

# Neonatal Septicaemia in Sub-Saharan Africa: A Protocol for Systematic Review and Meta-analysis.

**Micheal Abel Alao**

University College Hospital Ibadan

**Oluwakemi O Tongo**

University College Hospital Ibadan

**Idowu Adejumo Ayede**

UCH: University College Hospital Ibadan

**Michael Udochukwu Diala**

Jos University Teaching Hospital

**Olayinka Rasheed Ibrahim**

Federal Medical Centre Katsina

**Daniel A Gbadero**

Bowen University College of Health Sciences

**Emmanuel Okechukwu Nna** (✉ [e.nna@themping.org](mailto:e.nna@themping.org))

The Molecular Pathology Institute, Enugu <https://orcid.org/0000-0001-6791-2336>

**Tina M Slusher**

University of Minnesota Medical Center Fairview: University of Minnesota Health

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## Protocol

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# Abstract

**Background:** The morbidity and mortality from neonatal septicaemia (NNS) in low-middle income country remain high at the background of strained health care delivery system. The burden, pooled risks and outcomes of NNS are largely unknown. We aimed to produce a protocol for synthesizing evidence from available data for neonatal septicaemia in sub-Saharan Africa.

**Methods:** We developed a search strategy using MeSH, text words and entry terms. Nine databases will be searched: PubMed, Embase, CINAHL, AJOL, Google Scholar, Web of Science, Cochrane Library, Research gate and Scopus. Only Observational studies retrievable in the English Language will be included. The primary measurable outcome is the proportion of neonatal with septicaemia while secondary outcomes include proportion of bacterial isolates and their antibiogram, risk factors for NNS, in hospital mortality, length of hospital stay, frequency of necrotizing enterocolitis and other sequel . All identified studies will be screened based on the inclusion criteria. Data will be deduplicated in Endnote version 9, before exporting to Rayyan QCRI for screening. Extractable data will include first author's name and year of publication, the country and regions in sub-Saharan Africa, total neonatal admissions, number with sepsis, the sample size, bacterial isolates, antibiogram, in-hospital mortality, length of hospital stay and frequency of necrotizing enterocolitis.

All studies will be assessed for methodological, clinical and statistical heterogeneity. The NIH Quality assessment tool for observational studies and the Cochrane tool of risk of bias will be used to assess for the strength of evidence. Publication bias will be assessed using the funnel plot.

**Discussion:** Results will be presented as the prevalence, standard error and confidence interval of newborns with neonatal septicaemia in sub-Saharan Africa. Subgroup analysis using categorical data such as risk factors, bacterial isolates, antibiogram and outcomes of neonatal septicaemia will also be reported. A cumulative meta-analysis will be done to assess the time trend of the risk factors, pathogens and antibiogram. The CMA version 3 will be used for statistical analysis. Results will be presented in forest plots.

**Systematic Review Registration:** This protocol is registered in PROSPERO, registration number CRD42020219604.

## Background

The presence of bacteria in the bloodstream of a newborn with associated clinical evidence of systemic acute inflammatory response and multiorgan dysfunction syndrome describes the state of a newborn with septicaemia.<sup>1-4</sup> Globally, neonatal septicaemia (NNS) remains one of the leading causes of morbidity and mortality in the first four weeks of life accounting for 336,300 total deaths per annum.<sup>2, 5, 6</sup> The greatest burden disproportionately impact the low middle-income countries (LMICs) in contrast with high income countries.<sup>7, 8</sup>

Neonates compared with older children and adults are at increased risk for septicaemia.<sup>3, 6, 9</sup> They are immunologic, lacking quantitatively and qualitatively in the cellular response to infection.<sup>3, 6, 9</sup> The neonates have defective humoral defence mechanism.<sup>3</sup> The responses in the classic and alternate complement system pathways are suboptimal.<sup>3, 9</sup> The newborns have impaired chemotaxis, decreased neutrophil deformability, reduced complement receptor expression besides the poor oxidative metabolic response.<sup>3, 6, 9</sup> The inherent limitations in the immunological systems, suboptimal infection control and prevention, limited infection screening of high-risk mothers including the proportion of mothers with unknown HIV status, home deliveries practices, pervading cultural practices and myth that discourages safe deliveries in sub Saharan Africa; all these put the newborns at a higher risk for infection compared with neonates in the high-income countries.<sup>1</sup> There are several attempts to upscale the newborn survival strategies in sub Saharan African through essential newborn care, survival and thrive strategies.<sup>10-12</sup> But adequate measures and protocols for handling neonatal sepsis are still lacking.

However, there is increasing literature on NNS in the sub Saharan, even though the pooled burden in this setting is still lacking.<sup>12</sup> The variable definition of terms, small sample sizes with conflicting reports also makes the published data less generalizable, hence, its limited clinical application. Besides, recent literature has also shown a mismatch between empiric antibiotic choices and sensitivity pattern of isolates for neonatal sepsis in sub-Saharan Africa. This has implications for resource allocation, mobilization and programme implementation. The gap requires urgent attention if the sustainable development goal 3.2 of reducing neonatal mortality rate from 27 per 1,000 in 2019 to 12 per 1,000 will be achievable in all the member countries.<sup>13, 14</sup> We, therefore, aimed at developing a protocol to enable transparent, accurate and reproducible systematic review and meta-analysis, which will provide robust evidence for an informed decision in the care and future policy regarding newborn care in sub Saharan Africa.

## **Methods And Design**

### **Objectives:**

The main objective of this study is to determine the pooled prevalence of neonatal septicaemia in the sub Saharan Africa.

### **Review Questions:**

1. What is the pooled proportion of neonates with septicaemia in sub Saharan Africa?
2. What are the pooled frequency of risk factors of neonatal septicaemia in sub Saharan Africa?
3. What are the pooled frequency and types of pathogens and antibiogram of neonatal septicaemia in sub Saharan Africa?

4. What are the pooled outcomes of in-hospital mortality, length of hospital admission and frequency of necrotizing enterocolitis among neonatal with septicaemia in sub Saharan Africa?
5. What are the cumulative trends of neonatal septicaemia over the years?

## Study Design

This is a protocol for systematic review and meta-analysis of observational studies conducted in the Sub Saharan Africa. This protocol is design to enable a reliable, transparent and accurate systematic review and meta-analysis. Using this protocol will enable determination of pooled prevalence of neonatal sepsis, pooled prevalence of risk factors, sub-group analysis of pathogens, antibiogram and the pooled prevalence of outcomes of neonatal septicaemia and cumulative trends over the years in the sub Saharan Africa. There is no timeframe or restriction in selecting eligible studies using this protocol.

## INCLUSION CRITERIA:

- A. Observational studies: Cohort studies, case controls, cross-sectional studies, historic cohort studies.
- B. Studies must report the primary outcome: proportion of neonatal septicaemia.
- C. Studies must be retrievable in the English Language.
- D. Studies that report any of the following secondary outcomes, e.g risk factors, outcomes, bacterial isolates and antibiogram, in addition to primary outcome, will be included.

## Exclusion criteria:

- a. Reviews, editorials, commentaries, methodological articles, letters to editors, case reports
- b. Studies reporting in- vitro and animal studies.
- c. Duplicates/ replicates of studies.
- d. Studies not retrievable in the English Language.
- e. Studies on Surgical patients.
- f. Neonates with multiple congenital malformations.

**PICOs:** The details for participants, intervention, comparison and outcomes (PICOs) are shown in Table 1.

This review will be reported in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2015 Statement).<sup>15</sup> The Protocol has the PRISMA-P Checklist attached as a supplementary material.

## Information sources

The search will employ sensitive topic-based strategies designed for each database. The search will be carried out in the following databases: PUBMED, EMBASE, CINAHL, RESEARCHGATE, AJOL, GOOGLE

SCHOLAR, WEB OF SCIENCE, SCOPUS and COCHRANE LIBRARY. Only observational studies will be included. There is no time frame for selection of studies.

## **Search strategy**

The search strategy includes MESH terms, text words and entry terms. Table 2 shows the search strategies as used in the Pubmed. The same search strategy will be used in other databases with slight modifications.

## **Data Extraction and Management**

### **a. Data Extraction**

Four main tools will be used for data extraction and management: a) EndNote version 9, b) Rayyan QCRI systematic review screening tool and c) Microsoft Excel and d) CMA Version 3 Software

Five levels of data screening will be used for searched studies:

- i. Level 1 would involve screening of identified studies for the study design. Only observational studies, retrievable in the English Language would be selected.
- ii. Level 2 will involve screening of selected studies in the titles and abstracts using entry terms, keywords and meSH terms.
- iii. At Level 3, selected studies will be further screened for content by reading the full article using the same search strategy.
- iv. Level 4 will involve snowballing of literature on references from included studies.
- v. Level 5 will involve grey literature that report primary outcome and or secondary outcomes.

Seven reviewers are involved in this study. A pair of reviewers will independently screen the selected article for eligibility using Rayyan QCRI systematic review screening tool.<sup>16</sup> The two reviewers will be blinded from each other using the screening tool. Conflict between the paired reviewer shall be resolved by a third reviewer who would will server as a tie -breaker. The data of all screened studies will be exported into MICROSOFT EXCEL. Snowballing search of relevant studies through the review of the references of selected studies and grey literature will be performed manually.

### **b. Selection Process:**

Agreement between two independent and blinded reviewers who screened titles, abstracts, full texts of eligible observational studies, snowballed articles and grey literature will form the basis for selecting studies for inclusion for systematic review and meta-analysis. Where there are conflicts in decision, this will be resolved by a third reviewer. Authors of eligible studies with any missing data will be contacted via email and telephone.

### **c. Data Collection Process:**

Deduplication of studies will be done using End note version 9.<sup>17</sup> Eligible studies will be screened using Rayyan QCRI and exported into Microsoft Excel. All templates for housing extracted data items will be created in Excel.

The following data items will be extracted from eligible studies and entered into MICROSOFT EXCEL:

1. The last name of the first author and the year of publication
2. The country and region in sub-Saharan Africa
  - a. Number of neonates with sepsis
5. Number of neonates with confirmed sepsis (bacterial isolate identified by bacterial culture)
6. Number of neonates with probable sepsis (laboratory evidence supports sepsis but no isolate)
7. Number of neonates with presumed or possible sepsis (risk factors for sepsis but no laboratory evidence)
5. Sample size
8. Risk factors for septicaemia
9. Antibigram
10. Secondary outcomes
  - a) In-hospital mortality
  - b) Length of hospital admission
  - c) Frequency of necrotizing enterocolitis

Data from MICROSOFT EXCEL file will be exported in CMA software for meta- analysis

## **Data items/Measurable outcomes**

The measurable outcomes are

1. Proportion of neonates with septicaemia in sub Saharan Africa.
2. The proportion of risk factors in reported neonatal septicaemia in sub Saharan Africa.
3. The frequency of pathogens and patterns of antibiogram in neonatal septicaemia in sub Saharan Africa.
4. The frequency of outcomes such as mortality, length of hospital admission and necrotizing enterocolitis in neonatal septicaemia in sub Saharan Africa.

# Effect Sizes

The primary effect size is prevalence.

Different primary indexes in individual studies of same design and report outcome will be converted to prevalence in the CMA Software.

Categorical outcomes will be used for subgroup analysis.

Numerical outcomes will be used for meta-regression.

## Data synthesis

- a. Studies that passed the methodological quality assessment using the NIH quality assessment tool will be extracted. The results will be presented in tabular format.
- b. in addition to a narrative synthesis, the following will be included in the meta-analysis:
  1. The proportion of babies with neonatal septicaemia.
  2. Categorical variables for subgroup analysis
  3. Numerical variables for meta-regression

## c. Quantitative analysis

Pooled prevalence of neonatal septicaemia, standard error and variance will be calculated with 95% CI. This is the primary measurable outcome.

Sub-group analysis will be performed using categorical data on i) regions in Sub Saharan Africa, ii) types of pathogens, iii) the antibiogram, iv) risk factors and v) the secondary outcomes.

Subgroup analysis will be performed using categorical data such as geographical location, types of bacterial isolates, antibiogram, components of risk factors and outcomes as moderators. Results of subgroup analysis will be presented in forest plots.

Meta-regression will be performed on prevalence of neonatal septicaemia as outcome variable using frequency of risk factors, length of hospital admission, gestational age at birth and mortality as explanatory variables. This will establish a regression model for predicting prevalence of neonatal septicaemia.

A cumulative meta-analysis will be performed to check for trend in prevalence of neonatal septicaemia of the years.

Eligible studies will be quantitatively analysed using the Comprehensive Meta-Analysis (CMA) software version 3 (Biostat, USA).<sup>18</sup>.

## Criteria for Quantitative data Synthesis

The pooled prevalence, standard error, variance and 95% confidence interval, and. Heterogeneity will be assessed using the Q statistics and its p-value,  $\tau^2$  and the Higgins  $I^2$ .  $I^2$  values of less than 40% will be considered low heterogeneity while values > 40 but < 75% will be considered moderate and values > 75% are high. A random-effect model will be used for computation in this study. A sensitivity analysis will be performed to check for outlying studies and their effects on pooled prevalence of neonatal septicaemia. Publication bias in the selection of studies will be visually assessed on the funnel plot (trim and fill method) and tested for asymmetry. Other statistical tests such as Egger's regression intercept, Begg and Mazumdar's rank correlation and Orwin's fail-safe N will be used where appropriate.

## Risk of bias

The risk of bias in the included studies will be accessed for the individual article using the National Institute of Health (NIH) Quality assessment tool for observational cohort and cross-sectional studies. The NIH Quality assessment tool has 10 questions. This will be cross-checked with the Cochrane tool of risk of bias assessment for the strength of the body of evidence; i.e. using specific relevant items from this tool to assess the strength of the body of evidence.. Studies with extreme bias will be subjected to sensitivity testing using the include/exclude function in the CMA Software.

## Assessment of Meta-bias

Meta-bias will be assessed as follows:

- i. Method of testing/reporting of neonatal septicaemia at the outcome level.
- ii. Reporting of study: Studies that were reported in different units but similar in outcome and design will be converted based on individual case evaluation. This will be evaluated for individual studies by assessing the unit of reporting of studies, for example, whether prevalence with confidence intervals or incidence or proportion will be reported.
- iii. Heterogeneity will be assessed at the study level using the Q statistics and its p-value,  $\tau^2$  and the Higgins  $I^2$
- iv. Publication bias will be assessed at the study level using the funnel plot (trim and fill method) and test for asymmetry
- v. Sensitivity analysis will assessed at the study level using include and exclude function in the CMA Software

## Results

The study selection process will be summarized in a flow diagram according to the PRISMA 2015 Statement and PRISMA-P Checklist. A table of the search strategy in various databases showing text

words, MeSH and entry terms will be included. List of included studies will be summarized in a table. Quantitative data such as pooled prevalence, standard error and 95% CI, p values, relative weights assigned to studies and heterogeneity tests will be included in the forest plots. A table of quality scores and risk of bias of each eligible study will be included. Forest plots to show sub-group analysis will be included. Meta-regression and sensitivity analysis will be shown in Figures and Tables.

## **Discussion**

The study will examine the type of pathogen that predominantly causes neonatal septicaemia and the most widely used antibiotics (from antibiogram report). It will report associations, if any, between risk factors and secondary outcomes to prevalence of neonatal septicaemia. It will discuss the implications of the pooled prevalence of septicaemia in the sub Saharan Africa. The final study will be published in a peer-review journal and the findings will be disseminated to relevant health authorities and clinical groups that manage pregnant women and newborns.

## **Abbreviations**

GRADE: Grades of Recommendation, Assessment, Development and Evaluation;

PRISMA-P: Preferred Reporting Items for Systematic reviews and Meta-analyses Protocols

NIH: National Institute of Health

CMA: Comprehensive Meta-Analysis Software

NNS: Neonatal Sepsis

PROSPERO: International Prospective Register for Systematic Reviews

## **Declarations**

### **Authors' contributions:**

AMA conceived the project. AMA, EN and UMD designed the study, AMA, TOO, AIA, OO, TS and UMD and ORI did PubMed searches, screened and reviewed the articles; EN and TS performed CINAHL, Cochrane Database, Web of Science database search while AMA, TOO, AIA, OO, UMD and ORI screened and reviewed the articles from these databases. Article handpicked and those obtained through contact with experts in the field were equally screened by AMA, TOO, AIA, OO, UMD and ORI.

### **Ethical Approval/ Dissemination:**

The study will use published data, thus, no ethical approval is required.

### **Consent for Publication:**

All reviewers/authors consented to publication

### **Availability of data and materials:**

All research materials and datasets including search strategy will be made public without any hindrance.

### **Conflicting Interests:**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### **Acknowledgement:**

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### **Funding:**

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2. Sponsor: All the authors contributed to sponsor the project
3. **Guarantor of the review:** Dr Emmanuel Nna

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## Tables

Table 1

The details for participants, intervention, comparison and outcomes (PICOs)

<b>Population</b>	<b>Neonates with septicaemia</b>
Intervention	Antibiotics
Comparison	Neonates without septicaemia
Outcome	Primary outcome: prevalence of neonatal septicaemia Secondary outcomes: Risk factors, antibiogram sensitivity, mortality, mortality and recovery

Table 2

## The search strategy

Search No	Search strategy	No of articles
S17= S16 AND S12	((("Prevalence"[Mesh]) OR ("Prevalence"[TIAB])) OR ("Consequences"[TIAB])) OR ("Outcome"[TIAB])) AND (((("Infant, Newborn"[Mesh]) AND ("septicaemia [TIAB]")) OR ("neonatal septicaemia [TIAB]")) AND (((Sub-Saharan Africa OR Subsaharan Africa) OR ("Subsaharan Africa" [TIAB])) OR ("Sub-Saharan Africa" [TIAB])) OR (Angola[TIAB] OR Benin[TIAB] OR Botswana[TIAB] OR Burkina Faso [TIAB] OR Burundi[TIAB] OR Cameroon[TIAB] OR Central African Republic[TIAB] OR Chad[TIAB] OR Congo[TIAB] OR Cote d'Ivoire[TIAB] OR Eritrea[TIAB] OR Ethiopia[TIAB] OR [TIAB] OR Gabon[TIAB] OR Gambia[TIAB] OR Ghana[TIAB] OR Guinea[TIAB] OR [TIAB] OR Guinea-Bissau[TIAB] OR Kenya[TIAB] OR Lesotho[TIAB] OR Liberia[TIAB] OR Madagascar[TIAB] OR Malawi[TIAB] OR Mali[TIAB] OR Mauritania[TIAB] OR Mauritius[TIAB] OR Mozambique[TIAB] OR Namibia[TIAB] OR Niger[TIAB] OR Nigeria[TIAB] OR Rwanda[TIAB] OR Senegal[TIAB] OR Sierra Leone[TIAB] OR Somalia[TIAB] OR South Africa[TIAB] OR United Republic of Tanzania[TIAB] OR Togo[TIAB] OR Uganda[TIAB] OR Zaire[TIAB] OR Zambia, Zimbabwe[TIAB]))))	36
S16 = S14 AND S15	((("Infant, Newborn"[Mesh]) AND ("septicaemia [TIAB]")) OR ("neonatal septicaemia [TIAB]")) AND (((Sub-Saharan Africa OR Subsaharan Africa) OR ("Subsaharan Africa" [TIAB])) OR ("Sub-Saharan Africa" [TIAB])) OR (Angola[TIAB] OR Benin[TIAB] OR Botswana[TIAB] OR Burkina Faso [TIAB] OR Burundi[TIAB] OR Cameroon[TIAB] OR Central African Republic[TIAB] OR Chad[TIAB] OR Congo[TIAB] OR Cote d'Ivoire[TIAB] OR Eritrea[TIAB] OR Ethiopia[TIAB] OR [TIAB] OR Gabon[TIAB] OR Gambia[TIAB] OR Ghana[TIAB] OR Guinea[TIAB] OR [TIAB] OR Guinea-Bissau[TIAB] OR Kenya[TIAB] OR Lesotho[TIAB] OR Liberia[TIAB] OR Madagascar[TIAB] OR Malawi[TIAB] OR Mali[TIAB] OR Mauritania[TIAB] OR Mauritius[TIAB] OR Mozambique[TIAB] OR Namibia[TIAB] OR Niger[TIAB] OR Nigeria[TIAB] OR Rwanda[TIAB] OR Senegal[TIAB] OR Sierra Leone[TIAB] OR Somalia[TIAB] OR South Africa[TIAB] OR United Republic of Tanzania[TIAB] OR Togo[TIAB] OR Uganda[TIAB] OR Zaire[TIAB] OR Zambia, Zimbabwe[TIAB]))	107
S15 = S8 OR S9 OR S10 OR S11	((Sub-Saharan Africa OR Subsaharan Africa) OR ("Subsaharan Africa" [TIAB])) OR ("Sub-Saharan Africa" [TIAB])) OR (Angola[TIAB] OR Benin[TIAB] OR Botswana[TIAB] OR Burkina Faso [TIAB] OR Burundi[TIAB] OR Cameroon[TIAB] OR Central African Republic[TIAB] OR Chad[TIAB] OR Congo[TIAB] OR Cote d'Ivoire[TIAB] OR Eritrea[TIAB] OR Ethiopia[TIAB] OR [TIAB] OR Gabon[TIAB] OR Gambia[TIAB] OR Ghana[TIAB] OR Guinea[TIAB] OR [TIAB] OR Guinea-Bissau[TIAB] OR Kenya[TIAB] OR Lesotho[TIAB] OR Liberia[TIAB] OR Madagascar[TIAB] OR Malawi[TIAB] OR Mali[TIAB] OR Mauritania[TIAB] OR Mauritius[TIAB] OR Mozambique[TIAB] OR Namibia[TIAB] OR Niger[TIAB] OR Nigeria[TIAB] OR Rwanda[TIAB] OR Senegal[TIAB] OR Sierra Leone[TIAB] OR Somalia[TIAB] OR South Africa[TIAB] OR United Republic of Tanzania[TIAB] OR Togo[TIAB] OR Uganda[TIAB] OR Zaire[TIAB] OR Zambia, Zimbabwe[TIAB]))	318,885
S14 = S13 OR S7	((("Infant, Newborn"[Mesh]) AND ("septicaemia [TIAB]")) OR ("neonatal septicaemia [TIAB]"))	884

Search No	Search strategy	No of articles
S13= S5 AND S6	("Infant, Newborn"[Mesh]) AND ("septicaemia [TIAB]")	853
S12 = S1 OR S2 OR S3 OR S4	((("Prevalence"[Mesh]) OR ("Prevalence"[TIAB])) OR ("Consequences"[TIAB])) OR ("Outcome"[TIAB])	1,942,069
S11	Angola[TIAB] OR Benin[TIAB] OR Botswana[TIAB] OR Burkina Faso [TIAB] OR Burundi[TIAB] OR Cameroon[TIAB] OR Central African Republic[TIAB] OR Chad[TIAB] OR Congo[TIAB] OR Cote d'Ivoire[TIAB] OR Eritrea[TIAB] OR Ethiopia[TIAB] OR[TIAB] OR Gabon[TIAB] OR Gambia[TIAB] OR Ghana[TIAB] OR Guinea[TIAB] OR[TIAB] OR Guinea-Bissau[TIAB] OR Kenya[TIAB] OR Lesotho[TIAB] OR Liberia[TIAB] OR Madagascar[TIAB] OR Malawi[TIAB] OR Mali[TIAB] OR Mauritania[TIAB] OR Mauritius[TIAB] OR Mozambique[TIAB] OR Namibia[TIAB] OR Niger[TIAB] OR Nigeria[TIAB] OR Rwanda[TIAB] OR Senegal[TIAB] OR Sierra Leone[TIAB] OR Somalia[TIAB] OR South Africa[TIAB] OR United Republic of Tanzania[TIAB] OR Togo[TIAB] OR Uganda[TIAB] OR Zaire[TIAB] OR Zambia, Zimbabwe[TIAB]	200,861
S10	Sub-Saharan Africa OR Subsaharan Africa	222,553
S9	"Sub-Saharan Africa" [TIAB]	22,735
S8	"Subsaharan AfricA" [TIAB]	153
S7	"neonatal septicaemia [TIAB]"	190
S6	"septicaemia [TIAB]"	6,417
S5	"Infant, Newborn"[Mesh]	612,441
S4	"Consequences"[TIAB]	270,251
S3	"Outcome"[TIAB]	1,027,646
S2	"Prevalence"[TIAB]	639,414
S1	"Prevalence"[Mesh]	296,723

## Supplementary Files

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