The prevalence of *Angiostrongylus cantonensis* in rodent hosts in China and several Asian countries: a systematic review and meta-analysis

Huifang Bai[a,1*], Huiyuan Bai[b,1], Fei Bai[c,1], Yizhen Cao[a], Yunqiu Chen[a]

a Department of Pathogenic Biology, Medical College, Ji Nan University, Guangzhou 510632, PR China

b State Key Laboratory of Bioelectronics, School of Biological Science and Medical Engineering, Southeast University, Nanjing 210096, PR China

c College of Plant Science and Technology, Huazhong Agricultural University, Wuhan 430070, Hubei Province, PR China

[*] Corresponding author

E-mail address: bhfbhf92@sina.com

[1] These authors contribute equally to this work.

Abstract

Introduction

Angiostrogylus cantonensis (*A.cantonensis*) is a zoonotic parasitic nematode, with a worldwide distribution, causing eosinophilic meningitis or meningoencephalitis in human. Human infection with *A.cantonensis* typically occur from intentional or unintentional ingestion of infected intermediate or paratenic hosts, sometimes due to contaminated produce. Although the biology of *A.cantonensis* is relatively well known, little is understood about the transmission level in different zoogeographical regions, especially in Asia. Here, to evaluate the prevalence of *A.cantonensis* in

rodent hosts in China and several Asian countries, we conducted a systematic review registered with PROSPERO (CRD42020161665).

Methods

Records were selected systematically from 7 database (Medline via to Pubmed, Web of science, Scopus, Google Scholar, CNKI, Wangfang, CBM). Forest plots and random-effects model were used to display pooled estimates. The Freeman-Tukey double arcsine transformation of R software was used to conduct meta-analysis and statistical significance was set at 0.05.

Results

A total of 67 studies met the inclusion criteria and were included in the systematic review and meta-analysis. The pooled prevalence estimates of *A.cantonensis* infection in rodents was 0.1003 (95%CI: 0.0765, 0.1268). There was significant heterogeneity in reported outcomes ($p<0.0001$). And we considered that there was no publication bias in the included studies.

Conclusion

The *A.cantonensis* infection rate among rodent hosts were still high in Asia, particularly in China, especially in *Rattus norvegicus*, and thus comprehensive measures should be taken for rodent hosts control to avoid an angiostrongyliasis outbreak. Due to the wide distribution and movement of rodent hosts, people in all regions of China, even in other Asia area live at risk of an infection. Hence, the development of more reliable diagnostic tests will be key for an effective identification of cases as well as improved patient care. Consequently, further studies

are required to updated strategies for controlling *A.cantonensis* infection among human population.

Author summary

Angiostrongylus cantonensis (*A.cantonensis*) is a zoonotic parasitic nematode, with a worldwide distribution, causing eosinophilic meningitis or meningoencephalitis in human. Human infection with *A.cantonensis* typically occur from intentional or unintentional ingestion of infected intermediate or paratenic hosts, sometimes due to contaminated produce. Information about angiostrongyliasis burden, including its prevalence and incidence and geographic distribution in Asia, which is necessary to guide in planning appropriate control measures. In this study, we performed a systematic review and meta-analysis of published studies in China and several Asian countries on *A.cantonensis.* Our approach allowed evidence-based approximation to the estimations of the burden of *A.cantonensis* infection, for different rodent hosts groups, geographic regions, publication years and so on. At the same time, our review showed the *A.cantonensis* infection rate among rodent hosts were still high in Asia, particularly in China, especially in *Rattus norvegicus*. Finally, much bigger and longer-term studies are required to updated strategies for controlling *A.cantonensis* infection among human population.

Background

Angiostrongylus cantonensis (*A.cantonensis*) is a zoonotic parasitic nematode, with a worldwide distribution, causing eosinophilic meningitis or meningoencephalitis in human. Human infection with *A.cantonensis* typically occur from intentional or

67 unintentional ingestion of infected intermediate or paratenic hosts, sometimes due to
68 contaminated produce.
69 Traditionally, with the wider domain of climate and health, the neglected tropical
70 diseases (NTDs), a collection of infectious diseases affected hundreds of millions of
71 individuals living in tropical and subtropical countries. Recently, such dramatic
72 habitat changes are linked to accelerated biodiversity loss, which has been linked to
73 major changes in the epidemiology of human diseases: increased disease risks and the
74 emergence of novel pathogens resulting from increased contacts among wildlife,
75 domesticated animals, and humans[1-3]. In particularly, angiostrongyliasis, as a kind
76 of NTDs, was found in the Pacific Islands, Southeast Asia, parts of South and Central
77 America and the Caribbean, even in European countries[4-6]. Recently, although
78 researchers gradually pay more attention to investment towards reducing the burden
79 of NTDs, they still collectively contribute to productively loss, illness and suffering in
80 many countries[7,8]. Recent estimates of their overall burden suggest NTDs kill over
81 350,000 people per annum and cause the loss of between 27 and 56 million
82 disability-adjusted life years[9]. To date, more than 2000 cases of eosinophilic
83 meningitis have been recorded in China, even 100 cases in Taiwan and most human
84 cases of angiostrongyliasis (~1300 cases) have been reported in Thailand[5,10], where
85 between 0.3 and 2 people per 100,000 become infected annually[11,12]. These
86 findings indicate that the extensive distribution of *A.cantonensis* in global world is
87 high, human will be at high risk of *A.cantonensis* infection.
88 In recent decades, more than 20 species of feral rodents have been categorized as

89 pests in tropical and subtropical countries, and these species cause tremendous losses
90 and damages to crops and food stocks[13]. Feral rodents are known to transmit
91 diseases and act as reservoir hosts to many zoonotic parasites that pose health risks to
92 humans, including *A.cantonensis*, hantaviruses, *Leptospira spp.*, *Bartonella spp.*,
93 *Trypanosoma spp.*, and *Babesia spp.*[14-16]. For *A.cantonensis,* at least 17 rodent
94 species may behave as definitive hosts, capable of passing first stage (L1) larvae in
95 their feces. Simultaneously, snails and slugs (intermediate hosts) ingest these
96 larvae, which mature into the third stage (L3) larvae (infective form) that are passed
97 on to the definitive hosts again when the definitive hosts consume infected
98 intermediate hosts. Then, the worms travel to brain, especially in the subarachnoid
99 space, elicits an intense eosinophilic inflammation and causes acute eosinophilic
100 meningitis. Finally, it will become a molluscs-rodents cycle to lead infectious.
101 Humans become the incidental hosts by consuming the infected intermediate or
102 paratenic hosts (or ingestion of snail slime)[17]. Importantly, the development of
103 control methods against zoonotic parasites depends on knowledge of their life cycles
104 and transmission patterns in different zoogeographical regions. Therefore, it is
105 essential to survey the relationship between parasites and rodents in order to identify
106 the sources of zoonotic infections[18].
107 Surprisingly, despite rodents being the dominant vertebrate species in many of these
108 altered tropical systems and the key hosts for numerous zoonotic microparasites
109 (viruses, bacteria, and protists), consistent patterns between habitat fragmentation and
110 environment change with the epidemiology of multiple parasite diseases have yet to

111 be determined, and studies that address the context of pathogen circulation are
112 lacking. Indeed, simultaneous to the technical and targeted approaches being,
113 recommended by WHO are much wider attempts at sustainable development, most
114 visible through the lens of the sustainable development goals[19]. Meanwhile, there
115 are little diagnostic methods and effective treatment methods. Furthermore, we need
116 do more research to solve this challenge. Here, in this study, we aim to identify the
117 prevalence of *A.cantonensis* in rodent hosts in China and several Asian countries,
118 provided essential recommendations for the researchers and policy makers.

119 Materials and methods

120 The protocol for this systematic review was defined in advance and registered with
121 PROSPERO (CRD42020161665). This study was conducted in accordance with the
122 PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and
123 Meta-analysis) for systematic review and meta-analysis. The PRISMA checklist
124 (Table S1) was used to ensure inclusion of relevant information in the analysis.

125 Literature search

126 To evaluate the prevalence of *A.cantonensis* in rodent hosts in China and several
127 Asian countries, we carried out a systematic review of the literature (full-text)
128 published online in the English and Chinese between May 1946 and December 2019.
129 Records were selected systematically from 7 database (Medline via to Pubmed, Web
130 of science, Scopus, Google Scholar, CNKI, Wangfang, CBM). This range of years
131 was important to study the prevalence since the first study was reported. The modified
132 searches were performed by various combinations of the following terms using

133 Boolean operator “AND” and “OR”: (rat lungworm OR *Angiostrongylus cantonensis*
134 OR *Angiostrongyliasis OR Angiostrongylidae*) AND (prevalence OR distribution OR
135 epidemic OR incidence OR frequency OR occurrence OR detection OR identification
136 OR characterization OR investigation OR survey OR rate) AND Asia. The reference
137 lists of selected articles also were screened manually and appropriate articles were
138 included. Full text articles were downloaded or obtained through library
139 resources. .

140 **Study selection**

141 All selected articles had to meet the following inclusion criteria: (i) a cross-sectional
142 study or descriptive study; (ii) the study published between May 1946 and December
143 2019; (iii) the language was limited in Chinese or English; (iv) full-text article; (v)
144 infection cases in Asia, provided geographical location; (vi) reported as animal level
145 prevalence data; (vii) exact total numbers and positive cases numbers; (viii) rodent
146 hosts numbers higer than fifty.

147 Investigations without these criteria were excluded. Also, if the same study data were
148 published in both English and Chinese sources, the articles with less detailed
149 information would be excluded from this study. When any authors found articles
150 different to judge, the first author was consulted and eventual differences discussed to
151 reach a consensus decision on whether to include or exclude the article.

152 **Quality assessment**

153 The included articles were evaluated using a 10-items quality appraisal checklist (File
154 S1). An item would be scored ‘0’ if it was answered ‘no data available’ or ‘unclear’;

155 if it was answered 'yes', then the item scored '1'. Article quality was assessed as
156 follows: low quality = 0–3; moderate quality = 4–7; high quality = 8–10.

157 **Data extraction**

158 For the data extraction, the two independent assessors applied the inclusion criteria
159 selected the articles and extracted the data. Discrepancies were resolved by consensus.
160 The detailed characteristics of each study were extracted using a pre-designed
161 data-collection excel form. Information was collected as followings: first author, year
162 of publication, location, geographical region, sample size, number of positive cases,
163 diagnostic methods, types of rodent hosts, quality score of each study.

164 **Statistical analysis**

165 The statistical software used in the analysis was R software version (3.6.3). Estimated
166 pooled prevalence and 95% confidence intervals (CI) were calculated with the
167 Freeman-Tukey double arcsine transformation. Heterogeneity testing was performed
168 using the I^2 and Cochran' Q statistic methods. A significant value ($p<0.05$) in the
169 analysis suggested a real effect difference. The I^2 values of 25%, 50% and 75% were
170 considered as low, moderate and high heterogeneity, respectively. The risk of study
171 bias was assessed using the funnel plots, and the Egger's regression test. Furthermore,
172 subgroup analysis were done if the heterogeneity were overlapping moderate I^2. Four
173 potential sources of heterogeneity were examined: country, animal species,
174 publication year, quality score. The Q and I^2 statistics values were calculated for each
175 subgroup to determine the effective factors on the prevalence *A.cantonensis* and
176 heterogeneity about all the included studies.

Results

Study search and included studies

A total of 2103 articles were screened in the initial and 67 were obtained for the final analysis. Fig 1 showed our systematic workflow for identifying, screening and including studies in this study. Hence, 59 articles from China, 1 from Japan, 4 from Thailand, 1 from India and 2 from Philippines. The complete list of included articles with the extracted data can be found in the Fig 2 and Supporting information (File S2). A total of 45196 rodents were dissected and 4954 were identified with *A.cantonensis* infection. The detailed characteristics of each study were provided in Table 1.

Fig 1. Flow-chart of systematic review of *A.cantonensis*

Fig 2. Map of the geographical distribution in Asian countries of the surveys

Table 1. Characterizatics of the eligible studies

Study	Location	Method	Number	Positive rate	quality score
(Zhang et al. 2017)	Fujian	NE	5266(541)	10.30%	7
(Huang et al. 2017)	Guangdong, Shenzhen	NE	238(22)	9.24%	8
(Hu et al. 2017)	Guangdong, Nan'ao island	NE, PCR	110(32)	29.10%	8
(Lin et al. 2016)	Fujian, Zhangzhou	NE	1551(142)	9.20%	9
(Eamsobhana et al. 2016)	24 provinces in Thailand	NE	669(46)	6.90%	7
(Ribas et al. 2016)	Udon Thani province	Staining	98(3)	3.10%	5
(Yang et al. 2015)	Yunnan	ELISA	304(0)	0.00%	6
(Tujan et al. 2016)	Nueva Ecija, Philippines	PCR	209(64)	29%	8
(Zhang et al. 2014)	Yunnan	NE	174（0）	0.00%	7
(Castillo et al. 2018)	Nueva Ecija, Philippines	NE	600(600)	100%	9
(Liang et al. 2014)	Guangdong, Shenzhen	NE	195(21)	10.80%	6
(Hu et al. 2018)	Guangdong, Nan'ao island	NE, PCR	110(32)	29.10%	8
(Xie et al. 2013)	Guangxi, Beihai	NE	58(1)	1.70%	5
(Huang et al. 2019)	Guangdong, Shenzhen	NE, ELISA	238(22)	9.20%	8

(Yang et al. 2012)	Guangdong, Guangzhou	NA	432(23)	5.30%	8
(Chen et al. 2011)	Guangdong	NE	1391(132)	9.50%	9
(Huang et al. 2011)	Guangdong, Shenzhen	NE	331(50)	15.10%	7
(Hu et al. 2011)	Hainan island	NA	118(13)	11.00%	6
(Vitta et al. 2011)	Phitsanulok province	NE	62(1)	1.60%	7
(Zeng et al. 2011)	Jangxi	Microscopy	502(12)	2.40%	4
(Zhu et al. 2010)	Fujian, nanping	NE	291(42)	14.40%	7
(Li et al. 2010)	Fujian	NE	4890(434)	8.90%	6
(Fu et al. 2010)	Guangxi	NE	149(5)	3.40%	5
(Deng et al. 2010)	Guangdong	NE	491(56)	11.40%	7
(Zhang et al. 2009)	Guangdong, yangchun	NE	192(11)	5.70%	4
(Renapurkar et al. 1982)	Bombay	NA	937(12)	1.30%	6
(Lan et al. 2010)	Zhejiang, Lishui	NE	1937(70)	3.61%	6
(Zhang et al. 2008)	Guangdong, Shenzhen	NE	248(22)	8.90%	7
(Li et al. 2008)	Yunnan	NE	124(4)	3.20%	4
(Ye et al. 2008)	Fujian, Fuzhou	NE	1964(269)	13.70%	6
(Wang et al. 2008)	Fujian, Ximen	NE	957(64)	6.70%	4
(Zeng et al. 2007)	Jiangxi	Microscopy	187(3)	1.60%	3
(Luo et al. 2005)	Fujian, Fuzhou	NE	1487(246)	16.50%	9
(Shen et al. 2004)	Guangdong, Zhaoqing	NE	221(12)	5.40%	8
(Yang et al. 2003)	Fujian	NE	625(52)	8.30%	6
Chen et al. 2003)	Fujian, Changle	Microscopy	112(44)	39.30%	3
Pan et al. 2002)	Zhejiang, Wenzhou	NE	87(17)	19.50%	4
(Yang et al. 2001)	Fujian	NE	579(40)	6.90%	5
(Liang et al. 2000)	Zhejiang, Wenzhou	NE	2069(316)	15.30%	9
(Zhang et al. 1999)	Fujiang, Fuzhou	NE	113(18)	19.50%	7
(Tung et al. 2013)	Taiwan, Taichung	NE	51(8)	15.70%	5
(Tokiwa et al. 2013)	Ogasawara Archipelago, Japan	NE	136(46)	33.80%	5
(Pipitgool et al. 1997)	Ubon Ratchathani	NE	272(3)	1.10%	7
(Lv et al. 2009)	China	NE	711(32)	4.50%	6
(Zhang et al. 2008)	Guangdong, Jiangmen	NE	229(10)	4.40%	8
(Deng et al. 2012)	Guangdong	NA	491(56)	11.40%	7
(Barratt et al. 2016)	Guangdong, guangzhou	NA	432(23)	5.30%	7
(Duan et al. 2008)	Hunan	NE	60(1)	1.70%	6
(Ma et al. 2008)	Guangdong, shenzhen	NE	248(22)	8.90%	8
(Lin et al. 2007)	Fujian, lianjiang	NE	178(27)	15.20%	6
(Pan et al. 2011)	Guangdong	NE	5820(496)	8.50%	8
(Lan et al. 2009)	Zhejiang, Lishui	NE	218(12)	5.50%	6

(Feng et al. 2008)	Guangdong,guangzhou	NE	113(4)	3.50%	7
(Yu et al. 2008)	Guangdong, shenzhen	NE	1510(301)	19.90%	9
(Wang et al. 2007)	Fujaing, xiamen	NE	957(64)	6.70%	5
(Lin et al. 2010)	Guangdong, qingyuan	NE	387(37)	9.60%	8
(Tan et al. 2008)	Guangdong, jiangmen	NE	229(10)	4.40%	7
(Li et al. 2008)	Guangxi, wuzhou	NE	193(4)	2.10%	7
(Chen et al. 2009)	Guangdong, maoming	NE	196(21)	10.70%	5
(Tong et al. 2011)	Hainan	NE	124(14)	11.30%	8
(Lin et al. 2011)	Guangdong, jiangmen	NE	113(30)	26.50%	7
(Geng et al. 2011)	Guangdong, shenzhen	ELISA	331(40)	12.10%	10
(Huang et al. 2010)	Guangdong	NE	293(24)	8.20%	7
(Zhang et al. 2009)	Guangdong, maoming	NE	148(15)	10.10%	7
(Lin et al. 2011)	Guangdong, qingyuan	NE	844(96)	11.40%	9
(Qu et al. 2011)	Guangdong, qingyuan	NA	288(27)	9.40%	6
(Zhang et al. 2008)	Guangdong, shenzhen	NA	307(38)	12.40%	4

Pooling and heterogeneity analysis

The pooled prevalence estimates of *A.cantonensis* infection in rodent hosts with individual studies were shown in a forest plot (Fig 3). A substantial heterogeneity was observed among studies (χ^2=4979.77, P<0.05; I^2=99.0%). When calculated using a random-effects model, the overall infection rate was 0.1003 (95%CI: 0.0765,0.1268). The estimates of infection rates for different subgroups and heterogeneities were presented in Table 2 and Fig 4. All pooled infection rates for each subgroup were calculated using a random-effects model bacause of the observed high heterogeneity among studies within subgroups. Base on study periods, the estimate had been significantly increased since 2008 (≤2008: 0.0834 (95%CI: 0.0595, 0.1107)vs＞2008: 0.111 (95%CI: 0.0758, 0.1518)). In terms of the rodent hosts species, the estimate was highest in *Rattus norvegicus* (0.1441, 95%CI: 0.1100, 0.1818), followed by *Rattus flavipectus* (0.0428, 95%CI: 0.0062, 0.0987), *Bandicota indica* (0.0409, 95%CI:

0.0000, 0.1240), *Mus musculus* (0.0101, 95%CI: 0.0041, 0.0187), *Rattus rattus* (0.0093, 95%CI: 0.0004, 0.0299), *Rattus losea* (0.0044, 95%CI: 0.0000, 0.0176), and the lowest was *Suncus Murinus* (0.0006, 95%CI: 0.0000, 0.0086). In terms of Asia region, China (0.0893, 95%CI: 0.0773, 0.1020) was higher than Thailand (0.0299, 95%CI: 0.0053, 0.0700). Finally, in terms of score, the estimate was highest in high score(0.1266, 95%CI: 0.1021, 0.1560), followed by low score (0.0892, 95%CI: 0.0420, 0.1509), the lowest was middle score (0.0728, 95%CI: 0.0583, 0.0888).

Fig. 3 Random-effects model meta-analysis of *A.cantonensis* infection in Asian countries

Fig. 4 Subgroup froest plot of infection *A.cantonensis* in Asian countries

Table.2 Subgroup meta-analysis of *A.cantonensis* in Asian countries

variable	**population**	**No.of infected rodents**	**No. of total rodents**	**Pooled estimate Prevalence (%)**	**95%CI**	**Heterogeneity(Q)**			**Egger'test**	
						Q	**I²(%)**	**P-value**	**t**	**P**
Asia region										
China	42213(4179)	4179	42213	0.0893	(0.0773,0.1020)	1005.38	95.1	<0.0001	-0.5678	0.5724
Thailand	1101(53)	53	1101	0.0299	(0.0053,0.0700)	19.67	93.9	0.0002	-1.0502	0.4038
Japan	136(46)	46	136							
Philippines	809(664)	664	809							
india	937(12)	12	937							
Score										
≤4 (low)	2469(192)	192	2469	0.0892	（0.0420,0.1509）	139	96.8	<0.0001	1.0588	0.3304
＞4 to ≤7 (middle)	24578(2103)	2103	24578	0.0728	（0.0583,0.0888）	674.28	95.4	<0.0001	-0.8451	0.4035
＞7 to ≤10 (high)	18149(2659)	2659	18149	0.1266	(0.1021,0.1560)	421.26	96.5	<0.0001	0.4219	0.6781
Host species										
Rattus norvegicus	18479(3048)	3048	18479	0.1441	(0.1100,0.1818)	2320.32	98	<0.0001	-0.4383	0.663
Rattus flavipectus	7840（918）	918	7840	0.0428	(0.0062,0.0987)	2230.08	98.3	<0.0001	-0.409	0.6846

Suncus Murinus	5758（179）	179	5758	0.0006	（0.0000,0.0086）	164.89	87.2	<0.0001	-0.7805	0.4416
Mus musculus	1137（22）	22	1137	0.0101	（0.0041,0.0187）	34.88	44.6	0.2469	-2.2943	0.0292
Rattus losea	1697（69）	69	1697	0.0044	（0.0000,0.0176）	25.5	62.3	0.0841	1.8715	0.0797
Bandicota indica	800（66）	66	800	0.0409	（0.0000,0.1240）	90.17	93.1	<0.0001	0.3826	0.7109
Rattus rattus	797(19)	19	797	0.0093	（0.0004,0.0299）	35.34	79.3	0.0008	0.8389	0.4179
other species	4269(415)	415	4269							
publication year										
≤2008	14007(1602)	1602	14007	0.0834	(0.0595,0.1107)	665.2	97.1	<0.0001	-1.833	0.0798
＞2008	31189(3352)	3352	31189	0.111	(0.0758,0.1518)	4311.74	99.1	<0.0001	0.6216	0.5377
Overall	49156(4954)	4954	49156	0.1003	(0.0765,0.1268)	4979.77	99.0	<0.0001	0.1075	0.9147

Publication bias

Despite the significant heterogeneity, the funnel plot displayed a symmetric spread of studies in terms of relative weight and effect size, thereby we could not directly judge whether there was publication bias in the included studies (Fig. 5). The results of Egger's test showed P=0.9147 (P>0.05) (data not shown). Therefore, we considered that there was no publication bias in the included studies. Notably, the total number of studies was reasonable, and the individual studies were of variable sample size. Moreover, Duval and Tweedie's trim and fill procedure for the detection of publication bias did not support the possibility of missing studies from the analysis.

Fig. 5 Funnel plot of the arcsine transformed infection rates of *A.cantonensis* in Asian countries

Discussion

In previous study, rodents may play an important role in the transmission of certain zoonotic parasites to humans[18]. For *A.cantonensis*, the estimate was highest in *Rattus norvegicus*, *Rattus flavipectus* and *Bandicota indica*, followed by *Mus musculus*, *Rattus rattus* , *Rattus losea*, and *Suncus Murinus*. The difference of the

infection rates among seven kinds of rats may be relative to the factors: the susceptibility to *A. cantonensis*, rat's habitat, activity range and hunted objects, and so on. For example, the front several rodents : (i) be considered as dominant species in several Asian countries[20,21]; (ii) live close to human dwellings[22]; (iii) they were also known to prey on snails not plants[23]. The outcome is comparable to the previous report[24].

Before 2008, there were outbreaks in Beijing, Wenzhou, Guangzhou and so on in China, particularly, 160 cases infected in Beijing[25]. Then, investigator did more research across China by the national angiostrongyliasis control programme. They found this phenomenon was supported by the environment change, including soil, water and air. The climate changes influence global air and land surface temperatures. Also, soil and water are important to the natural history of many parasite or their vectors. In such environments, a high prevalence of parasite infection (hantavirus, Yersinia pestis) is often found in various rodents species[26]. In normal, *Rattus spp.* feces could be in water or soil. The major intermediate hosts (e.g. *Pomacea canaliculata* and *Achatina fulica*)[27] maybe infected by ingesting feces. Typically, soil and water properties' changes will affect the intermediate hosts and definitive hosts living time. Their living stages are an essential component of the *A.cantonensis* infection life cycle. Moreover, with the wide habitat alternation, the hosts may adapted and mitigated quickly to modify emissions and habitats. Finally, all factors mentioned earlier leads cases increased year by year.

Limitations

254 Though this study provided information for the prevalence of *A.cantonensis* in rodent
255 hosts in Asia, several limitations may merit attention. First, the estimations of
256 infection rates using a random-effect model was unavoidable, then subgroup analysis
257 was employed but could not fully explain the source of heterogeneity. Secondly, our
258 study didn't included all Asian countries because the relevant data were not available
259 or incomplete. Finally, in this study, we only focused on *Rattus norvegicus*, *Rattus*
260 *flavipectus*, *Bandicota indica*, *Mus musculus*, *Rattus rattus*, *Rattus losea* and *Suncus*
261 *Murinus*, because they were common and most important rodent hosts. However,
262 other rodents, like *Rattus tiomanicus*, *Rattus exulans* and so on, though difficulty to
263 collect them but should not be neglected. To fully elucidate the prevalence of
264 angiostrongyliasis, further studies should pay attention to the other species rodent
265 hosts.

266 **Conclusion**

267 In conclusion, our systematic review and meta-analysis estimated a national
268 prevalence of *A.cantonensis* in rodent hosts in Asia, particularly in China, which
269 provided a scientific basis for prevention a control of the spread of angiostrongyliasis.
270 The *A.cantonensis* infection rate among rodent hosts were still high in China,
271 especially in *Rattus norvegicus*, and thus comprehensive measures should be taken for
272 rodent hosts control to avoid an angiostrongyliasis outbreak. Due to the wide
273 distribution and movement of rodent hosts, people in all regions of China, even in
274 other Asia area live at a risk of an infection. Moreover, public health officials,
275 epidemiologists, researchers, clinical technicians, medical practitioners,

parasitologists, and veterinarians, as well as the general public, should be aware of such risks, and integrated strategies should be taken to reduce or eliminate such risks[28]. Hence, the development of more reliable diagnostic tests will be key for an effective identification of cases as well as improved patient care. Consequently, further studies are required to updated strategies for controlling *A.cantonensis* infection among human population.

Supporting information

Table S1. PRISMA checklist.

(DOC)

File S1.Quality assessment checklist.

(DOCX)

File S2. References of the selected articles included in the systematic review.

(DOCX)

Funding information

This work has received no specific funding.

Declaration of interests

We declare no competing interests.

Author Contributions

Conceptualization: Huifang Bai, Huiyuan Bai, Fei Bai.

Data curation: Huifang Bai, Huiyuan Bai, Fei Bai.

Formal analysis:Huifang Bai, Huiyuan Bai.

Investigation: Huiyuan Bai, Fei Bai.

298 Methodology: Huifang Bai, Huiyuan Bai, Fei Bai.

299 Validation: Huifang Bai, Yizhen Cao, Yunqiu Chen.

300 Visualization: Huifang Bai, Yizhen Cao, Yunqiu Chen.

301 Writing-original draft: Huifang Bai, Huiyuan Bai.

302 Writing-review & editing: Huifang Bai, Huiyuan Bai, Fei Bai, Yizhen Cao, Yunqiu

303 Chen.

304 References

305 1. Luis AD, Hayman DT, O'Shea TJ, Cryan PM, Gilbert AT, Pulliam JR, et al. A

306 comparison of bats and rodents as reservoirs of zoonotic viruses: are bats special?

307 Proc Biol Sci. 2013; 280(1756): 20122753. pmid:23378666

308 2. Civitello DJ, Cohen J, Fatima H, Halstead NT, Liriano J, McMahon TA, et al.

309 Biodiversity inhibits parasites: Broad evidence for the dilution effect. Proc Natl

310 Acad Sci U S A. 2015; 112(28): 8667-8671. pmid:26069208

311 3. Olival KJ, Hosseini PR, Zambrana-Torrelio C, Ross N, Bogich TL, Daszak P. Host

312 and viral traits predict zoonotic spillover from mammals. Nature. 2017; 546(7660):

313 646-650. pmid:28636590

314 4. Rosen L, Chappell R, Laqueur GL, Wallace GD, Weinstein PP. Eosinophilic

315 meningoencephalitis caused by a metastrongylid lung-worm of rats. Jama. 1962;

316 179(620-624. pmid:14493905

317 5. Wang QP, Lai DH, Zhu XQ, Chen XG, Lun ZR. Human angiostrongyliasis. Lancet

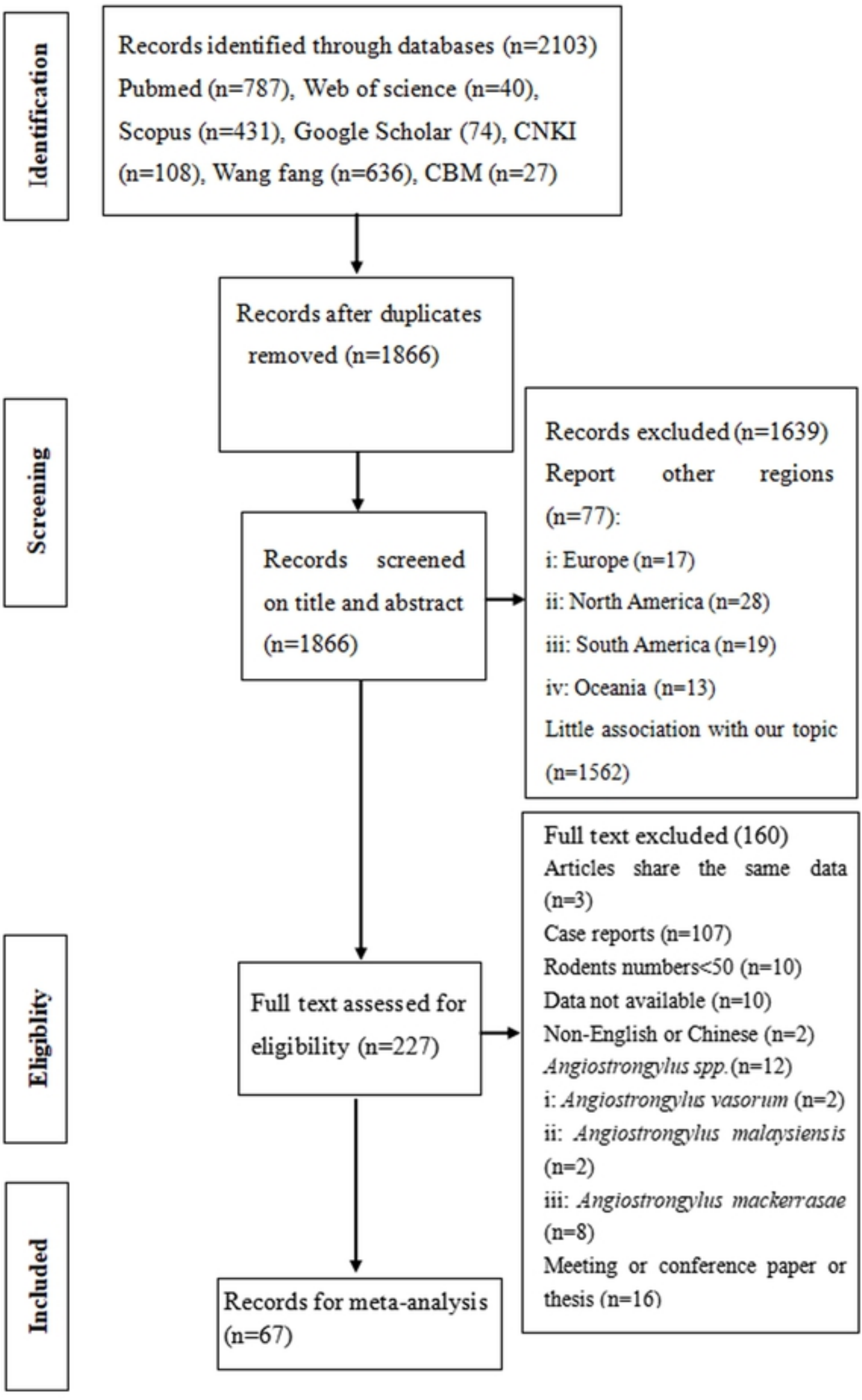
318 Infect Dis. 2008; 8(10): 621-630. pmid:18922484

319 6. Thiengo SC, Simões Rde O, Fernandez MA, Maldonado A, Jr. Angiostrongylus
320 cantonensis and rat lungworm disease in Brazil. Hawaii J Med Public Health. 2013;
321 72(6 Suppl 2): 18-22. pmid:23901376
322 7. Molyneux D, Sankara DP. Guinea worm eradication: Progress and challenges-
323 should we beware of the dog? PLoS Negl Trop Dis. 2017; 11(4): e0005495.
324 pmid:28426663
325 8. Conteh L, Engels T, Molyneux DH. Socioeconomic aspects of neglected tropical
326 diseases. Lancet. 2010; 375(9710): 239-247. pmid:20109925
327 9. Hotez PJ. Ten global "hotspots" for the neglected tropical diseases. PLoS Negl
328 Trop Dis. 2014; 8(5): e2496. pmid:24873825
329 10. Wang QP, Wu ZD, Wei J, Owen RL, Lun ZR. Human Angiostrongylus
330 cantonensis: an update. Eur J Clin Microbiol Infect Dis. 2012; 31(4): 389-395.
331 pmid:21725905
332 11. Suankratay C, Wilde H, Berger S. Thailand: country survey of infectious diseases.
333 J Travel Med. 2001; 8(4): 192-203. pmid:11703902
334 12. Eamsobhana P, Lim PE, Yong HS. Genetic diversity of the rat lungworm,
335 Angiostrongylus cantonensis, the major cause of eosinophilic meningitis. Hawaii J
336 Med Public Health. 2013; 72(6 Suppl 2): 15-17. pmid:23901375
337 13. Claveria FG, Causapin J, de Guzman MA, Toledo MG, Salibay C. Parasite
338 biodiversity in Rattus spp caught in wet markets. Southeast Asian J Trop Med
339 Public Health. 2005; 36 Suppl 4(146-148. pmid:16438200

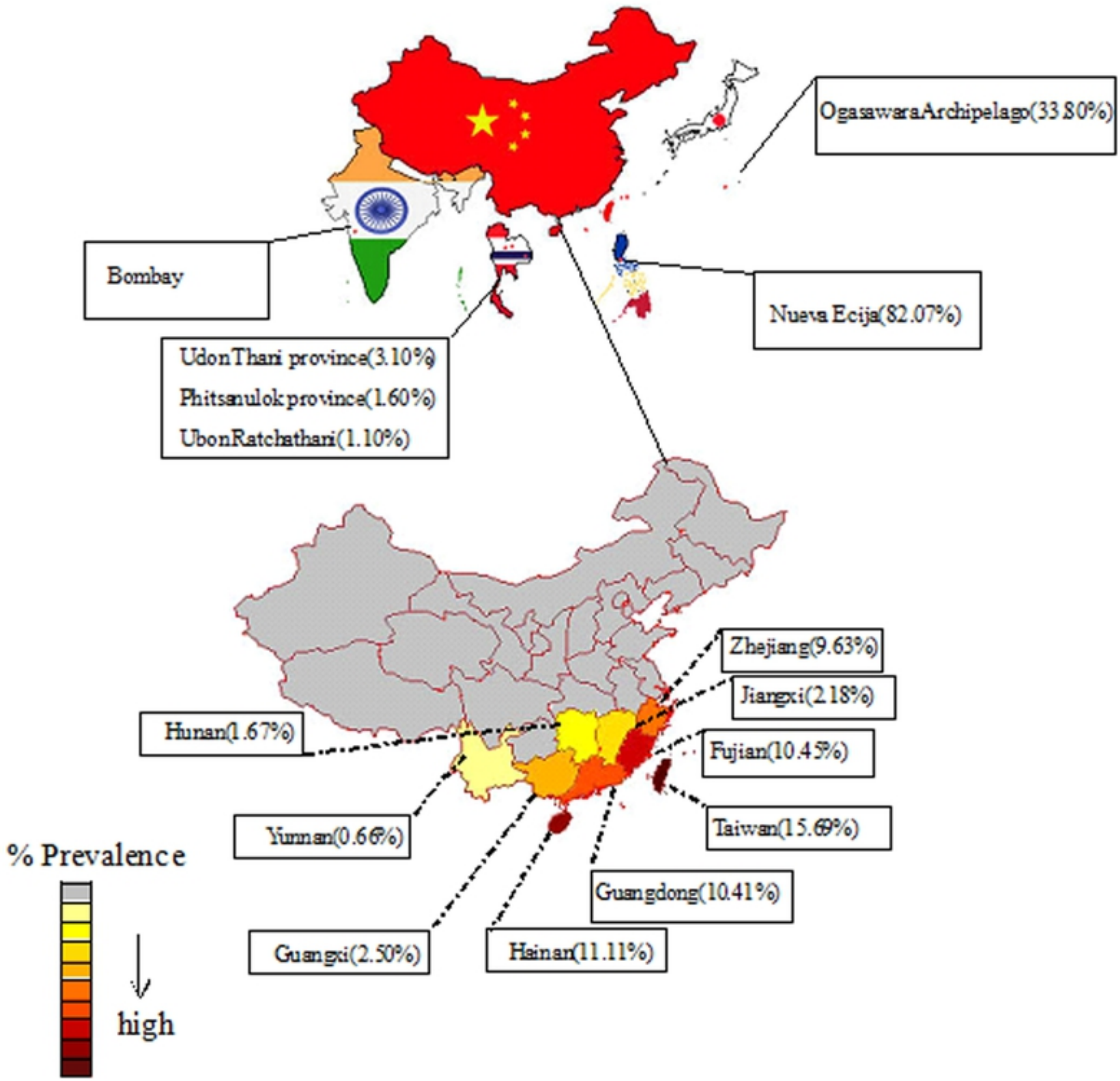
340 14. Tangkanakul W, Smits HL, Jatanasen S, Ashford DA. Leptospirosis: an emerging
341 health problem in Thailand. Southeast Asian J Trop Med Public Health. 2005;
342 36(2): 281-288. pmid:15916031
343 15. Truc P, Büscher P, Cuny G, Gonzatti MI, Jannin J, Joshi P, et al. Atypical human
344 infections by animal trypanosomes. PLoS Negl Trop Dis. 2013; 7(9): e2256.
345 pmid:24069464
346 16. Watt G, Pachirat O, Baggett HC, Maloney SA, Lulitanond V, Raoult D, et al.
347 Infective endocarditis in northeastern Thailand. Emerg Infect Dis. 2014; 20(3):
348 473-476. pmid:24572588
349 17. Sohal RJ, Lui F (2020) Angiostrongylus Cantonensis (Angiostrongliasis).
350 StatPearls. Treasure Island (FL): StatPearls Publishing
351 Copyright © 2020, StatPearls Publishing LLC.
352 18. Tung KC, Hsiao FC, Wang KS, Yang CH, Lai CH. Study of the endoparasitic
353 fauna of commensal rats and shrews caught in traditional wet markets in Taichung
354 City, Taiwan. J Microbiol Immunol Infect. 2013; 46(2): 85-88. pmid:22516746
355 19. Griggs D, Stafford-Smith M, Gaffney O, Rockström J, Ohman MC, Shyamsundar
356 P, et al. Policy: Sustainable development goals for people and planet. Nature. 2013;
357 495(7441): 305-307. pmid:23518546
358 20. Lv S, Zhang Y, Liu HX, Zhang CW, Steinmann P, Zhou XN, et al.
359 Angiostrongylus cantonensis: morphological and behavioral investigation within
360 the freshwater snail Pomacea canaliculata. Parasitol Res. 2009; 104(6): 1351-1359.
361 pmid:19172296

362 21. Salibay C. Distribution of Native and Non-native Rats (Rattus sp) Along an
363 elevational gradient in the tropical Rainforest of Southern Luzon, Philippines.
364 Ecotropica. 2008; 14(129-136.
365 22. Hu QA, Lv S, Guo YH, Liu HX, Zhang Y. Genetic diversity of Angiostrongylus
366 cantonensis in Nan'ao Island of Guangdong Province. Chin J Parasitol Parasit Dis.
367 2017; 35(2): 130-135.
368 23. Hu QA, Zhang Y, Guo YH, Lv S, Xia S, Liu HX, et al. Small-scale spatial
369 analysis of intermediate and definitive hosts of Angiostrongylus cantonensis. Infect
370 Dis Poverty. 2018; 7(1): 100. pmid:30318019
371 24. Chen D, Zhang Y, Shen H, Wei Y, Huang D, Tan Q, et al. Epidemiological survey
372 of Angiostrongylus cantonensis in the west-central region of Guangdong Province,
373 China. Parasitol Res. 2011; 109(2): 305-314. pmid:21301874
374 25. MacDonald R. Eating raw snails leads to angiostrongylus meningitis in Beijing.
375 The Lancet Infectious Diseases. 2006; 6(10): 622.
376 26. McCauley DJ, Salkeld DJ, Young HS, Makundi R, Dirzo R, Eckerlin RP, et al.
377 Effects of land use on plague (Yersinia pestis) activity in rodents in Tanzania. Am J
378 Trop Med Hyg. 2015; 92(4): 776-783. pmid:25711606
379 27. Lv S, Zhang Y, Steinmann P, Zhou XN. Emerging angiostrongyliasis in Mainland
380 China. Emerg Infect Dis. 2008; 14(1): 161-164. pmid:18258099
381 28. Zhang RL, Chen MX, Gao ST, Geng YJ, Huang DN, Liu JP, et al. Enzootic
382 angiostrongyliasis in Shenzhen, China. Emerg Infect Dis. 2008; 14(12): 1955-1956.
383 pmid:19046534

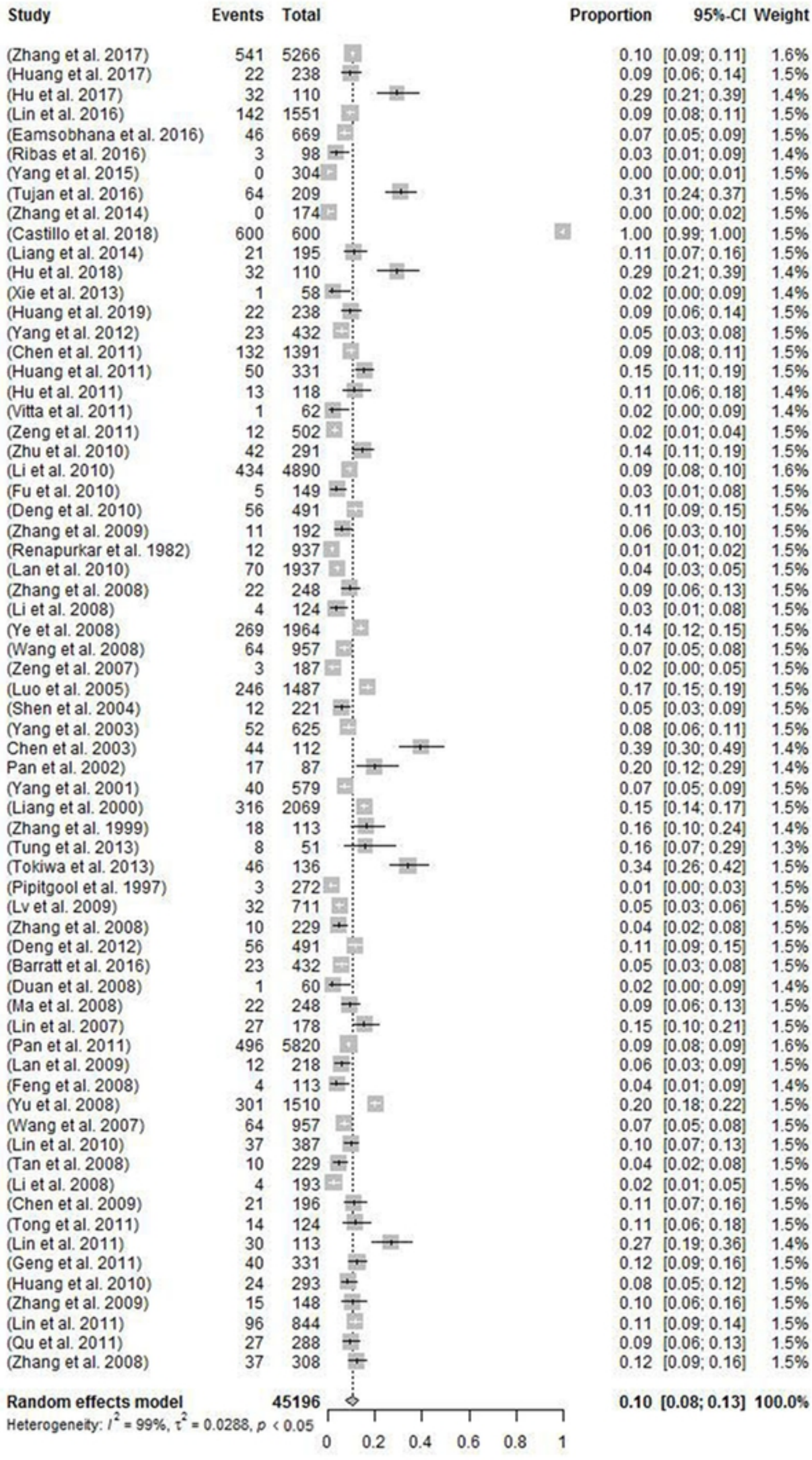
384


Identification
Records identified through databases (n=2103)
Pubmed (n=787), Web of science (n=40), Scopus (n=431), Google Scholar (74), CNKI (n=108), Wang fang (n=636), CBM (n=27)
Screening
Records after duplicates removed (n=1866)
Records screened on title and abstract (n=1866)
Records excluded (n=1639)
Report other regions (n=77):
i: Europe (n=17)
ii: North America (n=28)
iii: South America (n=19)
iv: Oceania (n=13)
Little association with our topic (n=1562)
Eligiblity
Full text assessed for eligibility (n=227)
Full text excluded (160)
Articles share the same data (n=3)
Case reports (n=107)
Rodents numbers<50 (n=10)
Data not available (n=10)
Non-English or Chinese (n=2)
Angiostrongylus spp. (n=12)
i: Angiostrongylus vasorum (n=2)
ii: Angiostrongylus malaysiensis (n=2)
iii: Angiostrongylus mackerrasae (n=8)
Meeting or conference paper or thesis (n=16)
Included
Records for meta-analysis (n=67)

Figure


OgasawaraArchipelago(33.80%)
Bombay
Nueva Ecija(82.07%)
UdonThani province(3.10%)
Phitsanulok province(1.60%)
UbonRatchathani(1.10%)
Zhejiang(9.63%)
Jiangxi(2.18%)
Hunan(1.67%)
Fujian(10.45%)
Taiwan(15.69%)
Yunnan(0.66%)
Guangdong(10.41%)
Guangxi(2.50%)
Hainan(11.11%)
% Prevalence
high

Figure


Study Events Total Proportion 95%-CI Weight
(Zhang et al. 2017) 541 5266 0.10 [0.09; 0.11] 1.6%
(Huang et al. 2017) 22 238 0.09 [0.06; 0.14] 1.5%
(Hu et al. 2017) 32 110 0.29 [0.21; 0.39] 1.4%
(Lin et al. 2016) 142 1551 0.09 [0.08; 0.11] 1.5%
(Eamsobhana et al. 2016) 46 669 0.07 [0.05; 0.09] 1.5%
(Ribas et al. 2016) 3 98 0.03 [0.01; 0.09] 1.4%
(Yang et al. 2015) 0 304 0.00 [0.00; 0.01] 1.5%
(Tujan et al. 2016) 64 209 0.31 [0.24; 0.37] 1.5%
(Zhang et al. 2014) 0 174 0.00 [0.00; 0.02] 1.5%
(Castillo et al. 2018) 600 600 1.00 [0.99; 1.00] 1.5%
(Liang et al. 2014) 21 195 0.11 [0.07; 0.16] 1.5%
(Hu et al. 2018) 32 110 0.29 [0.21; 0.39] 1.4%
(Xie et al. 2013) 1 58 0.02 [0.00; 0.09] 1.4%
(Huang et al. 2019) 22 238 0.09 [0.06; 0.14] 1.5%
(Yang et al. 2012) 23 432 0.05 [0.03; 0.08] 1.5%
(Chen et al. 2011) 132 1391 0.09 [0.08; 0.11] 1.5%
(Huang et al. 2011) 50 331 0.15 [0.11; 0.19] 1.5%
(Hu et al. 2011) 13 118 0.11 [0.06; 0.18] 1.4%
(Vitta et al. 2011) 1 62 0.02 [0.00; 0.09] 1.4%
(Zeng et al. 2011) 12 502 0.02 [0.01; 0.04] 1.5%
(Zhu et al. 2010) 42 291 0.14 [0.11; 0.19] 1.5%
(Li et al. 2010) 434 4890 0.09 [0.08; 0.10] 1.6%
(Fu et al. 2010) 5 149 0.03 [0.01; 0.08] 1.5%
(Deng et al. 2010) 56 491 0.11 [0.09; 0.15] 1.5%
(Zhang et al. 2009) 11 192 0.06 [0.03; 0.10] 1.5%
(Renapurkar et al. 1982) 12 937 0.01 [0.01; 0.02] 1.5%
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(Li et al. 2008) 4 124 0.03 [0.01; 0.08] 1.5%
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Chen et al. 2003) 44 112 0.39 [0.30; 0.49] 1.4%
Pan et al. 2002) 17 87 0.20 [0.12; 0.29] 1.4%
(Yang et al. 2001) 40 579 0.07 [0.05; 0.09] 1.5%
(Liang et al. 2000) 316 2069 0.15 [0.14; 0.17] 1.5%
(Zhang et al. 1999) 18 113 0.16 [0.10; 0.24] 1.4%
(Tung et al. 2013) 8 51 0.16 [0.07; 0.29] 1.3%
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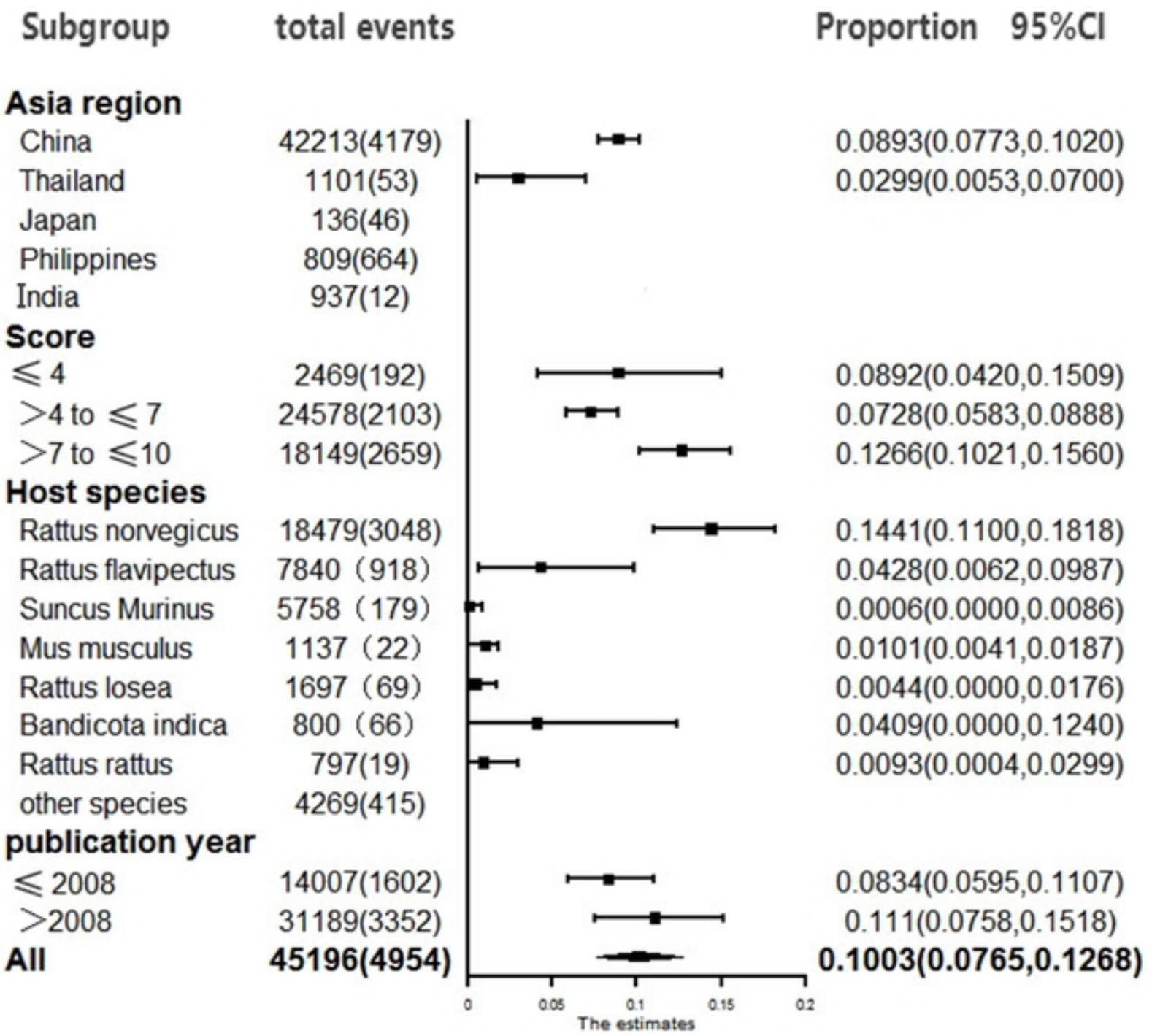
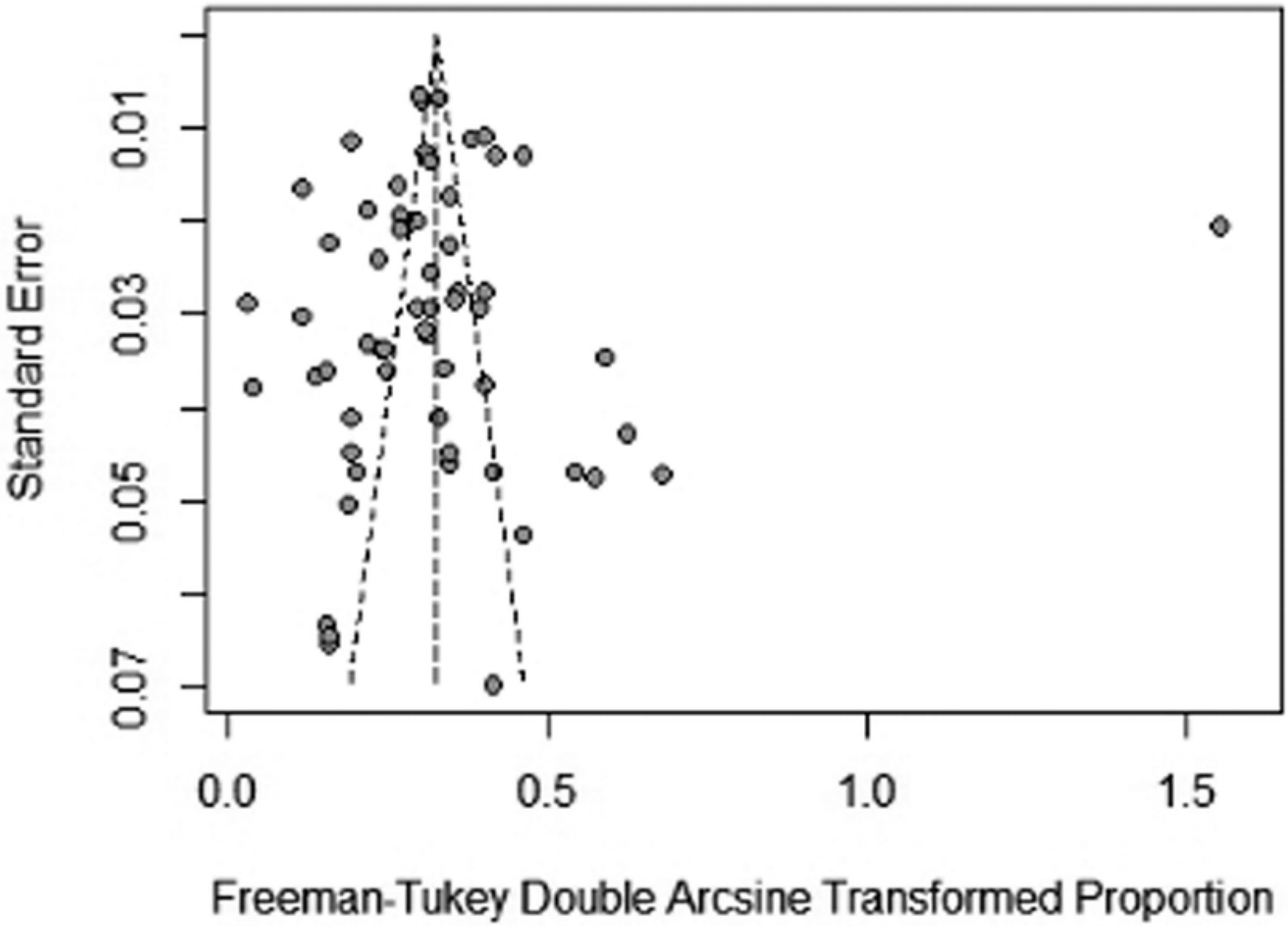
(Zhang et al. 2008) 10 229 0.04 [0.02; 0.08] 1.5%
(Deng et al. 2012) 56 491 0.11 [0.09; 0.15] 1.5%
(Barratt et al. 2016) 23 432 0.05 [0.03; 0.08] 1.5%
(Duan et al. 2008) 1 60 0.02 [0.00; 0.09] 1.4%
(Ma et al. 2008) 22 248 0.09 [0.06; 0.13] 1.5%
(Lin et al. 2007) 27 178 0.15 [0.10; 0.21] 1.5%
(Pan et al. 2011) 496 5820 0.09 [0.08; 0.09] 1.6%
(Lan et al. 2009) 12 218 0.06 [0.03; 0.09] 1.5%
(Feng et al. 2008) 4 113 0.04 [0.01; 0.09] 1.4%
(Yu et al. 2008) 301 1510 0.20 [0.18; 0.22] 1.5%
(Wang et al. 2007) 64 957 0.07 [0.05; 0.08] 1.5%
(Lin et al. 2010) 37 387 0.10 [0.07; 0.13] 1.5%
(Tan et al. 2008) 10 229 0.04 [0.02; 0.08] 1.5%
(Li et al. 2008) 4 193 0.02 [0.01; 0.05] 1.5%
(Chen et al. 2009) 21 196 0.11 [0.07; 0.16] 1.5%
(Tong et al. 2011) 14 124 0.11 [0.06; 0.18] 1.5%
(Lin et al. 2011) 30 113 0.27 [0.19; 0.36] 1.4%
(Geng et al. 2011) 40 331 0.12 [0.09; 0.16] 1.5%
(Huang et al. 2010) 24 293 0.08 [0.05; 0.12] 1.5%
(Zhang et al. 2009) 15 148 0.10 [0.06; 0.16] 1.5%
(Lin et al. 2011) 96 844 0.11 [0.09; 0.14] 1.5%
(Qu et al. 2011) 27 288 0.09 [0.06; 0.13] 1.5%
(Zhang et al. 2008) 37 308 0.12 [0.09; 0.16] 1.5%
Random effects model 45196 0.10 [0.08; 0.13] 100.0%
Heterogeneity: I^2 = 99%, τ^2 = 0.0288, p < 0.05
0 0.2 0.4 0.6 0.8 1

Figure


Subgroup
total events
Proportion 95%CI
Asia region
China 42213(4179) 0.0893(0.0773,0.1020)
Thailand 1101(53) 0.0299(0.0053,0.0700)
Japan 136(46)
Philippines 809(664)
India 937(12)
Score
⩽4 2469(192) 0.0892(0.0420,0.1509)
>4 to ⩽7 24578(2103) 0.0728(0.0583,0.0888)
>7 to ⩽10 18149(2659) 0.1266(0.1021,0.1560)
Host species
Rattus norvegicus 18479(3048) 0.1441(0.1100,0.1818)
Rattus flavipectus 7840 (918) 0.0428(0.0062,0.0987)
Suncus Murinus 5758 (179) 0.0006(0.0000,0.0086)
Mus musculus 1137 (22) 0.0101(0.0041,0.0187)
Rattus losea 1697 (69) 0.0044(0.0000,0.0176)
Bandicota indica 800 (66) 0.0409(0.0000,0.1240)
Rattus rattus 797(19) 0.0093(0.0004,0.0299)
other species 4269(415)
publication year
⩽2008 14007(1602) 0.0834(0.0595,0.1107)
>2008 31189(3352) 0.111(0.0758,0.1518)
All 45196(4954) 0.1003(0.0765,0.1268)
0
0.05
0.1
0.15
0.2
The estimates

Figure


Standard Error
0.07
0.05
0.03
0.01
0.0
0.5
1.0
1.5
Freeman-Tukey Double Arcsine Transformed Proportion

Figure