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Evidence of improved reporting of swine vaccination trials in the post-REFLECT statement publication period

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Abstract

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Materials and Methods: The study population was 61 studies that evaluated vaccines targeted at pathogens affecting swine health or pork safety. Two reviewers assessed the reporting of 18 of 22 REFLECT items and 5 risk-of-bias domains.

Results: Authors reported the method used to allocate experimental units in 33 of 42 (79%) and 14 of 19 (74%) studies published prior to and following REFLECT, respectively. There has been a substantial shift in the reporting of allocation approaches. Before 2011, only 2 of 25 (8%) studies that reported using random allocation provided supporting evidence. This increased in studies published between 2011-2017 (4 of 6; 66%). Before 2011, 8 of 33 (24%) studies reported using systematic allocation, which increased to 43% (6 of 14 studies) between 2011-2017. There has also been an increase in the prevalence of reporting for 14 of the 18 REFLECT items. There was an increase in the number of studies reporting evidence to support true randomization to group and data that suggests few baseline imbalances.

Implications: Data from this study suggests swine vaccination trial reporting improved, which may be due to researchers having more access to better quality information.

Keywords

swine, REFLECT, vaccine, risk-of-bias, randomization

Disciplines

Large or Food Animal and Equine Medicine | Veterinary Toxicology and Pharmacology

Comments

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Summary

Objectives: Describe and compare the proportion of studies reporting the method used to assign study units to treatment groups, reporting a random allocation approach, reporting 18 REFLECT items, and the proportion of studies having a low risk-of-bias assessment in swine vaccination trial studies published after the REFLECT statement, compared to studies published before.

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Resumen - Evidencia de un mejor reporte de los estudios de vacunación porcina en el período posterior de publicación a la declaración REFLECT

Objetivos: Describir y comparar la proporción de estudios que describen el método utilizado para asignar unidades de estudio a grupos de tratamiento, que reportan un enfoque de asignación aleatoria, reportando 18 ítems REFLECT y la proporción de estudios que tienen una evaluación de bajo riesgo de parcialidad en estudios de vacunación porcina publicados después de la declaración REFLECT, comparados con estudios publicados anteriormente.

Materiales y métodos: La población del estudio fue de 61 estudios que evaluaron vacunas contra patógenos que afectan la salud de los cerdos o la seguridad de la carne. Dos revisores evaluaron el informe de 18 de los 22 elementos REFLECT y 5 áreas de riesgo de parcialidad.

Resultados: Los autores reportaron el método utilizado para asignar unidades experimentales en 33 de 42 (79%) y 14 de 19 (74%) estudios publicados antes y después de REFLECT, respectivamente. Ha habido un cambio importante en el reporte de los enfoques de asignación. Antes de 2011, solo 2 de 25 (8%) estudios que informaron el uso de una asignación aleatoria proporcionaron evidencia de apoyo. Esto aumentó en los estudios publicados entre 2011-2017 (4 de 6; 66%). Antes de 2011, 8 de 33 (24%) estudios informaron el uso sistemático, que aumentó a 43% (6 de 14 estudios) entre 2011-2017. También ha habido un aumento en la prevalencia de reporte de 14 de los 18 ítems REFLECT. Hubo un aumento en el número de estudios que informaron evidencia para respaldar la asignación al azar real al grupo y los datos que sugieren pocos desequilibrios de base.

Implicaciones: Los datos de este estudio sugieren que los reportes de los estudios de vacunación porcina mejoraron, lo que puede deberse a que los investigadores tienen más acceso a información de mejor calidad.

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Moura CAA, Totton SC, Sargeant JM, et al. Evidence of improved reporting of swine vaccination trials in the post-REFLECT statement publication period. *J Swine Health Prod.* 2019;27(5):265-277.

Résumé – Évidence d'amélioration de la publication des essais de vaccination des porcs durant la période suivant la publication de l'énoncé REFLECT

Objectifs: Décrire et comparer la proportion d'études rapportant : la méthode utilisée pour attribuer les unités à l'étude aux groupes de traitement, une approche d'attribution aléatoire, 18 items REFLECT, et la proportion d'études ayant un risque faible de biais d'évaluation dans les essais de vaccination de porcs publiés après l'énoncé REFLECT, comparativement aux études publiées avant.

Matériels et méthodes: La population étudiée consistait en 61 études qui ont évalué des vaccins ciblant des agents pathogènes affectant la santé porcine ou la salubrité de la viande porcine. Deux réviseurs ont évalué la publication de 18 des 22 items REFLECT et cinq domaines de risque de biais.

Résultats: Les auteurs rapportaient la méthode pour distribuer les unités expérimentales dans 33 des 42 (79%) et 14 des 19 (74%) études publiées préalablement et après REFLECT, respectivement. Il y eu un changement notoire dans la publication des approches d'attribution. Avant 2011, seulement 2 des 25 (8%) des études qui rapportaient utiliser une attribution aléatoire fournissaient des preuves à cet effet. Ceci augmenta dans les études publiées entre 2011-2017 (4 de 6; 66%). Avant 2011, 8 des 33 (24%) études rapportaient utiliser une attribution aléatoire, proportion qui augmenta à 43% (6 de 14 études) entre 2011-2017. Il y eu également une augmentation de la prévalence à rapporter pour 14 des 18 items REFLECT. Il y avait une augmentation dans le nombre d'études qui rapportaient des preuves pour supporter une réelle randomisation pour regrouper et des données qui suggèrent peu de débalancements au départ.

Implications: Les données de la présente étude suggère que les rapports d'essais de vaccination chez le porc se sont améliorés, ce qui pourrait être dû au fait que les chercheurs ont accès à des information de meilleure qualité.

Infectious diseases of swine and infectious causes of foodborne illness impact the sustainability of the food supply. Diseases such as African swine fever, porcine reproductive and respiratory syndrome, and swine influenza can lead to reduced pork supply,[1] while outbreaks of foodborne pathogens associated with pork, such as *Salmonella,* lead to reduced demand and risk of public health-related problems.[2-4] Therefore, it is critical that swine veterinarians have access to comprehensive reports of vaccine efficacy, allowing them to make science-driven decisions on the best immunization process to control or eradicate diseases in the herd. Unfortunately, scientific reporting of intervention studies in swine production often lacks critical information that enables assessment of biases, and there is an apparent need to improve reporting.[5]

In 2010, the Reporting Guidelines for Randomized Controlled Trials for Livestock and Food Safety (REFLECT) statement and the companion Explanation and Elaboration document were published.[6-11] The REFLECT statement has a 22-item checklist developed by an international group to help investigators improve the reporting of livestock trials that have a production, health, or food-safety outcome. The long-term goal of reporting checklists such as the REFLECT statement and similar reporting guidelines, such as the CONSORT statement,[12] the ARRIVE statement for biomedical experiments,[13-17] and STROBE-Vet,[18-22] is to reduce research wastage and maximize research utility for decision-making through improved reporting. Therefore, it is critical to periodically evaluate reporting and determine if progress toward improved reporting is occurring. In 2018, a study was performed to assess the reporting characteristics of bovine respiratory disease clinical trials published before and following the publication of the REFLECT statement. The authors reported positive trends toward improved reporting after 2010.[23] However, to our knowledge, there are no studies in swine production assessing if reporting has improved in recent years coinciding with efforts such as the REFLECT statement and Meridian Network (`https://meridian.cvm.iastate.edu`), a website that acts as a clearinghouse for reporting guidelines related to animals used in research.

Reporting guidelines are designed to improve reporting with an underlying hope that once reporting is improved, end-users will be able to identify well-executed studies and clearly extract the results. It is also hoped that in reality the vast majority of studies are well executed, and that comprehensive reporting will enable this fact to be more obvious. Currently, it is often not possible to differentiate well-executed studies from poorly executed studies. If reporting is noncomprehensive then it is difficult, if not impossible, to differentiate between well-executed studies with a low risk-of-bias from poorly executed studies with a high risk-of-bias. For example, if 2 studies exist and one randomized properly and the other did not and neither reported randomization, then these differential risks-of-bias cannot be determined. However, not all aspects of reporting relate to risk-of-bias; some items are included to help end-users understand the generalizability of the results while other aspects are designed to help end-users properly comprehend the efficacy of the interventions. The lack of detail in reporting means that many studies with interventions of interest cannot be properly assessed by veterinarians, thus reducing the impact and utility of these studies. These aspects are still relevant as they ensure maximized utility of resources, including animals, involved in animal studies.

The objective of this study was to assess whether reporting and risk-of-bias standards have changed for swine vaccination trials in the publication period from 2011 to 2017 (post-REFLECT) compared to the publication period before 2011 (pre-REFLECT). Aim 1 described the proportion of studies reporting the allocation of study units to treatment group in studies published after the REFLECT statement compared to studies published before. Our hypothesis was that the proportion of articles reporting the allocation methods would have increased in recent years, as awareness of the impact of poor reporting has increased. Aim 2 described the proportion of studies reporting a random allocation approach in studies published after the REFLECT statement compared to studies published before. Our hypothesis was that the proportion of articles reporting a random allocation approach have increased in the last years; however, prior evidence suggests that there is some misunderstanding in the veterinary sciences of the difference between truly random and pseudo-random allocation approaches.[23] Aim 3 sought to describe the reporting prevalence of 18 REFLECT items in studies published after the REFLECT statement compared to studies published before. Our hypothesis was that the proportion of articles reporting the REFLECT items have increased over the years. Aim 4 sought to describe the proportion of studies having a low risk-of-bias assessment in studies published after the REFLECT statement compared to studies published before. Our hypothesis was that the proportion of articles having a low risk-of-bias assessment have increased over the years.

Materials and methods

Study protocol

A study protocol was developed and registered with the Open Science Framework.[24] For all aspects of the project (title and abstract screening, full-text screening, and risk-of-bias assessment), 2 reviewers independently completed forms in DistillerSR (Evidence Partners, Ottawa, Canada). Conflicts between reviewers were resolved by discussion or, when consensus could not be reached, by consulting a third reviewer. The authorship on the title page of each article was redacted before evaluation; however, because of the small community of researchers in this subject area, it was not possible to ensure that blinding occurred. Additionally, the reviewers could not be blinded to publication dates because the date on which the study was conducted was usually reported in the Methods section and was part of the comprehensive reporting assessment (Items 3 and 14). The screening form, the reporting assessment form, and the risk-of-bias form were pretested on 20, 2, and 4 studies respectively. All forms are provided in the online supplementary materials (`https://doi.org/10.25380/iastate.7946732.v1`).

Study population

For this cross-sectional observational survey, the population of interest was controlled trials where at least one study group received a vaccine targeting pathogens associated with swine health or food safety in pork. Further, the study had to be published in 1 of the 5 journals that published the REFLECT statement: *Preventive Veterinary Medicine*, *Journal of Food Protection*, *Journal of Veterinary Internal Medicine*, *Journal of Swine Health and Production*, and *Zoonoses and Public Health*. These journals were selected because they recommend authors to use the REFLECT statement. The outcome reported by the investigators did not impact eligibility. Controlled trials were defined as having a concurrent/parallel comparison arm with either artificial challenge or natural infection. The publication periods were defined as pre-REFLECT, which included 2010 and earlier, and post-REFLECT, which was 2011 and later. As REFLECT was published in 2010, we considered studies published in 2010 as being written before REFLECT.

Screening assessment

The literature search was conducted in Web of Science (Clarivate Analytics, United States) using the Centre for Agriculture and Bioscience International database using the search strategy presented in Table 1. Two levels of screening were used to identify eligible manuscripts: title and abstract followed by the full text.

Comprehensive reporting assessment

The reporting assessment form was based on a form developed for a bovine respiratory disease study,[23] which was in turn based on the REFLECT Statement[6-11] and was modified for use in swine. We assessed reporting 18 of the 22 REFLECT items (items 1 and 3-19). Items 2, 20, 21, and 22 were considered too subjective for a consistent and valid assessment. Signaling questions and notes that guided the consistent assessment of the items are included with the forms in the online supplementary materials (`https://doi.org/10.25380/iastate.7946732.v1`).

Risk-of-bias assessment

We used the Cochrane risk-of-bias 2.0 algorithm[25] to assess the risk-of-bias that arose from deviations from intended interventions, from missing outcome data, from measurement of the outcome, and from selection of the reported results. However, for assessing the risk-of-bias due to randomization process, we modified the algorithm so that it followed the schema in Figure 1. The risk-of-bias algorithm we used did not consider failure to report allocation concealment to be critical to assessing bias in swine vaccine trials, as is suggested by the Cochrane risk-of-bias algorithm. We would propose that the Cochrane risk-of-bias algorithm authors consider the allocation concealment important in human health because the knowledge of potential intervention might cause some recruiters to modify the allocation schedule. For example, Kahan et al,[26] described the following:

> If a recruiter believes the next allocation will be the intervention, they may wait to enroll a very sick patient, as they do not want to 'waste' an intervention allocation on a relatively healthy patient who is less likely to need it.

However, in swine vaccine studies, which are the topic of this study, we considered the probability that the recruiter had either differential personal attachment to the pig or *a priori* knowledge of the pig potential production value to be low.

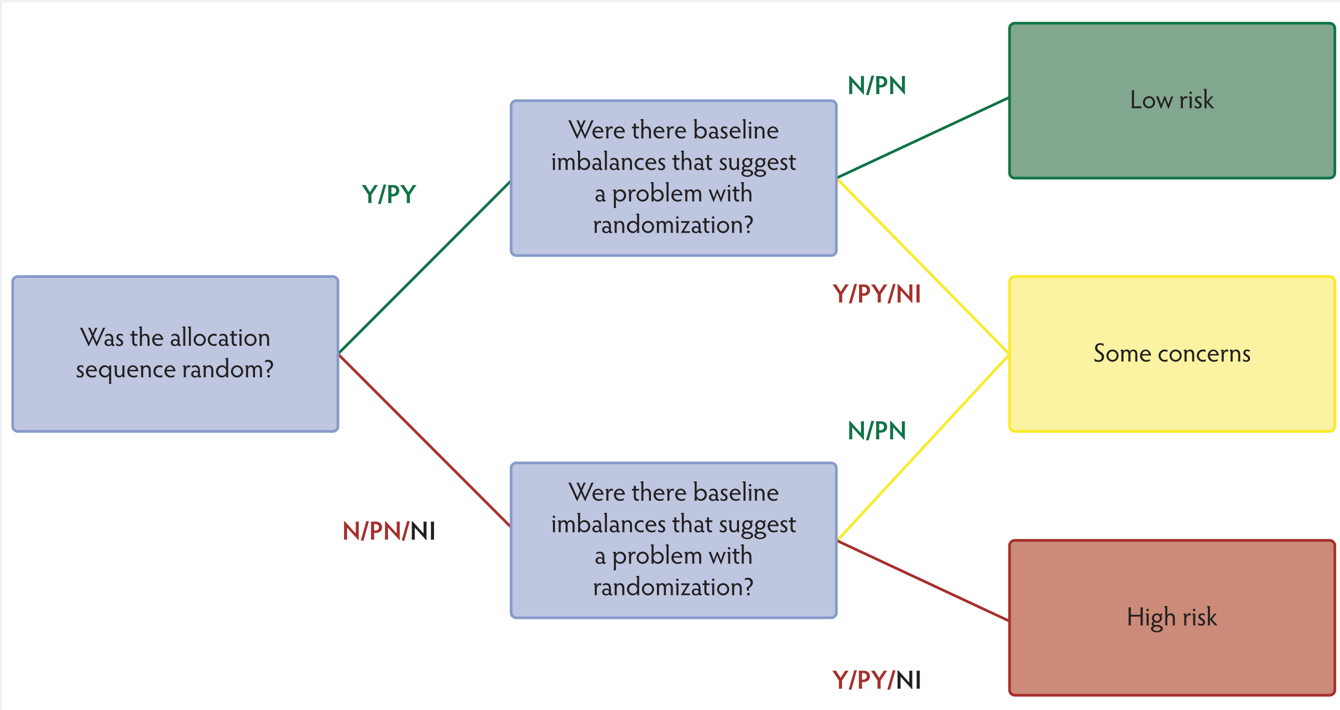
Therefore, we included the scenario where studies could fail to report allocation concealment and random method of allocation and this would result in a different pathway, with lower risk-of-bias, than the Cochrane Risk of Bias (ROB) 2.0 algorithm. We also

Table 1: Literature search for vaccination trials in swine from 1982-2017 conducted in Web of Science using the CABI database*

Search No.	Search string	No. of hits
1	Topic = (swine OR pig* OR piglet* OR gilt* OR boar* OR sow* OR weaner* OR hog* OR porcine OR pork* OR *Sus scrofa* OR *Sus domesticus*)	645,575
2	Topic = (Vaccin* OR immuniz*)	149,140
3	Journals = (*Preventive Veterinary Medicine* OR *Journal of Food Protection* OR *Journal of Veterinary Internal Medicine* OR *Swine Health and Production* OR *Journal of Swine Health and Production* OR *Zoonoses and Public Health*)	17,169
4	#1 AND #2 AND #3	239

* Search was conducted September 28, 2017.
CABI = Centre for Agriculture and Bioscience International.

Figure 1: Risk-of-bias algorithm arising from the allocation process used for 61 extracted swine vaccine studies published pre- or post-REFLECT publication. Y = yes; PY = probably yes; N = no; PN = probably no; NI = no information.



considered that providing no information about baseline differences to be more similar in risk to having evidence of baseline imbalances.

Our risk-of-bias assessment algorithm for individual and cluster-randomized trials (which are the trials that conduct the randomization at the group level, instead of at the individual animal level) are the same.

Statistical analysis

We estimated the prevalence ratios for the post-REFLECT publication period (numerator) compared to the pre-REFLECT publication period (denominator) for:

- reporting of any allocation method (Aim 1),
- reporting of a valid random allocation, given an allocation approach was reported (Aim 2),
- reporting 18 of the REFLECT items (Aim 3), and
- a low risk-of-bias assessment for the five bias domains (low versus high/some concerns; Aim 4).

We did not conduct any null hypothesis testing as they have limited value in an observational study of unknown pre-planned power. Additionally, since we sampled all available papers that met our eligibility criteria, we considered the population to be a census. Therefore, we did not calculate any measures of precision (confidence intervals), because we have no uncertainty about the point estimates reported. When we could not calculate the prevalence ratio due to zeros, we reported the results of a Fisher test for binomial proportions. All statistical analyses were done using R 3.4.1 program.

Results

Screening for eligibility and characteristics of included studies

The search retrieved 239 records. One hundred seventy-two records were excluded based on the title or abstract. Six papers were excluded based on the full-text assessment. For the 61 manuscripts assessed, 42 studies[27-68] were published before the REFLECT statement (date range: 1982-2010), while 19 studies[69-87] were published between 2011 and 2017. Forty-seven trials were published in the *Journal of Swine Health and Production* (formerly published as *Swine Health and Production*), 11 in *Preventive Veterinary Medicine*, 2 in *Zoonoses and Public Health*, and 1 in *Journal of Food Protection*. Only the *Journal of Swine Health and Production* and *Preventive Veterinary Medicine* had articles published from 2011 to 2017, with 14 and 5 papers, respectively. Fifty-six studies had individual allocation to an intervention group and 5 studies were cluster-randomized trials.

Aim 1: Reporting of an allocation method

Investigators reported in the title, abstract, or methods section the method used to allocate the experimental units to the interventions in 33 of 42 (79%) and 14 of 19 (74%) studies in the pre-REFLECT and post-REFLECT publication periods, respectively (Figure 2). The prevalence ratio was 0.94.

Aim 2: Approach to allocation reported

This outcome was limited to studies that reported an allocation approach in Aim 1. For 25 of 33 (76%) studies published before 2011 and 6 of 14 (43%) studies published between 2011-2017, the approach to allocation was reported as random. Before 2011, 23 of 25 (92%) studies that reported a random allocation approach did not provide any evidence of the randomization process, for example, the method used to generate the random allocation sequence, the method used to implement the random allocation sequence, or who conducted the randomization process. Yet, in the period from 2011-2017, this number had decreased to 2 of 6 (33%) studies (Figure 2). Before 2011, only 2 of 25 (8%) studies that reported a random allocation approach provided evidence of the randomization process, and this increased in studies published between 2011 and 2017 to 4 of 6 (67%). Of the studies that did report information about allocation, 8 of the 33 studies (24%) published before 2011 and 6 of 14 (43%) studies published between 2011 and 2017 reported using a systematic allocation method. In systematic random allocation approaches, the researcher picks the first individual at random and keeps selecting the other subjects by alternation. Two studies published post-REFLECT reported another allocation method (non-random and arbitrary selection).

Figure 2: Distribution of allocation approaches reported in 61 swine vaccine studies published pre- or post-REFLECT publication.

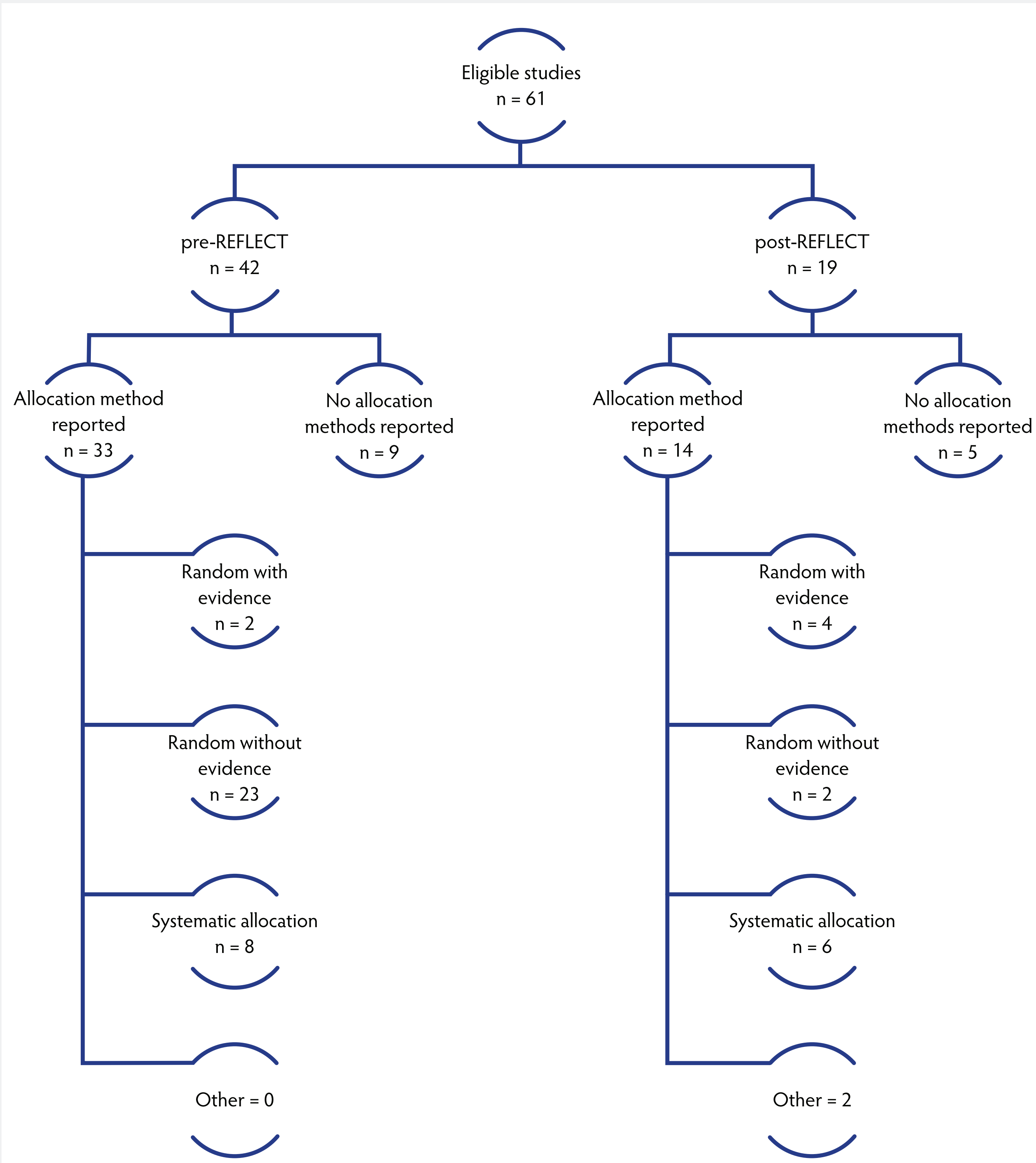


Table 2: Reporting characteristics of 18 REFLECT statement items from 61 extracted swine vaccine studies published pre- or post-REFLECT publication

	Published studies reporting, No. (%)		
REFLECT reporting items	**Pre-REFLECT studies**	**Post-REFLECT studies**	**Prevalence ratio**
Item 1: In the Title or Abstract, did the investigators report that the study units were randomly allocated to the interventions? (eg, "random allocation", "randomized", or "randomly assigned")	11/42 (26)	6/19 (32)	1.2
Item 3: In the Methods, did the investigators report eligibility criteria for owner/managers and study units at each level of the organizational structure, and did they describe the settings and locations where the data were collected?	2/42 (5)	4/19 (21)	4.4
Item 4: In the Methods, did the investigators give precise details of the interventions intended for each group, the level at which the intervention was allocated, and how and when interventions were administered?	28/42 (67)	15/19 (79)	1.2
Item 5: Did the investigators report the specific objectives and hypotheses of the study?	6/42 (14)	2/19 (11)	0.7
Item 6: Did the investigators give clearly defined primary outcome measures and the levels at which they were measured, and, when applicable, any methods used to enhance the quality of the measurements?	6/42 (14)	8/19 (42)	2.9
Item 7: Did the investigators report how the sample size was determined and, when applicable, explain any interim analyses and stopping rules?	7/42 (17)	7/19 (37)	2.2
Item 8: If the authors described an approach to allocation anywhere in the manuscript then did the investigators report the method used to generate the random allocation sequence at the relevant level of the organizational structure, including details of any restrictions (eg, blocking, stratification)?	2/25 (08)	4/6 (67)	8.3
Item 9: Did the investigators report the method used to implement the random allocation sequence at the relevant level of the organizational structure, (eg, numbered containers), clarifying whether the sequence was concealed until interventions were assigned?	0/25 (0)	0/6 (0)	*
Item 10: Did the investigators report who generated the allocation sequence, who enrolled study units, and who assigned study units to their groups at the relevant level of the organizational structure?	0/25 (0)	0/6 (0)	*
Item 11: Did the investigators report whether those administering the interventions, caregivers, and those assessing the outcomes were blinded to group assignment?	15/42 (36)	12/19 (63)	1.8
Item 12: Were statistical methods used to compare groups for all outcome(s)? Did the investigators clearly state the level of statistical analysis and methods used to account for the organizational structure (where applicable)? Were the methods for additional analyses, such as subgroup analyses and adjusted analyses reported?	34/42 (81)	17/19 (89)	1.1
Item 13: In the Results, did the investigators report the flow of study units through each stage for each level of the organization structure of the study (a diagram is strongly recommended)?	29/42 (69)	15/19 (79)	1.1
Item 14: Did the investigators report dates defining the periods of recruitment and follow-up?	12/42 (29)	5/19 (26)	0.9

Table 2 cont'd: Reporting characteristics of 18 REFLECT statement items from 61 extracted swine vaccine studies published pre- or post-REFLECT publication

REFLECT reporting items	Published studies reporting, No. (%)		Prevalence ratio
	Pre-REFLECT studies	Post-REFLECT studies	
Item 15: Did the investigators report the baseline demographic and clinical characteristics of each group, explicitly providing information for each relevant level of the organizational structure?	11/42 (26)	8/19 (42)	1.6
Item 16: Did the investigators report the number of study units (denominator) in each group included in each analysis?	25/42 (60)	15/19 (79)	1.3
Item 17: Did the investigators report a summary of results for each group, accounting for each relevant level of the organizational structure, and the estimated effect size and its precision?	1/42 (2)	3/19 (16)	6.6
Item 18: For the studies with 2 or more arms, did the investigators address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory?	8/28 (29)	6/12 (50)	1.75
Item 19: Did the investigators report all important adverse events or side effects in each intervention group?	4/42 (10)	2/19 (11)	1.1

* not calculated

Aim 3: Reporting of REFLECT checklist items

The reporting characteristics for the REFLECT checklist items are reported in Table 2 and Figure 3. After REFLECT publication, the prevalence of reporting the following REFLECT items had improved: randomization in the title and abstract (item 1), eligibility criteria for owner/managers and study units and the description of settings (item 3), details of the interventions (item 4), primary outcome (item 6), how the sample size was calculated (item 7), method used to generate the random allocation sequence (item 8), whether or not blinding was done (item 11), whether statistical methods were used (item 12), flow of study units through the study (item 13), baseline demographic and clinical characteristics of each group (item 15), number of study units used in analysis (item 16), summary of results for each group - estimated effect size and its precision (item 17), multiplicity (item 18), and adverse events or side effects (item 19). After REFLECT publication, the prevalence of reporting the objective and hypothesis (item 5) and dates defining the periods of recruitment and follow-up (item 14) decreased. Concealment of the allocation sequence (item 9) as well as who generated the allocation sequence/who enrolled study units/who assigned study units to their groups (item 10) were not reported for any of the 61 studies reviewed. Data about reporting characteristics of the challenge models (REFLECT item 4B) are not shown in Figure 3, as it could not be dichotomized, and these results are instead reported in Table 3. The percentage of challenge model studies was higher in studies published before 2011 (21 of 42 studies; 50%) than between 2011 and 2017 (6 of 19 studies; 32%).

Aim 4: Risk-of-bias assessment

Of the 61 manuscripts assessed, 5 were cluster-randomized and published before 2011, so there were no cluster-randomized trials identified in the post-REFLECT period. The reporting characteristics of the 61 extracted studies for the risk-of-bias assessments are shown in Table 4. There was an increase in the prevalence of low risk-of-bias studies, based on the randomization process domain, between the post- and pre-REFLECT studies. All the other risk-of-bias domains appeared to be unchanged.

Discussion

One of the main advantages of randomized controlled trials is their ability to reduce confounding, a significant source of bias in the assessment of interventions.[88] It is interesting therefore that the prevalence of reporting an allocation method to study units was virtually unchanged (or decreased) in the two publication periods (79% to 74%). However, although the proportion of studies that reported using a random allocation method has decreased, the proportion of studies that reported using a systematic method has increased. This finding also occurred in other veterinary studies.[89] Two hypotheses might explain this finding: 1) that there has been a change in the approach to allocation away from random allocation to systematic allocation, and 2) that there has been a change in the language used to report systematic or haphazard allocation approaches in veterinary sciences. Studies that previously described the allocation method as random have changed the description of the method to reflect the actual approach ie, systematic allocation. The first hypothesis suggests that there was no reporting improvement on studies published after REFLECT. The second hypothesis suggests that reporting is improving, if the studies published before 2011 that used systematic or haphazard methods were misreporting or misrepresenting those approaches as random allocation. This latter hypothesis is supported by the increase in the number of studies that provided evidence for the designation of random allocation from 8% to 66%.

Figure 3: The prevalence comparison plot of 18 REFLECT items reported in 42 studies published before 2011 and 19 studies published between 2011 and 2017. Item 4B had multiple categories and is not included. Items 2 and 20 to 23 were considered too subjective for assessment and were not included.

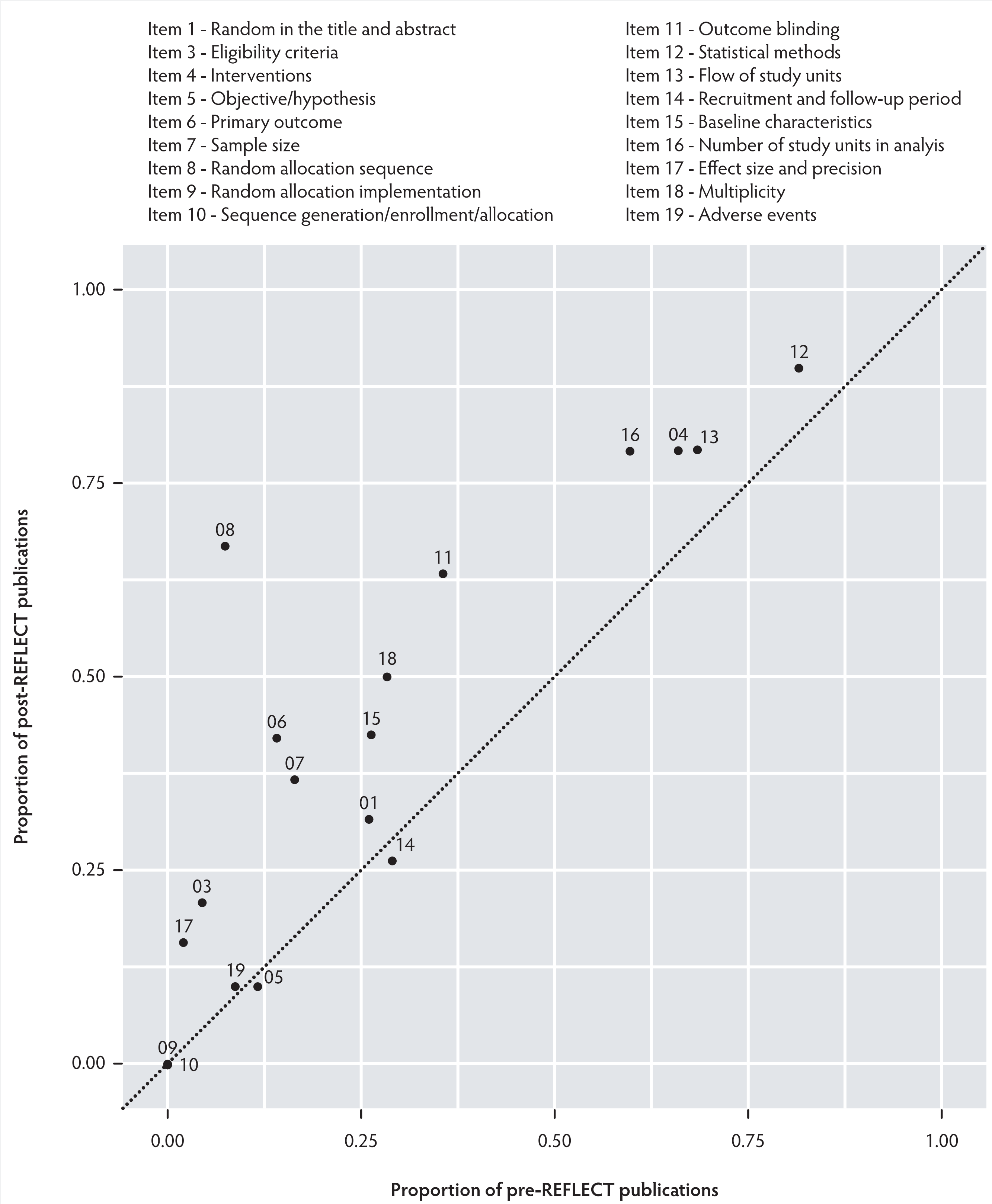


Table 3: Reporting characteristics of swine vaccine challenge studies (item 4B of REFLECT statement) published pre- or post-REFLECT publication.

Publication period	No. of challenge studies/ Total No. of studies (%)	No. of studies reporting item/ No. of challenge studies (%)
Pre-REFLECT studies	21/42 (50)	5/21 (24) – complete description: organism growth details, route of administration and dose of the organism
		13/21 (62) – partial description: route of administration and dose of the organism
		1/21 (5) – partial description: route of administration
		2/21 (10) – partial description: seeder pigs
Post-REFLECT studies	6/19 (32)	2/19 (11) – complete description: description of organism growth details, route of administration and dose of the organism
		4/19 (21) – route of administration and dose of the organism only

We attempted to identify in veterinary clinical trial texts where the concept of systematic or alternative allocation arose, and we cannot trace its origin. One study we are aware of discusses and recommends the use of alternative approaches as being equivalent to random allocation and practical, ie, every-other-calf or odd-and-even number schemes.[90] The authors suggested that valid random allocation is impractical in field settings and alternation could serve as a practical method under field conditions while still controlling confounding bias. We were not able to identify similar advice for swine studies, although apparently this approach is used commonly. What is unknown is if, and under what circumstances, a systematic allocation approach is an adequate replacement for random allocation. We were unable to find empirical evidence for this assumption.[90]

Another interesting finding is the number of studies that reported using a random allocation approach while providing no support for this statement. Although the percentage of studies reporting a random allocation approach was higher before 2011, most of those studies did not report details of the randomization process (23 of 25). The majority of studies (4 of 6) reporting a random allocation approach between 2011 and 2017 provided some information to support the randomization process. This finding suggests improved reporting.

For Aim 3, the results show an increase in the prevalence of reporting most of the REFLECT items and suggest that the overall reporting of swine intervention trials has improved. It is less clear whether improved reporting has translated into lower risk-of-bias. Although the risk-of-bias due to the randomization process appears to have decreased, the other risk-of-bias domains were unchanged. Even for the randomization process ROB domain, the evidence is poor because the low risk-of-bias was based on 2 studies published between 2011 and 2017 and 1 study before 2011.

Additional information is needed to determine if the increased reported use of systematic allocation is based on the tendencies of the industry and is, therefore, unlikely to change. It is also necessary to establish the true benefit of randomized over systematic allocation methods to determine if it is essential to use truly random approaches.[91] One approach would be to assess if there are differences in effect sizes in systematically allocated versus randomly allocated studies. Arguing against the need for such evidence is the fact that proper randomization to group is the established standard for intervention trials and the basis for inference. It is also not currently feasible to obtain empirical evidence that allocation concealment is associated with bias as there are too few studies that include this component for comparison to be made. Further, it is hard to envision veterinary schools and graduate programs teaching study design approaches that are not acceptable at the federal level for registration of drugs or vaccines, especially as so many livestock veterinarians are employed by the pharmaceutical and biologics industry to conduct trials. However, if evidence were found that some design elements identified by Cochrane ROB 2.0 are not relevant to livestock studies this would not be unprecedented. In human health, some groups have reported that some Cochrane risks-of-bias domains appear not to be related to empirical evidence of bias.[92]

Although reporting has improved, there remains room for improvement on all REFLECT items, since none of them were reported by all papers. However, it is unclear what would be the best way to make this improvement occur. The journals that published the studies all endorse the use of the REFLECT statement; however, none require a checklist be submitted or require that reviewers use REFLECT to assess the studies. Even if these journals did require that submitting authors include a completed reporting checklist there is no evidence that such an approach would improve reporting.[93] We would propose that several next steps are needed. It is essential that increased education efforts in veterinary schools, graduate programs, and groups involved in post-graduation professional development such as the American Association of Swine Veterinarians raise awareness of the value of improved reporting to veterinarians, especially as prior studies have shown that many editors are unaware of reporting guidelines.[94] These efforts will ensure that veterinarians are aware that poor reporting is associated with biased results and that veterinarians can recognize poor reporting. Further, more education of researchers

Table 4: The risk-of-bias assessment of the 61 extracted swine vaccine studies published pre- or post-REFLECT publication

Bias arising from	Published pre-REFLECT, No. (n = 42)			Published post-REFLECT, No. (n = 19)			Prevalence ratio*
	High	Some concerns	Low	High	Some concerns	Low	
Randomization process	32	9	1	11	6	2	4.42
Deviations from intended interventions	0	2	40	0	0	19	1.02
Missing outcome data	2	12	28	1	6	12	0.95
Measurement of the outcome	3	1	38	1	0	18	1.05
Selection of the reported results	2	40	0	1	18	0	†

* Prevalence ratio between low risk compared to some concerns and high risk combined.
† Not calculated.

about the obligation to provide stakeholders, including funding groups, veterinarians, and producers, with research reports that comprehensively describe the research is required. Providing comprehensive reports ensures that maximum value is obtained from the human and financial capital investment made in research studies. Also, very importantly, if the basic premise of the call for improved reporting is disputed, we would strongly support that such evidence be included in the peer-reviewed literature so that the role of comprehensive research reporting can be properly discussed among scientists and stakeholders.

Implications

- Substantially more studies are reporting the use of systematic allocation methods, and it is unclear if such an approach adequately ensures exchangeable groups.
- The prevalence of reporting a random allocation method decreased between the pre- and post-REFLECT studies; however, the prevalence of evidence to support a claim that valid random allocation was used has increased.
- The prevalence of reporting most REFLECT items increased between the pre- and post-REFLECT publication periods.
- The prevalence of low risk-of-bias due to the allocation approach might have increased between the pre- and post-REFLECT publication periods. Other risk-of-bias domains appear unchanged.

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Contributions

Dr Moura contributed to the development of the study concept, the risk-of-bias modifications, performed data extraction, risk-of-bias assessment, data analysis, and preparation of manuscript drafts. Dr Totton performed data extraction, risk-of-bias assessment, and provided feedback on drafts of the manuscript. Dr Linhares contributed to the development of the study concept and approved the final report. Dr Sargeant contributed to the development of the study concept, the risk-of-bias modifications, and approved the final report. Dr O'Sullivan contributed to the development of the study concept, the risk-of-bias modifications, and approved the final report. Dr O'Connor contributed to the development of the study concept, the risk-of-bias modifications, data analysis, preparation of manuscript drafts, and approved the final report.

Declarations

Ethical approval for animal use or human subjects was not required for this project. All preplanned results are reported and modifications from the protocol are reported.

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Conflict of interest

Drs O'Connor and Sargeant are co-authors of the REFLECT statement. Drs Moura, Linhares, Totton, and O'Sullivan have no conflicts of interest to declare.

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* Non-refereed references.

Conversion tables

Weights and measures conversions

Common (US)	Metric	To convert	Multiply by
1 oz	28.35 g	oz to g	28.4
1 lb (16 oz)	453.59 g	lb to kg	0.45
2.2 lb	1 kg	kg to lb	2.2
1 in	2.54 cm	in to cm	2.54
0.39 in	1 cm	cm to in	0.39
1 ft (12 in)	0.31 m	ft to m	0.3
3.28 ft	1 m	m to ft	3.28
1 mi	1.6 km	mi to km	1.6
0.62 mi	1 km	km to mi	0.62
1 in^2	6.45 cm^2	in^2 to cm^2	6.45
0.16 in^2	1 cm^2	cm^2 to in^2	0.16
1 ft^2	0.09 m^2	ft^2 to m^2	0.09
10.76 ft^2	1 m^2	m^2 to ft^2	10.8
1 ft^3	0.03 m^3	ft^3 to m^3	0.03
35.3 ft^3	1 m^3	m^3 to ft^3	35
1 gal (128 fl oz)	3.8 L	gal to L	3.8
0.264 gal	1 L	L to gal	0.26
1 qt (32 fl oz)	946.36 mL	qt to L	0.95
33.815 fl oz	1 L	L to qt	1.1

Temperature equivalents (approx)

°F	°C
32	0
50	10
60	15.5
61	16
65	18.3
70	21.1
75	23.8
80	26.6
82	28
85	29.4
90	32.2
102	38.8
103	39.4
104	40.0
105	40.5
106	41.1
212	100

°F = (°C × 9/5) + 32
°C = (°F - 32) × 5/9

Conversion chart, kg to lb (approx)

Pig size	Lb	Kg
Birth	3.3-4.4	1.5-2.0
Weaning	7.7	3.5
	11	5
	22	10
Nursery	33	15
	44	20
	55	25
	66	30
Grower	99	45
	110	50
	132	60
Finisher	198	90
	220	100
	231	105
	242	110
	253	115
Sow	300	135
	661	300
Boar	794	360
	800	363

1 tonne = 1000 kg
1 ppm = 0.0001% = 1 mg/kg = 1 g/tonne
1 ppm = 1 mg/L