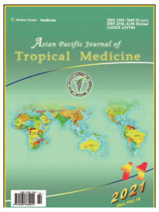

Meta-Analysis

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Tick–borne pathogens in Iran: A meta–analysis

Mehdi Khoobdel[1], Amir Sajad Jafari[2], Zakkyeh Telmadarraiy[3], Mohammad Mehdi Sedaghat[4], Hasan Bakhshi[5]✉

[1]*Health Research Center, LifeStyle Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran*

[2]*Department of Veterinary Medicine, Faculty of Veterinary Medicine, University of Zabol, Zabol, Iran*

[3]*Department of Medical Entomology and Vector Control, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran; Rahyan Novin Danesh (RND) University, Sari, Mazandaran, Iran*

[4]*Department of Medical Entomology and Vector Control, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran*

[5]*Vector–borne Diseases Research Center, North Khorasan University of Medical Sciences, Bojnurd, Iran*

ABSTRACT

Objective: Different studies have been performed on the prevalence of tick-borne pathogens in different areas of Iran; however, as far as our knowledge, there is no regional meta-analysis available for consideration and estimation of tick species infected with different pathogens in Iran.

Methods: In this review, among different databases, a total of 95 publications were included, and the infection of different tick species to different tick-borne pathogens was determined; furthermore, presence of pathogens (with 95% confidence intervals) in tick vectors was calculated separately for each province, using Comprehensive Meta-Analysis version 2 (Biostat, USA).

Results: Totally, among all 95 studies, 5 673 out of 33 521 investigated ticks were positive according to different detection methods. Overall estimated presence of pathogens in tick vectors in Iran was 8.6% (95% *CI* 7.0%-10.6%, *P*<0.001). Of all 46 species of ticks in 10 genera in Iran, 28 species in 9 genera, including *Alveonasus*, *Argas*, *Boophilus*, *Dermacentor*, *Haemaphysalis*, *Hyalomma*, *Ixodes*, *Ornithodoros*, and *Rhipicephalus* were infected with at least 20 pathogens in 10 genera including *Aegyptianella*, *Anaplasma*, *Babesia*, *Borrelia*, *Brucella*, *Orthonairovirus* [Crimean-Congo hemorrhagic fever virus (CCHFV)], *Coxiella*, *Ehrlichia*, *Rickettsia* and *Theileria* in 26 provinces of Iran. The presence of pathogens in ticks collected in western Iran was more than other regions. *Hyalomma anatolicum* (20.35%), *Rhipicephalus sanguineus* (15.00%), and *Rhipicephalus bursa* (14.08%) were the most prevalent infected ticks for different pathogens. In addition, most literatures were related to CCHFV and *Theileria*/*Babesia* spp.

Conclusions: Public health and veterinary professionals should be aware of diagnosing possible diseases or outbreaks in vertebrates.

KEYWORDS: Ticks; Tick-borne diseases; Vector-borne diseases; Iran

1. Introduction

Ticks are external obligatory blood-sucking parasites of vertebrates (phylum Arthropoda; class Arachnida) that fall into three families including Ixodidae (hard ticks), Argasidae (soft ticks), and Nuttalliellidae[1]. Ticks are the primary vectors and reservoirs for different pathogens including viruses, bacteria, and protozoa all over the world, which pose significant threats to human and animal health[2,3]. Tick-borne pathogens cause thousands of disease cases in human populations worldwide with the animal cases seeming to be more than humans[4]. Different species of ticks are able to transmit different diseases. And Crimean-Congo hemorrhagic fever (CCHF), Colorado tick fever, Q fever, borreliosis, relapsing fever, theileriosis, babesiosis, anaplasmosis, ehrlichiosis and Rocky Mountain spotted fever are

Significance

Several studies have shown the presence of tick-borne pathogens in ticks in Iran; however, as far as our knowledge, there is no meta-analysis available for estimation of ticks infected with tick-borne pathogens. Our analysis showed that the overall estimated presence of pathogens in tick vectors in Iran was 8.6% (95% *CI* 7.0%-10.6%, *P*<0.001). Furthermore, 28 tick species in 9 genera were found to be infected with at least 20 pathogens in 10 genera.

✉To whom correspondence may be addressed. E-mail: hbakhshi89@gmail.com

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among the most significant tick-borne diseases caused by these pathogens[5]. The spectrum of tick-borne diseases of both medical and veterinary importance has increased in recent years as a result of advances in molecular biology. New microorganisms are being detected in ticks collected in different countries, and the list of potential tick-transmissible pathogens is updating[6]. Problems caused by tick infestations are not limited only to transmission of pathogens. Bite stress, production loss, physical damage, anemia and poisoning are other aspects of tick bites[7]. Furthermore, the importance of animal productions in the economy and food industry around the world is undeniable[8]. Animal health can be altered by the direct and indirect effects caused by the bites of ticks and tick-borne diseases, leading to noteworthy production decrement of meat, milk, eggs, and leathers. In some severe cases, tick-borne pathogens lead to the death of humans and animals. Indirect effects are related to the costs associated to the treatment and control[8]. From past to present, ticks and tick-borne diseases have been recognized as a threat for human and animal health. Ticks are responsible for the majority of vector-borne diseases in Asia, America and Europe[9].

Iran, covering an area of 1 648 195 km^2, with a population of 83 million, is located in the Middle East. This country is located in Palearctic and Oriental zoogeographic regions, with different types of climate: mild and quite wet on the coast of the Caspian Sea, continental and arid in the plateau, cold in high mountains, desert and hot on the southern coast and in the southeast, resulting in diversity of tick species[10,11]. Ecology of ticks, their interactions with environment and risk of infection by tick-borne pathogens are directly related to the spatial and temporal variations. As a result, diversity of climate, as well as the vast geographical area, increases the diversity of tick populations which leads to the risk of transmission of different tick-borne pathogens[12]. To date, it has been reported that 46 species of ticks (10 Argasidae and 36 Ixodidae) in 10 genera occur in the country[13].

Tick species can be considered as sentinels to track the circulation of tick-borne pathogens before an outbreak breaks out in humans and animals. Although many studies revealed data about prevalence of different tick-borne pathogens in different areas of Iran, as far as our knowledge, there is no comprehensive data available for consideration and estimation of the damages caused by pathogens transmitted by ticks, on the economy and public health in Iran. For this reason, performing an updated regional review and meta-analysis on the studies conducted on the prevalence of tick-borne pathogens in different provinces of this country is highly necessary. Considering the damages caused by tick-borne diseases on the public health, animal husbandry, and Iran tourism industry, the current study attempted to determine and highlight the presence of pathogens in tick vectors and epidemiological aspects of tick-borne diseases in Iran.

2. Materials and methods

2.1. Searching approach

The present meta-analysis was performed according to the guidelines of preferred reporting items for systematic reviews and meta-analyses statement. In this regional meta-analysis study, nine English and Persian language databases including PubMed, Google Scholar, Science Direct, Scopus, Web of Science, Magiran, Civilica, Iranian Research Institute for Information Science and Technology (IranDoc), and Scientific Information Database (SID) were selected to explore the articles and data with no time limitation (last updated: 7 March, 2021). Duplicate articles, case series, animal-based studies, human-based studies and studies carried out in other countries were excluded. All studies, representing the prevalence of tick-borne pathogens in ticks as hosts/reservoirs were concerned and all PRISMA criteria have been met (Figure 1).

Totally, 95 articles and data fit into the criteria. Then, author(s) names, year of publication, province of study, tick vectors, pathogens, the number of examined ticks and the number of positive ticks were extracted from the collected data. The search was conducted using English and Persian language keywords with different patterns (*e.g.*: Tick, Iran, *Anaplasma*, *Babesia*, *Theileria*, Crimean-Congo hemorrhagic fever virus, CCHFV, *Ehrlichia*, *Agyptinella*, *Francisella*, *Brucella*, *Borrelia*, *Coxiella*, and *Rickettsia*). Advanced search options and Boolean operators 'AND' and 'OR' were also used to find more relevant records.

2.2. Paper selection

PICO process or framework (Population, Intervention, Comparator and Outcome) is a common method for formulating a systematic review queries. However, this format is not suitable for prevalence studies. Quality assessment for the included studies of the present research were setup and developed according to CoCoPop structure [Co (Condition) = infection by pathogens; Co (Context) = provinces of Iran; Pop (Population) = ticks]. Studies and the selected data were independently analyzed and the eligibility was determined by HB and ASJ. Disagreements were resolved by MK.

2.3. Meta-analysis

Initially, the prevalence of each genus of pathogen (with 95% confidence intervals) was calculated separately for each province (at least two studies were needed for calculation of each pathogen in separate provinces). Then, an overall prevalence was calculated for all pathogens in respect to each province. Furthermore, the total

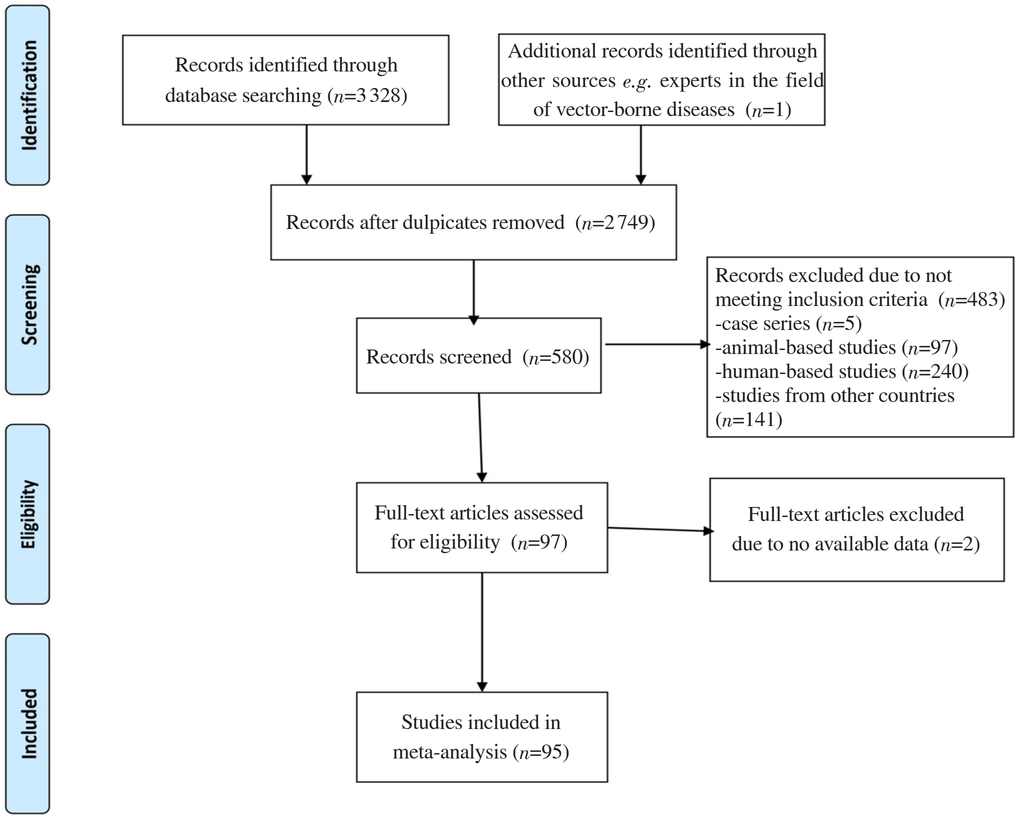

Figure 1. Fowchart of studies selection in terms of tick-borne pathogens in Iran.

prevalence for each pathogen in Iran was estimated. Cochran *Q* test (*P*<0.05 shows statistically significant heterogeneity) and I^2 test [25% (low), 50% (moderate), and 75% (high) heterogeneity] were used to evaluate heterogeneity among studies. To compute overall size effect (*Q*<0.05), random model was used; otherwise (*Q*>0.05), fixed model was assessed. For determination of publication bias, Egger's and Begg's tests were applied (*P*>0.05 indicates a reasonable publication bias). Also, a funnel plot was used to visualize the publication bias. *P*<0.05 was considered statistically significant for statistical analysis of prevalence. All statistical analyses were performed using Comprehensive Meta-Analysis version 2 (Biostat, USA).

3. Results

Among all databases screened, 3 328 records were identified through database searching; then, a total of 95 publications were selected and included in this review. Among these 95 publications, 33 521 ticks were surveyed and 5 673 were positive according to different detection methods in all provinces of Iran. Of all 46 species of ticks (in 10 genera) which occur in Iran[13], 28 species (in 9 genera) including *Alveonasus* (1 species: *Al. canestrinii*), *Argas* (2 species: *Ar. persicus*, *Ar. reflexus*), *Boophilus* (*Boophilus* spp.), *Dermacentor* (2 species: *D. marginatus*, *D. niveus*), *Haemaphysalis* (4 species: *Ha. concinna*, *Ha. inermis, Ha. punctata*, *Ha. sulcata*), *Hyalomma* (10 species: *H. aegyptium*, *H. anatolicum*, *H. asiaticum*, *H. detritum*, *H. dromedarii*, *H. excavatum*, *H. marginatum*, *H. rufipes*, *H. schulzei*, *H. scupense*, *H.* sp.), *Ixodes* (1 species: *I. ricinus*), *Ornithodoros* (3 species: *O. erraticus*, *O. lahorensis*, *O. tholozani*), and *Rhipicephalus* (5 species: *R. annulatus*, *R. appendiculatus*, *R. bursa*, *R. sanguineus*, *R. turanicus*, *R.* spp.) were found to be infected with at least 20 pathogens (in 10 genera) including *Aegyptianella* (1 species: *Ae. pullorum*), *Anaplasma* (4 species: *An. ovis*, *An. bovis*, *An. phagocytophilum*, *An. marginale*, *An.* spp.), *Babesia* (3 species: *Ba. ovis*, *Ba. bigemina*, *Ba. occultans*, *Ba.* spp.), *Borrelia* (3 species: *Bo. microti*, *Bo. anserina*, *Bo. persica*, *Bo.* sp.), *Brucella* (*Brucella* sp.), *Orthonairovirus* (1 virus: CCHFV), *Coxiella* (1 species: *Cx. burnetii*), *Ehrlichia* (2 species: *Eh. canis*, *Eh. ovina*, *Eh.* spp.), *Rickettsia* (1 species: *Ri. hoogstraalii*, *Ri.* sp.), *Theileria* (4 species: *Th. annulata*, *Th. lestoquardi*, *Th. ovis*, *Th. equi*, *Th.* spp.), as well as unspecified *An. centrale*/*An. bovis* (Table 1). In this review, *D. marginatus*, *D. niveus*, *H. detritum* and *H. scupense* were considered as separate species.

Among the provinces where ticks were found to be infected with different genera of pathogens (including CCHFV), Lorestan (7 genera), Ardabil (6 genera), Golestan (5 genera), and Sistan and Baluchestan (5 genera) provinces had the most number of ticks infected with different genera of pathogens (Table 2).

Among 31 provinces of Iran, 26 provinces were surveyed in

Table 1. Summary of tick-borne pathogens in tick species in different provinces of Iran.

Provinces	Pathogens screened*	Year of study	Total tested/ positive tick specimens	Tick vectors																															Ref.
				Al. canestrinii	*Ar. persicus*	*Ar. reflexus*	*Boophilus* spp.	*D. marginatus*	*D. niveus*	*Ha. concinna*	*Ha. inermis*	*Ha. punctata*	*Ha. sulcata*	*H. aegyptium*	*H. anatolicum*	*H. asiaticum*	*H. detritum*	*H. dromedarii*	*H. excavatum*	*H. marginatum*	*H. rufipes*	*H. schulzei*	*H. scupense*	*H.* sp.	*I. ricinus*	*O. erraticus*	*O. lahorensis*	*O. tholozani*	*R. annulatus*	*R. appendiculatus*	*R. bursa*	*R. sanguineus*	*R.* sp.	*R. turanicus*	
Ardabil	*Ba. ovis*	2017	200/10					2	8																										[14]
	Ba. sp.	2016	289/0																																[15]
	Total	2 studies	489/10					2	8																										
	Bo. sp.	2014	17/7																									7							[16]
	Bo. sp.[a,#]	2002	1421/NA																																[17]
	Total	2 studies	17/7																									7							
	CCHFV	2010	130/36											1						1		1		6			9				18				[18]
	Total	1 study	130/36											1						1		1		6			9				18				
	Cx. burnetii	2020	280/40												24				8													8			[19]
	Total	1 study	280/40												24				8													8			
	Eh. canis	2013	146/64					9							4	9															12	30			[20]
	Total	1 study	146/64					9							4	9															12	30			
	Th. annulata	2016	289/69												47	13			9																[15]
	Total	1 study	289/69												47	13			9																
	Total 7 pathogens	7 studies	1062/226					11	8					1	75	22			17	1		1		6			9	7			30	38			
Azerbaijan, East	*An./Eh.* sp.[b,##]	2021	168/37					2					2		16	5				4											5	3			[21]
	An. ovis	2016	215/122												3												119								[22]
	An./Ri. sp.[b]	2021	30/10					10																											[23]
	Total	3 studies	413/169					12					2		19	5				4							119				5	3			
	Ba./Th. sp.[c,##]	2021	182/0																																[21]
	Ba./Th. sp.[c]	2018	93/4					3																								1			[24]
	Total	2 studies	275/4					3																								1			
	Br. sp.[##,***]	2021	133/20					6					2			3				5											4				[21]
	Total	1 study	133/20					6					2			3				5											4				
	CCHFV	2016	177/9					6												2					1										[25]
	Total	1 study	177/9					6												2					1										
	Total 5 pathogens	5 studies	998/202					27					4		19	8				11					1		119				9	4			
Azerbaijan, west	*Ba. bigemina*	2017	530/52																										22		18	12			[26]
	Ba. ovis	2014	848/94																												94				[27]
	Ba. sp.	2013	211/9																												1	8			[28]
	Total	3 studies	1589/155																										22		113	20			
	Th. lestoquardi	2017	315/37					11												15														11	[29]
	Total	1 study	315/37					11												15														11	
	Total 4 pathogens	4 studies	1904/192					11												15									22		113	20		11	
Fars	*Ba. ovis*	2013	171/15												3					1				1										10	[30]
	Total	1 study	171/15												3					1				1										10	
	Eh. ovina	2005	89/23												23																				[31]
	Total	1 study	89/23												23																				

Table 1. Continued.

Provinces	Pathogens screened[a]	Year of study	Total tested/ positive tick specimens	Tick vectors																															Ref.
				Al. canestrinii	*Ar. persicus*	*Ar. reflexus*	*Boophilus* spp.	*D. marginatus*	*D. niveus*	*Ha. concinna*	*Ha. inermis*	*Ha. punctata*	*Ha. sulcata*	*H. aegyptium*	*H. anatolicum*	*H. asiaticum*	*H. detritum*	*H. dromedarii*	*H. excavatum*	*H. marginatum*	*H. rufipes*	*H. schulzei*	*H. scupense*	*H.* sp.	*I. ricinus*	*O. erraticus*	*O. lahorensis*	*O. tholozani*	*R. annulatus*	*R. appendiculatus*	*R. bursa*	*R. sanguineus*	*R.* sp.	*R. turanicus*	
	CCHFV	2016	200/9												3					2												4			[32]
	Total	1 study	200/9												3					2												4			
	Th. lestoquardi	2013	171/5												2																		1	2	[30]
	Th. lestoquardi/*Th.* sp.[c]	2005	89/53												53																				[31]
	Th. ovis	2013	90/5																															5	[33]
	Total	3 studies	350/63												55																		1	7	
	Total 5 pathogens	4 studies	550/110												84					3				1								4	1	17	
Gilan	*An. marginale*	2020	30/1																														1		[34]
	An. ovis	2016	53/25					24																								1			[22]
	Total	2 studies	83/26					24																								1	1		
	Bo. sp.	2020	507/2																						1				1						[35]
	Total	1 study	507/2																						1				1						
	Br. spp.[e]	2017	1/1				1																												[36]
	Total	1 study	1/1				1																												
	Total 4 pathogens	4 studies	591/29				1	24																	1				1			1	1		
Golestan	*An./ Eh.* sp.[b]	2017	48/12												2					1			2								2	5			[37]
	Total	1 study	48/12												2					1			2								2	5			
	Ba. occultans	2017	48/1												1																				[37]
	Ba. ovis	2017	48/2																				1									1			[37]
	Total	1 study	48/3												1								1									1			
	Bo. sp.	2020	507/42																						1							26		15	[35]
	Total	1 study	507/42																						1							26		15	
	CCHFV	2017	130/7												3			2		1												1			[38]
	Total	1 study	130/7												3			2		1												1			
	Th. ovis	2017	48/14												1			2	1	3	1		2								1	3			[37]
	Total	1 study	48/14												1			2	1	3	1		2								1	3			
	Total 6 pathogens	3 studies	685/78												7			4	1	5	1		5		1						3	36		15	
Hamadan	*Bo. persica*	2003	82/3																									3							[39]
	Bo. persica	1998	1 157/0																																[40]
	Total	2 studies	1 239/3																									3							
	CCHFV	2016	100/7													1															2	4			[41]
	CCHFV	2010	328/63			2									2		48															11			[42]
	CCHFV	2008	88/10									1			1			2		3											1	2			[43]
	Total	3 studies	516/80			2						1			3	1	48	2		3											3	17			
	Total 2 pathogens	5 studies	1 755/83			2						1			3	1	48	2		3								3			3	17			

Table 1. Continued.

Provinces	Pathogens screened*	Year of study	Total tested/ positive tick specimens	Tick vectors																															Ref.
				Al. canestrinii	*Ar. persicus*	*Ar. reflexus*	*Boophilus* spp.	*D. marginatus*	*D. niveus*	*Ha. concinna*	*Ha. inermis*	*Ha. punctata*	*Ha. sulcata*	*H. aegyptium*	*H. anatolicum*	*H. asiaticum*	*H. detritum*	*H. dromedarii*	*H. excavatum*	*H. marginatum*	*H. rufipes*	*H. schulzei*	*H. scupense*	*H.* sp.	*I. ricinus*	*O. erraticus*	*O. lahorensis*	*O. tholozani*	*R. annulatus*	*R. appendiculatus*	*R. bursa*	*R. sanguineus*	*R.* sp.	*R. turanicus*	
Hormozgan	*An.* sp.	2020	30/1															1																	[34]
Total	1 pathogen	1 study	30/1															1																	
Ilam	CCHFV[a]	2015	137/9																																[44]
Total	1 pathogen	1 study	137/9																																
Isfahan	CCHFV	2016	210/11										1		3	2								2								3			[45]
Total	1 pathogen	1 study	210/11										1		3	2								2								3			
Kerman	*An.* sp.	2020	96/23												2	1				11												9			[46]
	Total	1 study	96/23												2	1				11												9			
	Ba. sp.	2016	211/0																																[47]
	Total	1 study	211/0																																
	CCHFV	2020	258/0																																[48]
	CCHFV	2018	203/0																																[49]
	Total	2 studies	461/0																																
	Cx. burnetii	2018	375/47																													47			[50]
	Cx. burnetii	2011	245/18												15																	3			[51]
	Total	2 studies	620/65												15																	50			
	Eh. sp.	2016	408/25																													25			[52]
	Total	1 study	408/25																													25			
Total	5 pathogens	7 studies	1 796/113												17	1				11												84			
Kermanshah	CCHFV	2016	131/5												3	1																1			[53]
	Total	1 study	131/5												3	1																1			
	Th. annulata	2019	420/20												20																				[54]
	Th. lestoquardi	2019	420/50												10																			40	[54]
	Th. ovis	2019	420/60																	20														40	[54]
	Total	1 study	420/130												30					20														80	
Total	4 pathogens	2 studies	551/135												33	1				20												1		80	
Khorasan,	*Ba. caballi*	2014	37/0																																[55]
North	*Ba. ovis*	2014	44/2																	1														1	[56]
	Ba. motasi	2014	44/0																																[56]
	Total	2 studies	81/2																	1														1	
	CCHFV	2019	62/5												3																	2			[57]
	CCHFV	2016	134/0																																[58]
	Total	2 studies	196/5												3																	2			
	Th. equi	2014	37/3												2																1				[55]
	Th. lestoquardi	2012	220/5																	5															[59]
	Th. ovis	2012	220/10																	5														5	[59]

Table 1. Continued.

Provinces		Pathogens screened[*]	Year of study	Total tested/ positive tick specimens	Tick vectors																															Ref.
					Al. canestrinii	*Ar. persicus*	*Ar. reflexus*	*Boophilus* spp.	*D. marginatus*	*D. niveus*	*Ha. concinna*	*Ha. inermis*	*Ha. punctata*	*Ha. sulcata*	*H. aegyptium*	*H. anatolicum*	*H. asiaticum*	*H. detritum*	*H. dromedarii*	*H. excavatum*	*H. marginatum*	*H. rufipes*	*H. schulzei*	*H. scupense*	*H.* sp.	*I. ricinus*	*O. erraticus*	*O. lahorensis*	*O. tholozani*	*R. annulatus*	*R. appendiculatus*	*R. bursa*	*R. sanguineus*	*R.* sp.	*R. turanicus*	
		Th. lestoquardi/ Th. ovis[c]	2012	220/5																	5															[59]
		Total	2 studies	257/23												2					15											1			5	
	Total	7 pathogens	5 studies	497/30												5					16											1	2		6	
Khorasan, Razavi		*Ba.* sp.	2015	246/0																																[60]
		Ba. sp.	2013	429/0																																[61]
		Total	2 studies	675/0																																
		Bo. persica	2016	996/52																									52							[62]
		Total	1 study	996/52																									52							
		CCHFV	2020	100/6																	6															[63]
		CCHFV	2016	152/0																																[58]
		CCHFV	2015	105/4													1				1										1				1	[64]
		Total	3 studies	357/10													1				7										1				1	
		Th. annulata	2002	510/231													1			230																[65]
		Th. lestoquardi	2013	429/10																															10	[61]
		Th. lestoquardi	2013	169/5																															5	[66]
		Th. ovis	2013	429/25																															25	[61]
		Th. ovis	2013	169/10																															10	[66]
		Th.ovis/Th. lestoquardi[c]	2013	429/0																																[61]
		Th. sp.	2015	246/1																	1															[60]
		Total	4 studies	1354/282													1			230	1														50	
	Total	7 pathogens	8 studies	2707/344													2			230	8								52		1				51	
Khorasan, South		*An. ovis*[##]	2020	100/20																														20		[67]
		An. ovis	2016	59/25		1				1						9	3	1	4		4							1					1			[22]
		Total	2 studies	159/45		1				1						9	3	1	4		4							1					1	20		
		CCHF[##]	2020	100/7													3	3															1			[67]
		CCHFV	2016	194/49												7			42																	[58]
		Total	2 studies	294/56												7	3	3	42														1			
		Cx. burnetii[##]	2020	100/0																																[67]
		Total	1 study	100/0																																
	Total	3 pathogens	3 studies	553/101		1				1						16	6	4	46		4							1					2	20		
Khuzestan		*Th.* spp.	2018	655/67												54	10	2	1																	[68]
	Total	1 pathogen	1 study	655/67												54	10	2	1																	
Kohgiluyeh and Boyer-Ahmad		CCHFV	2019	469/1																												1				[69]
	Total	1 pathogen	1 study	469/1																												1				

Table 1. Continued.

Provinces	Pathogens screened*	Year of study	Total tested/ positive tick specimens	Tick vectors																															Ref.
				Al. canestrinii	*Ar. persicus*	*Ar. reflexus*	*Boophilus* spp.	*D. marginatus*	*D. niveus*	*Ha. concinna*	*Ha. inermis*	*Ha. punctata*	*Ha. sulcata*	*H. aegyptium*	*H. anatolicum*	*H. asiaticum*	*H. detritum*	*H. dromedarii*	*H. excavatum*	*H. marginatum*	*H. rufipes*	*H. schulzei*	*H. scupense*	*H.* sp.	*I. ricinus*	*O. erraticus*	*O. lahorensis*	*O. tholozani*	*R. annulatus*	*R. appendiculatus*	*R. bursa*	*R. sanguineus*	*R.* sp.	*R. turanicus*	
Kurdistan	*Ba.* sp.	2018	3 107/1 303									13			221	18	25		31										283		385	327			[70]
	Total	1 study	3 107/1 303									13			221	18	25		31										283		385	327			
	Bo. persica	2009	96/19																									19							[71]
	CCHFV	2012	90/5												1			1		3															[73]
	Total	1 study	90/5												1			1		3															
	Th. sp.	2018	3 107/939												431	101	41		78										77		113	98			[70]
	Total	1 study	3 107/939												431	101	41		78										77		113	98			
Total	4 pathogens	4 studies	3 393/2269									13			653	119	66	1	109	3								19	360		498	425			
Lorestan	*Ae. pullorum*	2018	20/5		5																														[74]
	Total	1 study	20/5		5																														
	An. ovis	2020	70/14													11																3			[34]
	Total	1 study	70/14													11																3			
	Bo. anserina	2017	212/140		140																														[75]
	Total	1 study	212/140		140																														
	Cx. burnetii	2020	160/80	60	20																														[76]
	Total	1 study	160/80	60	20																														
	CCHFV	2015	434/29												12	7				1												9			[77]
	Total	1 study	434/29												12	7				1												9			
	Ri. hoogstraalii	2020	64/6		6																														[78]
	Total	1 study	64/6		6																														
	Th. lestoquardi##	2015	54/5												5																				[79]
	Th. lestoquardi	2015	171/1														1																		[30]
	Th. lestoquardi##	2013	54/5												5																				[80]
	Total	3 studies	279/11												10		1																		
	Th. ovis##	2014	152/37																													37			[79]
	Th. ovis##	2015	152/37																													37			[80]
	Total	2 studies	304/74																													74			
Total	8 pathogens	9 studies	1 543/359	60	171										22	18	1			1												86			
Mazandaran	*An. bovis*	2013	618/364					4		22	6	105													5						119	8		95	[81]
	An. bovis/ *An. centrale*[b]	2014	101/50									1													14				1			34			[82]
	An. phagocytophilum	2004	98/5																						5										[83]
	Total	3 studies	817/419					4		22	6	106													24				1		119	42		95	
	Bo. sp.	2020	507/27																						16						1	7		3	[35]
	Total	1 study	507/27																						16						1	7		3	
	Cx. burnetii	2005	605/0																																[84]

Table 1. Continued.

Provinces		Pathogens screened*	Year of study	Total tested/ positive tick specimens	Tick vectors																															Ref.
					Al. canestrinii	*Ar. persicus*	*Ar. reflexus*	*Boophilus* spp.	*D. marginatus*	*D. niveus*	*Ha. concinna*	*Ha. inermis*	*Ha. punctata*	*Ha. sulcata*	*H. aegyptium*	*H. anatolicum*	*H. asiaticum*	*H. detritum*	*H. dromedarii*	*H. excavatum*	*H. marginatum*	*H. rufipes*	*H. schulzei*	*H. scupense*	*H.* sp.	*I. ricinus*	*O. erraticus*	*O. lahorensis*	*O. tholozani*	*R. annulatus*	*R. appendiculatus*	*R. bursa*	*R. sanguineus*	*R.* sp.	*R. turanicus*	
		Total	1 study	605/0																																
		CCHFV	2017	130/7												3			2		1												1			[38]
		CCHFV	2016	58/1																													1			[85]
		Total	2 studies	188/8												3			2		1												2			
		Th. ovis	2012	20/1																													1			[86]
		Th. /Ba. sp.[c]	2012	20/10																													10			[86]
		Total	1 study	20/11																													11			
	Total	7 pathogens	8 studies	2137/465					4		22	6	106			3			2		1					40				1		120	62		98	
Qazvin		*Bo. microti*[##]	2007	24/12																							12									[87]
		Bo. persica	2010	344/16																									16							[88]
		Bo. Persica[##]	2007	231/20																									20							[87]
		Bo. sp.	2010	344/3																								3								[88]
		Total	2 studies	599/51																								3	36							
	Total	3 pathogens	2 studies	599/51																							12	3	36							
Qom		CCHFV	2012	88/6																	6															[89]
	Total	1 Pathogen	1 study	88/6																	6															
Semnan		*Bo. persica*	1999	5938/243																									243							[90]
		Total	1 study	5938/243																									243							
		CCHFV	2018	93/4												1			2														1			[91]
		Total	1 study	93/4												1			2														1			
	Total	2 pathogens	2 studies	6031/247												1			2										243				1			
Sistan and Baluchestan		*An. / Eh.* sp.[b,**]	2019	256/175												79	24	2	32		36		2													[92]
		An. marginale	2021	248/12																															12	[93]
		An. ovis[##]	2020	100/20												20																				[94]
		An. ovis / Eh. sp.[b]	2014	53/14												8	3								1								2			[95]
		Total	4 studies	657/221												107	27	2	32		36		2		1								2		12	
		Cx. burnetii[##]	2020	100/0																																[94]
		Cx. burnetii	2017	583/18												7				6													5			[96]
		Cx. burnetii[a]	2016	1305/105																																[97]
		Total	3 studies	1988/123												7				6													5			
		Eh. sp.	2017	50/5																													5			[98]
		Total	1 study	50/5																													5			
		CCHFV[##]	2020	100/0																																[94]
		CCHFV	2017	49/3																	1												1	1		[99]
		CCHFV	2013	140/6								1													5											[100]
		Total	3 studies	289/9								1									1				5								1	1		
		Th. sp.	2019	110/18													9																4		5	[101]

Table 1. Continued.

Provinces		Pathogens screened*	Year of study	Total tested/ positive tick specimens	Tick vectors: *Al. canestrinii*	*Ar. persicus*	*Ar. reflexus*	*Boophilus* spp.	*D. marginatus*	*D. niveus*	*Ha. concinna*	*Ha. inermis*	*Ha. punctata*	*Ha. sulcata*	*H. aegyptium*	*H. anatolicum*	*H. asiaticum*	*H. detritum*	*H. dromedarii*	*H. excavatum*	*H. marginatum*	*H. rufipes*	*H. schulzei*	*H. scupense*	*H.* sp.	*I. ricinus*	*O. erraticus*	*O. lahorensis*	*O. tholozani*	*R. annulatus*	*R. appendiculatus*	*R. bursa*	*R. sanguineus*	*R.* sp.	*R. turanicus*	Ref.
		Th. sp.	2003	346/36												30																	6			[102]
		Th. / *Ba.* sp.[b]	2018	93/12					2																								10			[24]
		Total	3 studies	549/66					2							30	9																20		5	
	Total	7 pathogens	12 studies	3533/424					2			1				144	36	2	32	6	37		2		6								33	1	17	
Tehran		CCHFV	2017	89/0																																[103]
		Total	1 study	89/0																																
		Th. annulata	2020	27/18																													18			[104]
		Total	1 study	27/18																													18			
	Total	2 pathogens	2 studies	116/18																													18			
Yazd		CCHFV	2011	140/8												1	1	2	3		1															[105]
		Total	1 study	140/8												1	1	2	3		1															
		Th. annulata	2015	250/15												15																				[106]
		Th. lestoquardi	2015	250/0																																[106]
		Total	1 study	250/15												15																				
	Total	3 pathogens	2 studies	390/23												16	1	2	3		1															
Unspecified Locations[f]		*Ba.* sp.	2013	211/9																												1	8			[28]
		Ba. sp.	2007	269/34																												20	6		8	[107]
		Ri. sp.	2020	61/36		20						1		5			10																			[108]
	Total	2 pathogens	3 studies	541/79		20						1		5			10															21	14		8	
Total		22 pathogens[g]	95 studies	33521 /5673[h]	60	192	2	1	79	9	22	8	120	10	1	1155	238	125	94	363	146	1	3	5	15	43	12	132	360	384	1	799	851	23	303	NA

Totally, 95 studies were included; of 31 provinces, the infection of different ticks by different pathogens were recorded in 26 provinces; at least 20 pathogens (in 10 genera) were detected in 28 species of tick vectors (in 9 genera); Abbreviations: *Ba: Babesia; Bo: Borrelia; Cx: Coxiella; Eh: Ehrlichia; Ri: Rickettsia; Th: Theileria; An: Anaplasma; Ae: Aegyptianella; Br: Brucella, Brucellaceae; Al: Alveonasus; Ar: Argas; D: Dermacentor; Ha: Haemaphysalis; H: Hyalomma; I: Ixodes; O: Ornithodoros; R: Rhipicephalus*; NA: not applicable.

*: In this table, all unidentified species of pathogens (*e.g.*: *Ba.* sp.) have been considered as separate pathogens in the meta-analysis; in Ilam province, the species of CCHFV vector(s) have not been mentioned in the source.

**: In this review, total positive ticks have been reported as 175 in its source; however, the addition of individual positive ticks is reported as 174. For this reason, we changed the positive number of *H. anatolicum* from 78 to 79.

***: Abdoli *et al.*, have reported Brucellaceae in this research. We considered this finding as *Brucella* in our analysis.

#: In this study, the total number of positive (infected to pathogen) ticks as well as their species has not been reported. As a result, the number related to this research has not been concluded in our table.

##: In these studies, the total number of tested ticks has been reported in terms of each specific pathogen. As a result, total sample size of the study may be different from each pathogen's sample size.

a: In these investigations, only the exact number of positive ticks were reported and the number of positive species were not specified

b: In these investigations, further to insufficient data regarding genus of pathogen, we considered the pathogen of these studies as *Anaplasma* sp. in the meta-analysis.

c: In these investigations, further to insufficient data regarding genus of pathogen, we considered the pathogen of these studies as *Theileria* sp. in the meta-analysis.

d: In this study, due to insufficient data regarding the number of positive ticks, the percentage of infection was used as the number of positive samples.

e: This study was not included in the meta-analysis due to sample size less than 2.

f: In some investigations, the province of the infected tick(s) was not specified. We have grouped these studies as "unspecified location".

g: Of 22 pathogens investigated, the infection of ticks to *Ba. caballi* and *Ba. ovis* was not confirmed; ticks were found to be infected with 20 pathogens.

h: In some investigations, the species or genera of positive ticks have not been stated. In such cases, we have included the studies as well. So, the sum of the total positive ticks differs with the total number of the ticks morphologically identified at the genus/species level.

Table 2. Different genera of pathogens (as well as CCHFV) detected in tick vectors in different provinces of Iran.

Province	Total tested/positive tick(s)	Positive tick vector(s)	Pathogen(s)
Ardabil	1 062/226	*D. marginatus*; *D. niveus*; *H. aegyptium*; *H. anatolicum*; *H. asiaticum*; *H. excavatum*; *H. marginatum*; *H. schulzei*; *H.* sp.; *O. lahorensis*; *O. tholozani*; *R. bursa*; *R. sanguineus*	*Babesia*; *Borrelia*; CCHFV; *Coxiella*; *Ehrlichia*; *Theileria*
Azerbaijan, East	998/202	*D. marginatus*; *Ha. sulcata*; *H. anatolicum*; *H. asiaticum*; *H. marginatum*; *I. ricinus*; *O. lahorensis*; *R. bursa*; *R. sanguineus*	*Anaplasma*; *Babesia*; *Brucella*; CCHFV
Azerbaijan, West	1 904/192	*D. marginatus*; *H. marginatum*; *R. annulatus*; *R. bursa*; *R. sanguineus*; *R. turanicus*	*Babesia*; *Theileria*
Fars	550/110	*H. anatolicum*; *H. marginatum*; *H.* sp.; *R. sanguineus*; *R.* sp.; *R. turanicus*	*Babesia*; *Ehrlichia*; CCHFV; *Theileria*
Gilan	591/29	*Boophilus* spp.; *D. marginatus*; *I. ricinus*; *R. annulatus*; *R. sanguineus*; *R.* sp.	Anaplasma; Borrelia; Brucella
Golestan	685/78	*H. anatolicum*; *H. dromedarii*; *H. excavatum*; *H. marginatum*; *H. rufipes*; *H. scupense*; *I. ricinus*; *R. bursa*; *R. sanguineus*; *R. turanicus*	*Anaplasma*; *Babesia*; *Borrelia*; CCHFV; *Theileria*
Hamadan	1 755/83	*Ar. reflexus*; *Ha. punctata*; *H. anatolicum*; *H. asiaticum*; *H. detritum*; *H. dromedarii*; *H. marginatum*; *O. tholozani*; *R. bursa*; *R. sanguineus*	*Borrelia*; CCHFV
Hormozgan	30/1	*H. dromedarii*	*Anaplasma*
Ilam	137/9	NA	CCHFV
Isfahan	210/11	*Ha. sulcata*; *H. anatolicum*; *H. asiaticum*; *H.* sp.; *R. sanguineus*	CCHFV
Kerman	1 796/113	*H. anatolicum*; *H. asiaticum*; *H. marginatum*; *R. sanguineus*	*Anaplasma*; *Coxiella*; *Ehrlichia*
Kermanshah	551/135	*H. anatolicum*; *H. asiaticum*; *H. marginatum*; *R. sanguineus*; *R. turanicus*	CCHFV; *Theileria*
Khorasan, North	497/30	*H. anatolicum*; *H. marginatum*; *R. bursa*; *R. sanguineus*; *R. turanicus*	*Babesia*; CCHFV; *Theileria*
Khorasan, Razavi	2 707/344	*H. asiaticum*; *H. excavatum*; *H. marginatum*; *O. tholozani*; *R. appendiculatus*; *R. turanicus*	*Borrelia*; CCHFV; *Theileria*
Khorasan, South	553/101	*Ar. persicus*; *D. niveus*; *H. anatolicum*; *H. asiaticum*; *H. detritum*; *H. dromedarii*; *H. marginatum*; *O. lahorensis*; *R. sanguineus*; *R.* sp.	*Anaplasma*; CCHFV
Khuzestan	655/67	*H. anatolicum*; *H. asiaticum*; *H. detritum*; *H. dromedarii*	*Theileria*
Kohgiluye and Boyer-Ahmad	469/1	*R. bursa*	CCHFV
Kurdistan	3 393/2 269	*Ha. punctata*; *H. anatolicum*; *H. asiaticum*; *H. detritum*; *H. dromedarii*; *H. excavatum*; *H. marginatum*; *O. tholozani*; *R. annulatus*; *R. bursa*; *R. sanguineus*	*Babesia*; *Borrelia*; CCHFV; *Theileria*
Lorestan	1 543/359	*Al. canestrinii*; *Ar. persicus*; *H. anatolicum*; *H. asiaticum*; *H. detritum*; *H. marginatum*; *R. sanguineus*	*Aegyptianella*; *Anaplasma*; *Borrelia*; *Coxiella*; CCHFV; *Rickettsia*; *Theileria*
Mazandaran	2 137/465	*D. marginatus*; *Ha. concinna*; *Ha. inermis*; *Ha. punctata*; *H. anatolicum*; *H. dromedarii*; *H. marginatum*; *I. ricinus*; *R. annulatus*; *R. bursa*; *R. sanguineus*; *R. turanicus*	*Anaplasma*; *Borrelia*; CCHFV; *Theileria*
Qazvin	599/51	*O. erraticus*; *O. lahorensis*; *O. tholozani*	*Borrelia*
Qom	88/6	*H. marginatum*	CCHFV
Semnan	6 031/247	*H. anatolicum*; *H. dromedarii*; *O. tholozani*; *R. sanguineus*	*Borrelia*; CCHFV
Sistan and Baluchestan	3 533/424	*D. marginatus*; *Ha. inermis*; *H. anatolicum*; *H. asiaticum*; *H. detritum*; *H. dromedarii*; *H. excavatum*; *H. marginatum*; *H. schulzei*; *H.* sp.; *R. sanguineus*; *R.* sp.; *R. turanicus*	*Anaplasma*; *Coxiella*; *Ehrlichia*; CCHFV; *Theileria*
Tehran	116/18	*R. sanguineus*	*Theileria*
Yazd	390/23	*H. anatolicum*; *H. asiaticum*; *H. detritum*; *H. dromedarii*; *H. marginatum*	CCHFV; *Theileria*

Babesia (7 provinces), *Borrelia* (10 provinces), CCHFV (19 provinces), *Coxiella* (4 provinces), *Ehrlichia* (4 provinces), *Theileria* (14 provinces), *Anaplasma* (9 provinces), *Brucella* (2 provinces), *Aegyptianella* (1 province), *Rickettsia* (1 province); Positive tick species in different provinces are as follows: *Al. canestrinii* (1 province), *Ar. persicus* (2 provinces), *Ar. reflexus* (1 province), *D. marginatus* (6 provinces), *D. niveus* (2 provinces), *H. aegyptium* (1 province), *H. anatolicum* (17 provinces), *H. asiaticum* (13 provinces), *H. detritum* (7 provinces), *H. dromedarii* (10 provinces), *H. excavatum* (5 provinces), *H. marginatum* (17 provinces), *H. rufipes* (1 province), *H. schulzei* (2 provinces), *H. scupense* (1 province), *Ha. concinna* (1 province), *Ha. inermis* (2 provinces), *Ha. punctata* (3 provinces), *Ha. sulcata* (2 provinces), *I. ricinus* (4 provinces), *O. erraticus* (1 province), *O. lahorensis* (4 provinces), *O. tholozani* (6 provinces), *R. annulatus* (4 provinces), *R. appendiculatus* (1 province), *R. bursa* (9 provinces), *R. sanguineus* (18 provinces), *R. turanicus* (8 provinces), *Boophilus* spp. (1 province), *Hyalomma* spp. (4 provinces), *Rhipicephalus* sp. (4 provinces), NA (1 province).

terms of detection of infection of different pathogens in ticks; meanwhile, the status of tick infection with different pathogens remained unclear in Alborz, Bushehr, Chaharmahal and Bakhtiari, Markazi, and Zanjan provinces. The provinces in which the most studies have been carried out are Sistan and Baluchestan (12 studies), Lorestan (9 studies), Razavi Khorasan (8 studies), Mazandaran (8 studies), Kerman (7 studies), and Ardabil (7 studies). On the other hand, Hormozgan, Ilam, Isfahan, Khuzestan, Kohgiluyeh and Boyer-Ahmad, and Qom were among the least studied provinces (only one study in each province). More than 60 literatures were related to CCHFV and *Theileria*/*Babesia* spp., while *Aegyptianella*, *Brucella* and *Rickettsia* were limited to less than 10 publications (Table 1). According to a random effect model, the total prevalence of tick-borne pathogens in Iran was calculated as 8.6% (95% *CI* 7.0%-10.6%, *P*<0.001). The highest and lowest prevalence rate occurred in Kurdistan (20.5%; 95% *CI* 14.0%-29.1%, *P*<0.001), and Khorasan, Razavi (2.4%; 95% *CI* 0.8%-6.7%, *P*=0.008), respectively. In addition, *Anaplasma* sp. was the pathogen with the highest statistically significant prevalence (23.5%; 95% *CI* 15.1%-34.7%, *P*<0.001), while the lowest infection rate belonged to *Babesia* sp. (4.0%; 95% *CI* 1.9%-8.1%, *P*<0.001) (Table 3).

Statistical analysis revealed that the highest prevalence of *Anaplasma* sp., *Babesia* sp., *Borrelia* sp., CCHFV, *Coxiella* sp., and *Theileria* sp. occurred in East-Azerbaijan (36.5%; 95% *CI* 15%-63.9%, *P*=0.335), West-Azerbaijan (8.8%; 95% *CI* 6.1%-12.5%, *P*<0.001), Kurdistan (8.5%; 95% *CI* 1.2%-41.6%, *P*=0.022), South-Khorasan (14.3%; 95% *CI* 3.7%-42.0%, *P*=0.017), Kerman (9.9%; 95% *CI* 5.8%-16.4%, *P*<0.001), and Mazandaran (21.0%; 95% *CI* 1.5%-82.4%, *P*=0.009), respectively. *Brucella* sp., *Ehrlichia* sp., *Rickettsia* sp., and *Aegyptianella* sp. did not meet the criteria for entering province-specific meta-analysis (less than 2 publications in each province). A forest plot was used to show the prevalence of tick-borne pathogens across the country (Supplementary Figure 1). In addition, funnel plot revealed an asymmetry in the funnel which might indicate that some studies were missed on the right side of the plot (Figure 2). In line with funnel plot, the results of Egger's test (*P*<0.001) showed a publication bias among studies. Based on the funnel plot, most of the studies with low prevalence of tick-borne pathogens were included in this meta-analysis (Figure 2).

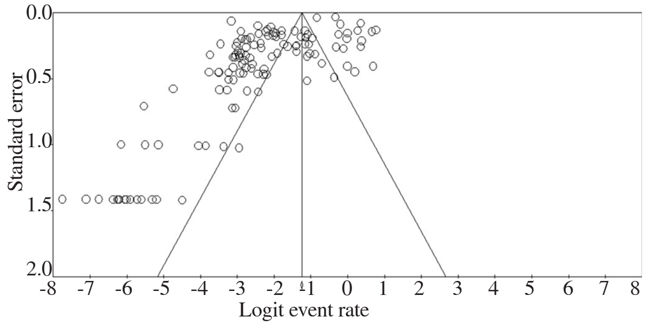

Figure 2. Funnel plot of standard error by logit event rate.

4. Discussion

As far as we know, the present meta-analysis is the first large-scale study that examined the prevalence of tick-borne pathogens in tick vectors in Iran. Overall estimated prevalence of tick-borne pathogens in Iran was 8.6% (95% *CI* 7.0%-10.6%, *P*<0.001). The greatest infection rates among tick vectors were dedicated to *Rickettsia* sp. (*P*>0.05), and *Anaplasma* sp., respectively. *Anaplasma* species are Gram-negative obligate intraerythrocytic bacteria (Rickettsiales; Anaplasmataceae) which are of great veterinary concern. *An. marginale*, the most probable causative agent of bovine anaplasmosis, has been reported worldwide. This pathogen mainly affects ruminants resulting in mild to severe febrile hemolytic anemia that leads to significant economic losses[109]. Other species are as follows *An. ovis* and *An. mesaeterum* (in sheep and goat), *An. phagocytophilum* (in horse, dogs and cats), *An. platys* (in dogs) and *An. centrale* in cattle[110,111]. Although medically important pathogens such as *Borrelia* sp., *Coxiella* sp., and CCHFV were less prevalent in ticks according to the pooled results of literature review, it should be noted that to determine the epidemiological status of a pathogen, all factors affecting pathogen's life cycle must be taken into consideration. For example, CCHF is endemic in Iran and its neighboring countries and a significant number of human cases are reported each year. In a recent review on distribution of ticks and their infection to CCHFV, the main vectors of CCHF, *H. marginatum* and *H. anatolicum*, have been reported in more than 38.7% of provinces of Iran[112]. In our review, among all pathogens, CCHFV positive ticks were reported in 19 provinces. The point may be that in Iran, the main way of CCHFV transmission is not tick bite. CCHFV infection in human mostly occurs due to direct contact with infected livestock (blood, tissues, secretions), which have been infected by ticks[113,114].

Q fever is a zoonosis caused by the bacterium *Cx. burnetii*. Human infection mainly occurs through inhalation of contaminated animal products, direct contact with infected animals and consumption of unpasteurized milk or other dairy products contaminated with this pathogen. Ticks play a key role in transmitting bacteria between animals, and are considered as reservoirs of *Cx. burnetii* bacteria and guarantee the long-term presence of this microorganism in nature[84]. *Borrelia* spp. is the causative agent of Lyme disease and relapsing fever which are zoonotic vector-borne diseases transmitted primarily by ticks[115]. In a descriptive and retrospective study during 1997-2006, Masoumi *et al*. reported that the disease is detected in humans in 18 provinces of the 31 provinces in Iran[116]. Other reports also revealed that *Borrelia* spp. is present in ticks and other vertebrates[35,117]. According to reports of *Cx. burnetii* and *Borrelia* spp. in ticks, humans, and animals in Iran, Q-fever, Lyme disease and relapsing fever can be considered as emerging diseases in the country[118–120].

The most infected provinces in terms of tick-borne pathogens

Table 3. Meta-analysis result of different genera of pathogens (including CCHFV), detected in each province as well as in the country.

Provinces	Pathogens	No. of studies	Sample size	Prevalence (pooled effect size)	95% *CI*		Heterogeneity		*P* values of prevalence	Publication bias	
					Lower	Upper	I^2(%)	*Q* test		Begg's test (2 tailed *P* value)	Egger's test (2 tailed *P* value)
Ardabil	*Babesia* sp.	2	489	0.012	0.000	0.255	81.938	5.537	0.009	NA	NA
	Tick borne pathogens	7	1 351	0.186	0.104	0.310	93.410	91.046	<0.001	0.763	0.357
Azerbaijan, East	*Anaplasma* sp.	3	413	0.365	0.158	0.639	95.564	45.088	0.335	1.000	0.678
	Theileria sp.	2	275	0.032	0.013	0.077	71.037	3.45	<0.001	NA	NA
	Tick borne pathogens	7	998	0.133	0.051	0.305	96.091	153.502	<0.001	0.367	0.051
Azerbaijan, West	*Babesia* sp.	3	1 589	0.088	0.061	0.125	75.961	8.320	<0.001	0.296	0.032
	Tick borne pathogens	4	1 904	0.097	0.074	0.125	67.142	9.130	<0.001	0.308	0.176
Fars	*Theileria* sp.	3	350	0.123	0.009	0.682	97.645	84.928	0.158	1.000	0.081
	Tick borne pathogens	6	810	0.115	0.035	0.316	96.359	137.321	<0.001	0.259	0.045
Gilan	*Anaplasma* sp.	2	83	0.169	0.008	0.830	89.515	9.537	0.326	NA	NA
	Tick borne pathogens	3	590	0.049	0.001	0.699	96.472	56.697	0.127	1.000	0.334
Golestan	*Babesia* sp.	2	96	0.033	0.011	0.097	0.000	0.331	<0.001	NA	NA
	Tick borne pathogens	6	829	0.066	0.030	0.139	87.992	41.639	<0.001	0.707	0.683
Hamedan	*Borrelia* sp.	2	1 239	0.005	0.000	0.278	88.288	8.538	0.017	NA	NA
	CCHFV	3	516	0.124	0.066	0.221	78.850	9.456	<0.001	0.296	0.126
	Tick borne pathogens	5	1 755	0.060	0.023	0.149	88.583	35.034	<0.001	0.027	0.001
Hormozgan							NA				
Ilam							NA				
Isfahan							NA				
Kerman	*Coxiella* sp.	2	620	0.099	0.058	0.164	75.927	4.154	<0.001	NA	NA
	CCHFV	2	461	0.002	0.000	0.015	0.000	0.014	<0.001	NA	NA
	Tick borne pathogens	7	1 796	0.060	0.029	0.119	88.637	88.637	<0.001	0.763	0.110
Kermanshah	*Theileria* sp.	3	1 260	0.096	0.055	0.164	90.249	20.511	<0.001	0.296	0.042
	Tick borne pathogens	4	1 391	0.082	0.047	0.139	88.747	26.659	<0.001	0.308	0.164
Khorasan, North	*Babesia* sp.	3	125	0.029	0.009	0.087	0.000	1.209	<0.001	1.000	0.050
	CCHFV	2	196	0.023	0.001	0.319	77.002	4.348	0.014	NA	NA
	Theileria sp.	4	697	0.036	0.024	0.054	37.422	4.794	<0.001	1.000	0.938
	Tick borne pathogens	9	1 018	0.038	0.027	0.054	31.263	11.639	<0.001	0.676	0.219
Khorasan, Razavi	*Babesia* sp.	2	675	0.002	0.000	0.014	0.000	0.000	<0.001	NA	NA
	CCHFV	3	357	0.044	0.024	0.078	52.013	4.168	<0.001	0.269	0.102
	Theileria sp.	7	2 381	0.033	0.007	0.139	98.126	327.182	<0.001	0.367	0.014
	Tick borne pathogens	13	4 409	0.024	0.008	0.067	97.677	516/536	<0.001	0.076	0.008
Khorasan, South	*Anaplasma* sp.	2	159	0.299	0.129	0.552	88.666	8.823	0.115	NA	NA
	CCHFV	2	294	0.143	0.037	0.420	12.466	91.978	0.017	NA	NA
	Tick borne pathogens	5	553	0.176	0.089	0.317	87.984	33.288	<0.001	0.426	0.243
Khuzestan							NA				
Kohgiluyeh and Boyer-Ahmad							NA				
Kurdistan	*Borrelia* sp.	2	196	0.085	0.012	0.416	90.511	10.538	0.022	NA	NA
	Tick borne pathogens	5	6 500	0.205	0.140	0.291	97.348	150.833	<0.001	0.462	0.240
Lorestan	*Theileria* sp.	5	583	0.125	0.064	0.228	83.837	24.748	<0.001	0.086	0.000
	Tick borne pathogens	11	1 543	0.172	0.087	0.314	96.425	279.715	<0.001	0.061	0.064
Mazandaran	*Anaplasma* sp.	3	817	0.323	0.131	0.601	96.098	51.254	0.207	0.296	0.231
	CCHFV	2	188	0.047	0.023	0.090	15.618	1.185	<0.001	NA	NA
	Theileria sp.	2	40	0.210	0.015	0.824	85.552	6.921	0.009	NA	NA
	Tick borne pathogens	9	2 157	0.100	0.031	0.277	97.765	357.961	0.001	0.754	0.049

Table 3. Continued.

Provinces	Pathogens	No. of studies	Sample size	Prevalence (pooled effect size)	95% *CI*		Heterogeneity		*P* values of prevalence	Publication bias	
					Lower	Upper	I^2(%)	*Q* test		Begg's test (2 tailed *P* value)	Egger's test (2 tailed *P* value)
Qazvin	*Borrelia* sp. = Tick borne pathogens	4	943	0.077	0.020	0.253	94.702	56.624	0.001	0.734	0.993
Qom	NA										
Semnan	Tick borne pathogens	2	6031	0.041	0.036	0.046	0.000	0.010	<0.001	NA	NA
Sistan and Baluchestan	*Anaplasma* sp.	4	657	0.241	0.054	0.641	98.232	169.554	0.193	0.734	0.083
	Coxiella sp.	3	1988	0.041	0.015	0.103	89.324	18.734	<0.001	1.000	0.374
	CCHFV	3	289	0.040	0.018	0.090	28.217	2.786	<0.001	1.000	0.430
	Theileria sp.	3	549	0.122	0.097	0.152	29.684	2.844	<0.001	1.000	0.471
	Tick borne pathogens	14	3533	0.093	0.043	0.188	97.420	503.959	<0.001	1.000	0.392
Tehran	Tick borne pathogens	2	116	0.110	0.000	0.975	93.702	15.878	0.477	NA	NA
Yazd	*Theileria* sp.	2	500	0.015	0.001	0.299	82.719	5.787	0.014	NA	NA
	Tick borne pathogens	3	640	0.055	0.037	0.081	65.569	5.809	<0.001	0.296	0.142
Unspecified location	*Babesia* sp.	2	480	0.077	0.026	0.208	89.207	9.265	<0.001	NA	NA
	Tick borne pathogens	3	541	0.175	0.033	0.565	97.476	79.225	0.093	1.000	0.982
Iran (all collected data)	*Anaplasma* sp.	18	2373	0.235	0.151	0.347	96.596	498.733	<0.001	0.080	0.000
	Babesia sp.	17	6943	0.040	0.019	0.081	97.737	706.904	<0.001	0.010	0.000
	Borrelia sp.	15	5124	0.068	0.029	0.150	97.567	534.363	<0.001	1.000	0.289
	Brucella sp.	NA									
	CCHFV	31	4819	0.056	0.039	0.081	86.951	199.253	0.001	0.091	0.000
	Coxiella sp.	9	3753	0.065	0.030	0. 138	96.738	245.246	<0.001	1.000	0.450
	Ehrlichia sp.	4	693	0.177	0.056	0.437	96.744	92.137	0.019	0.734	0.594
	Rickettsia sp.	2	125	0.283	0.029	0.839	96.370	27.552	0.480	NA	NA
	Theileria sp.	36	11076	0.093	0.067	0.129	96.157	910.777	<0.001	0.827	0.000
	Tick borne pathogens	135	35184	0.086	0.070	0.106	97.429	5211.303	<0.001	0.933	0.000

Note: In this analysis, each row of Table 1 was considered as an individual data. Furthermore, the sample size of each row of Table 1 was considered a separate sample size, and all pathogens were included. Provinces with less than two data were not included in meta-analysis. However, the pathogens detected in these provinces were calculated in Iran's total prevalence of pathogens section.

were Kurdistan (20.5%), Ardabil (18.6%), South Khorasan (17.6%), Lorestan (17.2%), East Azerbaijan (13.3%) and Fars (11.5%), respectively. Geographically, these provinces (except South Khorasan) are located in the western parts of Iran. Therefore, it can be concluded that although tick-borne pathogens have been reported from different regions of Iran, the western part of the country is more infected than other regions. This high prevalence can be justified due to high livestock population, common border with neighboring countries and traditional livestock holding methods with low hygiene.

In this analysis, 26 out of 31 provinces were surveyed regarding tick-borne pathogen detection in ticks; meanwhile, the status of infection of ticks to different pathogens remained unclear in five provinces: Alborz, Bushehr, Chaharmahal and Bakhtiari, Markazi, and Zanjan. Due to the importance of ticks and their impact on human and animal health, it is highly advisable to conduct studies concerning tick-borne diseases to clarify the status of these provinces. Vector surveillance seems to be vital for observing the presence or occurrence of emerging and reemerging tick borne diseases in Iran and provides a preliminary warning for predicting probable epidemics.

In our analysis, *H. anatolicum* (20.35%), *R. sanguineus* (15.00%), and *R. bursa* (14.08%), were the most prevalent infected ticks in Iran. Genera of *Hyalomma* species have received much attention due to the role in the transmission of *Theileria* spp., *Babesia* spp., *Rickettsia* spp., and CCHFV. *R. sanguineus* (brown dog tick, kennel tick) is found worldwide with an interest toward warmer climates (tropics and sub-tropics)[121]. Dogs are specific host for *R. sanguineus*, however, it can be found on domestic ruminants and other vertebrates. Several pathogens such as *Ba. canis*, *Cx. burnetii*, *Eh. canis*, *Ri. conorii*, *Ri. rickettsii*, *Theileria* sp., *Anaplasma* sp., and CCHFV have been isolated from *R. sanguineus*[122–124]. *R. bursa* is common among livestock transmitting the protozoans *Ba. bigemina*, *Ba. caballi*, *Th. equi* and *Ba. bovis*[125]. Following these highly infected vectors, much lower prevalence levels were detected in *R. appendiculatus*, *H. schulzei*, *H. rufipes*, *H. aegyptium* and *Boophilus* sp. These vectors should not be underestimated, as future investigations may reveal a high tendency of these species to transmit pathogens.

Controlling strategies against ticks and tick-borne diseases for prevention of significant losses due to both economic and public health problems are also seem to be important and helpful. Many attempts have been carried out for the control of ticks and tick-borne diseases[126]. Some other additional methods have been suggested: (1) livestock sheds should be checked regularly in terms of tick infestation; (2) different species of livestock should be held separately to avoid interspecies tick infection; (3) quarantine of newly purchased animals decreases the chance of tick transmission to existing animals; (4) periodic application of acaricide and chemotherapy according to regional and national guidelines is sometimes suggested; (5) clearance of vegetation cut off the connection between different stages of tick's life and disrupts their life cycle is also suggested; (6) some novel methods including application of vaccines against tick-borne pathogens, biological control, and genetically resistant livestock breeds are in the spotlight[127].

This investigation had some limitations: In the old classification of Iran provinces, some provinces are currently divided in two or more provinces, resulting in the less accuracy of the old literature, as they cover a larger area. In addition, access to the full text of some dissertations required a visit to the relevant center, which was very difficult due to the COVID-19 pandemic. In such cases, we missed some dissertations. Furthermore, the scientific name of some of tick species had changed since the publication of the associated papers, so we had to search with the old names as well.

In conclusion, the occurrence of at least 20 different pathogens (in 10 genera) in 28 species (in 9 genera) of ticks in 26 provinces of Iran, sheds light on the current status of the country in terms of tick-borne pathogens. Rate of infection to different pathogens in different regions, especially western parts of Iran, is a warning for public and animal health. Further investigations and persistent surveillance of vectors as well as vertebrate hosts will expand the chance of controlling tick-borne pathogens. In most parts of the meta-analysis concerning total pathogens of Iran, the results showed high heterogeneity ($I^2 > 75\%$). Similarly, meta-analysis of separate provinces revealed high heterogeneity. This is not unexpected due to the variations associated with the different detection methods, sample size, geographical traits, location, time of the study, and population of interest. While the significance of a meta-analysis in regarding to the prevalence of tick-borne pathogens is undeniable, it is suggested that meta-analysis should not be an adequate alternative for large-scaled epidemiological studies due to heterogeneous approaches, regions and times of different studies.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Authors' contributions

HB, MK, and ASJ planned for the study. HB, ASJ, MK, and MMS performed the literature search and data extraction. MK and ZT critically evaluated the manuscript. ASJ performed the meta-analysis. The final manuscript approved by all the authors.

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