ABSTRACT

Inadequate transfer of passive immunity (ITPI) in newborn dairy calves remains an important risk factor for mortality and morbidity. Most available studies are focused on calves delivered and raised on the same farms. This setting is far different from calves transported and commingled from different farms to be raised as veal or for other purposes. The aim of this systematic review and meta-analysis was to describe the association between ITPI and important health outcomes (mortality, bovine respiratory disease, and diarrhea) in multisource commingled dairy calves raised for veal or other purposes. We searched studies through CAB abstracts (via CAB direct), PubMed, and Web of Science (via ISI) databases until September 2, 2021. Observational studies and randomized trials written in English or French assessing ITPI association with any of the selected outcomes were included. Young dairy calves transported to commercial facilities and explicitly stated as being raised for veal production or not (then considered as “other”) were our populations of interest. If raw or adjusted data were available for ≥5 studies for a given outcome of interest, then random effect meta-analysis models were used to investigate ITPI effects on this outcome. Nineteen studies were selected from 6,221 abstracts retrieved in the initial search. We observed significantly higher odds of mortality in calves with ITPI compared with those with successful transfer of passive immunity [odds ratio (OR) = 2.46; 95% confidence interval (CI): 1.43–4.22, n = 8 studies]. Calves with ITPI had higher odds of diarrhea (OR = 3.03; 95% CI: 1.2–7.62, n = 7 studies). A significant publication bias toward publishing studies with positive results was found in studies reporting on bovine respiratory disease (n = 5 studies), which revealed nonsignificant associations after correction of publication bias (OR = 1.40; 95% CI: 0.77–2.6). Heterogeneity could not be thoroughly investigated for mortality and diarrhea due to the limited number of studies. Therefore, the pooled estimates of the random models should be interpreted with caution despite their robustness to sensitivity analyses. In this study, we also observed that multiple definitions for transfer of passive immunity and outcomes were used in the literature. Moreover, the raising system definition was often limited. There seems, therefore, to be a need for standardized definitions of these parameters, as well as a better description of systems used for multisource commingled dairy calves raised for veal production or other production purposes.

Key words: mortality, diarrhea, risk factors, odds ratio, publication bias

INTRODUCTION

Newborn male dairy calves are considered as dairy industry by-products and contribute to worldwide meat production (Sans and de Fontguyon, 2009). These young male calves are generally commingled and then transported for various purposes. They can be slaughtered within days of birth as bobby calves targeting niche marketing strategies, mostly in Australia and New Zealand (Cave et al., 2005). Also, such calves could be raised for veal meat production (Pardon et al., 2014; Renaud et al., 2018a) either on a milk-based diet (milk-fed or white veal) for approximately 6 mo or on a grain-based diet (grain-fed or rose veal) for 4 to 5 mo postweaning (Brscic et al., 2019). The finishing weights of both types of veal calves typically range from 230 to 250 kg for milk-fed calves and 320 kg for grain-fed calves (Renaud, 2017). These young male calves could also be fed for dairy-beef production for 6 mo in North America and Europe before being sold out to feedlots as “receiving” calves (Maas and Robinson, 2007; Endres and Schwartzkopf-Genswein, 2018). Dairy bull calves
are also raised for the beef industry in the US, where they are raised until weaning on the dairy farm, and then sold for backgrounding by a beef producer (Moore et al., 2002).

It is worthwhile noting that there is no specific universally accepted definition for “veal calf production,” which ultimately depends on the geographical area. In veal production, young calves (principally male ones) from multiple dairy herds, are generally collected by tradesmen, and transported to sorting centers (in Europe; Pardon et al., 2014) or directly to auction markets (in North America; Buczinski et al., 2021). They are then commingled with other calves from different farms and transported to their finishing facilities. Additionally, drover calves are those directly transported to veal facilities by some veal producers (Renaud et al., 2018b).

The age ranges of the calves when commingled and transported varies from a few days to a few weeks. This characteristic depends on specific country habits, country regulations, and the anticipated benefit between costs associated with keeping the calf on the dairy farm and sale price (Sans and de Fontguyon, 2009).

Coomingling young calves, after potential stressors such as different management practices on the dairy farm of origin (Renaud et al., 2018a), transport durations and conditions (Marcato et al., 2020), or risk factors related to their arrival at the veal facility puts these young calves at risk of a variety of health problems (Bähler et al., 2012; Pardon et al., 2015; Winder et al., 2016). Diseases such as the bovine respiratory disease complex (BRD) and diarrhea, are commonly reported in young male calves raising facilities where the morbidity risk for BRD varied between 7 and 61% (Brsecic et al., 2012; Pardon et al., 2013, 2015), whereas for diarrhea, it was varied between 5 and 23% (McDonough et al., 1994; Pardon et al., 2013). In a European study of 5,863 calves in 15 veal batches, the incidence rate of respiratory disease, diarrhea, arthritis, and otitis were 0.95, 0.30, 0.11, and 0.07 cases per 1,000 calf-days at risk, respectively (Pardon et al., 2012a).

These health issues are associated with increased antimicrobial use in raising facilities and with the emergence of antimicrobial resistance (Pardon et al., 2012b; Lava et al., 2016). Veal calves could serve as a reservoir for resistant bacteria, possibly transported to humans, and may jeopardize the efficacy of antibiotic treatment in humans (Di Labio et al., 2007).

Adequate transfer of passive immunity (TPI) is a key factor associated with calf health and growth on dairy farms (Urie et al., 2018a; Godden et al., 2019). The absorption of the immunoglobulins present in colostrum through the small intestine of the calf within the first 24 h after birth refers to the TPI. Various definitions of acceptable TPI have been proposed, and despite widespread use of IgG as an industry benchmark, there is no globally accepted threshold. By extension, calves’ relative degrees of passive immunity can be determined based on IgG levels (high vs. low) and other tests, including serum reflectance, could be used as a proxy for IgG levels (Buczinski et al., 2018). Inadequate transfer of passive immunity (ITPI) is generally defined when the IgG concentration is less than 10 g/L (Weaver et al., 2000) or serum total protein (STP) <5.2 g/dL (Buczinski et al., 2018) in calves between 24 h and 10 to 14 d of age (Raboisson et al., 2016; Buczinski et al., 2018). Different management factors are reported to increase the risk of ITPI including the cleanliness of colostrum, colostrum quality, the quantity of colostrum fed, and time of colostrum feeding after birth (Godden et al., 2019). However, these definitions have their own limitations because IgG is just a specific part of the immune components present in colostrum and it is difficult to find studies using the same definition of adequate versus inadequate TPI as reviewed in beef and dairy calves recently (Raboisson et al., 2016).

Inadequate transfer of passive immunity has been associated with increased odds of morbidity and mortality, increased production costs, and reduced average daily gains in ITPI calves (Urie et al., 2018b; Lombard et al., 2020). Inadequate transfer of passive immunity prevalence varied over time in US newborn dairy heifers sampled during their first week of age between 41% (USDA, 1993), 20% (Beam et al., 2009), and recently 13% (Urie et al., 2018a). In Canada, a recent study conducted on newborn dairy calves in 59 herds showed a median of 32% ITPI at the herd level (Morin et al., 2021). Renaud et al. (2020) found that 24% of dairy calves intended for veal production sampled twice at their dairy farms of origin plus at auction markets had ITPI. However, upon veal facility arrival, on average, 40% of veal calves suffered ITPI in a Belgian study (Pardon, 2012). Another study carried out by our research group in Quebec, on 80 batches of veal calves, reported an individual or calf level ITPI prevalence of 62.5% (Abdallah et al., 2020).

However, one should note that the association between ITPI and health outcomes may potentially depend on the various facets of newborn calves’ management settings, including the definition of ITPI, which depends on the test and cut-off used, age at sampling, as well as specific study effects. A recent systematic review and meta-analysis was conducted on the adjusted associations between ITPI and mortality, BRD, and diarrhea in dairy and beef calves (Raboisson et al., 2016). In this latter study, the adjusted risk ratios and 95% confidence intervals (CI) for mortality, BRD, and diarrhea in calves with ITPI were 2.12 (95% CI:
1.43–3.13), 1.75 (95% CI: 1.50–2.03), and 1.51 (95% CI: 1.05–2.17), respectively. The mean total costs per head were estimated to be €60 and €80 for dairy and beef calves with ITPI compared with the same breeds raised in control herds (Raboisson et al., 2016).

However, no systematic reviews and or meta-analyses are available to summarize the association between ITPI and negative health outcomes in dairy calves that are commingled from different sources to be processed for veal. This information would be potentially different from the previously reported studies in dairy and beef calves, which are classically kept at their original farms during their first months of life.

Therefore, there is a need to specifically study the association between ITPI and negative health outcomes in multisource commingled dairy calves raised for veal or other purposes using a systematic review and meta-analysis study. We aimed to synthesize the literature to identify the reported association between ITPI and the most important health outcomes in multisource commingled dairy calves raised for veal or other purposes including mortalities, BRD, diarrhea, arthritis, and otitis.

**MATERIALS AND METHODS**

The protocol was previously published online (Abdallah et al., 2018). Some amendments were made to this protocol, including (1) extending the inclusion of studies (either peer-reviewed or not) on multisource commingled dairy calves not raised in a typical veal system of milk-fed or grain-fed veal calves; and (2) risk of bias assessment, which was modified due to recent evidence mentioning the issues associated with risk of bias assessment tools, including the variability in study types and the absence of universally accepted criteria for assessing risk of bias in observational studies (Bero et al., 2018). No animals were used in this study, and ethical approval for the use of animals was thus deemed unnecessary.

**Review Question**

The review question was, “In multisource commingled dairy calves being raised for veal or other purposes, what is the association between TPI and: (1) mortality, (2) BRD, (3) diarrhea, (4) arthritis, and (5) otitis.” The following search terms were used: (“mortality” or “death*” or “dead” or “respiratory” or “pneumonia” or “BRD” or “diarrhea” or “diarrhea” or “diarrh*” or “scours” or “otitis” or “ear infection*” or “ear inflammation*” or “arthriti*” or “lameness”) AND (“veal” or “calf” or “calves”) AND (“passive and immunity” or “immunoglobulins” or “colostrum”). The search strategy aimed to be very sensitive at the cost of being less specific to be sure not to miss a relevant reference.

**Eligibility Criteria for Considering Studies for this Review**

**Eligible Study Types.** Longitudinal studies such as randomized controlled trials and observational studies using cohorts (prospective or retrospective), or case-control study types were eligible for inclusion. Each study had to report at least one of the targeted outcomes and the exposure of interest (ITPI assessment). Case series, case reports, and reviews were excluded. Articles written in languages other than English or French were excluded.

**Participant’s Eligibility.** The population of interest were multisource commingled dairy calves monitored in commercial facilities for veal or other production purposes. Studies following calf health at the farm of origin or conducted in experimental research/academic settings were excluded.

**Search Strategy for Identification of Studies.** We searched CAB abstracts (via CAB Direct, https://www.cabdirect.org/), PubMed (https://pubmed.ncbi.nlm.nih.gov/), and Web of Science (via ISI, https://www.webofscience.com/wos/woscc/advanced-search) up to September 2, 2021, for eligible studies using a Boolean search strategy developed with the help of a librarian (Supplemental File S1, https://figshare.com/s/bf59a5726554726b165a). The gray literature, defined as any research work that was not published through the peer-reviewed publishing channels, was then searched through Google Scholar. Moreover, the reference lists of the retrieved articles were consulted by the first author (A.A.) to look for any relevant references not included in the systematic review list.

Search results were uploaded into Covidence systematic review software (Veritas Health Innovation) and duplicates removed. A primary screening round was conducted by 2 independent reviewers, each title and abstract were reviewed for relevance by 2 authors (A.A. and S.B.). At this stage, any paper retained by 1 of the 2 reviewers was kept for full reading, if there was any disagreement, the full text was consulted. A second round of screening was then conducted to assess the full articles. Any discrepancy was resolved by recruiting a third reviewer (D.F.) and obtaining a consensual decision. When ≥2 reviewers agreed on including a study, it was included, otherwise, the study was excluded.

**Data Extraction from Included Studies.** For each study, information was extracted in parallel by...
2 reviewers (A.A. and S.B.) using predefined Excel spreadsheets as a basic extraction tool developed by both reviewers and piloted with 2 specific references. Regarding study characteristics, the extracted data were authors, year, season, country, and study type. Additionally, definitions of immunity transfer success and tests used in each study were retrieved. Transfer of passive immunity was defined by either direct serum concentration of IgG or indirect evaluation using, for example, STP concentration, which was measured directly or not (e.g., refractometry), or another way of indirect evaluation using a zinc sulfate or sodium sulfite test (Weaver et al., 2000). Being below versus above a specific cut-off was used to define inadequate versus adequate TPI, respectively. Other prespecified covariates that could affect the test accuracy (age, hydration, diseases status at test time) were extracted when available. Description of participants (veal or nonveal), raising systems, population size, and number of herds included in the study, were recorded.

Regarding outcomes, case definitions used, number of reported cases for calves with any one of the forementioned health outcomes, and number of calves at risk across ITPI status were retrieved. The classification method used for distinguishing calves with adequate or inadequate passive immunity transfer was based upon each specific study’s methods and cut-off points. For an outcome of interest when the 2 × 2 table was obtained, the odds ratio (OR) and CI were also compiled based on the following calculations:

\[
\text{OR} = \frac{(A \times D)}{(C \times B)},
\]

Upper 95% CI = \(e^{\ln(\text{OR}) + 1.96 \times \text{SE(\ln OR)}}\), and

Lower 95% CI = \(e^{\ln(\text{OR}) - 1.96 \times \text{SE(\ln OR)}}\),

where \(A\) = outcome and inadequate transfer of passive immunity are present, \(B\) = outcome is absent and inadequate transfer of passive immunity is present, \(C\) = outcome and adequate transfer of passive immunity are present, and \(D\) = outcome is absent and adequate transfer of passive immunity is present.

**Methodological Quality and Risk of Bias Assessment**

In contrast to that initially planned, no specific risk of bias analysis of the studies included in the meta-analysis was conducted because of the anticipated variability in study types and the absence of universally accepted standards for assessing risk of bias in observational studies (Bero et al., 2018). The authors specifically mention that the available tools are complex to use or irrelevant for many observational studies because most are derived from tools intended for use with intervention studies. However, a comprehensive analysis of the main study characteristics was performed to describe critical elements that may be associated with risk of bias. Such analysis was done whether ITPI was the main study objective or not, and even if the OR was adjusted or not.

**Statistical Analysis and Data Synthesis**

The analyses were summarized using meta-analysis conducted with metafor package in R 4.1.0 (https://r-project.org; Viechtbauer, 2010). A random effect meta-analysis was conducted whenever ≥5 studies were available for any a priori defined outcome of interest. The random effect model and its variance (\(t^2\)) was determined using the DerSimonian–Laird estimator through the metafor package in R (Viechtbauer, 2010). Summary effect measures were reported as OR with their 95% CI. The idea behind model construction was to compare odds of outcome occurrence in multisource commingled dairy calves with ITPI versus those with adequate TPI. Prediction intervals were also calculated as the range of the predicted OR in a new study given the past studies’ results accounting for model heterogeneity, in other words, the random variation of individual studies’ OR (Viechtbauer, 2010).

Heterogeneity was assessed in 2 ways, first using Cochran’s Q test that is computed by summing the squared deviations of each study’s effect estimate from the overall effect estimate. Then \(I^2\) statistic that could be explained as the total variability in a set of effect sizes due to true heterogeneity was also calculated (between-studies variability; Huedo-Medina et al., 2006).

Heterogeneity was hypothesized to be potentially affected by potential variables such as raising type of calves (veal vs. other purposes), geographic region (Europe vs. North America), season of study, TPI estimation methods, and definition of outcomes used. Due to the low number of included studies per outcome, (less than 10 studies for each model), sources of heterogeneity could not be thoroughly investigated through meta-regression or subgroup analysis (Michael et al., 2009).

Publication bias was explored in this systematic review using funnel plots and the Egger regression test analysis (Egger et al., 1997). An Egger test \(P\)-value <0.05 was interpreted as the presence of publication bias. When publication bias was detected, a trim-and-fill method correction was applied to obtain the publication bias adjusted estimate, and these adjusted estimates were then used for reporting summary estimates (Duval and Tweedie, 2000).
Sensitivity Analysis

The leave one out method was used to calculate the sensitivity of the overall or pooled estimate of each random effect meta-analysis model. This method removes a single study each time and repeats the analysis (Sahebkar, 2014). For a meta-analysis with n studies, (n-1) different estimates were therefore calculated. Changes in point estimates and 95% CI were appraised each time.

RESULTS

Characteristics of the Selected Studies

The database search returned 6,213 references. The search of CAB abstracts, PubMed/MEDLINE, and Web of Science databases provided 2,312, 2,836, and 1,065 studies, respectively. After removal of 1,313 duplicates, 4,908 articles were obtained for the first screening phase for titles and abstracts. Eight additional articles were retrieved from Google Scholar. From these, 50 full text articles were further evaluated. The complete selection strategy is summarized in Figure 1. A total of 19 articles were finally included in this systematic review; 31 articles were excluded for various reasons summarized in Figure 1.

Table 1 shows the characteristics of the 19 studies that were retained for analysis. Studies were published between 1973 and 2021. Ten studies were performed in North America, 9 studies were conducted in European countries. Thirteen studies were conducted on veal calves, and the remaining 6 studies were performed on calves raised for other purposes. Regarding the latter studies, all 6 studies were conducted on commingled dairy calves without further information on the end purpose of raising. Only Mormede et al. (1982) reported that the calves were slaughtered 105 d after fattening unit arrival.

From the 19 studies, 10, 11, and 13 studies reported mortality, BRD, and diarrhea as outcomes (2 × 2 tables obtained for 8, 7, and 5 studies), respectively. Lamineness was reported in 3 studies (2 × 2 table obtained only from 1 study), whereas only 1 study reported an incidence of otitis. Based on such results, the meta-analyses were only performed for mortality, BRD, and diarrhea.

From 50 (Hoet et al., 2003) to 39,619 (Cortese et al., 2020) calves were sampled for passive immunity transfer estimation in the included studies. Summarized results for passive immunity are presented in Table 1. Various methods and thresholds defining ITPI were observed; in most of the included studies, ITPI was considered when IgG < 10 g/L or STP < 5.2 or 5.5 g/dL. We initially aimed to use the ITPI definition as case moderators to explain part of the heterogeneity observed, as suggested by Raboisson et al. (2016). However, we were unable to include this analysis due to the low number of studies. Median ITPI prevalence was 24% in studies that were conducted in North America (range: 2–78%), whereas this was 43% in European countries (range: 30–67%). The sampling period for TPI estimation was generally performed either during the marketing day or during the first week after facility arrival.

The prevalence of mortality ranged from 2% in a prospective cohort study (Wilson et al., 1994) to 33% in a case-control study (Renaud et al., 2018c). The BRD prevalence ranged from 18% (Postema and Mol, 1984) to 61% (Pardon et al., 2015), whereas diarrhea prevalence ranged from 2% (Cortese et al., 2020) to 79% (McDonough et al., 1994).

When reported, BRD, diarrhea, and lameness definitions used in the included studies were quite variable, as summarized in Table 2. Briefly, 11 studies reported BRD as an outcome. Three studies did not report the case definitions. One study used the standardized scoring systems of Love et al. (2014). In 4 studies, the authors used their own scoring system. In the remaining 3 studies, the authors used the poor calf thrift index (without defined scoring) which included laborious breathing, fever, cough, nasal, and ocular discharges. Thirteen studies focused on diarrhea. In 4 studies, no case definitions were reported. Another 4 studies used their own scoring systems. The remaining 5 studies defined diarrheic cases with the presence of watery fecal contents with or without clots, depression, partial or complete anorexia, and fever.

Meta-analyses

Eight studies were included in mortality meta-analysis, with 5 studies performed on veal calves. The unconditional odds of mortality in calves with ITPI was 2.46 times higher (95% CI: 1.43–4.22; P = 0.001) than for calves with adequate TPI (Figure 2A, Table 3). Heterogeneity (I^2) was high (77.1%); no publication bias could be detected on the funnel plot (Figure 3A), nor with Egger’s regression test (P = 0.08). The leave one out sensitivity analysis revealed a median pooled estimate of 2.49 (ranging from 2.21 to 2.81, Table 3).

The main model for BRD included 5 studies (3 studies for calves raised for veal and 2 studies for calves raised for other purposes). The odds for BRD in calves with ITPI was 2.28 (95% CI: 1.31–3.97; P = 0.003) times higher than that of calves with adequate TPI. (Figure 2B, Table 3); the total heterogeneity I^2 in this model was 59.5%. A potential publication bias was observed in the funnel plot (Figure 3B) and was also indicated by
Egger’s regression test ($P = 0.003$). The trim-and-fill analysis revealed a nonsignificant association between ITPI and BRD (OR: 1.40; 95% CI: 0.77–2.6; $P = 0.26$, Figure 3B, Table 3). Results of the sensitivity analysis through the leave one out method showed a median pooled estimate of 2.26 (range: 1.73–3.12, Table 3).

Seven studies (3 for calves raised for veal and 4 for calves raised for other purposes) were included in the diarrhea model (Figure 2C, Table 3). Odds for diarrhea in calves with ITPI were 3.03 (95% CI: 1.2–7.62, $P = 0.02$) times higher than those with an adequate TPI. Total heterogeneity $I^2$ in this latter model was 91.8%. No evidence of publication bias was found [funnel plot, Figure 3C, Egger’s test ($P = 0.19$)]. Sensitivity analysis through the leave one out method revealed a median pooled estimate of 2.95 (range: 2.22–3.82, Table 3).

**DISCUSSION**

To the best of our knowledge, this is the first systematic review to investigate the effect of failure or inadequate passive immunity transfer on odds of

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**Figure 1.** Flow diagram of the study selection process; the search was performed on September 2, 2021. *The results of 4 articles were partially or completely repeated in 4 articles from the same authors (i.e., 2 different papers published from the same experimental study). Only 4 references were therefore included for full text screening, and the other 4 studies were excluded to avoid double counting.*
Table 1. Characteristics of the included studies (n = 19) reporting the effect of inadequate transfer of passive immunity (ITPI) on the negative health outcomes in commingled dairy calves raised for veal or other purposes.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study type</th>
<th>Season</th>
<th>Raising system/place2</th>
<th>Days on feed</th>
<th>ITPI definition</th>
<th>Method for passive immunity estimation</th>
<th>ITPI prevalence</th>
<th>Total no. of calves sampled for transfer of passive immunity (d since arrival)</th>
<th>Calf’s age at transport (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cagnasso et al., 2004</td>
<td>Italy</td>
<td>Prospective cohort</td>
<td>NR</td>
<td>Milk-fed veal calf facility</td>
<td>NR</td>
<td>IgG &lt;10 mg/mL</td>
<td>Radial immunodiffusion</td>
<td>0.3</td>
<td>117</td>
<td>0 &lt;21</td>
</tr>
<tr>
<td>Cortese et al., 2020</td>
<td>USA</td>
<td>Prospective cohort</td>
<td>2017–2018</td>
<td>Calf-raising facility</td>
<td>120</td>
<td>STP &lt; 5 g/dL</td>
<td>Digital refractometer, Palm Abbe Misco</td>
<td>0.02</td>
<td>39,619</td>
<td>1 2</td>
</tr>
<tr>
<td>Frankena et al., 1994</td>
<td>Netherlands</td>
<td>Randomized controlled trial/</td>
<td>Spring 1992</td>
<td>Milk-fed veal calf facility</td>
<td>200</td>
<td>NR</td>
<td>Light-scattering immunoassay</td>
<td>NR</td>
<td>116</td>
<td>1-7 7</td>
</tr>
<tr>
<td>Goetz et al., 2021</td>
<td>Canada</td>
<td>Prospective cohort</td>
<td>January 2017–April 2018</td>
<td>Grain-fed veal calf facility</td>
<td>78</td>
<td>IgG &lt;10 g/L</td>
<td>Radial immunodiffusion</td>
<td>0.14</td>
<td>989</td>
<td>1 3-7</td>
</tr>
<tr>
<td>Hoet et al., 2003</td>
<td>USA</td>
<td>Prospective cohort</td>
<td>Autumn 1999</td>
<td>Milk-fed veal calf facility</td>
<td>35</td>
<td>Ig ≤ 5 mg/mL</td>
<td>Sodium sulfite-precipitation test, ZST test</td>
<td>0.32</td>
<td>50</td>
<td>0 4-10</td>
</tr>
<tr>
<td>Irwin, 1974</td>
<td>England</td>
<td>Prospective cohort</td>
<td>NR</td>
<td>Commercial unit</td>
<td>42</td>
<td>ZST &lt; 25 units</td>
<td>ZST test</td>
<td>0.67</td>
<td>58</td>
<td>0 NR</td>
</tr>
<tr>
<td>Johnson et al., 1973</td>
<td>USA</td>
<td>Prospective cohort</td>
<td>Winter 1970</td>
<td>Milk-fed veal calf facility</td>
<td>66</td>
<td>2.5 ≤ Ig ≤ 10 g/L</td>
<td>ZST test</td>
<td>0.5</td>
<td>64</td>
<td>0 2-7</td>
</tr>
<tr>
<td>McDonough et al., 1994</td>
<td>USA</td>
<td>Prospective cohort</td>
<td>Summer 1990–autumn 1991</td>
<td>Special-fed veal calf facility</td>
<td>112</td>
<td>IgG &lt;8 g/L (failure), 8 g/L ≤ IgG ≤ 1,600 g/L (partial failure)</td>
<td>Radial immunodiffusion</td>
<td>0.78</td>
<td>460</td>
<td>1-7 2-7</td>
</tr>
<tr>
<td>Mormede et al., 1982</td>
<td>France</td>
<td>Randomized controlled trial/</td>
<td>NR</td>
<td>Fattening unit</td>
<td>105</td>
<td>NR</td>
<td>Radial immunodiffusion</td>
<td>NR</td>
<td>54</td>
<td>0 4-32</td>
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<tr>
<td>Pardon et al., 2015</td>
<td>Belgium</td>
<td>Prospective longitudinal study cohort</td>
<td>Winter 2014</td>
<td>Grain-fed veal calf facility</td>
<td>18</td>
<td>Ig &lt;10 g/L</td>
<td>Serum electrophoresis</td>
<td>0.41</td>
<td>150</td>
<td>0 12-41</td>
</tr>
<tr>
<td>Pempek et al., 2018</td>
<td>USA</td>
<td>Randomized controlled trial/</td>
<td>Summer 2016</td>
<td>Special-fed veal calf facility</td>
<td>42</td>
<td>STP &lt; 5.5 g/dL</td>
<td>Handheld refractometer (optical)</td>
<td>0.1</td>
<td>240</td>
<td>0 3-7</td>
</tr>
<tr>
<td>Postema and Mol, 1984</td>
<td>Netherlands</td>
<td>Prospective cohort</td>
<td>NR</td>
<td>Milk-fed veal calf facility</td>
<td>127</td>
<td>STP &lt;5.5 g/dL</td>
<td>Handheld refractometer (optical)</td>
<td>0.1</td>
<td>240</td>
<td>0 3-7</td>
</tr>
<tr>
<td>Postema et al., 1987</td>
<td>Netherlands</td>
<td>Prospective cohort</td>
<td>June 1984</td>
<td>Milk-fed veal calf facility</td>
<td>126</td>
<td>IgG &lt;10 g/L</td>
<td>Unclear</td>
<td>0.48</td>
<td>77</td>
<td>2 NR</td>
</tr>
<tr>
<td>Renaud et al., 2018c</td>
<td>Canada</td>
<td>Case-control</td>
<td>Autumn 2015–summer 2016</td>
<td>Milk-fed veal calf facility</td>
<td>21</td>
<td>IgG &lt;16.7 g/L</td>
<td>Radial immunodiffusion</td>
<td>0.54</td>
<td>405</td>
<td>0 NR</td>
</tr>
<tr>
<td>Stilwell and Carvalho, 2011</td>
<td>Canada</td>
<td>Prospective cohort</td>
<td>NR</td>
<td>Fattening unit</td>
<td>60</td>
<td>IgG &lt;10 mg/mL</td>
<td>Immunoassay IgG test</td>
<td>0.38</td>
<td>97</td>
<td>0 &lt;15</td>
</tr>
</tbody>
</table>

Continued
mortality, BRD, and diarrhea, in multisource commingled dairy calves raised for veal production (milk or grain), or those raised for other purposes. An association with lameness or arthritis and otitis could not be thoroughly investigated due to a lack of studies investigating these diseases. The results of our random effect models agreed with those reported in a recent meta-analysis in terms of a higher OR for negative health outcomes in association with ITPI (Raboisson et al., 2016). In this latter study, dairy or beef calves with ITPI were twice as likely to die (compared with 2.46 times as likely for multisource commingled dairy calves in our study) and were 1.5 times more likely to be treated for diarrhea (compared with 3.03 times more likely in our study) when compared with calves with adequate TPI.

For the mortality model in our meta-analysis, all included studies found that ITPI was associated with higher odds of mortality except Goetz et al. (2021) in which no association between ITPI and mortality was reported. The dynamics of mortality in veal facilities was characterized by 3 different periods of risk that occur 2 and 9 wk after facility arrival, and at the end of the production cycle (Pardon et al., 2012a). Winder et al. (2016) reported that almost 50% of mortalities occurred during the first month after facility arrival. Inadequate transfer of passive immunity, as well as additional on-arrival risk indicators such as dehydration, abnormal navel, increased rectal temperature, higher fecal score, as well as specific contextual effects of the batch of calves from different origins, could explain greater mortalities in the first few weeks of the production cycle (Renaud et al., 2018b; Scott et al., 2019). Furthermore, calves that suffered ITPI had a higher mortality rate up to 10 wk of age (Tyler et al., 1998). In our review, the median follow-up period until mortality in the included studies was 66 d, which is therefore mostly compatible with mortality occurring early in the production cycle.

Diarrhea has been found to be associated with higher morbidity and mortality rates among neonatal calves (McGuirk, 2008). In veal facilities, diarrhea was found to be the most prevalent disease during the first 4 wk of the production cycle (McDonough et al., 1994; Pardon et al., 2013). It was previously reported to be associated with significant weight loss (Postema and Mol, 1984) and a long-term effect on the hot carcass weight, with a reduction of 0.051 kg/d on feed (Pardon et al., 2013). Furthermore, diarrhea was found to be a major reason for antibiotic treatment in veal calves (Pardon et al., 2012b). In our meta-analysis, ITPI in all studies was associated with higher odds of diarrhea except for Postema et al. (1987), where ITPI was not associated with diarrhea.
### Table 2. Case definitions for bovine respiratory disease (BRD), diarrhea, and lameness as reported in 16 studies reporting morbidity outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>BRD</th>
<th>Diarrhea</th>
<th>Lameness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortese et al., 2020</td>
<td>Cases diagnosed according to the Love et al. (2014) scoring system</td>
<td>No case definition</td>
<td>No case definition</td>
</tr>
<tr>
<td>Frankena et al., 1994</td>
<td>Calves diagnosed for BRD if they had 2 or more of the criteria used for assessing disease</td>
<td>NA¹</td>
<td>NA</td>
</tr>
<tr>
<td>Goetz et al., 2021</td>
<td>Respiratory abnormalities (nasal and ocular discharge, abnormal respiration rate, and presence of a cough)</td>
<td>Three consecutive days of watery diarrhea, blood in loose or watery feces, or loose or watery feces in addition to refusing milk for 2 consecutive feedings</td>
<td>NA</td>
</tr>
<tr>
<td>Hoet et al., 2003</td>
<td>NA</td>
<td>Calves with scores ≥2 were classified as having diarrhea (0, normal feces; 1, pasty feces; 2, semi-liquid feces; 3, liquid feces with some solid material; 4, liquid feces)</td>
<td>NA</td>
</tr>
<tr>
<td>Irwin, 1974</td>
<td>NA</td>
<td>No case definition</td>
<td>NA</td>
</tr>
<tr>
<td>Johnson et al., 1973</td>
<td>No case definition</td>
<td>Diarrhea, inappetence, or body temperature &gt;39.7°C</td>
<td>NA</td>
</tr>
<tr>
<td>McDonough et al., 1994</td>
<td>NA</td>
<td>No case definition</td>
<td>NA</td>
</tr>
<tr>
<td>Mormede et al., 1982</td>
<td>No case definition</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Pardon et al., 2015</td>
<td>Depression, cough, rectal temperature, and nasal discharge, each category has a score from 0 to 3; animals with a score of ≥5 were considered as a case</td>
<td>Presence of diarrhea, (partial) anorexia, and depression</td>
<td>NA</td>
</tr>
<tr>
<td>Pempek et al., 2018</td>
<td>Respiratory disease score is the sum of points from rectal temperature, the character of nasal discharge, eye or ear appearance, and presence of a cough; calves with score 6 or higher had at least 2 clinical signs of respiratory disease</td>
<td>Calves with scores ≥2 were classified as having diarrhea (0, normal feces; 1, semi-formed, pasty, uncomplicated diarrhea; 2, loose, stays on top of slats; 3, watery, sifts through slats; 2 and 3 scores without fever or depression; 4, complicated diarrhea with fever ≥39.4°C)</td>
<td>NA</td>
</tr>
<tr>
<td>Postema and Mol, 1984</td>
<td>Calves with fever (above 39.6°C) and hyperpnea</td>
<td>All calves producing watery feces with clots</td>
<td>NA</td>
</tr>
<tr>
<td>Postema et al., 1987</td>
<td>Calves with fever (above 39.6°C) and hyperpnea</td>
<td>All calves producing watery feces</td>
<td>NA</td>
</tr>
<tr>
<td>Renaud et al., 2018c</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Wilson et al., 2000</td>
<td>Scores 1 and 2 classified as having BRD (1 = harsh breathing sounds, markedly elevated rate, coughing; 2 = breath sounds audible, rate elevated, coughing; 3 = breath sounds audible, rate slightly elevated, occasional cough; 4 = quiet, nonlaborered breathing, rate &gt;35/min; 5 = quiet, nonlaborered breathing, rate ~30/min)</td>
<td>Scores 1 and 2 classified as having diarrhea (1 = manure is fluid, color is yellow or pale, flecks of blood; 2 = manure is semi-solid, pale to yellow in color; 3 = manure is more fluid than normal, color is abnormal; 4 = manure is slightly loose, normal color; 5 = normal color and consistency)</td>
<td>Scores 1 and 2 classified as having arthritis; 1 = enlarged joints, purulent or serous discharge; 2 = visibly abnormal joints and effusion; 3 = visibly normal in appearance, palpable joint abnormalities, or effusion; 4 = mild joint deformities, small amount of palpable effusion; 5 = normal joint alignment, no swelling</td>
</tr>
<tr>
<td>Wilson et al., 2020</td>
<td>NA</td>
<td>Watery fecal consistency</td>
<td>NA</td>
</tr>
</tbody>
</table>

¹NA = not applicable, such disease condition was not reported in that study.
Figure 2. Forest plots for effect of inadequate transfer of passive immunity (ITPI) on odds ratios for mortality (A), bovine respiratory disease (BRD; B), and diarrhea (C). Calf types (veal vs. nonveal), ITPI prevalence (ITPI Prev), time until mortality (follow-up), and case definition were included in the forest plots. Pooled effect (center of red diamonds) and associated confidence intervals (lateral tips of diamond) are present at the bottom of each graph. Dashed lines right and left of the tips of the red diamonds represent the prediction intervals that account for the random variation of the individual studies’ values. RE = random effect; Q = Cochran’s Q heterogeneity test; QM = Cochran’s Q heterogeneity test for moderators; $\tau^2$ = variance; NR = not reported.
The BRD complex remains one of the leading causes of morbidity and mortality during the cycles of veal production (Sargeant et al., 1994; Leruste et al., 2012; Brscic et al., 2012). A single BRD bout led to an average 8.2 kg loss in the hot carcass weight in 10 white veal commercial veal farms in Northern Belgium (Pardon et al., 2013). Bovine respiratory disease was the primary cause of antibiotic treatment in a large veal unit in England (Miller et al., 1980). Recently, in 15 white veal operations studied in Belgium, BRD was the primary disease for group and individual antibiotic use (Pardon et al., 2012b). Bovine respiratory disease was the most common reason for individual treatment (73% of the cases) for white veal calves in a Swiss study (Lava et al., 2016). Surprisingly, a specific publication bias for BRD outcome was reported, meaning that reported effects in selected studies were biased toward reporting studies with higher effects, and unreported studies with lower effects. When correcting for publication bias, the results were not significantly different from one (i.e., absence of association).

Publication bias should always be investigated, as such bias could lead to incorrect conclusions of systematic reviews (Sutton et al., 2000). This bias can be evaluated either visually, through funnel plots (Sterne and Egger, 2001) or through the Egger statistical test (Egger et al., 1997). This test regresses the standardized effect sizes on the corresponding precisions. An intercept of 0 indicates no publication bias. The regression intercept, however, may lack the intuitive interpretation for asymmetry of the collected study results. The regression intercept only reflects the average of the standardized deviates of the models. Moreover, selection models have previously been reported to test publication bias (Dear and Begg, 1992; Hedges, 1992; Silliman, 1997; Sutton et al., 2000), but they are frequently complex and based on strong and largely untestable assumptions which limits their usefulness (Lin and Chu, 2018). Based on such uncertainty in testing publication bias, the low number of BRD studies (n = 5), even with significant Egger test results, the absence of association between ITPI and BRD should be interpreted with caution.

Diagnosis of BRD poses significant challenges because there are numerous infectious etiologies and clinical presentations (Woolums et al., 2009). Farmers usually lack sensitivity for detecting cases and when the diagnosis is performed, the delay in disease detection is associated with a later stage of the disease (Leruste et al., 2012; Pardon et al., 2013). Therefore, BRD dynamics are difficult to follow when only based on BRD treatment records. The variation in reported BRD cases could also result from a combination of differences in diagnostic criteria and definitions (Buczinski and Pardon, 2020). These specific factors could partly explain the heterogeneity of the meta-analysis model and wide variation of the true association between ITPI and BRD. Additionally, the clinical manifestation of BRD generally comes later than enteritis or diarrhea problems in veal farms, which may be associated with the decrease of the initial protective effect of TPI. The relative role of respiratory pathogen build-up and diffusion in the veal or commingled calves’ units versus on-arrival immunity status of the calves should be explored more in detail in various settings (i.e., low vs. high prevalence or incidence of BRD).

In our meta-analyses, the different heterogeneity sources including geographic region, type of calves (veal vs. nonveal), raising systems, season of study, estimation methods for passive immunity transfer, and definition of outcomes were planned to be investigated to explore their effect on the relationship between ITPI and negative health outcomes (i.e., mortality, BRD, and diarrhea). However, this exploration was incomplete due to the insufficient number of studies (<10) included in each of the random models and limited reported information in the included studies. Important variables such as calf-raising systems, passive immunity transfer testing methods, definitions for BRD, diarrhea, arthritis, and otitis were lacking. This may also provide an explanation for the high heterogeneity

<table>
<thead>
<tr>
<th>Item</th>
<th>Mortality (n = 8 studies)</th>
<th>BRD complex (n = 5 studies)</th>
<th>Diarrhea (n = 7 studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds ratio (95% CI)</td>
<td>2.46 (1.43–4.22)</td>
<td>2.12 (1.18–3.81)</td>
<td>2.37 (1.29–4.35)</td>
</tr>
<tr>
<td>Main model</td>
<td>2.49 (2.21–2.81)</td>
<td>2.26 (1.73–3.12)</td>
<td>2.95 (2.22–3.82)</td>
</tr>
<tr>
<td>Publication bias analysis¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median odds ratio (range)</td>
<td>NA</td>
<td>1.40 (0.77–2.60)</td>
<td>NA</td>
</tr>
<tr>
<td>Leave one out</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹NA = not applicable. No publication bias was detected using Egger’s test.

²When a publication bias was reported, a trim-and-fill imputation process was conducted to determine corrected estimates of the effect.
Figure 3. Contour-enhanced funnel plots for publication bias in models for mortality (A), diarrhea (C), and trimmed and filled funnel plot for the bovine respiratory disease (BRD) model (B). From the inside outward, the shaded regions in the funnel plots indicate different significance levels of $P < 0.1$, $0.05$, $0.01$, and $0.00$ respectively; effect sizes falling into the first 2 shaded regions are considered significant (i.e., indicating significant publication bias).
of results found. Following standard reporting of these diseases, such as reliable clinical scoring systems even if not 100% accurate, would be helpful in decreasing the variability of case definition between studies (Hayes et al., 2010).

A standardized and appropriate BRD definition is a crucial concern worldwide that will help in determining the disease prevalence plus early diagnosis and treatment. The Wisconsin and California respiratory scoring systems were previously developed to help in the earlier diagnosis or treatment of BRD in dairy calves (McGuirk, 2008; Love et al., 2014). Despite moderate accuracy, they are important tools to standardize case definition and for use by producers. However, users need to be trained to improving score reliability. These scoring systems, depending on clinical signs to be assessed, may yield low inter-rater reliability between scorers with different levels of experience (i.e., veterinary student, producers, technicians, and veterinarians; Buczinski et al., 2016; Berman et al., 2021). Adequate training is required to improve reliability within and between raters.

Different scoring systems were developed to identify calves with diarrhea based on the consistency of a fecal sample when calves were stimulated to defecate, and the feces was scored on a 4-point scale (McGuirk, 2008; Curtis et al., 2016; Gomez et al., 2017). Hide cleanliness assessment has also been proposed (Hughes, 2001; Jorgensen et al., 2017), but was shown to be poorly correlated with the total number of days with an abnormal fecal score in veal calves scored upon their facility arrival (Graham et al., 2018). A recent study focusing on a specific 4-category fecal scoring system adapted from Larson et al. (1977) correlates well with fecal DM content (Renaud et al., 2020). Using this score would, therefore, be very helpful and practical in defining diarrhea and should be recommended for future studies.

In most studies, sampling of calves was performed between arrival day and one week after facility arrival (i.e., during the first month of age because the exact age upon arrival is not generally precisely known). Various sampling times for immunity transfer evaluation could be a potential risk factor that may affect ITPI prevalence. This could be attributed to either diseases associated with protein loss or dehydration or with calf production of IgG and other proteins when becoming older. Passive transfer of immunity has only been validated in calves up to 9 d of age (Wilm et al., 2018), where IgG and STP values were found to be highly correlated during such a period and could easily be detected in blood upon sampling in that specified period. The correlation between IgG before 10 d of age and STP later is still not well studied, but interference with the passive immunity in the development of the active immunity component occurs (Chase et al., 2008). The case definition of ITPI (the type of test and threshold used) varied between studies and may explain part of the heterogeneity observed. However, it was impossible to use the TPI definition as a moderator in the meta-regression to quantify the potential effect of this definition on study heterogeneity, as previously done for dairy and beef calves (Raboisson et al., 2016) due to the different tests and or cut-off points used to quantify the passive immunity transfer. As a result, it is critical to consider this limitation in future studies to accurately characterize the size of the effect.

Based on our results, the true added value of an individual calf with an adequate or insufficient immunity transfer on the herd performance is difficult to determine. The different ITPI study prevalences (between 2 and 78%) could also affect the added effect or value of any calf regardless of its immunity status. The beneficial effect of adequate TPI for a specific calf will potentially not be the same in a group where ITPI prevalence is low versus groups where ITPI prevalence is high. This contextual effect is multifactorial. Better group immunity could lead to lower shedding of infectious agents by calves with adequate TPI and may mitigate the negative effect for calves with ITPI. In these conditions, this herd immunity has a protective effect on calves not adequately protected. Unfortunately, because of the low number of available studies, this hypothesis could not be explored in the meta-analyses. Future studies comparing the effect of individual versus group ITPI are strongly recommended.

Almost all the OR for different outcomes were obtained from $2 \times 2$ table data and no OR adjustment through regression models were performed; this could also be a study limitation. The BRD and diarrhea prevalence could not be used for adjusting OR for mortality in the included studies. However, the random effect models for mortality, BRD, and diarrhea were supported with publication bias only for the BRD outcome, and the sensitivity analyses investigations ensured the relative robustness of the study results, and this could be considered a strength of this study.

**CONCLUSIONS**

Inadequate transfer of passive immunity was found to be associated with mortality and diarrhea in finishing facilities for multisource commingled dairy calves raised for veal or other purposes. After adjusting for publication bias, ITPI was not associated with increased BRD risk. Inadequate transfer of passive immunity remains a critical determinant of future calf health. Our results raise concerns about the necessity of standardizing the definition of ITPI and the outcomes due to the dif-
ferent tests and or cut-off points for TPI definitions and varied case definitions used in the selected studies. Moreover, adequate definitions and reporting on raising systems for young multisource commingled dairy calves are recommended.

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REFERENCES


