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Impact of different search strategies on the results of a meta-analysis for mastitis in dairy cattle

Impacto de diferentes estratégias de busca sob os resultados de uma metanálise para a característica mastite em gado de leite

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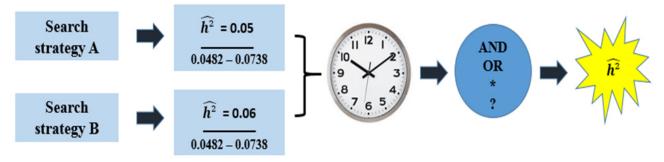
Abstract

Poorly formulated search strategies can have great influences on the results of a meta-analysis, since it directly impacts the amount and adherence to the theme of the works used for study, therefore, the formulation of a consistent and functional search strategy is essential for the review system to achieve its goals. The objective of this work was to study the impact of different search strategies in a systematic review by performing a meta-analysis to estimate heritability for the mastitis trait in dairy cattle. Once the search strategies were defined, the searches carried out in the Web of science, Scopus, Scielo and Pubmed databases returned 921 studies from which, after going through the identification, selection, eligibility and inclusion processes, 25 studies were selected. Withdrawals from selected articles, 26 heritability estimates were used in the meta-analysis. A random effect model was used, with all analyzes performed by the R program, through the Metafor package. The estimates obtained through the combined statistics of studies for mastitis, presented values of low magnitude (0.05 and 0.06). The effects of search strategies have a significant impact on the meta-analysis estimates produced. **Keywords:** Milk cattle; Heritability; Genetical enhancement

Resumo

Estratégias de buscas mal formuladas podem apresentar grandes influências nos resultados de uma metanálise, uma vez que impacta diretamente na quantidade e aderência ao tema dos trabalhos utilizados para estudo, portanto, a formulação de uma estratégia de busca consistente e funcional é fundamental para que a revisão sistemática atinja seus objetivos. O objetivo deste trabalho foi estudar o impacto de diferentes estratégias de busca em uma revisão sistemática por meio da realização de uma metanálise para estimação de herdabilidade para a característica mastite em gado de leite. Uma vez definidas as estratégias de busca, as pesquisas realizadas nas bases de dados Web of science, Scopus, Scielo e Pubmed retornaram 921 estudos dos quais, após passarem pelos processos de identificação, seleção, elegibilidade e inclusão, 25 estudos foram selecionados. Retiradas dos artigos selecionados, 26 estimativas de herdabilidades foram utilizadas na realização da metanálise. Utilizou-se um modelo de efeito aleatório, sendo todas as análises realizadas pelo programa R, por meio do pacote Metafor. As estimativas obtidas através da estatística combinada de estudos para mastite, apresentou valores de baixa magnitude (0,05 e 0,06). Os efeitos das estratégias de busca têm impacto significativo nas estimativas de metanálise produzidas.

Palavras Chaves: Bovinos de leite; Herdabilidade; Melhoramento genético



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The systematic review is a technique used by researchers to point out knowledge gaps that need to be filled, directing the use of resources to areas in which scientific investigation is a priority. In general, a fundamental question elaborated by the authors is sought to be answered using results already published in several studies.⁽¹⁾

When possible, the data collected in the systematic review are submitted to a methodology called metaanalysis, which is based on the application of wellestablished statistical procedures. Meta-analysis aims to obtain a single and reliable answer for the set of results on the same topic.⁽²⁾ These techniques can be used in the context of animal genetic improvement to obtain, for example, genetic parameters that serve as a reference for simulation studies or even increase the sample size to obtain more reliable estimates for use in future studies or even for decision-making in animal breeding programs.

Specifically in the context of dairy cattle, the systematic review can be used to study the characteristics of economic importance and their respective genetic parameters. Characteristics associated with welfare, such as mastitis, have gained importance in studies and animal breeding programs due to the growing awareness of the population. Thus, systematic reviews about mastitis seem to be interesting.

The first step in the review is to find studies related to the subject in the available databases. The formulation of a consistent and functional search strategy is essential at this stage for the systematic review to achieve its objectives. Problem search strategies may present great influences on the results of the meta-analysis, leading to under-or overestimation of results, as they directly impact the quantity and adherence to the theme of the articles for study.

Therefore, this research aimed to study the impact of different search strategies in a systematic review by performing a meta-analysis to estimate heritability for mastitis in dairy cattle.

2. Material and methods

2.1 Research question definition

The review question was defined in the POT strategy format: population (P), outcome (O), and type of study/methodology (T).

Holstein dairy cattle in production under any age group, country, production system, or management environment were considered as population (P) to verify the frequency of studies on the mastitis trait in dairy cattle breeding. For this study, we considered outcome (O) heritability estimates from the literature. These heritabilities were considered for the study when present in databases compiled to be explicitly used in studies of animal genetic improvement. The heritabilities were considered when estimated through an animal model with the REML or Bayesian (T) methodologies.

2.2. Literature search strategy

Data were collected from the literature of the following electronic databases: Scopus, Web of Science, Scielo, and PubMed. Searching in more than one database avoids possible publication bias by capturing literature that is not referenced in one or more databases. The keywords used for the search were formulated in English to reach the largest number of published articles, being divided into four groups: welfare group (welfare, behavior, indicator trait, health trait, emotion*), dairy cattle group (dairy cattle, milk, cow), animal breeding group (animal breeding, genomic, genetic, heritab*, genetic parameter, genetic correlation, genomic correlation, breeding), and statistics group (estimat*, predict*).

The search strategy was defined so that, necessarily, all groups are present with at least one search term. Therefore, the search for strategy 1 was carried out as follows: ("welfare" group) AND ("animal breeding" group) AND ("dairy cattle" group) AND ("statistics" group). The operator AND is used to create the need for all groups to appear simultaneously in the search, whereas the asterisk is intended to favor the appearance of any ending for the searched word. Within groups, the operator OR was used to guarantee at least one occurrence of the group's search terms. For instance, the "welfare" group was described as (welfare OR behavior OR "indicator trait*" OR "health trait*" OR emotion*).

Strategy 2 was defined as ("animal breeding" group) AND ("dairy cattle" group) AND ("statistics" group). The difference relative to strategy 1 was the removal of the animal welfare group.

2.3. Selection of articles

Initially, the articles were evaluated and selected using the title and abstract. The selected articles had information regarding the indicator trait mastitis and an associated heritability, estimated by the REML or Bayesian methods (eligibility criteria). Articles that did not meet any of the criteria were excluded in this first stage, and the selected ones were stored and organized with the help of the Zotero reference management software.⁽³⁾ The remaining articles from the first stage moved on to the second stage, in which the articles were read in full, and the eligibility criteria were verified. This entire article selection process was carried out by two evaluators.

2.4. Data extraction

The data extraction step was performed by two

evaluators, avoiding the selection preference for only one member, and eliminating the risk of measurement bias. The following data were extracted within each selected study: milk-producing breed, country of study, year of publication of the article and heritability found for the mastitis trait, applied methodology, and respective standard errors.

Data collection and information organization were carried out at the same time, using electronic spreadsheets to store the database, later facilitating the meta-analysis execution.

2.5. Data analysis

2.5.1. Publication bias analysis

Bias analysis was performed using the quantilequantile plot, which shows each standardized estimate against the value observed in the standardized normal distribution.

2.6. Meta-analysis

2.6.1. Statistical models

The following random model was applied after carrying out exploratory analyses:

$$\hat{h}_i^2 = \mathbf{h}^2 + s_{ij} + e_{ij}$$

where h_i is the estimated heritability in the i-th study, h^2 is the heritability parametric value, s_{ij} is the random effect of the i-th study($s_i^{indep} \sim N(0, \tau^2)$), and e_{ij} is the random error ($e_i^{indep} \sim N(0, \gamma^2)$).

2.6.2 Estimates of genetic parameters (heritability)

Standard error information associated with heritabilities is of paramount importance in this type of study, as they are used to obtain the combined estimates by the meta-analysis methodology. The inverse of the standard errors was used in this study as weighting values to obtain the estimates by meta-analysis.⁽⁴⁾

Thus, the combined estimate of heritabilities was found using the equation:

$$\hat{h}^2 = \sum_{i=l}^k w_i^* t_i^2 / \sum_{i=l}^k w_i^*$$

in which the weight is $w_i^* = l/(\gamma_i^2 + \hat{\tau}^2)$, t_i^2 is the parameter found in the literature, and k is the number of works used in the studies.

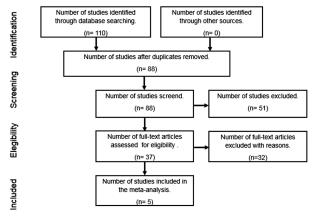
The combined standard deviation, associated with $\hat{\tau}^2$, was estimated by:

$$S_{+} = \sqrt{1/\sum_{i=l}^{k} (1/w_{i}^{*})}$$

All analyses were performed using the metafor⁽⁵⁾ package of the R⁽⁶⁾ software. The RStudio⁽⁷⁾ interface was used to make working with the R software easier.

3. Results and discussion

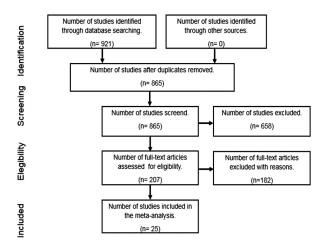
Searches in the databases (Web of Science, Scopus, PubMed, and Scielo) allowed identifying 110 publications for strategy 1 (Figure 1) and 921 publications for strategy 2 (Figure 2), and five strategy 1 studies and 25 strategy 2 studies were selected after passing all the stages. Heritability estimates were extracted from them to perform the meta-analysis.



Strategy 1

Figure 1. Flowchart of the selection process of primary studies carried out for strategy 1.

Source: Flowchart of the selection process of primary studies adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), translated by Galvão, Pansani, and Harrad.⁽⁸⁾



Strategy 2

Figure 2. Flowchart of the selection process of primary studies carried out for strategy 2.

Source: Flowchart of the selection process of primary studies adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), translated by Galvão, Pansani, and Harrad.⁽⁸⁾

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Table 1 shows descriptive statistics about heterogeneity and their respective confidence intervals found by using the random model. The welfare indicator

trait mastitis presented high values of I² and H², meaning significant variability of parametric values of the heritabilities collected in each study.

Table 1. Estimates of the total amount of heterogeneity (tau²), square root of total heterogeneity estimate (tau), percentage of total variability due to heterogeneity (I² %), total variability divided by within-study variance (H²) with their respective 95% confidence intervals, standard deviation (SD), and random model heterogeneity (Q) test for the welfare indicator trait mastitis.

	Estatísticas					
Estratégias	TAU^2	TAU	I^2 (%)	H^2	DP	Q p - valor
Estratégia 1	0,0012 0,0004 - 0,0659	0,0351 0,0198 – 0,2568	96,62 90,1129 – 99,934	29,61 10,1142 - 1529,569	0,0010	< ,0001
Estratégia 2	0,0009 0,0005 - 0,0024	0,0295 0,0227 – 0,0492	87,54 80,6655 – 95,139	8,03 5,1721 - 20,5757	0,0003	< ,0001

Strategy 1 - search considering the animal welfare group in the keywords.

Strategy 2 - search not considering the animal welfare group in the keywords.

The interval for I² was relatively short, allowing concluding that the variation found between heritability due to heterogeneity among studies is important in these cases. According to the test for the existence of heterogeneity between studies, the mastitis trait presented significant results (p<0.005). Values referring to I² and H² relative to mastitis 2 showed a decrease in values when compared to mastitis 1.

A significant decrease was observed when we compared the confidence intervals of the studies, mastitis 1 and 2 for the I^2 and H^2 statistics. The mastitis trait has been considered in dairy cattle breeding programs but only more recently this trait has been studied within the context of an indicator trait of animal welfare. In more recent studies, health-related characteristics, such as mastitis, have been studied as an important component within the multifactorial trait of animal welfare due to the population's awareness of welfare in production.

Given this more recent concern, considerably fewer works have focused on the study of mastitis to investigate welfare. Thus, the search strategy that included the group of keywords related to welfare returned a smaller number of results, resulting in different

Authors	and	years
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heritability estimates between the two strategies, both in terms of value but mainly regarding the accuracy.

Figure 2 shows an overview of the accuracy of the used heritability estimates and their contribution to the meta-analysis estimate. The study by Lund et al.⁽⁹⁾ presented the lowest precision and, therefore, the lowest contribution in the meta-analysis estimate, while the studies by Abdelsayed et al. (10) and Pritchard et al. (11) presented the highest contribution.

Figure 3 shows new contributions from studies by the search strategy that did not consider the keyword welfare. The study by Lund et al.⁽⁹⁾ still represents the lowest contribution to the heritability estimate and its long confidence interval implies lower reliability of the estimate. The new studies that presented the highest contribution were those by Wolf et al.,⁽¹²⁾ Hass et al.,⁽¹³⁾ Heringstad et al.,⁽¹⁴⁾ Zavadilova et al.,⁽¹⁵⁾ Carlen et al.,⁽¹⁶⁾ Mrod et al.,⁽¹⁷⁾ Heringastad et al.,⁽¹⁸⁾ Perez-Cabal et al.,⁽¹⁹⁾ Rupp and Boichard,⁽²⁰⁾ Abdelsayed et al.,⁽¹⁰⁾ Sorensen et al.,⁽²¹⁾ Urioest et al.,⁽²²⁾ Zadeh et al.,⁽²³⁾ Koeck et al.,⁽²⁴⁾ Chegini et al.,⁽²⁵⁾ Pritchard et al.,⁽¹¹⁾ and Zwald et al.⁽²⁶⁾ These studies had the lowest confidence intervals, contributing with higher weight to the obtained estimate.

Heritability [95%]-CI	
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Chegini et al., 2019 (25) 🖝	0.06 [0.04, 0.08]
Abdelsayed et al., 2017 (1	0.01 [0.00, 0.02]
Pritchard et al., 2013 (11)	0.04 [0.03, 0.05]
Zwald et al., 2004 (26)	0.09 [0.07, 0.11]
Lund et al., 1994 (9)	0.25 [0.05, 0.45]
Random model	0.05 [0.02, 0.09]
0 0.1 0.2 0.3 0.4 0.5	
Heritability	

Figure 3. Forest plot of heritability estimate for the welfare indicator trait mastitis with the inclusion of the animal welfare group.

Wang and Bushman (32) suggest the use of the quantile-quantile plot when the sample is small and also state that the absence of publication bias occurs when the points form a straight line starting from the origin and that most of them are aligned (Figure 4). The comparison

between quantile-quantile plots (which was adopted as the standard for the analysis of bias) presented little difference in the distribution of points, which means that there is no publication bias because the points remain within the expected range (Figure 5).

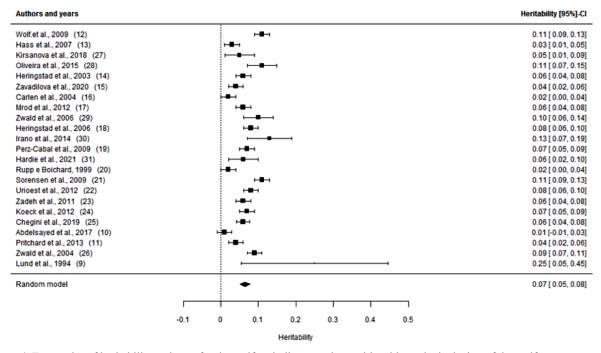


Figure 4. Forest plot of heritability estimate for the welfare indicator trait mastitis without the inclusion of the welfare group.

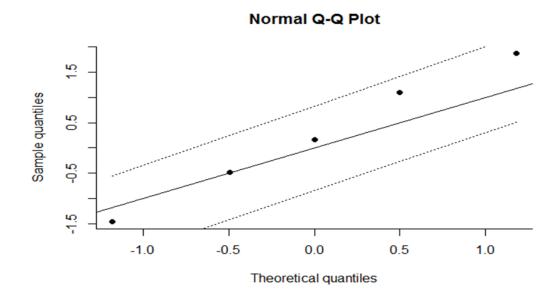


Figure 5 Quantile-quantile plot of heritability estimate for the welfare indicator trait mastitis with the inclusion of the animal welfare group.

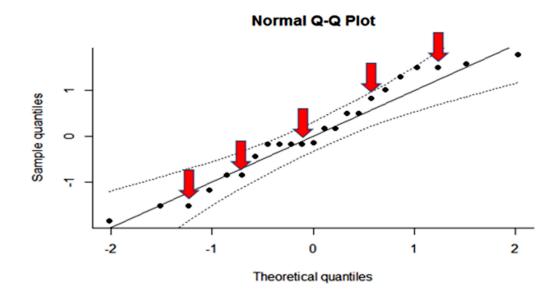


Figure 6. Quantile-quantile plot of heritability estimate for the welfare indicator trait mastitis without including the welfare group. *Arrows indicate the studies present in strategy 1 that returned in strategy 2

Table 2 shows the heritability estimates produced by meta-analysis with their respective standard errors and confidence interval at 95% probability. The estimated value presented low heritability and relatively low standard error. In addition, the confidence intervals are not long.

Table 2. Estimates of heritability by meta-analysis, standard error, and confidence interval at 95% probability (95% CI) for the animal welfare indicator trait mastitis.

Strategy	Estimated heritability	Standard error	95% CI
Strategy 1	0.05	0.0177	0.0202 - 0.0895
Strategy 2	0.06	0.0065	0.0482 - 0.0738

Strategy 1 – search considering the animal welfare group in the keywords. Strategy 2 – search not considering the animal welfare group in the keywords.

The comparison between heritabilities shows a small difference in the values. However, the increase in the number of studies included in the meta-analysis by strategy 2 provided higher precision of the estimate with a standard error almost three times lower than in strategy 1. This fact is reflected directly in the produced confidence intervals, with strategy 2 having the shortest interval.

The results show that a relatively small change in the search strategy can produce significantly more or less accurate estimates by meta-analysis. From the point of view of animal breeding programs, the precision of estimates is fundamental for making safe decisions about breeding strategies, which may have great economic impacts. Inaccurate estimates are more prone to errors, which can lead to great difficulties compared to competing programs if incorporated into the program since genetic progress must happen more slowly or not occur at all in more serious cases.

Thus, the search strategy must be very well worked out at the beginning of the studies, spending some time testing different strategies. For the tests to be effective, it is also necessary to delve into the logical and semantic operators available for building searches in the used databases, without which the searches will be significantly limited. Table 3 shows the individual effect of each study on the heritability estimate found, and the studies were removed one by one, and a new statistic was produced.

The removal of studies in strategy 1 caused oscillation in the heritability value and other statistics due to the smaller number of studies found. However, heritability did not change when applied in strategy 2, and little change was observed in the other statistics. It shows that a higher number of studies is important to provide accurate estimates with less dependence on specific studies within the meta-analytic studies.

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Table 3. Estimates of heritability by meta-analysis, standard error, and confidence interval at 95% probability (95% CI) for the animal
welfare indicator trait mastitis after removing individual studies.

Authors Removed	Estimated heritability	Standard error	95% CI
	St	rategy 1	
Chegini et al., 2009 (25)	0.05	0.0261	0.0064 - 0.1088
Abdelsayed et al., 2017(10)	0.065	0.0153	0.0365 - 0.0965
Pritchard et al., 2013 ⁽¹¹⁾	0.06	0.0261	0.0127 - 0.1152
Zwald et al., 2004 ⁽²⁶⁾	0.04	0.0155	0.0104 - 0.0820
Lund et al., 1994 ⁽⁹⁾	0.04	0.0168	0.0163 - 0.0820
	St	rategy 2	
Wolf et al., 2009 ⁽¹²⁾	0.06	0.0066	0.0497 - 0.0754
Hass et al., 2003 ⁽¹³⁾	0.06	0.0068	0.0534 - 0.0802
Kirsanova et al., 2018 ⁽²⁷⁾	0.06	0.0070	0.0521 - 0.0793
Oliveira et al., 2015(28)	0.06	0.0067	0.0501 - 0.0764
Heringstad et al., 2003(14)	0.06	0.071	0.0516 - 0.0793
Zavadilova et al., 2020 ⁽¹⁵⁾	0.06	0.0069	0.0528 - 0.0800
Carlen et al., 2004(16)	0.06	0.0067	0.0542 - 0.0802
Mrod et al., 2012 ⁽¹⁷⁾	0.06	0.0071	0.0516 - 0.0793
Zwald et al., 2006 ⁽²⁹⁾	0.06	0.0068	0.0504 - 0.0770
Heringstad et al., 2006(18)	0.06	0.0070	0.0507 - 0.0781
Irano et al., 2014 ⁽³⁰⁾	0.06	0.0066	0.0503 -0.0762
Perez-Cabal et al., 2009 ⁽¹⁹⁾	0.06	0.0071	0.0511 - 0.0787
Hardie et al., 2021(31)	0.06	0.0070	0.0517 - 0.0790
Rupp e Boichard, 1999 ⁽²⁰⁾	0.06	0.0062	0.0542 - 0.0802
Sorensen et al., 2009	0.06	0.0066	0.0497 - 0.0754
Urioest et al., 2012(22)	0.06	0.0070	0.0507 - 0.0781
Zadeh et al., 2011 ⁽²³⁾	0.06	0.0071	0.0516 - 0.0793
Koeck et al., 2012 ⁽²⁴⁾	0.06	0.0071	0.0511 - 0.0787
Chegini et al., 2009(25)	0.06	0.0071	0.0516 - 0.0793
Abdelsayed et al., 2017(10)	0.06	0.0064	0.0550 - 0.0802
Pritchard et al., 2013(11)	0.06	0.0069	0.0528 - 0.0800
Zwald et al., 2004 ⁽²⁶⁾	0.06	0.0069	0.0503 - 0.0773
Lund et al., 1994 ⁽⁹⁾	0.06	0.0067	0.0512 - 0.0773

4. Conclusion

Search strategy has a significant impact on the produced meta-analysis estimates either on the value of the estimate and/or the associated precision. Search strategies must be objective and specific while covering as many works as possible so that estimates and associated precision are not compromised.

Conflict of interests

The authors declare no conflict of interest.

Author contributions

Conceptualization: R. Fonseca, D.P. Silva, G.V. Polycarpo, S.A. Maestá. *Data curation:* D.P. Silva. *Formal analysis:* R. Fonseca, D.P. Silva, G.V. Polycarpo. *Methodology:* R. Fonseca, G.V. Polycarpo, D.P. Silva. *Writing (review and editing):* D.P. Silva, R. Fonseca, F. N. Aléssio, A. Queiroz, S.A. Maestá. *Resources:* F.N. Aléssio, A. Queiroz. *Supervision:* R. Fonseca.

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