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# *Anaplasma Phagocytophilum*, a Zoonotic Vector-Borne Bacterial Species in Rodents and Its Associated Tick Vector: Systematic Review

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## ABSTRACT

**Background:** The bacterium *Anaplasma phagocytophilum*, the causative agent of tick-borne fever, is alleged to be naturally maintained in a tick-rodent cycle, with human beings involved only as incidental impasse hosts. This study was undertaken to update scientific evidence on the occurrence of *A. phagocyphilum* in rodents and its associated tick species.

**Results:** The systematic review was executed using the PRISMA guidelines to assess and compile the relevant literature. Published journal articles from 1 January 2000 to August 2023 were sourced from three electronic databases, including PubMed, ScienceDirect and Google Scholar, and after evaluation of the articles, ultimately 23 were eligible for this systematic review. Of the eligible studies, 43.5% did not report on the detection of *A. phagocytophilum* in tick species but only in rodents, whilst 26.1% of the studies, reported on negative detection of *A. phagocytophilum* in both rodents and ticks. In terms of rodents, there were 11 genera observed from the eligible studies with *Apodemus* spp. being the most frequently reported host, followed by *Microtus* spp. and *Myodes* spp. *Ixodes* ticks including *I. ricinus* and *I. trianguliceps* were the most frequent tick species investigated as arthropod carriers/vectors in the studies, followed by *Dermacentor* and *Haemaphysalis* tick species.

**Conclusions:** This study has consolidated information from published articles on the role that rodents play as hosts or carriers of *A. phagocytophilum* and the possible role that related tick species play as vectors. Various tick species play a significant role as vectors of *Anaplasma phagocytophilum* and infect a wide array of rodent hosts that may possibly interact with humans

## 1 | Introduction

*Anaplasma phagocytophilum* is a zoonotic obligate intracellular bacterium, a causative agent of tick-borne fever disease affecting mammals (Holden et al. 2005; Urbanová et al. 2022). This bacterium infects the granulocytes, primarily the neutrophils, of rodents, thus resulting in granulocytic anaplasmosis with a substantial economic impact on other mammals, including domestic ruminants and humans (Holden et al. 2005; Urbanová et al. 2022). *A. phagocytophilum* is associated with a variety of tick species that facilitate its spread across different geographic regions (Stuen et al. 2013). As such, its prevalence is frequent during the seasons of tick activity and infestation of several mammalian host species (Stuen et al. 2013). The epidemiological

cycles of *A. phagocytophilum* are complex and involve a wide range of vectors and mammals, with human beings involved only as incidental impasse hosts (Urbanová et al. 2022). This bacterium is frequently detected in rodents, which serve as reservoir hosts, and in their associated tick vectors (Jiang et al. 2020). In the rodent reservoirs, *A. phagocytophilum* infection is transient, lasting one to two months (Kallio et al. 2014).

Studies have elucidated the association of *A. phagocytophilum* with a wide variety of tick species, such as the *Ixodes*, including *Ixodes ricinus*, *Ixodes scapularis*, *Ixodes pacificus* and *Ixodes persulcatus*, as well as other species such as *Amblyomma americanum*, *Dermacentor variabilis* and *Dermacentor andersoni*. (Kolo et al. 2020; Panthawong et al. 2020). A review by Karshima et al. (2022) supported this notion by showing that a number of hard ticks of the aforementioned genera, with the addition of *Haemaphysalis*, *Hyalomma* and *Rhipicephalu,s* are major vectors of *A. phagocytophilum*. These vectors may be found in almost every region globally (Mubashir et al. 2022). Ticks acquire the pathogen during the larval or nymphal stage when feeding on infected vertebrates such as rodent hosts and maintain infection throughout the next life stages (Urbanová et al. 2022). Rodents are important for the development of sub-adult tick stages and have a valuable role in the tick life cycle, serving as main feeding and maintenance hosts for the developmental stages (Szekeres et al. 2015).

Regardless of the important role played by rodents in zoonotic tick-borne infections, less attention is paid to them and their potential for human interaction. Furthermore, less attention was paid to diseases transmitted by rodents regardless of their potential role as a source of human contamination (Selmi et al. 2021). Rodents' natural habitats include woodlands and grasslands in rural and peri-urban landscapes. Rodents play an important role as a reservoir host and final host of many infectious zoonotic organisms (Ramatla et al. 2019). Therefore, they are involved in the natural cycle of various tick-borne bacterial pathogens (Barandika et al. 2007; Obiegala et al. 2019). Most of the rodents are agricultural pests whereby they feed on roots, berries, seeds and other parts of plants. This activity enables them to transmit various zoonotic disease-causing pathogens, including tickborne *A. phagocytophilum* (Eisen and Paddock 2021).

In their systematic review and meta-analysis on the prevalence and distribution of *A. phagocytophilum* in tick vectors, Karshima et al. (2022) indicated that diverse species of wildlife, domestic animals and birds were infected by *A. phagocytophilum*. Since the risk of transmitting pathogens, including *A. phagocytophilum* from ticks to animals and humans exists (Karshima et al. 2022), the emphasis on the importance of investigating the potential role of rodents in the transmission of *A. phagocytophilum* to humans is necessary. Thus, understanding the prevalence and distribution of *A. phagocytophilum* in rodent populations can assist in identifying areas of higher risk for human infection and inform public health interventions. Therefore, the dissemination of rodents and their close contact with humans, together with companion animals, may have an impact on the health status of the latter (Obiegala et al. 2019). Hence, this review aimed to synthesize the research outcomes on *A. phagocyphilum* in rodents and their associated tick species.

## 2 | Materials and Methods

### 2.1 | Study Design

The objective of this review was to consolidate and describe the available evidence regarding the occurrence of *A. phagocyphilum* in rodents and associated tick species. The systematic review was conducted using the recommended method as outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Page et al. 2021; Monyama et al. 2022). The following procedures were followed during the review: (i) articles that might be relevant were classified using database searches, (ii) assessments of the articles' applicability to the review, (iii) assessments of the quality of relevant articles and (iv) data extraction, screening and analysis.

### 2.2 | Review Questions

This review aimed to synthesize the research outcomes on *A. phagocytophilum* in rodents and their associated tick species, published from the 1st of January 2000 until the 1st of August 2023 from four scientific databases. The review question of this systematic review was, 'What is the prevalence of *A. phagocytophilum* in rodents and ticks?'

### 2.3 | Systematic Search Strategy and Selection Criteria of the Journal Articles

The study was carried out in accordance with the methodology endorsed by the PRISMA guidelines (Tawana et al. 2023). The keywords were used to retrieve studies from electronic databases, including PubMed (https://pubmed.ncbi.nlm.nih.gov/ from 11 July 2022 to 16 July 2022), Science Direct (https://www.sciencedirect.com/ 12 July 2022–16 July 2022), Google Scholar (https://scholar.google.com/, 13 October 2022–15 September 2022) and Scopus (https://www.scopus.com/, 22 January 2023–15 August 2023).

The systematic search was accomplished following the combination of free text and wordlist terms in diverse distinctions: '*Anaplasma* spp.' '*Anaplasma phagocytophilum*', *A. phagocytophilum* AND/OR, 'rodents', 'ticks' and 'mice'. Thereafter, titles and abstracts were assessed, and potential articles were reviewed and downloaded for analysis. The reference list from the potentially searched published articles was also screened for articles relating to this review. The following criteria were used to select the final list of articles: (a) duplicate articles were checked and removed from consideration, (b) articles that did not meet the inclusion criteria were also removed, (c) articles that did not fit the aim and scope were not taken into consideration, and (d) articles published before 2000 were also eliminated.

### 2.4 | Criteria for Evaluation and Selection

Records from the electronic databases were initially identified using the title and abstract. The redundant journal article copies and unnecessary records were eliminated. To determine

significant journal articles, all retrieved articles that were relevant based on their titles were further screened based on their abstracts. When the emphasis was not on rodents, *A phagocyphilum* or their associated ticks, the records were typically excluded. The thesis, dissertation and records with unclear methodology were also removed.

### 2.5 | Inclusion Criteria

Studies had to meet the following inclusion criteria:

The search was limited to only journal articles published in the English language and published from January 2000 to 15 August 2023. Only the published journal articles that met the predefined inclusion criteria as follows: reported *A. phagocytophilum* identified in rodents and ticks were included in this systematic review.

### 2.6 | Exclusion Criteria

Journal articles were excluded if they (i) were published only in abstract format, (ii) were not published in English, (ii) were editorials or reviews (iv) were experimental or observational studies, (v) were articles not published between 2000 and 2023 or (iv), the study was conducted on ticks sampled from other vertebrates but not rodents.

### 2.7 | Identifying the Bias Risk Assessment

A total of 23 articles were included and analysed for quality to avoid the risk of bias. Included articles were analysed according to the JBI critical appraisal checklist (JBI Evidence Synthesis Manual) and guidelines in the gradebook and Cochrane handbook for systematic reviews of interventions (Higgins et al. 2022). The risk assessment was conducted by evaluating the following variables: (i) study location, (ii) year of publication, (iii) type of samples from rodents and rodent species and (iv) tick species. (v) prevalence of *A. phagocytophilum* in collected ticks and rodents, (vi) indexed test used for the detection of *A. phagocytophilum* and (vii) specific gene detected. The quality of relevant studies was evaluated by a system of scoring through a modified checklist that was based on the following questions: (a) was the title and abstract of the study relevant? (b) were the methods and data analysis of the study clear and sufficiently covered? (c) does the study give a detailed description of the statistical approach and analysis? (d) was the sample size acceptable? (e) Was the interpretation of the results and discussion taking account of the aim/objectives of the study? (f) Were the rodent and tick samples randomly selected from the population? (g) Were the rodents randomly selected and allocated? (h) Were the study participants sampled in an appropriate manner? The assessment done on every paper was based on these eight questions and scored at $8/8 \times 100\%$ (Table S1). A score above 70% was signified as a high-quality journal article, between 69% and 50% as an average-quality journal article, and below 49% as a low-quality. Thus, no paper was omitted from this review manuscript based on the scores since any score obtained reflects the quality of the study on *A. phagocytophilum* infections in rodents and their associated ticks, but not the quality of this review article. Eligibility, inclusion, quality evaluation and data extraction were all handled by a single reviewer throughout the systematic review process.

### 2.8 | Data Collection and Analysis

The author surnames, the study's year of publication, the country, infested tick (number of ticks), the prevalence of *A. phagocytophilum* detected in ticks, rodent spp., and sample type were among the data extracted from studies that met the eligibility criteria. The extracted data was recorded on a spreadsheet. No further attempts were made to contact the authors of journal articles for additional or unpublished data.

### 2.9 | Countries from Which Published Studies Were Conducted

Articles were originally published in the following countries: China (Cao et al. 2006; Zhan et al. 2010, Zhan et al. 2010; Zhao et al. 2013; Y. J. Yang et al. 2013; Jiang et al. 2020), Slovakia (Blaňarová et al. 2014; Svitálková et al. 2015), Germany (Silaghi et al. 2012; Galfsky et al. 2019), Switzerland (Burri et al. 2011; Burri et al. 2014), Finland (Kallio et al. 2014), France (Chastagner et al. 2016), Italy (Rosso et al. 2017), Korea (Chae et al. 2008), South Africa (Kolo et al. 2020), Hungary (Szekeres et al. 2015), Spain (Barandika et al. 2007), Turkey (Güner et al. 2005), United Kingdom (Bown et al. 2003), the United States (Goodrich et al. 2020) and Canada (Dumas et al. 2022) were included in this systematic review.

## 3 | Results

### 3.1 | Article Selection

A total of 1385 articles were identified during the initial screening. During the database search, 45 additional articles were retrieved, bringing the total to 1430. Following the initial screening of titles/abstracts and duplicates, 1023 distinct articles resulted. When determining if the study was duplicated, the study was evaluated based on the same information it contained in the fields for authors, published year, title, volume and the page numbers of the article. The remaining 23 articles were finally chosen for data extraction and analysis after the articles that did not meet eligibility standards were eliminated (Figure 1).

### 3.2 | Quality Assessment of Studies

With a quality score between 62.5% and 100%, all studies included in this systematic review were deemed to have a low risk of bias (Table S1).

### 3.3 | Article Characteristics

To address the distribution of *A. phagocytophilum*, the study characteristics included the authors of each article and year of publication, the country where the study was conducted,

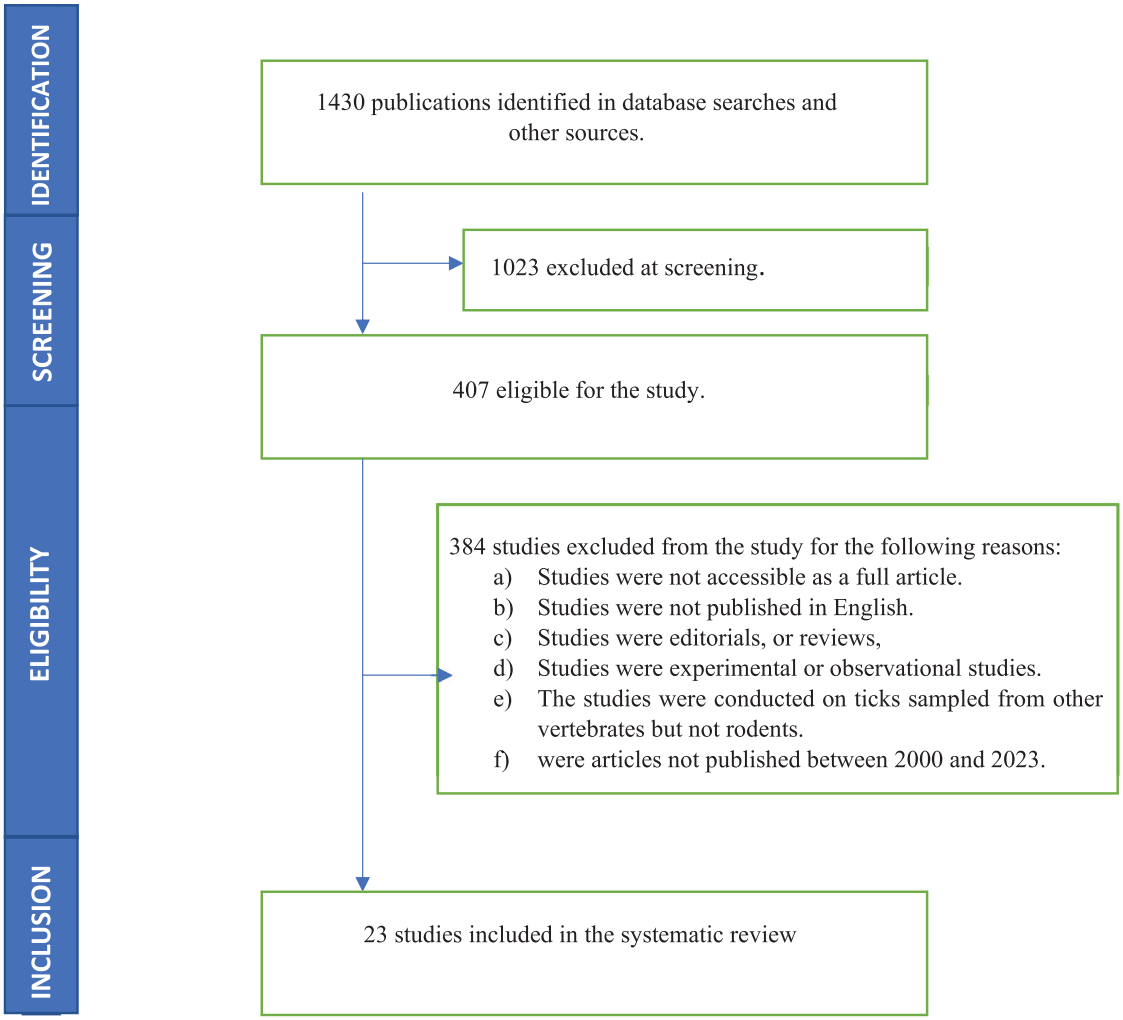


**FIGURE 1** | PRISMA flow diagram showing the process of finding and choosing published articles for the occurrence of *A. phagocyphilum* in rodents and associated tick species.

the identification method of ticks, the total number of rodents collected during sampling, the rodent species, sample type, the diagnostic method, as well as the prevalence of *A. phagocytophilum* (Table 1).

A total of six studies conducted in Switzerland, Canada, Germany, the Unites States and Turkey reported the negative results of *A. phagocytophilum* from all samples collected from the ticks and rodents, as shown in Table 2.

### 3.4 | Distribution of *A. Phagocytophilum*

Of the studies included in this systematic review, ten (10/23; 43.5%) of the eligible studies did not report on the detection of *A. phagocytophilum* in tick species but only in rodents. A total of six (6/23; 26.1%) eligible studies reported negative results on the detection of *A phagocytophilum* in both rodents and ticks (Burri et al. 2011; 2014; Dumas et al. 2022; Galfsky et al. 2019; Goodrich et al. 2020; Güner et al. 2005). The 23 eligible studies were reported in China ($n = 6$), Slovakia ($n = 2$), Germany ($n = 2$), Switzerland ($n = 2$), Finland ($n = 1$), France ($n = 1$), Italy ($n = 1$), Korea ($n = 1$), South Africa ($n = 1$), Southern Hungary ($n = 1$), Spain ($n = 1$), Turkey ($n = 1$), the United Kingdom ($n = 1$), the United States ($n = 1$) and Canada ($n = 1$), as shown in Figure 2.

Overall, 23 studies (Tables 1 and 2) were included and reviewed systematically for the prevalence of *A. phagocytophilum* in rodents and the associated tick vectors. Different diagnostic techniques were employed in the studies for the detection of *A. phagocytophilum*. The most widely employed detection method was the PCR technique 95.7% (22/23). Out of the 96%, only 4.5% (1/22) coupled PCR with another technique, which was the reverse line blot (RLB) hybridization due to a large number of screened rodent tissues. Furthermore, only 54.5% (12/22) employed conventional PCR, 31.8% (7/22) used qPCR and 9.1% (2/22) used nested PCR. All the eligible studies with positive detection of *A. phagocytophilum* used the PCR technique to screen for the presence of *A. phagocytophilum* in rodent tissues, with the spleen being the prime target, followed by the blood as the other frequent tissue used in a few other studies (Table 1). Thus, *A. phagocytophilum* was detected in 73.9% (17/23) of the studies dominated by 52.9% (9/17) of conventional PCR. The negative *A. phagocytophilum* reporting studies include one study that did not use a PCR-based technique as a diagnostic method; instead the enzyme-linked immunosorbent assay (ELISA) technique was employed.

**TABLE 1** | List and characteristics of eligible studies conducted in various countries included in the systematic review with positive detection of *Anaplasma phagocytophilum* by various detection methods from rodents and tick species.

| Country | Infested tick (number of ticks) | Prevalence of *A. phagocytophilum* detected in ticks | Rodent spp./host | Rodents spp. sample type (+ve/samples) | Indexed test | Gene | References |
|---|---|---|---|---|---|---|---|
| Slovakia | *I. ricinus** (2050)<br>*I. trianguliceps** (66) | 10/2050 (0.5%)<br>10/66 (15.0%) | *A. agrarius**<br>*A. flavicollis**<br>*M. glareolus** | Ear (11/669)<br>Spleen (9/407) | qPCR | *msp2**<br>*msp4*<br>*groEL*<br>*16S rRNA** | Blaňarová et al. (2014) |
| | *I. ricinus** (963) | 11/963 (1.1%) | *A. flavicollis**<br>*M. glareolus**<br>*M. arvalis*<br>*A. sylvaticus*<br>*M. minutus*<br>*M. subterraneus* | skin<br>Spleen<br>% or number? | qPCR | *msp2** | Svitálková et al. (2015) |
| Spain | — | — | *A. sylvaticus*<br>*A. flavicollis**<br>*Mus domesticus*<br>*C. glareolus* | Ear<br>Urinary bladder<br>Spleen<br>Liver<br>Kidney<br>Lung<br>Brain<br>1/281 (0.36%) | M-PCR<br>RLB hybridization | *msp2** | Barandika et al. (2007) |
| United Kingdom | *I. trianguliceps** (617) | 111/617 (18.0%) | *A. sylvaticus*<br>*C. glareolus* | Blood (7/902 ~1.8%) | PCR | — | Bown et al. (2003) |
| China | *I. persulcatus* (100)<br>*D. silvarum* (286) | 4/100 (4.0%)<br>2/286 (0.7%) | *A. peninsulae*<br>*A. agrarius**<br>*C. rufocanus*<br>*Mus musculus (-ve)*<br>*R norvegicus (-ve)* | Spleen (9/102 ~8.8%) | PCR | *16S rRNA** | Cao et al. (2006) |
| | *H. qinghaiensis* (1231) | 74/1231 (6.0%) | *A. agrarius** | Spleen (2/12 ~16.7 %) | PCR | *16S rRNA** | Y. J Yang et al. (2013) |
| | — | — | *A. agrarius**<br>*A. peninsulae*<br>*R. norvegicus*<br>*C. migratorius*<br>*T. triton* | Spleen (23/159 ~14.5%) | qPCR | *16S rRNA**<br>*mps2** | Zhan et al. (2010) |
| | — | — | *R. opimus* | Blood (58/490 ~ 11.8%) | PCR | 16*S rRNA** | Jiang et al. (2020) |

(Continues)

**TABLE 1** | (Continued)

| Country | Infested tick (number of ticks) | Prevalence of *A. phagocytophilum* detected in ticks | Rodent spp./host | Rodents spp. sample type (+ve/samples) | Indexed test | Gene | References |
|---|---|---|---|---|---|---|---|
| | — | — | *R. norvegicus*<br>*A. agrarius** | Spleen (33) | PCR | *16S rRNA**<br>*mps4*<br>*gltA* | Zhao et al. (2013) |
| | — | — | *R. norvegicus*<br>*C. migratorius*<br>*A. agrarius**<br>*A. peninsulae*<br>*T. triton* | Tissues (5/9 ~ 55.6%) | qPCR | *msp2**<br>*16S rRNA** | Zhan et al. (2010) |
| Korea | *H. longicornis* (570)<br>*H. flava* (306)<br>*I. nipponensis* (742) | 6/570 (1.1%)<br>0/306 (0.0%)<br>10/742 (1.4%) | *A. agrarius**<br>*R. norvegicus*<br>*T. triton*<br>*Mus musculus*<br>*Myodes regulus* | Spleen (20/369 ~ 5.4%) | PCR | *16S rRNA** | Chae et al. (2008) |
| France | — | — | *A. sylvaticus*,<br>*A. flavicollis**<br>*M. glareolus** | Blood<br>Spleen<br>(110/1163) 9.5% | qPCR | *msp2** | Chastagner et al. (2016) |
| Finland | — | — | *M. glareolus** | Blood (33/151) 21.0% | Nested PCR | 16*S rRNA**<br>*msp*4 | Kallio et al. (2014) |
| South Africa | — | — | Rodents spp. | Blood (166/282) 59.0% | PCR | *msp2**<br>*16S rRNA**<br>*gltA*<br>*msp4*<br>*alnkA* | Kolo et al. (2020) |
| Italy | *I. ricinus** (-)<br>*I. triaguliceps** (11) | — | *A. flavicollis**<br>*M. glareolus**<br>*A. sylvaticus*<br>*M. multiplex* | Ear<br>Biopsy<br>Larvae<br>Nymphs<br>52/964 (5.4%) | PCR | *16S rRNA**<br>*GroEL*<br>*Msp4* | Rosso et al. (2017) |
| Germany | *I. ricinus** (782)<br>*D. reticulatus** (814) | 79/782 (10.1%)<br>0/814 (0.0%) | *A. flavicollis**<br>*M. glareolus**<br>*A. agrarius** | Tissue | PCR | *16S rRNA** | Silaghi et al. (2012) |
| Southern Hungary | *I. ricinus** (75)<br>*D. reticulatus* (64)<br>*H. concinna* (80)<br>*I. acuminatus* (56)<br>*D. marginnatus* (68) | 2/75 (2.6%)<br>0/64 (0.0%)<br>0/80 (0.0)<br>0/56 (0.0%)<br>0/68 (0.0%) | *A. flavicollis**<br>*A. agrarius**<br>*M. glareolus**<br>*M. arvalis*<br>*M. minutus*<br>*Mus musculus* | Skin–23/348 (6.6%)<br>Spleen–9/177 (5.1%) | M-PCR | *groEL*<br>*msp2** | Szekeres et al. (2015) |

*denotes the most frequent variable type, that is, gene, tick or rodent spp. among the studies.

**TABLE 2** | List and characteristics of eligible studies conducted in various countries included in the systematic review with negative detection of *Anaplasma phagocytophilum* by various detection methods from rodents and tick species.

| Country | Infested tick (Number of ticks) | Prevalence of *A. phagocytophilum* detected in ticks | Rodent spp./host | Rodents spp. sample type (+ve/samples) | Indexed test | Gene | References |
|---|---|---|---|---|---|---|---|
| Switzerland | *I. ricinus** (465)<br>*I. trianguliceps** (14) | 0/465 (0.0%)<br>0/14 (0.0%) | *A. sylvaticus*<br>*M. glareolus**<br>*Apodemus spp.* | — | PCR | — | Burri et al. (2011) |
| | *I. ricinus** (103) | 0/103 (0.0%) | *A. flavicollis**<br>*M. glareolus**<br>*Apodemus spp.*<br>*A. sylvaticus* | Blood | Nested PCR | — | Burri et al. (2014) |
| Canada | *I. scapularis* (1) | 0/1 (0.0%) | *P. leucopus*<br>*M. gapperi* | — | qPCR | *msp2** | Dumas et al. (2022) |
| Germany | *I. ricinus** (1711)<br>*D. reticulatus* (122) | 0/1711 (0.0%)<br>0/122 (0.0%) | *A. agrarius**<br>*A. flavicollis**<br>*A. terrestris*<br>*M. glareolus** | — | PCR | *msp2** | Galfsky et al. (2019) |
| USA | — | — | *N. micropus*<br>*N. albigula*<br>*D. ordii* | Blood | M-qPCR | *msp4* | Goodrich et al. (2020) |
| Turkey | — | — | *A. flavicollis**<br>*A. sylvaticus*,<br>*M. epiroticus*<br>*Mus macedonicus*, | Blood | ELISA | — | Güner et al. (2005) |

*denotes the most frequent variable type, that is, gene, tick or rodent spp. among the studies.

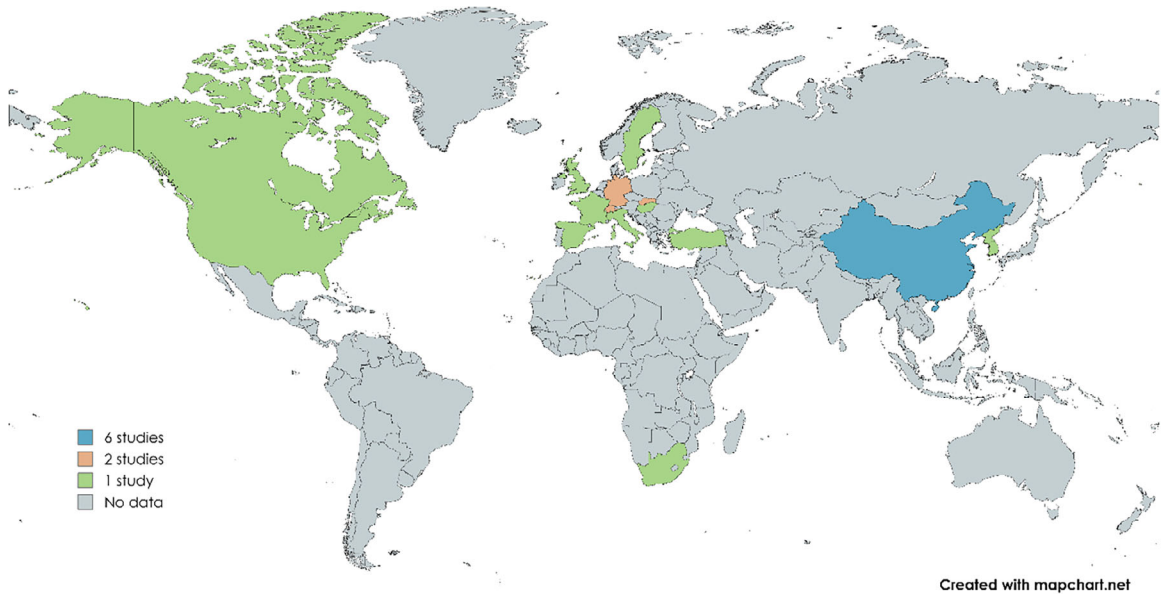


**FIGURE 2** | World map showing a number of articles from different countries that reported the *A. phagocytophilum* in rodents or ticks (https://www.mapchart.net/world.html (accessed on 16 March 2024).

The *Ixodes* ticks, including *I. ricinus* and *I. trianguliceps* were the most frequent ticks observed in the studies, followed by *Dermacentor* and *Haemaphysalis* tick species. In terms of rodents, there were 11 genera observed from the eligible studies, with *Apodemus* spp. being the most frequently screened rodent host, followed by *Microtus* spp. and *Myodes* spp. (Table 1). Additionally, there was an observation in studies where *Apodemus agrarius* and *A. flavicollis* were captured; there was a constant occurrence of both *Ixodes ricinus* and *I. trianguliceps* tick species identified.

## 4 | Discussion

*A. phagocytophilum* is the most important tick-borne bacteria of veterinary and public health significance in the family Anaplasmataceae (de La Fuente et al. 2016). This study undertook a systematic review to assess and compile consolidated data from relevant articles published on *A. phagocytophilum* in rodents and associated tick species. Since *A. phagocytophilum* is genetically diverse and has a broad host range, this bacterium has been detected in several tick and rodent species (Chastagner et al. 2016; Burri et al. 2014). Thus, the data reviewed in this study revealed that *A. phagocytophilum* infections have been detected from various rodent hosts and the associated ticks from different sites throughout the globe. It has been observed that 26.1% of studies that investigated *A. phagocytophilum* infection in both rodent and tick species showed negative results, with 73.9% of studies generating positive results. The absence of *A. phagocytophilum* observed in these studies could be due to the low number of examined hosts in each site (Burri et al. 2011).

The bacterium *A. phagocytophilum* has been detected in the yellow-necked mouse (*Apodemus flavicollis*) and field voles (*Microtus agrestis*) in European countries (Stuen et al. 2013; Kolo et al. 2020), while in the United States, the white-footed mouse (*Peromyscus leucopus*) is considered the primary and competent reservoir host of this pathogenic bacterium (Kolo et al. 2020). In England, the most common rodents associated with tick-borne diseases are wood mice (*A. sylvaticus*), bank voles (*Myodes glareolus*) and yellow-necked mice (*A. flavicollis*) (Cull et al. 2017). In Jilin Province, China, *A. phagocytophilum* was detected in black-striped field mice (*A. agrarius*) and great long-tailed hamsters (*T. triton*) (Zhan et al. 2010).

The bacterium *A. phagocytophilum* is well documented to be associated with *Ixodes* ticks that may act as vectors; however, the agent has also been reported in *Dermacentor* ticks, including *D. reticulates, D. silvarum* and *D. variabilis*. Data reviewed in this study revealed that *A. phagocytophilum* has been detected from other tick species such as *H. longicornis* and *H. qinghaiensis*, though the detection rate in this species as compared to *Ixodes* tick species is minimal. This is in accordance with the review by Karshima et al. (2022) where they observed the highest infection rate in *Ixodes* ticks. This is a further indication that numerous tick species may maintain or be involved in the transmission of *A. phagocytophilum*. This highlights the need for further investigations into the roles of these non-*Ixodes* ticks in the epidemiology of *A. phagocytophilum* (Karshima et al. 2022; J. Yang et al. 2015). The non-*Ixodes* ticks, including the *Dermacentor* and *Haemaphysalis* genera that are reported in this systematic review, mostly feed on a variety of hosts, including humans, which indicates potential transmission of pathogens, including *A. phagocytophilum* across different species (Ben and Lozynskyi 2019; Dykstra et al. 2020; Zhang et al. 2024). Thus, the presence of *A. phagocytophilum* in these non-*Ixodes* ticks highlights the complexity of tick-borne disease ecology. This suggests a need for comprehensive surveillance and control measures to be put in place to curb the spread of pathogens, including *A. phagocytophilum* (Eisen and Paddock 2021). Also, this underscores the need for public awareness about the risks of tick-borne diseases, especially in areas with high rodent-tick-human interactions (Eisen and Paddock 2021).

Though some species of ticks are strongly tied to specific groups of vertebrates, rodents are important hosts in the ecology of tick-

borne pathogens, including *A. phagocytophilum* as they support both nymphal and larval stages (Cull et al. 2017; Estrada-Peña et al. 2015). Notably, the infestation of small mammals, including rodents, with infected nymphs is sufficient to transmit pathogens to the host in order for a feeding larva to acquire the infectious agent (Cull et al. 2017). The *A. phagocytophilum* first infects the midgut cells of ticks before developing in the salivary glands and spreading to hosts that are vulnerable to tick feeding, where the pathogen preferentially infects neutrophils and granulocytic cells (de La Fuente et al. 2016).

The presence of small mammal hosts and their contribution to supporting different tick species can vary considerably across countries (Cull et al. 2017). The overall distribution frequency of genera of rodents in this review was identified as *Apodemus, Arvicola, Crocidura, Diporodyms, Microtus, Myodes, Mus, Neotoma, Clethrionomys, Crseomys, Rattus, Coregonus, Tscherkia, Microryzomys, Peromyscus* and *Rhombomys*. This illustrates the correlation between the diversity and varying distribution of rodents across the globe, which are important reservoirs for numerous zoonotic diseases, including *A. phagocytophilum* (Chen et al. 2022). In this review, *A. agrarius, A. flavicollis* and *M. glareolus* were the most often occurring varied rodent species. *Myodes glareolus* is thought to be a superior reservoir for a number of tick-borne infections, despite the fact that tick infestation rates are typically reported to be higher in *Apodemus* spp. than in *M. glareolus* (Kurtenbach et al. 1995; Talleklint and Jaenson 1997).

A significant variation was noted in the number of studies conducted on *A. phagocytophilum* harboured by rodents and their associated ticks per continent. Thus, Europe had the highest number of eligible studies, followed by Asia, North America and Africa, which is the continent with the fewest studies conducted. This is due to the fact that surveillance reports on *A. phagocytophilum* infections in tick vectors are on the increase worldwide (Karshima et al. 2022). This is an indication that an excessive rodent population may lead to an increasing number of ticks, which have a higher chance of biting humans and transmitting disease-causing pathogens (Krawczyk et al. 2020. Since rodents can amplify tick-borne diseases by increasing the density of infected ticks, this raises the risk of human infection mostly in the regions with high interaction among rodents, ticks and humans (Krawczyk et al. 2020). Thus, effective rodent control measures can minimize the overall tick population and the risk of disease transmission to the public (Krawczyk et al. 2020; Akhtar et al. 2023).

Molecular techniques appear to be much more utilized to identify *A. phagocytophilum* than culture or serological tests. PCR tests have been crucial in the laboratory identification of HGA, a tick-borne infection caused by the bacterium *A. phagocytophilum* in clinical and environmental specimens due to their rapidity and relative ease of performance (J. Yang et al. 2016). Thus, this review noted that, of the diagnostic procedures utilized in primary studies, 95.7% used PCR techniques, which revealed significantly higher detection of *A. phagocytophilum* than other employed diagnostic assays. This suggests that PCR amplification is one of the most reliable and cost-effective techniques for the detection of *A. phagocytophilum* molecular diagnostic assays.

The result shows that *I. ricinus* and *I. trianguliceps* were the most frequent tick species observed as compared to other tick species. The *I. trianguliceps* has only been well studied in a few regions of Europe (Bown et al. 2009, 2003) and in many small mammal studies this species may be overlooked in favour of studying *I. ricinus*, which is more abundant and more important in terms of public and veterinary health. The *I. ricinus* is an indigenous hard tick species with a wide geographical distribution. It is widely distributed in the European regions and North Africa. It is reported that *I. ricinus* shows a low degree of host specificity, considering that it has been proven to be associated with more than 300 terrestrial vertebrate species. It is also reported to be attracted to rodent odours (van Duijvendijk et al. 2017). Hence the frequent occurrence in this study. It has been reported that larval and nymphal stages of *I. ricinus* may be able to feed more successfully on mice than on voles (Talleklint and Jaenson 1997), and this may be related to the development of acquired resistance to feeding. In this review, *I. trianguliceps* and *I. ricinus* were the most often occurring varied tick species. The role of *I. trianguliceps* in circulating tick-borne pathogens among hosts has gained increasing attention. For example, the transmission of certain *A. phagocytophilum* and *Babesia microti* strains has been shown to depend on *I. trianguliceps* rather than the coexisting *I. ricinus* (Bown et al. 2008). The incidence of *A. phagocytophilum* infection in host species rose with tick burden throughout all stages of the *I. ricinus* life cycle (Fabri et al. 2022). Thus, the chance of a host getting infected with *A. phagocytophilum* likely increases when it feeds on more ticks and again if a host is infected with *A. phagocytophilum*, likely feeds on more ticks that could become infected (Fabri et al. 2022).

## 5 | Conclusion

This study increased our understanding of the host/carrier role that rodents play in the spread of *A. phagocytophilum* and the possible role that related tick species play as potential vectors. Most of the rodents included in the studies are agricultural pests that feed on roots, berries, seeds and other parts of plants. This activity enables them to distribute various zoonotic disease-causing agents, including *A. phagocytophilum*. The results of this review underscore the significance of developing and successfully implementing a rodent and tick management strategy globally. Thus, several measures should be taken to minimize the likelihood of becoming infected with these zoonotic pathogens from rodents and their associated tick species. This systematic review only focused on studies that were published in English and potentially excluded research in other languages. This can lead to limitations in the understanding of the global distribution of rodents, ticks and *A. phagocytophilum* they harbour.

### Author Contributions

**Maropeng C Monyama:** conceptualization, methodology, validation, investigation, formal analysis, writing – review and editing, writing – original draft. **Tsepo Ramatla:** methodology, validation, writing – review and editing, formal analysis. **Bradly Khosa:** writing – review and editing, formal analysis, resources, methodology. **Tshepo Mafokwane:** writing – review and editing, validation. **Oriel Thekisoe:** conceptualization, writing – review and editing, formal analysis.

### Ethics Statement

The authors have nothing to report.

### Conflicts of Interest

The authors declare no conflicts of interest.

### Data Availability Statement

The datasets generated and analysed will be available on request to the corresponding author.

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**Supporting Information**

Additional supporting information can be found online in the Supporting Information section.