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A Meta-Analysis of the Inclusion of Bio-Mos® in Milk or Milk Replacer Fed to Dairy Calves on Daily Weight Gain in the Pre-Weaning Period

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Abstract

Objective: This meta-analysis determines the effect of Bio-Mos®, a mannan-oligosaccharide, supplementation to pre-weaned dairy source calves on average daily weight gain (ADG) pre-weaning.

Methods: A literature search was performed and peer-reviewed studies and abstract proceedings were included. Studies were included where Bio-Mos®- supplemented calves were compared to control calves and weights were measured pre-weaning. A random effect meta-analysis was performed for overall effect and also comparing the effect stratified on type of liquid feed that the calves received.

Results: A total of 23 cohort studies performed in USA, United Kingdom, Brazil, Chile, the Czech republic, India, Japan, Peru, Poland, Spain and Turkey between 1993 and 2012 were included in the meta-analysis. The Bio-Mos® supplementation ranged from 2-10 g per day, with an average inclusion of 3.8 g per day. Twenty-one studies reported an increased daily weight gain in calves fed Bio-Mos® in milk or milk replacer compared to control calves. The random effects meta-analysis model estimated that Bio-Mos®- supplemented calves gained 0.064 kg/day (95% CI 0.047-0.081 kg/day) more than unsupplemented control calves (P-value <0.01). When stratified on type of feed, the estimates were similar; for milk replacer calves a 0.055 kg/day increased weight gain, for milk feed calves a 0.071 kg/day weigh gain and for waste milk/milk replacer calves a 0.068 kg/day weight gain advantage in Bio-Mos®-supplemented calves compared to unsupplemented control calves. Funnel plots indicated no publication bias or reporting bias.

Conclusion: The meta-analysis concludes that Bio-Mos® supplementation of milk or milk replacer can be expected to on average result in 64 g more weight gain per day in pre-weaned dairy calves, which would correspond to 3.8 kilo higher weights for calves weaned at 2 months of age.

Keywords: Meta-analysis; Milk replacer; Dairy calves

Introduction

The health status of young calves is one of the most important factors contributing to growth and performance. Diarrhoea in young calves is a major issue in the dairy and beef sector. The most common cause of disease and death in pre-weaned dairy calves is diarrheal disease [1]. Diseases and deaths are usually the tip of the iceberg of enteric sub-optimal health, and sub-optimal gut health contributes to dysbiosis and poor digestion, with resulting poor feed efficiency and growth performance. A recent meta-analysis of calf studies performed over the last 20 years has indicated that pre-weaning growth is linked to future milk production, and heifer that grow 100 g more pre-weaning can produce 155 kg more milk in the first lactation [2].

Mannan-oligosaccharides are prebiotics derived from the cell wall of Saccharomyces cerevisiae that have been shown to optimize gut health and overall health in numerous production animals [3]. It has been showing consistent results across various production species in improving performance in terms of improved feed intake, feed efficiency and growth. Bio-Mos®, Alltech's mannan-oligosaccharide based nutritional supplement derived from the cell wall of S. cerevisiae, have been most extensively researched and published [3].

Mannan-oligosaccharides can bind various pathogenic bacteria such as Escherichia coli and Salmonella enterica and it can modify and help to improve the composition of the intestinal microflora [3]. Mannan-oligosaccharides have been shown to improve faecal consistency, respiratory health, growth performance and increase concentrate intake [1, 4-7]. The performance-enhancing effects are most likely due to improvement in gut health, gut immunity and digestive function. Numerous trials have been performed to evaluate the influence of Bio-Mos® in the milk or milk replacer feed of pre-weaned calves on performance, whereas few other commercial mannan-oligosaccharide studies have been published. The aim of this paper is to perform a meta-analysis of the effect of inclusion of Bio-Mos® in milk or milk replacer feed to pre-weaned calves on their estimated daily growth rate during the pre-weaning period.

Material and Methods

A literature search was performed where all articles where calves were supplemented with mannan-oligosaccharides and weight gains were reported. PubMed searches where performed with various combinations of mannan-oligosaccharide, calves, pre-weaning, weight, average daily gain, prebiotics, oligosaccharides, and dairy. Due to the lack of peer-review studies published with mannan-oligosaccharides from other companies than Alltech, the decision was made to limit the study to Bio-Bio-Mos®. All published or elsewhere reported clinical or field trials presented at conferences and found in proceedings were included in this analysis where calves were supplemented with various quantities of Bio-Mos® in the milk replacer or milk or combinations of milk and milk replacers during the pre-weaning period. The company Alltech provided all studies using Bio-Mos® in calves. The studies that were eligible for inclusion were cohort studies where Bio-Mos® -supplemented calves were compared with control calves that did not receive any supplement and included weight or weight gain measures of the calves from the first week to some point during the pre-weaning period. Only studies where Bio-Mos® supplementation was started within one week of birth were included.

The meta-analysis was performed using Comprehensive Meta-Analysis Software 2.0. The mean reported average daily gain (ADG) was either used as reported or calculated based on reported weights. Standard error estimates were used to derive standard deviations and, where missing, the average standard deviation of daily gains across the studies was used. Only one ADG estimate per study was used in the analysis.

The 'inverse variance method' was used for meta-analysis and both fixed effects models and random effect models were developed [8]. The average effect size across all trials was computed as a weighted mean, whereby the weights are equal to the inverse variance of each trial's effect estimator. In the random effects model, larger studies and studies with less random variation were given greater weight than smaller studies. In the fixed effects model, studies were given equal weight. Forest plots and statistical tables were created for average daily gain shown in **Table 1 and Figure 1**. Funnel plots were created to evaluate selection bias or publication bias of studies **(Figure 2).** The level of significance was set at α=0.05 and 95% confidence intervals were produced for the effect estimates.

Results

A total of 23 studies were eligible for inclusion in the meta-analysis **(Table 1)** and 454 calves were Bio-Mos® supplemented and 446 calves were control calves. The first trial was performed in 1993 in the United States and the last study included was performed in Brazil in 2012. Six studies were performed in USA, five in the United Kingdom, three in Brazil and one each in Chile, the Czech Republic, India, Japan, Peru, Poland, Spain and Turkey.

The Bio-Mos® supplementation ranged from 2 g to 10 g per calf and day, with an average inclusion of 3.84 g per calf and day. The calves were followed from first week of life until at least 28 days of age and at the most until 60 days of age, the average age at the end of the studies and final weighing was 46 days. In 13 studies calves were fed conventional milk replacer, in two studies calves were fed a combination of pasteurized waste milk and milk replacer and in eight studies the calves were fed either whole milk or pasteurized waste milk. The calves were mostly limit-fed milk around half a kilo of milk replacer powder per day, or 4 liters of milk, and the maximum quantities fed were 8 liters of whole milk.

Twenty-one studies reported an increased daily weight gain in Bio-Mos® supplemented compared with control calves **(Table 1** and **Figure 1)**. Two studies reported a slightly lower weight gain in Bio-Mos® -supplemented calves compared with control calves. The outcome of interest was the difference in mean ADG between Bio-Mos® -supplemented calves compared with the control calves. The fixed effects model indicated that the estimated ADG in Bio-Mos® -supplemented calves was 0.061 kg/day (95% CI 0.048-0.074 kg/day) higher than non-supplemented calves (P-value <0.01) (**Table 2**).

The random effects model gave a very similar estimate of 0.064 kg/day (95% C.I. 0.047-0.081 kg/day) (P-value <0.01) (**Table 2**). When stratified by type of feed (milk replacer, milk or combinations of waste milk and milk replacer), the estimated ADG increase compared to unsupplemented control calves were similar; 0.055 kg/day for milk replacer calves, 0.071 kg/day for milk feed calves and 0.068 kg/day for waste milk/milk replacer calves (**Table 2**).

The funnel plots indicate that the estimated effect is true and not due to a publication or selection bias. The funnel plot puts study size on the vertical axis and effect size on the horizontal axis **(Figure 2).** Large studies are found towards the top of the graph and tend to cluster near the mean effect size, and the smaller studies are toward the bottom and (since there is more sampling variation in effect size estimates in the smaller studies) will be dispersed across a range of values.

In the absence of publication bias it is expected that studies are distributed symmetrically about the combined effect size. One concern of publication bias is that some non-significant studies are missing from the analysis and that these studies, if included, would nullify the observed effect. This meta-analysis yielded a z-value of 9.017 and a corresponding 2-tailed p-value<0.00001. The fail-safe N is 464, which means there would be need to be more than 20 missing studies for every observed study for the effect to be nullified.

Table 1: Basic trial design and mean difference in ADG in Bio-Mos®-supplemented calves compared to control calves in 23 studies

		Bio-MOS supplemented calves				Control calves					
Study	Feed	g/d	Calves	mean ADG	Std ADG	Calves	mean ADG	Std ADG	Mean diff	S.E.	References
USA 1993 a	MR	2	14	0,48	0,07	15	0,36	0,08	0,121	0,028	[15]
USA 1993 b	MR	2	7	0,40	0,11	7	0,34	0,11	0,064	0,059	[16]
USA 1994	MR	4	18	0,49	0,11	18	0,43	0,11	0,064	0,037	[17]
USA 1996	MR	2	17	0,40	0,11	17	0,36	0,11	0,040	0,038	[18]
JP 1996	MR	4	9	0,83	0,11	8	0,64	0,11	0,190	0,053	[19]
PL 1996	MILK	2	12	0,68	0,11	12	0,50	0,11	0,180	0,045	[20]
USA 1997 a	MR	2	60	0,39	0,11	60	0,33	0,11	0,059	0,020	[4]
USA 1997 b	WM-MR	4	81	0,46	0,11	81	0,39	0,11	0,066	0,017	[21]
PE 1998	MILK	6	20	0,72	0,11	20	0,67	0,11	0,050	0,035	[22]
BR 2000	MILK	4	12	0,43	0,11	12	0,37	0,11	0,060	0,045	[23]
USA 2003	MR	4	24	0,34	0,15	24	0,36	0,15	-0,020	0,042	[5]
UK 2005	MILK	4	28	0,55	0,11	28	0,47	0,11	0,080	0,029	[24]
TR 2005	MILK	4	20	0,45	0,09	20	0,43	0,09	0,021	0,027	[25]
UK 2006	WM-MR	4	28	0,55	0,16	29	0,47	0,16	0,081	0,043	[26]
ES 2006	MR	4	30	0,91	0,09	30	0,90	0,09	0,010	0,024	[13]
UK 2007 a	MR	4	15	0,48	0,12	15	0,42	0,11	0,063	0,041	[27]
UK 2007 b	MILK	4	17	0,57	0,08	17	0,51	0,08	0,060	0,028	[28]
CZ 2008	MR	5	10	0,55	0,11	9	0,47	0,11	0,080	0,051	[29]
CL 2009	MR	10	10	0,37	0,11	10	0,35	0,11	0,024	0,049	[30]
BR 2009	MILK	5	16	0,70	0,11	16	0,57	0,11	0,121	0,039	[14]
UK 2010	MR	4	19	0,26	0,11	12	0,26	0,11	-0,003	0,041	[31]
BR 2012	MR	4	8	0,41	0,12	8	0,35	0,12	0,058	0,061	[32]
IN 2012	MILK	4	18	0,32	0,06	18	0,26	0,06	0,058	0,021	[10]
Study contains Country code and year of study. MR: Milk replacer, MILK: whole milk/pasteurized waste milk, WM-MR: Pasteurized waste milk and milk replacer											

Table 2: Meta-analysis overall fixed and random models, and feed stratified random models of effect of Bio-Mos®-supplementation to pre-weaned calves on average daily gain.

Model	Milk type	Number studies	Diff in means	S.E.	Lower limit	Higher limit	Z-value	P-value
Fixed	All	23	0,061	0,007	0,000	0,048	0,07	<0,01
Random	All	23	0,064	0,009	0,000	0,047	0,08	<0,01
Random	MR	13	0,055	0,014	0,000	0,027	0,08	<0,01
Random	Milk	8	0,071	0,015	0,000	0,042	0,10	<0,01
Random	WM-MR	2	0,068	0,016	0,000	0,037	0,10	<0,01

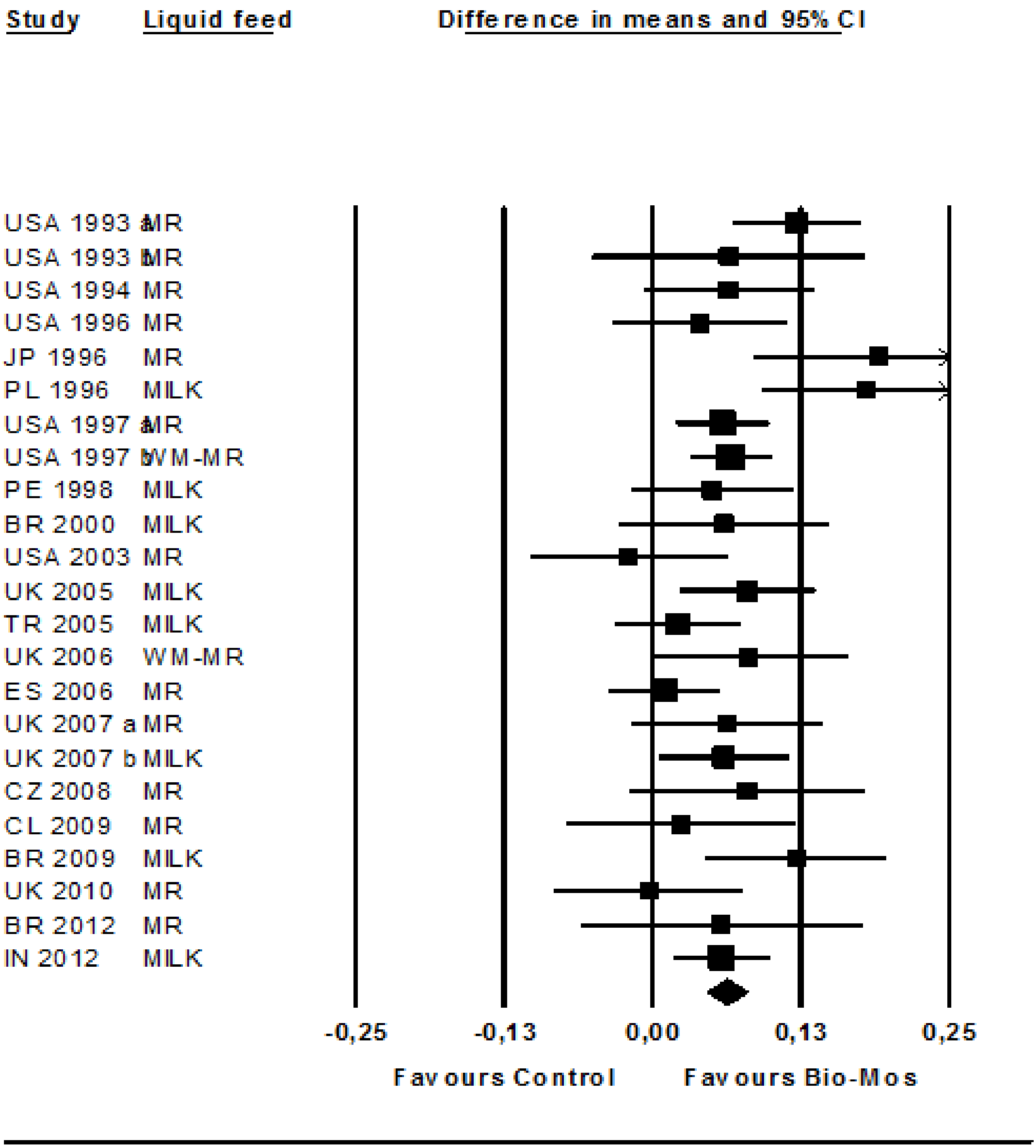

Figure 1: Forest plot of difference in ADG (kg/d) between Bio-Mos® -supplemented calves and control calves pre-weaning.

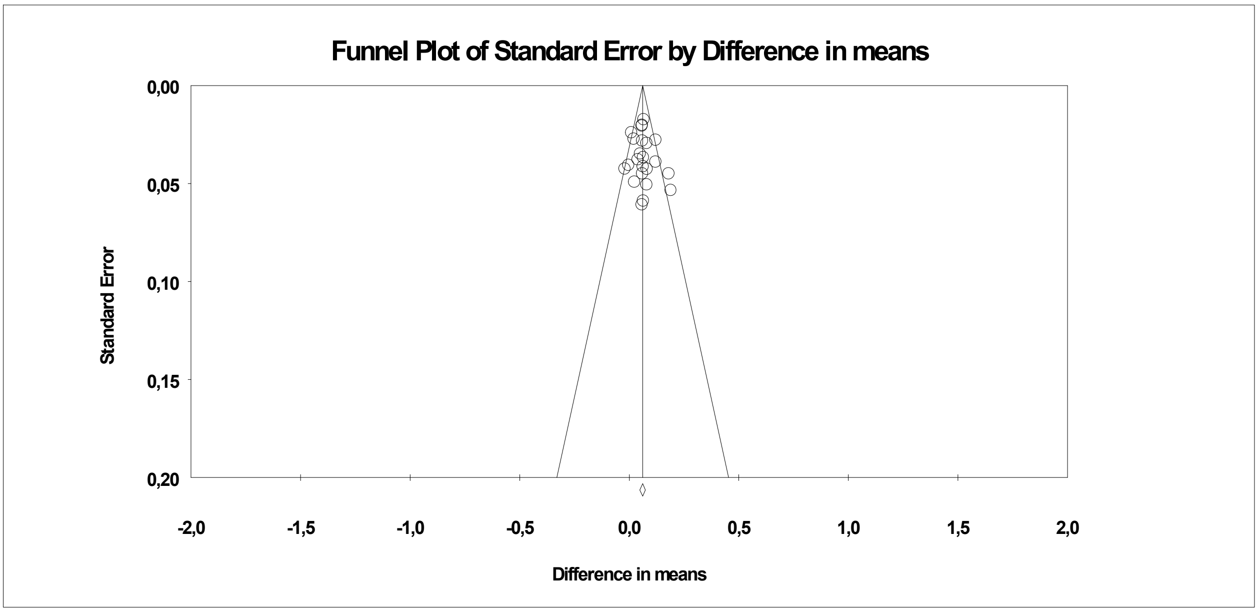

Figure 2: Funnel plot of standard error by difference in means of ADG in pre-weaned calves supplemented with Bio-Mos® in the milk or milk replacer.

Discussion

This meta-analysis indicates that pre-weaning calves when supplemented with Bio-Mos® at an average inclusion rate of 4 g per calf per day, achieved an additional 64 g weight gain per day pre-weaning. This increased ADG in Bio-Mos® -supplemented calves would correspond to an estimated 3.8 kg heavier calf at weaning at 60 days of age.

Mannan-oligosaccharides are prebiotics that have been shown to modify the gut microbial flora, increase the intestinal mucus-layer, improve intestinal immunity through interactions at the Peyer's patches and directly bind potential pathogens by binding to mannose-sensitive lectins [3,9]. The initial aim of the meta-analysis was to evaluate numerous performance and health parameters in pre-weaning calves supplemented with mannan-oligosaccharides. Several studies included in this meta-analysis also recorded health parameters and showed improved faecal consistency, reduced diarrhoeal incidence and improved gut immunity in Bio-Mos®-supplemented calves [5,10]. However the varied units of measurements and the description of the studies did not provide sufficient information to perform a meta-analysis. Few studies recorded feed intake or feed efficiency, and did not allow for further analysis. Since improved digestive health, less disease, improved feed intake and feed efficiency all translates into an improved weight gain, it is highly likely that observed weight gain were due to a combination of these factors.

Peer-reviewed or elsewhere published studies of mannan-oligosaccharides in pre-weaning calves were almost exclusively from Alltech with their proprietary mannan-oligosaccharide Bio-Mos®. Due to the lack of studies published from other companies, it was decided to limit the meta-analysis to Bio-Mos®. Commercial mannan-oligosaccharides vary in composition and purity and thereby efficacy. For example, a study in Turkey supplementing calves daily with 7 g mannan-oligosaccharides (not Bio-Mos®) could not detect any improvement in gut health or microbial community, as well as no significant difference in weight gain compared with control calves [11]. Therefore, caution should be taken when extrapolating the results of this meta-analysis to other commercial mannan-oligosaccharides.

Meta-analysis is a powerful tool to synthesize results from a series of studies and yield a more powerful test and a more precise estimate of the effect of an intervention. The fixed-effect model assumes that there is one true effect size, which underlies all the studies in the analysis and that all differences in observed effects are due to sampling error. This model can be used to define summary effects of the study results. The random effect model assumes that the true effect could vary from study to study based on various study conditions. There may be different effects of supplementation in different studies. For drawing inference from these studies to apply to other calves, then the random effect model results should be used. In this paper both the fixed effect and the random effect model results are presented allowing the reader to evaluate the underlying assumptions of the meta-analysis, however, the random effect model is the most appropriate. The outcomes of the two models are very similar and this strengthens the conclusions regarding the estimated improvement in daily gain obtained through Bio-Mos® supplementation in pre-weaned calves. The funnel plots indicate that the estimated effect is true and not due to a publication or selection bias.

The improved growth performance in calves supplemented with Bio-Mos® can be attributed to enhanced gut health and digestive function, as well as overall well-being of the calf, as the supplementation provides no nutritional supplementation to the diet. Enteric diseases are most prevalent in pre-weaned calves and disease is often accompanied by suppressed appetite of both milk and grain resulting in reduced growth rates [12]. Several studies included in this paper noted an improved grain intake in Bio-Mos®-supplemented calves and an improved feed efficiency [5,10,13,14]. The improved daily gain may be partly attributed to an increased nutrient intake and partly to an improved feed efficiency. The long-term improved performance in heifers with improved pre-weaning growth would be equivalent to 100 kg more milk in the first lactation and generates additional return on investment for the Bio-Mos®, including reduced treatment costs [2].

Conclusion

This meta-analysis consisting of 23 studies including 454 Bio-Mos® -supplemented calves and 446 control calves indicates that the inclusion of Bio-Mos® at levels of 2 to 10 g per calf per day in the milk or milk-replacer feed significantly improves average daily gain in pre-weaned calves by an estimated 64 g. This increased ADG in Bio-Mos® -supplemented calves would correspond to an improved return for the producer through enhanced productivity.

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