Animal review

This record cannot be edited because it has been marked as out of scope

1. * Review title.

Give the working title of the review. This must be in English. The title should have the interventions or exposures being reviewed and the associated health or social problems.

Prioritising host genes implicated in Bronchopulmonary Dysplasia: a systematic review and meta-analysis by information content of non-human mammal omic studies.

2. Original language title.

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

Not applicable

3. * Anticipated or actual start date.

Give the date when the systematic review commenced, or is expected to commence.

01/06/2024

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

31/01/2025

5. * Stage of review at time of this submission.

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.

Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.

This field should be updated when any amendments are made to a published record and on completion and publication of the review.

The review has not yet started: Yes

Review stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

6. * Named contact.

The named contact acts as the guarantor for the accuracy of the information presented in the register record.

Chris Happs

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Chris

7. * Named contact email.

Enter the electronic mail address of the named contact.

s2143609@ed.ac.uk

8. * Named contact address.

Enter the full postal address for the named contact.

Baillie Lab, Roslin Institute, Easter Bush Campus, Midlothian, United Kingdom, EH25 9RG

9. Named contact phone number

Enter the telephone number for the named contact, including international dialling code.

0131 651 9100

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'none' if the review is not affiliated to any organisation.

The University of Edinburgh

Organisation web address:

https://www.ed.ac.uk

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country are now mandatory fields for each person.**

Mr Chris Happs. University of Edinburgh
Dr Sara Clohisey Hendry. The University of Edinburgh
Dr Jonathan Millar. The University of Edinburgh
Professor J Kenneth Baillie. The University of Edinburgh

12. * Funding sources/sponsors.

Give details of the individuals, organisations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the individuals or bodies listed should be included.

None

Grant number(s)

None

13. * Conflicts of interest.

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

None

14. Collaborators.

Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.

15. * Review question.

Give details of the question to be addressed by the review, clearly and precisely.

In non-human mammalian animal models of Bronchopulmonary Dysplasia, which genes are prioritised as being implicated in the host-response?

Context and rationale

Provide a brief description of the context and rationale of the review, including information on the relevance of your review for human health (max 250 words).

Up to 40% of extreme and early preterm babies develop Bronchopulmonary Dysplasia (BPD), in which alveolar lung tissue is damaged. BPD can occur as a result of the treatments necessary for survival, inflammation secondary to infection, or developmental abnormalities.

Research to date has yet to identify a statistically significant single nucleotide polymorphism (SNP) linked to BPD. Rodent models are widely used in research, in BPD however, they cannot provide an accurate environment to simulate the condition. Rodents are born at an earlier stage of lung development than humans and are prepared for gas exchange in a hyperoxic environment. Human lungs, at a similar stage, are not.

The results from this review will be compared with human results to identify animal models suitable for further study of BPD.

16. * Searches.

Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.

Primary search

OVID MEDLINE and Epub Ahead of Print, In-Process, In-Data Review & Other Non-Indexed Citations, Daily and Versions 1946 to January 31, 2024.

AND

Embase Classic + Embase 1947 to January 31, 2024.

Secondary search

- Search of [bioRxiv](https://www.biorxiv.org) and [medRiv](https://www.medrxiv.org) using relevant keywords.

- Single-level forward and backward citation searches of the reference lists of included articles.

- Extraction of references contained in the [ARDS DB](https://doi.org/10.3389/fgene.2021.750568).

- Correspondence with corresponding authors of included studies.

No language restrictions will be imposed.

Inclusion will be restricted to studies published after 1967.

The full search strategy is described at the link below.

17. URL to search strategy.

Give a link to the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies).

https://www.dropbox.com/scl/fi/4h9b3ldnomblsrfdf314f/BPD_Animal_Search.txt?rlkey=uvdkwozkeyclr2ym4bq6jvu1p&dl=0

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Human disease modelled.

Give a short description of the disease, condition or healthcare domain being modelled.

Bronchopulmonary Dysplasia.

19. * Animals/population.

Give summary criteria for the animals being studied by the review, e.g. species, sex, details of disease model. Please include details of both inclusion and exclusion criteria.

Inclusion criteria:

- Animal Studies that use any non-human mammal

Exclusion criteria:

--Human studies animal model studies

20. * Intervention(s), exposure(s).

Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed (e.g. dosage, timing, frequency). Please include details of both inclusion and exclusion criteria.

Inclusion criteria:

Not applicable

Exclusion criteria:

Not applicable

21. * Comparator(s)/control.

Where relevant, give details of the type(s) of control interventions against which the experimental condition(s) will be compared (e.g. another intervention or a non-exposed control group). Please include details of both inclusion and exclusion criteria.

Inclusion criteria:

Not applicable

Exclusion criteria:

Not applicable

22. * Study designs to be included.

Give details of the study designs eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. Please include details of both inclusion and exclusion criteria.

Inclusion criteria:

We are seeking to include whole-genome studies which report an association between genes, transcripts, or proteins and susceptibility to BPD or with severity or outcome.

We will include studies employing the following methodologies: CRISPR screen, RNAi screen, protein-protein interaction, host proteins incorporated into virion or virus-like particle, genome-wide association, transcriptomic study, or proteomic study.

Exclusion criteria:

We will exclude studies in which only results from human studies.

We will exclude studies employing the following methodologies: candidate transcriptomic or proteomic studies (50 genes investigated) and candiate gene association studies.

23. Other selection criteria or limitations applied.

Give details of any other inclusion and exclusion criteria, e.g. publication types (reviews, conference abstracts), publication date, or language restrictions.

Exclude reviews, case studies, meta-analysis, in-silico analyses.

24. * Outcome measure(s).

Give detail of the outcome measures to be considered for inclusion in the review. Please include details of both inclusion and exclusion criteria.

Inclusion criteria:

Ranked list of genes associated with BPD susceptibility, severity, and/or outcome in non-human mammalian animal models.

Exclusion criteria:

Not applicable

25. N/A.

This question does not apply to systematic reviews of animal studies for human health submissions.

26. * Study selection and data extraction.

Procedure for study selection

Give the procedure for selecting studies for the review, including the screening phases (title and/or title-abstract and/or full-text), the number of researchers involved, and how discrepancies will be resolved.

Article titles and abstracts obtained using the search strategy will be stored using reference management software (endNote X9, Clarivate Analytics, United States). Initial screening of titles will be conducted by single authors against eligibility criteria, using the Screenatron tool (Systematic Review Accelerator, Bond University, Australia). Thereafter, screening of abstracts against eligibility criteria will be conducted by two authors independently. Inconsistencies will be resolved in discussion with a third author. Full text articles will be retrieved for studies matching the eligibility criteria.

Prioritise the exclusion criteria

Multiple exclusion criteria may apply to an abstract/paper, which can cause discrepancies between reviewers in the reason for exclusion recorded. To avoid this, it is helpful to prioritize the exclusion criteria (e.g. 1) not an animal study; 2) not a myocardial infarction model, etc.) and record the highest ranking applicable criterion as the reason for exclusion. Please sort the exclusion criteria defined in questions 19 to 24. If applicable, do so for each screening phase.

Not applicable

Methods for data extraction

Describe methods for data extraction, including the number of reviewers performing data extraction, extraction of data from text and/or graphs, whether and how authors of eligible studies will be contacted to provide missing or additional data, etc.

Data will be extracted by two independent reviewers using a pre-piloted proforma.

Data to be extracted: study design

Specify the data to be extracted related to characteristics of the study design, e.g. controlled versus cross-over, number of experimental groups, etc.

Gene lists will be extracted as a text file and their ranking preserved if possible. Ranking may be based on magnitude of effect or signficance (continuous data). Where multiple measures are available we will preference magnitude of effect. Similarly, adjusted P values will be preferred over raw P values. If studies report multiple time points we will rank genes based on their minimum P value. We will exclude genes for which the magnitude of effect or significance fall outside the authors threshold, or when this information is not available, for which P 0.05, or z score 1.96, or log fold change 1.5. Gene, transcript, or protein identifiers will be mapped to its HUGO Gene Nomenclature Committee (HGNC) symbol. If one is not available we will use an equivalent Ensembl or Refseq symbol.

Data to be extracted: animal model

Specify the data to be extracted related to characteristics of the animal model, e.g. species, sex of the animals, etc.

In addition, we will extract information relating to study design, methodology, animal model, severity, and outcomes.

Data to be extracted: intervention of interest

Specify the data to be extracted related to characteristics of the intervention of interest, e.g. dose, timing, etc.

Not applicable

Data to be extracted: primary outcome(s)

Define the primary outcome measure(s). For each outcome measure, specify in which format data will be extracted, including the eligible units of measurement, and data type (continuous/dichotomous). A description of any other manipulation or transformation of the extracted data that is planned may be included.

Not applicable

Data to be extracted: secondary outcome(s)

Define the secondary outcome measure(s). For each outcome measure, specify in which format data will be extracted, including the eligible units of measurement, and data type (continuous/dichotomous). A description of any other manipulation or transformation of the extracted data that is planned may be included.

Not applicable

Data to be extracted: other

Specify any other data or study characteristics to be extracted, e.g. bibliographical details, such as author, year and language.

Not applicable

21. * Risk of bias and/or quality assessment. [21.changed]

State whether and how risk of bias and/or study quality will be assessed. Assessment tools specific for pre-clinical animal studies include SYRCLE's risk of bias tool and the CAMARADES checklist for study quality

No risk of bias and/or quality assessment planned

No

By use of SYRCLE's risk of bias tool

No

By use of SYRCLE's risk of bias tool adapted as follows:

No

By use of the CAMARADES checklist for study quality

No

By use of the CAMARADES checklist for study quality, adapted as follows:

No

Other criteria, namely

Yes

Q-genie tool

Method for risk of bias and/or quality assessment

Give the procedure for the risk of bias and/or quality assessment, including the number of reviewers involved, their contribution, and how discrepancies will be resolved.

All genome-wide association studies will be assessed for risk of bias using domain-based evaluation as described in the [Q-Genie tool](https://doi.org/10.1186/s12863-015-0211-2). Studies will be classified as low, moderate, or high quality from their overall score.

For each gene ranked in the "top 50" by our meta-analysis we will rate the cumulatative evidence for genetic association using the [Venice interim guidelines](https://doi.org/10.1093/ije/dym159).

2 authors will assess the studies independently.

28. * Strategy for data synthesis.

Planned approach

For each outcome measure, specify whether a quantitative or narrative synthesis is planned and how this decision will be made.

We will conduct a meta-analysis by information content (MAIC) of extracted gene lists. We have previously described our MAIC methodolgy in detail (https://doi.org/10.1038/s41467-019-13965-x , https://doi.org/10.1038/s41598-020-79033-3 , https://doi.org/10.1038/s41586-020-03065-y). All components of our core algorithm can be found at https://github.com/baillielab/maic.

If a meta-analysis is planned, please specify the following:

Effect measure

For each outcome measure, specify the effect measure to be used (e.g. mean difference, odds ratio etc.).

Not applicable

Effect models

For each outcome measure, specify the statistical model of analysis (e.g. random-effects or fixed-effect model).

Not applicable

Heterogeneity

Specify the statistical methods to assess heterogeneity (e.g. I^2, Q). For further guidance please refer to the introduction and practical guide to pre-clinical meta-analysis.

Not applicable

Other

Specify other details of the meta-analysis methodology (e.g. correction for multiple testing, correction for multiple use of control group).

We will conduct gene set enrichment analysis based on rankings by MAIC score. We will use two methods: 1. FGSEA in R () using the full ranked list, and 2. over-enrichment analysis using Enrichr () on the "top 100" genes.

We will control for false discovery using the Benjamini-Hochberg procedure (FDR 0.05).

29. * Analysis of subgroups or subsets.

[1 change]

Subgroup analyses

Give any planned exploration of subgroups or subsets within the review. ‘None planned’ is a valid response if no subgroup analyses are planned.

We will conduct sub-group analyses based on species e.g., rodent vs livestock.

Sensitivity

For each outcome measure, specify any sensitivity analyses you propose to perform.

Not applicable

Publication bias

Specify whether an assessment of publication bias is planned. If applicable, specify the method for assessment of publication bias.

None

30. * Review type.

Type of review

Animal model review

Yes

Experimental animal exposure review

No

Pre-clinical animal intervention review

No

31. Language.

Select each country individually to add it to the list below, use the bin icon to remove any added in error.

English

There is not an English language summary

32. * Country.

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.

Scotland

33. Other registration details.

List other places where the systematic review protocol is registered. The name of the organisation and any unique identification number assigned to the review by that organisation should be included.

Not applicable

34. Reference and/or URL for published protocol.

Give the citation and link for the published protocol, if there is one.

Not applicable

Add web link to the published protocol.

Or, upload your published protocol here in pdf format. Note that the upload will be publicly accessible.

No I do not make this file publicly available until the review is complete

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

No

Give brief details of plans for communicating review findings.?

We will make our manuscript available on medRxiv simultaneously with submission for publication.

We will make the curated list of references and genes, as well as the results of our meta-analysis, available at following the publication of our manuscript.

36. * Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line.

Bronchopulmonary Dysplasia; Genetics; Genomics; Animal Models; Mammal; Susceptibility.

37. Details of any existing review of the same topic by the same authors.

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

Our group has previously employed similar methodology to study the host genetics of [Influenza A](https://doi.org/10.1038/s41467-019-13965-x) and [SARS-CoV-2](https://doi.org/10.1038/s41598-020-79033-3) infection.

38. * Current review status.

Review status should be updated when the review is completed and when it is published.

Please provide anticipated publication date

Review_Ongoing

39. Any additional information.

Provide any further information the review team consider relevant to the registration of the review.

Not applicable

40. Details of final report/publication(s) or preprints if available.

This field should be left empty until details of the completed review are available OR you have a link to a preprint. Give the full citation for the preprint or final report or publication of the systematic review.

Give the link to the published review or preprint.