



## Frequency and Clinical Manifestations of Pediatric Brucellosis in Iran: A Systematic Review

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### Abstract

#### Background

Brucellosis is a zoonotic disease that is widely distributed throughout the developing countries. Children are considered as at risk groups for infection. The aim of this study was to assess the frequency and clinical manifestations of Brucellosis in Iranian children and adolescents.

**Materials and Methods:** We systematically searched international databases; ISI, Medline (via PubMed), Scopus, and national databases Irandoc, Barakat knowledge network system, Magiran, and Scientific Information Database (SID). The search strategy was developed based on main terms of "Brucellosis," "Brucella fever", "Gibraltar", "Rock Fever", "Undulant Fever", "Cyprus Fever", "Malta Fever", and "Bang Disease".

**Results:** A total of 885 studies were identified, from them a total of 12 studies that were conducted between 2001 and 2016 were included. Following the relevancy assessments and quality control, data from the 1,429 participants were presented in our review. The age of the patients ranged from 2 to 18 years. Only one out of twelve studies provided the prevalence of 4.30% and 3.4 incidence. Studies varied greatly in reporting high risk behavior of animal contact (8.4 to 76.0%) and unpasteurized dairy (22.4 to 91.6%).

#### Conclusion

Our finding reveals the disparity of reported prevalence and clinical manifestations of Brucellosis in Iranian children. Fever and joint pain were the most frequent reported signs. Differences in study design, measurement tools and methods, and sub population sampling, does not provide the possibility of aggregation of data for more comprehensive inference.

**Key Words:** Brucellosis, Children, Clinical manifestations, Iran.

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## 1- INTRODUCTION

Brucellosis is one of the most common zoonotic infections worldwide (1, 2). Scientific evidence reveals it is widely distributed throughout the developing countries (3-5). Recent evidence warns about the increasing trends of infection, especially in undetected cases (2, 6, 7). These gram-negative facultative intracellular pathogens could lead to high morbidity diseases in humans and many species of domesticated and wild animals. The infection mostly causes flu-like symptoms, including weakness, fever, malaise and weight loss (5, 7). To date, there are eight different identified species as: *Brucella melitensis* (*B.melitensis*), *B. abortus*, *B. suis*, *B. canis*, *B. neotomae*, *B. ovis*, *B. ceti* and *B. pinnipedialis*, except for *B. neotomae* and *B. ovis*, the others are pathogenic for humans (8).

The importance of adverse health effects of this disease is not limited to physical complications, its widespread increasing trends have become one of the most important challenges for economic development in many countries such as Iran, whose economic growth and employment to a great extent depend on animal husbandry and agriculture (9, 10). Children and young people, students and farmers, especially in rural areas are considered as at risk groups (11, 12). In children early diagnosis and treatment are crucial factors for the prevention of morbidity and mortality (13, 14). Considering the increasing trends and burden of disease, access to reliable reports and evidence have become crucial to set priorities in the health care systems (15-17). Policy makers and health providers require information to gain a better insight into the preventive and controlling approaches (18,19). Childhood brucellosis as a challenging problem in Iran has serious complications like arthritis (4, 20). To the best of our knowledge, despite the high priority given to the

problem, there is no comprehensive related literature on these topics (4, 10, 17). To respond to the evident gap in related literature, present study aimed to systematically review all of the studies on the prevalence and clinical manifestations of Brucellosis in Iranian children. We followed a comprehensive approach to conducting an up-to-date systematic review of all available studies. We believe that results from this study will enhance understanding about the epidemiology of brucellosis in Iranian children and assist the policy makers in improving their preventive and controlling strategies.

## 2- MATERIALS AND METHODS

### 2-1. Searching

In order to assess the prevalence and clinical manifestations of Brucellosis in Iranian children, using Medical Subject Headings (MeSH) terms, and Emtree pathways, in April 10 2018, three international databases of Medline (via PubMed), Web of Science, and Scopus were searched for published scientific evidence and peer review studies. We also searched all of the systematic national databases of Irandoc, Magiran, Barakat knowledge network system, and Scientific Information Database (SID) for English and their equivalent Persian key terms. The search strategy, developed based on main terms of "Brucellosis", "Brucella fever", "Gibraltar", "Rock fever", "Undulant fever", "Cyprus fever," "Malta fever", "Bang disease". All of the related MeSH terms and key words were added to search queries. The results were limited to human subject. For international searches there was not any restriction for language and time (**Table.1**). National databases were searched based on English developed search strategy and its equivalent Persian key words. Reference Manager bibliographic software was used to manage searched citations. Duplicate entries were identified by considering the title of the

papers, authors, the year of publication, and specifications of the sources. In questionable cases, the abstract texts were compared.

**Table-1:** Search strategy for frequency and clinical manifestation in Iran

PubMed
((("Brucellosis "[Mesh] OR " Brucellosis, Bovine "[Mesh] OR "Brucella" [ MeSH Terms] OR "Brucella" [ All Fields] OR "Brucellosis"[ MeSH Terms] OR "Brucellosis" [ All Fields] OR "Gibraltar"[ All Fields] OR "Brucellosis "[ All Fields] OR "Fever"[ All Fields] OR "Rock Fever" [ All Fields] OR "Undulant Fever" [ All Fields] OR "Cyprus Fever" [ All Fields] OR "Malta Fever" [ All Fields] OR "Bang Disease" [ All Fields] ) AND ("Iran "[ MeSH] OR "Iran"[All Fields]" OR "persia" [ Mesh])).
Scopus
(( ( TITLE-ABS-KEY ("Bang Disease) OR TITLE-ABS-KEY ("Malta AND fever ") OR TITLE-ABS-KEY (" cyprus AND fever ") OR TITLE-ABS-KEY (" undulant AND fever ") OR TITLE-ABS-KEY ("rock AND fever ") OR TITLE-ABS-KEY (" Gibraltar AND fever" ) OR TITLE-ABS-KEY ("Brucella" ) OR TITLE-ABS-KEY ( Brucellosis ) ) ) AND ( ( TITLE-ABS-KEY ( Iran* ) OR TITLE-ABS-EY ( Persia* ) ) ).
ISI/WOS
TOPIC: (Se) OR ("Bang Disease") OR TOPIC: ("Malta Fever") OR TOPIC: ("Cyprus Fever") OR TOPIC: (Brucellosis) OR ("Undulant Fever") OR TOPIC: ("Rock Fever") OR TOPIC: ("Gibraltar Fever") OR TOPIC: (Brucella) TOPIC: (Iran*) OR TOPIC: (Persia*) Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years.

**2-2. Inclusion and exclusion criteria**

All available studies that were conducted on relevant subjects were included. Studies in sub- groups of specific population such as non-Iranian populations were excluded. In case of more than one extracted document from the one specific study, paper with reporting of more complete data was considered. We also excluded papers with duplicate citations. Papers for which the required data for classification and analyzing could not be obtained were

considered for possible future work and assessment of availability of resources. Non peer reviewed, conference proceedings and book chapters were followed for more data availability.

**2-3. Validity Assessment and data extraction**

After three steps of data refinement for titles, abstracts and full texts, the full text of each selected article was retrieved for detailed analysis. According to standard forms (2, 21) quality assessment and data extraction were conducted by a check list which recorded: citation, publication year, study year, place of study, type of study, population characteristics and methodological criteria (sample size, mean age, type of measure, results of measures and other information). All processes from systematic search to the data extraction were followed independently by two research experts (Kappa statistic for agreement for quality assessment; 0.92). Under the supervision of main investigator, probable classification discrepancies were resolved by discussion. Based on brucellosis literature (22), a comprehensive list of clinical manifestations of Brucellosis cases was designed. Through reviewing papers, data recorded under each specification of: general criteria (documented fever, sweats, chills, fatigue, headache, malaise, weight loss, nausea/vomiting); abdominal signs or symptoms (abdominal pain, splenomegaly, hepatomegaly, hepatitis); musculoskeletal details (arthralgia, arthritis, myalgia, back pain, spondylitis, and sacroiliitis), and specific organ involvement (epididymo-orchitis, abortion, endocarditis, respiratory and neurological signs, and cutaneous changes) the number of subjects with each symptom/syndrome was recorded for each study, as well as the number of male and female patients.

**2-4. Statistical analysis**

For all available data, the interested results were presented as prevalence and incidence of disease and also clinical manifestations in infected cases. The Chi-square based Q test and I square statistics were used to assess the heterogeneity between the studies reported prevalence. The result of Q test was regarded as statistically significant at  $P < 0.1$ . Due to severe heterogeneity among studies regarding reported values, pooled prevalence was not possible through random-effect meta-analysis model. The analyses were conducted using STATA software version 11.0.

### 2-5. Ethical considerations

Present study was approved by the ethical committee of Alborz University of Medical Sciences. All of the included studies were cited in all reports and all extracted publications. When more information was needed about a certain study, the corresponding author was contacted.

## 3- RESULTS

### 3-1. Searching

We refined data for prevalence and clinical manifestations of Brucellosis in Iranian children. **Figure.1** shows the review flowchart of the databases searched and the number of hits in each steps. A total of 885 studies were identified, from them 760 papers were found through international databases and 43.72% were duplicates.

### 3-2. Flow of the included studies

**Figure.1** shows a flow diagram of the process for the selection of articles included in the review. In total, 289 frequency and morbidity studies were selected, for which full text was available for 153. However, 14 of these were in languages in which the team was not competent [Croatian (6), Turkish (4), Korean (2), Persian (1), Mandarin (1)],

leaving 96 morbidity studies for quality assessment. Some articles contained both frequency and morbidity data and were thus counted in both categories. According to our search strategy 254 records were found; of them, 185 were from international databases and the remaining 69 were obtained from national databases. After removing duplicates, via the refining steps, only 53 articles were found related to our study domain. Considering inclusion and exclusion criteria, 34 articles that met eligible criteria remained for data extraction. The flow diagram of the study selection process is shown in the **Figure.1**.

### 3-3. Study Characteristics

A total of 12 studies that were conducted between 2001 and 2016 were included (**Table.2**). Considering the assigned inclusion/exclusion criterion, following the relevancy assessments and quality control, totally, data from the 1,429 participants were presented in our investigation. The age of the patients ranged from 2 to 18 years. Studies varied greatly in reporting high risk behavior of animal contact (8.4-76.0%), and unpasteurized dairy (22.4-91.6%). One out of twelve studies provided the prevalence of 4.30% in Kohak district of Qom province (**Table.2**) (*Please see the table at the end of paper*).

Considering the clinical manifestations, fever and joint pain were the most frequent reported signs which were described in 10 studies. The prevalence of fever in infected children ranged from 32.0% up to 97.0%. The joint pain problem prevalence differs from 49.5 to 83.0%. After these, Splenomegaly as the second most frequent sign in 9 studies fluctuated between 16.9% and 43.2%. Sweating and hepatomegaly were mentioned in 7 studies reporting 44.0-76.4%, and 4.0- 59.0%, respectively. Cough (6.0-15.0%), and chills (16.2-45.8%) were the least reported sign (**Table.3**) (*Please see the table at the end of paper*).

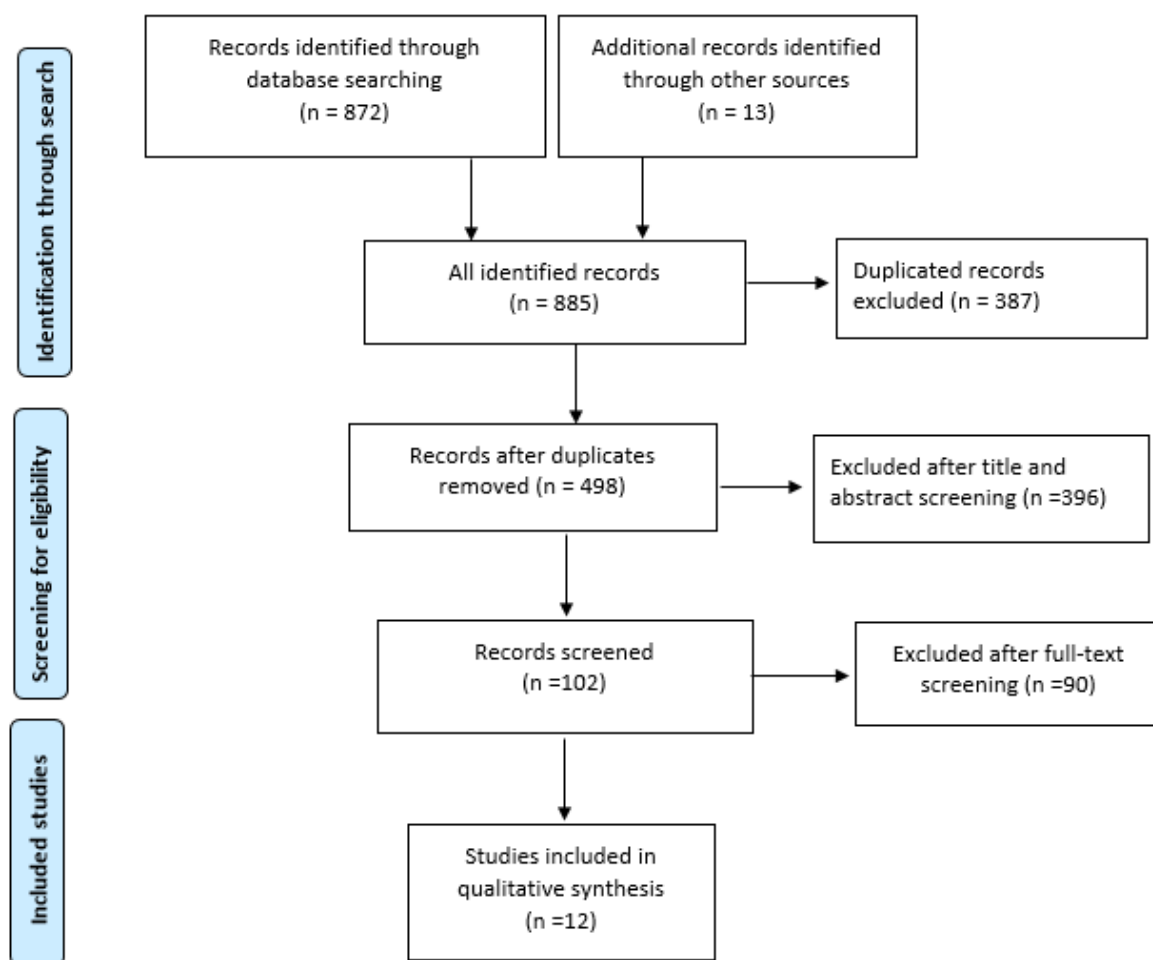


Fig.1: PRISMA flowchart of present study.

#### 4- DISCUSSION

Despite the conducted studies, brucellosis remains a challenging health problem in Iran (12). This is the first systematic review on reported prevalence and clinical manifestations of Brucellosis in Iranian children according to gender, age, and levels of reported values, which is conducted with no limitation of time and language. In our study, from a total of 885 searched papers, 12 studies were eligible for inclusion. Our findings provide an evidence-based view for better insight for relevant stakeholders and policy makers. A total of 885 studies were identified, from them 760 papers were found through international databases. A total of 12 studies that were conducted between 2001

and 2016 were included. Following the relevancy assessments and quality control, data from the 1429 participants were presented in our investigation. The age of the patients ranged from 2 to 18 years. Studies varied greatly in reporting high risk behavior of animal contact (8.4-76.0%), and unpasteurized dairy (22.4-91.6%). The clinical signs of brucellosis presented in our systematic review are consistent with other literature (13). In Iranian children such as other studied populations, the clinical manifestations vary from a sub-acute clinical disease to a chronic disease (17). In related literature, the arthritis and fever are the most common clinical findings of brucellosis (17). Other related studies emphasized on



a widely distributed infection throughout the developing countries (1, 2). Annually more than 500,000 new cases are recorded in the world, most of them are reported from the developing regions where the disease is endemic (3, 25). The results of studies show that the highest prevalence is found in the Mediterranean basin, the Arabian Peninsula, the Indian subcontinent and parts of Central and South America (26-28). According to World Health Organization (WHO) report, every year, more than 45,000 new cases of infection are reported from countries of Eastern Mediterranean region (29); the evidence also emphasized on considerable trends in Iran (28, 30). Unfortunately, there is very limited information about the problem in Iran (8, 10, 12, 30, 31). Considering the specific criteria for Iran, the geographic situation of the country is discussed as an important risk factor for the propagation of contagious diseases, mainly in contact with the eastern and western neighbors such as Iraq, Pakistan and Afghanistan (1). Some central parts of the country have been some of the most important endemic areas of brucellosis for many years. In 1964, nearly 80% of all infection reported to WHO were from these areas (8, 32).

According to one study in 2003, the average incidence of infection with brucellosis in adult Iranian population was 21 cases per 100,000 population. Based on this estimation, in different parts of the country, incidence of disease varied between 1.5 and 107.5 per 100,000 population (33). Based on the other documents, the prevalence of diseases in Iranian adults has been reported from 0.5 to 10.9% in different provinces. In a study in Tehran province the incidence of brucellosis was reported as 17.5 per 100,000 population (34). Children and young people, students and farmers, especially in rural areas are considered as at risk groups (8, 9, 11). A retrospective descriptive study on children in Tehran

showed that from 96 children diagnosed with brucellosis, 24 (25%) had Brucella arthritis, 14 (58.3%) males and 10 (41.7%) females. Most common manifestations were fever (87.5%) and fatigue (75%). Mono arthritis was recorded in 15 patients (62.5%) of the cases with involvement of the knee in 8 (45%) and hip in 5 (29%), the ankle in 2 (8%) patients while 9 (37.5%) patients suffered from poly arthritis. None of the patients had axial joints involvement (12). In other research the most frequent symptom in 79.7% of the cases was joint pain, 72.9% had history of fever during the course of the disease. Arthritis, splenomegaly and lymphadenopathy were found in 60.97%, 16.9%, 7.5%, of patients, respectively (20). In other experience 57% of patients were from rural areas, and 43% were from cities. About 65% had a positive history of consuming unpasteurized milk products. The most frequent symptoms found were arthralgia (79%), and fever (78%). The most common physical symptoms were fever (51%), and arthritis (26%) (19).

Other studies in Iranian children reported that in comparison with previous reports from this center (1988 to 2001), the incidence of brucellosis remained unchanged over the years (nearly 3-4 patients per year) (21); in most of the studies boys are at higher risk than girls. The probable reason that the boys are more affected than girls may be the more exposure to the domestic animals. Regarding age distribution, seven (16%) patients were under 3 years old (17). Other researches showed the same results (24, 31, 32). The epidemiological research on the clinical manifestations in 469 adult brucellosis infected patients in the northern part of Iran shown that consumption of fresh cheese (22.4%), animal husbandry (11.3%), working in a laboratory (8.1%), and veterinary profession (1.5%) were the main risk factors for contamination (30). As suggestions for prevention and control

of problem, some important health related safety considerations such as delivery and milking of livestock, not consuming non-pasteurized dairy products, promotion of the health surveillance system must be improved by the public and private sectors (8). It is emphasized that, in children, like adults, prescriptions for early diagnosis and treatment are crucial factors for the prevention of morbidity and mortality (10, 24). Many studies reveal that in Iran there are significant differences in the geographic distribution of brucellosis, with the incidence rates being highest in most of the cities in the west and north-west of the country (4, 9, 10).

## 5- CONCLUSIONS

To the best of our knowledge, this is the first systematic review of clinical manifestations of Brucellosis in Iranian children that provides practical information for better health policy and more targeted planning studies in this field. Incidence rates were highest in most of the cities in the west and north-west of the country. Fever and joint pain were the most frequent reported signs. Studies varied greatly in reporting high risk behavior of animal contact and unpasteurized dairy. These also can be used for future complementary studies.

## 6- CONFLICT OF INTEREST

All the authors declare that they have no conflict of interest.

## 7- ACKNOWLEDGMENTS

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## 8. AUTHORS' CONTRIBUTIONS

SD, RA and MQ developed the main design of manuscript. MG, YS and HA extracted data. All co-authors

contribution and participated in the revision of the manuscript.

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**Table-2:** General characteristics of included studies.

No	Author (reference)	Year	City	Sample size	Gender (%)		Living area (%)		High Risky behavior (%)		Age group	Prevalence	Incidence
					Male	Female	Urban	Rural	Animal Contact	Unpasteurized dairy			
1	Savadkuhi & Zoghi (23)	2001	Tehran	116	-	-	-	-	-	56.0	<12	-	-
2	Hasanjani et al. (24)	2005	Babul	111	55.0	45.0	59.5	40.5	-	-	3-15	-	-
3	Ettehad (25)	2007	Ardabil	51	76.5	23.5	66.0	34.0	-	62.0	1-12	-	-
4	Afsharpaiman & Mamishi (26)	2008	Tehran	44	65.9	34.0	39.0	61.0	-	65.9	≤ 14	-	-
5	Soleimani (27)	2010	Zahedan	42	68.8	24.4	67.0	33.0	33.3	-	≤ 15	-	-
6	Ayazi et al. (28)	2011	Ghazvin	175	61.0	39.0	57.0	43.0	58.0	65.0	< 12	-	-
7	Zamani et al. (20)	2011	Tehran	96	58.3	41.7	25.0	75.0	8.4	83.4	2-12	-	-
8	Sasan et al. (29)	2012	Khorasane Razavi	82	60.0	40.0	70.2	29.8	76.0	91.6	10-16	-	-
9	Fanni et al. (30)	2013	Tehran	34	65.0	35.0	00.0	100	15.0	65.0	2-14	-	-
10	Khalili et al. (31)	2014	Zahedan	32	75.0	25.0	-	-	-	-	7-19	-	-
11	Aghaali et al. (32)	2015	Qom	186	51.0	49.0	00.0	100	17.7	29.0	7-12	4.3%*	3.4% <sup>‡</sup>
12	Khazaei et al. (33)	2016	Hamedan	460	69.0	31.0	87.8	12.2	37.0	22.4	< 11	-	41.4 <sup>€</sup>

\*Asymptomatic brucellosis; <sup>‡</sup>Appearance of symptoms after one year follow up; <sup>€</sup> Per 100 000 population.

**Table-3:** Clinical manifestations of brucellosis in Iranian children.

No	Author (reference)	Year	Clinical manifestations (%)												
			Fever	Joint pain	Sweating	Anorexia	Fatigue	Weight loss	Abdominal pain	Headache	Cough	Chills	Splenomegaly	Hepatomegaly	Lymphadenopathy
1	Savadkuhi & Zoghi (23)	2001	97.0	72.0	44.0	78.0	-	-	12.0	-	-	-	20.0	4.0	6.0
2	Hasanjani et al. (24)	2005	73.9	49.5	67.6	-	-	-	-	-	-	16.2	18.0	-	-
3	Ettehad (25)	2007	84.2	81.2	60.2	-	-	-	-	-	-	-	21.0	31.0	18.0
4	Afsharpaiman & Mamishi (26)	2008	77.4	79.5	52.3	61.4	-	-	-	-	-	-	43.2	34.1	13.6
5	Soleimani (27)	2010	32.0	83.0	76.4	16.0	20.0	6.0	-	-	6.0	-	38.0	59.0	-
6	Ayazi et al. (28)	2011	78.0	79.0	44.0	28.0	40.0	14.0	20.0	18.0	15.0	41.0	20	16	12
7	Zamani et al. (20)	2011	87.5	62.5	-	-	75.0	20.8	-	58.3	-	45.8	25.0	16.7	-
8	Sasan et al. (29)	2012	73.0	79.7	-	-	-	-	-	-	-	-	16.9	-	7.5
9	Fanni et al. (30)	2013	74.0	65.0	59.0	71.0	68.0	50.0	24.0	21.0	14.0	-	32.0	24.0	18.0
10	Khalili et al. (31)	2014	39.0	83.0	-	-	45.0	-	21.0	55.0	-	-	-	-	-
11	Aghaali et al. (32)	2015	-	-	-	-	-	-	-	-	-	-	-	-	-
12	Khazaei et al. (33)	2016	-	-	-	-	-	-	-	-	-	-	-	-	-