Maximizing value and minimizing waste in clinical trial research in swine: Selecting interventions to build an evidence base

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Summary

Researchers conduct a trial to compare an intervention of interest to a comparison group. Initially, researchers should determine whether a trial is evaluating superiority, equivalence, or noninferiority. This decision will guide the choice of a placebo versus active comparison group. Interventions, as well as baseline management, should be comprehensively reported to allow replication or clinical application. It is necessary to build a body of evidence across multiple trials to apply evidence-based decision-making. To achieve this, at least one intervention in every trial should be an intervention that has been used in at least one previously published trial.

Keywords: swine, clinical trial, evidence, interventions, linking networks

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Resumen - Maximizar el valor y minimizar el desperdicio en la investigación de ensayos clínicos en cerdos: Selección de intervenciones para construir una base de evidencia

Los investigadores realizan un estudio para comparar una intervención de interés con un grupo comparativo. Inicialmente, los investigadores deben determinar si un ensayo está evaluando la superioridad, la equivalencia, o la no inferioridad. Esta decisión guiará la elección de un placebo versus grupo la comparación activa de grupo. Las intervenciones, así como el manejo basal, deben informarse íntegramente para permitir la replicación o la aplicación clínica. Es necesario construir un cuerpo de evidencia a través de múltiples estudios para aplicar la toma de decisiones basada en evidencia. Para lograr esto, al menos una intervención en cada estudio debe ser una intervención que se haya utilizado en al menos un estudio publicado anteriormente.

Résumé - Maximiser la valeur et minimiser le gaspillage en recherche lors d'essais cliniques chez le porc: Sélectionner des interventions pour constituer une base de données probantes

Les chercheurs effectuent des essais afin de comparer une intervention d'intérêt à un groupe de comparaison. Au départ, les chercheurs devraient déterminer si l'essai vise à évaluer la supériorité, l'équivalence, ou la non-infériorité. Cette décision guidera le choix du placebo versus le groupe actif de comparaison. Les interventions, ainsi que la gestion de base, devraient être rapportées de manière exhaustive afin de permettre la reproduction ou l'application clinique. Il est nécessaire de constituer un ensemble de preuves à partir de multiples essais afin de mettre en place la prise de décisions fondée sur des preuves. Pour y parvenir, au moins une intervention dans chaque essai devrait être une intervention qui a été utilisée dans au moins une autre étude publiée précédemment.

In swine health and production, as in veterinary medicine in general, there is increasing emphasis on the use of evidence to inform decisions related to health and management. This evidence comes from research.[1] However, in the biomedical research field, it has been estimated that 85% of the research that is conducted is wasted (ie, not useful) because the questions asked are not relevant, the design and methods are inadequate, full reports are not accessible, or the results are biased or unusable.[2] The extent of research wastage is unknown and may be an issue in swine research, or whether there are ways the research community can better maximize the value of our research. However, a consideration of this issue and reflection on how we as a research community can maximize the value of our research is warranted.

In this commentary, we focus on clinical trials intended to assess the efficacy of an intervention to prevent or treat a clinical problem or to improve productivity, although the concepts have applicability to all study designs and research questions. Of the primary research designs, well-conducted clinical trials provide the highest level of evidence for evaluating the efficacy of an intervention when it is ethical and feasible to allocate study subjects to intervention groups.[3,4] A hallmark of a clinical trial is the use of a comparison group. A comparison group, which may be a placebo or another intervention, allows the investigator

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to distinguish between the impact of the intervention on outcomes (preselected factors that are hypothesized to be a result or consequence of the intervention) versus other factors, such as the natural progression of disease, veterinarian or producer expectations, or other interventions.[5]

In designing a clinical trial, the selection of intervention and comparator groups is of paramount importance. An individual researcher may select an intervention because they are interested in evaluating the efficacy of that specific intervention. However, researchers also should consider the potential for the results of the trial to contribute to building a body of evidence for the prevention or treatment of a clinical problem or productivity issue. This does not restrict the selection of the intervention of interest. Rather, the selection of the comparison group(s) can impact the larger usability of the trial in contributing to a body of evidence. Selecting interventions to build a body of evidence will be the focus of this article. The intention is to focus on principles of trial design, and not drug regulatory requirements.

Defining the trial purpose and intervention type

Prior to selecting the comparison group(s), the trial purpose should be determined. A trial may be intended to evaluate whether the intervention of interest is superior to another intervention (superiority), has the same efficacy as another intervention (equivalence), or is not worse than another intervention (noninferiority).[6,7] With a superiority trial, the null hypothesis is that there is no difference between the intervention groups; therefore, the alternative hypothesis is that the intervention groups differ. With an equivalence design, the null hypothesis is that the interventions differ by at least a prespecified amount, with the alternative hypothesis being that there is no difference between the interventions. A new intervention that has equivalent efficacy to an existing intervention still may be preferable based on cost, few side effects, easier dosing,[8] or shorter withdrawal time for livestock. Finally, for a noninferiority trial, the null hypothesis is that the intervention of interest is worse than the comparator by more than a margin of noninferiority (a predetermined acceptable difference) and the alternative hypothesis is that the intervention of interest is not worse than the comparator by the margin of noninferiority.[6,9] The decision on the study purpose is important, as it will impact the required sample size and the analysis and interpretation of the trial results. Typically, superiority trials have the smallest sample size, followed by noninferiority trials, with equivalence trials having the largest required sample size.[6] The use of intention to treat (ITT) versus per-protocol (PP) analysis also will differ. With ITT analysis, individuals remain in the group to which they were originally allocated, regardless of whether they completed the intervention as intended. With PP analysis, individuals are only included in an intervention group if they completed the intervention protocol as intended. Therefore, PP analysis reflects the biological efficacy of an intervention whereas ITT analysis relates to the real-world effectiveness, where not all individuals comply with or complete the exact intervention protocol. While ITT is the recommended approach to analysis of superiority trials, both ITT and PP analysis should be conducted for noninferiority and equivalence trials.[6-8]

Based on common statistical approaches and narrative interpretations of trial results provided by authors, it might reasonably be assumed that most trials in the swine literature are intended to evaluate superiority. However, explicit reporting of the trial purpose is uncommon. A word search of 179 clinical trials from 146 articles included in a recent systematic review and network meta-analysis of vaccinations for bacterial respiratory diseases in swine[10] revealed that none of the studies were explicitly described by the authors as superiority trials. Two of the trials were described by the authors as intending to evaluate equivalence of interventions[11,12] and the authors of one trial stated in the discussion section that the primary aim was to evaluate noninferiority.[13] Additional examples in the swine literature include a noninferiority trial comparing antibiotic treatments for *Actinobacillus pleuropneumoniae* in growing-fattening pigs in Europe[14] and an equivalence trial evaluating concurrent vaccinations for respiratory illness.[15]

The trial purpose also has implications for the type of comparison group, specifically to whether a placebo or an active intervention is the appropriate comparator. Using a placebo, sham, or nontreated control as the comparison group allows the investigator to evaluate whether an intervention is better than nothing. Thus, placebo comparators only make sense for trials intended to evaluate superiority. In the initial stages of identifying efficacious interventions for a clinical problem, there may not be any interventions that have consistently been shown to be superior to a nonactive control. In this instance, the use of placebo comparison groups may be appropriate. However, using placebo controls often does not address a question of interest to producers and veterinarians who generally want to know what product to use rather than whether to treat or prevent at all. Additionally, if an efficacious alternative is available, it may be inconsistent with animal welfare concerns and uneconomical to expose animals to a placebo control.[5,16] Unless there is previous empirical evidence that another intervention is consistently superior to a placebo, the results of head-to-head comparisons of active ingredients are not interpretable; if two interventions are found to be equivalent (or a new intervention is found to be noninferior), it is possible that both are highly efficacious or that both are not efficacious at all.[9,17,18] In addition, if multiple intervention options exist, researchers planning trials designed to evaluate noninferiority or equivalence might use the least efficacious alternative intervention as the comparator. This could potentially lead to progressively less efficacious interventions being identified as equivalent or noninferior, a phenomenon referred to as "biocreep."[8,18] Although more costly to perform, a viable option to consider is to add a placebo arm to a trial. For example, if the intention was a pairwise comparison of the intervention of interest to an intervention known to be efficacious, adding a placebo arm will ensure confirmation of the superiority of the comparator in the study population.[17] The sample size required for the superiority comparison will be less than the equivalence comparison, so the additional cost may be manageable.

Defining the intervention

When writing the report of a clinical trial, it is essential that the intervention groups are described in sufficient detail to allow replication. The REFLECT-statement reporting guidelines for clinical trials in livestock, highlighted in the instructions to authors by the *Journal of Swine Health and Production*, recommend that a trial report include "precise

details of the interventions intended for each group, the level at which the intervention was allocated, and how and when interventions were actually administered."[19] The REFLECT-statement explanation and elaboration document provides an example of comprehensive intervention reporting, as well as further information on the detail needed to allow for replication.[20] Moura et al[21] compared the completeness of reporting of REFLECT-statement items in clinical trials in swine prior to and after publication of the REFLECT-statement. The clinical trials included in this evaluation were published in 1 of the 5 journals that had published the REFLECT-statement (*Journal of Swine Health and Production*, *Preventive Veterinary Medicine*, *Journal of Food Protection*, *Journal of Veterinary Internal Medicine*, and *Zoonoses and Public Health*). After publication of the REFLECT-statement, 79% the intervention groups were fully described in the evaluated swine trials compared to 67% prior to publication. The improvement is encouraging; however, this still means that reporting of interventions is not comprehensive in approximately 1 in 5 trials. In addition to the REFLECT-statement, expanded guidelines on reporting of active interventions (TIDieR guidelines)[22] and reporting of placebo groups (TIDieR-Placebo)[23] in the human healthcare literature are available and may provide additional guidance for complete reporting of interventions.

A further consideration when describing interventions is the baseline management used in the herd(s) enrolled in a trial. Swine management of important health outcomes often is multifaceted; for instance, there may be a vaccination protocol in place for respiratory illness in a herd that is participating in a clinical trial on metaphylactic antibiotic use to control respiratory disease. Interventions compared to no intervention in the absence of other management practices (such as vaccination) may appear more efficacious than if the comparison was made in a population with other standard industry practices in place. Similarly, it may be important to know about management practices more broadly used to control multiple diseases, such as all-in all-out management. If all trials on an intervention have been conducted in all-in all-out herds, the results may not be as applicable to herds with continuous flow systems. This is more critical when comparing across swine production regions or systems where common production practices can be quite variable. Therefore, to allow the reader to interpret the trial results, it is important that baseline management practices that all trial animals have been exposed to are completely described.

Building a body of research by linking interventions

A final consideration moves beyond the design of a single trial to the building of a body of evidence that can be used for evidence-informed decision-making. Replication is a hallmark of science; trials evaluating the efficacy of the same intervention may reach different conclusions and it is not uncommon for highly cited clinical research showing efficacy of interventions to subsequently be contradicted.[24] Results from a single trial are based on a sample of study subjects. Therefore, it would be expected that different samples of animals from the same target population would lead to somewhat different study findings due to chance (sampling error).[25] In addition to the statistical argument for replication, there is a scientific argument wherein the efficacy of interventions is more likely to be correctly identified if the results have been seen in multiple trials with the same interventions and outcomes evaluated under similar conditions and in similar populations.[25,26]

When making clinical decisions, the relative (comparative) efficacy of all available intervention options is of interest; veterinarians and producers usually want to know which intervention is best, rather than whether to use any one specific intervention. Network meta-analysis is an extension of meta-analysis wherein relative efficacy can be estimated for all interventions for a specific condition and outcome.[27,28] However, to estimate relative efficacy in a network meta-analysis, at least one intervention arm in the trial needs to have been evaluated in at least one other trial with the same outcome. As a case study to explore this issue in swine health, Figures 1 and 2 were created using data from a systematic review of preventive antibiotics for respiratory disease in swine[29] to illustrate the relationships between the interventions in the included trials. Each node represents an intervention used in at least one trial, with the lines between nodes illustrating the comparisons between interventions that were evaluated in the trials. Figure 1 shows the network of each unique intervention as described by the trial authors; for instance, if a trial compared high dose to low dose for the same antibiotic or if different modes of administration for a single antibiotic were compared, these were considered as unique interventions. The majority of comparisons were to a nonactive control (the green central node in the larger cluster of interventions), with very few head-to-head comparisons outside of a single trial. In addition, there were 8 head-to-head comparisons with no replication (the 2-node clusters not connected to the larger cluster) and therefore no possibility of estimating the efficacy of these interventions compared to other interventions that had been evaluated in the literature. In Figure 2, interventions were amalgamated, such that each node represents an antibiotic, with all doses and routes of administration for each antibiotic combined into a single intervention. When interventions were combined in this manner, there was only one trial that did not have a common intervention arm with any other trial. There also was more replication and more connections between the interventions. However, considerable detail on the efficacy of each unique intervention was lost by combining different doses and routes of administration together. End-users may also have concerns about the assumptions made to amalgamate interventions into a single intervention ie, different doses and baselines representing the same intervention. To maximize the value of individual trials, consideration should be given to designing trials to ensure that at least one intervention in their trial has been included in a previous trial (preferably with the same parameters, eg, the same dose and route of administration), so that a comparative body of evidence can be developed over time.

Where to go from here

Researchers select an intervention to evaluate in a clinical trial because they are interested in exploring whether the intervention is efficacious in preventing or treating a condition of interest. However, by carefully considering the comparison groups that are selected, the results of the trial can contribute to the larger body of evidence on the prevention or treatment of the condition of interest. For instance, in Figure 2, the inclusion of a nonactive intervention group in the trial that did not connect to the network would have allowed that

Figure 1: Network of interventions used in trials evaluating the efficacy of preventive antibiotics for respiratory disease in swine[29] where each node represents a unique intervention.

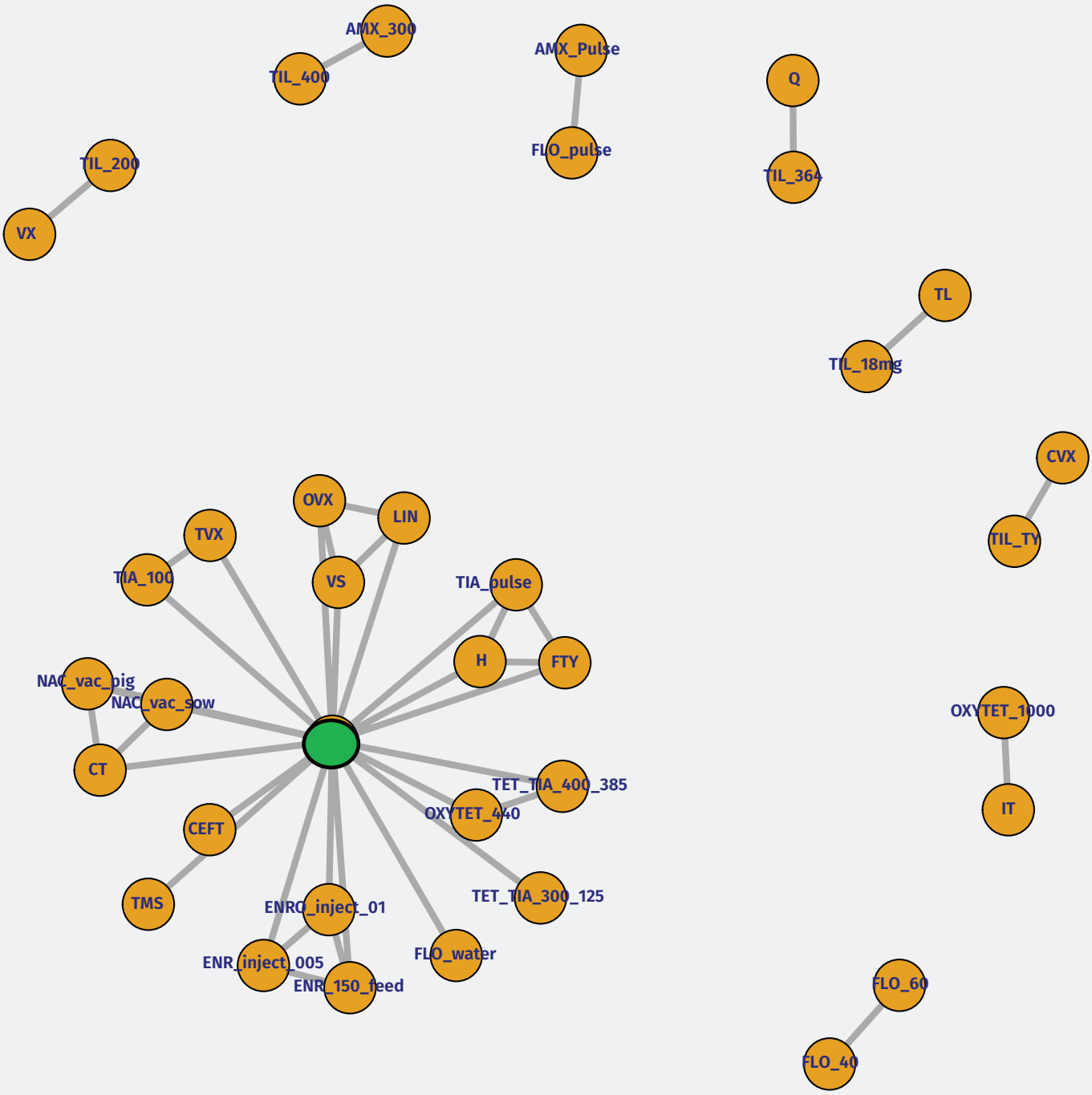
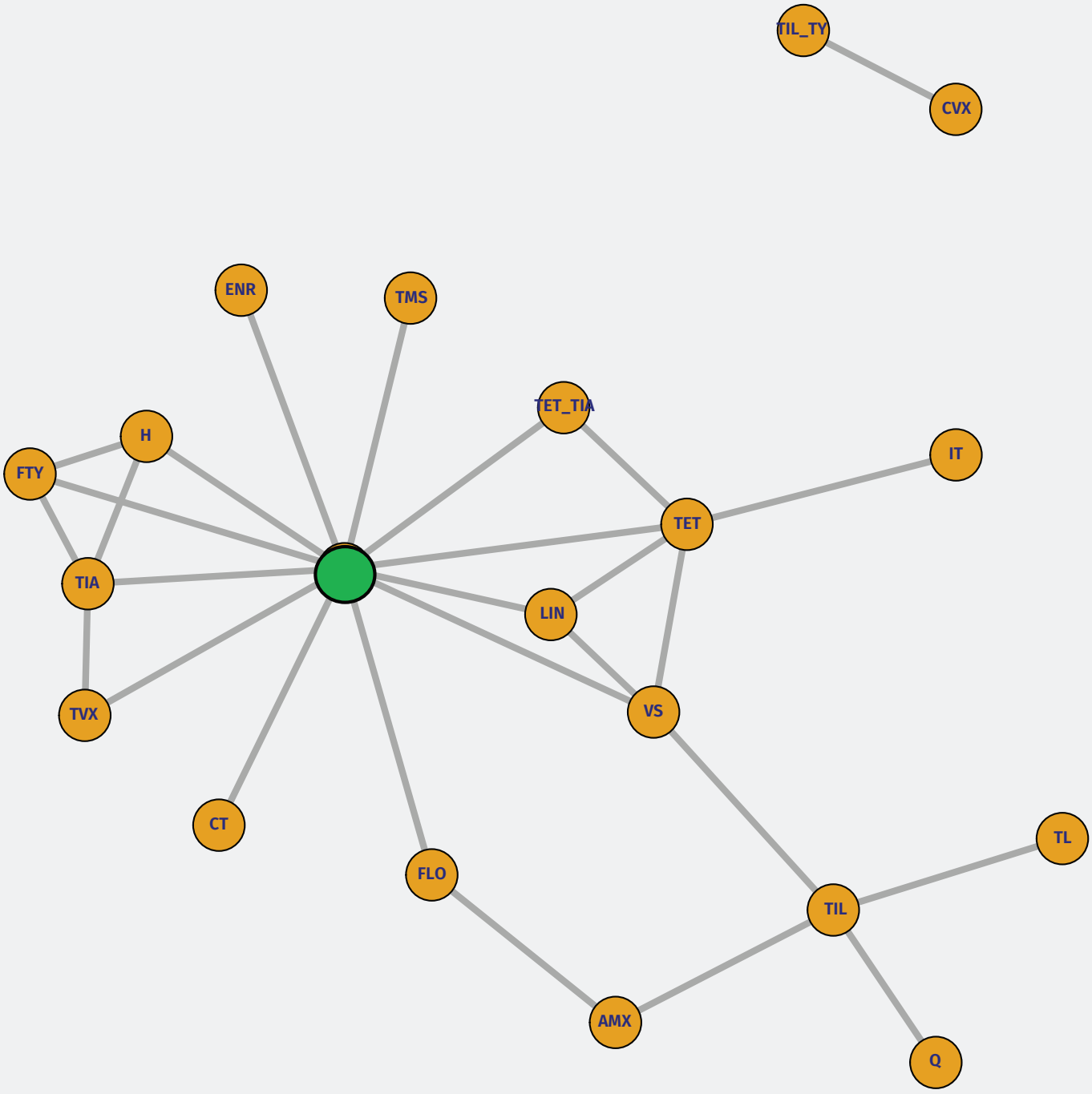


Figure 2: Network of interventions used in trials evaluating the efficacy of preventive antibiotics for respiratory disease in swine[29] where each node represents an antibiotic, with different doses or modes of administration combined into a single intervention.



trial to be linked into the larger body of literature. The appropriate comparison group will vary over time, as more research on efficacious interventions for a given outcome becomes available. Initially, superiority trials comparing a new intervention to a placebo are appropriate. As efficacious interventions are identified, head-to-head comparisons using superiority, equivalence, or noninferiority approaches may be employed. Determining whether an efficacious intervention exists may require a search of the literature and evaluation of multiple trials if no systematic review is available on the topic of interest. However, systematic reviews are increasingly being published in the veterinary literature; a scoping review of systematic reviews and meta-analyses related to animal health, performance, or on-farm food safety identified 240 systematic reviews involving swine.[30]

Regardless, at least one intervention arm in a clinical trial should have been evaluated in a previously published report, to allow linking of trials across all intervention options. Systematic reviews, meta-analyses, and network meta-analyses provide useful information of whether there are interventions shown to be superior to a placebo and on the interventions that have been evaluated for researchers designing a clinical trial. Network meta-analysis provide information on all possible interventions evaluated in the literature for a given outcome. However, these review types are still relatively uncommon in swine health; there are two network meta-analyses published on swine respiratory illness that provide intervention maps detailing all of the intervention groups that have been evaluated in the literature for that topic,[10,31] a mixed treatment meta-analysis for porcine circovirus type 2 vaccines,[32] and a network meta-analysis on antibiotic alternatives.[33] Thus, until more network meta-analyses are conducted, it may be necessary for researchers to conduct a scan of the literature to determine what intervention comparisons have been conducted and to select an intervention group in common with at least one other trial. Ultimately, selecting intervention groups with a view to building a body of evidence will benefit the entire industry, will enhance clinical decision-making by practitioners, and will also improve the health and welfare of swine.

Implications

- Existing efficacious interventions will guide trial purpose and comparison group type.
- Complete description of interventions and baseline management is essential.
- Linking interventions with other published trials builds a body of evidence.

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Conflict of interest

None reported.

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