Title: The efficacy of litter management to prevent disease and/or antibiotic use in broiler poultry: A protocol for a systematic review

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Author contributions:
All authors contributed to the development of the review question and the methodology described in this proposal. CBW drafted the protocol, with input of all co-authors.

Registration:
This protocol is archived in the University of Guelph's institutional repository (The Atrium; https://atrium.lib.uoguelph.ca/xmlui/handle/10214/10046) and published online with Systematic Reviews for Animals and Food (SYREAF) available at: http://www.syreaf.org/. The systematic review will be reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines (Liberati et al., 2009). This protocol is reporting using the items (headings) recommended in the PRISMA-P guidelines (Moher et al., 2015).

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Introduction.

Rationale:

To control and prevent major causes of disease in broiler production, it is important that contributing risk factors are identified and managed (USAHA, 2017). A crucial part of broiler production is litter management (Chen and Jiang, 2014), which, if managed improperly, leads to higher incidence of disease (Dunlop et al., 2016). Poor litter management is typically observed as excessively wet or dry litter. The development of wet litter is multifactorial, but the main triggers are improper ventilation, bird illness, equipment malfunction, diet composition, and extreme environmental temperatures and humidity. Wet litter (above 25-35% moisture) provides a better medium for pathogenic organisms to thrive (Lister, 2009), is associated with necrotic enteritis outbreaks (Hermans and Morgan, 2007). Wet litter also is associated with

higher ammonia levels, which can damage birds' respiratory lining, and can cause foot pad dermatitis (Shepherd and Fairchild, 2010). Dry litter can lead to dusty conditions which can be an issue with the bird's, and people's, respiratory health (Homidan et al., 2003). Typically, many of these causes of morbidity are treated or prevented with antibiotics. As a result, litter management is linked to the use of antimicrobials, which in turn is a driver of antimicrobial resistance. The World Health Organization is urging all stakeholders concerned with both food-producing animals and humans to establish recommended steps to enhance the prudent use of antimicrobials (WHO, 2015). Similarly, the World Animal Health Organization has also published recommendations and position statements regarding prudent use and risk management related to antimicrobial use in animals (OIE, 2017).

Understanding the impact of litter management on morbidity, mortality, and antibiotic use is essential to helping reduce the need for antibiotics while maximizing health, welfare, and productivity. Systematic reviews of studies examining the effect of different management strategies, and network meta-analysis (if possible) to provide input on relative efficacy, will yield the highest level of evidence for efficacy of interventions under field conditions (Sargeant and O'Connor, 2014).

Objectives: The objective of this protocol is to describe the methods for a systematic review – network meta-analyses to address the question: "What is the efficacy of litter management strategies to reduce morbidity, mortality, or antibiotic use in broiler chickens?"

The specific PICO/PECO elements, which will define the eligibility criteria, are as follows:

i. *Population:* Broiler poultry.
ii. *Intervention/Exposure:* Litter management strategies (as defined by the authors)
iii. *Comparator:* Another litter management strategy, or a no intervention control.
iv. *Outcomes:* Morbidity (as defined by the authors), condemnations at slaughter, mortality, and total antibiotic use.

Methods

Eligibility criteria: In addition to eligibility criteria inherent in the PICO/PECO elements described above, eligibility includes publication in English. Both journal articles and other forms of research reports are eligible, provided they report the results of a primary research study with a concurrent comparison group using an eligible study design and with a full text of more than 500 words.

Study designs eligible: Controlled trials with natural disease exposure (only cluster allocation is expected) will be eligible for inclusion, as will analytical observational studies. Controlled trials with deliberate disease challenge will be documented at full text screening; we will identify the litter management interventions and whether any of the outcomes of interest were assessed for these challenge trials, but will not be included in meta-analysis.

Information sources:

We will conduct the literature search in a range of relevant bibliographic databases and other information sources containing both published and unpublished literature. Table 1 presents the resources to be searched.

Table 1: Databases and information sources to be searched

Database / information source	Interface / URL
MEDLINE	PubMed
CAB Abstracts	CAB Interface
Science Citation Index	Web of Science
Conference Proceedings Citation Index – Science	Web of Science
Agricola	Proquest

Most of the key poultry conferences provide short abstracts (<500 words) in their conference proceedings, which do not provide the detail necessary to include in a systematic review. However, the Western Poultry Disease Conference and the World's Poultry Science Association conference proceedings provide full papers. Therefore, one reviewer will hand-search these resources for potentially relevant study reports. Any articles thus identified will be entered into DistillerSR for level 2 screening by 2 reviewers.

A single reviewer will check the reference lists of all included studies for any eligible studies that may have been missed by the database searches.

Search strategy:

A Science Citation Index (Web of Science) search strategy designed to identify studies of litter management interventions to reduce morbidity, condemnation at slaughter, mortality, and antibiotic use is presented in Table 2. The search strategy employs a multi-stranded approach to maximize sensitivity. The conceptual structure is as follows:

- Broilers;

AND

- Litter management;

AND

- Disease reduction and/or reduced antibiotic use

Table 2: Search strategy to identify studies examining litter management strategies to reduce morbidity, mortality, or antibiotics use in broilers using Science Citation Index (Web of Science)

#1 TS=(Chicken* OR Poultry* OR flock* OR gallus* OR broiler*) 193,862

#2 TS=((cake AND litter) OR (caking AND litter) OR (de-caking AND litter) OR (litter AND (sand OR "sunflower husks" OR "rick husks" OR shavings OR straw OR sawdust OR paper OR "orange peel")) OR "litter reuse" OR "reused litter" OR "wet litter" OR "litter management" OR "fresh litter" OR "reused-litter" OR "litter condition" OR "recycled litter" OR "litter treatment" OR "litter condition" OR "litter quality" OR "bedding" OR "litter moisture" OR "litter deterioration" OR "litter type" OR "litter quantity" OR "litter friability" OR "litter drying" OR "litter flowability" OR "litter moisture" OR "litter score" OR "litter amendment") 17,674

#3 TS=((litter OR bedding) AND (enzyme OR "NSP-degrading" OR xylanase OR "phytate-degrading" OR phytase OR "electrolyte balance" OR "dietary Ca" OR "dietary Na" OR "dietary P" OR "dietary K" or "dietary potassium" OR "dietary phosphorus" OR "dietary calcium" OR "dietary sodium" OR "water quality" OR "hard water" OR betaine OR trimethyl OR chloride OR sulphate OR sulfate OR "sodium bisulfate" OR acidification OR "aluminum sulfate" OR clay OR diatomaceous earth OR "heat drying" OR "ferric sulphate" OR "ferric sulfate" OR KLASP OR "poultry guard" OR "all clear" OR peat OR windrowing)) 23,455

#4 TS=(morbidity OR mortality OR antibiotic OR antimicrobial OR dysbacterosis OR dermatitis OR "foot-burn" OR pododermatitis OR FPD OR "paw score" OR "paw quality" OR "gait score" OR "foot pad" OR "hock burn" OR "breast blister" OR coccidiosis OR Eimeria OR clostridium OR coli OR Escherichia OR coliform OR colisepticaemia OR collibacillosis OR coligranuloma OR Hjarre's OR "air sac disease" OR cellulitis OR peritonitis OR salphingitis OR osteomyelitis OR peritonitis OR salpingitis OR synovitis OR panopthalmitis OR omphalitis OR enteritis OR bronchitis OR "bursal disease" OR proventriculitis OR runting OR stunting OR "hemorrhagic septicemia" OR "respiratory disease" OR "swollen head syndrome" OR coliform OR osteomyelitis) 2,020,977

#2 OR #3 38,793

#1 AND (#2 OR #3) 2,642

#1 AND (#2 OR #3) AND #4 664

The search strategies will not be limited by date, language, or publication type.

We will conduct searches using each database listed in the protocol, translating the strategy appropriately to reflect the differences in database interfaces and functionality.

Study records:

Data management: We will download the results of searches in a tagged format, load them into bibliographic software (EndNote) and de-duplicate the citations. We will save results from resources that do not allow export in a format compatible with EndNote in Word or Excel documents as appropriate and manually de-duplicate. The de-duplicated search results will be uploaded into online systematic review software (DistillerSR®, Ottawa, ON, Canada). Reviewers

will have training in epidemiology and in systematic review methods. Prior to both abstract and full-text screenings, data extraction, and risk of bias assessment, the reviewers assigned to each step will undergo training to ensure consistent data collection using the forms created in DistillerSR®.

Selection process: In the first round of screening, abstracts and titles will be screened for eligibility. Two reviewers will independently evaluate each citation for relevance using the following questions:

1) Is this a primary study evaluating litter management to reduce morbidity, condemnations at slaughter, mortality, or antibiotic use in broilers?
   YES (neutral response), NO (EXCLUDE), UNCLEAR (neutral response)
2) Is there a concurrent comparison group? (i.e. controlled trial with natural or deliberate disease exposure or analytical observational study)?
   YES (neutral response), NO (EXCLUDE), UNCLEAR (neutral response)
3) Is the full text available in English? [language of publication can be included as a field in DistillerSR]
   YES (include for full text screening), NO (EXCLUDE), UNCLEAR (include for full text screening)

Citations will be excluded if both reviewers responded "no" to any of the questions. Any disagreements will be resolved by consensus. If consensus cannot be reached, the article will be marked as "unclear" and will advance to full text screening. A pre-test will be conducted by all reviewers on the first 250 abstracts to ensure clarify of questions and consistency of understanding of the questions.

Following title/abstract screening, eligibility will be assessed through full-text screening, using the questions included below. Two reviewers will independently evaluate the full text articles, with any disagreements resolved by consensus. If consensus cannot be reached, a third reviewer will be used. A pre-test will be conducted by all reviewers on the first 10 full texts to ensure clarify of questions and consistency of understanding of the questions.

1) Is the full text available with > 500 words?
   YES (neutral response), NO (EXCLUDE)
2) Is the full text available in English? [language of publication can be included as a field in DistillerSR]
   YES (neutral response), NO (EXCLUDE)
3) Eligible population: Does the study evaluate broilers?
   YES (neutral response), NO (EXCLUDE)
4) Eligible intervention: Does the study assess one or more litter management strategies?
   YES (neutral response), NO (EXCLUDE)
5) Are at least one of the following outcomes described: morbidity, condemnations at slaughter, mortality, antibiotic use.
   YES (neutral response), NO (EXCLUDE)

6) Is there a concurrent comparison group? (i.e. controlled trial with natural or deliberate disease exposure or analytical observational study)?
   YES (neutral response), NO (EXCLUDE)
7) Eligible study design: what is the study design?
   Analytical observational study (move to data extraction)
   Controlled trial with natural disease exposure (move to data extraction stage),
   Controlled trial with deliberate disease induction (indicate the litter management strategy(ies) evaluated, but exclude from data extraction)

Data collection process: Data will be extracted by two reviewers working independently. Any disagreements will be resolved by consensus or, if consensus cannot be reached, a third reviewer will be used. Authors will not be contacted to request missing data or to clarify published results. A form for data extraction will be created for this review in DistillerSR® and pre-tested on 4 full text articles to ensure question clarity.

Data items:

Study level data to be extracted include:

- Country where trial was conducted (if not stated, use country affiliation of corresponding author)
- Commercial versus research flocks
- Number of flocks enrolled in study
- Year(s) the study was conducted
- Months of data collection
- Age of the flock
- Age at market
- Strain of the birds
- Conventionally reared or if specific antibiotic restrictions exist in the population, e.g. “antibiotic free” or organic flocks (with further text description of the restriction)

Arm level data collected:

- Description of the intervention/exposure group
- Stage of production when the intervention/exposure was used
- Length of the intervention/exposure period
- Unit of allocation (individual, pen, floor, barn)
- Description of comparison group
- Number of birds enrolled
- Number of pens / rooms / flocks enrolled
- Number of animals / pens / rooms / flocks lost to follow up
- Number of animals / pens/ rooms / flocks analyzed
- Any additional concurrent treatments given to both intervention groups.
- The approach used in the analysis to account for non-independent observations (not applicable, not reported, random effects, GEE, other)

Outcomes and prioritization:

- Morbidity,
- Condemnation at slaughter,
- Mortality,
- Total antibiotic use,

These outcomes were prioritized based on their impact on animal health and welfare and their economic importance. Formal evaluation of these criteria for prioritization was not undertaken.

The specific outcome data, as described below, will be extracted only for experimental studies with natural disease exposure and for analytical observational studies.

Outcome data to be collected:

1) Morbidity
    a. Case definition
    b. Time period for assessing outcome, frequency of outcome assessment
    c. Level at which outcome data were measured (animal / room / flock)

2) Condemnation at slaughter
    a. Case definition
    b. Age / weight at slaughter

3) Mortality
    a. Level at which outcome data were measured (animal / room / flock)
    b. Time period for assessing outcome

4) Total antibiotic use
    a. Measure used to define outcome
    b. Time period for assessing outcome
    c. Antibiotic(s) used

For each outcome, we will extract the possible metrics in the following order:

- 1st priority: Adjusted summary effect size ($_{adjusted}$ risk ratio or $_{adjusted}$ odds ratio, mean differences for continuous outcomes) and variables included in adjustment and corresponding precision estimate
- 2nd priority: Unadjusted summary effect size
- 3rd priority: Arm level risk of the outcome, or arm level mean of the outcome (continuous outcomes)
- Variance components.

Risk of bias in individual studies: Risk of bias for controlled trials with natural disease exposure will be performed at the outcome level for each outcome using the Cochrane risk of bias instrument, ROB-2.0 for clustered RCTs (Higgins et al., 2016) which is available at https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool. . For analytical observational studies, we will use the Cochrane ROBINS-I tool (Risk of bias in non-randomized studies of interventions) (Sterne et al., 2016), modified as appropriate for studies in poultry. The tool is available at https://sites.google.com/site/riskofbiastool/welcome/home .

Data synthesis:

Network meta-analysis. Network meta-analysis (aka mixed treatment comparison meta-analysis) will be conducted separately for observational and intervention studies, and will be done separately for each outcome. Network meta-analysis will use the approach described by NICE Decision Support Unit technical document (Dias et al., 2014; O'Connor et al., 2013; O'Connor et al., 2016). The approach to reporting will use the PRISMA- NMA (http://www.prisma-statement.org/Extensions/NetworkMetaAnalysis.aspx). Planned a priori sub-group analyses will be conducted for randomized versus non-randomized trials, if at least 2 of each type are included for the same outcome.

Meta-bias(es): Small study effects ("publication bias") will be assessed for all antibiotic-comparator combinations where there are at least 10 studies in the meta-analysis. If feasible, we will use approaches to assessing publication bias in the network of evidence using previously proposed approaches (Mavridis et al., 2013; Mavridis et al., 2014).

Confidence in cumulative evidence: The quality of evidence for each outcome will be assessed using the approach proposed by GRADE (GRADE, 2015, Puhan et al., 2014), while also considering the nature of the network meta-analysis (Jansen et al., 2011). If feasible, we will use the framework from the CINeMA platform for conveying the impact of risk of bias on the network performance.

Discussion:

This systematic review will provide a synthesis of the current evidence regarding the efficacy of litter management strategies used to reduce morbidity, mortality, and antibiotic use in poultry. Results will be helpful for veterinarians and poultry producers when making evidence-informed decisions regarding litter management options to reduce disease and use. The results also will be helpful for identifying specific gaps in knowledge related to the efficacy of litter management strategies to target additional research.

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