Failed transfer of passive immunity is a component cause of pre-weaning disease in beef and dairy calves: A systematic review and meta-analysis

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Abstract

Pre-weaned beef and dairy calves that fail to receive maternal antibodies are more susceptible to disease. A systematic review and meta-analysis were performed to evaluate the association between failed transfer of passive immunity (FTPI) and disease in pre-weaned beef and dairy calves. Three databases were searched for relevant studies that evaluated calves diagnosed with FTPI at ≤8 days of age and recorded incidence of disease pre-weaning. Twenty-three, out of 182 identified references, were relevant and contained 46 studies. Twelve studies evaluated the effect of FTPI on morbidity, 18 on mortality, 8 on diarrhea, and 8 on pneumonia. Forty-two of 46 studies (91.3%) reported greater risk for disease among FTPI calves. The strength of association between FTPI and disease varied and was not resolved by subgrouping by outcome, animal type, test, cut-off point, or cumulative incidence of disease. Failed transfer of passive immunity is a component cause of calf disease that may have a greater impact in some populations than others.

Key words: diarrhea, pneumonia, risk ratio, morbidity, mortality, failed transfer of passive immunity.

Introduction

Newborn beef and dairy calves that fail to receive maternal antibodies are more susceptible to disease. Failed transfer of passive immunity (FTPI) is associated with negative health outcomes such as neonatal calf diarrhea, pneumonia, treatment with an antimicrobial, or death compared to calves that have adequate transfer of passive immunity (ATPI).[13,34,51] Calves that are diseased may have a decreased average daily gain and weaning weight.[10,14,55]

The serum concentration of immunoglobulin G (IgG) is most commonly measured to classify FTPI because it is the most abundant immunoglobulin in neonates that have consumed colostrum.[7] Immunoglobulin G can be measured with a radial immunodiffusion assay (RID), turbidimetric immunoassays (TIA), or enzyme-linked immunosorbent assay (ELISA). Because measuring IgG uses a laboratory-based test, other more rapid and less costly methods for classifying calves as having FTPI are commonly used. Handheld refractometers measure refractive index, or how much light is bent as it moves through a solution and crosses an optically more dense medium.[15] The refractometer is used to convert the refractive index of serum into a value quantifying serum total protein concentration. Serum total protein is correlated with IgG concentration as immunoglobulins are the largest fraction of soluble protein in the blood of calves that have consumed colostrum.[27] Calves with larger refractive indexes and serum total protein values are assumed to have larger quantities of IgG circulating in their bloodstream. Another method of FTPI classification is through serum turbidity. In this method, a solution of zinc or sodium sulfate is added to a sample of the calf's blood serum that causes an insoluble precipitate of zinc or sodium and proteins to form.[28] Serum samples with greater concentrations of IgG are expected to result in an opaque solution consisting of the suspension of the precipitate that classifies a calf as having ATPI.[48]

While low IgG concentrations and low serum total protein measurements are associated with disease, many IgG and serum total protein cut-off points have been proposed for classifying a calf as having FTPI. Studies that evaluate the risk of mortality have often used lower cut-off points than studies that evaluate morbidity as calves with lower IgG concentrations are at greater risk of death than disease.[5,47,56] Studies evaluating beef calves have often used higher cut-off points than dairy calves as beef calves are thought to achieve greater concentrations of serum IgG.[47]

The objective of this study was to conduct a systematic review and meta-analysis of literature regarding FTPI and evaluate the strength of association between FTPI and disease in pre-weaned calves.

Materials and methods

A systematic review of the literature and meta-analysis were performed to quantify the overall risk of disease for pre-weaned calves classified as having FTPI utilizing the standardized meta-analysis guidelines provided by PRISMA.[31] The question to be answered was "how strongly is an FTPI diagnosis associated with the risk of disease in pre-weaned calves?" Populations of interest included beef, dairy, or mixed breed cattle prior to weaning. Outcomes of interest included morbidity, mortality, antimicrobial treatment, diarrhea, and pneumonia. Failed transfer of passive immunity was defined as an immunological measurement below a cut-off point specified by a study and measured in calves between 24 hours and 8 days of age. Calves with values above the cut-off point were classified as having ATPI.

A systematic search of the literature was performed independently by two evaluators for studies published between 1950 and January 2020 using three searchable databases to identify relevant studies that classified calves as having FTPI and reported morbidity or mortality.[a,b,c] The time frame was

from 1950 to 2020 to include papers related to FTPI from the discovery and common usage of refractometry and RID.[12,15,26] Reference lists of retrieved articles were consulted for any relevant references not included in the literature search. Three combinations of search terms were used in the databases:

- attributable AND risk OR risk AND difference OR risk AND fraction OR population AND attributable AND risk AND (passive AND immunity OR passive AND transfer OR maternal AND immunity) AND (calves OR calf)
- (morbidity OR mortality) AND (passive AND immunity OR passive AND transfer OR maternal AND immunity) AND (calf OR calves OR bos OR bovine)
- (total AND protein OR IgG OR immunoglobulin AND G) AND (morbidity OR mortality) AND (calf OR calves).

Longitudinal study designs, including randomized controlled trials and observational studies using cohorts, were eligible for use in determining the relative risk of FTPI on the disease outcome. Included studies must have 1) reported at least one of the targeted outcomes, 2) defined a cut-off point for FTPI, and 3) either quantify the number of calves with FTPI and ATPI or provide enough information to determine the number of calves with FTPI and ATPI. Exclusion criteria include case reports, case series, case-control, and review study designs, as well as publications written in languages other than English. Challenge studies were also excluded as the study design does not mimic natural infection. Studies involving hoof stock other than domesticated cattle were excluded.

For the primary screening round, each title and abstract were reviewed for relevance. Studies were deemed relevant if the title or abstract contained a diagnostic test for FTPI and at least one health outcome. Studies that passed the first screening were uploaded into a bibliographical management software and duplicates were removed.[d] The second screening round was used to assess the full articles for all inclusion criteria. Reasons for exclusions were categorized as calf age, FTPI/ATPI classification, morbidity/mortality, and study design (Figure 1). The conditions for each exclusion category are as follows: 1) studies which collected blood from calves for FTPI/ATPI classification at greater than 8 days of age or did not state what age calves underwent blood collection were classified as "calf age"; 2) studies that failed to state the test and cut-off point for FTPI/ATPI or the number of calves in each category were classified as "FTPI/ATPI classification"; 3) studies that did not classify morbidity/mortality by ATPI or FTPI were classified as "morbidity/mortality"; and 4) studies that only collected blood from a subset of calves, reported odds or risk ratios without stating the number of calves in each group or had an excludable study design were classified as "study design". If a study was excluded for FTPI/ATPI classification or morbidity/mortality, but met all other inclusion criteria, the authors were contacted for the missing information.

For each study, the following data were extracted and compiled using spreadsheet software.[e] Study characteristics included author, year, country, study design, type of test used to determine FTPI, cut-off value used, number of calves in each outcome, and the length of observation. Participant characteristics included animal type (beef or dairy), population size, and number of calves classified as FTPI or ATPI. Animal type was classified for calves based on sire and dam breeds. Calves born with both parents classified as dairy breeds were classified as dairy. Calves born with both parents classified as a beef breed were classified as beef. Calves born with one parent classified as beef and one as dairy were classified as dairy if the calves were removed from their dam shortly after birth and hand- reared, or as beef if the calves remained with their dam prior to weaning. Outcomes included case definitions used, number of reported cases for calves with disease, and the number of calves at risk based on FTPI status. If a study reported a marginal or partial immune status, those calves were included as FTPI. Cumulative incidence of morbidity was defined as the total number of calves that experienced a morbidity event during the length of observation divided by the total number of calves starting the study. Studies that measured more than one cause of morbidity, such as pneumonia and diarrhea, were excluded from the total morbidity analysis, because a calf with both diseases could be counted twice, unless there was an overall treatment or morbidity category. Studies with a cumulative incidence of morbidity greater than or equal to 10%, an empirically selected threshold, were classified as high while studies with less than 10% were classified as low. Cumulative incidence of mortality was defined as the total number of calves that died during the length of observation divided by the total number of calves starting the study. Studies with a cumulative incidence of mortality greater than or equal to 5% were classified as high while less than 5% was low.[32,51] The strength of association between FTPI and disease outcome (morbidity, mortality, diarrhea, pneumonia) for each study was assessed by the non-adjusted risk ratio (RR) and 95% confidence intervals using a meta-analysis software.[f]

$$\text{Risk ratio} = \frac{\textit{Number of calves with FTPI and disease / Number of calves with FTPI}}{\textit{Number of calves with ATPI and disease / Number of calves with ATPI}}$$

Studies that reported more than one disease outcome had more than one RR calculated. Attributable fraction was calculated for each disease outcome by study to determine the proportion of disease in calves with FTPI that is due to FTPI.

$$\textit{Attributable fraction} = \frac{(RR - 1)}{RR}$$

Attributable fraction 95% confidence intervals were also calculated.[19] The preventable fraction was calculated for studies with a negative attributable fraction.

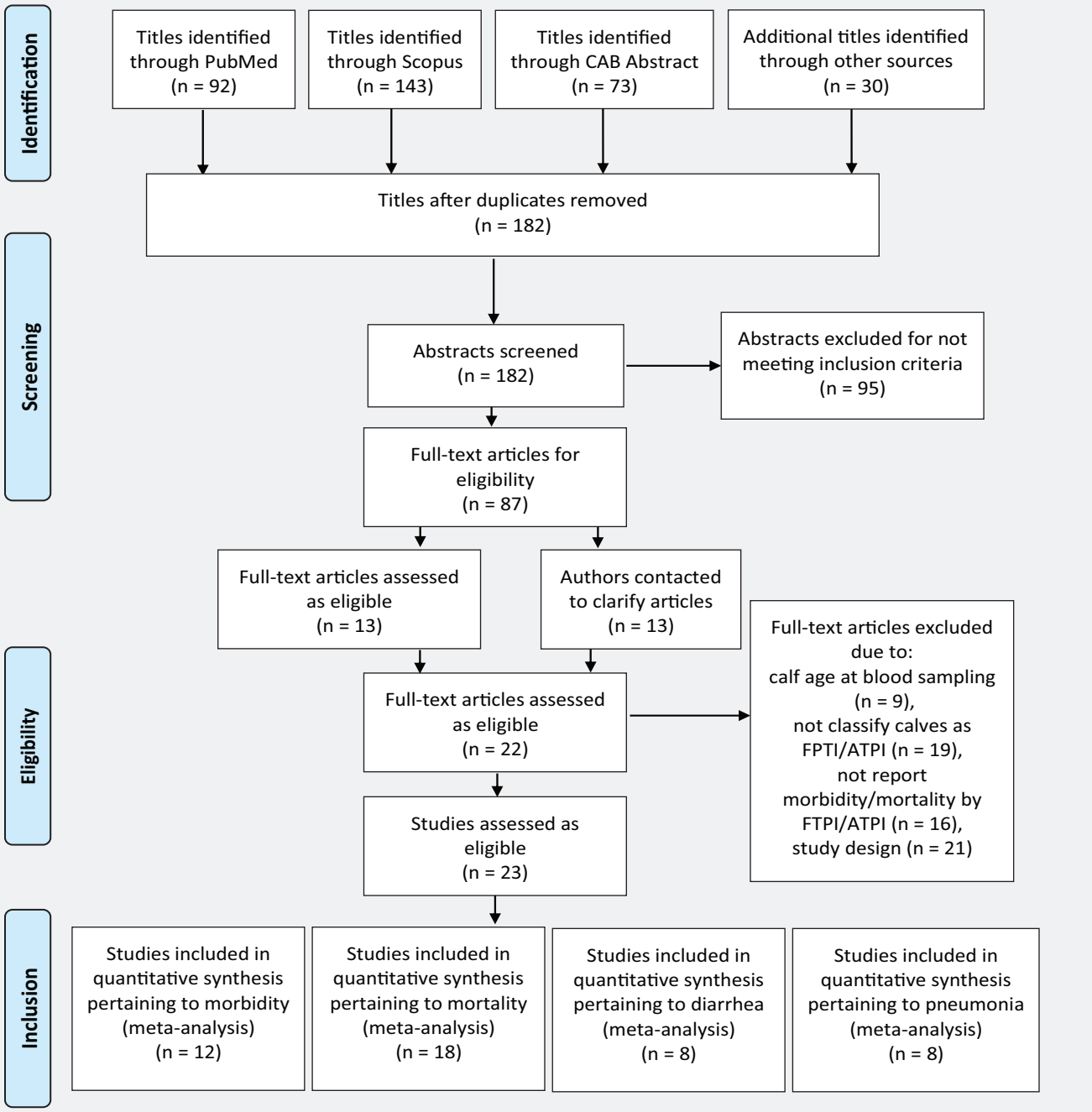
$$\textit{Preventable fraction} = \frac{\textit{(Cumulative incidence of disease in calves with ATPI) – (Cumulative incidence of disease in calves with FTPI)}}{\textit{Cumulative incidence of disease in calves with ATPI}}$$

Population attributable fraction was calculated for each disease outcome by study to determine the proportion of disease in a population due to FTPI.[2]

$$\textit{Population attributable fraction} = \frac{\textit{Proportion of calves with FTPI} * (RR - 1)}{[\textit{Proportion of calves with FTPI} * (RR\text{-}1)] + 1} * 100\%$$

A meta-analysis was performed to determine an overall risk ratio (RR) for an outcome when three or more studies with a homogenous RR were available. Risk ratio homogeneity

Figure 1: The flow of the selection process. The search was completed on July 15, 2022. FTPI, failed transfer of passive immunity; ATPI, adequate transfer of passive immunity.



was assessed using a random effects approach and weighting of primary studies using the Mantel-Haenszel method in a meta-analysis software.[f] Homogeneity between studies was assessed with the Q-test and I^2 statistic with the assumption that the RR were normally distributed.[30] Studies were labeled as heterogenous, with a significant Q-test ($P < 0.10$) indicating a significant variability between studies that prevented them from being combined, or homogenous, with a non-significant Q-test ($P \geq 0.10$) indicating similar variability between studies indicating that they could be combined. A significance level of $\alpha = 0.10$ was selected to reduce the chance of a type II error. If heterogeneity existed, studies were sub-grouped to assess contextual heterogeneity first by outcome then animal type, test type, cumulative incidence classification, and cut-off point. For comparisons lacking at least three studies or homogeneity, data was reported as a narrative synthesis.

Study quality was assessed using Research Triangle Institute item bank for non-randomized trials.[18,53] The Research Triangle Institute item bank contains 29 questions to evaluate risk of bias in observational studies. Six questions were selected, based on applicability to experimental and observational study designs, to evaluate study quality in this review.[33] The six questions (Q) were: **Q1:** Do the inclusion/exclusion criteria vary across the comparison groups of the study?; **Q2:** Does the strategy for recruiting participants into the study differ across groups?; **Q3:** Is the selection of the comparison group

appropriate, after taking into account feasibility and ethical considerations?; **Q4**: Are interventions/exposures assessed using valid and reliable measures, implemented consistently across all study participants?; **Q5:** Are outcomes assessed using valid and reliable measures, implemented consistently across all study participants?; **Q6:** Is the length of follow-up the same for all groups? Two individuals independently evaluated the studies for risk of bias and any discrepancies were discussed to reach a consensus. A low study quality was assigned to studies with 3 or more negative responses, high was defined as all study questions had positive responses, and moderate was assigned to studies that did not meet the criteria for high or low quality.[33]

Results

The flow diagram summarizing the study selection process is shown in Figure 1. A total of 22 full text articles consisting of 23 studies were found to assess the effect of FTPI on disease in the pre-weaning period. The publication year range for included studies was from 1977 to 2019.[29,32] Two of the 18 dairy articles used the same population to sample calves and 3 of the 4 beef articles were performed on the same herd, but in different years.[10,34,49,50,57] Twelve studies were included in the systematic review on overall morbidity or treatment. Overall mortality included 18 studies in the systematic review. Studies that evaluated calves with diarrhea or pneumonia were assessed in separate systematic reviews consisting of 8 studies each. The study characteristics are presented in Table 1. One manuscript altered the cut-off point, 5.2 g/dL or 5.7 g/dL, depending on if the outcome was mortality or pneumonia, respectively.[56]

The study quality for each study is presented in Figure 2. All studies were high- to moderate- quality. Most moderate-quality studies failed to describe how outcomes were measured or provided vague definitions that resulted in a subjective assessment. Most studies provided sufficient information about test performance, how the diagnostic tests were used to assess the immunological indicator quantity, and classification of FTPI. A summary of evidence is presented in Table 2. Most study outcomes favored ATPI over FTPI (42/46; 91.3%). A forest plot of the RR for all studies and disease outcomes is displayed in Figure 3. The association between FTPI and overall disease was heterogeneous ($P < 0.0001$).

Of the 12 studies that evaluated the association between FTPI and overall morbidity or treatment, 9 studies observed morbidity in dairy calves and 3 studies were of beef calves. In studies evaluating morbidity, 5 different tests were used to categorized calves as having FTPI, RID (n = 6), TIA (n = 2), refractometry (n = 2), biuret (n = 1), and gamma glutamyltransferase test (GGT; n = 1). Seven cut-off points were used to classify calves as having FTPI in morbidity studies, complete GGT opacity (n = 1), 1000 mg/dL of IgG (n = 4), 1500 mg/dL of IgG (n = 1), 1600 mg/dL of IgG (n = 2), 2400 mg/dL of IgG (n = 1), 5.2 g/dL of serum total protein (n = 1), and 5.5 g/dL of serum total protein (n = 2). Most of the studies evaluating morbidity had a high cumulative incidence (n = 11). The strength of association (RR = 0.96 to 5.24) between FTPI and overall morbidity or treatment differed by study ($P < 0.0001$) that was not resolved by subgrouping by animal type, test, cut-off point, or cumulative incidence. The attributable fraction for morbidity ranged from -4 to 81% (Figure 4A) and the population attributable fraction was -1 to 59% (Figure 5A). Two studies had negative attributable risk fractions and, therefore, had preventable fractions of 3 and 4%.[25,32]

Of the 18 studies that evaluated the association between FTPI and mortality, 15 studies observed mortality in dairy calves and 3 studies were of beef calves. In studies evaluating mortality, 6 different tests were used to categorized calves as having FTPI, RID (n = 10), refractometry (n = 3), TIA (n = 2), biuret (n = 1), electrophoresis (n = 1), and GGT (n = 1). Nine cut-off points were used to classify calves as having FTPI in mortality studies, complete GGT opacity (n = 1), 800 mg/dL of IgG (n = 1), 1000 mg/dL of IgG (n = 7), 1200 mg/dL of IgG (n = 1), 1500 mg/dL of IgG (n = 1), 1600 mg/dL of IgG (n = 2), 2400 mg/dL of IgG (n = 1), 5.2 g/dL of serum total protein (n = 1), and 5.5 g/dL of serum total protein (n = 3). Most of the studies evaluating mortality had a high cumulative incidence (n = 12). The strength of association (RR = 0.80 to 12.99) between FTPI and mortality differed by study ($P < 0.0001$) that was not resolved by subgrouping by animal type, test, cut-off point, or cumulative incidence. The attributable fraction for mortality ranged from -26 to 92% (Figure 4B) and the population attributable fraction was -9 to 86% (Figure 5B). Two studies had negative attributable risk fractions and, therefore, had preventable fractions of 12 and 20%.[36,52]

Of the 8 studies that evaluated pneumonia, 7 studies observed pneumonia in dairy calves and 1 study was of beef calves. In studies evaluating pneumonia, 3 different tests were used to categorized calves as having FTPI, RID (n = 5), TIA (n = 2), and refractometry (n = 1). Four cut-off points were used to classify calves as having FTPI in pneumonia studies, 800 mg/dL of IgG (n = 1), 1000 mg/dL of IgG (n = 5), 1600 mg/dL of IgG (n = 1), and 5.7 g/dL of serum total protein (n = 1). Seven of the 8 studies (88%) had a high cumulative incidence of pneumonia. The strength of association (RR = 1.05 to 5.56) between FTPI and pneumonia differed by study ($P < 0.0001$) that was not resolved by subgrouping by animal type, test, cut-off point, or cumulative incidence. The attributable fraction for pneumonia ranged from 4 to 82% (Figure 4C) and the population attributable fraction was 1 to 55% (Figure 5C).

Of the 8 studies that evaluated diarrhea, 7 studies observed diarrhea in dairy calves and 1 study was of beef calves. In studies evaluating diarrhea, 3 different tests were used to categorize calves as having FTPI, RID (n = 5), TIA (n =2), and electrophoresis (n = 1). Three cut-off points were used to classify calves as having FTPI in diarrhea studies, 800 mg/dL of IgG (n = 1), 1000 mg/dL of IgG (n = 6), and 1600 mg/dL of IgG (n = 1). Seven of the 8 studies (88%) had a high cumulative incidence of diarrhea. The strength of association (RR = 1.15 to 2.13) between FTPI and diarrhea differed by study ($P = 0.0004$) that was not resolved by subgrouping by animal type, test, cut-off point, or cumulative incidence. The attributable fraction for diarrhea ranged from 13 to 53% (Figure 4D) and the population attributable fraction was 3 to 27% (Figure 5D).

Discussion

All but four studies found that calves with FTPI were at greater risk for disease compared to calves with ATPI. This meta-analysis found a variable strength of association between FTPI and the risk of pre-weaning disease that could not be summarized by a single value. Attributable fraction estimates the importance of an exposure among those exposed. Whereas population attributable fraction estimates the importance of the exposure on the disease burden of the population. In some studies, but not all, FTPI was an important factor explaining pre-weaning disease among those that failed to

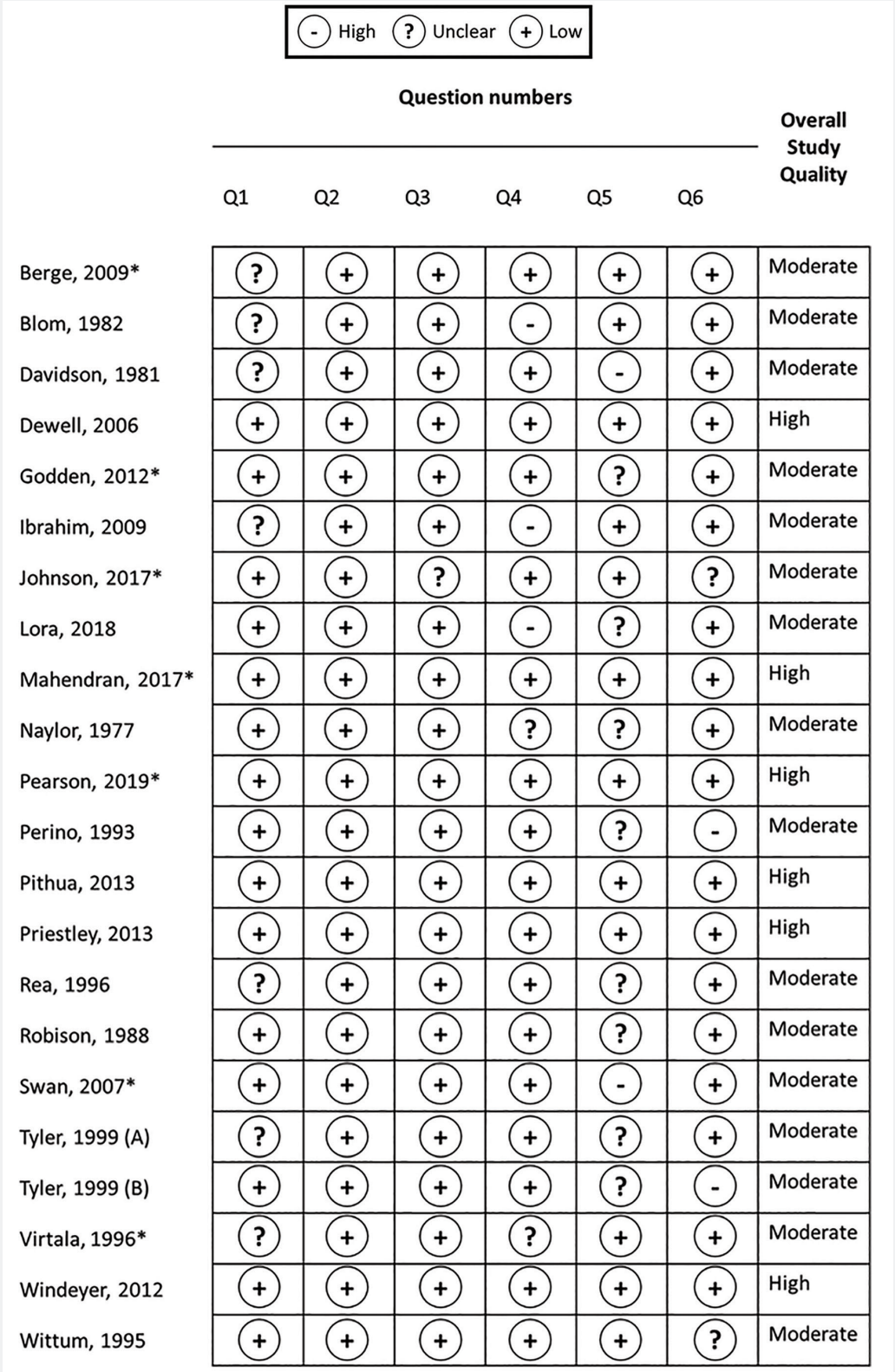
Table 1: Characteristics of studies reporting the quantity of calves with failed and adequate transfer of passive immunity and measured health events.

Study, Year	Population	Study design†	Country	Test†	Test Cut-off	Number of animals in study	Outcome	Cumulative incidence of morbidity†	Cumulative incidence of mortality†	Duration of follow-up (days)
Berge, 2009*	Dairy	RCT	US	RID	1000 mg/dL	272	Diarrhea, mortality, and pneumonia	High	High	28
Blom, 1982	Dairy	Cohort	Netherlands	GGT	Complete	193	Morbidity and mortality	High	High	90
Davidson, 1981	Dairy	RCT	US	RID	1500 mg/dL	186	Morbidity and mortality	High	High	63
Dewell, 2006	Beef	Cohort	US	RID	1600 mg/dL	1559	Morbidity and mortality	High	Low	200
Godden, 2012*	Dairy	RCT	US	TIA	1000 mg/dL	1071	Diarrhea, mortality, pneumonia, and treatment	High	Low	56
Ibrahim, 2009	Dairy	Cohort	Ethiopia	Biuret	5.5 g/dL	354	Morbidity and mortality	High	High	180
Johnson, 2017*	Dairy	Cohort	UK	RID	1000 mg/dL	492	Diarrhea and pneumonia	High		56
Lora, 2018	Dairy	Cohort	Italy	Electrophoresis	1000 mg/dL	78	Diarrhea and mortality	High	High	30
Mahendran, 2017*	Dairy	Cohort	UK	Refractometry	5.2 g/dL	468	Morbidity	High		56
Naylor, 1977	Dairy	Cohort	US	Refractometry	5.5 g/dL	32	Morbidity	High		36
Pearson, 2019*	Beef	RCT	Canada	RID	2400 mg/dL	225	Morbidity and mortality	Low	High	42
Perino, 1993	Beef	Cohort	US	RID	1600 mg/dL	48	Diarrhea and pneumonia	Low		150
Pithua, 2013	Dairy	Cohort	US	RID	1000 mg/dL	561	Diarrhea, mortality, pneumonia, and treatment	High	High	60
Priestley, 2013	Dairy	RCT	US	RID	1000 mg/dL	147	Morbidity and mortality	High	High	56
Rea, 1996	Dairy	Cohort	US	RID	1000 mg/dL	246	Mortality		High	100
Robison, 1988	Dairy	Cohort	US	RID	1200 mg/dL	1000	Mortality		Low	70
Swan, 2007*	Dairy	RCT	US	TIA	1000 mg/dL	508	Diarrhea, mortality, pneumonia, and treatment	High	High	56
Tyler, 1999 (A)	Dairy	Cohort	US	Refractometry	5.5 g/dL	3479	Mortality		High	112
Tyler, 1999 (B)	Dairy	RCT	US	Refractometry	5.5 g/dL	864	Mortality		Low	100
Virtala, 1996*	Dairy	Cohort	US	RID	800 mg/dL	408	Diarrhea, mortality, and pneumonia	High	High	90
Windeyer, 2012 (A)	Dairy	RCT	Canada/US	Refractometry	5.2 g/dL	2874	Mortality		Low	90
Windeyer, 2012 (B)	Dairy	RCT	Canada/US	Refractometry	5.7 g/dL	2874	Pneumonia	High		90
Wittum, 1995	Beef	Cohort	US	RID	1600 mg/dL	263	Morbidity and mortality	High	Low	163

* denotes studies that additional data was requested

† RCT = randomized controlled trial; RID = Radial immunodiffusion; GGT = gamma glutamyltransferase test; TIA = turbidimetric immunoassays; cumulative incidence of mortality ≥ 5% = high; cumulative incidence of mortality < 5% = low; Cumulative incidence of morbidity ≥ 10% = high; Cumulative incidence of morbidity < 10% = low

Figure 2: Study quality for included studies.



Q1: Do the inclusion/exclusion criteria vary across the comparison groups of the study?; **Q2:** Does the strategy for recruiting participants into the study differ across groups?; **Q3:** Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?; **Q4:** Are interventions/exposures assessed using valid and reliable measures, implemented consistently across all study participants?; **Q5:** Are outcomes assessed using valid and reliable measures, implemented consistently across all study participants?; **Q6:** Is the length of follow-up the same for all groups?

* denotes studies that additional data was requested

receive colostrum. Similarly, in some studies, but not all, FTPI was an important component explaining the disease burden of the population studied. Variability in RR, attributable fraction, and population attributable fraction suggests that colostrum consumption was an important factor in some studies but not in others. Other factors contribute to pre-weaning disease and may be more important than colostrum consumption depending on the study. From these observations, we might conclude that consumption of colostrum is a component cause of disease in pre-weaned calves.

A potential limitation of this meta-analysis is the various ways studies classified both disease and FTPI. The potential for misclassification by exposure or disease may introduce misclassification bias. Each study used a different case definition for disease and may have been biased by the observer, where calves identified as diseased in one study may not have in another. In most studies, disease was identified by a variety of individuals which may contribute to misclassification. When evaluating disease, mortality is a more definitive clinical outcome compared to morbidity, which can vary in presentation, case definition, and severity, but mortality lacks specificity to a disease process. Previous studies have observed a lack of sensitivity and specificity when visually classifying morbidity in cattle.[6,17,46,54] Additionally, this meta-analysis found a lack of uniformity when classifying calves with FTPI as many test and cut-off points were used and could lead to misclassification of FTPI status. However, there is not perfect system for predicting which calves will become disease or have FTPI. When evaluating disease, some studies used scoring systems[3,20,21,25,37,56] or performed personnel training[10,34,36,37,52,57] to limit potential misclassification. For classifying FTPI status, correlation between tests for FTPI using serum total protein and IgG have shown good agreement.[1,5,11,29,35,40,43,48] Confounding, when an extraneous variable accounts for the association between the intended variables, is a common bias with observational studies.[45] Fourteen of the included studies were observational studies and the association between FTPI and disease may have been influenced by factors outside of the observed variables. However, a repeatable relationship was observed between FTPI and disease across studies that confirms the association between FTPI and disease. Unaccounted variables may have contributed to the observed variability.

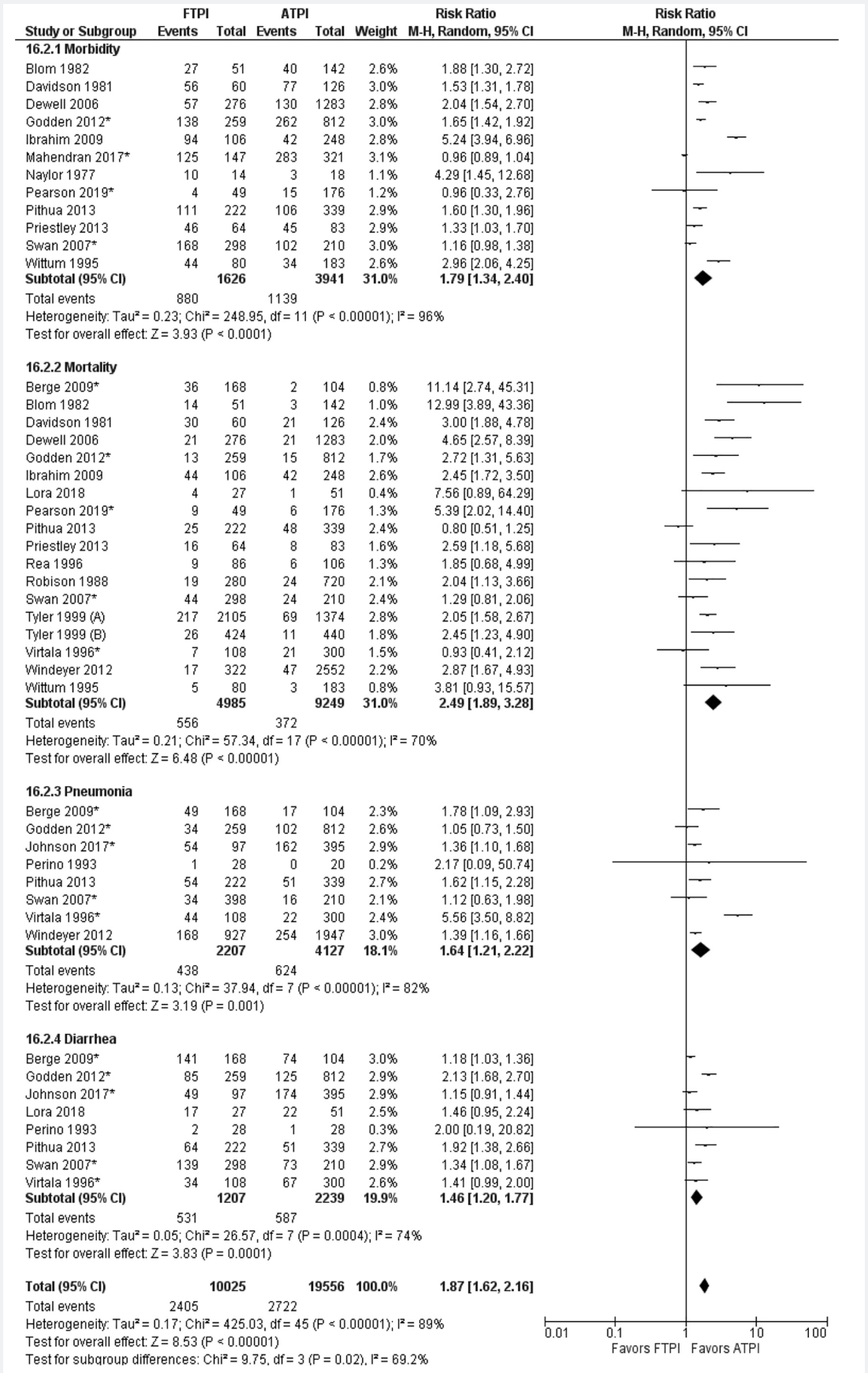
The subjective nature of the risk of bias assessment may depend upon the evaluator of the study. To assess the risk of bias between various study designs, 6 questions were selected. The selected questions highlighted the ambiguity in diagnostic test strategies for FTPI and the varying disease classifications used which may contribute to misclassification noted by the heterogenous risk ratios.

Beef and dairy studies were included due to the limited number of studies available on FTPI and pre-weaning disease. Beef and dairy calves with FTPI were found to be at a greater risk of disease, however, beef and dairy herds have different colostrum management and calf rearing practices which could contribute to the observed heterogeneity in the strength of association. Limiting the studies to only dairy studies still produced a heterogenous RR. This finding could be an artifact of colostrum allocation as some dairy studies randomly allocated calves to receive different types of colostrum replacers or only used colostrum replacers.[21,36,37,44] Colostrum contains other nutrients besides IgG that may reduce pre-weaning disease, however, a previous study found no difference in disease between calves with ATPI that received maternal colostrum compared to a colostrum replacer.[23] The type of colostrum that calves received was not analyzed in this meta-analysis. Additionally, the length of observation differed between beef and dairy articles. Most of the articles evaluating beef calves followed calves out to weaning at approximately 5 to 6 months of age while articles evaluating dairy calves followed calves until weaning at 8 to 9 weeks of age. The additional 4 months that beef calves were observed may have artificially inflated the cumulative incidence of disease and included disease events not associated with colostrum consumption resulting in a RR closer to 1. Censoring the length of observation to 45 or 60 days after birth would control for a possible time influence, but insufficient data was available within the articles to evaluate this. Publication bias, typically assessed by examining a funnel plot for small-study effects, could not be performed for this meta-analysis due to a lack of homogeneity in the strength of association. Publication bias is commonly recommended when there are greater than or equal to 10 homogenous studies.[18] The present study had an insufficient number of homogenous studies to reliably assess symmetry.

Heterogeneity in the strength of association between FTPI and disease is consistent with the findings of a previous meta-analysis.[38] The strength of association may differ over time and between populations as the prevalence of the exposure changes.[8] For this meta-analysis the estimation of attributable fraction describes the impact of colostrum consumption on the individual calf. Just like RR, the attributable fraction varied by study and outcome. In some studies, the RR was high and the attributable fraction was high indicating that for calves with FTPI failure to achieve adequate colostral immunity was an important cause of mortality.[3,20,24] For other studies where the strength of association between FTPI and disease was low and the attributable fraction was also low suggests that other causes of morbidity besides FTPI were more important in calves with FTPI.[16,32] Other factors, such as nutrition, may contribute to morbidity and are not impacted by colostrum consumption. Additionally, some studies had negative attributable fractions where not receiving colostrum was protective.[25,32,36,52] Poor colostrum hygiene may have contributed to the negative effects of receiving colostrum.

Population attributable fraction has the underlying assumption of causality between the exposure (FTPI) and outcome (disease) within a population.[22] Therefore, for this meta-analysis the estimation of population attributable fraction describes the impact of colostrum consumption on the population. In studies with a high population attributable fraction, failure to achieve adequate colostral immunity was an important contributor to mortality in the population and if sufficient colostral immunity were achieved, there would have been a large reduction in the incidence of diseased calves.[3,4] Other studies with a low population attributable fraction suggest that other component causes of morbidity were more important in those herds.[21,36] In these populations, the disease process might not be mitigated by achieving colostral immunity and the elimination of FTPI from these might have resulted in minimal change in the incidence of diseased calves. However, for some populations, the attributable fraction was relatively high (e.g., greater than 50%) but the population attributable fraction was relatively low (e.g., less than 20%).[10,56] In these situations, colostrum consumption was an important factor for mortality in calves with FTPI, but the proportion of calves with FTPI in the population was low. Therefore, on the population level, colostrum consumption did not greatly impact mortality.

Figure 3: Forest plot of relative risk of disease from studies that evaluated transfer of passive immunity in beef or dairy calves in the pre-weaned period.



* denotes studies that additional data was requested

Table 2: Summary of evidence to assess the effect of failed transfer of passive immunity in calves on morbidity, mortality, diarrhea and pneumonia.

Study, Year	Outcome	Exposure†	Event rate§	Relative risk (95% confidence)	Attributable fraction (%; 95% confidence)	Population attributable fraction (%)
Berge, 2009*	Diarrhea	FTPI	141/168	1.18 (1.03, 1.36)	15 (5, 25)	10
		ATPI	74/104	Reference		
	Mortality	FTPI	36/168	11.14 (2.74, 45.31)	91 (83, 100)	86
		ATPI	2/104	Reference		
	Pneumonia	FTPI	49/168	1.78 (1.09, 2.93)	44 (33, 54)	33
		ATPI	17/104	Reference		
Blom, 1982	Morbidity	FTPI	27/51	1.88 (1.30, 2.72)	47 (32, 62)	19
		ATPI	40/142	Reference		
	Mortality	FTPI	14/51	12.99 (3.89, 43.36)	92 (83, 101)	76
		ATPI	3/142	Reference		
Davidson, 1981	Morbidity	FTPI	56/60	1.53 (1.31, 1.78)	35 (21, 48)	15
		ATPI	77/126	Reference		
	Mortality	FTPI	30/60	3.00 (1.88, 4.78)	67 (53, 80)	39
		ATPI	21/126	Reference		
Dewell, 2006	Morbidity	FTPI	57/276	2.04 (1.54, 2.70)	51 (47, 55)	16
		ATPI	130/1283	Reference		
	Mortality	FTPI	21/276	4.65 (2.57, 8.39)	78 (76, 81)	39
		ATPI	21/1283	Reference		
Godden, 2012*	Diarrhea	FTPI	85/259	2.13 (1.68, 2.70)	53 (48, 59)	21
		ATPI	125/812	Reference		
	Mortality	FTPI	13/259	2.72 (1.31, 5.63)	63 (61, 65)	29
		ATPI	15/812	Reference		
	Pneumonia	FTPI	34/259	1.05 (0.73, 1.50)	4 (0, 9)	1
		ATPI	102/812	Reference		
	Treatment	FTPI	138/259	1.65 (1.42, 1.92)	39 (33, 46)	14
		ATPI	262/812	Reference		
Ibrahim, 2009	Morbidity	FTPI	94/106	5.24 (3.94, 6.96)	81 (70, 92)	56
		ATPI	42/248	Reference		
	Mortality	FTPI	44/106	5.15 (3.19, 8.29)	81 (72, 89)	55
		ATPI	20/248	Reference		
Johnson, 2017*	Diarrhea	FTPI	49/97	1.12 (0.89, 1.41)	13 (2, 24)	3
		ATPI	174/395	Reference		
	Pneumonia	FTPI	54/97	1.36 (1.10, 1.68)	26 (15, 37)	7
		ATPI	162/395	Reference		
Lora, 2018	Diarrhea	FTPI	17/27	1.46 (0.95, 2.24)	31 (8, 55)	14
		ATPI	22/51	Reference		
	Mortality	FTPI	4/27	7.56 (0.89, 64.29)	87 (75, 98)	69
		ATPI	1/51	Reference		

Table 2 continued on next page

Table 2 continued:

Study, Year	Outcome	Exposure†	Event rate§	Relative risk (95% confidence)	Attributable fraction (%; 95% confidence)	Population attributable fraction (%)
Mahendran, 2017*	Morbidity	FTPI	125/147	0.96 (0.89, 1.04)	-4 (-10, 3)	-1
		ATPI	283/321	Reference		
Naylor, 1977	Morbidity	FTPI	10/14	4.29 (1.45, 12.68)	77 (42, 111)	59
		ATPI	3/18	Reference		
Pearson, 2019*	Morbidity	FTPI	4/49	0.96 (0.33, 2.76)	-4 (-13, 4)	-1
		ATPI	15/176	Reference		
	Mortality	FTPI	9/49	5.39 (2.02, 14.40)	81 (74, 89)	49
		ATPI	6/176	Reference		
Perino, 1993	Diarrhea	FTPI	2/28	1.43 (0.14, 14.70)	30 (16, 44)	20
		ATPI	1/20	Reference		
	Pneumonia	FTPI	1/28	2.17 (0.09, 50.74)	54 (46, 62)	41
		ATPI	0/20	Reference		
Pithua, 2013	Diarrhea	FTPI	64/222	1.92 (1.38, 2.66)	48 (41, 55)	27
		ATPI	51/339	Reference		
	Mortality	FTPI	25/222	0.80 (0.51, 1.25)	-26 (-31, -20)	-9
		ATPI	48/339	Reference		
	Pneumonia	FTPI	54/222	1.23 (0.90, 1.69)	19 (12, 26)	8
		ATPI	67/339	Reference		
	Treatment	FTPI	111/222	1.60 (1.30, 1.96)	37 (29, 46)	19
		ATPI	106/339	Reference		
Priestley, 2013	Morbidity	FTPI	46/64	1.33 (1.03, 1.70)	25 (9, 40)	12
		ATPI	45/83	Reference		
	Mortality	FTPI	16/64	2.59 (1.18, 5.68)	61 (49, 73)	41
		ATPI	8/83	Reference		
Rea, 1996	Mortality	FTPI	9/86	1.85 (0.68, 4.99)	64 (58, 70)	39
		ATPI	6/106	Reference		
Robinson, 1988	Mortality	FTPI	19/280	2.04 (1.13, 3.66)	51 (48, 54)	22
		ATPI	24/720	Reference		
Swan, 2007*	Diarrhea	FTPI	139/298	1.34 (1.08, 1.67)	25 (17, 34)	17
		ATPI	73/210	Reference		
	Mortality	FTPI	44/298	1.29 (0.81, 2.06)	23 (17, 29)	15
		ATPI	24/210	Reference		
	Pneumonia	FTPI	34/298	1.50 (0.85, 2.64)	33 (28, 38)	23
		ATPI	16/210	Reference		
	Treatment	FTPI	168/298	1.16 (0.98, 1.38)	14 (5, 23)	9
		ATPI	102/210	Reference		
Tyler, 1999 (A)	Mortality	FTPI	217/2105	2.05 (1.58, 2.67)	51 (49, 53)	39
		ATPI	69/1374	Reference		

Table 2 continued on next page

Table 2 continued:

Study, Year	Outcome	Exposure†	Event rate§	Relative risk (95% confidence)	Attributable fraction (%; 95% confidence)	Population attributable fraction (%)
Tyler, 1999 (B)	Mortality	FTPI	26/424	2.45 (1.23, 4.90)	59 (57, 62)	42
		ATPI	11/440	Reference		
Virtala, 1996*	Diarrhea	FTPI	34/108	1.41 (0.99, 2.00)	29 (20, 39)	10
		ATPI	67/300	Reference		
	Mortality	FTPI	7/108	0.93 (0.41, 2.12)	-8 (-14, -2)	-2
		ATPI	21/300	Reference		
	Pneumonia	FTPI	44/108	5.56 (3.50, 8.82)	82 (74, 90)	55
		ATPI	22/300	Reference		
Windeyer, 2012 (A) ‡	Mortality	FTPI	17/322	2.87 (1.67, 4.93)	65 (63, 67)	17
		ATPI	47/2552	Reference		
Windeyer, 2012 (B) ‡	Pneumonia	FTPI	168/927	1.39 (1.16, 1.66)	28 (25, 31)	11
		ATPI	254/1947	Reference		
Wittum, 1995	Morbidity	FTPI	44/80	2.96 (2.06, 4.25)	66 (54, 78)	37
		ATPI	34/183	Reference		
	Mortality	FTPI	5/80	3.81 (0.93, 15.57)	74 (69, 78)	46
		ATPI	3/183	Reference		

* Denotes studies that additional data was requested
† ATPI = adequate transfer of passive immunity; FTPI = failed transfer of passive immunity
‡ Windeyer, 2012 used a serum total protein cut-off point of 5.2 g/dL for mortality (A) and 5.7 g/dL for pneumonia (B)
§ Event rate is the number of individuals with the exposure and outcome divided by the number of individuals with the exposure

Disease is an interaction between an infectious agent, a susceptible host, and an environment that brings the agent and host together.[8] Failed transfer of passive immunity increases a calf's susceptibility to an agent and is therefore one component of the many contributing causes of disease in pre-weaned calves. However, pre-weaning disease is not always caused by an infectious etiology which can be mitigated by colostral immunity. Individual factors or exposures that contribute to the development of disease are called component causes and are pictorially represented in Figure 6 as a pie slice. When a pie is complete, the collective exposures cause the disease and the combination of factors that complete the pie is termed a sufficient cause. Some factors, such as factor C in Figure 6, are present in all the sufficient causes of disease and are considered a necessary cause. In diseases that are caused by multiple factors, most identified component causes are neither necessary nor sufficient to produce disease.[8] Failed transfer of passive immunity is a component cause of pre-weaning disease, but the RR for disease was also dependent on the distribution of other component causes within the population. Other potential component cause of pre-weaning disease such as stocking density, pathogen density, nutrition, management factors, and other stressors were not measured within this meta-analysis but may have contributed to disease in the various studies.[42] Different distribution of component causes can explain the lack of repeatability and difference in RR observed in studies with similar designs and populations but were performed in different years.[10,34,49,50,57]

Failed transfer of passive immunity is a component cause of disease in pre-weaned calves. However, the impact of FTPI on a calf or herd's risk of developing disease depends on the presence of other component causes of disease. Interventions to prevent FTPI may reduce the risk of disease in some calves and in some populations but have less impact in others.

Endnotes

[a]Scopus (https://www.scopus.com/search/form.uri?display=basic#basic, Elsevier, Netherlands)

[b]Pubmed (https://pubmed.ncbi.nlm.nih.gov/, National Institute for Health, Bethesda, MD)

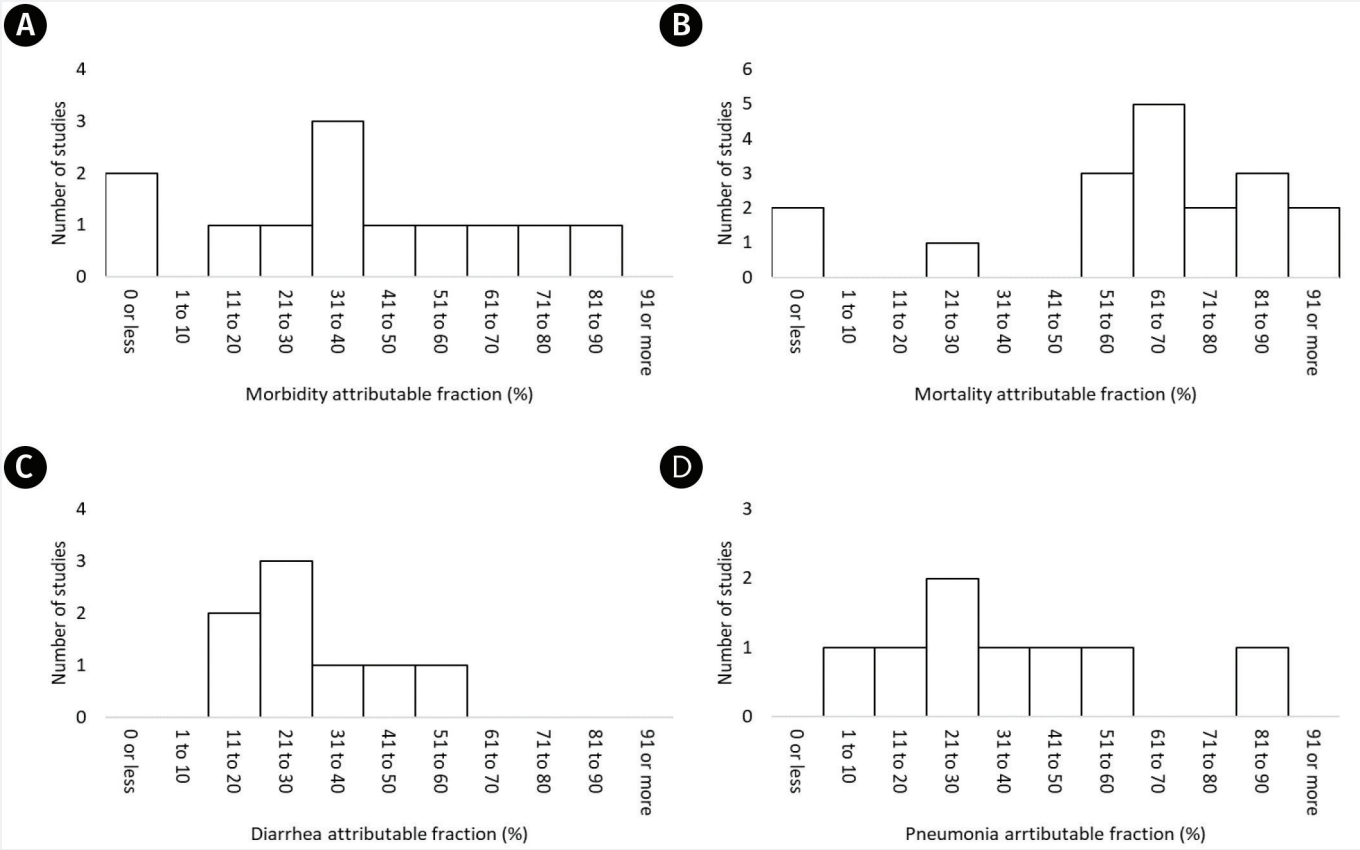
[c]CAB Abstract (https://www.cabdirect.org/, United Kingdom)

[d]Zotero 5.0 (http://www.zotero.org, George Mason University, Fairfax, VA)

[e]Microsoft Excel (Excel 2016, Microsoft Corp, Redmond, WA)

[f]Review Manager (RevMan 2014 Version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration)

Figure 4: Histogram of attributable fraction for morbidity (A), mortality (B), diarrhea (C) and pneumonia (D) from studies that evaluated transfer of passive immunity in beef or dairy calves in the pre-weaned period.



Conflict of interest

The authors declare no conflicts of interest.

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Author contributions

AT: Conceptualization and design, data acquisition, analysis, and interpretation, and manuscript drafting

DS: Data acquisition and interpretation, and manuscript revisal and approval

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Figure 5: Histogram of population attributable fraction for morbidity (A), mortality (B), diarrhea (C) and pneumonia (D) from studies that evaluated transfer of passive immunity in beef or dairy calves in the pre-weaned period.

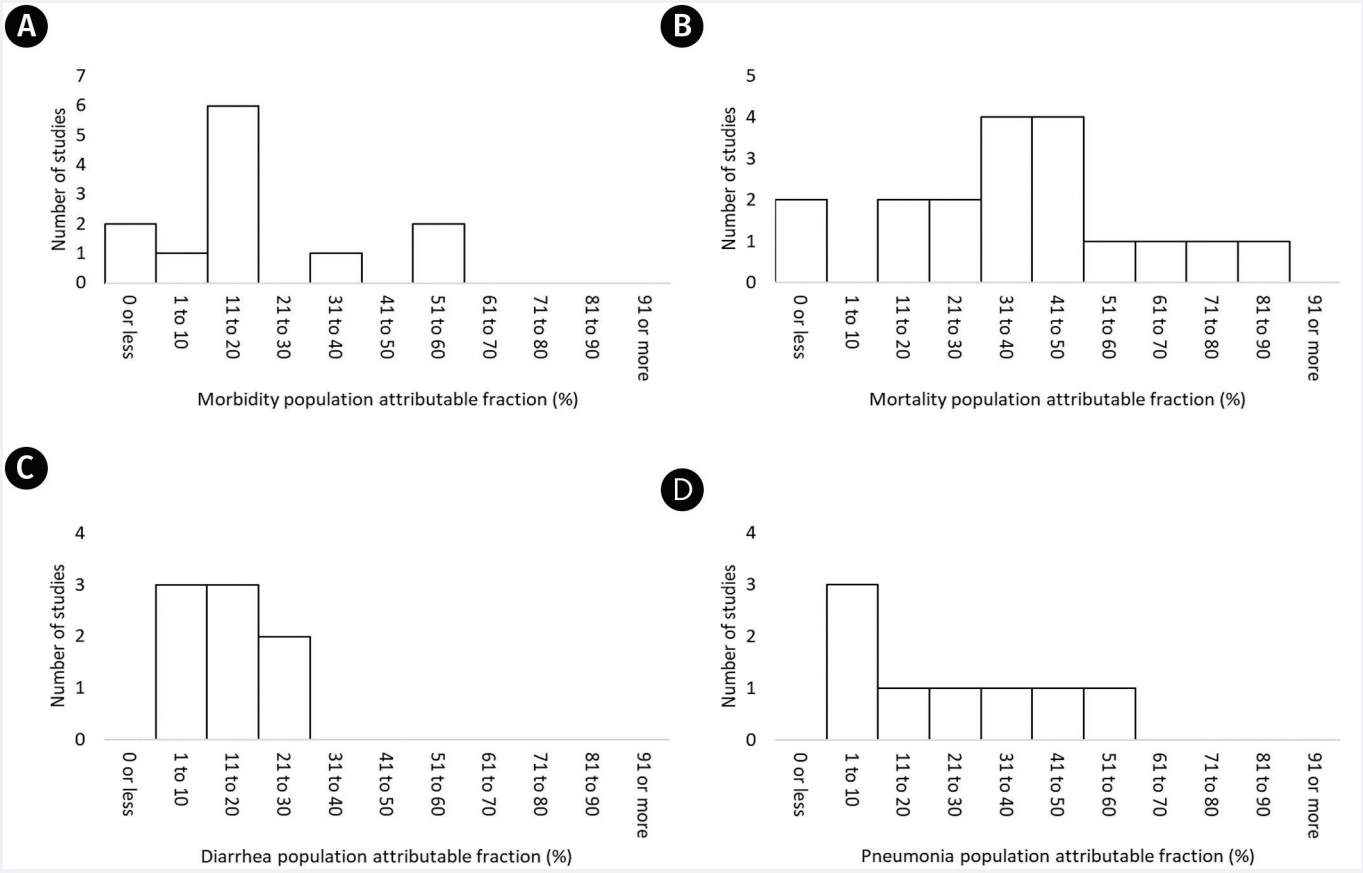
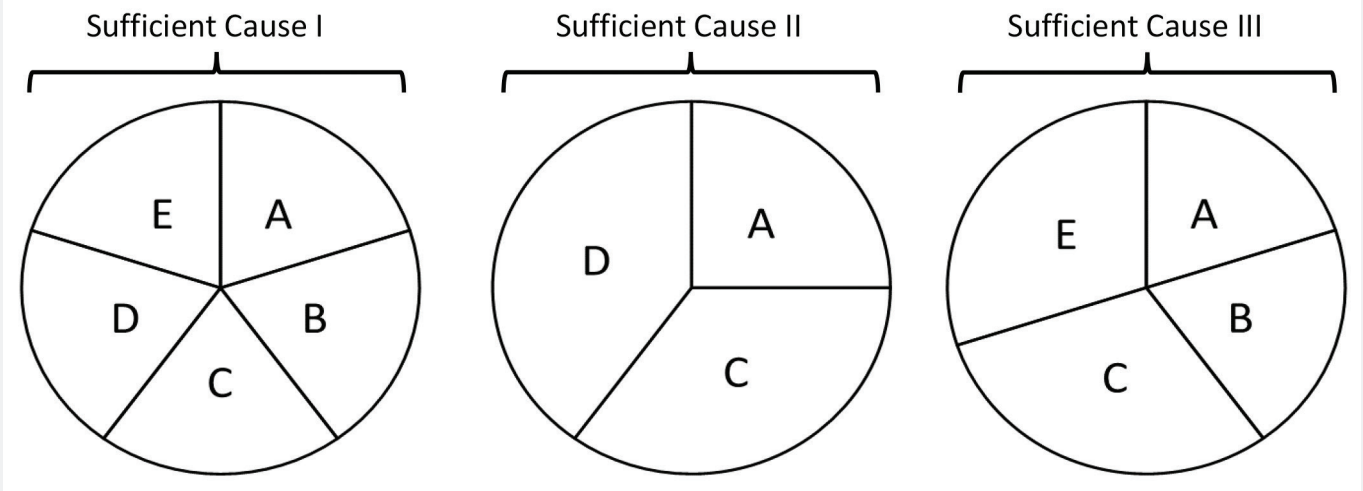


Figure 6: Hypothetical sufficient causes of disease adapted from Rothman, 1978.



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