



Comparing two approaches for meta-analysis of binary outcomes

YOGESH C BANGAR¹ and MED RAM VERMA²

ICAR-Indian Veterinary Research Institute, Izatnagar, Uttar Pradesh 243 122 India

ABSTRACT

In the present study, meta-analysis of binary outcome was undertaken by using two approaches namely Summary Statistics (SS) and Individual Animal Data (IAD) approach for obtaining more reliable estimates of the association of risk factors [breed (crossbred & indigenous), parity (primiparous & multiparous), age (< 5 years & > 5 years) and milk yield (kg)] with clinical mastitis [binary outcome (yes or No)] in dairy cows in India. For the present study the data on mastitis were compiled from three organized cattle farms. The results of bootstrapping showed that the pooled estimates under Individual Animal Data (IAD) approach were significantly higher than Summary Statistics (SS) approach for all unadjusted risk factors. However the results of both approaches were similar under covariate-adjusted circumstances. In case of heterogeneity of effects across farms, Individual Animal Data (IAD) approach provides more reliable information than Summary Statistics (SS) approach. Therefore it was also concluded that the crossbreds (adjusted for age) cows (1.47 times), older cows (1.85 times) multiparous cows (2.21 times) and high yielders (1.67 times) cows were at higher risk of mastitis than their respective reference categories. Therefore Individual Animal Data (IAD) approach is an appropriate approach for animal science data as it is more reliable and perform better in heterogenous conditions.

Key words: Bootstrap, Clinical mastitis, Dairy cows, Meta-analysis

One of the key areas in the research related to animal health and production is to determine the associated risk factors of important diseases by studying animal characteristics and managerial practices. The studies of factor-outcome associations are useful to identify the individual animals in which the risk of getting a disease is high and then, to adopt necessary preventive and therapeutic measures to minimise the economic losses to the dairy sector. Clinical mastitis is one of the most important diseases in dairy cows throughout the world. It causes heavy economic losses by reducing milk production, affecting herd structure and treatments costs (Hogeveen *et al.* 2011). Several studies have investigated the cow-level risk factors associated with incidence of clinical mastitis (Steenefeld *et al.* 2008, Nakov and Trajcev 2012). The studies which carried out to assess the risk of various diseases in animal population have described the various kinds of statistical models and also use the several datasets from various locations or time periods or the data from the previous studies/reports.

Meta-analysis is a quantitative statistical technique used to generalize findings and to derive conclusions about the point of interest by conducting a systematic review of previous research studies (Lean *et al.* 2009). It provides

the pooled estimates of effects and offers an opportunity to test the homogeneity of effects across studies (Walker *et al.* 2008). Several studies have carried out a meta-analysis of risk factors of disease by using the data from previously published studies (Wang *et al.* 2014, Asmare *et al.* 2014, Bangar *et al.* 2015, Bangar *et al.* 2016).

There are two approaches available for conducting the meta-analysis if individual animal records are available (Dutton 2010, Debray *et al.* 2013). The first approach combines summary statistics obtained from each study to provide the pooled estimate about the point of interest. Second approach of meta-analysis uses individual animal records obtained from each study to generalize the results. The comparison between these two approaches can be useful to determine the appropriate approach and further the precision and accuracy can be increased in the process of estimation of associations of risk factors with the disease conditions.

The present study was undertaken to compare Individual Animal Data (IAD) approach of meta-analysis with Summary Statistics (SS) approach in the context of risk factors of clinical mastitis in dairy cows and to obtain the pooled estimates of risk of mastitis in dairy cows in various cow-level risk factors by using appropriate approach of meta-analysis.

MATERIALS AND METHODS

Study area: Meta-analysis of prevalence and risk factors of clinical mastitis in dairy cows under farm conditions was done by collecting data on mastitis in dairy cows from 3

Present address: ¹Scientist (yogeshbangar07@gmail.com), Department of Animal Genetics and Breeding, Lala Lajpat Rai University of Veterinary and Animal Sciences, Hisar, Haryana. ²Principal Scientist (medramverma@rediffmail.com), Division of Livestock Economics, Statistics and Information Technology, ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly, Uttar Pradesh.

organized cattle farms, viz. Cattle and Buffalo Farm, LPM Section, ICAR-Indian Veterinary Research Institute (IVRI), Izatnagar, Uttar Pradesh; Research Cum-Development Project on Cattle (RCDP), Mahatma Phule Krishi Vidyapeeth (MPKV), Rahuri (Maharashtra); Livestock Research Center, ICAR-National Dairy Research Institute (NDRI), Karnal (Haryana) located in India from April 2012 to March 2013.

Data variables: The data of all dairy cows were completely recorded to collect essential information on related aspects of animal particulars, production records and status of mastitis by reviewing animal history sheets, production records, disease registers etc. The occurrence of mastitis was considered binary outcome (yes/no) and different risk factors were used to assess association of mastitis occurrence in three farms.

Statistical analysis: All cow and farm level data including mastitis status were entered into Microsoft excel spreadsheet. Preliminary analysis was done to explore different cow-level risk factors of mastitis such as breed (crossbred & indigenous), age (< 5 & ≥ 5 yrs), parity (primiparous & multiparous) and milk yield (< 8 & ≥ 8 kg). The prevalence of mastitis was calculated as number of cows with mastitis during reference period divided by population at risk which was taken as number of lactating cows in the reference period.

Meta-analysis of binary outcome was carryout using approaches (i) Summary Statistics (SS) approach and (ii) Individual Animal Data (IAD) approach (Dutton 2010), as follows.

Summary Statistics Approach

This approach was performed into two stages.

Stage 1: All data on mastitis were analyzed separately for each farm to obtain summary statistics of risk of mastitis for each risk factor. Binary logistic regression was used under considering a single risk factor with $i=1, 2, \dots, k$ and $j = 1, 2, \dots, N_i$ as follows:

$$\text{Logit}(p) = \log \left(\frac{p_{ij}}{1-p_{ij}} \right) = \alpha_i + \beta_i x_{1ij}$$

where α_i represent intercept for i^{th} farm and β_i (log-odds ratio) represent slope as the association of risk factor x_{1ij} with binary outcome for i^{th} farm. The estimates ($\hat{\beta}_i$) were considered as summary statistics of risk effects for each farm, which were used in stage 2.

Stage 2: In this stage, two types of models, viz. fixed effect model and random effects model were considered and summary statistics ($\hat{\beta}_i$) of each risk factor at each farm were used to obtain the pooled estimate by appropriate model.

Fixed effect model

The observed effect of y_i risk factor of mastitis for any farm is given by the population mean plus the sampling error in that farm under fixed effect model,

$$y_i = \mu + \varepsilon_i$$

where μ is grand mean and ε_i is distributed normally with mean 0 and variance σ^2 . Here, only within-study variance (s^2_1) was considered and therefore, the weight (w_i) was allotted to each farm under the inverse variance of respective farm ($1/s^2_1$) and the pooled estimate ($\bar{\beta}_w$) of risk factor associated with disease was calculated (Borenstein *et al.* 2009) and given by,

$$\bar{\beta}_w = \frac{\sum_{i=1}^k w_i \times \hat{\beta}_i}{\sum_{i=1}^k w_i} \text{ and } SE(\bar{\beta}_w) = \frac{1}{\sqrt{\sum_{i=1}^k w_i}} \text{ where } w_i = \frac{1}{s^2_1}$$

Homogeneity of the effects across farms was tested using Q statistic (Cochran, 1954) and quantified using I² index (Higgins and Thompson 2002) as follows:

$$Q = \sum_{i=1}^k \left[w_i (\hat{\beta}_i - \hat{\beta}_w)^2 \right] \text{ and } I^2 = \frac{Q - df}{Q} \%$$

Random effects model

In case of heterogeneity of estimates across farms, random effects model was considered (Poolsup *et al.* 2014) as follows:

$$y_i = \mu + \zeta + \varepsilon_i$$

Which considers two deviation, i.e. the deviation of the true study effect from the grand mean and the deviation of the observed study effect from the true study effect. Thus there are two source of variation, i.e. between-farm variance (δ^2 , an estimate of the between-farm variance, τ^2) and within-farm variance (s^2_1). The weight assigned to each farm under the inverse variance scheme (DerSimonian and Laird 1986) is given by,

$$w_i^* = \frac{1}{S^2_1 + \delta^2} \text{ where } \delta^2 = \frac{Q - (k-1)}{C} \text{ and}$$

$$C = \sum_{i=1}^k w_i - \left(\sum_{i=1}^k w_i^2 \right) \div \left(\sum_{i=1}^k w_i \right)$$

and the pooled estimate ($\bar{\beta}_w^*$) of risk factor associated with occurrence of mastitis under random effects model was calculated by the formula explained earlier except with different weights W_i^* .

Individual Animal Data Approach

Meta-analysis of binary outcome using Individual Animal Data (IAD) approach was done to obtain the pooled estimates of risk effects from all farms in a single step by considering as data were from a single large study (Dutton 2010). This approach was performed by including farm as an indicator variable in the model, with one risk factor. The fixed and mixed effects models were used in the meta-analysis as follows:

Fixed Effect Model

The general logistic regression model was used to estimate the probability of occurring mastitis assuming farm

and risk factor as fixed effects and given by (Whitehead 2002) with $i=1,2,\dots,k$ and $j=1,2,\dots,N_i$ as follows:

$$\text{Logit}(p) = \log \left(\frac{p_{ij}}{1-p_{ij}} \right) = \alpha + \beta_{0i} + \beta_1 x_{1ij}$$

where α represent intercept and (β_{0i}) represent farm effect with (β_{0k}) being constrained to zero. β_1 (log-odds ratio) was considered as the pooled estimate of association of mastitis occurrence with respective risk factor, which was assumed common across all intercept and farms.

The hypothesis $H_0: \delta^2=0$ (homogeneity of estimates across farms) was tested using Likelihood Ratio Tests (LRT) of the fixed model with and without interaction of farm and risk factor. Under homogeneity across farms, results of fixed effect model were considered, otherwise mixed effects model was preferred to obtain the pooled estimate (Tobias *et al.* 2004).

Mixed Effects Model

Generalized linear mixed model was used for meta-analysis of binary outcome by considering risk factor as fixed effect and both farm and farm by risk factor interaction as random effects (Whitehead 2002) as follows.

$$\text{Logit}(p) = \log \left(\frac{p_{ij}}{1-p_{ij}} \right) = \alpha + \gamma_{0i} + \gamma_1 x_{1ij}$$

where $\gamma_{0i} = \beta_0 + v_{0i}$ and $\gamma_{1i} = \beta_1 + v_{1i}$. V_{0i} & V_{1i} are normally distributed random effects. Grouping separately fixed and random effect, above model can be written as,

$$\text{Logit}(p) = \log \left(\frac{p_{ij}}{1-p_{ij}} \right) = \alpha_h + \beta_{0i} + \beta_1 x_{1ij} + V_{0i} + V_1 x_{1ij}$$

The bootstrap procedure was used to compare two approaches of meta-analysis (Efron 1979; Dutton 2010). Total of 1000 bootstrap replicates were drawn from original data by stratified resampling with replacement and two approaches of meta-analysis were applied to these replicates. The distribution of the paired difference between estimates of two approaches of meta-analysis were summarized and compared to find out significant difference between two approaches of meta-analysis. If zero is within the 95% bootstrap percentile confidence interval of the paired difference of estimates, then it was concluded that the results of the two approaches of meta-analysis were statistically similar.

Finally, appropriate approach was suggested on the basis of bootstrap criteria, thereby the pooled estimates of risk of mastitis in dairy cows were provided by appropriate approach. The statistical analyses were conducted software using PROC LOGISTIC, PROC GENMOD and PROC GLIMMIX in SAS 9.3 software. The bootstrapping was performed using PROC SURVEYSELECT in SAS 9.3 software.

RESULTS AND DISCUSSION

Meta-analysis using Summary Statistics (SS) approach

Stage 1: Farm-wise analysis of risk of mastitis: The

binary logistic regression analysis of risk of mastitis with respect to each risk factor was done separately for each farm to obtain summary statistics (estimates) and the results are shown in Table 1. The data on total 878 lactating cows for study period (April 2012 – March 2013) were collected from three farms, out of which 248 (28.25%), 172 (19.59%) and 458 (52.16%) cows were maintained at IVRI, MPKV and NDRI farm, respectively. The factor-wise odds ratios indicated that the risk of mastitis was more in crossbred, cows with age < 5 yrs, primiparous and high yielders (≥ 8 kg) than their counter parts. However the significance of these factors was varied at each farm.

Stage 2: Obtaining the pooled estimates

The results of meta-analysis using summary statistics including both fixed and random effects models with respect to unadjusted and adjusted risk factors are shown in Table 2. The test of homogeneity was not significant ($p > 0.05$) for breed (unadjusted and adjusted), age and parity and it was concluded that there was consistency for the effects of these factors between three farms. Therefore, the results according to fixed effect model were considered and the pooled estimates of risk of mastitis in the crossbred cows (unadjusted), crossbred cows (adjusted), older cows and multiparous cows were observed as 1.35 (95% CI: 0.95, 1.92; $p=0.09$), 1.47 (95% CI = 1.03, 2.11; $p = 0.03$), 1.85 (95% CI: 1.37, 2.50; $p < 0.001$) and 2.18 (95% CI: 1.55, 3.05; $p < 0.001$) respectively. In case of milk yield factor, the heterogeneity ($Q= 6.58$; $I^2=69.60\%$; $p < 0.05$) was observed between farms. The pooled estimate of the risk of mastitis under random effects model was not significant ($p > 0.05$) for milk yield.

Meta-analysis using Individual Animal Data (IAD) approach

The pooled estimate of risk of mastitis due to each risk factor was obtained by IAD approach (Table 2). The results showed that there was homogeneity of effects of all risk factors across farms except milk yield. The results due to fixed effect model indicated that pooled estimates of risk of mastitis in the crossbred cows (unadjusted), crossbred cows (adjusted), older cows and multiparous cows were observed as 1.37 (95% CI: 0.97, 1.93; $P=0.07$), 1.51 (95% CI: 1.06, 2.13; $p = 0.02$), 1.85 (95% CI: 1.37, 2.51; $p < 0.001$) and 2.21 (95% CI: 1.57, 3.10; $p < 0.001$) respectively. The results under mixed effects model for milk yield showed that the risk of mastitis due to milk yield was found significantly higher for the high yielding cows (OR= 1.67; 95% CI: 1.03, 2.73; $p < 0.04$) than low yielding cows.

Comparison between two approaches of meta-analysis

The results of comparing the estimates of risk of mastitis obtained by Summary Statistics (SS) approach and Individual Animal Data (IAD) approach for various risk factors using the bootstrap method are shown in Table 3. The results for breed (unadjusted, adjusted), age and parity were compared using estimates from fixed effect model

Table 1. Binary logistic regression analysis of association of mastitis with potential cow-level risk factors in cows at three organised cattle farms

Farm	Factor	level	Total	Affected (%)	OR	95% CI	P value
IVRI	Overall		248	71 (28.63)			
	Breed	Crossbred	196	62 (31.63)	2.21	1.01 , 4.82	0.05
		Indigenous	52	9 (17.31)	Reference		
	Age	< 5 yrs	173	41 (23.70)	Reference		
		≥ 5 yrs	75	30 (40.00)	2.15	1.20 , 3.83	0.01
	Parity	Primiparous	110	18 (16.36)	Reference		
		Multiparous	138	53 (38.41)	3.19	1.73 , 5.87	<0.001
	Milk Yield	< 8 kg	120	26 (21.67)	Reference		
		≥ 8 kg	128	45 (35.16)	1.96	1.11 , 3.45	0.02
MPKV	Overall		172	60 (34.88)			
	Breed	Crossbred	155	55 (35.48)	1.32	0.44 , 3.94	0.62
		Indigenous	17	5 (29.41)	Reference		
	Age	< 5 yrs	82	25 (30.49)	Reference		
		≥ 5 yrs	90	35 (38.89)	1.45	0.77 , 2.73	0.25
	Parity	Primiparous	50	11 (22.00)	Reference		
		Multiparous	122	49 (40.16)	2.38	1.11 , 5.09	0.03
	Milk Yield	< 8 kg	84	20 (23.81)	Reference		
		≥ 8 kg	88	40 (45.45)	2.67	1.39 , 5.13	<0.001
NDRI	Overall		458	126 (27.51)			
	Breed	Crossbred	263	76 (28.90)	1.18	0.78 , 1.79	0.44
		Indigenous	195	50 (25.64)	Reference		
	Age	< 5 yrs	216	45 (20.83)	Reference		
		≥ 5 yrs	242	81 (33.47)	1.91	1.25 , 2.92	<0.001
	Parity	Primiparous	135	28 (20.74)	Reference		
		Multiparous	323	98 (30.34)	1.66	1.03 , 2.69	0.04
	Milk Yield	< 8 kg	197	53 (26.90)	Reference		
		≥ 8 kg	261	73 (27.97)	1.06	0.70 , 1.60	0.80

OR: Odds Ratio; CI: Confidence Interval

Table 2. Meta-analysis of association of mastitis with potential cow-level risk factors using summary statistics (SS) and individual animal data (IAD)

Factor	Approach	Model	$\hat{\alpha}$ (SE)	Q^S / LRT [#]	I^2 (%)	OR	95% CI	p value
Breed (Unadj.) ^a	SS	Fixed	0.30 (0.18)	1.95 ^{NS}	0.00	1.35	0.95 , 1.92	0.09
		Random	0.30 (0.18)			1.35	0.95 , 1.92	0.09
	IAD	Fixed	0.31 (0.18)	2.06 ^{NS}		1.37	0.97 , 1.93	0.07
		Mixed	0.36 (0.17)			1.43	1.03 , 1.99	0.03
Age	SS	Fixed	0.62 (0.15)	0.84 ^{NS}	0.00	1.85	1.37 , 2.50	<0.001
		Random	0.62 (0.15)			1.85	1.37 , 2.50	<0.001
	IAD	Fixed	0.62 (0.15)	0.84 ^{NS}		1.85	1.37 , 2.51	<0.001
		Mixed	0.61 (0.15)			1.84	1.37 , 2.47	<0.001
Parity	SS	Fixed	0.78 (0.17)	2.76 ^{NS}	27.54	2.18	1.55 , 3.05	<0.001
		Random	0.80 (0.21)			2.23	1.48 , 3.34	<0.001
	IAD	Fixed	0.79 (0.17)	2.77 ^{NS}		2.21	1.57 , 3.10	<0.001
		Mixed	0.82 (0.22)			2.28	1.49 , 3.48	<0.001
Milk Yield	SS	Fixed	0.42 (0.15)	6.58*	69.60	1.52	1.13 , 2.05	0.01
		Random	0.53 (0.29)			1.69	0.96 , 2.98	0.07
	IAD	Fixed	0.43 (0.15)	6.64*		1.53	1.14 , 2.06	0.01
		Mixed	0.52 (0.25)			1.67	1.03 , 2.73	0.04
Breed (Adj) ^b	SS	Fixed	0.39 (0.18)	2.06 ^{NS}	3.03	1.47	1.03 , 2.11	0.03
		Random	0.40 (0.19)			1.49	1.03 , 2.15	0.04
	IAD	Fixed	0.41 (0.18)	2.35 ^{NS}		1.51	1.06 , 2.13	0.02
		Mixed	0.45 (0.17)			1.58	1.12 , 2.22	0.01

OR: Odds Ratio; CI: Confidence Interval; ^STest of homogeneity under SS approach; [#]Test of homogeneity under IAD approach;^aNot-adjusted for age variation; ^bAdjusted for age variation; *Significant at 5% level of significance; ^{NS}Non-significant.

Table 3. Comparison of two approaches of meta-analysis of binary outcome

Factor	Difference	2.5th Percentile	97.5th percentile	Conclusion
Breed (Unadj.) ^a	0.024	0.002	0.089	*IAD larger than SS
Age	0.002	0.001	0.01	*IAD larger than SS
Parity	0.025	0.001	0.091	*IAD larger than SS
Milk yield	0.013	0.001	0.038	*IAD larger than SS
Breed (Adj.) ^b	0.034	-0.014	0.092	^{NS} Both are similar

^aNot-adjusted for age variation; ^bAdjusted for age variation
*Significant at 5% level of significance; ^{NS}Non-significant.

whereas for milk yield, random/mixed effects model was used. The bootstrap method showed that there was significant difference between the pooled estimates obtained from two approaches of meta-analysis for all risk factors except breed adjusted for age. Among two approaches, IAD approach provides significantly higher estimates of risk of mastitis than the SS approach. Due to adjustment to breed to reduce the variation of age across farms, both approaches produce similar results for risk of mastitis in both breeds.

The results of the present study has provided the estimates (Range: 27.51% to 34.88%) of prevalence of clinical mastitis in dairy cows maintained at three farms. Similar estimates were also reported by several authors (Khalate 2009, Bangar *et al.* 2016).

The present study demonstrated and compared two approaches (SS and IAD) of meta-analysis for estimating the risk of mastitis in dairy cows using the data from three cattle farms. The study of these two approaches is essential for appropriate selection of procedure because of either approach can interpret differently (Debray *et al.* 2013). Several studies have been conducted meta-analysis of binary outcome using Individual Animal Data (IAD) and Summary Statistics (SS) approaches (Leonardi-Bee 2005, Mathew and Nordstrom 2010, Debray *et al.* 2013). The analysis in the present study deals with both fixed and random/mixed models since comparison between these two models provides insight to the data (Riley *et al.* 2013). The choice of model was based on the significance of the homogeneity of effects across farms. Further, in case of mixed effects model, both farm and its interaction with risk factor were considered as random effects as it provides more accurate estimate than either farm or its interaction as random effects (Tobias *et al.* 2004).

Both Statistics (SS) and Individual Animal Data (IAD) approaches has showed gain in statistical power and concluded significance of risk factors despite of their non-association with mastitis at individual farm. It was conventionally believed that these two procedures of meta-analysis produces similar estimates and thus, same conclusions (Whitehead 2002; Mathew and Nordstrom 2010, Stewart *et al.* 2012), but the results of the study showed that this is not true.

The comparison between two approaches of meta-

analysis using Bootstrap method suggested that these approaches provide significantly different results for each risk factor. These findings were also reported by Debray *et al.* (2013) who stated that the choice of implementation of procedure leads to different conclusions about which factor associated with the outcome. The estimates from Individual Animal Data (IAD) approach were significantly higher than those obtained from Summary Statistics (SS) approach. This difference between the results of two approaches may be due to the assumption of normality for combining of log odds ratios under SS approach whereas Individual Animal Data (IAD) approach uses the exact binomial distribution (Whitehead 2002, Leonardi-Bee 2005). Further, it was also observed that the estimates of standard error under Individual Animal Data (IAD) approach was equal to or less than that of Summary Statistics (SS) approach. For milk yield factor, Individual Animal Data (IAD) approach not only narrowed confidence interval (95% CI=1.03, 2.73) under mixed effects model as compared to SS approach (95% CI=0.96, 2.98) under random effects model but provided significant association of milk yield with mastitis. Furthermore, the study compared the two approaches for age-adjusted breed factor and it was found that the results of both approaches of meta-analysis are similar. Lin and Zeng (2010) observed that Individual Animal Data (IAD) approach is not relative efficient than Summary Statistics (SS) approach under covariate adjustment. However, standard error of risk estimates for age-adjusted breed factor was lower in Individual Animal Data (IAD) approach.

The results of the study indicated that Individual Animal Data (IAD) approach provides more reliable information than Summary Statistics (SS) approach. This finding was in accordance of the results of several studies (Clarke *et al.* 1998; Debray *et al.* 2013). Therefore, the study interprets the association of various risk factors with mastitis on the basis of IAD approach.

In the present study, the indigenous cows were older in age at MPKV farm than other farms and furthermore the study results in high incidences of mastitis in older cows. This may be reason for non-significant effect of breed with mastitis despite of high prevalence of mastitis in crossbred cows for all farms. To provide uniformity in the analysis, the effect of breed was re-evaluated by making adjustment for variation in age. After adjustment, crossbred cows showed significantly higher risk of mastitis (1.47 times) than indigenous cows. This finding was in accordance with reports of Dego and Tareke (2003). The older lactating cows were at greater (1.85 times) risk of mastitis than younger lactating cows. Similarly, the multiparous cows were more (2.21 times) susceptible to mastitis than the primiparous cows. Similar results were reported by several authors (Van den Borne *et al.* 2010). It was also observed that the occurrence of mastitis was associated with High yielding cows (Grohn *et al.* 2004; Wilson *et al.* 2004).

It was concluded that Individual Animal Data (IAD) approach provides more reliable information than Summary Statistics (SS) approach mainly in heterogeneous effects

across studies. However both Individual Animal Data (IAD) and Summary Statistics (SS) approaches produce similar results under homogenous and covariate-adjusted conditions. According to Individual Animal Data (IAD) approach, breed (age-adjusted) was found significant with mastitis occurrence and it was concluded that the crossbreds cows (1.47 times), older cows (1.85 times) multiparous cows (2.21 times) and high yielders (1.67 times) cows were at higher risk of mastitis than their respective reference categories.

ACKNOWLEDGEMENTS

The authors are thankful to Late Dr B. Singh, Ex-Head, Division of LES & IT, Indian Veterinary Research Institute, Izatnagar (Uttar Pradesh) for valuable guidance during the study programme. The authors are highly thankful to Incharge, LPM section, IVRI, Bareilly (Uttar Pradesh); Director of Research, MPKV, Rahuri, (Maharashtra) and Joint Director (Research), NDRI, Karnal (Haryana) for permission to use data on mastitis from the cattle farms of their institutes/university. The authors are also thankful to the learned referees and the Editor for the valuable suggestions on the original version of the paper.

REFERENCES

- Asmare K, Krontveit R I, Ayelet G, Sibhat B, Godfroid J and Skjerve E. 2014. Meta-analysis of Brucella seroprevalence in dairy cattle of Ethiopia. *Tropical Animal Health and Production* **46**(8): 1341–50.
- Bangar Y C, Singh B, Dohare A K and Verma M R. 2015. A systematic review and meta-analysis of prevalence of subclinical mastitis in dairy cows in India. *Tropical Animal Health and Production* **47**(2): 291–97.
- Bangar Y C, Verma M R, Dohare A K and Mukherjee R. 2016. Meta-analysis of prevalence of clinical mastitis in crossbred cows in India (1995–2014). *Journal of Animal Research* **6**(6): 933–38.
- Borenstein M, Hedges L V, Higgins J P T and Rothstein H R. 2009. Introduction to Meta-analysis, Wiley, Chichester.
- Clarke M, Stewart L, Pignon J P and Bijlens L. 1998. Individual patient data meta-analysis in cancer. *British Journal of Cancer* **77**(11): 2036–44.
- Cochran W G. 1954. The combination of estimates from different experiments. *Biometrics* **10**(1): 101–29.
- Debray T P, Moons K G, Abo-Zaid G M, Koffijberg H and Riley R D. 2013. Individual participant data meta-analysis for a binary outcome: one-stage or two-stage? *PLoS ONE* **8**(4): e60650.
- Dego O K and Tareke F. 2003. Bovine mastitis in selected areas of southern Ethiopia. *Tropical Animal Health and Production* **35**(3): 197–205.
- DerSimonian R and Laird N. 1986. Meta-analysis in clinical trials. *Controlled Clinical Trials* **7**(3): 177–88.
- Dutton M T. 2010. Individual Patient-Level Data Meta-Analysis: A comparison of methods for the diverse populations collaboration data set. (Published PhD Thesis, The Florida State University).
- Efron B. 1979. Bootstrap methods: Another look at the Jackknife. *Annals of Statistics* **7**(1): 1–26.
- Grohn Y T, Wilson D J, Gonzalez R N, Hertl J A, Schulte H, Bennett G and Schukken Y H. 2004. Effect of pathogen-specific clinical mastitis on milk yield in dairy cows. *Journal of Dairy Science* **87**(10): 3358–74.
- Higgins J P and Thompson S G. 2002. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* **21**(11): 1539–58.
- Hogeveen H, Huijps K and Lam T J G M. 2011. Economic aspects of mastitis: New developments. *New Zealand Veterinary Journal* **59**(1): 16–23.
- Khalate N. 2009. Logistic Regression Analysis of Morbidity and Mortality in Organised Farms of Maharashtra. MVSc Thesis, Deemed University, Indian Veterinary Research Institute, India.
- Lean I J, Rabiee A R, Duffield T F and Dohoo I R. 2009. Invited review: Use of meta-analysis in animal health and reproduction: methods and applications. *Journal of Dairy Science* **92**(8): 3545–65.
- Leonardi-Bee J. 2005. Exploring heterogeneity in meta-analyses using summary and individual patient data methodologies from stroke trials. PhD Thesis, University of Nottingham.
- Lin D Y and Zeng D. 2010. On the relative efficiency of using summary statistics versus individual-level data in meta-analysis. *Biometrika* **97**(2): 321–32.
- Mathew T and Nordstrom K. 2010. Comparison of one-step and two-step meta-analysis models using individual patient data. *Biomedical Journal* **52**(2): 271–87.
- Nakov D and Trajcev M. 2012. Udder quarter risk factors associated with prevalence of bovine clinical mastitis. *Macedonian Veterinary Review* **35**(2): 55–64.
- Poolsup N, Suksomboon N and Amin M. 2014. Effect of treatment of gestational diabetes mellitus: a systematic review and meta-analysis. *PLoS ONE* **9**(3): e9248.
- Riley R D, Kauser I, Bland M, Thijs L, Staessen J A, Wang J, Gueyffier F and Deeksa J J. 2013. Meta-analysis of randomised trials with a continuous outcome according to baseline imbalance and availability of individual participant data. *Statistics in Medicine* **32**(16): 2747–66.
- Steenefeld W, Hogeveen H, Barkema H W, VandenBroek J and Huirne R B M. 2008. The Influence of cow factors on the incidence of clinical mastitis in dairy cows. *Journal of Dairy Science* **91**(4): 1391–1402.
- Stewart G B, Altman D G, Askie L M, Duley L, Simmonds M C and Stewart L A. 2012. Statistical analysis of individual participant data meta-analyses: a comparison of methods and recommendations for practice. *PLoS ONE* **7**(10): e46042.
- Tobias A, Saez M and Kogevinas M. 2004. Meta-Analysis of results and individual patient data in epidemiological studies. *Journal of Modern Applied Statistical Methods* **3**(1): 176–85.
- Van den Borne B H, van Schaik G, Lam T J and Nielsen M. 2010. Variation in herd level mastitis indicators between primi- and multiparae in Dutch dairy herds. *Preventive Veterinary Medicine* **96**(1–2): 49–55.
- Walker E, Hernandez A V and Kattan M W. 2008. Meta-analysis: Its strengths and limitations. *Cleveland Clinic Journal of Medicine* **75**(6): 431–39.
- Wang Y, Li P, Wu Y, Sun X, Yu K, Yu C and Qin A. 2014. The risk factors for avian influenza on poultry farms: A meta-analysis. *Preventive Veterinary Medicine* **117**(1): 1–6.
- Whitehead A. 2002. Meta-Analysis of Controlled Clinical Trials. Wiley, Chichester.
- Wilson D J, Gonzalez R N, Hertl J, Schulte H F, Bennett G J, Schukken Y H and Grohn Y T. 2004. Effect of clinical mastitis on the lactation curve: a mixed model estimation using daily milk weights. *Journal of Dairy Science* **87**(7): 2073–84.