

# Meta-analysis for Non-Common Events: *Rabies*

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**Abstract** Meta-analysis of common events is readily available when a literature search is carried out for use in a meta-analysis. Usually, the fixed and random effect models work well with the common events. Non-common events are associated with effect estimates that are undefined or unstable when data is needed to carry out a meta-analysis. The application of the single mean imputation technique provided a complete data set in the meta-analysis of four studies that encountered loss of data. Data was sourced via Google scholar, jstor website, MEDLINE, Infectious Diseases Journal, Veterinary Medicine Journal, Public Health Journal and Cochrane database. Twelve studies out of sixteen had complete data and were meta-analyzed, resulting in a summary effect of 4.77 and a 95% confidence interval of (3.34, 6.81), I-squared = 26.7% with p-value = 0.182. After tackling missing values of the four studies using the MATLAB software for imputation of missing values, another meta-analysis was carried out with the 16 studies, the resulting summary effect was 5.4 and 95% confidence interval of (3.36, 8.67), I-squared=66.9%, p-value<0.001. Sequential sensitivity analyses and publication bias tests led to the exclusion of 2 studies. The final meta-analysis consisted of 14 studies and resulted in a summary effect of 5.69, 95% confidence interval of (3.51, 9.23) in favour of mortality, I-squared=69.9%, p-value<0.001. The result of the meta-analysis involving 14 studies was accepted over that of 12 studies going by the P-value significance (Table 3). Protective measures should be used by the individuals who are exposed to rabies by slaughtering or consumption of infected species because rabies is extremely fatal.

**Keywords** Non-common events, Missing Values, Rabies, Sensitivity Analysis, Subgroup Analysis

## 1. Introduction

Non-common events occur in everyday circumstances, the events may be avoided by researchers because data may be undefined, unstable or missing. Non-inclusion of such studies where meta-analysis is inevitable reduces statistical power on the inferences there-off or may result in misleading conclusions. Non-common events are also associated with high levels of heterogeneity which may be managed using sequential sensitivity analysis or subgroup analysis [1]. Rabies is a non-common event and it is a fatal illness with almost 100% case fatality rate. In rabid animals, the rabies virus confines mainly to the nerves and adipose tissues even though it can also be found in all parts of the body [2]. Transmission is possible following consumption of carcasses of animals that died of rabies and by consumption of raw dog meat [3]. No intervention is effective in stopping the disease after the onset of symptoms. Hence, there is

need to prevent the disease. Rabies is transmitted by contamination of wound with infectious material especially saliva from rabid animals and from bites by rabid animals. In Nigeria, dogs are responsible for over 96% of rabies cases in animals [4]. Rabies remains an endemic and neglected tropical disease in Nigeria and is often misdiagnosed, under-diagnosed and under-reported [12, 15]. In some cases, despite proper vaccination, the disease has been reported [12, 17].

## 2. Materials & Methods

Data for rabies was sourced via Google scholar, jstor website, MEDLINE, Infectious Diseases Journal, Veterinary Medicine Journal, Public Health Journal and Cochrane database. The quality of the studies was rated either good or excellent based on the Downs & Black [5] checklist (Table 1). The inclusion criteria were studies that recorded: -

1. odd ratios for risk of mortality related to rabies.
2. results from Nigeria.
3. sample size.

Altogether, 16 studies were included for the meta-analysis.

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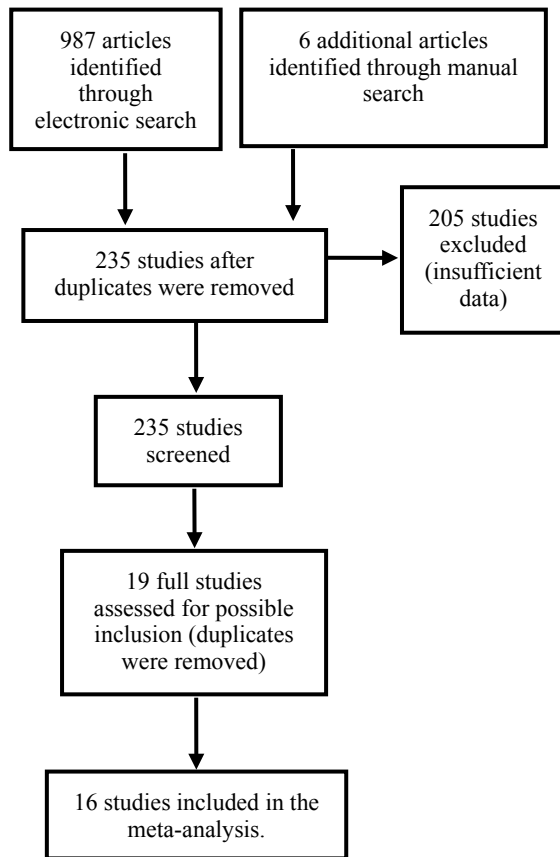
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**Table 1.** Downs and Black checklist for quality assessment of studies included in the systematic review and meta-analysis (Downs & Black, 1998)

Author/year	Reporting				External validity	Internal validity-bias			Internal validity-confounding (selection bias)				Quality score*
	1	2	3	4		6	7	8	9	10	11	12	
[12]	1	1	1	1	1	NR	1	1	1	1	NR	1	10
[13]	1	1	1	1	1	NR	1	1	1	1	NR	0	9
[7]	1	1	1	1	1	NR	1	1	1	1	NR	1	10
[14]	1	1	1	1	1	NR	1	0	1	1	NR	0	10
[15]	1	1	1	1	1	NR	1	1	1	1	NR	1	10
[16]	1	1	1	1	1	NR	1	1	1	1	NR	1	10
[17]	1	1	1	1	0	NR	1	1	1	1	NR	0	8
[18]	1	1	1	1	1	NR	1	1	1	1	NR	1	10
[8a]	1	1	1	1	0	NR	1	1	1	1	NR	0	8
[8b]	1	1	1	1	1	NR	1	1	1	1	NR	1	10
[8c]	1	1	1	1	1	NR	1	1	1	1	NR	1	10
[8d]	1	1	1	1	0	NR	1	1	1	1	NR	1	9
[19]	1	1	1	1	1	NR	1	1	1	1	NR	1	10
[20]	1	1	1	1	1	NR	1	1	1	1	1	NR	10
[2]	1	1	1	1	0	NR	1	1	1	1	NR	1	9
[3]	1	1	1	1	1	NR	1	1	1	1	1	1	10

\*Excellent (10-12), good (8-9), fair (5-7), poor (<5), Y = Yes, N = No

**Figure 1.** Flow diagram for selected 16 studies for review and meta-analysis of rabies data

The meta-analysis of non-common disease outcomes is associated with loss of data due to death, lack of response owing to stigma of disease, recovery of patients or simply attitude of patients. Such missing information are needed for meta-analyses especially because fewer studies are available in non-common cases. The pattern of missing data from four studies could not be determined, the four studies were derived from [8] and did not have an effect measure neither was it computable from available data. The single mean imputation method of missing data management involving sequential imputation of mean as explained in [9, 10] was adopted using MATLAB software to obtain odd ratios that were used in the meta-analysis.

The statistical methods that was used for the meta-analysis are those explained in [6] combined with both the DerSimonian & Laird (D & L) methods and inverse variance (IV) methods based on standard fixed or random effects models which were modified to provide a solution to the meta-analysis of non-common outcomes [1].

Consider a collection of  $k$  non-common primary studies, the  $i^{\text{th}}$  of which has estimated effect size  $Y_i$  and true effect size  $\mathcal{Q}_i$ . The general models are: -

$$Y_i = \begin{cases} \mathcal{Q} + E_i & \text{fixed effect} \\ \mu + \mathcal{Q}_i + e_i & \text{random effect} \end{cases} \quad (1)$$

where  $E_i$  and  $e_i \sim N(0, \sigma_i^2)$ ,  $i = 1, 2, \dots, k$

$E_i$  is the sampling error,

$e_i$  is the random deviations of study's observed effect from the true effect size,

$\mathcal{G}$  is the population mean,

$\mathcal{G}_i$  is the deviation of study's true effect from the grand mean,

$\mu$  is the grand mean

The fixed effects model assumes  $\mathcal{G}_i = \mu$  for  $i = 1, 2, \dots, k$ , implying that each study in the meta-analysis has the same underlying effect. The estimator of  $\mu$  is generally a simple weighted average of the  $Y_i$ , with the optimal weights equal to the inverse of the variance

$$W_i = \frac{1}{V_{Y_i}} \quad (2)$$

where  $V_{Y_i}$  is the within study variance for study  $i$ .

The weighted mean ( $M$ ) is then computed as

$$M = \frac{\sum_{i=1}^k W_i Y_i}{\sum_{i=1}^k W_i} \quad (3)$$

where  $\sum_{i=1}^k W_i Y_i$  is, the sum of the products  $W_i Y_i$  (effect size multiplied by weight) and is divided by the sum of the weights  $\sum_{i=1}^k W_i$ .

The variance of the summary effect is estimated as the reciprocal of the sum of the weights,

$$V_M = \frac{1}{\sum_{i=1}^k W_i} \quad (4)$$

and the estimated standard error of the summary effect is the square root of the variance,

$$SE_M = \sqrt{V_M} \quad (5)$$

Then,  $(1 - \alpha)\%$  lower and upper limits for the summary effect are estimated thus,

$$\left. \begin{aligned} LL_M &= M - t_{\alpha/2} \times SE_M \\ UL_M &= M + t_{\alpha/2} \times SE_M \end{aligned} \right\} \quad (6)$$

Finally, a t-test to test the null hypothesis that the common true effect  $\mathcal{G}$  is zero can be computed using

$$t = \frac{M}{SE_M} \quad (7)$$

for a one-tailed test the p-value is given by

$$P = 1 - \varphi(\pm |t|) \quad (8)$$

where we choose positive if the difference is in the expected direction and negative otherwise, and for a two-tailed test by

$$P = 2[1 - (\varphi|t|)] \quad (9)$$

and  $\varphi|t|$  is the standard normal cumulative distribution.

To compute a study's variance under the random-effects model, we need to know both the within-study variance and  $\tau^2$ , since the study's total variance is the sum of the two values. One method for estimating  $\tau^2$  is the method of moments (or the D & L method). The parameter  $\tau^2$  (tau-squared) is the between studies variance (the variance of the effect size parameters across the population of studies).

It is possible that  $T$  is negative due to sampling error, which is unacceptable as a value for  $\tau^2$ , so we define;

$$\tau^2 = \begin{cases} T & \text{if } T > 0 \\ 0 & \text{if } T \leq 0 \end{cases} \quad (10)$$

Let  $T^2$  be an estimator for  $\tau^2$

$$T^2 = \frac{Q - df}{C} \quad (11)$$

where

$$Q = \sum_{i=1}^k W_i Y_i^2 - \frac{\left(\sum_{i=1}^k W_i Y_i\right)^2}{\sum_{i=1}^k W_i} \quad (12)$$

$df = k - 1$

where  $k$  is the number of studies, and

$$C = \sum_{i=1}^k W_i - \frac{\sum_{i=1}^k W_i^2}{\sum_{i=1}^k W_i} \quad (13)$$

under the random-effects model the weight assigned to each study is

$$W_i^* = \frac{1}{V_{Y_i}^*} \quad (14)$$

where  $V_{Y_i}^*$  is the within-study variance from study  $i$  plus the between-study variance,  $\tau^2$ .

$$V_{Y_i}^* = V_{Y_i} + T^2 \quad (15)$$

The weighted mean,  $M^*$ , is

$$M^* = \frac{\sum_{i=1}^k W_i^* Y_i}{\sum_{i=1}^k W_i^*} \quad (16)$$

that is, the sum of the products (effect size multiplied by weight) divided by the sum of the weights.

The variance of the summary effect is estimated as the reciprocal of the sum of the weights, or

$$V_{M^*} = \frac{1}{\sum_{i=1}^k W_i^*} \quad (17)$$

and the estimated standard error of the summary effect is the square root of the variance,

$$SE_{M^*} = \sqrt{V_{M^*}} \quad (18)$$

The  $(1-\alpha)\%$  lower and upper limits for the summary effect would be computed as

$$\left. \begin{aligned} LL_{M^*} &= M^* - t_{\alpha/2} \times SE_{M^*} \\ UL_{M^*} &= M^* + t_{\alpha/2} \times SE_{M^*} \end{aligned} \right\} \quad (19)$$

Finally, a t-value to test the null hypothesis that the mean effect  $\mu$  is zero could be computed as

$$P^* = 1 - \varphi\left(\pm |t^*|\right) \quad (20)$$

where we choose positive if the difference is in the expected direction or negative otherwise.

For a two-tailed test by

$$P^* = 2 \left[ 1 - \left( \varphi\left(|t^*|\right) \right) \right] \quad (21)$$

The  $I^2$ -Statistic is an alternative and stronger measure compared to the Q-measure [11].

$$I^2 = \left( \frac{Q - df}{Q} \right) \times 100\% \quad (22)$$

use value of Q from (12).

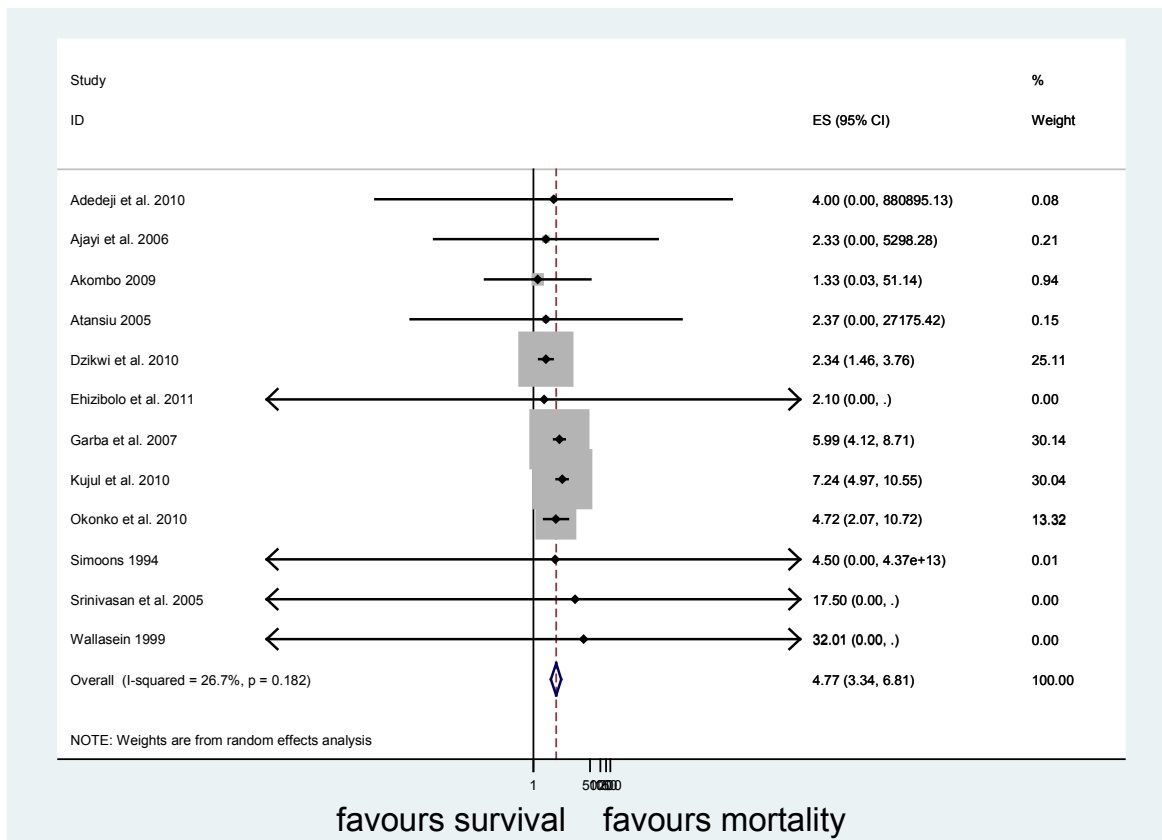
Heterogeneity in the  $I^2$ -Statistics may be termed low, moderate, or high based on the intervals  $0 \leq I^2 < 25\%$ ,  $25\% \leq I^2 < 50\%$ , or  $I^2 \geq 50\%$  respectively.

### 3. Results

The studies from [8] had missing odd ratio values that were not computable from available data. Before the imputation of missing values, the meta-analysis of 12 studies (Figure 2) resulted in I-squared = 26.7%, p-value > 0.001, with odds ratio = 4.77 in favour of mortality, at 95% confidence interval (3.34, 6.81).

Egger's and Begg's tests (Figure 3&4) were at variance with respect to publication bias, as such, we could not conclude the presence of bias.

However, sensitivity analysis (Figure 5) indicated that study [7] may be a source of bias.



**Figure 2.** Meta-analysis of 12 studies on risk of mortality of rabies data

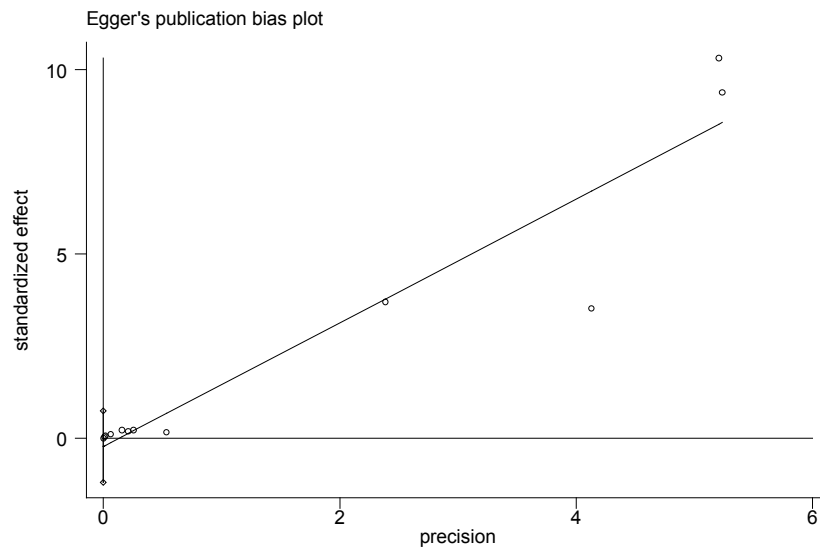


Figure 3. Egger's publication bias plot of rabies data

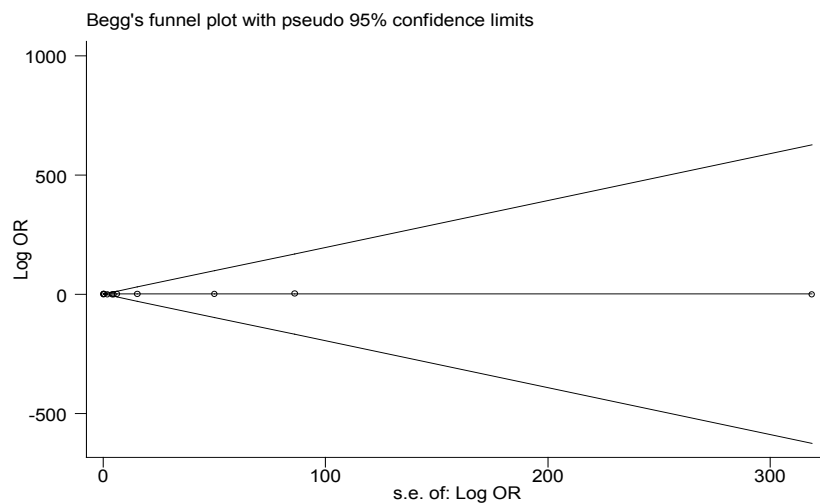


Figure 4. Begg's funnel plot of rabies data

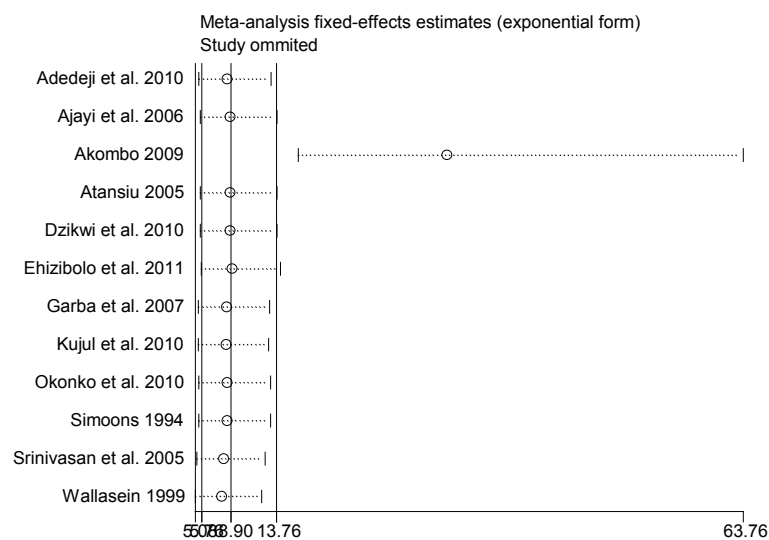


Figure 5. Sensitivity analysis of rabies data

In a sequential pattern, the MATLAB software, using the single imputation of mean method from the available values, the odd ratios were imputed before meta-analysis was carried out on 16 studies altogether. The meta-analysis resulted in I-Squared = 66.9%, p-value < 0.001, with odds ratio = 5.4 in favour of mortality, at 95% confidence interval (3.36, 8.67) (Figure 6).

Egger's test (Figure 7) detected the presence of bias, while Begg's test (Figure 8) indicated the absence of bias.

Sensitivity analysis (Figure 9) also showed that the [7] study may be a source of bias.

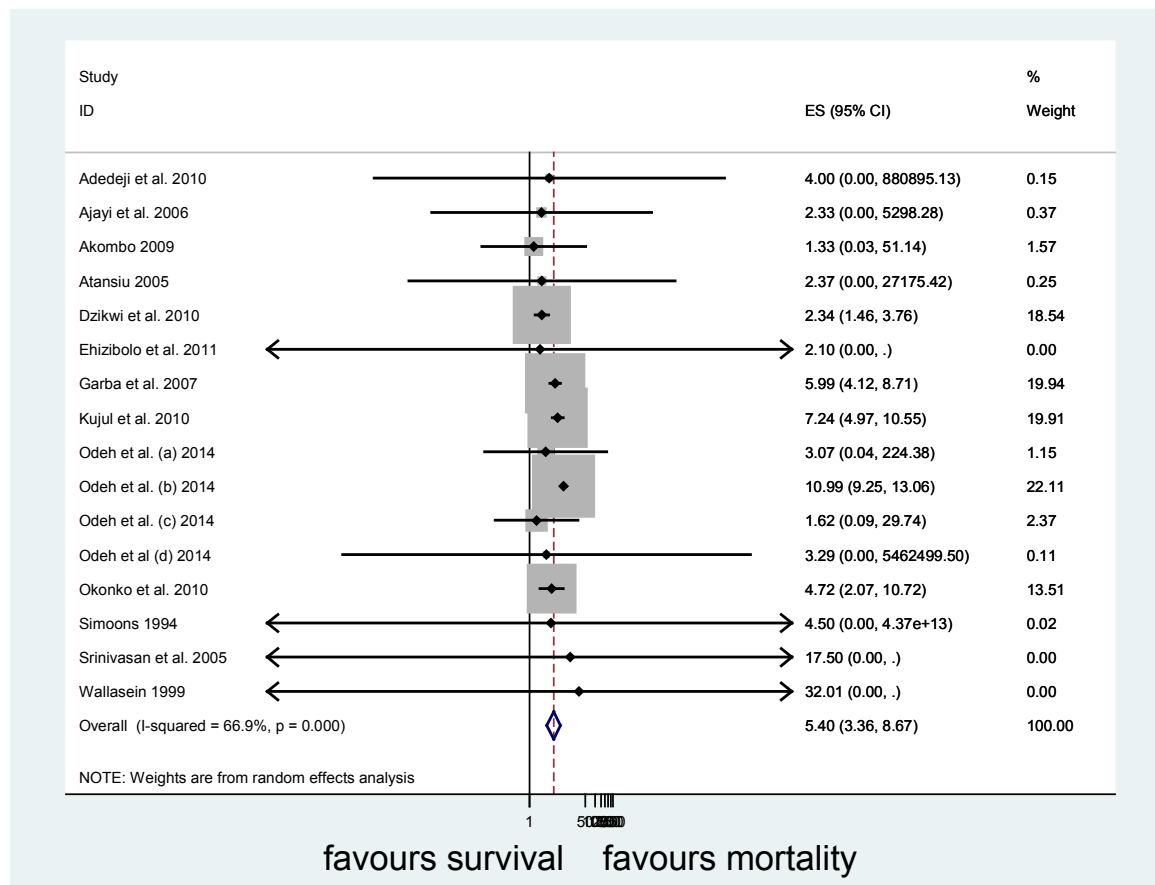


Figure 6. Meta-analysis of 16 studies of rabies data

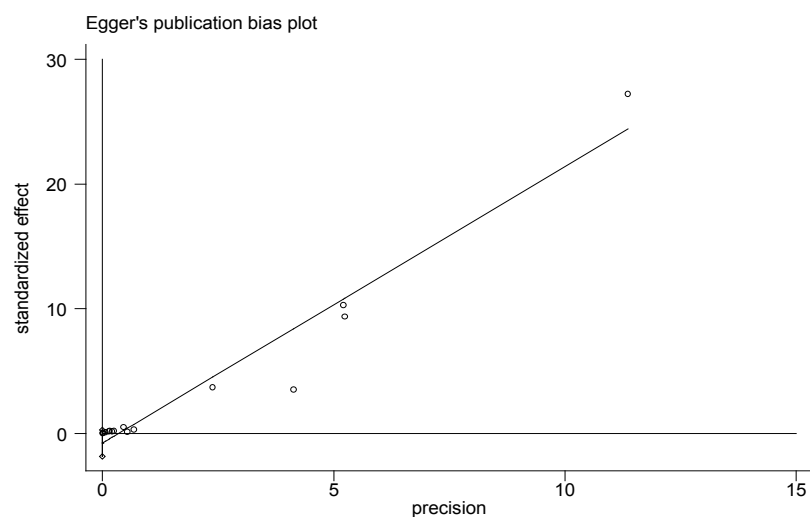


Figure 7. Egger's test of 16 studies of rabies data

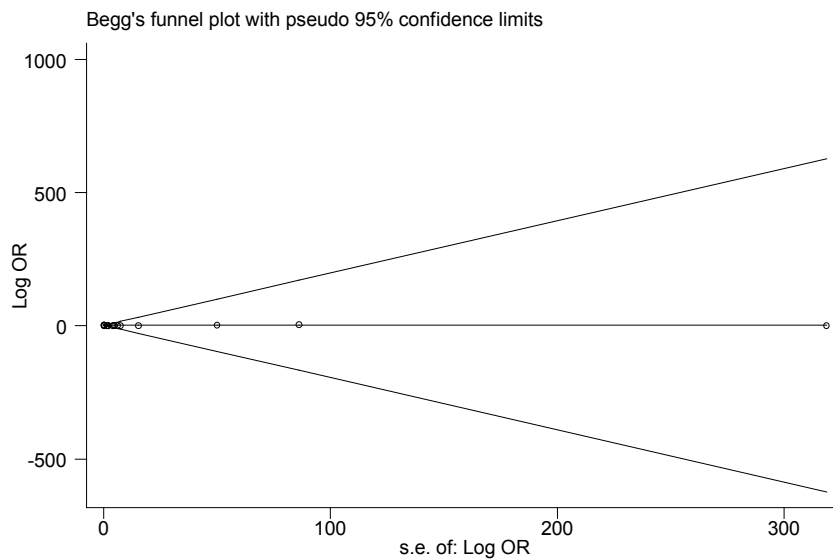


Figure 8. Begg's test of 16 studies of rabies data

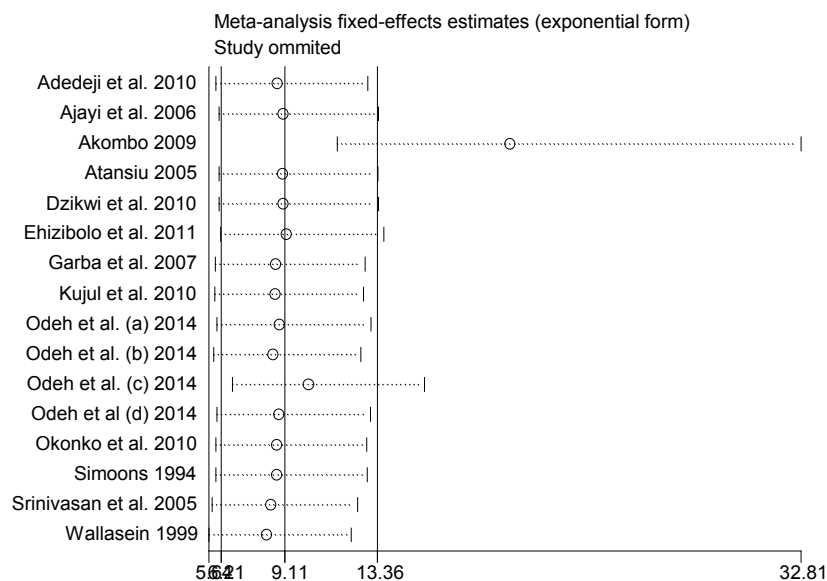


Figure 9. Sensitivity analysis showing Akombo study as a source of bias

The [7] study was excluded and another meta-analysis was carried out (Figure 10). It yielded I-Squared = 68.4%,  $p$ -value < 0.001, with odds ratio = 5.52 in favour of mortality at 95% confidence interval (3.42, 8.9).

Sensitivity analysis (Figure 11) showed [8] may be a source of bias & heterogeneity, after excluding it and

meta-analysing, I-Squared = 69.9%,  $p$ -value < 0.001, with odds ratio = 5.69 in favour of mortality (Figure 12), at 95% confidence interval (3.51, 9.23).

Table 3 is a comparison of the meta-analysis of the 12 studies (Figure 2) versus that of 14 studies (Figure 12).

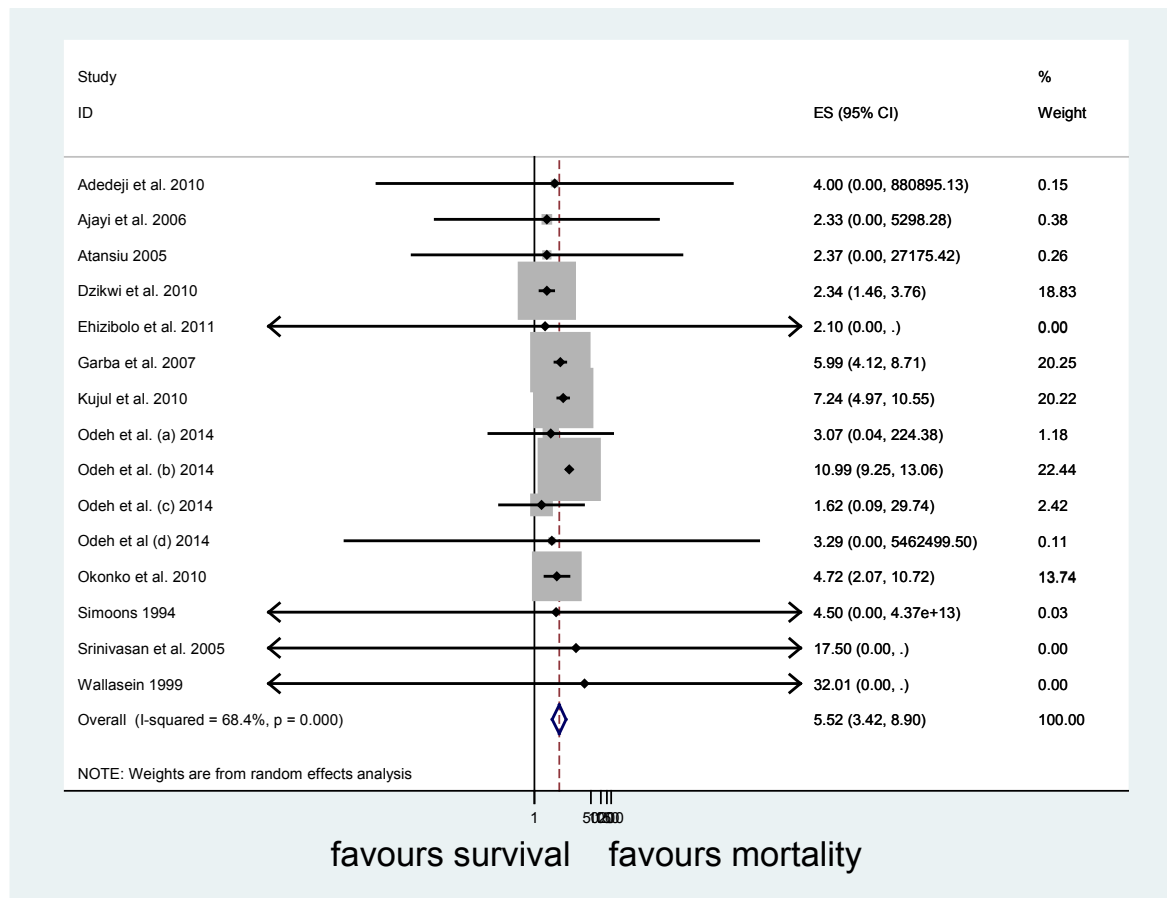


Figure 10. Meta-analysis of 15 studies of rabies data

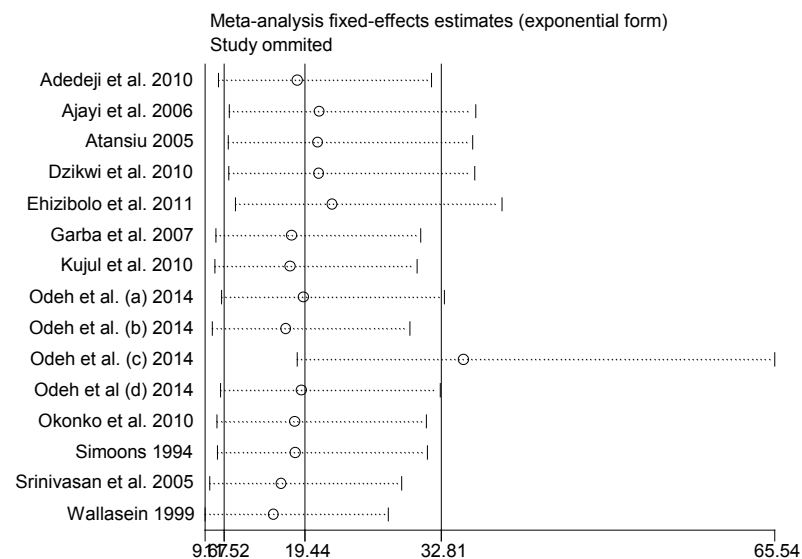


Figure 11. Sensitivity analysis showing Odeh (c) 2014 study as source of bias



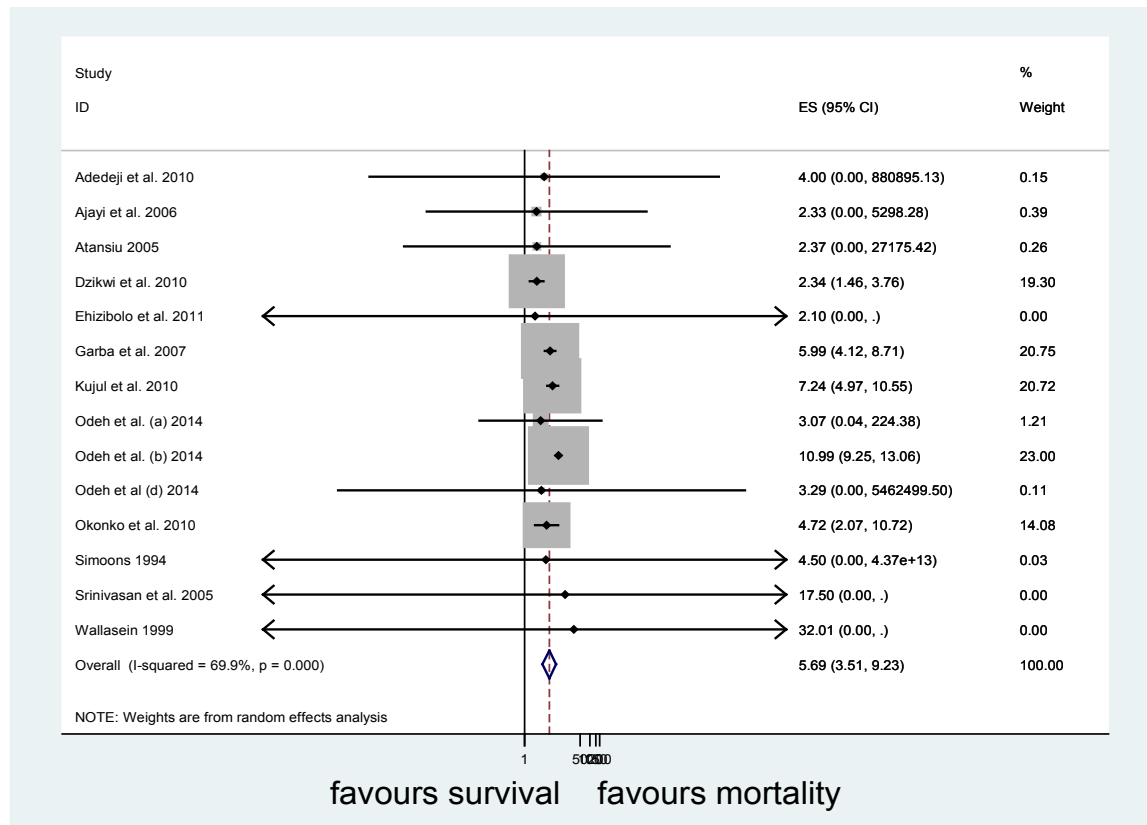


Figure 12. Showing meta-analysis of 14 studies

Table 2. Subgroup analyses to identify sources of methodological heterogeneity in rabies data

Characteristic		K	I <sup>2</sup> -statistic (%)	OR (95% CI)	Comment
Study quality:	Excellent	7	61.3	4.43 (1.4 – 2.38)	Quality of studies could affect accuracy of estimates.
	Good	5	88.5	5.71 (0.80 – 3.89)	
Gender:	Female	6	75.3	2.91 (1.31 – 2.91)	Both male and female are at higher risk of mortality.
	Male	9	95.2	2.71 (1.11 – 3.12)	
Age:	< 20 years	6	97	1.73 (0.85 – 3.5)	Older patients may provide more reliable estimates.
	≥ 20 years	10	68.9	1.88 (1.46 – 2.69)	
Sample size:	< 50	9	87.2	1.23 (0.84 – 2.96)	Larger sample size may be associated with higher risk of mortality.
	≥ 50	7	52.1	1.95 (1.46 – 2.43)	
Region:	North	3	0	2.98 (1.99 – 3.59)	Northerners have significantly high risk of mortality from HIV-related depression.
	West	7	1.8	1.29 (1.14 – 1.45)	
	East	3	95.8	1.32 (0.9 – 9.64)	
	South	2	82.5	1.11 (0.70 – 11.84)	

Table 3. Meta-analysis results on risk of mortality in persons exposed to rabies before &amp; after imputing missing values

S/N	ANALYSIS	14 STUDIES	12 STUDIES	REMARK
1	Summary effect	5.69(3.51,9.23)	4.77(3.34,6.81)	higher risk with 14 studies
2	I-Squared	69.9%	26.7%	Higher bias with 14 studies
3	P-value	0	0.182	Results of 14 studies accepted

## 4. Discussion

Non-common events are characterized by missing data because the events occur in adverse situations that portends such. The application of the missing data statistical tool is an attempt to gather more studies for meta-analysis when non-common outcomes are involved. Treatment of such data as a complete frame is beneficial to the overall power of results.

The alternative methods provided for the meta-analysis are easy to apply when rare events are involved. Most times, the number of studies,  $k$ , is small, as such, the  $t$ -test is recommended instead of the standard normal distribution.

## 5. Conclusions

In conclusion, meta-analysis of rare events poses difficulties such as incomplete data, heterogeneity etc. These problems may be tackled effectively using missing data mechanisms, sensitivity analysis and subgroup analysis. In this paper, sensitivity and subgroup analysis did not completely reduce heterogeneity, however, the power of the final summary effect measure is reliable,  $P$ -value  $< 0.001$ . In the field of meta-analysis, non-common outcomes have been neglected in the past, probably because of some of the problems that were encountered in this research. Some of such problems include non-availability of data, presence of publication bias, few studies available, lack of statistical knowledge, case of missing data. An attempt has been made in this research to resolve some of the set-backs, with the hope that more researchers will survey the use of the techniques to meta-analyze non-common outcomes of primary studies.

Downs and Black checklist items: 1- aims/objectives clearly outlined; 2- major outcomes clearly mentioned; 3- patients characteristics provided; 4- major findings clearly mentioned; 5-sample representative of population; 6-appropriate statistical tests done; 7- primary outcome valid; 8- were measures to curtail bias applied; 9- cases and controls recruited from same population; 10- cases and controls recruited over same time period; 11- adjustment for confounders done; 12- addressed lost to follow up.

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