Supplementary File 1: PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

| Section/Topic | Item # | Checklist Item                                                                                                                                                                                                 | Reported on Page # |
|---------------|--------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| TITLE         | Title 1 | Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*                                                                                       | 1                 |
| ABSTRACT      | Structured summary 2 | Provide a structured summary including, as applicable:  

  **Background**: main objectives  

  **Methods**: data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.*  

  **Results**: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed.* Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.  

  **Discussion/Conclusions**: limitations; conclusions and implications of findings.  

  **Other**: primary source of funding; systematic review registration number with registry name. | 2-3               |
| INTRODUCTION  | Rationale 3 | Describe the rationale for the review in the context of what is already known, *including mention of why a network meta-analysis has been conducted.* | 4                 |
|               | Objectives 4 | Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 4                 |
| METHODS       |              |                                                                                                                                                                                                                   |                    |
| Protocol and registration | 5 | Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number. |
|--------------------------|---|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Eligibility criteria     | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification). |
| Information sources      | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. |
| Search                   | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. |
| Study selection          | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). |
| Data collection process  | 10| Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. |
| Data items               | 11| List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. |
| Geometry of the network  | S1| Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers. |
| Risk of bias within individual studies | 12| Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. |
| Summary measures         | 13| State the principal summary measures (e.g., risk ratio, difference in means). Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses. |
| Planned methods of analysis | 14| Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to:  
  - Handling of multi-arm trials; |
### Assessment of Inconsistency
- Selection of variance structure;
- Selection of prior distributions in Bayesian analyses; and
- Assessment of model fit.

**Assessment of Inconsistency** | S2 | Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.
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**Risk of bias across studies** | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).

**Additional analyses** | 16 | Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following:
- Sensitivity or subgroup analyses;
- Meta-regression analyses;
- *Alternative formulations of the treatment network; and*
- *Use of alternative prior distributions for Bayesian analyses (if applicable).*

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### RESULTS†

#### Study selection
- Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.

**Study selection** | 17 | 8, Figure 1

#### Presentation of network structure
- Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.

**Presentation of network structure** | S3 | Supp. File 3

#### Summary of network geometry
- Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.

**Summary of network geometry** | S4 | 8, Supp. File 3,
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#### Study characteristics
- For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.

**Study characteristics** | 18 | 8, Table 1,
---|---|---|---
| Section                                      | Item | Description                                                                                                                                                                                                 | Supp. References |
|----------------------------------------------|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| Risk of bias within studies                  | 19   | Present data on risk of bias of each study and, if available, any outcome level assessment.                                                                                                                      | Supp. Table 2    |
| Results of individual studies                | 20   | For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. Modified approaches may be needed to deal with information from larger networks. | Supp. File 5 to   |
|                                              |      |                                                                                                                                                                                                            | Supp. File 7     |
| Synthesis of results                          | 21   | Present results of each meta-analysis done, including confidence/credible intervals. In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons. If additional summary measures were explored (such as treatment rankings), these should also be presented. | 8,9              |
| Exploration for inconsistency                | S5   | Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, $P$ values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network. | Supp. Table 5    |
| Risk of bias across studies                  | 22   | Present results of any assessment of risk of bias across studies for the evidence base being studied.                                                                                                | 10,              |
|                                              |      |                                                                                                                                                                                                            | Table 2 to Table 5|
| Results of additional analyses                | 23   | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth). | NA              |
### DISCUSSION

| Summary of evidence | 24 | Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers). |
|---------------------|----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Limitations         | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).* |
| Conclusions         | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.                                                                 |

### FUNDING

| Funding            | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network. |

**PICOS** = population, intervention, comparators, outcomes, study design.

* Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.
† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

Reference: Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, Ioannidis JP, Straus S, Thorlund K, Jansen JP, Mulrow C, Catalá-López F, Gotzsche PC, Dickersin K, Boutron I, Altman DG, Moher D. The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions: Checklist and Explanations. *Ann Intern Med.* 2015;162(11):777-784.
We attempted to identify all relevant studies regardless of language or publication status (published, unpublished, in press, ongoing) by searching the Cochrane Pregnancy and Childbirth’s Trials Register (1).

Briefly, the Cochrane Pregnancy and Childbirth’s Trials Register is maintained by their Information Specialist and contains trials identified from monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), weekly searches of MEDLINE (Ovid), weekly searches of Embase (Ovid), monthly searches of CINAHL (EBSCO); handsearches of 30 journals and the proceedings of major conferences; weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts. The Register contains over 25,000 reports of controlled trials in the field of pregnancy and childbirth. It represents over 30 years of searching.

For compiling the Register, search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth review topic (or topics), and is then added to the Register.

When searching for a systematic review, the Information Specialist searches the Register for each review using this topic number rather than keywords. This results in a more specific search set that will be fully accounted for in the relevant review sections (Included, Excluded, Awaiting Classification or Ongoing).

Topics searched for this review included ‘preterm,’ ‘premature,’ ‘labour,’ ‘labor,’ ‘risk’ and ‘prevention.’

In addition to searches via the Information Specialist, we searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for unpublished, planned and ongoing trial reports using transparent search methods based on key terms.

**ClinicalTrials.gov (Advanced search)**

prevention | Interventional Studies | Preterm birth

risk | Interventional Studies | Preterm Labor

**ICTRP (each line run separately)**

risk AND preterm

risk AND premature

Initial searches for the review were conducted in July 2019, updated on 11 January 2020 and the most recent search for the review was conducted on 8 August 2021.

(1) Cochrane Pregnancy and Childbirth’s Trials Register. Available from: [https://pregnancy.cochrane.org/pregnancy-and-childbirth-groups-trials-register](https://pregnancy.cochrane.org/pregnancy-and-childbirth-groups-trials-register) (accessed 18/01/2021)
Supplementary File 3: Network Diagrams

Abbreviations for Network Diagrams

17-OHPC= 17alpha hydroxyprogesterone caproate; Amox = Amoxicillin; BR = bed rest; Cerc (McD)= McDonald Cerclage; Cerc (Sh)= Shirodkar Cerclage; Cerclage (Unspec.) = unspecified Cerclage; Clind = Clindamycin; Eryth = Erythromycin; Met = metronidazole; No TMT= no treatment; OP= oral progesterone; VP = vaginal progesterone

Outcomes for pregnant women

1. preterm birth less than 37 weeks' gestation

2. preterm birth less than 34 weeks' gestation
3. spontaneous preterm birth less than 34 weeks' gestation

4. preterm birth less than 28 weeks' gestation
5. maternal death

6. preterm prelabour rupture of membranes
7. maternal infection

Outcomes for offspring

1. perinatal death

2. neonatal death
3. Gestational age at birth
4. low birthweight, less than 2500 g

5. neonatal respiratory distress syndrome
6. neonatal pulmonary disease

7. intraventricular haemorrhage
8. periventricular leukomalacia

9. necrotising enterocolitis
10. Proven neonatal sepsis

11. Admission to neonatal intensive care unit
Supplementary File 4: Reference list of included studies (primary reference).

1. Ahuja R, Sood A, Pal A, Mittal R. Role of micronized progesterone in prevention of preterm labour in women with previous history of one or more preterm births: a research study at a tertiary care hospital. International Journal of Reproduction, Contraception, Obstetrics and Gynecology 2015;4(4):1176-80.

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Supplementary File 5: Summary of results of studies disconnected from the network

Four trials were disconnected from the network for at least one outcome. All four studies included an intervention which combined McDonald cerclage with another intervention. We calculated odds ratios or mean differences (with 95% confidence intervals) of the intervention compared to control for each individual study.

| Study | Intervention                                      | Control                                      | Outcome                                | Result               |
|-------|--------------------------------------------------|----------------------------------------------|----------------------------------------|----------------------|
| Althuisius 2001 | McDonald cerclage and bed rest and antibiotics [amoxicillin plus metronidazole] (n=19) | Bed rest and antibiotics [amoxicillin plus metronidazole] (n=16) | Preterm birth < 37 weeks gestation | **OR 0.16 (95% CI 0.04 to 0.72)** |
|        |                                                  |                                              | Preterm birth < 34 weeks gestation    | **OR 0.06 (95% CI 0.003 to 1.06)** |
|        |                                                  |                                              | Preterm birth < 28 weeks gestation    | **OR 0.10 (95% CI 0.005 to 2.08)** |
|        |                                                  |                                              | Preterm prelabour rupture of membranes | **OR 0.03 (95% CI 0.001 to 0.50)** |
|        |                                                  |                                              | Maternal infection                    | **OR 0.04 (95% CI 0.005 to 0.40)** |
|        |                                                  |                                              | Perinatal Death                       | **OR 0.10 (95% CI 0.005 to 2.08)** |
|        |                                                  |                                              | Neonatal Death                        | **OR 0.10 (95% CI 0.005 to 2.08)** |
|        |                                                  |                                              | Gestational age at birth (weeks)     | **MD 4.8 (95% CI 1.62 to 7.98)** |
| Berghella 2004 | McDonald cerclage and bed rest (n=29)          | Bed rest (n=28)                              | Spontaneous preterm birth < 34 weeks gestation | **OR 0.78 (95% CI 0.26 to 2.31)** |
|        |                                                  |                                              | Preterm prelabour rupture of membranes | **OR 0.76 (95% CI 0.25 to 2.33)** |
|        |                                                  |                                              | Perinatal Death                       | **OR 1.33 (95% CI 0.27 to 6.58)** |
| Keeler 2009  | McDonald cerclage and clindamycin (n=37)        | 17-OHPC and clindamycin (n=42)               | Preterm birth < 37 weeks gestation    | **OR 0.75 (95% CI 0.31 to 1.83)** |
|        |                                                  |                                              | Preterm birth < 28 weeks gestation    | **OR 0.75 (95% CI 0.25 to 2.21)** |
|        |                                                  |                                              | Preterm prelabour rupture of membranes | **OR 1.21 (95% CI 0.47 to 3.09)** |
|        |                                                  |                                              | Maternal infection                    | **OR 0.69 (95% CI 0.25 to 1.93)** |
|        |                                                  |                                              | Neonatal death                        | **OR 1.11 (95% CI 0.28 to 4.50)** |
|        |                                                  |                                              | Gestational age at birth (weeks)     | **MD -0.10 (95% CI -2.81 to 2.61)** |
| Rust 2001 | McDonald cerclage and clindamycin (n=55)        | Clindamycin (n=58)                           | Gestational age at birth (weeks)     | **MD 0.00 (95% CI -2.13 to 2.13)** |

17-OHPC = 17alpha hydroxyprogesterone caproate, CI = Confidence Interval, MD = Mean Difference, OR = Odds Ratio

1. See Supplementary File 4 for references of studies
2. OR<1 or MD>0 indicates an advantage to the intervention over the control, and statistically significant results are highlighted in bold.

Fewer preterm births at less than 37 weeks gestation, preterm prelabour rupture of membranes and cases of maternal infection occurred on McDonald cerclage and bed rest and antibiotics compared to bed rest and antibiotics. Gestational age at birth was also later on cerclage and bed rest and antibiotics compared to bed rest and antibiotics.

No statistically significant differences were demonstrated for preterm birth less than 34 weeks or 28 weeks gestation, nor for perinatal or neonatal death. There were also no statistically significant differences for any outcomes between McDonald cerclage and bed rest compared to bed rest and McDonald cerclage and clindamycin compared to Clindamycin alone or 17-OHPC and clindamycin.
However, due to small numbers of patients included in the trials and low numbers of events, confidence intervals of the individual study results are wide and therefore the magnitude of any difference between the any of the treatments is associated with great uncertainty.
Supplementary File 6: Network meta-analysis results of outcomes for pregnant women

Results are presented for the best fitting NMA model for each outcome (see Supplementary Table 5).

Results expressed as odds ratio (OR) and 95% credible interval (CI). OR<1 indicates an advantage to the treatment over the reference. A credible interval is interpreted as the interval where there is a 95% probability that the values of the OR will lie.

Due to the large number of pairwise comparisons made in NMAs, for practical reasons, comparisons to control, vaginal progesterone and intramuscular progesterone only are presented.

Extremely wide credible intervals were estimated for some treatment comparisons, particularly for the outcomes preterm birth <28 weeks, maternal death and maternal infection, where few events occurred and data were sparse. These results are very uncertain and should be interpreted with extreme caution.

Preterm Birth at <37 weeks (Random Effects, Consistency model)
Preterm Birth at <34 weeks (Random Effects, Consistency model)

| Treatment | Odds (95% CI) |
|-----------|--------------|
| Reference: Control (Placebo / No Treatment) | |
| Vaginal Progesterone | 0.50 (0.34, 0.70) |
| Oral Progesterone | 0.42 (0.12, 1.40) |
| 17-OHPC | 0.68 (0.43, 1.02) |
| McDonald Cerclage | 0.66 (0.21, 2.03) |
| Shidrokar Cerclage | 0.06 (0.00, 0.84) |
| Unspecified Cerclage | 0.66 (0.29, 1.44) |
| Pessary | 0.65 (0.39, 1.08) |
| Fish Oil | 0.30 (0.06, 1.23) |
| Bed Rest | 0.41 (0.05, 3.18) |
| Clindamycin | 2.95 (0.63, 15.55) |
| Combo (Pessary + Vaginal Progesterone) | 0.79 (0.18, 4.33) |
| Combo (McDonald Cerclage + Clindamycin) | 2.75 (0.37, 22.31) |
| Combo (Shirodkar Cerclage + Erythromycin) | 0.79 (0.25, 2.52) |
| Combo (17-OHPC + Clindamycin) | 0.98 (0.17, 5.70) |
| Combo (Omega3 + 17-OHPC) | 0.63 (0.20, 1.96) |
| Combo (McDonald Cerclage + Bed Rest) | 0.32 (0.02, 3.92) |

| Reference: Vaginal Progesterone | |
| Oral Progesterone | 0.83 (0.24, 3.03) |
| 17-OHPC | 1.34 (0.87, 2.12) |
| McDonald Cerclage | 1.32 (0.42, 4.40) |
| Shidrokar Cerclage | 0.13 (0.00, 1.76) |
| Unspecified Cerclage | 1.32 (0.59, 2.99) |
| Pessary | 1.29 (0.74, 2.39) |
| Fish Oil | 0.59 (0.12, 2.63) |
| Bed Rest | 0.82 (0.10, 6.65) |
| Clindamycin | 5.89 (1.22, 27.75) |
| Combo (Pessary + Vaginal Progesterone) | 1.58 (0.38, 6.86) |
| Combo (McDonald Cerclage + Clindamycin) | 5.48 (0.72, 46.81) |
| Combo (Shirodkar Cerclage + Erythromycin) | 1.58 (0.48, 5.47) |
| Combo (17-OHPC + Clindamycin) | 1.95 (0.33, 12.05) |
| Combo (Omega3 + 17-OHPC) | 1.26 (0.46, 4.08) |
| Combo (McDonald Cerclage + Bed Rest) | 0.64 (0.05, 8.20) |

| Reference: 17-OHPC | |
| Oral Progesterone | 0.62 (0.17, 2.27) |
| McDonald Cerclage | 0.98 (0.30, 3.34) |
| Shidrokar Cerclage | 0.10 (0.00, 1.32) |
| Unspecified Cerclage | 0.98 (0.41, 2.36) |
| Pessary | 0.96 (0.51, 1.88) |
| Fish Oil | 0.44 (0.09, 1.98) |
| Bed Rest | 0.61 (0.07, 5.01) |
| Clindamycin | 4.38 (0.89, 24.83) |
| Combo (Pessary + Vaginal Progesterone) | 1.17 (0.26, 5.40) |
| Combo (McDonald Cerclage + Clindamycin) | 4.07 (0.53, 35.34) |
| Combo (Shirodkar Cerclage + Erythromycin) | 1.17 (0.35, 4.12) |
| Combo (17-OHPC + Clindamycin) | 1.46 (0.24, 9.04) |
| Combo (Omega3 + 17-OHPC) | 0.94 (0.33, 2.72) |
| Combo (McDonald Cerclage + Bed Rest) | 0.48 (0.04, 6.19) |
### Spontaneous Preterm Birth at <34 weeks (Random Effects, Consistency model)

| Treatment                      | Odds Ratio (95% CI) |
|--------------------------------|---------------------|
| Reference: Control (Placebo / No Treatment) |                      |
| Vaginal Progesterone | 0.85 (0.15, 4.68) |
| 17-OHPC | 0.65 (0.09, 4.19) |
| Pessary | 0.63 (0.20, 1.99) |
| Reference: Vaginal Progesterone |                      |
| 17-OHPC | 0.76 (0.10, 5.41) |
| Pessary | 0.74 (0.13, 4.47) |
| Reference: 17-OHPC |                      |
| Pessary | 0.98 (0.12, 8.45) |

### Preterm Birth at <28 weeks (Fixed Effects, Consistency model)

| Treatment                      | Odds Ratio (95% CI) |
|--------------------------------|---------------------|
| Reference: Control (Placebo / No Treatment) |                      |
| Vaginal Progesterone | 0.91 (0.71, 1.17) |
| Oral Progesterone | 0.07 (0.00, 1.13) |
| 17-OHPC | 0.77 (0.48, 1.22) |
| McDonald Cerclage | 0.75 (0.55, 1.02) |
| Shidrokar Cerclage | 0.76 (0.00, 559.48) |
| Unspecified Cerclage | 1.64 (0.27, 10.89) |
| Pessary | 0.86 (0.59, 1.25) |
| Bed Rest | 0.80 (0.00, 546.21) |
| Combo (Shirodkar Cerclage + Erythromycin) | 0.85 (0.40, 1.82) |
| Combo (McDonald Cerclage + Bed Rest) | 0.83 (0.00, 663.15) |
| Reference: Vaginal Progesterone |                      |
| Oral Progesterone | 0.07 (0.00, 1.25) |
| McDonald Cerclage | 0.84 (0.52, 1.33) |
| Shidrokar Cerclage | 0.82 (0.55, 1.22) |
| Unspecified Cerclage | 0.84 (0.00, 599.44) |
| Pessary | 1.80 (0.30, 11.82) |
| Bed Rest | 0.94 (0.61, 1.44) |
| Combo (Shirodkar Cerclage + Erythromycin) | 0.87 (0.00, 611.55) |
| Combo (McDonald Cerclage + Bed Rest) | 0.94 (0.42, 2.07) |
| Reference: 17-OHPC |                      |
| Oral Progesterone | 0.09 (0.00, 1.55) |
| McDonald Cerclage | 0.98 (0.56, 1.72) |
| Shidrokar Cerclage | 1.00 (0.00, 716.95) |
| Unspecified Cerclage | 2.16 (0.34, 14.92) |
| Pessary | 1.12 (0.63, 2.03) |
| Bed Rest | 1.05 (0.00, 745.46) |
| Combo (Shirodkar Cerclage + Erythromycin) | 1.12 (0.46, 2.72) |
| Combo (McDonald Cerclage + Bed Rest) | 1.10 (0.00, 879.19) |
Maternal Death (Random Effects, Consistency model)

| Treatment                      | Reference: Control (Placebo / No Treatment) | Odds Ratio (95% CI) |
|-------------------------------|---------------------------------------------|---------------------|
| Vaginal Progesterone          |                                             | 1.00 (0.00, 4217.51) |
| 17-OHPC                       |                                             | 0.52 (0.00, 2230.54) |
| Unspecified Cerclage          |                                             | 0.89 (0.00, 103777.05) |
| Pessary                       |                                             | 1.01 (0.00, 225.88)  |

Reference: Vaginal Progesterone

| Treatment                      | Reference: Vaginal Progesterone | Odds Ratio (95% CI) |
|-------------------------------|---------------------------------|---------------------|
| 17-OHPC                       |                                 | 0.53 (0.00, 57526.45) |
| Unspecified Cerclage          |                                 | 0.90 (0.00, 3718.22)  |
| Pessary                       |                                 | 0.96 (0.00, 16531.13) |

Reference: 17-OHPC

| Treatment                      | Reference: 17-OHPC | Odds Ratio (95% CI) |
|-------------------------------|--------------------|---------------------|
| Unspecified Cerclage          |                    | 1.68 (0.00, 2235554.50) |
| Pessary                       |                    | 1.87 (0.00, 35596.39)  |

Preterm Rupture of Membranes (Fixed Effects, Consistency model)

| Treatment                      | Reference: Control (Placebo / No Treatment) | Odds Ratio (95% CI) |
|-------------------------------|---------------------------------------------|---------------------|
| Vaginal Progesterone          |                                             | 0.90 (0.73, 1.12)  |
| Oral Progesterone             |                                             | 0.76 (0.42, 1.37)  |
| 17-OHPC                       |                                             | 1.13 (0.77, 1.65)  |
| McDonald Cerclage             |                                             | 1.65 (0.75, 3.77)  |
| Unspecified Cerclage          |                                             | 2.41 (0.84, 7.68)  |
| Pessary                       |                                             | 0.76 (0.49, 1.18)  |
| Combo (Pessary + Vaginal Progesterone) |                     | 0.83 (0.31, 2.20)  |
| Combo (Shirodkar Cerclage + Erythromycin) |                     | 1.25 (0.64, 2.45)  |

Reference: Vaginal Progesterone

| Treatment                      | Reference: Vaginal Progesterone | Odds Ratio (95% CI) |
|-------------------------------|---------------------------------|---------------------|
| Oral Progesterone             |                                 | 0.84 (0.45, 1.57)  |
| 17-OHPC                       |                                 | 1.24 (0.85, 1.84)  |
| McDonald Cerclage             |                                 | 1.83 (0.81, 4.28)  |
| Unspecified Cerclage          |                                 | 2.66 (0.93, 8.44)  |
| Pessary                       |                                 | 0.84 (0.53, 1.33)  |
| Combo (Pessary + Vaginal Progesterone) |                     | 0.92 (0.36, 2.36)  |
| Combo (Shirodkar Cerclage + Erythromycin) |                     | 1.38 (0.69, 2.80)  |

Reference: 17-OHPC

| Treatment                      | Reference: 17-OHPC | Odds Ratio (95% CI) |
|-------------------------------|--------------------|---------------------|
| Oral Progesterone             |                    | 0.68 (0.34, 1.36)  |
| McDonald Cerclage             |                    | 1.47 (0.61, 3.66)  |
| Unspecified Cerclage          |                    | 2.13 (0.70, 7.19)  |
| Pessary                       |                    | 0.68 (0.38, 1.20)  |
| Combo (Pessary + Vaginal Progesterone) |                 | 0.74 (0.27, 2.05)  |
| Combo (Shirodkar Cerclage + Erythromycin) |                 | 1.11 (0.51, 2.41)  |
Supplementary File 7: Network meta-analysis results of outcomes for offspring

Results are presented for the best fitting NMA model for each outcome (see Supplementary Table 5).

Results expressed as odds ratio (OR) or mean difference (MD) and 95% credible interval (CI). OR<1 or MD>0 indicates an advantage to the treatment over the reference. A credible interval is interpreted as the interval where there is a 95% probability that the values of the MD or the OR will lie.

Due to the large number of pairwise comparisons made in NMAs, for practical reasons, comparisons to control, vaginal progesterone and intramuscular progesterone only are presented.

Extremely wide credible intervals were estimated for some treatment comparisons, particularly for outcomes perinatal death, periventricular leukomalacia, necrotising enterocolitis and sepsis, where few events occurred and data were sparse. These results are very uncertain and should be interpreted with extreme caution.

### Perinatal Death (Fixed Effects, Consistency model)

| Treatment | Odds Ratio (95% CI) |
|-----------|---------------------|
| Reference: Control (Placebo / No Treatment) | |
| Vaginal Progesterone | 0.66 (0.44, 0.97) |
| 17-OHPC | 0.78 (0.50, 1.21) |
| McDonald Cerclage | 0.59 (0.33, 1.03) |
| Unspecified Cerclage | 0.77 (0.53, 1.11) |
| Pessary | 0.90 (0.52, 1.54) |
| Clindamycin | 4.01 (0.44, 130.97) |
| Combo (Pessary + Vaginal Progesterone) | 1.66 (0.12, 54.82) |
| Combo (McDonald Cerclage + Clindamycin) | 7.59 (0.64, 274.24) |
| Combo (Shirodkar Cerclage + Erythromycin) | 0.72 (0.28, 1.78) |
| Combo (Omega3 + 17-OHPC) | 0.70 (0.30, 1.61) |
| Reference: Vaginal Progesterone | |
| 17-OHPC | 1.18 (0.65, 2.15) |
| McDonald Cerclage | 0.89 (0.44, 1.79) |
| Unspecified Cerclage | 1.17 (0.70, 1.96) |
| Pessary | 1.37 (0.73, 2.59) |
| Clindamycin | 6.12 (0.64, 202.76) |
| Combo (Pessary + Vaginal Progesterone) | 2.52 (0.19, 81.45) |
| Combo (McDonald Cerclage + Clindamycin) | 11.60 (0.94, 431.38) |
| Combo (Shirodkar Cerclage + Erythromycin) | 1.10 (0.40, 2.95) |
| Combo (Omega3 + 17-OHPC) | 1.07 (0.43, 2.69) |
| Reference: 17-OHPC | |
| McDonald Cerclage | 0.76 (0.36, 1.54) |
| Unspecified Cerclage | 0.99 (0.55, 1.76) |
| Pessary | 1.16 (0.57, 2.34) |
| Clindamycin | 5.21 (0.54, 171.23) |
| Combo (Pessary + Vaginal Progesterone) | 2.14 (0.15, 72.68) |
| Combo (McDonald Cerclage + Clindamycin) | 9.85 (0.79, 358.88) |
| Combo (Shirodkar Cerclage + Erythromycin) | 0.93 (0.32, 2.53) |
| Combo (Omega3 + 17-OHPC) | 0.91 (0.45, 1.83) |
Neonatal Death (Fixed Effects, Consistency model)

| Treatment                        | Odds (95% CI) |
|----------------------------------|---------------|
| Reference: Control (Placebo / No Treatment) |               |
| Vaginal Progesterone             | 0.29 (0.19, 0.46) |
| Oral Progesterone                | 0.26 (0.12, 0.55) |
| 17-OHPC                          | 0.56 (0.34, 0.93) |
| McDonald Cerclage                | 0.73 (0.13, 3.60) |
| Shidrokar Cerclage               | 0.13 (0.00, 6.09) |
| Unspecified Cerclage             | 0.57 (0.25, 1.26) |
| Pessary                          | 0.79 (0.37, 1.69) |
| Bed Rest                         | 0.73 (0.03, 17.83) |
| Combo (Pessary + Vaginal Progesterone) | 0.30 (0.01, 11.52) |
| Combo (Shirodkar Cerclage + Erythromycin) | 0.82 (0.25, 2.61) |
| Combo (McDonald Cerclage + Bed Rest) | 0.53 (0.01, 19.41) |
| Reference: Vaginal Progesterone  |               |
| Oral Progesterone                | 0.89 (0.36, 2.13) |
| 17-OHPC                          | 1.91 (1.12, 3.33) |
| McDonald Cerclage                | 2.48 (0.42, 13.08) |
| Shidrokar Cerclage               | 0.44 (0.00, 21.31) |
| Unspecified Cerclage             | 1.93 (0.78, 4.69) |
| Pessary                          | 2.70 (1.11, 6.55) |
| Bed Rest                         | 2.48 (0.10, 64.01) |
| Combo (Pessary + Vaginal Progesterone) | 1.03 (0.03, 38.13) |
| Combo (Shirodkar Cerclage + Erythromycin) | 2.79 (0.78, 9.59) |
| Combo (McDonald Cerclage + Bed Rest) | 1.79 (0.05, 67.90) |
| Reference: 17-OHPC               |               |
| Oral Progesterone                | 0.46 (0.18, 1.14) |
| McDonald Cerclage                | 1.29 (0.22, 6.87) |
| Shidrokar Cerclage               | 0.23 (0.00, 11.21) |
| Unspecified Cerclage             | 1.01 (0.39, 2.55) |
| Pessary                          | 1.41 (0.57, 3.49) |
| Bed Rest                         | 1.29 (0.05, 33.08) |
| Combo (Pessary + Vaginal Progesterone) | 0.54 (0.01, 20.66) |
| Combo (Shirodkar Cerclage + Erythromycin) | 1.45 (0.40, 5.12) |
| Combo (McDonald Cerclage + Bed Rest) | 0.93 (0.02, 35.77) |
Low Birthweight (Random Effects, Consistency model)

Reference: Control (Placebo / No Treatment)
- Vaginal Progesterone
- Oral Progesterone
- 17-OHPC
- McDonald Cerclage
- Unspecified Cerclage
- Pessary
- Zinc
- Combo (Pessary + Vaginal Progesterone)
- Combo (Omega3 + 17-OHPC)

Reference: Vaginal Progesterone
- Oral Progesterone
- 17-OHPC
- McDonald Cerclage
- Unspecified Cerclage
- Pessary
- Zinc
- Combo (Pessary + Vaginal Progesterone)
- Combo (Omega3 + 17-OHPC)

Reference: 17-OHPC
- Oral Progesterone
- McDonald Cerclage
- Unspecified Cerclage
- Pessary
- Zinc
- Combo (Pessary + Vaginal Progesterone)
- Combo (Omega3 + 17-OHPC)

Odds Ratio (95% CI)
- Reference worse
  - Vaginal Progesterone: 0.59 (0.31, 1.07)
  - Oral Progesterone: 0.38 (0.08, 1.76)
  - 17-OHPC: 0.71 (0.38, 1.31)
  - McDonald Cerclage: 0.61 (0.18, 1.87)
  - Unspecified Cerclage: 0.84 (0.20, 3.50)
  - Pessary: 0.59 (0.27, 1.24)
  - Zinc: 0.42 (0.06, 2.82)
  - Combo (Pessary + Vaginal Progesterone): 0.86 (0.15, 4.87)
  - Combo (Omega3 + 17-OHPC): 0.54 (0.11, 2.52)

- Reference better
  - Vaginal Progesterone: 0.65 (0.13, 3.42)
  - Oral Progesterone: 1.21 (0.55, 2.76)
  - 17-OHPC: 1.05 (0.26, 3.75)
  - McDonald Cerclage: 1.43 (0.31, 6.80)
  - Unspecified Cerclage: 1.00 (0.42, 2.41)
  - Pessary: 0.72 (0.09, 5.34)
  - Zinc: 1.46 (0.29, 7.47)
  - Combo (Pessary + Vaginal Progesterone): 0.91 (0.18, 4.69)

- 17-OHPC
  - Oral Progesterone: 0.54 (0.11, 2.80)
  - McDonald Cerclage: 0.86 (0.21, 3.06)
  - Unspecified Cerclage: 1.18 (0.26, 5.64)
  - Pessary: 0.82 (0.31, 2.15)
  - Zinc: 0.59 (0.08, 4.34)
  - Combo (Pessary + Vaginal Progesterone): 1.21 (0.20, 7.45)
  - Combo (Omega3 + 17-OHPC): 0.75 (0.18, 3.14)
Intraventricular haemorrhage (Fixed Effects, Consistency model)

| Comparison                                      | Odds Ratio (95% CI) |
|------------------------------------------------|---------------------|
| Reference: Control (Placebo / No Treatment)    |                     |
| Vaginal Progesterone                           | 0.66 (0.42, 1.03)   |
| Oral Progesterone                              | 0.65 (0.24, 1.71)   |
| 17-OHPC                                        | 0.64 (0.32, 1.31)   |
| McDonald Cerclage                              | 0.11 (0.00, 2.05)   |
| Unspecified Cerclage                           | 0.64 (0.08, 4.90)   |
| Pessary                                        | 1.07 (0.54, 2.12)   |
| Nifedipine                                     | 0.18 (0.00, 5.53)   |
| Combo (Shirodkar Cerclage + Erythromycin)      | 0.40 (0.01, 5.24)   |
| Combo (Omega3 + 17-OHPC)                       | 0.68 (0.22, 2.23)   |

Reference: Vaginal Progesterone

| Comparison                                      | Odds Ratio (95% CI) |
|------------------------------------------------|---------------------|
| Oral Progesterone                              | 0.99 (0.32, 2.85)   |
| 17-OHPC                                        | 0.97 (0.47, 1.99)   |
| McDonald Cerclage                              | 0.16 (0.00, 3.22)   |
| Unspecified Cerclage                           | 0.96 (0.13, 7.06)   |
| Pessary                                        | 1.62 (0.73, 3.63)   |
| Nifedipine                                     | 0.27 (0.00, 8.66)   |
| Combo (Shirodkar Cerclage + Erythromycin)      | 0.61 (0.02, 8.26)   |
| Combo (Omega3 + 17-OHPC)                       | 1.04 (0.32, 3.40)   |

Reference: 17-OHPC

| Comparison                                      | Odds Ratio (95% CI) |
|------------------------------------------------|---------------------|
| Oral Progesterone                              | 0.99 (0.30, 3.38)   |
| McDonald Cerclage                              | 0.10 (0.00, 3.52)   |
| Unspecified Cerclage                           | 0.99 (0.12, 9.24)   |
| Pessary                                        | 1.67 (0.63, 4.41)   |
| Nifedipine                                     | 0.29 (0.00, 9.31)   |
| Combo (Shirodkar Cerclage + Erythromycin)      | 0.62 (0.02, 9.12)   |
| Combo (Omega3 + 17-OHPC)                       | 1.07 (0.43, 2.78)   |

Periventricular Leukomalacia (Fixed Effects, Consistency model)

| Comparison                                      | Odds Ratio (95% CI) |
|------------------------------------------------|---------------------|
| Reference: Control (Placebo / No Treatment)    |                     |
| Vaginal Progesterone                           | 0.99 (0.03, 37.83)  |
| 17-OHPC                                        | 5.29 (0.66, 158.22) |

Reference: Vaginal Progesterone

| Comparison                                      | Odds Ratio (95% CI) |
|------------------------------------------------|---------------------|
| 17-OHPC                                        | 5.89 (0.08, 727.78) |
Necrotising enterocolitis (Fixed Effects, Consistency model)

| Treatment                          | Odds Ratio (95% CI) |
|------------------------------------|---------------------|
| Reference: Control (Placebo / No Treatment) |                      |
| Vaginal Progesterone               | 0.79 (0.49, 1.24)   |
| Oral Progesterone                  | 0.48 (0.14, 1.51)   |
| 17-OHPC                            | 0.40 (0.16, 0.93)   |
| McDonald Cerclage                  | 1.03 (0.11, 9.87)   |
| Unspecified Cerclage               | 4.17 (0.13, 2145.23)|
| Pessary                            | 1.24 (0.55, 2.65)   |
| Combo (Omega3 + 17-OHPC)           | 0.27 (0.04, 1.67)   |

Reference: Vaginal Progesterone

| Treatment                          | Odds Ratio (95% CI) |
|------------------------------------|---------------------|
| Oral Progesterone                  | 0.62 (0.16, 2.09)   |
| 17-OHPC                            | 0.51 (0.20, 1.22)   |
| McDonald Cerclage                  | 1.31 (0.13, 13.08)  |
| Unspecified Cerclage               | 5.28 (0.17, 2694.59)|
| Pessary                            | 1.58 (0.65, 4.00)   |
| Combo (Omega3 + 17-OHPC)           | 0.35 (0.05, 2.14)   |

Reference: 17-OHPC

| Treatment                          | Odds Ratio (95% CI) |
|------------------------------------|---------------------|
| Oral Progesterone                  | 1.22 (0.27, 5.19)   |
| McDonald Cerclage                  | 2.62 (0.23, 29.46)  |
| Unspecified Cerclage               | 10.67 (0.30, 5602.68)|
| Pessary                            | 3.14 (0.98, 10.51)  |
| Combo (Omega3 + 17-OHPC)           | 0.70 (0.13, 3.37)   |

Sepsis (Fixed Effects, Consistency model)

| Treatment                          | Odds Ratio (95% CI) |
|------------------------------------|---------------------|
| Reference: Control (Placebo / No Treatment) |                      |
| Vaginal Progesterone               | 0.43 (0.24, 0.77)   |
| 17-OHPC                            | 0.65 (0.37, 1.17)   |
| Unspecified Cerclage               | 0.40 (0.05, 2.98)   |
| Pessary                            | 0.86 (0.58, 1.28)   |
| Clindamycin                        | 24.56 (1.72, 13413.27)|
| Combo (Shirodkar Cerclage + Erythromycin) | 2.78 (0.55, 22.31) |
| Combo (Omega3 + 17-OHPC)           | 1.11 (0.23, 6.31)   |

Reference: Vaginal Progesterone

| Treatment                          | Odds Ratio (95% CI) |
|------------------------------------|---------------------|
| 17-OHPC                            | 1.52 (0.76, 3.06)   |
| Unspecified Cerclage               | 0.92 (0.12, 6.57)   |
| Pessary                            | 2.00 (1.00, 4.11)   |
| Clindamycin                        | 57.63 (3.75, 31257.05)|
| Combo (Shirodkar Cerclage + Erythromycin) | 6.52 (1.15, 56.71) |
| Combo (Omega3 + 17-OHPC)           | 2.58 (0.52, 15.00)  |

Reference: 17-OHPC

| Treatment                          | Odds Ratio (95% CI) |
|------------------------------------|---------------------|
| Unspecified Cerclage               | 0.61 (0.07, 4.73)   |
| Pessary                            | 1.32 (0.65, 2.66)   |
| Clindamycin                        | 38.13 (2.46, 20292.37)|
| Combo (Shirodkar Cerclage + Erythromycin) | 4.28 (0.76, 36.38) |
| Combo (Omega3 + 17-OHPC)           | 1.69 (0.39, 8.80)   |
| Treatment Comparison | Odds Ratio (95% CI) |
|----------------------|---------------------|
| **Reference: Control (Placebo / No Treatment)** | |
| Vaginal Progesterone | 0.61 (0.40, 0.86) |
| Oral Progesterone | 0.23 (0.10, 0.52) |
| 17-OHPC | 0.82 (0.48, 1.22) |
| McDonald Cerclage | 0.07 (0.00, 0.63) |
| Pessary | 0.90 (0.46, 1.71) |
| Nifedipine | 0.94 (0.02, 37.68) |
| Combo (Pessary + Vaginal Progesterone) | 1.13 (0.19, 7.73) |
| Combo (Omega3 + 17-OHPC) | 0.90 (0.28, 2.44) |
| **Reference: Vaginal Progesterone** | |
| Oral Progesterone | 0.38 (0.16, 0.97) |
| 17-OHPC | 1.34 (0.83, 2.08) |
| McDonald Cerclage | 0.12 (0.00, 1.09) |
| Pessary | 1.47 (0.76, 3.10) |
| Nifedipine | 1.55 (0.04, 64.39) |
| Combo (Pessary + Vaginal Progesterone) | 1.86 (0.32, 12.50) |
| Combo (Omega3 + 17-OHPC) | 1.47 (0.48, 4.22) |
| **Reference: 17-OHPC** | |
| Oral Progesterone | 0.28 (0.12, 0.77) |
| McDonald Cerclage | 0.09 (0.00, 0.84) |
| Pessary | 1.09 (0.53, 2.54) |
| Nifedipine | 1.17 (0.03, 49.21) |
| Combo (Pessary + Vaginal Progesterone) | 1.39 (0.23, 10.12) |
| Combo (Omega3 + 17-OHPC) | 1.09 (0.41, 2.91) |
### Supplementary Table 1: Summary of key trial and participant baseline characteristics

| Trial          | High Risk Population                                                                 | Total | GA at initiation of intervention | GA at stopping intervention | Nulliparous | History of PTB or SPTB < 37 weeks | History of PTB or SPTB < 34 weeks | Short cervix < 25mm | Smoking at start of pregnancy | Black or African race |
|----------------|--------------------------------------------------------------------------------------|-------|----------------------------------|-----------------------------|-------------|----------------------------------|-----------------------------------|---------------------|---------------------------|----------------------|
| Ahuja 2015     | History of PTB < 37 wks                                                              | 80    | 24 to 26 weeks                   | 34 weeks                    | NR          | 25%                              | NR                                               | NR                  | NR                       | NR                   |
| Akbari 2009    | History of sPTB, cervical cerclage or uterine malformation, 18 - 35 yrs old         | 150   | 24 weeks                         | 36 weeks                    | NR          | 93%                              | NR                                               | NR                  | NR                       | NR                   |
| Althuisius 2001| 1. History PTB/PPROM < 34 wks, 2. Uterine anomaly, knife cone biopsy 3. Short CL < 25mm 15-27wks on TVU | 36    | before 27 weeks                  | 37 weeks                    | 20%         | 80%                              | NR                                               | 100%                | NR                       | NR                   |
| Ashoush 2017   | History of sPTB < 37 wks                                                              | 212   | 14 to 18 weeks                   | 37 weeks                    | 0%          | 100%                             | NR                                               | NR                  | NR                       | NR                   |
| Azargoon 2016  | Prior PTB, prior PTB and short cervix < 28 mm, prior cerclage, uterine anomalies    | 103   | 16 to 22 weeks                   | 36 weeks                    | NR          | 53%                              | NR                                               | 27%                 | NR                       | NR                   |
| Bafghi 2015    | History of previous preterm delivery or a short cervix (< 25 mm) on TVU. Women with both risk factors excluded. | 78    | 16 to 20 weeks                   | delivery                    | NR          | 42%                              | NR                                               | 58%                 | NR                       | NR                   |
| Berghella 2004 | Asymptomatic women high risk due to: 1) > 1 PTB between 14-34 weeks of gestation, 2) >2 curettage procedures for spontaneous/voluntary abortions, 3) diethylstilbestrol (DES) exposure, 4) cone biopsy, or 5) Mullerian anomaly and who were identified to have a short cervix (< 25 mm) or significant funnelling (> 25%) between 14 weeks 0 days of gestation and 23 weeks 6 days of gestation. (Twin data excluded) | 61    | 14 to <24 weeks                  | delivery                    | NR          | 64%                              | NR                                               | 100%                | 28%                      | 77%                  |
| Study Year | Study Details                                                                 | Participants | Pregnancy Weeks | Delivery Weeks | Preterm Delivery | Preterm Rate | NR Rate | NR Rate | NR Rate |
|------------|-------------------------------------------------------------------------------|--------------|-----------------|----------------|------------------|--------------|---------|---------|---------|
| 2020 Blackwell | Previous singleton sPTB                                                      | 1708         | 16 to 20 weeks   | delivery       | 0%               | 100%        | NR      | 2%      | 8%      | 7%      |
| 1979 Breart  | 20-34 weeks incidental finding of short cervix with effacement or premature cervical dilatation in asymptomatic women | 211          | 24 to 34 weeks   | 37 weeks       | NR               | NR          | NR      | NR      | NR      | NR      |
| 2015 Cabrera-Garcia | Pregnant women with a short cervix (<25 mm) as identified by TVU at 19 to 22 weeks | 254          | 20 to 23 weeks   | 37 weeks       | 46%              | 11%         | NR      | 100%    | 17%     | 4%      |
| 2019 Care    | 16-24 weeks' gestation, history of sPTB, cervix < 3rd centile for gestation, 18+, treating physician in equipoise as to the best treatment | 18           | 16 to 24 weeks   | 37 weeks       | NR               | 78%         | NR      | 100%    | 45%     | NR      |
| 2011 Cetingoz | High risk pregnancy including twin (twin data excluded), prior sPTB or uterine malformation | 150          | 24 weeks         | 34 weeks       | NR               | NR          | NR      | NR      | NR      | NR      |
| 2010 Chandirani | Pregnant women (14 to 24 weeks’ gestation) with at least 1 previous preterm delivery and short cervix (< 25 mm) at < 24 weeks’ gestation were randomised. A third arm of controls were not randomised and not eligible for this review. | 37           | 14 to 24 weeks   | 37 weeks       | NR               | NR          | 31%     | 100%    | 6%      | NR      |
| 2020 Choi    | Singleton pregnancy, >20yrs, with history of sPTB or short cervix (<25mm) at 15-22weeks. | 247          | 16-22 weeks      | 36 weeks       | 20%              | 58%         | NR      | 48%     | NR      | NR      |
| 2017 Crowther | Singleton or twin pregnancy 18-24 weeks' gestation; history of PTB < 37 weeks (Twin data excluded) | 787          | 18 weeks         | 24 weeks       | 0%               | 100%        | 64%     | NR      | NR      | NR      |
| 2003 da Fonseca | Asymptomatic high risk women with singleton pregnancy (history of sPTB, | 156          | 24 weeks         | 34 weeks       | NR               | 94%         | NR      | NR      | NR      | 30%     |
| Study | Population Details | n | Follow-up | Outcome | Delivery Rate | Pre-eclampsia Rate | Preeclampsia Rate | Intrauterine Growth Restriction Rate | NTD Rate | Macrosomia Rate | Perinatal Mortality Rate | Small For Gestational Age Rate | Preterm Labor Rate | Preterm Birth Rate | Preterm Birth Rate |
|-------|---------------------|---|------------|---------|--------------|-------------------|------------------|-------------------------------|--------|----------------|------------------------|---------------------------|-----------------|-----------------|------------------|
| Danesh 2010 | Healthy pregnant women with previous PTB, 12 to 16 weeks' gestation, age 19 - 35 | 110 | 12 to 16 weeks | Delivery | 0% | 100% | NR | NR | NR | NR | NR |
| Danti 2014 | Singleton pregnancy with CL ≤ 25 mm between 24 and 32 weeks gestation, without uterine contractions | 87 | 24 to 32 weeks | 28 days after start of treatment | 38% | NR | NR | 100% | NR | NR | NR |
| Dugoff 2018 | 18 - 50 yrs, CL ≤ 20 mm, singleton pregnancy | 122 | 18 to <24 weeks | 37 weeks | 66% | 0% | 0% | 100% | 7% | 61% |
| El-Gharib 2013 | 20 - 34 years, history of PTB, singleton pregnancy, cervical length ≥ 15mm at 20-24 weeks, uterine malformation, or symptomatic bacteriuria | 160 | 20 to 24 weeks | 36 weeks | NR | NR | NR | NR | NR | NR | NR |
| Elimian 2016 | Singleton pregnancy 16 - 20 weeks gestation and history of sPTB | 174 | 16 to 20 weeks | before 37 weeks or delivery | 0% | 100% | NR | NR | 17% | NR | NR |
| Elzachi 2004 | History of PTB <37 | 81 | 14 weeks | NR | 0% | 100% | NR | NR | NR | NR | NR |
| Fonseca 2007 | All women with singleton or twin pregnancy with short cervix < 15 mm detected on US at 20-25 weeks' gestation (twin data excluded from this review) | 274 | 24 weeks | before 34 weeks | 56% | NR | NR | 100% | 6% | 55% |
| Glover 2011 | < 20 weeks gestation, history of sPTB | 33 | 16 to 20 weeks | 34 weeks | 0% | 100% | NR | NR | 53% | 46% |
| Goya 2012 | Singleton pregnancy, 18 to 43 years, 18 to 22 weeks gestation, CL ≤ 25 mm | 385 | 18 to 22 weeks | 37 weeks | 50% | 11% | NR | 100% | 20% | 13% |
| Grobman 2012 | Nulliparous with a viable singleton gestation and had a CL<30 mm between 16 weeks 0 days and 22 weeks 3 days. | 657 | 16 to 22 weeks | before 37 weeks | 100% | NR | NR | 100% | 17% | 52% |
| Harper 2010 | Prior singleton preterm delivery from 20 to 36.6 weeks' gestation due | 852 | 20 weeks | 37 weeks | 0% | 100% | NR | NR | 16% | 34% |
| Study (Year) | Description | n | First Trimester | Mid-Trimester | Late Trimester | Delivery | 5-Year | 1-Year | 2-Year | 5-Year | 1-Year | 2-Year |
|--------------|-------------|---|----------------|---------------|---------------|----------|--------|--------|--------|--------|--------|--------|
| Hassan 2011  | Singleton, 19 to 23 + 6 weeks, CL 10 - 20 mm on US, asymptomatic of PTL | 465 | 20 to < 24 weeks | before 37 weeks | 55% | 13% | NR | 100% | NR | 31% |
| Hui 2013     | Singleton pregnancy, CL < 25 mm at 20 to 24 weeks gestation | 108 | 20 to 24 weeks | 37 weeks | 64% | 8% | NR | 100% | 4% | NR |
| Ibrahim 2010 | Singleton pregnancy in the second trimester with previous PTB | 50 | second trimester | 36 weeks | 0% | 100% | NR | NR | NR | NR |
| Ionescu 2011 | Singleton pregnancy, CL < 25 mm at 19 to 24 weeks' and history of PTB | 92 | 19 to 24 weeks | NR | 0% | 100% | NR | 100% | NR | NR |
| Jabeen 2012  | Singleton pregnancy, history of PTB, 16 to 20 weeks' gestation | 60 | 16 to 20 weeks | 36 weeks | 0% | 100% | NR | NR | NR | NR |
| Jafarpour 2020 | Singleton pregnancy, history of PTL. | 100 | 16 weeks | 37 weeks | 0% | 100% | NR | NR | NR | NR |
| Johnson 1975 | History of PTB or second trimester pregnancy loss. | 50 | 12 to 24 weeks | 36 weeks | 0% | 100% | NR | NR | NR | 55% | 78% |
| Karbasian 2016 | Singleton pregnancy, CL ≤ 25 mm at 18 to 22 weeks gestation | 146 | 18 to 22 weeks | 37 weeks | NR | 13% | NR | 100% | NR | NR |
| Keeler 2009  | US evidence of short cervix ≤ 25 mm | 79 | 16 to 24 weeks | 36 weeks | NR | 23% | NR | 100% | NR | NR |
| Maher 2013   | History of PTB or cerclage in previous pregnancy, singleton, 14 to 18 weeks gestation | 518 | 14 to 18 weeks | 36 weeks | NR | 95% | NR | 6% | NR | NR |
| Majhi 2009   | History of sPTB, singleton pregnancy, 16 to 24 weeks gestation | 100 | 20 to 24 weeks | 36 weeks | 0% | 100% | NR | NR | 1% | NR |
| Meis 2003a   | Prior sPTB, 15 - 20 weeks gestation | 463 | 16 to 20 weeks | 36 weeks | 0% | 100% | NR | NR | 21% | 59% |
| MRC/RCOG 1993 | History of PTB or cervical surgery | 1292 | up to 29 weeks (80% before 20 weeks) | NR | NR | 71% | NR | NR | NR | NR |
| Nicolaides 2016 | Singleton, 16+ years of age, CL < 25 mm on US between 20+0 to 24+6 week's gestation | 935 | 20 to < 25 weeks | 37 weeks or labour | 54% | 16% | NR | 29% | 14% | 27% |
| Norman 2016  | +fFN plus any risk factor for PTB history, prior cervical | 1228 | 22 to 24 weeks | 34 weeks or delivery | 6% | 79% | NR | 36% | 20% | 15% |
| Study      | Criteria                                                                                                                                                                                                 | N  | Duration | Pregnancy Outcome | 0% | 100% | NR  | NR  | NR  | NR  | Percentage |
|------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|----------|-------------------|----|------|-----|-----|-----|-----|------------|
| O'Brien 2007 | 18 - 45 yrs old, 16 to 22 weeks gestation, history of sPTB                                                                                                                                          | 659| 18 to < 23 weeks | 37 weeks            | 0% | 100% | NR  | NR  | NR  | 26% |
| Olsen 2000  | history of preterm delivery, 16 - 20 weeks gestation, singleton pregnancy.                                                                                                                             | 232| 20 weeks   | delivery           | 0% | 100% | NR  | NR  | 43% | NR  |
| Otsuki 2016 | CL 25mm or less, 16-26 weeks with or without history of sPTB                                                                                                                                           | 106| 16 to 26 weeks | 37 weeks            | NR | 13%  | NR  | 100%| 5%  | NR  |
| Owen 2009   | 16 to 21 weeks, history of sPTB < 34 and short CL < 25 mm                                                                                                                                               | 302| 16 to 21 weeks | 37 weeks            | 0% | 100% | NR  | 100%| 18% | 57% |
| Pirjani 2017| Singleton pregnancy, 16-24 weeks gestation, CL < 25 mm, asymptomatic of PTL                                                                                                                           | 304| 16 to 24 weeks | 36 weeks            | 66%| NR   | NR  | 100%| NR  | NR  |
| Rai 2009    | Asymptomatic women age 18 - 35 between 18 and 24 weeks gestation, history of sPTB, singleton pregnancy                                                                                               | 150| 18 to 24 weeks | 36 weeks            | 0% | 100% | NR  | NR  | NR  | NR  |
| Rush 1984   | history of sPTB                                                                                                                                                                                             | 194| 15 to 21 weeks | 37 weeks            | 0% | 100% | NR  | 0%  | 0%  | NR  |
| Rust 2001   | 16 - 24 weeks gestation, internal os dilation, membrane prolapse into the endocervial canal but not beyond the external os, shortened CL < 25 mm, and exacerbation of these with fundal pressure                                | 113| 16 to 24 weeks | 36 weeks            | NR | 45%  | NR  | NR  | NR  | NR  |
| Saccone 2017| 18 - 50 yrs of age, singleton pregnancy, CL < or = 25 mm on US at 18 - 23+6 weeks                                                                                                                     | 300| 18 to < 24 weeks | 37 weeks            | 70%| 0%   | 0%  | 100%| 13% | 4%  |
| Saghahi 2011| history of PTB                                                                                                                                                                                             | 100| 16 to 20 weeks | 37 weeks            | 0% | 100% | NR  | NR  | NR  | NR  |
| Shadab 2018 | < 20 weeks' gestation in the current pregnancy; history of preterm birth; women intending to delivery elsewhere                                                                                     | 132| 16 to 20 weeks | 36 weeks            | 0% | 100% | NR  | NR  | NR  | NR  |
and < 12 weeks' gestation were excluded

Shahgheibi 2016 Women considered to be high risk of sPTB including history of preterm labour and uterine malformation. | 100 | 24 weeks | 34 weeks | NR | 9% | NR | NR | NR | NR

Shambhavi 2018 history of sPTB, singleton pregnancy, 16 to 24 weeks' gestation | 100 | 16 to 24 weeks | 37 weeks | 0% | 90% | NR | NR | 0% | NR

To 2004 CL < 15 mm at 22-24 weeks' gestation | 253 | 22 to 24 weeks | 37 weeks | NR | NR | 19% | 100% | 11% | 54%

van Os 2015 CL ≤ 30 mm, no history of sPTB, singleton pregnancy | 80 | 18 to 22 weeks | 34 weeks | 69% | 0% | 0% | 100% | 23% | NR

Vanda 2020 Singleton pregnancy at high risk of PTB; 15-45yrs, one or more risk factors including history of PTB or late miscarriage, short CL 16-18wks. | 166 | unclear | Labour | 40% | 27% | NR | NR | NR | NR

Vermuelen 1999 sPTB in the previous pregnancy with or without PPROM, < 36 weeks's gestation, a viable pregnancy without fetal anomalies | 168 | during week 26 and week 32 gestation | Unclear | 0% | 100% | NR | NR | NR | NR

Wajid 2016 18 to 35 years old, 20 to 24 weeks' gestation with prior history of PTB | 800 | 20 to 24 weeks | 37 weeks | 0% | 100% | NR | NR | NR | NR

Winer 2015 asymptomatic singleton pregnancies from 20(+0) through 31(+6) weeks of gestation with a CL< 25 mm and a history of preterm delivery or cervical surgery or uterine malformation or prenatal DES exposure. | 105 | 24 to 31 weeks | 36 weeks | NR | 56% | NR | 100% | 15% | NR

Abbreviations: GA = gestational age; NR = not reported; PTB = preterm birth; SPTB = spontaneous preterm birth
### Supplementary Table 2: Risk of bias of included studies

| Trial          | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias |
|----------------|---------------------------------------------|-----------------------------------------|--------------------------------------------------------|------------------------------------------------|------------------------------------------|-------------------------------------|-----------|
| Ahuja 2015     | Unclear risk                                | Unclear risk                            | Low risk                                               | Unclear risk                                   | Low risk                                  | Low risk                            | Low risk   |
| Akbari 2009    | Unclear risk                                | Unclear risk                            | High risk                                              | Unclear risk                                   | Low risk                                  | Low risk                            | Low risk   |
| Althuisius 2001| Unclear risk                                | Low risk                                | High risk                                              | Unclear risk                                   | Low risk                                  | Low risk                            | Low risk   |
| Ashoush 2016   | Low risk                                    | Low risk                                | Low risk                                               | Low risk                                       | Low risk                                  | Low risk                            | Low risk   |
| Azargoon 2015  | Low risk                                    | Low risk                                | Low risk                                               | Unclear risk                                   | Low risk                                  | Low risk                            | Low risk   |
| Bafghi 2015    | Low risk                                    | Low risk                                | High risk                                              | Low risk                                       | Low risk                                  | Low risk                            | Low risk   |
| Berghella 2004 | Low risk                                    | Low risk                                | High risk                                              | Unclear risk                                   | Low risk                                  | Low risk                            | Low risk   |
| Blackwell 2020 | Low risk                                    | Low risk                                | Low risk                                               | Low risk                                       | Low risk                                  | Low risk                            | Low risk   |
| Breart 1979    | Low risk                                    | High risk                               | Unclear risk                                           | Unclear risk                                   | Low risk                                  | Low risk                            | Low risk   |
| Cabrera-Garcia 2015 | Low risk                                    | Low risk                                | High risk                                              | Unclear risk                                   | Low risk                                  | Low risk                            | Low risk   |
| Care 2019      | Low risk                                    | Low risk                                | High risk                                              | Unclear risk                                   | Low risk                                  | Low risk                            | Unclear risk |
| Chandiramani 2003 | Low risk                                    | Low risk                                | Low risk                                               | Low risk                                       | Low risk                                  | Low risk                            | Unclear risk |
| Choi 2020      | Low risk                                    | Low risk                                | Unclear risk                                           | Unclear risk                                   | Low risk                                  | Low Risk                            | Low Risk   |
| Crowther 2017  | Low risk                                    | Low risk                                | Low risk                                               | Low risk                                       | Unclear risk                               | Low risk                            | Low risk   |
| da Fonseca 2003 | Low risk                                    | Low risk                                | Low risk                                               | Low risk                                       | Unclear risk                               | Low risk                            | Low risk   |
| Danesh 2010    | Low risk                                    | Low risk                                | Low risk                                               | Unclear risk                                   | High risk                                 | Unclear risk                       | Unclear risk |
| Danti 2014     | Low risk                                    | Low risk                                | Low risk                                               | Low risk                                       | Low risk                                  | Low risk                            | Low risk   |
| Dugoff 2018    | Low risk                                    | Low risk                                | High risk                                              | Unclear risk                                   | Low risk                                  | Low risk                            | Low risk   |
| El-Gharib 2013 | Unclear risk                                | Low risk                                | Low risk                                               | Unclear risk                                   | Low risk                                  | Low risk                            | Unclear risk |
| Elimian 2016   | Low risk                                    | Unclear risk                            | High risk                                              | High risk                                      | Low risk                                  | Un unclear risk                      | Low risk   |
| Ezechi 2004    | Unclear risk                                | Unclear risk                            | High risk                                              | Unclear risk                                   | Low risk                                  | Low risk                            | Low risk   |
| Fonseca 2007   | Low risk                                    | Low risk                                | Low risk                                               | Low risk                                       | Low risk                                  | Low risk                            | Low risk   |
| Glover 2011    | Low risk                                    | Low risk                                | Low risk                                               | Low risk                                       | Low risk                                  | Low risk                            | Low risk   |
| Goya 2012      | Low risk                                    | Low risk                                | High risk                                              | Unclear risk                                   | Low risk                                  | Low risk                            | Low risk   |
| Grobman 2012   | Low risk                                    | Low risk                                | Low risk                                               | Low risk                                       | Low risk                                  | Low risk                            | Low risk   |
| Harper 2010    | Low risk                                    | Low risk                                | Low risk                                               | Low risk                                       | Low risk                                  | Low risk                            | Low risk   |
| Hassan 2011    | Low risk                                    | Low risk                                | Low risk                                               | Low risk                                       | Low risk                                  | Low risk                            | Low risk   |
| Hui 2013       | Low risk                                    | Low risk                                | High risk                                              | Unclear risk                                   | Low risk                                  | Low risk                            | Unclear risk |
| Ibrahim 2010   | Unclear risk                                | Low risk                                | Unclear risk                                           | Low risk                                       | Un unclear risk                           | Low risk                            | Low risk   |
| Ionescu 2011   | Unclear risk                                | Unclear risk                            | High risk                                              | Unclear risk                                   | Low risk                                  | Un unclear risk                      | Low risk   |
| Jabeen 2012    | Unclear risk                                | Unclear risk                            | High risk                                              | Unclear risk                                   | Low risk                                  | Un unclear risk                      | Low risk   |
| Jafarpour 2020 | Low risk                                    | Low risk                                | Unclear risk                                           | Unclear risk                                   | Low risk                                  | Unclear risk                       | Low risk   |
| Johnson 1975   | Unclear risk                                | Low risk                                | Unclear risk                                           | Unclear risk                                   | Low risk                                  | Low risk                            | Low risk   |
| Karbaskan 2016 | Low risk                                    | Unclear risk                            | Unclear risk                                           | Unclear risk                                   | Low risk                                  | Low risk                            | Low risk   |
| Keeler 2009    | Low risk                                    | Low risk                                | High risk                                              | Unclear risk                                   | Low risk                                  | Low risk                            | Un unclear risk |
| Maher 2013     | Low risk                                    | Unclear risk                            | High risk                                              | Unclear risk                                   | Low risk                                  | Low risk                            | Low risk   |
| Majhi 2009     | Low risk                                    | Low risk                                | High risk                                              | Unclear risk                                   | Low risk                                  | Low risk                            | Low risk   |
| Meis 2003 a    | Low risk                                    | Low risk                                | Low risk                                               | Unclear risk                                   | Low risk                                  | Unclear risk                       | Low risk   |
| MRC/RCOG 1993  | Low risk                                    | Low risk                                | High risk                                              | High risk                                      | Low risk                                  | Low risk                            | Low risk   |
| Nicolaides 2016| Low risk                                    | Low risk                                | High risk                                              | Low risk                                       | Low risk                                  | Low risk                            | Low risk   |
| Norman 2016    | Unclear risk                                | Unclear risk                            | Low risk                                               | Unclear risk                                   | Low risk                                  | Unclear risk                       | Low risk   |
| O’Brien 2007   | Low risk                                    | Low risk                                | Low risk                                               | Low risk                                       | Low risk                                  | Low risk                            | Low risk   |
| Olsen 2000     | Low risk                                    | Low risk                                | Low risk                                               | Low risk                                       | Low risk                                  | Unclear risk                       | Low risk   |
| Otsuki 2016    | Low risk                                    | Low risk                                | High risk                                              | Unclear risk                                   | Low risk                                  | Low risk                            | Low risk   |
| Owen 2009      | Low risk                                    | Low risk                                | High risk                                              | Unclear risk                                   | Low risk                                  | Low risk                            | Low risk   |
| Pirjani 2017   | Unclear risk                                | Unclear risk                            | Unclear risk                                           | Unclear risk                                   | Low risk                                  | Low risk                            | Low risk   |
| Study        | Risk Level 1 | Risk Level 2 | Risk Level 3 | Risk Level 4 | Risk Level 5 | Risk Level 6 | Risk Level 7 | Risk Level 8 |
|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|
| Rai 2009     | Unclear risk | Low risk     | Low risk     | Unclear risk | Low risk     | Low risk     | Low risk     | Low risk     |
| Rush 1984    | Unclear risk | Unclear risk | High risk    | Unclear risk | Low risk     | Low risk     | Low risk     | Low risk     |
| Rust 2001    | Unclear risk | Unclear risk | High risk    | Unclear risk | Unclear risk | Low risk     | Low risk     | Unclear risk |
| Saccone 2017 | Low risk     | Low risk     | High risk    | Low risk     | Low risk     | Low risk     | Low risk     | Low risk     |
| Saghafi 2011 | Unclear risk | Unclear risk | High risk    | Unclear risk | Unclear risk | Low risk     | Unclear risk | Unclear risk |
| Shadab 2018  | Low risk     | Low risk     | Low risk     | Low risk     | Low risk     | Low risk     | Low risk     | Low risk     |
| Shambhavi 2018 | Unclear risk | Unclear risk | Low risk     | Unclear risk | Low risk     | Unclear risk | Unclear risk | Unclear risk |
| To 2004      | Low risk     | Low risk     | High risk    | Unclear risk | Low risk     | Low risk     | Low risk     | Low risk     |
| van Os 2015  | Low risk     | Low risk     | Low risk     | Low risk     | Low risk     | Low risk     | Unclear risk | Unclear risk |
| Vanda 2020   | Low risk     | Low risk     | Unclear risk | Unclear risk | Unclear risk | Unclear risk | Unclear risk | Unclear risk |
| Vermuellen 1999 | Low risk    | Low risk     | Low risk     | Low risk     | High risk    | Unclear risk | Unclear risk | Unclear risk |
| Wajid 2016   | Low risk     | Unclear risk | High risk    | Unclear risk | Low risk     | Unclear risk | Unclear risk | Unclear risk |
| Winer 2015   | Low risk     | Low risk     | High risk    | Unclear risk | Low risk     | Low risk     | Low risk     | Unclear risk |
### Supplementary Table 3: Total studies and participants contributing to each outcome

| Study             | Outcomes: Pregnant women | Outcomes: Offspring |
|-------------------|--------------------------|---------------------|
|                   | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| Ahuja 2015        | ✓ | ✓ |   |   |   |   |   | ✓ | ✓ |   |   |   |   |   |   |   |   |   | ✓  |
| Akbari 2009       | ✓ |   |   |   |   |   |   | ✓ | ✓ |   |   |   |   |   |   |   |   |   | ✓  |
| Althuisius 2001   | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |   |   |   |   |   |   |   |   |   |   |
| Ashoush 2017      | ✓ | ✓ |   |   |   |   |   | ✓ | ✓ | ✓ |   |   |   |   |   |   |   |   |   |
| Azargoon 2016     | ✓ | ✓ |   |   |   |   |   | ✓ | ✓ | ✓ |   |   |   |   |   |   |   |   |   |
| Bafghi 2015       | ✓ |   |   |   |   |   |   | ✓ | ✓ |   |   |   |   |   |   |   |   |   |   |
| Berghella 2004    | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |   |   |   |   |   |   |   |   |   |   |
| Blackwell 2020    | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |   |   |   |   |   |   |   |
| Breart 1979       | ✓ |   |   |   |   |   |   | ✓ | ✓ |   |   |   |   |   |   |   |   |   |   |
| Cabrera-Garcia 2015 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |   |   |   |   |   |   |   |
| Care 2019         | ✓ |   | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |   |   |   |   |   |   |   |   |   |   |
| Cetingoz 2011     | ✓ | ✓ |   |   |   |   |   |   |   | ✓ | ✓ | ✓ |   |   |   |   |   |   |   |
| Chandiramani 2010 | ✓ | ✓ |   |   |   |   |   | ✓ | ✓ | ✓ |   |   |   |   |   |   |   |   |   |
| Choi 2020         | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |   |   |   |   |   |   |   |   |   |   |
| Crowther 2017     | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |   |   |   |   |   |   |   |   |   |   |
| da Fonseca 2003   | ✓ | ✓ |   |   |   |   |   | ✓ | ✓ | ✓ |   |   |   |   |   |   |   |   |   |
| Danesh 2010       | ✓ |   |   |   |   |   |   | ✓ | ✓ |   |   |   |   |   |   |   |   |   |   |
| Danti 2014        | ✓ |   |   |   |   |   |   | ✓ | ✓ |   |   |   |   |   |   |   |   |   |   |
| Dugoff 2018       | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |   |   |   |   |   |   |   |   |   |   |
| El-Gharib 2013    | ✓ |   |   |   |   |   |   | ✓ | ✓ | ✓ |   |   |   |   |   |   |   |   |   |
| Elimian 2016      | ✓ | ✓ |   |   |   |   |   | ✓ | ✓ | ✓ |   |   |   |   |   |   |   |   |   |
| Ezeki 2004        | ✓ |   | ✓ |   |   |   |   | ✓ | ✓ | ✓ |   |   |   |   |   |   |   |   |   |
| Fonseca 2007      | ✓ |   | ✓ |   | ✓ | ✓ | ✓ | ✓ | ✓ |   |   |   |   |   |   |   |   |   |   |
| Glover 2011       | ✓ |   |   |   |   |   |   | ✓ | ✓ | ✓ |   |   |   |   |   |   |   |   |   |
| Goya 2012         | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |   |   |   |   |   |   |   |   |   |   |
| Grobman 2012      | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |   |   |   |   |   |   |   |   |   |   |
| Harper 2010       | ✓ | ✓ |   |   |   |   |   | ✓ | ✓ | ✓ |   |   |   |   |   |   |   |   |   |
| Hassan 2011       | ✓ | ✓ |   |   |   |   |   | ✓ | ✓ | ✓ |   |   |   |   |   |   |   |   |   |
| Hui 2013          | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |   |   |   |   |   |   |   |   |   |   |
| Ibrahim 2010      | ✓ |   |   |   |   |   |   | ✓ | ✓ | ✓ |   |   |   |   |   |   |   |   |   |
| Ionescu 2011      | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |   |   |   |   |   |   |   |   |   |   |
| Jabeen 2012       | ✓ | ✓ |   |   |   |   |   | ✓ | ✓ | ✓ |   |   |   |   |   |   |   |   |   |
| Jafapour 2020     | ✓ |   |   |   |   |   |   | ✓ | ✓ | ✓ |   |   |   |   |   |   |   |   |   |
| Johnson 1975      | ✓ |   |   |   |   |   |   | ✓ | ✓ | ✓ |   |   |   |   |   |   |   |   |   |
| Karbasian 2016    | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |   |   |   |   |   |   |   |   |   |   |
| Keeler 2009       | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |   |   |   |   |   |   |   |   |   |   |
| Study                      | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
|----------------------------|---|---|---|---|---|---|---|---|---|---|---|
| Maher 2013                 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Majhi 2009                 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Meis 2003a                 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| MRC/RCOG 1993              | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Nicolaides 2016            | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Norman 2016                | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| O'Brien 2007               | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Olsen 2000                 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Otsuki 2016                | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Owen 2009                  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Pirjani 2017               | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Rai 2009                   | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Rush 1984                  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Rust 2001                  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Saccone 2017               | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Shagha 2011                | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Shadab 2018                | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Shahgheibi 2016            | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Shambhavi 2018             | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| To 2004                    | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| van Os 2015                | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Vanda 2020                 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Vermuelen 1999             | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Wajid 2016                 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Winer 2015                 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **Total trials**           | 55 | 41 | 9 | 25 | 5 | 24 | 19 | 32 | 36 | 29 | 23 | 27 | 14 | 28 | 4 | 23 | 23 | 25 |

| Study                      | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
|----------------------------|---|---|---|---|---|---|---|---|---|---|---|
| **Total participants**     | 13,913 | 13,345 | 4,057 | 8,122 | 3,766 | 7,687 | 8,056 | 12,211 | 11,890 | 6,569 | 7,233 | 9,714 | 7,469 | 10,641 | 2,034 | 10,443 | 8,566 | 8,400 |

| Study                      | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
|----------------------------|---|---|---|---|---|---|---|---|---|---|---|
| **N (%) of participants**  | 4,563 | 3 | 2,222 | 467 | 759 | 0 | 788 | 252 | 511 | 344 | 1886 | 894 | 151 | 184 | 7 | 139 | 219 | 1,490 |

| Study                      | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
|----------------------------|---|---|---|---|---|---|---|---|---|---|---|
| **Total (%)**              | 32.7% | (0%) | 16.7% | (10.3%) | 9.3% | (3.1%) | 0% | (4.2%) | (2.9%) | NA | (26.1%) | (9.2%) | (2.0%) | (1.7%) | (0.3%) | (1.3%) | (2.6%) | (17.7%) |

1. See Supplementary File 3 for list of outcomes for pregnant women and offspring
### Supplementary Table 4: Treatments included in the analysis of each outcome (number of trials)

| Treatment                                      | Outcomes: Pregnant women | Outcomes: Offspring |
|------------------------------------------------|--------------------------|---------------------|
| Control: Placebo or no treatment               | 36 26 6 14 4 15 12      | 12 21 4 17 18      |
| Progesterone: vaginal                          | 23 19 3 10 2 11 8       | 12 7 8 3 14 10 14  |
| 17alpha hydroxyprogesterone caproate (17-OHPC)| 20 11 2 5 1 4 5         | 7 9 9 8 7 1 7 9 2  |
| Progesterone: oral                             | 4 1 1 1 1 1 1 1 1 1 2  |                  |
| Cerclage: McDonald                             | 4 2 1 1 1 1 1 1 1 1 1  |                  |
| Cerclage: Shirodkar                            | 1 1 1 1 1 1 1 1 1 1 1  |                  |
| Cerclage: Unspecified                         | 4 3 1 1 1 1 1 1 1 1 1  |                  |
| Pessary                                        | 6 6 5 7 2 6 5           | 6 5 3 4 6 2 6 5 6 3 |
| Antibiotics: Clindamycin                       | 1 1 1 1 1 1 1 1 1 1 1  |                  |
| Bed rest                                       | 2 2 1* 2 1* 1* 1* 1* 1* |                  |
| Tocolytics: Nifedipine                         | 1 1 1 1 1 1 1 1 1 1 1  |                  |
| Nutritional supplements: Zinc                  | 1 1 1 1 1 1 1 1 1 1 1  |                  |
| Omega 3 / Fish Oil                            | 1 1 1 1 1 1 1 1 1 1 1  |                  |
| Pessary + vaginal progesterone                 | 1 1 1 1 1 1 1 1 1 1 1  |                  |
| McDonald cerclage + clindamycin                | 1* 1* 1* 1* 1* 1* 1* 1* |                  |
| Cerclage (Shirodkar) + Erythromycin            | 1 1 1 1 1 1 1 1 1 1 1  |                  |
| Omega 3 + 17-OHPC                             | 1 1 1 1 1 1 1 1 1 1 1  |                  |
| Clindamycin + 17-OHPC                         | 1* 1* 1* 1* 1* 1* 1* 1* |                  |
| Cerclage (McDonald) + Bed Rest                 | 1 1 1* 1* 1* 1* 1* 1* 1* 1|                  |
| Cerclage (McDonald) + Bed Rest + Amoxicillin + Metronidazole | 1* 1* 1* 1* 1* 1* 1* 1* 1* 1* 1* 1|                  |
| Bed Rest + Amoxicillin + Metronidazole         | 1* 1* 1* 1* 1* 1* 1* 1* 1* 1* 1* 1|                  |

1. See Supplementary File 3 for list of outcomes for pregnant women and offspring. Treatments marked with an asterisk (*) are disconnected from the network for the outcome.
## Supplementary Table 5: Network meta-analysis models and model fit statistics

| Outcome | Clinical heterogeneity observed? | Continuity correction used? | Model | Number of data points | Posterior mean residual deviance | pD | DIC | Between-trial variance (Tau-squared) |
|---------|----------------------------------|-----------------------------|-------|-----------------------|---------------------------------|----|-----|-------------------------------------|
| **Outcomes for pregnant women** |                                  |                             |       |                       |                                 |    |     |                                     |
| 1. preterm birth <37 weeks' gestation | No                               | No                          | FE, consistency | 108 | 222.35 | 68.38 | 290.73 | NA |
|                                   | RE, consistency                   |                             | 108 | 110.88 | 93.18 | 204.06 | 0.28 (0.14 to 0.57) |
|                                   | FE, inconsistency                 |                             | 108 | 211.58 | 72.32 | 283.89 | NA |
|                                   | RE, inconsistency                 |                             | 108 | 111.52 | 95.36 | 206.88 | 0.31 (0.15 to 0.64) |
| 2. preterm birth <34 weeks' gestation | No                               | No                          | FE, consistency | 81 | 123.39 | 56.64 | 180.03 | NA |
|                                   | RE, consistency                   |                             | 81 | 82.56 | 70.53 | 153.08 | 0.22 (0.07 to 0.60) |
|                                   | FE, inconsistency                 |                             | 81 | 126.27 | 59.68 | 185.95 | NA |
|                                   | RE, inconsistency                 |                             | 81 | 81.75 | 72.78 | 154.53 | 0.28 (0.10 to 0.77) |
| 3. spontaneous preterm birth <34 weeks' gestation | Yes                             | No                          | FE, consistency | 16 | 41.86 | 11.02 | 52.88 | NA |
|                                   | RE, consistency                   |                             | 16 | 15.90 | 15.34 | 31.24 | 0.83 (0.17 to 6.42) |
|                                   | FE, inconsistency                 |                             | 16 | 40.70 | 13.16 | 53.86 | NA |
|                                   | RE, inconsistency                 |                             | 16 | 16.21 | 16.00 | 32.21 | 1.55 (0.22 to 16.5) |
| 4. preterm birth <28 weeks' gestation | No                               | Yes                         | FE, consistency | 48 | 54.18 | 34.24 | 84.42 | NA |
|                                   | RE, consistency                   |                             | 48 | 54.18 | 34.24 | 84.42 | NA |
|                                   | FE, inconsistency                 |                             | 48 | 54.18 | 34.24 | 84.42 | NA |
|                                   | RE, inconsistency                 |                             | 48 | 54.18 | 34.24 | 84.42 | NA |
| 5. maternal death | Yes                             | Yes                         | FE, consistency | 10 | 10.96 | 10.96 | 21.92 | NA |
|                                   | RE, consistency                   |                             | 10 | 11.69 | 11.69 | 23.38 | 4.00 (0.01 to 23.8) |
|                                   | FE, inconsistency                 |                             | NA | NA | NA | NA | NA |
|                                   | RE, inconsistency                 |                             | NA | NA | NA | NA | NA |
| 6. preterm prelabour rupture of membranes | No                               | Yes                         | FE, consistency | 43 | 55.49 | 29.43 | 84.92 | NA |
|                                   | RE, consistency                   |                             | 43 | 48.88 | 35.06 | 83.95 | 0.14 (0.00 to 1.17) |
|                                   | FE, inconsistency                 |                             | 43 | 54.39 | 32.71 | 87.09 | NA |
|                                   | RE, inconsistency                 |                             | 43 | 47.18 | 38.14 | 85.32 | 0.23 (0.00 to 1.76) |
| Outcomes for offspring | No | Yes |
|------------------------|----|-----|
| **7. maternal infection** | No | Yes |
| FE, consistency | 35 | 31.86 | 24.00 | 55.86 | NA |
| RE, consistency | 35 | 32.08 | 25.78 | 57.87 | 0.05 (0.00 to 0.79) |
| FE, inconsistency | 35 | 34.28 | 27.77 | 62.05 | NA |
| RE, inconsistency | 35 | 34.35 | 29.36 | 63.71 | 0.06 (0.00 to 1.22) |
| **Outcomes for offspring** | | | | |
| **1. perinatal death** | No | No |
| FE, consistency | 61 | 124.06 | 38.75 | 162.81 | NA |
| RE, consistency | 61 | 121.29 | 42.60 | 163.89 | 0.07 (0.00 to 0.66) |
| FE, inconsistency | 61 | 125.03 | 40.94 | 165.97 | NA |
| RE, inconsistency | 61 | 120.90 | 45.47 | 166.37 | 0.13 (0.00 to 1.06) |
| **2. neonatal death** | No | Yes |
| FE, consistency | 69 | 66.09 | 47.43 | 113.53 | NA |
| RE, consistency | 69 | 63.67 | 51.14 | 114.81 | 0.09 (0.00 to 0.67) |
| FE, inconsistency | 69 | 68.23 | 49.71 | 117.94 | NA |
| RE, inconsistency | 69 | 65.09 | 53.74 | 118.83 | 0.12 (0.00 to 0.85) |
| **3. gestational age at birth** | No | No |
| FE, consistency | 57 | 38.78 | 37.93 | 76.71 | NA |
| RE, consistency | 57 | 39.78 | 39.05 | 78.83 | 0.72 (0.00 to 9.07) |
| FE, inconsistency | 57 | 39.70 | 38.99 | 78.68 | NA |
| RE, inconsistency | 57 | 40.52 | 39.89 | 80.41 | 0.73 (0.00 to 9.99) |
| **4. low birthweight <2500 g** | No | No |
| FE, consistency | 44 | 86.30 | 31.18 | 117.49 | NA |
| RE, consistency | 44 | 44.61 | 40.82 | 85.42 | 0.41 (0.13 to 1.26) |
| FE, inconsistency | 44 | 87.40 | 33.18 | 120.58 | NA |
| RE, inconsistency | 44 | 44.56 | 41.77 | 86.33 | 0.51 (0.16 to 1.71) |
| **5. neonatal respiratory distress syndrome** | No | No |
| FE, consistency | 54 | 81.78 | 35.66 | 117.44 | NA |
| RE, consistency | 54 | 57.43 | 45.95 | 103.38 | 0.26 (0.05 to 0.87) |
| FE, inconsistency | 54 | 83.82 | 37.73 | 121.55 | NA |
| RE, inconsistency | 54 | 57.33 | 47.78 | 105.11 | 0.33 (0.08 to 1.11) |
| **6. neonatal pulmonary disease** | No | No |
| FE, consistency | 28 | 27.38 | 19.60 | 46.98 | NA |
| RE, consistency | 28 | 27.29 | 21.50 | 48.79 | 0.08 (0.00 to 1.55) |
| FE, inconsistency | 28 | 28.26 | 20.67 | 48.93 | NA |
| RE, inconsistency | 28 | 28.04 | 22.59 | 50.63 | 0.11 (0.00 to 2.30) |
### Table 1: Clinical Heterogeneity and Model Specifications

| Outcome                                    | No       | Yes       | FE, consistency | RE, consistency | FE, inconsistency | RE, inconsistency |
|--------------------------------------------|----------|-----------|----------------|----------------|------------------|------------------|
| 7. intraventricular haemorrhage            | No       | Yes       | 56             | 58.15          | 39.45            | 97.59            | NA               |
|                                            |          |           |                | 56             | 57.36            | 41.68            | 99.04            | 0.17 (0.00 to 1.32) |
|                                            |          |           | 56             | 54.98          | 43.65            | 98.64            | NA               |
|                                            |          |           | 56             | 55.20          | 45.19            | 100.39           | 0.14 (0.00 to 1.37) |
| 8. periventricular leukomalacia            | No       | No        | 8              | 8.56           | 5.72             | 14.28            | NA               |
|                                            | 8        |           | 6.63           | 5.31           | 11.93            | 0.05             | 0.04 to 24.2     |
|                                            | NA       |           | NA             | NA             | NA               | NA               | NA               |
| 9. necrotising enterocolitis               | No       | Yes       | 46             | 47.40          | 34.06            | 81.46            | NA               |
|                                            | 46       |           | 45.12          | 37.33          | 82.45            | 0.16             | 0.00 to 1.32     |
|                                            | 46       |           | 46.87          | 36.41          | 83.28            | NA               | 0.13             | 0.00 to 1.34     |
| 10. proven neonatal sepsis                 | No       | Yes       | 45             | 51.10          | 31.33            | 82.43            | NA               |
|                                            | 45       |           | 44.36          | 36.61          | 80.97            | 0.25             | 0.00 to 1.33     |
|                                            | 45       |           | 53.17          | 33.62          | 86.79            | NA               |                  |
|                                            | 45       |           | 45.64          | 39.19          | 84.83            | 0.32             | 0.01 to 1.66     |
| 11. admission to neonatal intensive care   | No       | No        | 50             | 72.22          | 33.65            | 105.87           | NA               |
| unit                                       | 50       |           | 54.78          | 43.12          | 97.90            | 0.17             | 0.01 to 0.65     |
|                                            | 50       |           | 72.27          | 35.69          | 107.96           | NA               |                  |
|                                            | 50       |           | 51.89          | 44.39          | 96.27            | 0.21             | 0.04 to 0.75     |

DIC=deviance information criterion; FE=fixed effects; pD=effective number of parameters; RE=random effects

1. We judged clinical heterogeneity by visual inspection of trial and participant characteristics (Supplementary Table 1). Where we considered clinical heterogeneity to be present (important differences in proportions of women with short cervix or a history of pre-term birth), random-effects models were used (regardless of model fit).
2. Continuity corrections (i.e. adding 0.5 to all event counts) were used where model convergence issues were encountered, likely due to zero cell counts.
3. Values highlighted in **bold** indicate the model used for each analysis. Results of other models were similar for each outcome, and available from the authors on request. Where model fit was similar and no clinical heterogeneity was present, the simplest model (fixed-effects assumed to be simpler than random-effects and consistency models assumed to be simpler than inconsistency models) was used.
4. Between trial variance (median and 95% credible interval of tau-squared) calculated only for random-effects models.
5. No closed loops were present within networks, therefore only consistency models could be considered.
Supplementary Table 6: Probability each treatment is the best (outcomes for pregnant women)\textsuperscript{1}

| Treatment | 1. preterm birth < 37 weeks’ gestation | 2. preterm birth < 34 weeks’ gestation | 3. spontaneous preterm birth < 34 weeks’ gestation | 4. preterm birth < 28 weeks’ gestation | 5. maternal death | 6. preterm prelabour rupture of membranes | 7. maternal infection |
|-----------|----------------------------------------|----------------------------------------|----------------------------------------|----------------------------------------|-----------------|------------------------------------------|-------------------|
| Control: Placebo or no treatment   | 0.0%                                   | 0.0%                                   | 4.7%                                   | 0.0%                                   | 7.8%            | 0.1%                                     | 6.9%              |
| Progesterone: vaginal               | 0.3%                                   | 0.2%                                   | 17.5%                                  | 0.0%                                   | 14.5%           | 2.7%                                     | 0.8%              |
| Progesterone: oral                  | 8.1%                                   | 3.6%                                   | NA                                     | 63.0%                                  | NA              | 31.9%                                    | 62.7%             |
| 17-OHPC                              | 0.1%                                   | 0.0%                                   | 39.4%                                  | 0.7%                                   | 31.4%           | 0.9%                                     | 1.4%              |
| Cerclage: McDonald                  | 0.4%                                   | 0.1%                                   | NA                                     | 0.6%                                   | NA              | 1.2%                                     | NA                |
| Cerclage: Shirodkar                 | 26.0%                                  | 71.0%                                  | NA                                     | 15.9%                                  | NA              | NA                                       | NA                |
| Cerclage: Unspecified               | 0.3%                                   | 0.3%                                   | NA                                     | 0.9%                                   | 28.1%           | 0.6%                                     | 2.3%              |
| Pessary                              | 0.8%                                   | 0.0%                                   | 38.4%                                  | 0.2%                                   | 18.1%           | 28.2%                                    | 18.2%             |
| Omega 3 / Fish Oil                  | 5.7%                                   | 10.3%                                  | NA                                     | NA                                     | NA              | NA                                       | NA                |
| Nutritional supplements: Zinc       | 8.5%                                   | NA                                     | NA                                     | NA                                     | NA              | NA                                       | NA                |
| Bed rest                            | 3.2%                                   | 1.0%                                   | NA                                     | 8.5%                                   | NA              | NA                                       | NA                |
| Antibiotics: Clindamycin            | 0.2%                                   | 0.0%                                   | NA                                     | NA                                     | NA              | NA                                       | NA                |
| Tocolytics: Nifedipine              | 11.3%                                  | NA                                     | NA                                     | NA                                     | NA              | NA                                       | NA                |
| Pessary + vaginal progestosterone   | 6.4%                                   | 1.1%                                   | NA                                     | NA                                     | NA              | 31.2%                                    | 7.8%              |
| McDonald cerclage + clindamycin     | NA                                     | 0.2%                                   | NA                                     | NA                                     | NA              | NA                                       | NA                |
| Cerclage (Shirodkar) + Erythromycin | NA                                     | 0.3%                                   | NA                                     | 0.8%                                   | NA              | 3.3%                                     | NA                |
| Clindamycin + 17-OHPC               | NA                                     | 1.2%                                   | NA                                     | NA                                     | NA              | NA                                       | NA                |
| Omega 3 + 17-OHPC                   | 8.2%                                   | 0.9%                                   | NA                                     | NA                                     | NA              | NA                                       | NA                |
| Cerclage (McDonald) + Bed Rest      | 20.6%                                  | 9.4%                                   | NA                                     | 9.4%                                   | NA              | NA                                       | NA                |

Abbreviations: 17-OHPC= 17-alpha hydroxyprogesterone caproate; NA=not applicable (treatment not included in the network)

1. Values highlighted in \textbf{bold} indicate the treatment with the highest probability of being the best for the outcome.
**Supplementary Table 7: Ranking of treatments (outcomes for pregnant women)**

| Treatment                                                                 | 1. preterm birth < 37 weeks' gestation | 2. preterm birth < 34 weeks' gestation | 3. spontaneous preterm birth < 34 weeks' gestation | 4. preterm birth < 28 weeks' gestation | 5. maternal death | 6. preterm prelabour rupture of membranes | 7. maternal infection |
|---------------------------------------------------------------------------|----------------------------------------|----------------------------------------|--------------------------------------------------|----------------------------------------|------------------|---------------------------------------------|-----------------------|
| Control: Placebo or no treatment                                          | 14 (10 to 16)                          | 13 (9 to 16)                           | 3 (1 to 4)                                       | 8 (5 to 11)                            | 3 (1 to 5)      | 5 (3 to 7)                                  | 3 (1 to 4)            |
| Progesterone: vaginal                                                     | 7 (3 to 11)                            | 6 (3 to 11)                           | 3 (1 to 4)                                       | 7 (3 to 10)                            | 3 (1 to 5)      | 4 (1 to 6)                                  | 5 (2 to 6)            |
| Progesterone: oral                                                       | 5 (1 to 12)                            | 5 (1 to 15)                           | NA                                               | 1 (1 to 8)                             | NA              | 2 (1 to 7)                                  | 1 (1 to 5)            |
| 17-OHPC                                                                  | 8 (4 to 12)                            | 9 (5 to 14)                           | 2 (1 to 4)                                       | 5 (2 to 10)                            | 3 (1 to 5)      | 6 (2 to 8)                                  | 4 (2 to 6)            |
| Cerclage: McDonald                                                      | 9 (3 to 14)                            | 9 (3 to 16)                           | NA                                               | 5 (2 to 9)                             | NA              | 8 (2 to 9)                                  | NA                    |
| Cerclage: Shirodkar                                                      | 3 (1 to 15)                            | 1 (1 to 10)                           | NA                                               | 5 (1 to 11)                            | NA              | NA                                          | NA                    |
| Cerclage: Unspecified                                                   | 12 (4 to 16)                           | 9 (3 to 15)                           | NA                                               | 9 (2 to 11)                            | 3 (1 to 5)      | 9 (3 to 9)                                  | 6 (2 to 7)            |
| Pessary                                                                  | 8 (2 to 13)                            | 9 (4 to 14)                           | 2 (1 to 4)                                       | 6 (2 to 10)                            | 3 (1 to 5)      | 2 (1 to 6)                                  | 3 (1 to 6)            |
| Omega 3 / Fish Oil                                                       | 8 (1 to 16)                            | 4 (1 to 14)                           | NA                                               | NA                                    | NA              | NA                                          | NA                    |
| Nutritional supplements: Zinc                                            | 8 (1 to 16)                            | NA                                    | NA                                               | NA                                    | NA              | NA                                          | NA                    |
| Bed rest                                                                | 8 (1 to 16)                            | 5 (2 to 16)                           | NA                                               | 5 (1 to 11)                            | NA              | NA                                          | NA                    |
| Antibiotics: Clindamycin                                                 | 15 (5 to 16)                           | 16 (9 to 17)                          | NA                                               | NA                                    | NA              | NA                                          | NA                    |
| Tocolytics: Nifedipine                                                  | 8 (1 to 16)                            | NA                                    | NA                                               | NA                                    | NA              | NA                                          | NA                    |
| Pessary + vaginal progesterone                                           | 9 (1 to 16)                            | 11 (2 to 17)                          | NA                                               | NA                                    | 3 (1 to 9)      | 7 (1 to 7)                                  | NA                    |
| McDonald Cerclage + Clindamycin                                         | NA                                    | 16 (5 to 17)                          | NA                                               | NA                                    | NA              | NA                                          | NA                    |
| Cerclage (Shirodkar) + Erythromycin                                     | NA                                    | 11 (3 to 16)                          | NA                                               | 6 (2 to 11)                            | NA              | 7 (1 to 9)                                  | NA                    |
| Clindamycin + 17-OHPC                                                   | NA                                    | 13 (2 to 17)                          | NA                                               | NA                                    | NA              | NA                                          | NA                    |
| Omega 3 + 17-OHPC                                                       | 6 (1 to 15)                            | 9 (2 to 16)                           | NA                                               | NA                                    | NA              | NA                                          | NA                    |
| Cerclage (McDonald) + Bed Rest                                           | 5 (1 to 16)                            | 4 (1 to 17)                           | NA                                               | 6 (1 to 11)                            | NA              | NA                                          | NA                    |

*Abbreviations: 17-OHPC= 17alpha hydroxyprogesterone caproate; NA=not applicable (treatment not included in the network)*

1. Ranks presented as Median and 95% credible interval. A CrI is interpreted as the interval where there is a 95% probability that the values of the MD (or OR) will lie. Values highlighted in **bold** indicate the treatment with the highest rankings.
### Supplementary Table 8: Probability each treatment is the best (outcomes for offspring)¹

| Treatment                                      | 1. perinatal death | 2. neonatal death | 3. GA at birth | 4. low birthweight < 2500 g | 5. neonatal RDS | 6. neonatal pulmonary disease | 7. IVH | 8. PVL | 9. necrotising enterocolitis | 10. proven neonatal sepsis | 11. admission to neonatal ICU |
|-----------------------------------------------|--------------------|-------------------|----------------|-----------------------------|----------------|-------------------------------|-------|-------|----------------------------|----------------------------|---------------------------|
| Control: Placebo or no treatment              | 0.0%              | 0.0%              | 1.9%           | 0.0%                        | 0.8%           | 0.0%                          | 46.7% | 0.0% | 0.0%                       | 0.0%                       | 0.0%                      |
| Progesterone: vaginal                         | 10.4%             | 5.3%              | 0.4%           | 1.9%                        | 1.6%           | 5.8%                          | 0.2%  | 49.7% | 0.4%                       | 36.4%                      | 0.0%                      |
| Progesterone: oral                            | NA                | 11.9%             | 4.8%           | 30.1%                       | 22.5%          | 24.9%                         | 1.0%  | 3.6%  | 18.0%                      | NA                         | 13.3%                     |
| 17-OHPC                                       | 2.0%              | 0.0%              | 0.9%           | 0.4%                        | 0.4%           | NA                           | 0.4%  | NA    | 14.7%                      | 4.5%                       | 0.0%                      |
| Cerclage: McDonald                            | 27.3%             | 0.6%              | 4.6%           | 7.6%                        | 2.0%           | NA                           | 45.4% | NA    | 10.1%                      | NA                         | 76.2%                     |
| Cerclage: Shirodkar                           | NA                | 45.3%             | 6.9%           | NA                          | NA             | NA                           | NA    | NA    | NA                         | NA                         | NA                        |
| Cerclage: Unspecified                         | 2.5%              | 0.5%              | 23.1%          | 4.2%                        | 52.8%          | NA                           | 4.3%  | NA    | 5.2%                       | NA                         | NA                        |
| Pessary                                       | 2.0%              | 0.1%              | 4.3%           | 3.5%                        | 1.1%           | 30.9%                        | 0.0%  | NA    | 0.2%                       | 0.7%                       | 0.0%                      |
| Omega 3 / Fish Oil                            | NA                | NA                | 11.5%          | NA                          | NA             | NA                           | NA    | NA    | NA                         | NA                         | NA                        |
| Nutritional supplements: Zinc                 | NA                | NA                | 14.1%          | NA                          | NA             | NA                           | NA    | NA    | NA                         | NA                         | NA                        |
| Bed rest                                      | NA                | 2.0%              | 16.4%          | NA                          | NA             | NA                           | NA    | NA    | NA                         | NA                         | NA                        |
| Antibiotics: Clindamycin                      | 2.4%              | NA                | NA             | NA                          | NA             | NA                           | NA    | 0.0%  | NA                         | NA                         | NA                        |
| Tocolytics: Nifedipine                        | NA                | NA                | 11.0%          | NA                          | 18.8%          | NA                           | 33.9% | NA    | NA                         | 9.2%                       | NA                        |
| Pessary + vaginal progesterone                | 16.4%             | 23.6%             | NA             | 6.9%                        | NA             | NA                           | NA    | NA    | NA                         | NA                         | 0.9%                      |
| McDonald cerclage + clindamycin               | 0.5%              | NA                | NA             | NA                          | NA             | NA                           | NA    | NA    | NA                         | NA                         | NA                        |
| Cerclage (Shirodkar) + Erythromycin           | 19.0%             | 0.5%              | 0.2%           | NA                          | NA             | 24.4%                        | 13.7% | NA    | 0.8%                       | NA                         | NA                        |
| Omega 3 + 17-OHPC                             | 17.6%             | NA                | NA             | 14.9%                       | 0.9%           | 13.2%                        | 1.1%  | NA    | 51.4%                      | 7.2%                       | 0.4%                      |
| Cerclage (McDonald) + Bed Rest                 | NA                | 10.2%             | NA             | NA                          | NA             | NA                           | NA    | NA    | NA                         | NA                         | NA                        |

Abbreviations: 17-OHPC= 17alpha hydroxyprogesterone caproate; GA=gestational age, ICU=intensive care unit; IVH=intraventricular haemorrhage; NA=not applicable (treatment not included in the network); PVL= periventricular leukomalacia; RDS=respiratory distress syndrome

¹ Values highlighted in bold indicate the treatment with the highest probability of being the best for the outcome.
### Supplementary Table 9: Ranking of treatments (outcomes for offspring)

| Treatment                          | 1. perinatal death | 2. neonatal death | 3. GA at birth | 4. low birthweight < 2500 g | 5. neonatal RDS | 6. neonatal pulmonary disease | 7. IVH | 8. PVL | 9. necrotising enterocolitis | 10. proven neonatal sepsis | 11. admission to neonatal ICU |
|-----------------------------------|--------------------|-------------------|----------------|-----------------------------|----------------|-----------------------------|-------|-------|-----------------------------|---------------------------|----------------------------|
| Control: Placebo or no treatment  | 8 (5 to 10)        | 10 (7 to 12)      | 4 (2 to 8)     | 8 (6 to 10)                 | 7 (5 to 9)     | 4 (2 to 6)                   | 8 (5 to 10) | 2 (1 to 3) | 6 (4 to 7)                 | 5 (3 to 7)                 | 7 (5 to 9)                  |
| Progesterone: vaginal             | 3 (1 to 7)         | 4 (1 to 7)        | 8 (3 to 12)    | 5 (2 to 8)                  | 4 (2 to 6)     | 4 (1 to 6)                   | 5 (3 to 8) | 2 (1 to 3) | 4 (2 to 7)                 | 2 (1 to 4)                 | 4 (3 to 6)                  |
| Progesterone: oral                | NA                 | 3 (1 to 7)        | 7 (1 to 13)    | 2 (1 to 10)                 | 2 (1 to 8)     | 2 (1 to 5)                   | 5 (2 to 10) | 3 (1 to 3) | 3 (1 to 7)                 | NA                        | 2 (1 to 4)                  |
| 17-OHPC                           | 5 (2 to 9)         | 7 (3 to 10)       | 8 (2 to 12)    | 6 (2 to 9)                  | 5 (2 to 8)     | NA                          | 5 (2 to 9) | NA     | 2 (1 to 5)                 | 3 (1 to 5)                 | 6 (3 to 8)                  |
| Cerclage: McDonald                | 2 (1 to 8)         | 8 (2 to 12)       | 8 (1 to 13)    | 5 (1 to 10)                 | 7 (2 to 9)     | NA                          | 2 (1 to 10) | NA     | 6 (1 to 8)                 | NA                        | 1 (1 to 4)                  |
| Cerclage: Shirodkar               | NA                 | 2 (1 to 12)       | 10 (1 to 13)   | NA                          | NA            | NA                          | NA     | NA     | NA                          | NA                        | NA                         |
| Cerclage: Unspecified             | 5 (1 to 9)         | 7 (2 to 11)       | 11 (1 to 13)   | 7 (1 to 10)                 | 1 (1 to 7)     | NA                          | 5 (1 to 10) | NA     | 8 (1 to 8)                 | 1 (1 to 7)                 | NA                         |
| Pessary                           | 7 (2 to 10)        | 9 (4 to 12)       | 8 (1 to 13)    | 5 (1 to 9)                  | 5 (2 to 8)     | 2 (1 to 6)                   | 8 (4 to 10) | NA     | 6 (3 to 8)                 | 4 (2 to 6)                 | 6 (3 to 9)                  |
| Omega 3 / Fish Oil                | NA                 | NA                | 7 (1 to 13)    | NA                          | NA            | NA                          | NA     | NA     | NA                          | NA                        | NA                         |
| Nutritional supplements: Zinc     | NA                 | NA                | 5 (1 to 13)    | 3 (1 to 10)                 | NA            | NA                          | NA     | NA     | NA                          | NA                        | NA                         |
| Bed rest                          | NA                 | 8 (2 to 12)       | 8 (1 to 13)    | NA                          | NA            | NA                          | NA     | NA     | NA                          | NA                        | NA                         |
| Antibiotics: Clindamycin          | 10 (2 to 11)       | NA                | NA            | NA                          | NA            | NA                          | NA     | NA     | NA                          | NA                        | 8 (7 to 8)                  |
| Tocolytics: Nifedipine            | NA                 | NA                | 5 (1 to 12)    | NA                          | 7 (1 to 9)     | 2 (1 to 10)                 | NA     | NA     | NA                          | NA                        | 7 (1 to 9)                  |
| Pessary + vaginal progesterone    | 9 (1 to 11)        | 4 (1 to 12)       | NA            | 7 (1 to 10)                 | NA            | NA                          | NA     | NA     | NA                          | 8 (2 to 9)                 | NA                         |
| McDonald cerclage + clindamycin   | 11 (4 to 11)       | NA                | NA            | NA                          | NA            | NA                          | NA     | NA     | NA                          | NA                        | NA                         |
| Cerclage (Shirodkar) + Erythromycin| 4 (1 to 10)      | 9 (3 to 12)       | 7 (3 to 11)   | NA                          | 4 (1 to 6)     | 3 (1 to 10)                 | NA     | NA     | 7 (3 to 8)                 | NA                        | NA                         |
| Omega 3 + 17-OHPC                 | 4 (1 to 9)         | NA                | NA            | 4 (1 to 10)                 | 8 (2 to 9)     | 5 (1 to 6)                   | 6 (2 to 10) | NA     | 1 (1 to 7)                 | 6 (1 to 7)                 | 6 (2 to 9)                  |
| Cerclage (McDonald) + Bed Rest    | NA                 | 6 (1 to 12)       | NA            | NA                          | NA            | NA                          | NA     | NA     | NA                          | NA                        | NA                         |

Abbreviations: 17-OHPC= 17α-hydroxyprogesterone caproate; GA=gestational age, ICU=intensive care unit; IVH=intraventricular haemorrhage; NA=not applicable (treatment not included in the network); PVL= periventricular leukomalacia; RDS=respiratory distress syndrome

2. Ranks presented as Median and 95% credible interval. A CrI is interpreted as the interval where there is a 95% probability that the values of the MD (or OR) will lie. Values highlighted in **bold** indicate the treatment with the highest rankings.
### Supplementary Table 10: Summary of direct evidence

| Treatment comparison | Outcome | Direct pairwise meta-analysis | NMA results \( ^4 \) |
|----------------------|---------|-------------------------------|----------------------|
|                      |         | Number of trials and participants | OR (95% CrI) \( ^2,3 \) | OR (95% CrI) \( ^2 \) |
| **Reference:** Control (placebo or no treatment) | | | |
| **Vaginal progesterone** | | | |
| Preterm birth < 37 weeks gestation (RE) | 10 trials, 2594 participants | 0.55 (0.31 to 0.88) | 0.47 (0.33 to 0.64) |
| Preterm birth < 34 weeks gestation (RE) | 9 trials, 3023 participants | 0.41 (0.18 to 0.74) | 0.50 (0.34 to 0.70) |
| Preterm birth < 28 weeks gestation (FE) | 3 trials, 1856 participants | 0.84 (0.13 to 5.20) | 0.91 (0.71 to 1.17) |
| Preterm prelabour rupture of membranes (FE) | 5 trials, 2818 participants | 0.97 (0.77 to 1.23) | 0.90 (0.73 to 1.12) |
| Maternal Infection (FE) | 3 trials, 1034 participants | 1.26 (0.76 to 2.11) | 1.42 (0.90 to 2.27) |
| Perinatal death (FE) | 7 trials, 3499 participants | 0.69 (0.45 to 1.07) | 0.66 (0.44 to 0.97) |
| Neonatal death (FE) | 10 trials, 3835 participants | 0.29 (0.17 to 0.48) | 0.29 (0.19 to 0.46) |
| Low birthweight < 2500 g (RE) | 5 trials, 1048 participants | 0.61 (0.20 to 1.52) | 0.59 (0.31 to 1.07) |
| Neonatal respiratory distress syndrome (RE) | 8 trials, 2534 participants | 0.51 (0.26 to 0.90) | 0.54 (0.34 to 0.82) |
| Neonatal pulmonary disease (FE) | 4 trials, 2482 participants | 0.97 (0.59 to 1.62) | 0.94 (0.58 to 1.52) |
| Intraventricular haemorrhage (FE) | 8 trials, 3200 participants | 0.71 (0.45 to 1.14) | 0.66 (0.42 to 1.03) |
| Periventricular leukomalacia (FE) | 3 trials, 1389 participants | 0.98 (0.02 to 37.9) | 0.99 (0.03 to 37.8) |
| Necrotising enterocolitis (FE) | 8 trials, 3568 participants | 0.90 (0.56 to 1.46) | 0.79 (0.49 to 1.24) |
| Proven neonatal sepsis (FE) | 6 trials, 1851 participants | 0.40 (0.19 to 0.79) | 0.43 (0.24 to 0.77) |
| Admission to neonatal intensive care unit (RE) | 8 trials, 2176 participants | 0.46 (0.19 to 0.84) | 0.61 (0.40 to 0.86) |
| Gestational age at birth (mean difference) (FE) | 5 trials, 2191 participants | 1.62 (-1.89 to 5.12) | 1.96 (-1.05 to 4.98) |
| **Oral progesterone** | | | |
| Preterm birth < 37 weeks gestation (RE) | 3 trials, 368 participants | 0.41 (0.07 to 1.94) | 0.37 (0.18 to 0.75) |
| Neonatal death (FE) | 2 trials, 335 participants | 0.26 (0.12 to 0.55) | 0.26 (0.12 to 0.55) |
| Admission to neonatal intensive care unit (RE) | 2 trials, 335 participants | 0.23 (0.01 to 7.51) | 0.23 (0.10 to 0.52) |
| Gestational age at birth (mean difference) (FE) | 2 trials, 220 participants | 1.32 (-4.03 to 6.68) | 1.30 (-3.96 to 6.60) |
| **17alpha hydroxyprogesterone caproate (17-OHPC)** | | | |
| Preterm birth < 37 weeks gestation (RE) | 11 trials, 3509 participants | 0.42 (0.20 to 0.74) | 0.53 (0.37 to 0.72) |
| Preterm birth < 34 weeks gestation (RE) | 5 trials, 2987 participants | 0.76 (0.47 to 1.16) | 0.68 (0.43 to 1.02) |
| Preterm prelabour rupture of membranes (FE) | 2 trials, 760 participants | 0.87 (0.52 to 1.44) | 1.13 (0.77 to 1.65) |
| Maternal Infection (FE) | 3 trials, 2822 participants | 1.49 (0.92 to 2.46) | 1.34 (0.86 to 2.12) |
| Perinatal death (FE) | 6 trials, 3038 participants | 0.78 (0.50 to 1.21) | 0.78 (0.50 to 1.21) |
| Neonatal death (FE) | 5 trials, 2917 participants | 0.59 (0.32 to 1.07) | 0.56 (0.34 to 0.93) |
| Low birthweight < 2500 g (RE) | 6 trials, 1413 participants | 0.75 (0.30 to 1.79) | 0.71 (0.38 to 1.31) |
| Condition                                      | Trials | Participants | Ratio (95% CI)          |
|------------------------------------------------|--------|--------------|-------------------------|
| Neonatal respiratory distress syndrome (RE)    | 4      | 2851         | 0.82 (0.60 to 1.12)     |
| Neonatal pulmonary disease (FE)                | 4      | 2850         | 0.67 (0.31 to 1.46)     |
| Intraventricular haemorrhage (FE)              | 4      | 2853         | 0.43 (0.16 to 1.06)     |
| Necrotising enterocolitis (FE)                  | 3      | 2753         | **0.22 (0.01 to 0.70)** |
| Proven neonatal sepsis (FE)                    | 4      | 2850         | 0.68 (0.35 to 1.32)     |
| Admission to neonatal intensive care unit (RE) | 4      | 2462         | 1.03 (0.48 to 1.91)     |
| Gestational age at birth (mean difference)     | 3      | 750          | 2.42 (-2.37 to 7.20)    |
| McDonald cerclage                              |        |              |                         |
| Preterm birth < 37 weeks gestation (RE)        | 3      | 576          | 0.54 (0.04 to 5.99)     |
| Preterm birth < 28 weeks gestation (FE)        | 2      | 495          | 0.72 (0.03 to 23.06)    |
| Perinatal death (FE)                           | 3      | 575          | 0.59 (0.33 to 1.03)     |
| Low birthweight < 2500 g (RE)                  | 2      | 275          | 0.55 (0.01 to 27.09)    |
| Pessary                                        |        |              |                         |
| Preterm birth < 37 weeks gestation (RE)        | 4      | 906          | 0.51 (0.10 to 3.00)     |
| Preterm birth < 34 weeks gestation (RE)        | 5      | 1830         | 0.70 (0.18 to 2.92)     |
| Spontaneous preterm birth < 34 weeks' gestation (RE) | 4  | 1722         | 0.58 (0.09 to 3.94)     |
| Preterm birth < 28 weeks gestation (FE)        | 5      | 1830         | 0.86 (0.57 to 1.28)     |
| Maternal death (RE)                            | 2      | 1239         | 0.99 (0.00 to 225.7)    |
| Preterm prelabour rupture of membranes (FE)    | 4      | 906          | 0.65 (0.39 to 1.10)     |
| Maternal Infection (FE)                        | 4      | 1724         | 0.98 (0.50 to 1.97)     |
| Perinatal death (FE)                           | 4      | 1730         | 0.79 (0.44 to 1.42)     |
| Neonatal death (FE)                            | 5      | 1823         | 0.80 (0.37 to 1.70)     |
| Low birthweight < 2500 g (RE)                  | 3      | 1612         | 0.54 (0.04 to 6.40)     |
| Neonatal respiratory distress syndrome (RE)    | 5      | 1812         | 0.70 (0.17 to 3.31)     |
| Neonatal pulmonary disease (FE)                | 2      | 418          | 0.73 (0.34 to 1.57)     |
| Intraventricular haemorrhage (FE)              | 5      | 1808         | 1.18 (0.59 to 2.41)     |
| Necrotising enterocolitis (FE)                  | 4      | 1706         | 1.10 (0.46 to 2.64)     |
| Proven neonatal sepsis (FE)                    | 5      | 1812         | 0.76 (0.23 to 2.08)     |
| Admission to neonatal intensive care unit (RE) | 2      | 1014         | 1.06 (0.04 to 32.43)    |
| Gestational age at birth (mean difference) (FE) | 3      | 788          | 1.69 (-3.95 to 7.31)    |

Reference: Vaginal progesterone

| Condition                                      | Trials | Participants | Ratio (95% CI)          |
|------------------------------------------------|--------|--------------|-------------------------|
| Preterm birth < 37 weeks gestation (RE)        | 8      | 2327         | 1.38 (0.95 to 1.87)     |
| Preterm birth < 34 weeks gestation (RE)        | 5      | 1289         | 1.21 (0.52 to 2.70)     |
| Treatment                  | Outcome                                                                 | Trials, Participants | OR (95% CI)                                                                 |
|---------------------------|-------------------------------------------------------------------------|----------------------|-----------------------------------------------------------------------------|
| 17α-hydroxyprogesterone   | Preterm birth < 28 weeks gestation (FE)                                 | 4, 987               | 0.93 (0.51 to 1.70)                                                         |
| caproate (17-OHPC)        |                                                                         |                      | 0.84 (0.52 to 1.33)                                                         |
|                           | Preterm prelabour rupture of membranes (FE)                             | 2, 600               | 1.68 (0.98 to 2.96)                                                         |
|                           |                                                                         |                      | 1.24 (0.85 to 1.84)                                                         |
|                           | Maternal Infection (FE)                                                 | 2, 649               | 0.56 (0.18 to 1.62)                                                         |
|                           |                                                                         |                      | 0.94 (0.53 to 1.68)                                                         |
|                           | Neonatal death (FE)                                                    | 4, 827               | 1.79 (0.86 to 3.88)                                                         |
|                           |                                                                         |                      | 1.91 (1.12 to 3.33)                                                         |
|                           | Neonatal respiratory distress syndrome (RE)                             | 3, 745               | 1.23 (0.15 to 10.91)                                                        |
|                           |                                                                         |                      | 1.36 (0.75 to 2.49)                                                         |
|                           | Neonatal pulmonary disease (FE)                                         | 2, 647               | 1.03 (0.23 to 4.63)                                                         |
|                           |                                                                         |                      | 0.78 (0.36 to 1.69)                                                         |
|                           | Intraventricular haemorrhage (FE)                                       | 3, 747               | 1.61 (0.58 to 4.76)                                                         |
|                           |                                                                         |                      | 0.97 (0.47 to 1.99)                                                         |
|                           | Necrotising enterocolitis (FE)                                          | 3, 747               | 1.08 (0.27 to 4.38)                                                         |
|                           |                                                                         |                      | 0.51 (0.20 to 1.22)                                                         |
|                           | Proven neonatal sepsis (FE)                                             | 3, 745               | 1.39 (0.51 to 3.99)                                                         |
|                           |                                                                         |                      | 1.52 (0.76 to 3.06)                                                         |
|                           | Admission to neonatal intensive care unit (RE)                          | 4, 1022              | 1.00 (0.24 to 3.41)                                                         |
|                           |                                                                         |                      | 1.34 (0.83 to 2.08)                                                         |
|                           | Gestational age at birth (mean difference) (FE)                         | 6, 1524              | -0.41 (-3.58 to 2.77)                                                       |
|                           |                                                                         |                      | -0.14 (-2.92 to 2.69)                                                       |
| Unspecified Cerclage      | Preterm birth < 28 weeks gestation (FE)                                 | 2, 103               | 1.50 (0.02 to 117.5)                                                        |
|                           |                                                                         |                      | 1.80 (0.30 to 11.4)                                                         |
|                           | Maternal Infection (FE)                                                 | 2, 107               | 2.23 (0.40 to 19.4)                                                         |
|                           |                                                                         |                      | 2.19 (0.50 to 12.21)                                                        |
|                           | Neonatal death (FE)                                                    | 2, 122               | 2.67 (0.38 to 34.7)                                                         |
|                           |                                                                         |                      | 1.93 (0.78 to 4.69)                                                         |
|                           | Neonatal respiratory distress syndrome (RE)                             | 2, 128               | 0.49 (0.11 to 1.81)                                                         |
|                           |                                                                         |                      | 0.44 (0.08 to 2.01)                                                         |
|                           | Proven neonatal sepsis (FE)                                             | 2, 50                | 0.84 (0.11 to 6.62)                                                         |
|                           |                                                                         |                      | 0.92 (0.12 to 6.57)                                                         |
|                           | Preterm prelabour rupture of membranes (FE)                             | 2, 254               | 0.98 (0.43 to 2.27)                                                         |
|                           |                                                                         |                      | 0.84 (0.53 to 1.33)                                                         |

3. Results are presented for the best fitting NMA model for each outcome (see Supplementary Table 5). Direct pairwise meta-analysis conducted with fixed effects (FE) or random effects (RE) corresponding to the approach taken for the NMA model.

4. Results expressed as odds ratio (OR) or mean difference (MD) and 95% credible interval (CrI). A CrI is interpreted as the interval where there is a 95% probability that the values of the MD (or OR) will lie. OR<1 or MD>0 indicates an advantage to the treatment over the reference. Values highlighted in **bold** indicate statistically significant results.

5. For most outcomes, non-informative prior distributions (Normal ~ (0, 0.0001)) were used for trial baselines (mu) and treatment effects (d). For two outcomes (maternal death and Neonatal respiratory distress syndrome), where model convergence issues were encountered, weakly informative prior distributions were used (Normal ~ (0, 0.001)). Continuity corrections (i.e. adding 0.5 to all event counts) were used when zero cell counts were encountered to alleviate where model convergence issues.

6. See Supplementary Table 3 for numbers of trials and participants contributing to NMAs for each outcome.