**Additional file 4\_doc1\_Appendices**

***Appendix 1: Modified Newcastle-Ottawa Scale: Cohort Studies tool***

**Selection**

1. *Representativeness of the exposed cohort*
2. Truly representative of the elderly population (at least 65 years old) **\***
3. Subgroup of the exposed population are elderly (at least 65 years) **\***
4. Exposed population was under 65 years.
5. Exposed participants drawn from non-representative group e.g., hospital patients.
6. No description of the derivation of the exposed cohort

1. *Selection of the non-exposed cohort*
2. Drawn from the same community as the exposed cohort **\***
3. Drawn from a different source.
4. No description of the derivation of the non-exposed cohort

1. *Ascertainment of exposure*
2. Secure record (i.e., medical records) describing initial and/or ongoing exposure to antimicrobial **\***
3. Self-reporting of exposure
4. No description of exposure

1. *Demonstration of the absence of the outcome of interest at the beginning of the study*
2. Yes **\***
3. No

**Comparability**

1. *Comparability of cohorts based on design and analysis.*
2. Study controls for sex, age, and disease severity at baseline \*
3. Study controls for the above plus any other additional factors **\*\***
4. Limited or no attempt to control for differences between the cohorts.

**Outcome**

1. *Assessment of Outcome*
2. Independent or blind assessment, or confirmation of the outcome by reference tosecure records (i.e. medical records, laboratory results etc) **\***
3. Identified through ICD codes on database records**\***
4. Self-report i.e. no reference to original medical records to confirm the outcome.
5. No description

1. *Was follow-up long enough for outcomes to occur.*
2. Yes **\***
3. No
4. Length of follow-up not stated.
5. *Adequacy of follow-up of cohorts*
6. Complete follow-up – all subjects accounted for **\***
7. Loss to follow-up less than 20% or description given for those lost **\***
8. Follow-up rate less than 50% and no description of those lost
9. No statement

**Thresholds for converting the Newcastle-Ottawa scales to risk of bias/or quality of study.**

|  |  |
| --- | --- |
| **Risk/Quality**  | **Threshold**  |
| Low risk/Good quality  | 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain  |
| Medium risk/Fair quality  | 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain  |
| High risk/Poor quality  | 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome domain  |

***Appendix 2: Cochrane risk of bias assessment tool for randomised studies***

Version 2 of the **Cochrane** **risk-of-bias assessment tool for randomised trials**: bias domains, signalling questions, response options, and risk-of-bias judgments.

|  |  |
| --- | --- |
| Bias domain and signalling question\*  | Response options  |
| Lower risk of bias  | Higher risk of bias  | Other  |  Comments  |
| **Bias arising from the randomisation process**  |   |
| 1.1 Was the allocation sequence random?  | Y/PY  | N/PN  | NI  |   |
| 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?  | Y/PY  | N/PN  | NI  |   |
| 1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?  | N/PN  | Y/PY  | NI  |   |
| Risk-of-bias judgment (low/high/some concerns)  |   |
| Optional: What is the predicted direction of bias arising from the randomisation process?  |   |
| **Bias due to deviations from intended interventions**  |   |
| 2.1 Were participants aware of their assigned intervention during the trial?  | N/PN  | Y/PY  | NI  |   |
| 2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?  | N/PN  | Y/PY  | NI  |   |
| 2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?  | N/PN  | Y/PY  | NA/NI  |   |
| 2.4 If Y/PY/NI to 2.3: Were these deviations likely to have affected the outcome?  | N/PN  | Y/PY  | NA/NI  |   |
| 2.5 If Y/PY to 2.4: Were these deviations from intended intervention balanced between groups?  | Y/PY  | N/PN  | NA/NI  |   |
| 2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?  | Y/PY  | N/PN  | NI  |   |
| 2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?  | N/PN  | Y/PY  | NA/NI  |   |
| Risk-of-bias judgment (low/high/some concerns)  |   |
| Optional: What is the predicted direction of bias due to deviations from intended interventions?  |   |
| **Bias due to missing outcome data**  |   |
| 3.1 Were data for this outcome available for all, or nearly all, participants randomised?  | Y/PY  | N/PN  | NI  |   |
| 3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?  | Y/PY  | N/PN  | NA  |   |
| 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?  | N/PN  | Y/PY  | NA/NI  |   |
| 3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?  | N/PN  | Y/PY  | NA/NI  |   |
| Risk-of-bias judgment (low/high/some concerns)  |   |
| Optional: What is the predicted direction of bias due to missing outcome data?  |   |
| **Bias in measurement of the outcome**  |
| 4.1 Was the method of measuring the outcome inappropriate?  | N/PN  | Y/PY  | NI  |   |
| 4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?  | N/PN  | Y/PY  | NI  |   |
| 4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?  | N/PN  | Y/PY  | NI  |   |
| 4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?  | N/PN  | Y/PY  | NA/NI  |   |
| 4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?  | N/PN  | Y/PY  | NA/NI  |   |
| Risk-of-bias judgment (low/high/some concerns)  |   |
| Optional: What is the predicted direction of bias in measurement of the outcome?  |   |
| **Bias in selection of the reported result**  |
| 5.1 Were the data that produced this result analysed in accordance with a prespecified analysis plan that was finalised before unblinded outcome data were available for analysis?  | Y/PY  | N/PN  | NI  |   |
| Is the numerical result being assessed likely to have been selected, on the basis of the results, from:  |   |
|  5.2 ... multiple eligible outcome measurements (eg, scales, definitions, time points) within the outcome domain?  | N/PN  | Y/PY  | NI  |   |
|  5.3 ... multiple eligible analyses of the data?  | N/PN  | Y/PY  | NI  |   |
| Risk-of-bias judgment (low/high/some concerns)  |   |
| Optional: What is the predicted direction bias due to selection of the reported results?  |   |
| **Overall bias**  |
| Risk-of-bias judgment (low/high/some concerns)  |   |
| Optional: What is the overall predicted direction of bias for this outcome?  |   |

Y=yes; PY=probably yes; PN=probably no; N=no; NA=not applicable; NI=no information.

* \* Signalling questions for bias due to deviations from intended interventions relate to the effect of assignment to intervention.

**Approach to reaching an overall risk-of-bias judgment for a specific result**

|  |  |
| --- | --- |
| Overall risk-of-bias judgment  | Criteria  |
| Low risk of bias  | The study is judged to be at low risk of bias for all domains for this result  |
| Some concerns  | The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain  |
| High risk of bias  | The study is judged to be at high risk of bias in at least one domain for this result, or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result  |