#### **REVIEWS**

# Meta-analysis of Brucella seroprevalence in dairy cattle of Ethiopia

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Abstract This meta-analysis estimates a single-group summary (effect size) for seroprevalence of Brucella spp. exposure in dairy cattle of Ethiopia. It also attempts to identify study-level variables that could explain the variation in apparent seroprevalence. The literature search was restricted to studies published in English language from January 2000 to December 2013. A template was designed to retrieve the most biologically plausible and consistent variables from the articles. A total of 29 published papers containing 40 animal-level studies were used in the analyses. The single-group summary of Brucella seroprevalence in cattle was estimated to reach 3.3 % with 95 % confidence interval (CI) (2.6–4.2 %). Of all the variables considered, region was the only specific factor identified to explain about 20 % of between-study variation. Accordingly, the region-based meta-analysis forest plot revealed the highest prevalence in central Ethiopia followed by southern part. The lowest prevalence estimate was observed in the western part of the country. The visual inspection of the funnel plot demonstrated the presence of possible publication bias which might dictate shortage of studies with higher prevalences or variance inflation due to infectiousness of *Brucella*. In conclusion, the quantitative review showed the seroprevalence to be low but widely distributed. More importantly, the review underscores the need for isolation and characterization of the circulating *Brucella* spp. to capture the type of *Brucella* spp. involved and its distribution in cattle in Ethiopia.

**Keywords** Seroprevalence *Brucella* spp · Brucellosis · Cattle · Ethiopia · Meta-analysis · Meta-regression · Heterogeneity

# Introduction

Ever since the discovery of Bang's bacillus or bacillus of cattle abortion by a Danish veterinarian, Benhard L.F. Bang, in the year 1897, *Brucella abortus* has been known as cause of abortion in cattle (Seleem et al. 2010). Importantly, brucellosis can also be due to *Brucella melitensis*, where mixed herding of cattle and small ruminants are common husbandry systems in Africa (Godfroid et al. 2013), and also *Brucella suis*, which has for the first time being described in Egypt (Menshawy et al. 2014). Brucellosis is a disease of economic and public health significance globally (Godfroid et al. 2005; WHO 2009; FAO 2009). It occurs worldwide, but bovine brucellosis has been eradicated in most of the developed nations (Seleem et al. 2010).

In Sub-Saharan Africa, the introduction of exotic animals with better productivity merit for food of animal origin is partly constrained by infectious diseases of which bovine brucellosis is one of them (Mangen et al. 2002; McDermott and Arimi 2002). Evidence of brucellosis and associated impact in cattle have been produced by a range of reports

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from countries including Egypt, Kenya, Uganda, Zambia, and Zimbabwe (Chimana et al. 2010; Holt et al. 2011; Magona et al. 2009; Matope et al. 2011; Muendo et al. 2012).

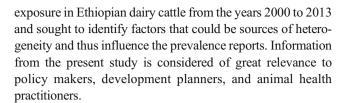
Like any other developing nation, the animal health service delivery and disease reporting system in Ethiopia are constrained by a range of technical and logistical hurdles (MoARD 2006). However, surveys have been conducted on various livestock diseases including brucellosis. In this regard, published reports on livestock brucellosis began to emerge since 1970th (Domenech 1977; Meyer 1980), and most of the reports from the last three decades focused on cattle brucellosis (Asfaw et al. 1998; Bekele et al. 2000; Berehe et al. 2007; Jergefa et al. 2009; Dinka and Challa 2009; Haileselassie et al. 2010; Asmare et al. 2010; Tolosa et al. 2010a; Megersa et al. 2011a; Asmare et al. 2013; Tschopp et al. 2013). The cited studies used serological methods to estimate the seroprevalence which range from 0.0 to 23.6 % in Ethiopia (Belihu 2002; Teklehaimanot and Gangwar 2011). Such variability in prevalence report may be attributed to differences in the study population, management systems, study designs, differences in sample sizes, or diagnostic tests used.

Although no single conclusive evidence on the presence and type of *Brucella* species involved in cattle infection in Ethiopia is available, the disease is presumed endemic in most parts of the country (Berehe et al. 2007). It is needless to mention that the lack of bacteriological isolates of *Brucella* from Ethiopia is one of the reasons for not fully capturing the zoonotic importance and epidemiological pattern of brucellosis in the country (Asmare et al. 2013). Yet, the information from various serological studies could be used as an available platform to suggest a reasonable estimate on the prevalence of livestock brucellosis at a national level.

As systematic reviews and meta-analysis have been developed for summarizing the scientific evidence from the literature (Dohoo et al. 2009; Higgins and Green 2011), we used the approach to make an overall weighted estimate (effect size) of the parameter of interest based on the existing reports and attempted to assess reasons for dispersion (i.e., heterogeneity) among the results of the primary studies. Thus, we believe that systematic reviews and meta-analyses of *Brucella* exposure in cattle help to overcome some of the shortcomings of individual reports where the precision of each study-specific estimate is accounted for when the overall estimate is computed.

# **Objectives**

This systematic review and meta-analysis focused on estimation of animal-level seroprevalence indicating *Brucella* spp.



#### Materials and methods

#### Literature search

Literature searches were conducted using the PubMed, ISI, and Google scholar search engines. Additional studies were identified by scanning the African Journal Online (AJOL) that includes the Ethiopian Veterinary Journal and Bulletin of Animal Health and Production in Africa. All searches were performed between the first week of November and mid-December 2013. The following keywords and combinations were used and rearranged to phrases close to Brucella prevalence in cattle in Ethiopia: bovine, cattle, intensive/semiintensive/extensive management, prevalence, and brucellosis. Searches were restricted to peer-reviewed articles published nationally or internationally in English language from January 1, 2000 GC to December 15, 2013 GC. Articles published before 2000 GC and those focusing on livestock other than cattle were not included.

#### Data extraction and assessment

Information on study methods, study animals, and relevant study-level covariates were retrieved using a predesigned template. The template was crafted after scanning relevant papers to identify the most consistent information to be retrieved for the analysis. The final template was tested using data from four papers extracted by the first author. Each article was reviewed and evaluated, and data were extracted. The data then compiled in Microsoft® Excel (Microsoft Corporation, Redmond, WA, USA) and subsequently imported into Stata (2009) (SE/12 for Windows, Stata Corporation, College Station, TX 778445, USA) which was used for all statistical analyses.

# Prevalence estimates

Apparent prevalence estimates were taken from each report after checking in line with production systems, number of test positives, and total sample size per system. Confidence intervals (95 %) were calculated for those reports limited to point estimates. In some case, number of positives, number of



animals sampled, and prevalence estimates were also calculated from a single article in line with geographical location, breed, or management. The prevalence estimates were then normalized using the logit transform, and the standard errors of the logit prevalence were computed as follows:

Logit prevalence = 
$$In \frac{P}{1-p}$$
,  $SE = \sqrt{\frac{1}{n*p*(1-p)}}$ 

# Meta-analysis

Due to the sampling frame, random effects meta-analyses of the logit prevalences were performed using the method of DerSimonian and Laird. The estimate of heterogeneity was taken from the inverse variance of random effect model using Stata metan command (Sterne et al. 2009; Dohoo et al. 2009; Borenstein et al. 2009). The basic results from the meta-analysis were presented in the plots. In the forest plot, each horizontal line represents the results from a single study, where the length of the line represents the 95 % confidence interval (CI) for the effect size (ES) from the individual study. The center of the shaded gray box marks the point estimate for the study, and the area of the gray box is proportional to the weight assigned to each study in the meta-analyses. Studies with large influence on the ES will get larger boxes than studies with less influence. A dashed vertical line indicates the ES, and a diamond-shaped box at the bottom of the dashed line shows the CI for the ES. A solid vertical line will be marked in the plot where the ES is 0.

The metan command generates an estimate of the Cochran's Q indicating differences in true ESs, an estimate of the true variance of ESs between studies (our estimate of  $\tau^2$ ) and Higgins  $I^2$  which is an estimate of what proportion of the observed variance that reflects

real differences in ES (Sterne et al. 2009; Borenstein et al. 2009):

$$I^2 = \left(Q - \frac{df}{Q}\right) * 100$$

where Q is the Cochran's Q statistic and df is the degrees of freedom (n-1). If  $I^2$  is close to 0, then almost all the observed variation is spurious, and there is nothing to explain. If  $I^2$  is large, then reasons for the observed variance should be evaluated (Borenstein et al. 2009).

#### Meta-regression

Animal-level random effects meta-regression models using the Stata metareg command were evaluated to identify sources of heterogeneity in prevalence estimates among studies and to evaluate the association between selected study-level predictors and prevalence estimates. Restricted maximum likelihood (REML) was used to estimate the additive (between-study) component of the variance tau<sup>2</sup>.

$$logit prevalence j = \beta_0 + \beta_{xj} + \mu_J + \varepsilon_j$$

where  $\beta_0$  represents the intercept or overall mean if no other predictor was included in the model,  $\beta$  represents the coefficient for the  $j^{th}$  predictor, and  $\mu_j$  represents the effect of study "j." The  $\varepsilon_j$  represents the differences between studies due to sampling variation. Variables were first assessed by univariable meta-regression, and variables with a p value <0.2 were considered for multivariable meta-regression. In the multivariable analyses, only variables with a p value <0.05 were retained. The proportion of variance explained was estimated as

$$R^2 = 1 - \frac{\tau^2 \text{unexplained}}{\tau^2 \text{total}}$$

**Table 1** Study characteristic variables selected for the meta-regression analyses in a systematic review and meta-analysis of *Brucella* seroprevalence in Ethiopia

Variable	Descriptions	Categories
Sample size	Number of animals	
Geography	Zones in line with administrative boundaries	
Region	Geographical region of Ethiopia	Central, Northern, Western, Eastern, and Southern Ethiopia
Data source	Data obtained from survey using questionnaire and farm record in some case	Primary
Study type	Study design	Cross-sectional, random, and convenience
Study population	Dairy cattle	Intensive, semi-intensive, and extensive management system
Type of diagnostic test	Serological testes	RBPT, CFT, and ELISA
Agro ecology	Covers the prominent agroecology in the country	Highland, midland, and lowland
Breed	Breed of the included cattle	Zebu, exotic, and their cross

RBPT Rose Bengal Plate Test, CFT complement fixation test, ELISA enzyme-linked immunosorbent assay



Table 2 Study quality variables included in a systematic review and meta-analysis of Brucella seroprevalence in Ethiopia

Variable	Description in MM section of the papers	Categories
Method of sample size determination	Did the paper describe how sample size was determined?	Yes/No
Sampling protocol	Did the paper describe how sampling was carried out?	Yes/No
Inclusion criteria	Is inclusion criteria set in sampling method or analysis	Yes/No
Details of diagnostic procedure	Did the paper have recipes and how decision was made?	Yes/No

where  $\tau^2_{\rm unexplained}$  was estimated from the null model without any variables and  $\tau^2_{\rm total}$  was unexplained

between-study variance with a given variable in the model. The selected study-level variables were evaluated

Table 3 List of the studies included in a meta-analysis of Brucella seroprevalence in dairy cattle in Ethiopia

Author (year)	Sample size	Apparent seroprevalence	Sampling group (management system)	Diagnostic test  RBPT, CFT	
Bekele et al. (2000)	4,243	4.9	Semi-intensive and extensive		
Eshetu et al. (2005)	552	10	Semi-intensive and intensive	RBPT, CFT	
Asmare et al. (2007)	811	2.5	Semi-intensive and intensive		
Berehe et al. (2007)	816	3.2	Extensive	RBPT, CFT	
Hailemelekot et al. (2007a)	864	3.8	Semi-intensive and intensive	RBPT, CFT	
Hailemelekot et al. (2007b)	326	3.7	Semi intensive and intensive	RBPT, CFT	
Tolosa et al. (2008)	1,305	0.8	Extensive	RBPT, CFT	
Kebede et al. (2008)	497	9.7	Extensive	RBPT, CFT	
Kebede et al. (2008)	619	12.4	Semi-intensive	RBPT, CFT	
Jergefa et al. (2009)	336	4.5	Semi-intensive	RBPT, CFT	
Jergefa et al. (2009)	902	2.2	Extensive	RBPT, CFT	
Dinka and Challa (2009)	1,106	11.2	Extensive	RBPT	
Abebe et al. (2009)	177	3.9	Semi-intensive and intensive	RBPT	
Haileselassie et al. (2010)	1,120	7.7	Semi-intensive	RBPT, CFT	
Haileselassie et al. (2010)	848	1.2	Extensive	RBPT, CFT	
Asmare et al. (2010)	1,627	1.7	Extensive	RBPT, CFT	
Megersa et al. (2011a)	283	10.6	Extensive	RBPT, CFT	
Amenu et al. (2010)	408	2.6	Semi-intensive and extensive	RBPT	
Ibrahim et al. (2010)	610	1.9	Semi-intensive	RBPT, CFT	
Tolosa et al. (2010a)	950	1.1	Extensive	RBPT, CFT	
Tolosa et al. (2010b)	780	0.5	Extensive	RBPT, CFT	
Degefa et al. (2011)	370	0.5 Extensive		RBPT, CFT	
Degefu et al. (2011)	435	1.4	Extensive	RBPT, CFT	
Megersa et al. (2011b)	900	1.6	Extensive	RBPT, CFT	
Teklehaimanot and Gangwar (2011)	72	23.6	Extensive	RBPT, CFT	
Teklehaimanot and Gangwar (2011)	232	11.2	Semi-intensive	RBPT, CFT	
Tesfaye et al. (2011)	1,202	1.5	Intensive	RBPT, CFT	
Haileselassie et al. (2011)	1,354	6.1	Extensive	RBPT, CFT	
Ibrahim et al. (2010)	985	3.9	Extensive	RBPT, CFT	
Yohannes et al. (2012)	55	3.6	Semi-intensive	RBPT, CFT	
Yohannes et al. (2012)	351	1.7	Extensive	RBPT, CFT	
Megersa et al. (2012)	575	8	Extensive	RBPT, CFT	
Asmare et al. (2013)	2,334	1.9	Semi-intensive and intensive		
Tschopp et al. (2013)	417	1.7 Extensive and semi-intensive		RBPT, ELISA	
Gumi et al. (2013)	862	1.4			



to determine how much of the between-study variance was accounted for by each predictor.

# Study characteristics and variables

The study characteristic variables selected for the metaregression analyses were selected based on biological relevance and consistency in reports and are defined in Table 1, while Table 2 presents the study quality variables included.

## Assessment of potential bias

The Begg's and Egger's tests were used in combination with a funnel plot to assess potential publication bias (Sterne et al. 2009; Borenstein et al. 2009). An influence plot was used to identify any influential studies.

#### Results

#### Literature search result

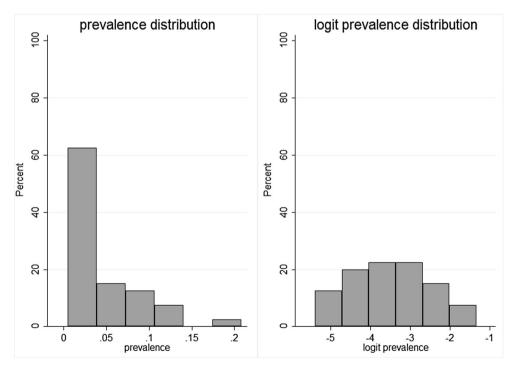
A total of 29 studies out of 50 reports from 124 retrieved references were included. All these studies were peer reviewed, written in English language, and published from January 2000 to December 2013. Due to a lack of consistency of reports on herd level prevalence, the ES estimate was limited to individual animal level. Eleven of the studies had covered the extensive management system exclusively on indigenous breed while eight studies were done on exotic

Fig. 1 Raw and logit apparent prevalence distributions for the animal-level studies for the meta-analysis of *Brucella* seroprevalence in dairy cattle in Ethiopia

agement systems. Ten studies considered both the indigenous cattle in extensive management system and exotic crosses in the semi-intensive management system. Regarding screening tests, three of study reports were based on Rose Bengal Plate Test (RBPT) alone while the remaining reports were based on a confirmatory test using complement fixation test (CFT) or enzyme-linked immunosorbent assay (ELISA) (Table 3). Ten of the papers reported more than one estimate of seroprevalence, and hence, the dataset consisted of 40 unique studies. The apparent Brucella seroprevalence distribution was skewed to the right reflecting the low seroprevalence level and infectious nature of the disease. Raw and logit-transformed figures by unit of analysis are depicted in Fig. 1. The logit transformation tended to normalize the data and was subsequently used in the meta-analysis. Meta-analysis and meta-regression

cattle and their crosses on intensive and semi-intensive man-

The ES of the logit prevalence from the random effects metaanalysis was -3.386 with 95 % CI -3.639, -3.136, corresponding to an apparent prevalence of 3.3 % with 95 % CI (2.6-4.2 %). A forest plot presenting the results from each study along with the ES is shown in Fig. 2. Based on the metaanalyses, the Cochran's Q was 624.94 (df 39, p<0.001), indicating significant variance in true effects. The estimate of  $\tau^2$  was 0.558 and  $I^2$  at 93.8 %, indicating a high proportion of between-study variance. Factors that could explain some of this variance were tested in the subsequent meta-regression.





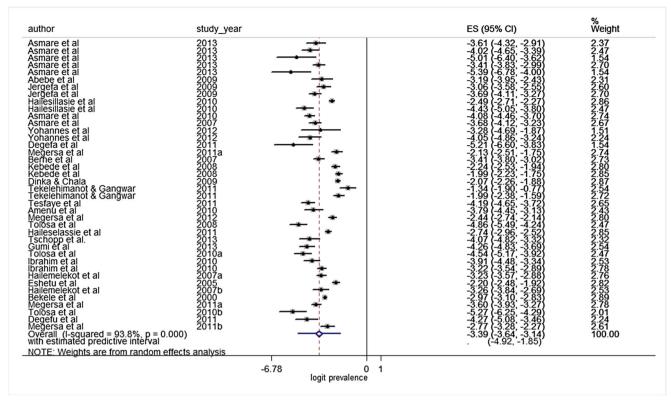


Fig. 2 Forest plot of the logit prevalence of Brucella seroprevalence in Ethiopia. The overall estimate was derived from a random effects meta-analysis

Results with coefficients and p values from the univariable meta-regression analyses are outlined in Table 4. Despite the high proportion of between-study variances, only region and study year had a univariable p value <0.2 and were selected for multivariable meta-regression (Table 4). Accordingly, region

was the only variable that showed a significant effect (p= 0.028), indicating a time-stable pattern. Central Ethiopia had the highest prevalence (ES closest to 0) and was chosen as baseline in the meta-regression. Compared to Central Ethiopia, Western Ethiopia had a significant decrease in logit prevalence

**Table 4** Regression coefficients and *p* values from univariable animal-level meta-regression of *Brucella* seroprevalence in Ethiopian dairy cattle (*n*=40 studies)

Variable	Category	n	Coefficient	p Value	Over all p value
Management	Extensive	21	Reference		
	Semi-intensive and intensive	17	0.11	0.724	
	Extensive and semi-intensive	28	0.46	0.516	0.717
Herd contact	Yes	23	Reference		
	No	17	-0.14	0.672	0.672
Mixed herd	Yes	23	Reference		
	No	17	-0.15	0.624	0.624
Breed	Indigenous	22	Reference		
	Exotic and their crosses	16	0.10	0.974	
	Mixed	2	-0.53	0.477	0.763
Regions	Central E.	11	Reference		
C	Southern E.	10	-0.85	0.044	
	Western E.	8	-1.44	0.002	
	Northern E.	8	-0.57	0.140	
	Eastern E.	3	-0.74	0.208	0.028
Diagnostic test	RBPT/CFT	35	Reference		
	RBPT	2	-1.19	0.470	
	ELISA	3	-0.42	0.194	0.423



by -1.44, p=0.002, while Northern Ethiopia had less decrease of logit prevalence by -0.85, p=0.044. Southern and Eastern Ethiopia was not significantly different from Central Ethiopia. Region explained 19.1 % of the between-study variance ( $R^2$ =0.191,  $\tau^2_{\rm unexplained}$ =0.674,  $\tau^2_{\rm total}$ =0.833). In addition, a subgroup analysis by region was performed to visualize the regional effect in a forest plot (Fig. 3). From the subgroup meta-analyses, the estimated prevalence for the different regions was calculated to be 5.9 % for Central, 1.5 % for Western, and 2.7 % for Northern Ethiopia. For Southern and Eastern regions of the country, the estimated prevalences were 3.5 and 2.9 %, respectively.

#### Publication bias

Both the Begg's and the Egger's tests were significant (p= 0.006 and p=0.001, respectively). Visual inspection of the funnel plot (Fig. 4) suggested that publication bias might have been present and there might be a shortage of studies with

higher prevalences (ES closer to 0). None of the studies were deemed influential according to the influence plot (data not shown).

# Discussion

These presumptive diagnoses of bovine brucellosis in Ethiopia were performed with a variety of serological tests. Ideally, such tests would detect *Brucella* spp.-exposed animals and none that were not. Brucellosis is one of the known cattle diseases for which a large number of reports are available from different production systems all over the country. However, all the reports made available so far are limited to serological studies that include RBPT, CFT, and ELISA. In the specified time period, we found 40 prevalence reports from 29 articles published in peer-reviewed journals. The highest numbers of reports (11) were from the central

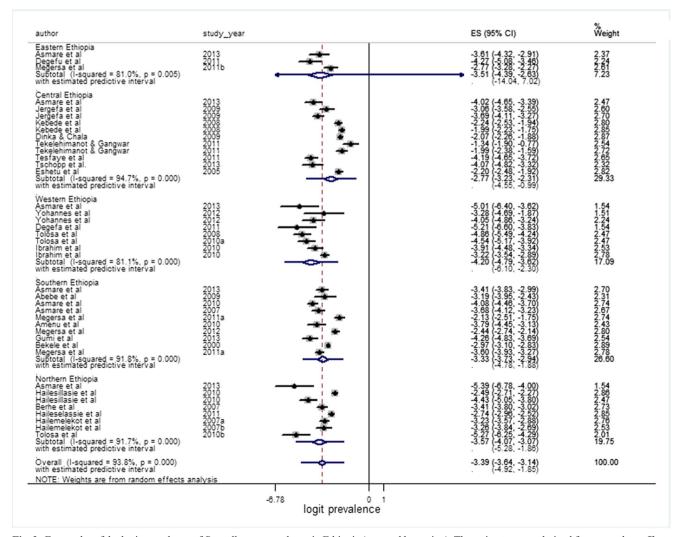
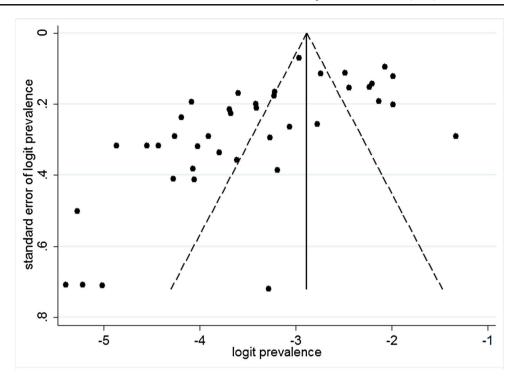


Fig. 3 Forest plot of the logit prevalence of *Brucella* seroprevalence in Ethiopia (grouped by region). The estimates were derived from a random effects meta-analysis



Fig. 4 Funnel plot of the point estimates of the logit prevalence of *Brucella* species exposure in Ethiopian dairy cattle



highlands while the lowest (3) were obtained from eastern part of the country. The reported apparent prevalence ranged from 0.5 % in the west (Tolosa et al. 2010b) to 23.6 % in the central highland of Ethiopia (Teklehaimanot and Gangwar 2011). In fact, the cumulative frequency diagram was skewed to the right which signifies the dominance of reports with low apparent prevalence.

The single-group summary (ES) in our meta-analysis was found to be 3.3 % with 95 % CI 2.6–4.2 %. The meta-analysis indicated that almost 95 % of the observed variance came from real differences between studies, and to elaborate sources of this variability and explain some heterogeneity meta-regression analysis was done on the study-level variables, i.e., studied regions, management systems, breed, herd composition, diagnostic test used, study year, and herd contact. Beside region, none of the factors were shown to influence the result much. Perhaps, the failure to capture the attributed difference could be due to limited number of contrasting categories within the variables under investigation or low overall prevalence. The subsequent subgroup analysis on region showed that the ES varied considerably between regions and prevalences ranged from 1.5 % in Western Ethiopia to 5.9 % in Central Ethiopia. The ES for Eastern, Northern, and Southern Ethiopia were 2.9, 2.7, and 3.5 %, respectively. The actual meaning of these different seroprevalences is not known. It is worth to re-emphasize that in case of spillover of *B. melitensis* from small ruminants to cattle, the seroprevalence in cattle will remain low over time, even in the absence of a control program, whereas in case of B. abortus infection in cattle, the seroprevalence will be higher and the infection will over time reach enzootic stability, characterized by a seroprevalence that will remain stable over time (Godfroid et al. 2013). The  $I^2$  was lower in the subgroups Western and Northern but still high and indicating that other factors also contributed to the heterogeneity. In fact, region explained only approximately 20 % of the between-study variance.

In the consecutive Begg's and Egger's test statistics and visual inspection of the funnel plot, likely evidence for possible publication bias or limitation of articles reporting higher prevalence were observed. The bias could be partly explained by our conservative estimate which excluded unpublished reports, workshop proceedings, and dissertation theses. Exclusions effected to avoid redundancy as most of the articles were part of dissertation thesis of graduate and undergraduate studies in various academic institutions. Besides, some studies lack clarity on the study designs which limit inference.

The lack of bias due to serological methods used was reassuring and underlines that the major differences found between regions truly represent differences in the epidemiology of *Brucella* in various areas of Ethiopia. The infectious nature of the disease also leads to a variance inflation in itself and may also be a reason for the irregular funnel plot observed and the strong right skewness of the original plot. In a nutshell, the meta-analysis allowed us to balance a wide range of studies and present a more reliable overall seroprevalence estimate for Ethiopia.



Nevertheless, an important and often forgotten shortcoming of brucellosis serology is the impossibility to infer which (smooth) *Brucella* spp. induced antibodies in the animal or human host. As a consequence, infection with *B. abortus*, *B. melitensis*, or *B. suis* will induce the same serological pattern, and antibodies induced by these different *Brucella* species are actually detected by the same serological tests (Godfroid et al. 2013). We acknowledge that the preceding fact to be part of the shortcomings of our review.

#### **Conclusions**

To our knowledge, this is the first quantitative review attempt ever made on cattle brucellosis in Ethiopia. In this metaanalysis and systematic review, we observed that the group summary (ES) for *Brucella* seroprevalence in cattle is low; yet, higher degree of variability was observed between regions. Comparatively, the highest prevalence was observed in central highland of Ethiopia followed by the southern part of the country. As these regions are serving as source of breeding stock, particularly for intensive and semi-intensively managed dairy cattle throughout the country, isolation and characterization of the circulating agent are mandatory to produce clearer picture on the dynamics of *Brucella* infections which possibly dictate the future intervention strategy in cattle. To this end, the use of the Farrell's medium for the isolation of Brucella spp. should be given due attention complying with technical and safety requirement.

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# Conflict of interest None

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