiologies of preterm birth, and evaluate short, medium and long exposure to antibiotics. Infectious etiology of preterm birth will be defined by maternal symptoms of *chorioamnionitis* as outlined by the American College of Obstetrics and Gynaecology (ACOG) such as maternal fever ≥38°C and two of the following: fetal tachycardia (>160/'), maternal tachycardia >80/', uterine tenderness, maternal leukocytosis > $15x10^6$, foul smelling discharge[6]. Histological evidence of *chorioamnionitis* is present in >70% of women who become febrile after an epidural (a common procedure during labour). Despite the lack of other symptoms, these cases will also be considered at risk of EOS together

with preterm premature rupture of membranes (pPROM), preterm labour and maternal colonisation with group B streptococcus [4]. Non-infectious reasons will include causes such as IUGR, fetal distress, maternal preeclampsia (hemolysis, elevated liver enzymes, low platelet count) and placental abruption. Antibiotic exposure will be defined as short (≤72h), medium (>72h to ≤7days) or longer-term (>7days) empiric therapy.

Types of outcome measures

Primary outcomes

- Early onset sepsis defined as positive blood or cerebral spinal fluid within the first 48-72 hours of life[4].
- Late onset sepsis defined as positive blood or cerebral spinal fluid after 72 hours of life[7].
- Necrotizing enterocolitis according to Bell's criteria[8].

Secondary outcomes

- Length of hospital stay.
- Neonatal death.
- Poor neurodevelopmental outcomes.

Data extraction items will include funding, geographic region of study, study characteristics (e.g. sample size, duration of follow-up and funding); population characteristics and eligibility criteria; intervention characteristics (e.g. type of antibiotics, dose, frequency, duration); exposure definitions, measurement tool and cut-offs; number randomized into each group and number analyzed; number exposed and unexposed; missing data and reasons for missing data; outcome definition, time-point, measurement tool employed, cut-offs, and metric; statistical analysis and

adjustments; and items necessary to assess risk of bias. For question 1, other data extraction items reported in the CHARMS checklist for risk prediction models will also be extracted [9].

One reviewer will extract data. Another reviewer will verify outcomes data independently. Discrepancies will be cross-checked against the full-text of the record and, where applicable, data entries will be corrected.

A table presenting review eligibility criteria is presented in appendix 1.

Search methods for identification of studies.

Studies will be identified through searches of bibliographic databases and trial registries, cited and citing references, contacting experts and general Internet searching. Database search strategies will be developed by a librarian experienced in systematic review searching. The MEDLINE strategy will be developed first, with input from the research team. The search will then be adapted for the other databases. Medline, Embase and Cochrane Central Register of Controlled Trials will be searched using the Ovid platform. ClincialTrials.gov and WHO International Clinical Trials Registry Platform will be searched to identify in progress or completed but not yet published trials. Searches will be restricted to the last 30 years but no study design or language restrictions will be imposed. We will include articles available by 28 February 2018. As preliminary searches suggest that approximately 15% of the records are published in a language other than English, studies in languages other than English will be excluded during screening as described below. The search will be updated toward the end of the review, after being validated to ensure that the MEDLINE strategy retrieves a high proportion of eligible studies found through any means but indexed in MEDLINE. A draft MEDLINE search strategy is included in Appendix 2.

Data collection and analyses

Selection of studies

Records identified through searching will be imported into Reference Manager were duplicate records will be removed, Remaining records will be uploaded to CrowdscreenSR (InsightScope), a website for crowdsourcing systematic reviews, which enables cooperation between reviewers during the study selection process. The selection process will be piloted by applying the inclusion criteria to a sample of publications to ensure inter-rated reliability. After that, all publications will be assessed independently by two researchers (JSS and JR) at two levels. First, titles and abstracts will be assessed, requiring consensus of two reviewers to exclude a record. Then, full text articles. Two reviewers assess the full text to determine final eligibility.. Disagreements will be resolved by consensus or third-party adjudication.

Data extraction

An electronic data extraction form will be used to extract key study characteristics (methods, participants and outcomes) (appendix 3). Data extraction will be piloted with five randomly selected eligible studies. Data extraction will be performed by two researchers (JSS and JR). Data corrections or amendments will be logged.

Assessment of risk of bias in included studies

Risk of bias assessment is an assessment of the internal validity of studies. Two reviewers will assess risk of bias independently for each outcome of interest. Disagreements will be resolved by consensus or third-party adjudication.

For question 1, we will use the *CHARMS checklist* to assess study validity [9]. For question 2, the *Quality In Prognosis Studies* (QUIPS) tool that covers six domains, namely, study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting will be used [10]. When evidence for Question 3 originates in randomized controlled trials, the *Cochrane risk of bias tool* will be employed. Assessment of risk of bias of non-randomized studies addressing question 3 will be based on our generic assessment of selection bias (including attrition bias or missing data), confounding (including time-varying changes in treatment/confounders), information bias and bias due to use of co-interventions [11]. Risk of bias assessment will be undertaken for all biasing domains, and each will be judged as high, moderate, low or unclear risk of bias. Overall risk of bias of a study will be judged across domains as high, moderate or low. A domain rating of high risk of bias will automatically lead to a judgment of high overall risk of bias. When no domain-specific assessment of the risk of bias was rated as high, the study's overall risk of bias will not be judged as high.

Publication bias will be investigated for the body of evidence from randomized controlled trials if the following criteria are met [12]:

- ≥ 10 studies contributing data for an outcome
- studies of unequal sizes
- no substantial clinical and methodological differences between smaller and larger studies
- quantitative results accompanied by measures of dispersion

Applicability

Characterization of study applicability or generalizability will be made by two reviewers and categorised as major concerns, minor concerns or no concern with corresponding rationales documented. Determinants of applicability incorporate population characteristics, study environmental settings, intervention dose/frequency/timing, definition of outcomes and exposures and their measurement techniques, adequacy of follow-up and background standards of care.

Measures of treatment effect

Question 1 investigates whether infectious and non-infectious aetiologies of birth ≤32 weeks would remain a significant predictor of a number of adverse neonatal and longer-term health outcomes in risk prediction models including other candidate predictors. This will be answered through a descriptive synthesis of relevant literature, informed by judgments of overall study risk of bias. No quantitative data pooling of these statistical estimates will be conducted. We will report the parameters of models from studies assessed as low risk of bias and generalizable models.

For Question 2, the decision to conduct a meta-analysis will be based on an assessment of between study heterogeneity, measured by the I-squared statistic. Between-study heterogeneity (i.e. I squared > 50%) can be explained by study level clinical or methodological covariates. Statistical heterogeneity between studies will be quantified with I-squared statistics and the P value from the chi-squared test ($P \leq 0.10$) will be used to determine statistical significance. As well as statistically heterogeneity, clinical and methodological heterogeneity will be explored with methodological covariates including study design, study risk of bias and funding and clinical covariates such as the severity of preterm birth, Apgar scores, antibiotic therapy protocol,

mode of delivery, and specific laboratory testing protocols. Such heterogeneity would be investigated in subgroup analyses or meta-regression. Where meta-analysis is warranted, data will be pooled using random effects generic inverse variance or Mantel–Haenszel method because group sizes are likely to be different in contributing observational studies. Other random effects models (e.g. Peto odds or inverse variance method) may be used as recommended by previously published guidance [13]. Adjusted estimates of association will be preferentially selected over crude estimates in meta-analyses. Pooled data will be reported as odds ratio, hazards ratio, relative risk or mean difference. Sensitivity analyses by study risk of bias will be undertaken as required. Evidence originating in studies that used prophylactic/empiric maternal or neonatal antibiotic therapy will be synthesized separately from those that did not. *Post hoc* subgroup analyses may be undertaken if warranted by the data.

Approach to meta-analysis for evidence pertaining to Question 3 will be similar to the approach described for Question 2. Randomized controlled trial data will not be combined with non-randomized studies. Sparse data will not be included in the meta-analysis but rather described narratively. Studies with zero events in both arms will be excluded from the meta-analysis.

Data synthesis

For continuous outcomes, which follow discrete distribution, mean difference will be calculated. Dichotomous data will be presented using relative risk, while count data will be expressed using rate ratios. Time-to-event outcomes will be reported as hazard ratios. All estimates will be presented together with 95% confidence intervals.

Studies comparable with respect to methodology and reporting the same outcomes will be combined in a meta-analysis. Between-study heterogeneity will be examined using the χ^2 test and the I^2 statistics. Fixed-effect meta-analysis will be permitted only when p value of χ^2 test >0.1

and I^2 <40% indicating that the between-studies differences are not statistically significant and observed heterogeneity might not be important[11 14]. Random-effect meta-analysis will be carried out using either DerSimonian & Laird or inverse variance methods of weight assignment for either continuous data or all remaining outcomes[14]. Fixed-effect meta-analysis will be conducted using the algorithm proposed by Mantel and Haenszel as well as the inverse variance method for cardinal and all other types of outcomes, respectively[15]. Significance of the overall effect will be tested with two-tailed Z-test assuming $p < 0.05$ as the level of significance.

Qualitative synthesis with either narrative description or tabular representation will be presented when studies could not be quantitatively combined due to inacceptable heterogeneity of missing data precluding meta-analysis.

All statistical analyses will be conducted using dedicated software. R statistical software with 'metafor' package will preferentially be used for all calculations and generation of corresponding plots, but the use of other statistical programs cannot be excluded [16].

Assessment of Certainty of Evidence

For each outcome, when prognostic or effect estimates are not very wide and can be conclusively interpreted, we will grade the certainty of evidence as per the published GRADE approach [17] [18]. For example, if for Question 3, short duration of empiric antibiotic therapy versus long-term therapy yields wide confidence interval for the outcome necrotizing enterocolitis, such that one cannot exclude the possibility that short duration may be harmful, equivalent or superior to long-term, then results are inconclusive and, as such, grading of the certainty of evidence will not be attempted for this outcome.

Dealing with missing data

The data will be analysed on an intention-to-treat principle. In case of missing data, which preclude inclusion of the outcome into quantitative accumulation, we will attempt to contact the corresponding author in order to obtain required information. The extent and implications of missing data will be reported.

Assessment of heterogeneity and sensitivity analysis

Between-study heterogeneity will be examined using the χ^2 test and the I^2 statistics, as described above. When between-trials variability reaches statistical significance (p value for heterogeneity < 0.1), attempts to explain heterogeneity will be undertaken using sensitivity analyses with either subgroup meta-analysis or meta-regression. Factors or continuous measures that may potentially influence the results will be analysed as covariates. For subgroup meta-analysis, identified studies will be stratified according to the following explanatory variables: study quality, race (Black vs non-Black), ethnicity (Hispanic versus non-Hispanic) or region (developing vs developed). Between-subgroup effects will be assessed using the test for interaction as proposed by Borenstein et al. with $p < 0.05$ indicating statistically significant impact of the covariate on observed effect size[19]. The contribution of continuous covariates (i.e.: mean maternal age, mean gestational age at delivery, percent of Black infants, mean birth weight, mean Apgar score) to between-study heterogeneity will be explored with random-effect meta-regression provided that at least ten studies will be available for each explanatory variable[11].

Assessment of publication biases

For meta-analyses with at least 10 studies the risk of publication bias will be examined by visual inspection of funnel plots and statistically assessed with the use of both Egger's and Begg's tests with $p < 0.05$ considered statistically significant.

Patient and Public Involvement

Patients and public were not involved in the study.

DISCUSSION

By conducting this systematic review, we plan to establish whether preterm infants born at ≤ 32 weeks of gestation due to non-infectious reasons should receive prophylactic antibiotic therapy. We will use the findings of this systematic review to prepare a future multicenter randomized-control study in order to establish safe and adequate antibiotics policies for extreme, severe, or moderately preterm infants. Furthermore, we will provide up-to-date evidence of the harms and benefits of chemoprophylaxis in the most premature group of newborns. Additionally, we plan to discuss how our findings may be applied in future guidelines and hospital policies.

ETHICS AND DISSEMINATION

We did not submit for ethical approval, as the study does not include individuals. All significant modifications in the protocol will be reported to PROSPERO. The full protocol will be widely available due to open access. We plan to submit our findings to international peer-reviewed journals (paediatric, infectious, epidemiology). Abstracts will be submitted to local and international conferences.

The Systematic Review will be used to prepare a multicenter prospective trial with the aim of evaluating the safety of using a more targeted antibiotic approach in low risk preterm infants,

including a delay in antibiotic initiation until laboratory tests results and blood culture results are available.

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Authors' contributions

Dr's Joanna Seliga-Siwecka, Mohammed Ansari, Justyna Romanska conceptualized and designed the study; drafted the initial manuscript, and approved the final manuscript as submitted.

Dr Judy Aschner critically reviewed the manuscript, and approved the final manuscript as submitted.

Dr Margaret Sampson developed the electronic search strategies, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Funding and competing interests statement

- This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors'.
- All authors have no competing interests to declare.

Appendix 1- Table 1. Review eligibility criteria

Question	Criteria	Population	Intervention/ Exposure	Comparator	Outcome*	Study design	Timing
1	Inclusion	Newborns ≤ 32 weeks GA	Infectious/non-infectious etiology of preterm birth	Other candidate variables	Early onset sepsis, late onset sepsis, necrotizing enterocolitis, length of hospital stay, neonatal death, poor neurodevelopment outcomes	Prospective or retrospective cohort (including cohorts obtained from RCTs), nested case-control, case-cohort studies, or admin database/registries All types of prediction model studies, i.e., model development studies with/without validation, model validation studies, model re-development or updating studies	Prognostication at birth Follow-up adequate for outcome of interest
	Exclusion	Non-English language literature, cross-sectional and case-control designs and models predicting composite outcomes					
2	Inclusion	As above	As above	Infectious indications for preterm birth	As above	As above, but not risk prediction models	Follow-up adequate for outcome of interest
	Exclusion	Non-English language literature, cross-sectional and case-control designs					
3	Inclusion	Newborns ≤ 32 weeks GA due to: Infectious indication (only) Non-infectious indication (only)	Short (≤72h), medium (>72h to ≤7days) or longer-term (>7days) empiric antibiotic therapy	No empiric antibiotic therapy or alternative duration of therapy	All of the above and total major or serious adverse events	Independent intervention-control comparative experimental or observational study	Follow-up adequate for outcome of interest
	Exclusion	Non-English language literature and cross-sectional studies					

* Outcomes will not be considered as eligibility criterion during screening. GA= gestational age; RCTs= randomized controlled trials; h= hours

Appendix 2 – Electronic search strategies

MEDLINE
1. Cesarean section/
2. Labor, induced/
3. Obstetric Labor, Premature/
4. (induc* or cesar*).mp.
5. or/1-4
6. exp Premature Birth/
7. exp Infant, Premature/
8. (pre-term or preterm or prematur*).mp.
9. or/6-8
10. exp Anti-Bacterial Agents/
11. exp Chemoprevention/
12. prophyla*.mp.
13. exp Sepsis/
14. (septic* or sepsis).tw.
15. or/10-14
16. 5 and 9 and 15
17. limit 16 to animals
18. limit 16 to humans
19. 16 not (17 not 18)
20. remove duplicates from 19

Embase
1. cesarean section/
2. exp labor induction/
3. ((induc* adj2 lab*) or cesar*).mp.
4. or/1-3
5. prematurity/
6. (pre-term or preterm or prematur*).mp.
7. or/5-6
8. exp antiinfective agent/
9. prophylaxis/ or exp antibiotic prophylaxis/ or exp chemoprophylaxis/ or exp infection prevention/
10. prophyla*.mp.
11. exp sepsis/
12. (septic* or sepsis).tw.
13. or/8-9,11-12
14. 4 and 7 and 13
15. limit 14 to human

16. limit 14 to animals
17. 14 not (16 not 15)
18. limit 17 to embase

CENTRAL
1. ((induc* adj2 lab*) or cesar*).mp.
2. (pre-term or preterm or prematur*).tw.
3. 1 and 2
4. (Antibiot* or anti-bacterial or antibacter*).tw.
5. (Anti-infect* or antiinfect*).tw.
6. (prophyla* or chemoprev*).tw.
7. (septic* or sepsis).tw.
8. or/4-7
9. 3 and 8

Appendix 3 Electronic data extraction sheet

General information		
Researcher		
Date of data extraction		
Record number		
Author		
Article title		
Citation		
Type of publication	journal article	conference abstract
Country of origin		
Source of funding		

Study characteristics	
Aim/objectives of the study	
Study design	
Study inclusion and exclusion criteria	
Recruitment procedures used (e.g. details of randomization, blinding)	
Unit of allocation	

Participant characteristics	
Age	
Gender	
Ethnicity	
Socio-economic status	
Disease characteristics	
Co-morbidities	

Intervention and setting	
Settings in which antibiotics where delivered (Level !, II, III care).	
Dose, route of administration, number of cycles	
Description of co-interventions	

Outcome data/results*	
Unit of assessment/analysis	
Statistical techniques used	
Whether reported	
Definition used in study	
Measurement tool or method used	
Unit of measurement (if appropriate)	
Length of follow-up, number and/or times of follow-up measurements	

*For each specified outcome

	Study group	**Control group**
Number of participants		
Number of participants included in analysis		
Number of withdrawals, exclusions, lost to follow-up		
Summary outcome data		
Dichotomous: number of events,		
Dichotomous: number of participants,		
Continuous: mean		
Continuous: standard deviation		

Type of analysis used in study (e.g. intention to treat, per protocol)	
Results of study analysis	
Dichotomous: odds ratio, risk ratio and confidence intervals, p-value	
Continuous: mean difference, confidence intervals	

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	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			1
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	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	13
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	n/a
Support:			
Sources	5a	Indicate sources of financial or other support for the review	n/a
Sponsor	5b	Provide name for the review funder and/or sponsor	n/a
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	n/a
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
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	7
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	8
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	8-9

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8-9
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)	8-10
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	8-10
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	8-10
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8
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	10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	10-12
	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)	12
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	n/a

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.