Heliyon 8 (2022) e08718

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Development of acaricide resistance in tick populations of cattle: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Prevalence
Resistance
Acaricides
Cattle
Tick populations
Meta-analysis
Rhipicephalus (Boophilus) microplus

ABSTRACT

The development of acaricide resistance in ticks infesting cattle is a major problem in the livestock industry in tropical and subtropical regions worldwide. To determine the current global trends and prevalence of acaricide resistance development (ARD) in tick populations of cattle, a systematic review and meta-analysis with an emphasis on *Rhipicephalus (Boophilus) microplus* was conducted. Data searches from five English electronic databases yielded 88 journal articles published between 1992 and 2020. In total, 218 *in-vitro* bioassays were used to investigate 3939 tick populations of cattle; of these, the 57.6% that exhibited ARD were largely limited to South America (Brazil), Central America (Mexico), and Asia (India). A total of 3391 of these tick populations were *R. (B.) microplus*, of which 2013 exhibited ARD. Random effects meta-analyses indicated that the exhibition of ARD was higher in *R. (B.) microplus* (66.2%) than in other tick species. Global prevalence estimates of ARD in *R. (B.) microplus* vary as a function of geography, detection methods, and acaricide compounds. In general, high heterogeneity was noted among the studies. However, homogeneity was observed among studies from India, suggesting the establishment of acaricide resistance in Indian *R. (B.) microplus* populations. Current tick control interventions are urgently required to limit the evolution and implications of resistance development.

1. Introduction

In tropical and sub-tropical regions of the world, beef and dairy production has been negatively impacted by ticks (Acari: Ixodidae), which infest approximately 80% of cattle (Yessinou et al., 2018a). The voracious blood-feeding habit of ticks, injection of toxins, and transmission of pathogens have resulted in severe economic losses, estimated to be US$ 18.7 billion annually (Sungirai et al., 2018). This has led to the use of synthetic acaricidal compounds that have been extensively used to control ticks in cattle (Abbas et al., 2014; Rodriguez-Vivas et al., 2018). However, the frequent and indiscriminate use of acaricides has resulted in a reduction in tick susceptibility to these compounds and a subsequent failure to control ticks (Wyk et al., 2016). Acaricide resistance is defined as the selection of specific heritable trait(s) in a population of ticks due to the population's exposure to an acaricide, which results in a significant increase in the percentage of the population that will survive after exposure to a standard dose of the acaricide used as recommended (slightly modified from Rodriguez-Vivas et al., 2018). Resistance in tick populations is an evolutionary adaptation owing to selection pressure that results from intensive exposure to acaricides (Aguilar et al., 2018). Most of these chemicals act on the tick nervous system. For example, organochlorines are gamma-aminobutyric acid (GABA)-gated chloride channel antagonists, organophosphates (OP) are acetylcholine esterase inhibitors, carbamates are cholinesterase inhibitors, synthetic pyrethroids (SP) are sodium channel modulators, macrocyclic lactones (ML) are chlorine channel activators, and formamidines are octopamine agonists (Abbas et al., 2014). The major mechanisms by which ticks resist acaricide action are enhanced metabolic detoxification and point mutations at target sites, which prevent the action of chemical products (Hernandez et al., 2002; CMPV, 2018).

Acaricide resistance development (ARD) has seriously hindered cattle producers' efforts to manage and control ticks and tick-borne diseases (Guerrero et al., 2014). The development of acaricide resistance in ticks has become a topic of research worldwide (Yessinou et al., 2018a), particularly with respect to the difficulties and expenses involved in developing new acaricides and producing tick-resistant cattle breeds

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https://doi.org/10.1016/j.heliyon.2022.e08718
Received 4 June 2021; Received in revised form 25 October 2021; Accepted 4 January 2022

(Abbas et al., 2014; Vudriko et al., 2016). The most suitable method to assess acaricide resistance in tick populations of cattle is by studying its effectiveness against ticks under field conditions. However, *in-vitro* laboratory bioassays provide valuable information related to ARD and the efficacy of acaricides under field conditions (Guerrero et al., 2014). Numerous *in-vitro* studies on the characterisation of resistance to acaricides in tick populations have been undertaken worldwide, such as those in Africa (Mekonnen et al., 2002; Ntondini et al., 2008; Wyk et al., 2016; Lovis et al., 2013a, b; Adehan et al., 2016; Vudriko et al., 2016; Sungirai et al., 2018; Yessinou et al., 2018a, b), South America (Puerta et al., 2015; Villar et al., 2016; Klafke et al., 2017), Central America (Rodrigues-Vivas et al., 2012; Miller et al., 2013 Busch et al., 2014) and Asia (Kumar et al., 2017; Sharma et al., 2018; Sagar et al., 2020).

To better understand the nature of ARD and the control of resistant ticks, selective reviews of different aspects of acaricide resistance in ticks have been presented by George et al. (2004), FAO (2004), Abbas et al. (2014), and Rodriguez-Vivas et al. (2018). Syntheses of selected records on the global status of acaricide resistance with special emphasis on *Rhipicephalus (Boophilus) microplus* have been presented by Abbas et al. (2014) and Rodriguez-Vivas et al. (2018). Despite the availability of numerous studies on the development of resistance to acaricides in tick populations, no study has systematically integrated quantitative findings from separate studies to determine the overall magnitude of the ARD problem. Therefore, to provide an overview and to estimate the pooled prevalence of ARD in tick populations of cattle, a systematic review and meta-analysis, with an emphasis on *R (B.) microplus,* was conducted.

2. Materials and methods

2.1. Search approach

A systematic literature search was conducted to identify all publications over the last three decades that have reported phenotypic acaricide resistance development in tick populations of cattle worldwide. A literature search was performed on 15 March 2020 for articles published between 1 January 1990 and 15 March 2020; this search used a combination of search keywords, namely, "Synthetic acaricide" OR "Synthetic ectoparasiticide" OR "Synthetic ixodicide" AND "Acaricide resistance OR Acaricide efficacy OR Susceptibility to acaricides" AND Cattle ticks OR Cow ticks". The literature search was performed using the North-West University library search engine and four English databases: Google Scholar, Science Direct, PubMed, and Web of Science. Manual searches of the reference list of peer-reviewed publications were also conducted. The titles and abstracts of the identified publications were copied into a Microsoft Word file and later screened for relevance to the study objectives according to our inclusion and exclusion criteria.

2.2. Inclusion and exclusion criteria for eligible publications

A systematic review (SR) and meta-analysis (MA) of studies that assessed phenotypic acaricide resistance in tick populations of cattle were carried out following the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines (Moher et al., 2015). Initially, the publications identified for inclusion in the MA and SR were screened based on relevant information in their titles and abstracts. Publications that met the following criteria were excluded from the study: (i) papers that were repetitive in the different databases searched and included the same information in their titles and abstracts, (ii) references unrelated to the study objectives, (iii) papers that evaluated the acaricidal activity of plant extracts, (iv) review articles or book chapters on acaricides or acaricide resistance in cattle ticks, (v) papers on the molecular and/or biochemical assessment of acaricide resistance, (vi) papers with titles and abstracts not in the English language, (vii) papers that assess acaricide efficacy in mites and ticks of "non-cattle" hosts, (viii) papers on tick borne diseases or the effects of acaricides on cattle, (ix) papers assessing the efficacy of bio-pesticides, siloxanes or growth regulators on ticks, (x) papers that determine *in-vivo* acaricide resistance in cattle ticks and (xi) surveys. The full texts of the portable document format (PDF) files of publications retained after the initial screening were obtained online through the North-West University and University of Edinburgh libraries. A detailed review of full-text articles on the characterisation of phenotypic acaricide resistance in tick populations of cattle was conducted. Articles were included in the SR and MA studies based on the following inclusion criteria: (i) the articles were full-text, related to the study objectives and available in the English language; (ii) the articles were on the *in-vitro* assessment of ARD, acaricide efficacy, or susceptibility to acaricides in cattle ticks and were based on a minimum of two populations/farms; (iii) the articles described the occurrence of phenotypic acaricide resistance in at least one tick population or farm assessed; and (iv) the article contained data on the geographical location (country) of the study, cattle tick species resistant to a named acaricide chemical compound, and the detection technique used in diagnosing acaricide resistance.

Publications that did not meet the inclusion criteria were also excluded. Article eligibility, inclusion, and data extraction were conducted by two authors working independently to ensure data quality and accuracy. Discrepancies in data collection were discussed by both authors, and corrections were performed after common agreement.

2.3. Data extraction and statistical analysis

The following data were extracted from the eligible full-text articles and recorded into Microsoft Excel spreadsheets: first author's surname, year of publication, country and study area, name of the acaricide, cattle tick species encountered, bioassays used for the detection of acaricide resistance (Larval Packet test, LPT; Adult Immersion test, AIT; Larval immersion test, LIT; Larval tarsal test, LTT), parameters for the quantification of acaricide resistance (Resistance factor, RF; Resistance ratio, RR; Percentage Acaricide Efficacy, %AE; Percentage Reproductive estimate, %RE; Percentage Larval mortality, %LM; Percentage egg laying, %EL; Percentage resistance, %R), number of cattle farms or tick populations/isolates assessed for acaricide resistance, and number of tick populations that exhibited acaricide resistance development.

In the SR of studies, descriptive statistics were applied to the group and the included studies were enumerated, based on the acaricide chemical compounds that were encountered, the acaricide resistance detection method, parameters for quantification of acaricide resistance, geography, and year of publication. For each eligible study, the frequency (prevalence) of ARD was expressed as the proportion of resistant cattle tick populations relative to those sampled. Meta-analyses were conducted to statistically combine the proportions of resistant cattle tick populations from separate studies to determine the pooled prevalence estimates of ARD in cattle tick populations. Prior to the meta-analysis, eligible studies were sorted according to different cattle tick species to ensure that the studies analysed were sufficiently homogeneous in terms of participants, interventions, and outcomes (Borenstein et al., 2009). For each study, the point prevalence estimate of ARD was determined based on the weight attributed to its sample size in a group of studies. The pooled prevalence estimate of ARD was obtained using a random effects model (Borenstein et al., 2009). This model assumes that the rate of ARD in tick populations varies among studies and that the summary effect is the weighted average of the effects reported in different studies (Borenstein et al., 2009).

The variation across studies (heterogeneity) was assessed using the Cochran's Q-test, whereas the Higgins I^2 statistic was used to estimate the percentage variation across studies due to heterogeneity rather than chance, with values of $I^2 < 25\%$ indicating low heterogeneity and $I^2 > 50\%$ indicating substantial heterogeneity (Higgins et al., 2003). Probability values of $P < 0.1$ indicated heterogeneity. Furthermore, separate meta-analyses (subgroup analysis) were conducted to determine the pooled prevalence estimates of ARD in *R. (B.) microplus* populations as a

function of geography, detection methods, year of publication, and acaricide compounds.

Assessment of heterogeneity was omitted when there were fewer than four studies, as Cochran's Q-test has a low power in estimating heterogeneity when the number of studies is small (Higgins et al., 2003). The overall and point prevalence estimates (with 95% confidence intervals) of ARD in cattle tick populations were expressed as forest plots to visualise the results from the meta-analyses. Meta--analyses were conducted using the Comprehensive Meta-Analysis (CMA) software version 3.

3. Results

3.1. Characteristics of the studies on acaricide resistance development in tick populations of cattle

The initial literature search resulted in 2252 publications retrieved from the North-West University library search engine (n = 518), Google Scholar (n = 879), Science Direct (n = 640), PubMed (n = 81), Web of Science (n = 76) databases, and manual searches (n = 58) (Figure 1). After the title and abstract screening, 1988 publications were excluded from the study. Of the 264 journal articles selected for full-text screening, 88 were published between 1992 and March 2020 and met our eligibility criteria (Figure 1). Of the 88 included studies, 218 bioassays investigated ARD in tick populations of cattle from 17 countries (Tables 1 and 2). Acaricide resistance development studies were mostly reported from Asia (n = 35, 75 bioassays) and South America (n = 24, 60 bioassays). Fewer studies were conducted in Central America (n = 13, 28 bioassays), Africa (n = 10, 38 bioassays), and Oceania (n = 6, 17 bioassays). Reports on the development of tick resistance in cattle from Europe and North America are unavailable.

Data on the number of ARD studies in tick populations published annually during the study period (1992–2020) are shown in Figure 2. Within the ten years' period from 1992 to 2001, only 3 eligible studies were included. The next ten years, from 2002 to 2011, saw an increase in the number of identified studies, averaging 2.5 per annum. The years 2012–2020 witnessed a noticeable increase with a total of 60 eligible studies, averaging 6.0 references per year (Figure 2).

A total of 21 acaricide active ingredients or compounds were assessed for resistance development in tick populations worldwide within the study period (Table 2). Resistance development studies were often conducted to investigate resistance to cypermethrin (n = 42), deltamethrin (n = 40), amitraz (n = 29), ivermectin (n = 15), and diazinon (n = 13) (Table 2). The larval packet test (LPT) has been widely used in the diagnosis of resistance in ticks (Table 2). Detection and quantification of phenotypic resistance were mostly conducted with the dose-mortality bioassay (n = 66), in which tick populations were described as susceptible or resistant, based on resistance ratios (RR), resistance factors (RF), or factor for resistance (FOR) values (Table 2). Percentage larval mortality (% LM), acaricide efficacy (% AE), resistance (% R), reproductive estimate (% RE), and egg-laying (% EL) were also used, although in only a few of the included studies (Tables 1 and 2).

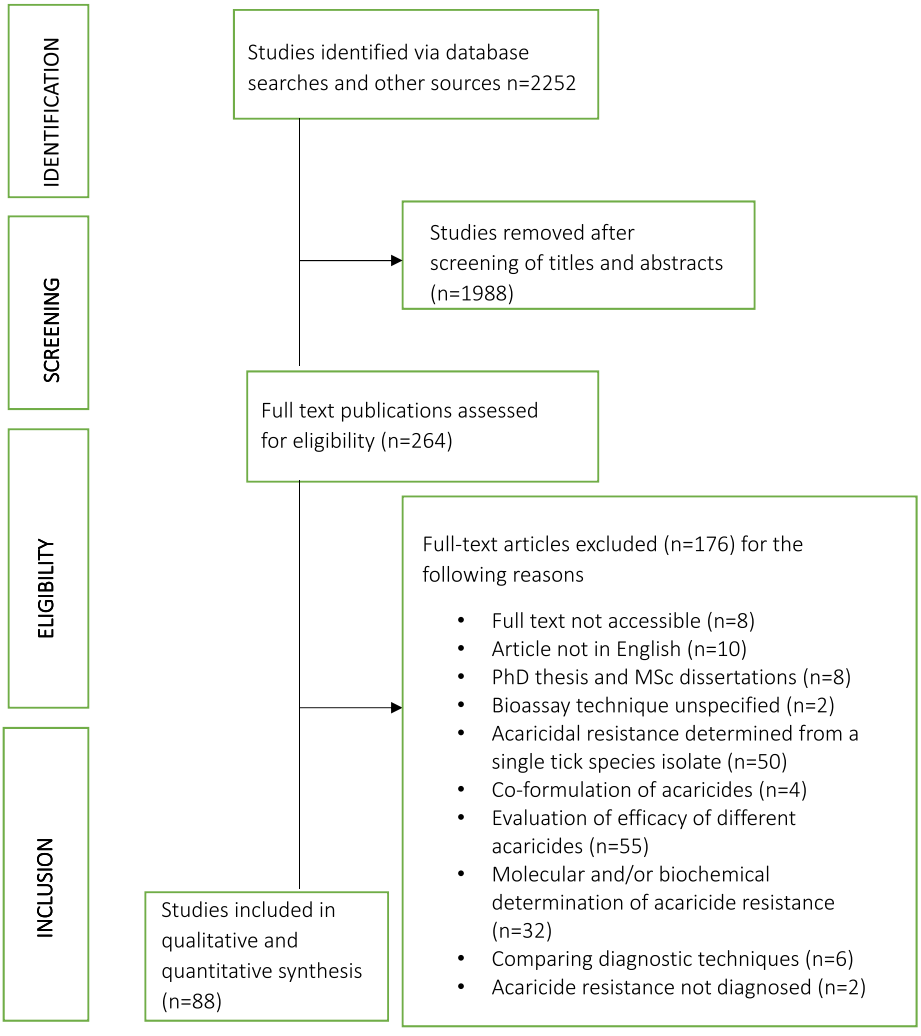

Figure 1. Flowchart of the selection process of studies included in systematic review and meta-analysis informed by PRISMA.

Table 1. List of eligible studies on acaricide resistance in tick populations of cattle worldwide during the study period (1992–2020).

Continent/Country	Acaricide name (Tick isolates or farms with ARD/Total tick isolates or farms sampled)	Cattle tick species	Bioassay technique	AR quantification parameter	References
AFRICA					
Ethiopia	Dieldrin (4/4); Diazinon (4/4) Chlorfenvinphos (1/4); Coumaphos (1/4)	*R. (B.) decoloratus*	LPT	% LM	Yilma et al. (2001)
	Coumaphos (1/4)	*R. evertsi*			
South Africa	Cypermethrin (6/11); Chlorfenvinphos (7/11); Amitraz (3/6)	*R. (B.) decoloratus*	LIT	OR	Mekonnen et al. (2002)
	Chlorfenvinphos (1/5)	*Amblyomma hebraeum*			
	Chlorfenvinphos (1/2)	*R. evertsi*			
South Africa	Amitraz (1/3); Chlorfenvinphos (3/3); Cypermethrin (1/3)	*R. (B.) decoloratus*	LIT & AIT	FOR, % RE, % EL	Mekonnen et al. (2003)
South Africa	Amitraz (3/45); Cypermethrin (1/44); Chlorfenvinphos (10/36)	*R. (B.) microplus*	LIT & AIT	FOR, % RE, % EL	Ntondini et al. (2008)
	Chlorfenvinphos (11/34)	*R. evertsi evertsi*			
	Cypermethrin (1/34)	*R. appendiculatus*			
South Africa	Cypermethrin (1/3); Flumethrin (1/3); Pyripol (1/3)	*R. (B.) microplus*	LTT	RR	Lovis et al. (2013a)
Benin	Deltamethrin (5/5); Alpha-cypermethrin (4/5); Amitraz (5/5)	*R. (B.) microplus*	LPT	RR	Adehan et al. (2016)
Uganda	Amitraz (1/13); Deltamethrin (2/13); Cypermethrin (12/13) Chlorfenvinphos (1/13)	*R. appendiculatus*	LPT	% LM	Vudriko et al. (2016)
	Amitraz (3/16); Deltamethrin (15/16); Cypermethrin (15/16); Chlorfenvinphos (4/16)	*R. (B.) decoloratus*			
Egypt	Deltamethrin (2/3)	*R. annulatus*	LPT	RF	Mahrous and Kamel (2016)
Benin	Alpha-cypermethrin (2/2); Deltamethrin (2/2)	*R. (B.) microplus*	AIT	RF	Yessinou et al. (2018a)
Benin	Alpha-cypermethrin (2/2); Deltamethrin (2/2)	*R. (B.) microplus*	LPT	RF	Yessinou et al. (2018b)
Egypt	Deltamethrin (10/11)	*R. annulatus*	LPT	RF	Aboelhadid et al. (2018)
SOUTH AMERICA					
Brazil	Amitraz (11/15)	*R. (B.) microplus*	LPT	RR	Li et al. (2004)
Bolivia	Flumethrin (35/83); Deltamethrin (73/83); Cypermethrin (63/83)	*R. (B.) microplus*	LPT	% LM	Villarro-Alvarez et al. (2006)
Brazil	Ivermectin (1/2)	*R. (B.) microplus*	LIT	RR	Klafke et al. (2006)
Brazil	Cypermethrin (10/12); Deltamethrin (9/12); Chlorpyriphos (5/12)	*R. (B.) microplus*	LPT	RF	Mendes et al. (2007)
Uruguay	Fipronil (4/4)	*R. (B.) microplus*	LIT	RR	Castro-Janer et al. (2010)
Brazil	Cypermethrin (19/23); Deltamethrin (20/23); Chlorpyriphos (17/24)	*R. (B.) microplus*	LPT	RR	Mendes et al. (2011)
Uruguay	Ivermectin (5/18); Fipronil (6/27)	*R. (B.) microplus*	LIT	RR	Castro-Janer et al. (2011)
Brazil	Alpha-cypermethrin (18/19); Cypermethrin (10/14); Amitraz (14/17)	*R. (B.) microplus*	AIT	% AE	Andreotti et al. (2011)
Brazil	Cypermethrin (18/20); Amitraz (1/20)	*R. (B.) microplus*	AIT	% AE	Veiga et al. (2012)
Brazil	Cypermethrin (7/7); Chlorpyriphos (7/7)	*R. (B.) microplus*	LPT	RR	Domingues et al. (2012)
Brazil	Amitraz (4/5); Cypermethrin (5/5); Deltamethrin (5/5)	*R. (B.) microplus*	AIT	% AE	Ueno et al. (2012)
Brazil	Ivermectin (6/9)	*R. (B.) microplus*	LIT	RR	Klafke et al. (2012)
Brazil	Cypermethrin (10/10); Deltamethrin (10/10); Flumethrin (6/8)	*R. (B.) microplus*	LPT	RF	Mendes et al. (2013)
Brazil	Chlorpyriphos (11/17); Coumaphos (14/17); Amitraz (15/17); Fipronil (11/17); Pyripol (7/17); Ivermectin (1/17)	*R. (B.) microplus*	LTT	RR	Lovis et al. (2013a)
Argentina	Amitraz (3/8); Cypermethrin (7/8); Flumethrin (2/8)	*R. (B.) microplus*	LTT	RR	Lovis et al. (2013b)
Argentina	Amitraz (2/2); Cypermethrin (2/2); Flumethrin (2/2)	*R. (B.) microplus*	LTT	RR	Cutelle et al. (2013)
Brazil	Cypermethrin (7/7); Deltamethrin (7/7); Amitraz (7/7)	*R. (B.) microplus*	AIT	% AE	Raynal et al. (2013)
Colombia	Cypermethrin (2/2); Amitraz (2/2)	*R. (B.) microplus*	AIT	% AE	Lopez-Arias et al. (2014)
Colombia	Cypermethrin (2/2); Amitraz (2/2)	*R. (B.) microplus*	AIT	% AE	Puerta et al. (2015)
Brazil and Uruguay	Lindane (13/16); Fipronil (16/16)	*R. (B.) microplus*	LPT LIT	RR	Castro-Janer et al. (2015)
Brazil	Amitraz (13/14); Cypermethrin (12/14)	*R. (B.) microplus*	AIT	% AE	Barros de Santana et al. (2015)
Colombia	Ivermectin (3/3)	*R. (B.) microplus*	LIT	LC_{50} & LC_{99}	Villar et al. (2016)
Ecuador	Amitraz (8/12); Alpha-cypermethrin (6/12); Ivermectin (3/12)	*R. (B.) microplus*	AIT	% R	Rodriguez-Hidalgo et al. (2017)
Brazil	Cypermethrin (102/104); Amitraz (80/104); Chlorpyriphos (63/104); Ivermectin (63/104); Fipronil (56/104)	*R. (B.) microplus*	LIT & LPT	RR	Klafke et al. (2017)

(*continued on next page*)

Table 1 (*continued*)

Continent/Country	Acaricide name (Tick isolates or farms with ARD/Total tick isolates or farms sampled)	Cattle tick species	Bioassay technique	AR quantification parameter	References
CENTRAL AMERICA					
USA (Texas)	Coumaphos (4/44); Permethrin (11/36); Amitraz (3/14); Ivermectin (1/32); Fipronil (6/8)	*R. (B.) microplus*	LPT	% LM	Busch et al. (2014)
Mexico	Carbaryl (7/7)	*R. (B.) microplus*	LPT	RR	Li et al. (2005)
Mexico	Diazinon (79/98); Coumaphos (45/98); Chlorfenvinphos (35/98); Flumethrin (63/98); Deltamethrin (60/98); Cypermethrin (58/98)	*R. (B.) microplus*	LPT	% LM	Rodrigues-vivaz et al. (2006a)
Mexico	Amitraz (19/98)	*R. (B.) microplus*	LIT	% LM	Rodrigues-vivaz et al. (2006b)
Mexico	Amitraz (3/3)	*R. (B.) microplus*	LIT	RR	Rosado-Aguilar et al. (2008)
Mexico	Ivermectin (6/6)	*R. (B.) microplus*	LIT	RR	Perez-Cogollo et al. (2010a)
Mexico	Ivermectin (30/30)	*R. (B.) microplus*	LIT	RR	Perez-Cogollo et al. (2010b)
Mexico	Cypermethrin (5/11)	*R. (B.) microplus*	LPT	% LM	Rodrigues-vivas et al. (2011)
Mexico	Cypermethrin (17/49)	*R. (B.) microplus*	LPT	RF	Rodriquez- vivaz et al. (2012)
Mexico	Ivermectin (40/53)	*R. (B.) microplus*	LIT	RR	Fernandez-Salas et al. (2012a)
Mexico	Amitraz (29/53); Cypermethrin (48/53)	*R. (B.) microplus*	LIT & LPT	% LM	Fernandez-Salas et al. (2012b)
Mexico	Fipronil (5/5); Permethrin (4/5); Coumaphos (4/5); Amitraz (1/5)	*R. (B.) microplus*	LPT	% LM	Miller et al. (2013)
Mexico	Chlorpyriphos (24/24); Coumaphos (13/24); Diazinon (24/24)	*Amblyomma cajennense*	LPT	% LM	Alonso-Diaz et al. (2013)
OCEANIA					
New Caledonia	Deltamethrin (1/2)	*R. (B.) microplus*	LPT	RF	Brun (1992)
New Caledonia	Deltamethrin (3/12); Flumethrin (1/6); Fenvalerate (3/7); Ethion (1/3); Chlorpyriphos (1/6); Diazinon (1/3)	*R. (B.) microplus*	LPT	RF	Beugnet and Chardonnet (1995)
New Caledonia	Ethion (15/107); Deltamethrin (52/114)	*R. (B.) microplus*	LPT	RF	Bianchi et al. (2003)
New Caledonia	Amitraz (4/19)	*R. (B.) microplus*	LPT	RR	Ducornez et al. (2005)
New Caledonia	Deltamethrin (17/19); Amitraz (8/35)	*R. (B.) microplus*	LPT	RR	Chevillon et al. (2007)
New Caledonia	Deltamethrin (4/6); Amitraz (4/5)	*R. (B.) microplus*	LPT	RR	Barre et al. (2008)
Australia	Coumaphos (2/2); Cypermethrin (2/2); Flumethrin (2/2)	*R. (B.) microplus*	LTT	RR	Lovis et al. (2013a)
ASIA					
Iran	Propetamphos (7/8)	*R. bursa*	LPT	RR	Enayati et al. (2009)
Iran	Lambda Cyhalothrin (5/11); Cypermethrin (12/12)	*R. bursa*	LPT	RR	Enayati et al. (2010)
India	Diazinon (17/19)	*R. (B.) microplus*	AIT	RF	Kumar et al. (2011)
India	Deltamethrin (6/6)	*R. (B.) microplus*	LPT	RF	Vatsya and Yadav (2011)
India	Deltamethrin (10/20); Cypermethrin (10/20); Diazinon (6/20)	*Hyalomma anatolicum*	LPT	RF	Shyma et al. (2012)
India	Cypermethrin (16/27); Deltamethrin (18/27)	*R. (B.) microplus*	AIT	RF	Sharma et al. (2012)
India	Deltamethrin (7/12)	*R. (B.) microplus*	LPT	RF	Abdullah et al. (2012)
India	Deltamethrin (2/2); Cypermethrin (1/2); Diazinon (2/2)	*R. (B.) microplus*	LPT	RF	Shyma et al. (2013)
India	Deltamethrin (15/18)	*R. (B.) microplus*	AIT	RF	Kumar et al. (2013)
India	Cypermethrin (4/6); Fenvalerate (3/6)	*R. (B.) microplus*	LPT	RF	Abdullah et al. (2013a)
India	Cypermethrin (5/7); Fenvalerate (1/7)	*R. (B.) microplus*	LPT	RF	Abdullah et al. (2013b)
India	Deltamethrin (6/6); Cypermethrin (2/6); Deltamethrin (5/6)	*H. anatolicum* *R. (B.) microplus*	LPT	RR	Nandi et al. (2015)
India	Amitraz (10/11)	*R. (B.) microplus*	AIT	RF	Kumar et al. (2014)
India	Cypermethrin (11/13); Deltamethrin (13/14)	*R. (B.) microplus*	AIT	RF	Singh et al. (2014)
India	Deltamethrin (3/3) Deltamethrin (1/2)	*R. annulatus* *R. (B.) microplus*	LPT	RF	Jyothimol et al. (2014)
India	Cypermethrin (11/13); Deltamethrin (13/14)	*R. (B.) microplus*	AIT	RF	Singh and Rath (2014)
India	Deltamethrin (6/6)	*R. (B.) microplus*	AIT	RF	Ahanger et al. (2015)
India	Deltamethrin (6/7); Cypermethrin (5/7); Diazinon (6/7)	*R. (B.) microplus*	AIT	RF	Ghosh et al. (2015)
India	Ivermectin (4/5)	*R. (B.) microplus*	LIT	RR	Singh et al. (2015)
India	Diazinon (1/2); Deltamethrin (1/2)	*R. (B.) microplus*	AIT & LPT	RF	Gaur et al. (2016)
	Diazinon (1/2); Deltamethrin (1/2)	*H. anatolium*	AIT		
India	Amitraz (3/4); Malathion (2/4)	*R. (B.) microplus*	AIT	RF	Dutta et al. (2017)
Iran	Cypermethrin (1/17); Lambda-Cyhalothrin (1/12)	*R. (B.) annulatus*	LPT	RR	Ziapour et al. (2016)
Iran	Deltamethrin (5/7)	*R. (B.) microplus*	LPT	RF	Lenka et al. (2016)
India	Malathion (12/18)	*R. (B.) microplus*	AIT	RF	Jyoti et al. (2016)
India	Deltamethrin (5/5)	*R. (B.) microplus*	AIT	% R	Kumari and Sangwan (2016)
	Deltamethrin (2/2); Amitraz (2/2)	*H. anatolicum*			

(*continued on next page*)

Table 1 (*continued*)

Continent/Country	Acaricide name (Tick isolates or farms with ARD/Total tick isolates or farms sampled)	Cattle tick species	Bioassay technique	AR quantification parameter	References
India	Deltamethrin (4/4); Cypermethrin (4/4); Diazinon (4/4)	*R. (B.) microplus*	AIT	RF	Chigure et al. (2018)
India	Deltamethrin (1/2); Diazinon (1/2)	*R. (B.) microplus*	AIT	RF	Gaur et al. (2017)
	Deltamethrin (1/2); Diazinon (1/2)	*H.anatolicum*			
Iran	Cypermethrin (7/29); Lambda Cyhalothrin (4/29)	*R. annulatus*	LPT	RF	Ziapour et al. (2017)
India	Deltamethrin (3/6); Cypermethrin (3/6)	*R. (B.) microplus*	LPT	RF	Kumar et al. (2017)
India	Deltamethrin (6/6); Cypermethrin (6/6); Diazinon (6/6)	*R. (B.) microplus*	AIT	RF	Nagar et al. (2018)
India	Ivermectin (7/7)	*R. (B.) microplus*	AIT	RF	Nandi et al. (2018)
India	Ivermectin (14/14)	*R. (B.) microplus*	LIT	RF	Khangembam et al. (2018)
India	Deltamethrin (3/10); Cypermethrin (4/10);	*H. anatolicum*	LPT	RF	Sharma et al. (2018)
	Deltamethrin (5/8); Cypermethrin (3/8)	*R. (B.) microplus*			
India	Coumaphos (4/5); Deltamethrin (5/5); Cypermethrin (4/5)	*R. (B.) microplus*	LPT & AIT	RF	Upadhaya et al. (2020)
India	Ivermectin (5/6); Cypermethrin (5/5); Deltamethrin (6/6); Coumaphos (6/6); Diazinon (3/3)	*R. (B.) microplus*	AIT	RF	Sagar et al. (2020)

Abbreviations: LPT, larval packet test; AIT, adult immersion test; LIT, larval immersion test; LTT, larval tarsal test; RF, resistance factor; RR, resistance ratio; FOR, factor for resistance; % AE, percentage acaricide efficacy; % RE, percentage reproductive estimate; % LM, percentage larval mortality; % EL, percentage egg laying; % R, percentage resistance; AR, acaricide resistance.

3.2. Meta-analyses on acaricide resistance development in tick populations of cattle

In total, 88 studies were included in the MA, representing 218 bioassays and 3939 tick populations, of which 2269 (57.6%) exhibited ARD (Table 3). A total of 77 (87.5%) of the 88 included studies reported ARD in *R.(B.) microplus*, of which 171 bioassays were conducted on 3391 tick populations from 14 countries worldwide (Table 3). The global pooled prevalence estimate (PPE) of ARD in populations of *R.(B.) microplus* was 66.2% (95% CI: 61.6–70.5), with a high level of heterogeneity ($P < 0.0001$; $I^2 = 75.5\%$) among studies (Table 3). Fewer than 7 included studies reported ARD in *R. (B.) decoloratus*, *R. appendiculatus*, *R. annulatus*, *R. evertsi evertsi*, *R. bursa*, *Hyalomma anatolicum*, *Amblyomma hebraeum*, and *A. cajennense* populations. Separate MAs were performed to determine the PPE of ARD in *R. (B.) decoloratus, Hyalomma anatolicum, R. appendiculatus,* and *R. annulatuswith* pooled ARD prevalence estimates of 56.5% (95% CI: 37.6–73.7), 45.7% (95% CI: 35.7–56.1), 32.0% (95% CI: 3.3–86.7) and 27.4% (95% CI: 10.0–56.1), respectively (Table 3). The measurement of heterogeneity of ARD in populations of *R. evertsi evertsi, R. bursa, Amblyomma hebraeum,* and *A. cajennense* was omitted because the number of included studies was small, and there were fewer than four bioassays.

Subgroup meta-analyses were conducted to describe the distinctive nature of ARD in populations of *R. (B.) microplus* with regard to geographical regions (continent and country), detection methods, publication years, and acaricide chemical compounds (Tables 4, 5, 6). Approximately 85% (n = 65) of the included studies on ARD in populations of *R. (B.) microplus* were from Asia, Central, and South America. The pooled prevalence of ARD in populations of *R. (B.) microplus* differed significantly ($\chi^2 = 84.5$; $P < 0.001$) across continents, and higher PPEs (>50%) were recorded in Asia [73.3%; 95% CI: 61.6–70.5)], South America [72.0% (95% CI: 65.7–77.6)], and Central America [54.7 % (95% CI:43.6–65.3)]. Tests for heterogeneity showed high variation ($P < 0.0001$; I^2>70%) among studies from Africa, Oceania, South and Central America, whereas the percentage of variation among studies from Asia was very low ($P < 0.336$; $I^2 = 6.6\%$) (Table 4). The continents of Africa (5) and Oceania (2) recorded the lowest numbers of eligible studies within the study period (1992–2020), as well as the lowest PPEs (<50%) of 48.4% (95% CI: 24.5–73.0) and 41.4% (95% CI: 27.9–56.5), respectively. A greater majority (53/77) of the included studies were from three countries, namely Brazil, Mexico, and India, with PPE values of 75.5% (95% CI: 68.6–81.2), 62.7% (95% CI: 51.6–72.2), and 73.5% (95% CI: 68.0–78.3), respectively (Table 5). A significantly high degree of heterogeneity was observed among studies from Brazil ($P < 0.0001$; $I^2 = 67.8\%$) and Mexico ($P < 0.0001$; $I^2 = 86.7\%$), whereas homogeneity ($P < 0.302$; $I^2 = 8.3\%$) existed among studies from India. The number of countries with reported cases of resistance development in *R. (B.) microplus* to acaricides increased from 1992 to 2020 (Table 4).

The pooled prevalence estimates differ significantly ($\chi 2 = 77.40$, $P < 0.001$) among detection methods, with the AIT being significantly ($P < 0.001$) sensitive in detecting ARD in populations of *R. (B.) microplus,* with a PPE of 78.9% (95% CI:73.4–83.5) compared to 61.0% (95% CI: 54.9–66.9) and 59.9% (95%CI: 46.5–71.9) with the LPT and LIT, respectively (Table 4). However, there was a considerably low level of heterogeneity ($P = 0.039$; $I^2 = 26.7\%$) among studies that detected ARD with AIT. Significantly higher levels of variation ($P < 0.0001$; I^2>79%) existed among studies that detected ARDs with LPT and LIT (Table 4). LPT and AIT are frequently used to investigate the resistance to synthetic pyrethroids, organophosphates, ivermectin, and amitraz. LIT was mainly used for the diagnosis of resistance to amitraz, ivermectin, and fipronil (Table 6).

Development of resistance to deltamethrin, cypermethrin, amitraz, and ivermectin in *R. (B.) microplus* populations was noted in a majority of the included studies (n ≥ 15). A total of 688, 569, 522 and 318, populations of *R. (B.) microplus* were assessed for resistance to these acaricide compounds. Pooling these large trials gave prevalence estimates of resistance development of 76.4% (95% CI: 68.5–82.8), 74.1% (95% CI: 65.1–81.5), 58.8% (95% CI:43.2–72.8), and 61.7% (95% CI: 42.7–77.7), respectively, with a significantly high level ($P < 0.0001$) of heterogeneity among the studies (Table 4). The points and pooled prevalence estimates of resistance development to these acaricides and measures of dispersion are presented in Figures 3, 4, 5, 6.

4. Discussion

Characterisation of acaricide resistance in resistant tick populations using bioassay tools is an important first step in providing phenotypic data on the level of tick resistance (Kumar, 2019). This study combined and analysed phenotypic data from published articles on acaricide resistance to provide pooled prevalence estimates of acaricide resistance

development worldwide. Most reports on phenotypic resistance development in tick populations worldwide refer to *R. (B.) microplus* (Rodriguez-Vivas et al., 2018). Indeed, among the 3939 tick populations that were investigated for resistance development, 3391 (86%) were *R. (B.) microplus,* which exhibited a global pooled prevalence estimate of acaricide resistance development of 66.2%. Acaricide resistance development worldwide has been faster in *R. (B.) microplus* followed by *R. (B.) decoloratus* (Guerrero et al., 2014). However, lower rates of acaricide resistance were observed in*, R. appendiculatus, R. annulatus, R. evertsi evertsi, R. bursa, Hyalomma anatolicum, Amblyomma hebraeum*, and *A. cajennense.* Both *R. (B.) microplus* and *R. (B.) decoloratus* are single host ticks, and their higher rates of resistance development has been attributed to their shorter life cycle and higher reproductive rates, which entail frequent treatment with acaricides (Guerrero et al., 2014). Frequent subjection of large proportions of tick populations to acaricides promotes the selection of resistant ticks, thereby increasing the evolution and spread of resistance. Acaricide resistance is generally uncommon in multi-host ticks (Mekonnen et al., 2002), as these ticks have a wide variety of hosts ranging from domestic to wild animals. In addition, they generally have longer life cycles, with the parasitic phase often shorter than the inter-treatment intervals used by most farmers. Therefore, a higher proportion of these ticks usually escape acaricide treatment (*refugia*), resulting in a low selection intensity for acaricide resistance (Guerrero et al., 2014). Based on the Higgins I^2 statistic, we noted high levels of variation across studies that reported acaricide resistance development in *R. (B.) microplus* populations worldwide. These differences might be attributed to the geography, economic status of farmers, breed of cattle, dose and frequency of acaricide application (Shyma et al.,

Table 2. Characteristics of studies included in the systematic review of acaricide resistance in tick populations of cattle.

Factor	Sub-category	No of studies	No of experiments	No of countries	List of countries
Acaricides	Dieldrin (OC)	1	1	1	Ethiopia
	Lindane (OC)	1	1	2	Brazil, Uruguay
	Carbaryl (Ca)	1	1	1	Mexico
	Pyripol (PYZ)	1	2	2	South Africa, Brazil.
	Fipronil (PYZ)	7	7	4	Uruguay, Brazil, Mexico, USA (Texas).
	Amitraz (FOM)	29	30	10	India, New Caledonia, USA (Texas), Brazil, Ecuador, Colombia, Mexico, Uganda, Benin, South Africa.
	Ivermectin (ML)	15	15	7	India, USA (Texas), Brazil, Ecuador, Colombia, Mexico, Uruguay.
	Alpha-cypermethrin (SP)	5	5	3	Benin, Brazil, Ecuador.
	Cypermethrin (SP)	42	46	10	India, Iran, Australia, Argentina, Brazil, Colombia, Mexico, Uganda, Bolivia, South Africa.
	Deltamethrin (SP)	40	47	9	India, Iran, New Caledonia, Brazil, Bolivia, Mexico, Egypt, Benin, Uganda.
	Flumethrin (SP)	7	8	7	South Africa, Mexico, Bolivia, Argentina, New Caledonia, Australia, Brazil.
	Permethrin (SP)	2	2	2	Mexico, USA (Texas).
	Lambda-Cyhalothrin (SP)	3	3	1	Iran
	Fenvalerate (SP)	3	3	2	India, New Caledonia.
	Coumaphos (OP)	8	10	6	Ethiopia, Mexico, Brazil, India, USA (Texas), Australia.
	Diazinon (OP)	13	15	4	India, Mexico, Ethiopia, New Caledonia.
	Chlorpyriphos (OP)	7	7	3	Brazil, Mexico, New Caledonia.
	Chlorfenvinphos (OP)	6	10	3	South Africa, Uganda, Mexico
	Malathion (OP)	2	2	1	India
	Ethion (OP)	2	2	1	New Caledonia
	Propetamphos (OP)	1	1	1	Iran
Bioassay technique	LPT	45	116	11	Ethiopia, Benin, Uganda, Egypt, Brazil, Mexico, Bolivia, USA (Texas), New Caledonia, Iran, India.
	AIT	28	67	6	India, Ecuador, Brazil, Colombia, Benin, South Africa.
	LIT	18	37	6	South Africa, Brazil, Mexico, Uruguay, Colombia, India.
	LTT	3	18	4	South Africa, Brazil, Argentina, Australia.
AR diagnostic parameter	RF/RR/FOR	66	147	11	India, Iran, New Caledonia, Australia, Brazil, Uruguay, Argentina, Mexico, Egypt, Benin, South Africa.
	% LM	10	39	4	Uganda, Mexico, Bolivia, USA (Texas).
	% R	2	6	2	India, Ecuador.
	% RE & % EL	2	8	1	South Africa
	% AE	7	17	2	Brazil, Colombia.
	LC_{50} & LC_{99}	x	1	1	Colombia
Geographical location	South America	24	60	6	Brazil, Colombia, Bolivia, Uruguay, Argentina, Ecuador,
	Central America	13	28	2	USA (Texas), Mexico
	Asia	35	75	2	India, Iran
	Africa	10	38	5	South Africa, Benin, Uganda, Egypt, Ethiopia,
	Oceania	6	17	2	New Caledonia, Australia
	Total	88	218	17	

Abbreviations: LPT, larval packet test; AIT, adult immersion test; LIT, larval immersion test; LTT, larval tarsal test; RF, resistance factor; RR, resistance ratio; FOR, factor for resistance; % AE, percentage acaricide efficacy; % RE, percentage reproductive estimate; % LM, percentage larval mortality; % EL, percentage egg laying; % R, percentage resistance; OC, organochlorine; SP, synthetic pyrethroid; OP, organophosphate; FOM, formamidine; Ca, carbamates; PYZ, phenylpyrazole; ML, macrocyclic lactone.

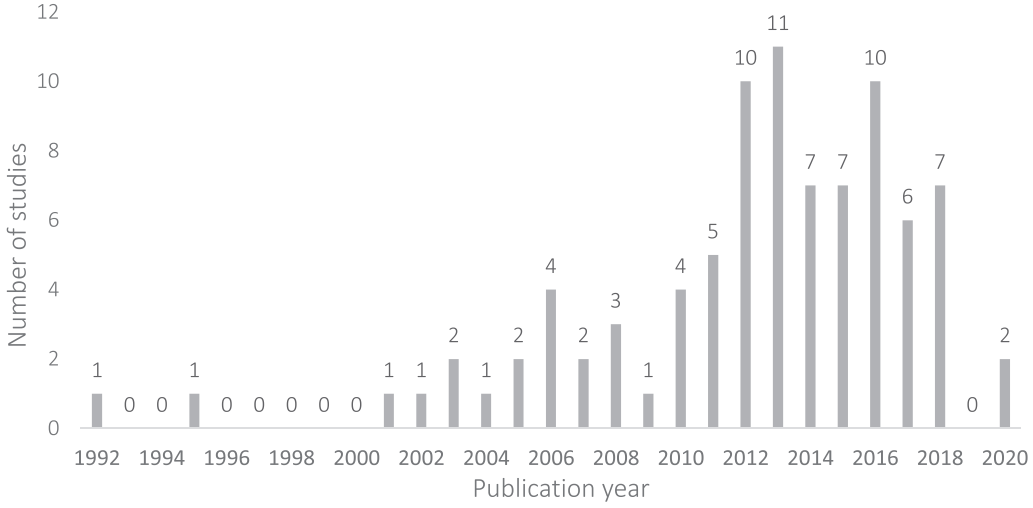

Figure 2. Annual distribution of studies on acaricide resistance in tick populations of cattle.

Table 3. Pooled prevalence estimates of acaricide resistance development in cattle tick species.

Tick species	Included studies[a]	No. of bioassays	Pooled prevalence estimates			Measurement of heterogeneity[b]			No of countries	List of countries
			No. of isolates	Isolates with ARD	Prevalence (%) (95% CI)	Q –value	I^2 (%)	P-value		
R. (B) microplus	77	171	3391	2013	66.2 (61.6–70.5)	692.9	75.5	<0.0001	14	South Africa, Benin, Brazil, Mexico, Bolivia, Uruguay, Argentina, Colombia, Ecuador, USA (Texas), New Caledonia, Australia, India & Iran
R. (B.) decoloratus	4	14	117	68	56.5 (37.6–73.7)	32	59.3	0.002	3	Ethiopia, South Africa, Uganda
Hyalomma anatolicum	6	12	98	47	45.7 (35.7–56.1)	9.5	0.0	0.578	1	India
R. appendiculatus	2	5	95	27	32.0 (3.3–86.7)	33.6	88.1	<0.0001	2	South Africa, Uganda
R. annulatus	4	6	90	15	27.4 (10.0–56.1)	18.6	73.1	0.002	2	Egypt, India
R. bursa	2	3	31	24	79.8 (33.6–96.9)	-	-	-	1	Iran
R evertsi evertsi	3	3	40	13	32.6 (19.9–48.5)	-	-	-	2	Ethiopia, South Africa
Amblyomma cajennense	1	3	72	61	91.7 (36.6–99.5)	-	-	-	1	Mexico
A. hebraeum	1	1	5	1	-	-	-	-	1	South Africa
Total	88	218	3939	2269						

[a] Multiple studies have reported ARD in several cattle tick species.
[b] Measurements of heterogeneity for subgroups with fewer than four trials were omitted.

2015), and sensitivity of the acaricide resistance detection methods employed. This indicates that monitoring the acaricide resistance status of each tick population is essential for the optimal and strategic use of acaricides. Monitoring acaricide resistance is crucial for preserving acaricide efficacy and preventing the spread of resistant populations (de Oliveira Souza Higa et al., 2015).

Globally, *R. (B.) microplus* is endemic in tropical and subtropical regions, but not in continental Europe, and has been eradicated from the USA (CMPV, 2018). Hence, this study found no reports on the development of resistance in *R. (B.) microplus* of cattle from Europe and North America. However, most reports on phenotypic acaricide resistance in *R. (B.) microplus* populations have emanated from South America (Brazil), Central America (Mexico), and Asia (India). Mexican acaricide-resistant *R. (B.) microplus* populations have been reported, particularly in the Veracruz and Yucatan regions (Rodrıguez-Vivas et al., 2006a, b; Perez-Cogollo et al., 2010a, b; Fernandez-Salas et al., 2012a, b). These Mexican *R. (B.) microplus* populations are mostly resistant to organophosphates, synthetic pyrethroids, amitraz, ivermectin, and fipronil (Rodriguez-Vivas et al., 2014). Organophosphates were heavily used in the national tick eradication program between 1974 and 1984, whereas pyrethroids and amitraz were introduced to Mexico in 1986 (Rodriguez-Vivas et al., 2014). In Brazil, reports of tick populations exhibiting resistance to acaricides are mainly from the southern Brazilian states of Rio Grande do Sol, São Paulo, and Mato Grosso do Sul Brazil (Klafke et al., 2006, 2017; Castro-Janer et al., 2010; Andreotti et al., 2011; Mendes et al., 2011, 2013). According to de Oliveira Souza Higa et al. (2015), acaricide resistance development in Brazilian populations of *R. (B.) microplus* has been attributed to the lack of an official tick control policy that leaves the responsibility of selecting control criteria in the hands of cattle producers, the continuous and inadequate application of acaricides for an extended period, and the rearing of European cattle breeds, which are more susceptible to ticks. Reports of acaricide resistance development in Indian populations of *R. (B.) microplus* have been reported, particularly in the Punjab state (Sharma et al., 2012; Kumar et al., 2013; Singh et al., 2014; Nandi et al., 2015; Singh and Rath, 2014; Singh et al., 2015; Jyoti et al., 2016; Khangembam et al., 2018; Sagar et al., 2020). The pooled prevalence estimate of acaricide resistance in the Indian R. *(B.) microplus* populations was observed to range from 68 to 78%. A lack of variation across studies ($P > 0.1$; $I^2 = 8.3$) was observed, implying that the rate of

Table 4. Pooled prevalence estimates of resistance development in *Rhipicephalus (Boophilus) microplus*.

Risk factor	No. of countries	Included studies	No of bioassays	Pooled prevalence estimates			Measure of heterogeneity		
				No of isolates of *R. (B.) microplus*	No of isolates with RD	Prevalence (%) (95% CI)	Q -value	I^2 (%)	P-value
Continent									
Africa	2	5	13	157	39	48.4 (24.5–73.0)	41.1	70.8	<0.0001
Asia	2	29	56	422	327	73.3 (68.0–78.0)	58.9	6.6	0.336
Central America	2	13	25	1105	583	54.7 (43.6–65.3)	190.6	87.4	<0.0001
Oceania	2	7	17	350	121	41.4 (27.9–56.5)	55.6	71.2	<0.0001
South America	7	24	60	1357	943	72.0 (65.7–77.6)	208.0	71.6	<0.0001
Detection method[b]									
LPT	9	35	82	2294	1344	61.0 (54.9–66.9)	390.4	79.3	<0.0001
AIT	5	27	55	488	385	78.9 (73.4–83.5)	73.7	26.7	0.039
LIT	6	16	23	986	564	59.9 (46.5–71.9)	186.0	88.2	<0.0001
LTT	4	3	18	147	86	59.8 (45.1–73.0)	33.0	48.5	0.011
Years of publication									
1992–2001	1	2	7	39	11	29.3 (16.8–45.9)	2.0	0.0	0.917
2002–2011	7	22	41	1669	871	59.0 (49.8–67.6)	338.0	88.2	<0.0001
2012–2020	12	53	123	1683	1131	70.7 (65.8–75.2)	305.7	60.1	<0.0001
Acaricides[b]									
Deltamethrin	7	36	36	569	406	76.4 (68.5–82.8)	82.8	57.8	<0.0001
Cypermethrin	8	37	37	688	488	74.1 (65.1–81.5)	114.8	69.5	<0.0001
Flumethrin	7	8	8	210	112	51.3 (35.3–67.0)	17.2	59.3	0.016
Alpha-cypermethrin	3	5	5	40	32	78.1 (51.3–92.4)	6.8	41.1	0.148
Fenvalerate[a]	2	3	3	20	7	37.8 (18.7–61.6)	-	-	-
Permethrin[a]	2	2	2	41	15	50.7 (11.1–89.4)	-	-	-
Chlorpyriphos	2	6	6	170	104	59.9 (46.1–72.3)	8.8	42.1	0.119
Coumaphos	5	7	7	177	79	63.5 (33.9–85.5)	32.4	81.5	<0.0001
Diazinon	3	10	10	146	120	80.6 (73.1–86.4)	7.1	0.00	0.631
Ethion[a]	1	2	2	110	16	14.7 (9.2–22.7)	-	-	-
Chlorfenvinphos[a]	2	2	2	134	45	33.7 (26.2–42.1)	-	-	-
Malathion	1	2	2	22	14	63.5 (42.0–80.7)	-	-	-
Amitraz	10	25	25	522	254	58.8 (43.2–72.8)	149.9	84.0	<0.0001
Fipronil	5	7	7	181	104	65.3 (43.4–82.2)	21.0	71.4	0.002
Pyripol[a]	2	2	2	20	8	40.0 (21.4–62.1)	-	-	-
Ivermectin	7	15	15	318	189	61.7 (42.7–77.7)	59.5	76.5	<0.0001
Carbaryl[a]	1	1	1	7	7	-	-	-	-
Lindane[a]	1	1	1	16	13	-	-	-	-

Abbreviations: RD, resistance development.

[a] Measurement of heterogeneity for subgroups with fewer than four trials were omitted.

[b] Multiple studies reported more than one detection method and acaricide.

ARD in the included studies was consistently high. This indicates the establishment of acaricide resistance in the Indian R. *(B.) microplus* populations. FAO (2004) predicted the establishment of widespread acaricide resistance in tick populations in India. Factors contributing to the development of acaricide resistance in India include poor infrastructure and management practices that provide conducive sites for the easy proliferation of ticks and climatic conditions conducive to the growth and survival of ticks throughout the year (Kumar et al., 2020). Furthermore, the liberalisation of the veterinary drug industry has made acaricides easily accessible to farmers, and limited control has led to improper dosing, higher application frequency, limited rotational use of acaricides, and non-adherence to acaricide usage principles. In addition, the unavailability of framed policies to manage tick infestations and the lack of concerted efforts by veterinarians to monitor the efficacy of widely used acaricides in field conditions have also contributed to the development of resistance in India (Kumar et al., 2020). Research on acaricide resistance development in tick populations of cattle in Africa is still in its infancy, and relatively few publications were obtained from the databases searched (Mekonnen et al., 2003; Ntondini et al., 2008; Adehan et al., 2016; Vudriko et al., 2016; Aboelhadid et al., 2018; Yessinou et al., 2018a, b). A potential reason for this result might be the low demand for research by policymakers as well as the lack of funding and researchers.

Globally, *R. (B.) microplus* populations have developed resistance to multiple acaricide compounds, predominantly SP (deltamethrin, cypermethrin, flumethrin), OP (diazinon), amitraz, fipronil, and ivermectin, emphasising the need for quick intervention strategies to combat the spread of resistant tick populations. In the past 15 years, SP has been the most aggressively marketed acaricide for tick control in cattle (Kumar et al., 2020). Continuous use and/or inadequate application of these products over a long period has promoted population selection for acaricide-resistant ticks, thereby increasing the rate of resistance development (de Oliveira Souza Higa et al., 2015). Higher levels of resistance to these SP compounds in populations of *R. (B.) microplus* have been

Table 5. Pooled prevalence estimates of resistance development in *Rhipicephalus (Boophilus) microplus* stratified by countries.

Country	No. of studies	No. of bioassays	Pooled prevalence estimates			Measurement of heterogeneity[a]		
			No. of isolates	No. of isolates with RD	Prevalence (%) (95% CI)	Q-value	I^2 (%)	P-value
South Africa	2	6	134	17	16 (6.4–34.3)	12.1	58.6	0.034
Benin	3	7	23	22	85.4 (66.9–94.5)	0.5	0.0	0.90
Brazil	14	38	950	682	75.5 (68.6–81.2)	114.9	67.8	<0.0001
Mexico	11	20	971	558	62.7 (51.6–72.2)	142.8	86.7	<0.0001
Bolivia	1	3	249	171	71.6 (40.0–90.5)	-	-	-
Uruguay	3	5	81	44	64.7 (27.7–89.7)	23.2	82.7	<0.0001
Argentina	2	6	30	18	62.0 (33.5–84.1)	8.6	42.0	0.125
Colombia	3	5	11	11	84.3 (58.1–95.4)	0.1	0.0	0.988
Ecuador	1	3	36	17	47.4 (25.2–70.6)	-	-	-
USA (Texas)	1	5	134	25	21.4 (7.9–46.4)	18.3	78.1	0.001
New Caledonia	6	14	344	115	36.9 (23.9–52.1)	49.3	73.6	<0.0001
Australia	1	3	6	6	83.3 (46.4–96.7)	-	-	-
India	28	55	415	322	73.5 (68.0–78.3)	58.9	8.3	0.302
Iran	1	1	7	5	-	-	-	-

Abbreviations: RD, resistance development.
[a] Measurements of heterogeneity for subgroups with fewer than four trials were omitted.

Table 6. Effect of detection method on pooled prevalence estimates of acaricide resistance development in *R (B.) microplus*.

Acaricides[b]	Detection Method[c]	No. of studies	Pooled prevalence estimates			Measurement of heterogeneity		
			No. of isolates	No. of isolates with RD	Prevalence (%) (95% CI)	Q- value	I^2 (%)	P-value
Deltamethrin	LPT	22	443	296	71.1 (60.3–80.0)	60.4	65.2	<0.0001
	AIT	15	126	108	80.9 (72.2–87.3)	11.2	0.00	0.672
Cypermethrin[d]	LPT	17	490	361	71.6 (58.4–81.9)	73.9	78.4	<0.0001
	AIT	14	139	114	77.8 (69.5–84.4)	11.8	0.00	0.543
	LIT[a]	2	148	103	53.0 (0.0–100)	-	-	-
	LTT	4	15	12	74.8 (45.4–91.4)	3.0	0.00	0.394
Flumethrin	LPT	4	195	105	52.7 (33.6–71.0)	12.6	76.3	0.006
	LTT	4	15	7	48.1 (18.8–78.8)	4.1	26.7	0.253
Alpha-cypermethrin	LPT[a]	2	7	6	81.2 (42.2–96.2)	-	-	-
	AIT[a]	3	33	26	79.3 (33.8–96.6)	-	-	-
Chlorpyriphos[d]	LPT	5	153	93	58.3 (40.5–74.2)	8.6	53.7	0.071
	LIT[a]	1	104	63	-	-	-	-
	LTT[a]	1	17	11	-	-	-	-
Coumaphos	LPT	4	152	57	45.8 (15.6–79.4)	19.5	84.6	<0.0001
	AIT[a]	1	6	6	-	-	-	-
	LTT[a]	2	19	16	82.5 (59.8–93.7)	-	-	-
Diazinon[d]	LPT	4	105	83	73.7 (52.5–87.6)	3.8	20.5	0.287
	AIT	7	43	38	84.3 (69.1–92.8)	3.7	0.00	0.714
Amitraz[d]	LPT	8	202	116	49.2 (24.8–74.1)	50.3	86.1	<0.0001
	AIT	10	94	64	76.3 (54.6–89.6)	21.3	57.7	0.012
	LIT	5	303	134	44.2 (15.3–74.6)	79.2	95.0	<0.0001
	LTT[a]	3	27	20	71.7 (28.5–94.2)	-	-	-
Fipronil[d]	LPT[a]	3	117	67	65.3 (40.4–84.0)	-	-	-
	LIT	4	151	82	66.2 (28.5–87.2)	16.0	81.3	0.001
	LTT[a]	1	17	11	-	-	-	-
Ivermectin[d]	LPT[a]	2	136	64	20.2 (0.6–91.7)	-	-	-
	AIT[a]	3	25	15	69.8 (17.2–96.3)	-	-	-
	LIT	10	244	172	72.0 (55.5–84.1)	25.2	64.3	0.003
	LTT[a]	1	17	1	-	-	-	-

Abbreviations: RD, resistance development; LPT, larval packet test; AIT, adult immersion test; LIT, larval immersion test; LTT, larval tarsal test.
[a] Measurements of heterogeneity for subgroups with fewer than four trials were omitted.
[b] Acaricides with fewer than four trials were not considered.
[c] Bioassay techniques with no trials were omitted.
[d] Two bioassay techniques were used in multiple trials.

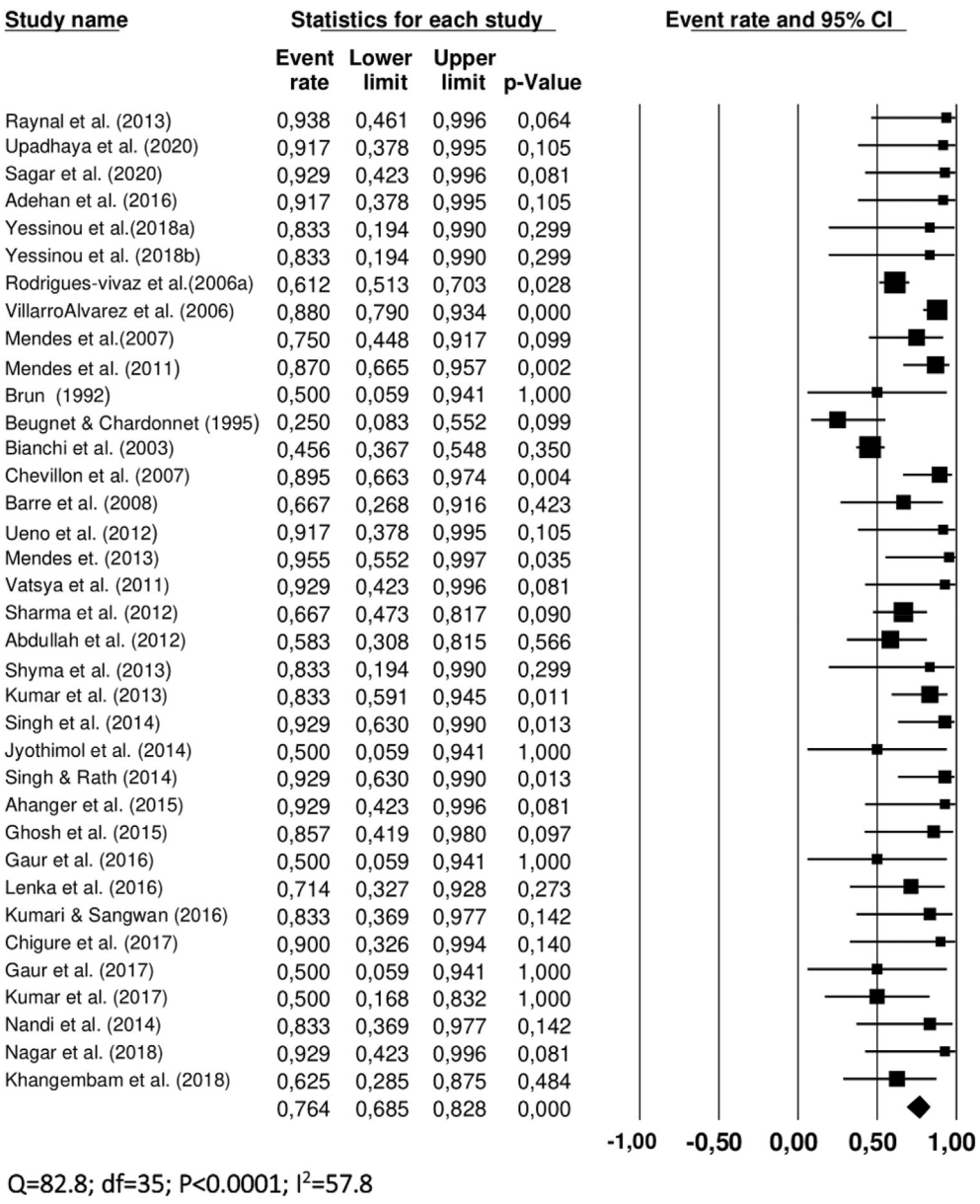

Figure 3. Point and pooled prevalence estimates of resistance development in *R. (B.) microplus* isolates to deltamethrin.

reported in many countries, including Benin (Yessinou et al., 2018a), Brazil (Mendes et al., 2011; Klafke et al., 2017), Mexico (Fernandez-Salas et al., 2012b) and India (Kumar et al., 2013; Singh and Rath, 2014; Sagar et al., 2020). Amitraz is one of the most popular acaricides used to control *R. (B.) microplus* in Australia, southern Africa, and Latin America (Jonsson and Hope, 2007). Amitraz was introduced at almost the same time (1970s) as SP to control OP-resistant tick populations, but its usage became limited owing to its higher cost (Jonsson and Hope, 2007). However, when tick populations began to exhibit SP resistance, the use of amitraz for tick control in cattle became frequent. Thus, the incessant and indiscriminate use of amitraz, especially at improper concentrations, probably contributed to the high rates (>80%) of amitraz resistance in *R. (B.) microplus* populations reported in many countries, including Brazil (Andreotti et al., 2011; Ueno et al., 2012; Lovis et al., 2013a; Raynal et al., 2013; Barros de Santana et al., 2015), Mexico (Rosado-Aguilar et al., 2008), Argentina (Cutellea et al., 2013), Colombia (Lopez-Arias et al., 2014; Puerta et al., 2015), New Caledonia (Barre et al., 2008), India (Kumar et al., 2014) and Benin (Adehan et al., 2016). Ivermectin (macrocyclic lactone) is a broad-spectrum drug commonly used to control gastrointestinal parasites and tick populations of cattle. For example, ivermectin is one of the best-selling antiparasitic drugs in the Mexican veterinary market (Rodriguez-Vivas et al., 2014). However, its use over the last 30 years has led to the development of resistance in *R. (B.) microplus* populations. Although several studies have demonstrated the efficacy of ivermectin for controlling *R. (B.) microplus* populations resistant to OP, SP, and amitraz (Rodriguez-Vivas et al., 2018), the results of this study indicate that many (189/318) populations of *R. (B.) microplus* have become resistant to ivermectin, with pooled prevalence estimates ranging from 43 to 78%. In *R. (B.) microplus* populations, high levels (>80%) of ivermectin resistance have been reported in Mexico (Perez-Cogollo et al., 2010a; 2010b) India (Khangembam et al., 2018; Nandi et al., 2018; Sagar et al., 2020) and Colombia (Villar et al., 2016).

Currently, four bioassays, AIT (FAO, 2004), LPT (FAO, 2004), LIT (Shaw, 1966) and LTT (Lovis et al., 2013a, b) have been used to test for

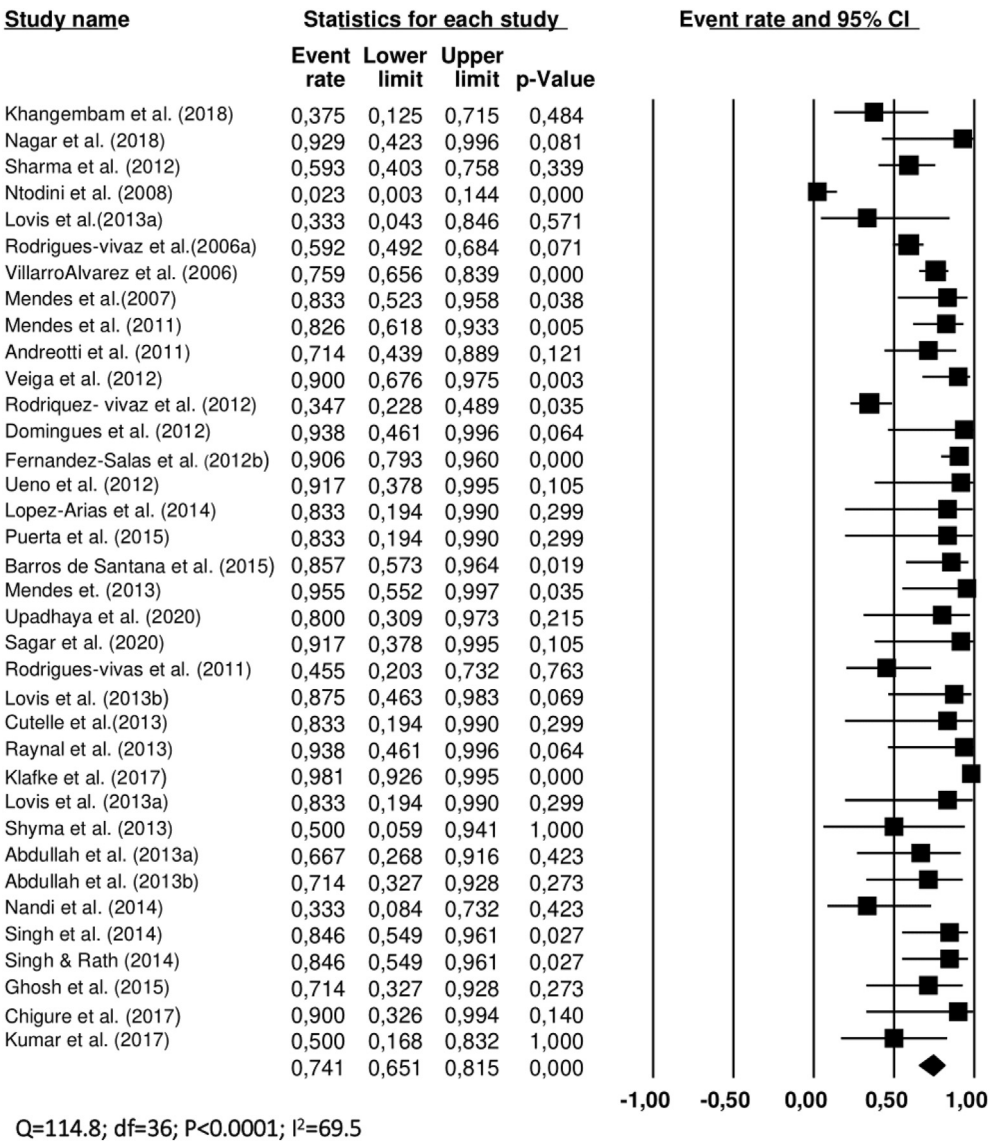

Figure 4. Point and pooled prevalence estimates of resistance development in *R. (B.) microplus* isolates to cypermethrin.

resistance to acaricides, where resistance mechanisms are unknown. The findings from this study are in complete agreement with those of Rodriguez-Vivas et al. (2018) that LPT is the most extensively used bioassay for the diagnosis of resistance to acaricides in *R. (B.) microplus* populations. Although AIT was observed to be significantly sensitive ($P < 0.001$) in detecting phenotypic acaricide resistance in *R. (B.) microplus*, it has been shown to be a poor test for detecting resistance in ticks (Jonsson and Hope, 2007). LPT is considered to be a highly repeatable bioassay, and comparative studies from bioassay results have shown that there is an acceptable level of agreement between LPT and LIT (FAO, 2004). This corroborates the findings of this study, in which the rates of resistance to acaricides in *R. (B.) microplus* detected with LPT [61.0% (95% CI: 54.9–66.9)] and LIT [59.9% (95%CI: 46.5–71.9)] were almost comparable and exhibited completely overlapping ranges. Consistent with the results reported by Rodriguez-Vivas et al. (2018), this study noted that LPT and AIT were often used to diagnose resistance to SPs and OPs in ticks, while LIT was often used to diagnose resistance to amitraz, ivermectin, and fipronil. Larval immersion test is currently the most widely used bioassay for detecting ivermectin resistance (Gutierrez et al., 2019).

Over the last three decades, there has been a drastic increase in the prevalence of acaricide resistance in *R. (B.) microplus* populations. This has been mainly attributed to the incessant and indiscriminate use of acaricides, which has led to the selection of tick populations resistant to acaricides (Klafke et al., 2017). Genes responsible for the onset of resistance are naturally present at minute levels in tick populations before the introduction and application of acaricides. The frequency of these naturally present resistance genes usually increases with continuous selection pressure from acaricide treatments, leading to declining efficacy of acaricides (Kumar, 2019). In the Brazilian state of Rio Grande do Sul, between 2005-2011, Santos and Vogel (2012) found that the percent of acaricide resistant *R. (B.) microplus* samples ranged from 29 to 75%. However, in later years (2013–2015), acaricide resistance in the same tick population had risen to 98% (Klafke et al., 2017).

Meta-analysis can be used to integrate data from different studies to inform decision making, but is associated with the weakness of publication bias. In this study, publication bias was not quantified because variability was expected within and among the studies. In addition, studies designed to investigate acaricide resistance in tick populations

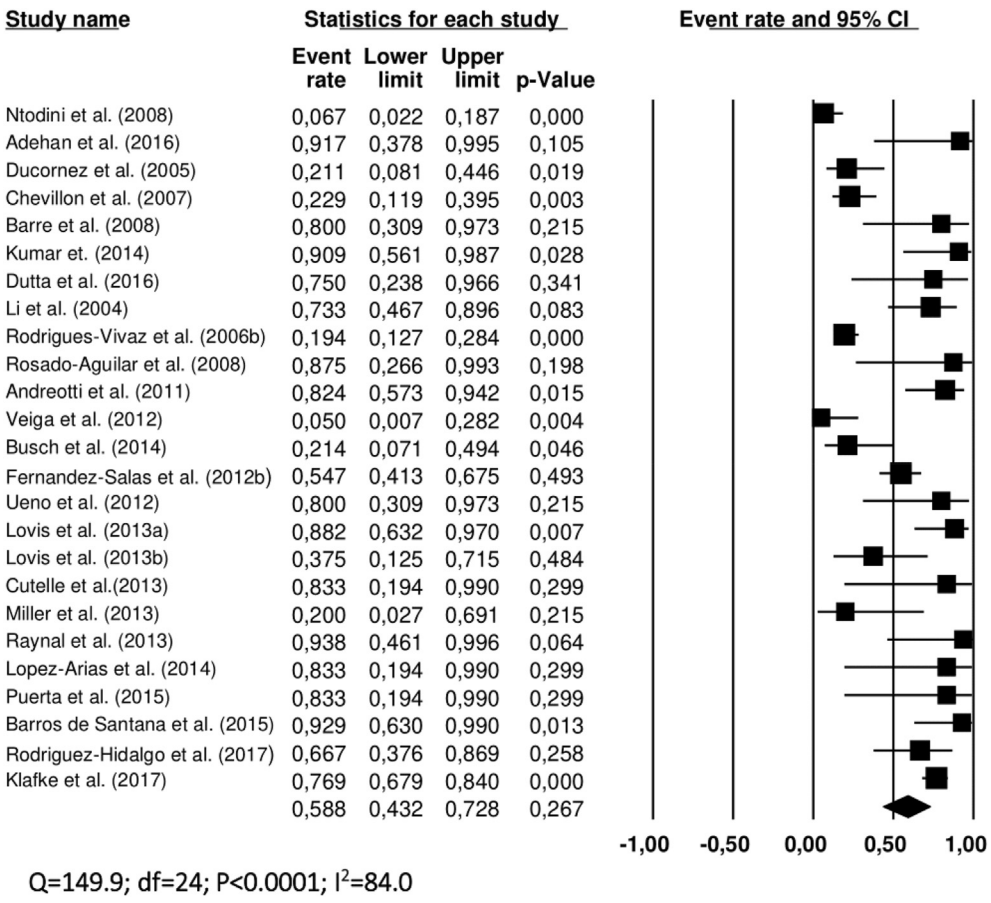

Figure 5. Point and pooled prevalence estimates of resistance development in *R. (B.) microplus* isolates to amitraz.

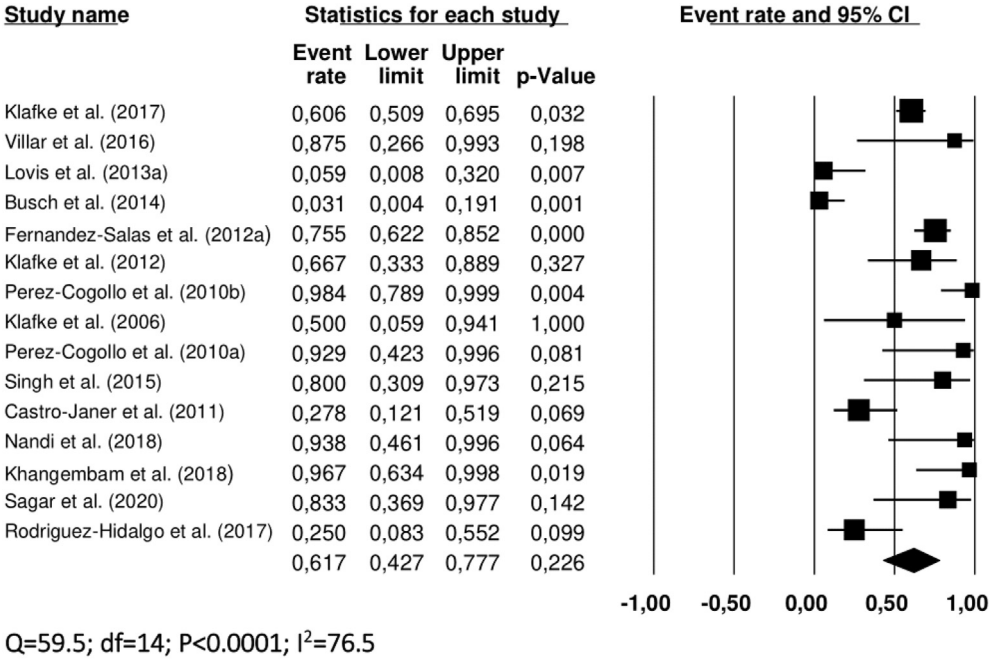

Figure 6. Point and pooled prevalence estimates of resistance development in *R. (B.) microplus* isolates to ivermectin.

are often undertaken and published only when treatment failure has been reported by livestock farmers. Hence, the impact of publication bias was considered minimal, although data were obtained only from published full-text reports written in the English language. Therefore, the findings of the present study could be considered sufficient to justify the need for formulation and adoption of appropriate tick control measures to lessen the impact of acaricide resistance in cattle production.

5. Conclusion

Many populations of tick species, especially *R. (B.) microplus,* have become resistant to majority of acaricide chemicals registered for use against them. As a result, continuous monitoring of the acaricide resistance status of each tick population is necessary to optimally and strategically use acaricides to prevent the proliferation of resistant tick populations, limit the effects of acaricide resistance, and preserve acaricide efficacy. Furthermore, policymakers and veterinary regulatory bodies, especially in tick-endemic countries, need to be acquainted with tick management strategies that could reduce dependency on acaricides.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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