Atiya imteyaz

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Submission date: 23-Jul-2022 05:43AM (UTC-0400)
Submission ID: 1843754652
File name: final_nisha_dissertation.docx (1.14M)
Word count: 8895
Character count: 49615

DISSERTATION SUBMITTED FOR THE MASTER'S DEGREE IN MEDICAL MICROBIOLOGY

TITLE

"Brucellosis in India and global picture-Meta analysis"

SUBMITTED BY

Atiya Imteyaz

2022

DEPARTMENT OF MICROBIOLOGY INTEGRAL INSTITUTE OF MEDICAL SCIENCES AND RESEARCH INTEGRAL UNIVERSITY LUCKNOW- 226026, U.P, INDIA

INTEGRAL INSTITUTE OF MEDICAL SCIENCE AND RESEARCH
INTEGRAL UNIVERSITY, LUCKNOW

"Brucellosis in India and global picture-Meta analysis"

DISSERTATION

SUBMITTED TO: -INTEGRAL UNIVERSITY

In partial fulfilment of the need for the award of the degree of Master of Science

In

Medical Microbiology

BY: -Atiya Imteyaz

Enrolment No: - 1900103437

UNDER THE GUIDANCE OF

Guide:

DR. NOOR JAHAN (MBBS., MD)

PROFESSOR & HOD DEPARTMENT OF MICROBIOLOGY

IIMS&R, LUCKNOW

INTEGRAL UNIVERSITY
Established Under U.P. Act No. 09 of 2004 by State Legislation Approved by University Grants Commission
Phone No.+91(0552)2890812,2890730,3296117,6451039Fax No.0522-2890809
Kursi Road, Lucknow-226026, Uttar Pradesh(INDIA)

DECLARATION OF CANDIDATE

I hereby declare that this dissertation entitled **"Brucellosis in India and global picture-Meta** analysis" is bonafide and genuine research work carried out by me under the guidance **of DR. NOOR JAHAN (MBBS., MD) PROFESSOR & HOD**, Department of Microbiology, Integral Institute of Medical Sciences and Research, Lucknow.

DATE:15/07/2022 ATIYA IMTEYAZ

PLACE:Lucknow

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Phone No.+91(0552)2890812,2890730,3296117,6451039Fax No.0522-2890809
Kursi Road, Lucknow-226026, Uttar Pradesh(INDIA)

ENDORSEMENT BY THE HOD

This is to certify that the dissertation entitled "*Brucellosis in India and global picture-Meta analysis*" is a bonafide and genuine research work carried out by Atiya imteyaz under the guidance of **DR. NOOR JAHAN MBBS., MD) PROFESSOR & HOD DEPARTMENT OF MICROBIOLOGY IIMS&R, LUCKNOW** in partial fulfilment of the requirement for the degree of Master of Science in Medical Microbiology. The research methods and procedure described have been done by the candidate and the results have been observed by the guides periodically.

DATE:

PLACE:

DR. NOOR JAHAN MBBS, MD)
PROFESSOR & HOD
DEPARTMENT OF MICROBIOLOGY
IIMS&R, LUCKNOW

INTEGRAL UNIVERSITY
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Phone No.+91(0552)2890812,2890730,3296117,6451039Fax No.0522-2890809
Kursi Road, Lucknow-226026, Uttar Pradesh(INDIA)

CERTIFICATE BY THE GUIDE AND CO-GUIDE

This is to certify that the dissertation entitled **"*Brucellosis in India and global picture-Meta analysis*"** is a bonafide and genuine research work done by Atiya imteyaz in partial fulfilment of the necessity for the degree of Masters of Science in Medical Microbiology.

The research methods and procedures described are done by the candidate and results are observed by the guide periodically.

DATE:

GUIDE:	CO-GUIDE:	CO-GUIDE:
DR. NOOR JAHAN MBBS, MD) PROFESSOR & HOD DEPARTMENT OF MICROBIOLOGY IIMS&R, LUCKNOW	**Dr Siraj ahmad** PROFESSOR & HOD DEPARTMENT OF Community medicine IIMS&R, LUCKNOW	**Dr Ausaf Ahmad**, Associate Professor Dept. of community medicine IIMS&R, Lucknow
SIGNATURE: ……	SINGATURE ……	SIGNATURE ……

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CERTIFICATE

This is to certify that research work entitled **"Brucellosis in India and global picture A meta - analysis"** submitted by **Atiya Imteyaz, Dr.Noor Jahan Dr.Siraj Ahmad, Dr.Ausaf Ahmad** for ethical approval before the Institutional Ethics Committee IIMS&R.

The above mentioned research work has been approved by Institutional Ethics Committee, IIMS&R with consensus in the meeting held on **19 May 2022**.

Dr.Deepak Chopra
(Jt.Member Secretary)
IRC/IEC
IIMS &R

Dr.Q.S.Ahmed
(Member Secretary)
IRC/IEC
IIMS &R

ACKNOWLEDGEMENT

I take this opportunity to extend my sincere gratitude and appreciation to all the helping hands who made my dissertation work a huge success.

Thanks to Allah for giving me strength and energy to finish this study.

I am thankful to the Integral University, Lucknow for providing the opportunity, laboratory equipment, materials, and valuable support, to complete this study.

First and foremost, I am extremely thankful to **DR. NOOR JAHAN (MBBS., MD) PROFESSOR & HOD DEPARTMENT OF MICROBIOLOGY IIMS&R, LUCKNOW,** whose benevolent guidance and constant encouragement helped me a lot doing my dissertation.

I express my heartful gratitude and regards to our esteemed teacher and my co- guide **Dr Siraj ahmad** PROFESSOR & HOD DEPARTMENT OF Community medicine IIMS&R,LUCKNOW**. Dr. Ausaf Ahmad**, Associate Professor Dept. of community medicine IIMS&R, Lucknow, for providing excellent guidance, motivation and keep interest in my dissertation. It was a great opportunity and wonderful experience to work under his supervision.

I express my heartiest thanks to Mrs. Sandeepika Dubey, Dr. Karuna Katiyar, Faculty members, Department of Microbiology, IIMS&R for their ready to help, support and guidance.

I am highly thankful to Dr. Ausaf Ahmad Statistician & Associate Professor, Department of Community Medicine for his kind interest, valuable guidance and statistical analysis in the dissertation work.

I am also thankful to Mr. Salman (Computer Operator), Mr. Dheeraj (Lab Technician), Mr. Dhirendra (Lab Technician), Mr. Mohsin (lab Technician)

for providing laboratory facilities and guidance during the period of work.

Finally, Special thanks to my entire family members who encouraged me to believe in hard work and not to worry about the results.

DATE: ATIYA IMTEYAZ

DEDICATED TO
TEACHER
"FAMILY"
&
"FRIENDS"

CONTENTS

LIST OF ABBREVIATIONS	
DALYs	Disability adjusted life years
BC	Blood culture
RBT	Rose Bengal test
SAT	Standard agglutination test
CF	Complement fixation
ELISA	Enzyme-linked immunosorbent assay
IFA	Indirect fluorescent-antibody
TR-FRET	Time-resolved fluorescent resonance energy transfer
FPA	Fluorescent polarization immunoassay
NAATs	Nucleic acid amplification tests
PCR	Polymerase chain reaction
PCR-EIA	PCR enzymatic immuno-assay
RT-PCR	Real-time PCR
M-RT-PCR	Multiplex real-time PCR
Q-RT-PCR	Quantitative real-time PCR
LAMP	Loop-mediated isothermal amplification
FISH	Fluorescence in situ hybridization
WGS	Whole genome sequencing

LIST OF TABLES

INTRODUCTION

Brucellosis is a disease caused by a bacterium of the genus Brucella, which is likely to be a zoonotic disease. **Brucella is a small, gram-negative cocci that most often lack the capsule, endospores, or native plasmids** [(1)]**.** They live inside the cells inside the host organism & exhibit environmental persistence outside the host. Intracellular transport involves 2 or 3 major steps, begins with the endosome vacuole, the endoplasmic reticulum compartment, and finally the vacuole with multiple markers of atypical autophagy. They withstand extreme temperatures, pH, & humidity, and withstand frozen and worn materials. They may infect many species, but also have some specificity [(2).]

The lysovialess group of alphaproteobacteria classes includes the Brucella species. Agrobacterium tumefaciens, Sinorhizobium meliloti, and Ochrobactrum anthropi are examples of unipolar growing organisms. The replication and separation of their two chromosomes, which are the norm, are coordinated over time. [(3).]

The disease has an impact on human health and is a major public health concern in underdeveloped nations [(4).] The Mediterranean Sea, the Middle East, the Arabian Peninsula, Africa, Latin America, and Asia are among the regions where it is endemic. It is also known that the four Brucella species—Brucella abortos, Brucella melitensis, Brucella Switzerland, and Brucella canis—can make people sick on a regular basis. Other Brucella species, such as Brucella inopinata, Brucella ceti and Brucella microti, inflict illness in animals but very infrequently on people (5). The World Organization for Animal Health (OIE) and the World Health Organization (WHO) both claim that brucellosis is a zoonotic disease that has a negative impact on both human health and animal production.

This bacterial disease not only causes a very debilitating and debilitating disease, but also has a great economic impact as patients lose time from their normal daily activities and animal production [(6).] In a review of 76 animal diseases and syndromes, brucellosis is in the top 10 in terms of its impact on the poor. To calculate disability-adjusted life years (DALYs), a brucellosis disorder weight of 0.2 has been previously proposed based on pain and reduced productivity known to be caused by infection [(6, 7).] However, more informed estimates are needed to Accurately assess the burden of illness. Brucellosis has long been known, but the description in humans as a clinical term, "Mediterranean gastric remission fever," was created by JA Marston in 1860 only in the 19th century.

In 1887, David Bruce (1865–1931) used the assistance of a Maltese scientist to describe the bacterium as a "micrococcus."
Scicluna Carruana Maltese physician Zammit demonstrated diseased goats and recognised the illness in 1905. [(7)] Bruce visited Africa and discovered"Trypanosoma brucei " as a cause of sleeping sickness.

Brucellosis is a chronic illness with a low fatality rate. With more than 500,000 new cases annually, human brucellosis nonetheless continues to be the most prevalent zoonotic illness worldwide. The illness is a significant contributor to travel-related morbidity and is associated with severe residual disability [8]. Over the past few decades, this disease's global epidemiology has seen a significant change. The most severe form of the illness, known as neurobulcellosis, affects 5-7 percent of those who contract it. Around the world, there are numerous nations that are affected. From China to the United States as well as the Mediterranean coast (8-9). Over the past ten years, incidence has once more decreased despite better surveillance and frequent reports of animal cases.
In order to identify human cases, microbiological examination is crucial because the clinical manifestations:

(I) Using cultures for direct diagnosis

(ii) Using serological testing for indirect diagnosis

(iii) Direct rapid diagnosis using molecular PCR-based methods.

Because of their clinical and epidemiological relevance, cultures are the "gold standard" in laboratory diagnosis of brucellosis despite the well-established experience of serological testing and sensitive nucleic acid amplification testing (NAATs) [10,11]. The automated BC system is also now

BC is now more sensitive, and the time it takes to detect it is shorter.

Brucella species [12]. The lack of universally accepted criteria for interpretation and inadequate specificity because of cross-reactivity are the main drawbacks of serological testing.

Limited sensitivity in the early stages of the illness stage and species differences. However, serological testing continues to be the primary diagnostic method, particularly

due to its inexpensive cost, simplicity of usage, and excellent negative predictive value, in endemic areas [12,13]. Recently, promising serological diagnostics based on novel synthetic antigens

The clinical signs and symptoms of brucellosis are varied, frequently ambiguous, can continue for a few days to a year or longer, and are frequently misdiagnosed as a result. Disorders and illnesses [16] that can result in difficult treatment and chronic illness Patients may show signs of osteoarthritis, malaise, perspiration, fever, and even more severe problems in other organ systems. Brucellosis not only harms the physical and mental wellbeing of people but also has a significant negative economic impact on society by reducing animal productivity. Humans can contract brucellosis by coming into close touch with diseased animals or by consuming milk from contaminated, unpasteurized animals [16,17].

There have been reports of vertical and sexual human-to-human transmission (HHT). Blood transfusions and other human-to-human transmission methods used anaesthetics. This in-depth analysis highlights a number of factors. Studies with the following criteria were excluded [23]

Articles about brucellosis in animals.

(B) Reported data that duplicated content from previously published publications

(C) Articles that couldn't offer patients' original data

(D) Articles discussing subjects like therapy intervention and exploratory laboratory experiments that had nothing to do with the clinical characteristics of human brucellosis.

Studies that met the aforementioned requirements were included [23, 24].

(A) There must be more than 10 research participants in each document and literature describing the clinical signs and symptoms of human brucellosis.

(B) The issues that have been discussed in the literature and who must reside in China and/or India.

(C) Studies that presented pertinent laboratory findings and data from general brucellosis cases fall under category .

The data were released by two independent reviewers which included data collection, research design, study area, patient characteristics, and number of male and female patients, clinical manifestations, case studies for each symptom and problem record for each of the study, diagnostic process, and laboratory parameters [25]. The study population was regarded as the sole male group in the study population for the sexually related outcomes of epididymo/orchitis. Patients in paediatric care should be aged 0 to 15 years. Additionally, we kept records about the time before therapy, any delays in diagnosis, and any exposure to relevant risk factors [25,26]. The data release results should be accepted and endorsed by all reviewers.

Treatment is administered to reduce illness duration, prevent relapse, and avoid consequences such arthritis, sacroiliac joint inflammation, spondylitis, encephalitis, endocarditis, epididymotrichitis, and abortion. A combination of two medications is presently employed since monotherapies historically had significant rates of relapse. There are conflicting recommendations for particular regimens in reference sources. In place of the previously advised regimen of tetracycline for six weeks combined with streptomycin for the first two to three weeks, the World Health Organization's guidelines, last issued in 1986, advocated doxycycline with rifampicin for six weeks. These two regimens' comparative advantages are still up for debate. Other antibiotics including fluoroquinolones, co-trimoxazole, and their mixtures with rifampicin are available as alternatives. Doxycycline-streptomycin and doxycycline-rifampicin were suggested in recent consensus recommendations of an expert group.
A previous meta-analysis, including six trials that were published up to 1992, found that doxycycline-streptomycin was superior to doxycycline-rifampicin. Since then, many more trials assessing the WHO recommended regimens have been published. Recent trials assessed the effect of quinolone based combination therapy and triple drug regimens [27]. Streptomycin been replaced by newer aminoglycosides and their effects on brucellosis have not been summarised. Finally ,the advantage of combination therapy over mono therapy has not been quantified.

In the past 50 years, brucellosis has only been discovered through culture in a small number of wildlife species in Africa, despite the fact that exposure to Brucella spp. has been found through serological research in a variety of wildlife species. Brucella species, including marine creatures, have been isolated in a wide range of wildlife species on other continents. When evaluating the research of this review, flaws and a lack of validation of brucellosis serological tests are significant limitations, especially if the number of animals tested is small. Since 2010, there has been a noticeable increase in the number of papers published on brucellosis in Africa, indicating a growing interest in the disease in animals. In comparison to other species, buffalo populations have greater prevalences of infection. Evidence from epidemiological, serological, and bacterial studies suggests that buffalo is a reservoir species and can withstand B. abortus infection [28,29,30].

Therefore, brucellosis exposure was predicted by livestock contact in antelopes and carnivores (spillover species), but not in buffalo (reservoir species). Understanding wildlife brucellosis and its potentially shifting epidemiology is crucial because population growth encourages the loss of wildlife habitat and increases livestock and wildlife duplication. Future research on brucellosis in Africa, particularly West and North Africa, must concentrate on the isolation, molecular characteristics, and environmental changes of Brucella spp. in order to comprehend the causes, patterns of transmission, and drivers of wildlife illnesses.

Laboratory Test A polymerase chain reaction (PCR) exhibits high specificity (100%), high sensitivity of 80% (1.25GE / µl), and higher reliability. The sensitivity of 94.1% enzyme-linked immunosorbent assay (ELISA) and 97.1% specificity can be determined between IgG, IgM, and IgA, in addition to being more beneficial and sensitive in the genus Brucella. Rose Bengal Agglutination (RBAT) is a rapid test, but less sensitive and specific. The standard agglutination reaction (SAT) has a sensitivity of 95.6% and a specificity of 100.0%, making it the most accurate and preferred for diagnosis [31].

The actual incidence of brucellosis may be higher rather than the incidence reported because of misdiagnosis or wrong reporting. Human knowledge and awareness of brucellosis among healthcare providers can help predict and accurately estimate the true incidence of brucellosis. Therefore, the main purpose was to study the perception of human brucellosis among medical professionals in Gujarat, India. This study evaluated expert knowledge of suspicion, diagnosis, prevention and treatment of brucellosis. This improves the level of care for human illness. India is one of the world's leading milk producers and the main occupations of the village are agriculture and livestock. Therefore, a high prevalence of brucellosis is expected [32]. In India, direct contact between humans and animals is common due to livestock breeding, occupations such as veterinarians and dairy workers, and consumption of unpasteurized milk and dairy products [32,33].

Overall cognitive level – Overall, 66/69 (95.65%) of respondents have heard of brucellosis. This was only 100% for symptomatic practitioners and 89% for AYUSH practitioners [33].

Newspapers and media as sources were cited by 62% of participants, while academic meetings such as conferences / workshops / CMEs were cited by only 52% of participants [34].

When asked if brucellosis is an animal disease, out of 69 there were 29 (42%) participants who knew about the correct answer, 35(51%) participants knew that brucellosis is a disease of "Both" (Animal and Human beings). On asking if a Human being is infected by coming in contact with the infected animal or animal products, 62 (98%) participants gave the right response. Total 58 (84%) participants knew about brucellosis being an occupational hazard for some professions.

Disinfection- The most widely used disinfectants, such as hypochlorite solutions, 70% ethanol, isopropanol, iodophores, phenolic disinfectants, formaldehyde, glutaraldehyde, and xylene, are effective at killing Brucella species. It was noted that citric acid diluted to 1 percent had less impact Xylene and calcium cyanamide decontaminated liquid manure, according to one study, after 2 to 4 weeks. However, some sources advise keeping such treated manure on hand for considerably longer (36,37). Acid pH 3.5 causes Brucellae to inactivate pretty quickly. Additionally, they can be eliminated by pasteurisation, gamma irradiation, wet heat of 121°C (250°F) for at least 15 minutes, dry heat of 320°F (160°C) for at least 1 hour, and heat of 320°F (160°C). For liquids, boiling for 10 minutes typically works.

Infections in Human- The acute symptoms of brucellosis often start to show up between two and four weeks after exposure, but the onset can be sneaky and some cases have been identified up to six months later. Clinical Signs The effects of B. melitensis infection range from asymptomatic infections to various syndromes that may manifest slowly or suddenly. Common symptoms of acute brucellosis include fever, chills, headache, malaise, back pain, myalgia, and lymphadenopathy, which may be accompanied by nonspecific flu-like symptoms.

Hepatomegaly & splenomegaly. Patients may get drenched in perspiration, especially at night (40). Constipation, vomiting, diarrhoea, and anorexia are examples of non-specific gastrointestinal symptoms. While some individuals have spontaneous recovery, others experience recurrent, non-specific symptoms (such as fever and weakness) that often wax and wane.Sepsis, pneumonia and other syndromes have been reported in congenitally infected infants, but some infected newborns are asymptomatic. Deaths are uncommon except in infants, and are usually caused by endocarditis or infections affecting the brain.

Diagnostic procedures Blood or clinical samples taken from the diseased organ can be used to cultivate B.melitensis. The bone marrow is more likely to contain it than the blood. Bone marrow sampling, however, is more challenging and is often only done in cases of suspected brucellosis after other methods of diagnosis have failed. B. Mellitensis cannot usually be distinguished, particularly in chronic instances. Nucleic acids can be found in clinical specimens using PCR. Serology is frequently used to diagnose human clinical conditions. The Rose Bengal Test, the Rose Bengal Confirmation Test, the Rose Bengal Test, and the the Serum Tube Agglutination Test (SAT) using 2-ME or DTT, or both.

The Coombs Test, the MicroAgglutination Test, and Brucella Capt (commercially available test for immunocapture agglutination).

Recently, researchers published a universal indirect ELISA that can identify antibodies to both smooth and rough brucellosis. On a serological test, a fourfold increase in titer is conclusive, albeit occasionally it is still undetected. In cases of neurological involvement,

antibodies are also checked in the cerebrospinal fluid. Problems can arise from cross-reactivity with other bacteria, particularly in agglutination (Y. enterocolitica O: 9, Salmonella urbana group N, Leptospira sp., Vibrio cholerae, Francisella tularensis, E. coli O157, Stenotrophomonas maltophilia, etc) [43,44]. Treatment For brucellosis in humans, long-term antibiotic dosing that combines two or more medications for some or all of the treatment time is the norm. According to reports, monotherapy has a significant recurrence rate. Various antibiotics may be suggested based on the patient's age, pregnancy, and other factors.

A recent universal indirect ELISA that can detect antibodies to both smooth and rough brucellosis was published by researchers. A fourfold increase in titer is conclusive on a serological test, albeit it can infrequently go undetected. Antibodies in the CSF fluid are also examined in situations with neurological involvement. Cross-reactivity with other microorganisms, especially in agglutination, might cause issues (Y. enterocolitica O: 9, Salmonella urbana group N, Leptospira sp., Vibrio cholerae, Francisella tularensis, E. coli O157, Stenotrophomonas maltophilia, etc) [43,44]. Treatment Long-term antibiotic dosing that incorporates two or more drugs for some or all of the treatment time is typical for brucellosis in humans. Monotherapy has a high rate of recurrence, according to reports. Depending on the patient's age, pregnancy, and other factors, different antibiotics may be recommended.

AIM & OBJECTIVES

AIM:

Here I determine the epidemiology and statistics of prevalence of human brucellosis in India and at global level.

OBJECTIVES:

My main objective is to study the transmission of human brucellosis by analysis of current and old epidemiology situation across the different states of India and across the world

REVIEW OF LITERATURE

.A study by. (Kadri, 2000) reported a prevalence of 0.8% in a larger group of PUO patients [7].

. In a study by Sen et al. (2002) 6.8% of seropositive cases were found among patients with PUO [4].

. Raw milk drinking history (87%) and occupational contact with animals (81%) as well as handling infectious organisms (62%) were highlighted as key risk factors in the study by kochar et al. (2007) [9]

• Study by Boral et al. (2009): Brucellosis has been reported as the leading cause of fever of unknown origin (PUO) [10]

. In India, disease has been reported sporadically, but the actual incidence is estimated to be much higher than reported due to misdiagnosis or underreporting .

• A study by Yohannes and Sing (2011) found a higher seroprevalence (27%) in the target sample population, Ludhiana [12].

• (Yohannesetal. 2011): Of the occupational groups, veterinarians were most affected, followed by agricultural workers [12].

• Study by Pathaket.al. (2014) We also found a 6% seroprevalence in patients with PUO [13].

•Because aerosolization is the method of infection in this setting, brucellosis is one of the most prevalent illnesses in laboratories.
(Robichaud and others, 2004) [14].

•Fresh goat milk and close contact with animals are reported to have had a history in more than 60% of brucellosis patients. Additionally, illness was mentioned.
In 2004 (Mantur et al) [15].

•If the patient has a history of interaction with animals or the ingestion of raw milk, there should be a high degree of clinical suspicion. (2003) Gokhale et al. [16]

•Less than 10% of brucellosis cases in humans are thought to be clinically diagnosed, treated, or reported in India. (2007) Mantur et al [17]. Due to its various clinical manifestations, brucellosis may frequently go unnoticed.

- Due to its numerous clinical symptoms, brucellosis is frequently proven and was previously thought (Mathai et al., 1996) [19]

- Patients with brucellosis have been identified as having a variety of symptoms that affect nearly all systems. Serum-positive patients, however, might not have any symptoms. (Handa and others, 1998) [20].

- As seen in the brucellosis outbreak in Kanwari village, Churu district, Rajasthan, polyarthritis sufferers should always be on the lookout for the disease. positive (Kalla et al, 2001) [22]

- The central and peripheral nervous systems are also impacted by neurobulcellosis, a rare yet devastating condition. This disease's clinical profile resembles common neuropathies, such as tuberculous meningitis aseptic meningitis, brain malaria, viral encephalopathy, and viral encephalitis Kochar and others (2000) [23]

- Patients with fever of unknown origin (FUO) who test negative on regular diagnostics are advised to get a bone marrow culture. Brucellosis testing using serology).

- Additionally, medical professionals should check for brucellosis in samples from patients with bacterial endocarditis, leukaemia, typhoid fever, rheumatoid arthritis, urogenital infections, karaazal, liver cirrhosis, and filariasis. In 2002, Thakur et al. [28]

- In the fight against Brucella, there are apparently new obstacles that the medical and veterinary sectors must overcome. I The possibility of Brucellosis in livestock Expansion of wild storage in (ii) The appearance of B. recent discovery of meritensis infections in cattle with unproven protective benefits of existing vaccinations, and (iii) huge animal depots of marine mammals for which the pathogenicity of potential animals remains uncertain [31]

- Additionally, it was noted that the decline in human occurrence was not linear and only occurred when the animal vaccination rate was above 30% (Minas et al.)

- If brucellosis is correctly diagnosed and treated as directed, the cure rate is very high (Kochar et al., 2000) [35]

- In addition to sanitation, vaccinations, and efficient heating and pasteurisation of dairy products and related commodities, prevention of human brucellosis should primarily concentrate on the eradication of infection in cattle (Mudaliar et al., 2003) [34]

- Recently identified marine mammal Brucellae that may also be human infections include Brucella pinnipediae and cetaceae (Sohn et al. 2003; McDonald et al. 2006) [36]

- Hunters may contract the disease through skin wounds or by unintentionally consuming the bacterium after killing deer, elk, moose, or wild pigs. According to Robson et al. (1993), a large portion of cases in abattoir workers are frequently caused by inhalation [37]

- Although brucellosis affects humans, Certain risk groups, such as slaughterhouse workers, also had much higher seroprevalence (Barbuddhe et al. 2000; Chadda et al. 2004) [42]

- Both the latex agglutination assay (Abdoel and Smits 2007) and the Brucella IgM and IgG lateral flow assay (Smits et al. 2003) have demonstrated quick, easy, high sensitivity, and specificity in cases verified in culture. These tests are perfect for use as point-of-care tests in hospitals and medical facilities as well as distant field diagnostics [43]

- Doctors and other healthcare personnel need to take precautions because there aren't any compassionate immunizations or effective controls. Workplace brucellosis may be decreased by using protective gear and barriers when handling stillbirth and pregnancy products and culture. (Young 1995) [44]

- Human brucellosis is not regarded as an infectious disease. Consequently, accumulation can happen when a common source emerges that raises the risk of infection or when a certain factor temporarily accumulates 1994; Chomeletalreported 175 cases of brucellosis.

- Patients enrolled in Karnataka Medical College, Hubli (Mantur1988) showed a prevalence of 3%. [50]

- The Manturetal. by studying (2004a) 93 children with brucellosis were reported in Villapur, 1.6 percent prevalence after SAT (1: 160) [50]

- The Manturetal. (2006) reported 495 adult patients in recent publications Villapur has a 1.8 percent prevalence [50]

- The investigation was continued in Bijapur, where an additional 111 cases were reported (Mantur et al. 2007a, 2008a, b; Tikare et al. 2008). In a different investigation, Mantur and his associates at the Belagavi Institute for Medical Sciences in Belgaum discovered 63 cases (Mantur BG and associates, unpublished report) [46]

MATERIAL AND METHODS

Search Strategy

I used a meta-analysis of the literature to find photographs of India and the rest of the world as well as publications about the clinical characteristics of human brucellosis in different nations. Wei Pu Data, Medline, CNKI, Wan Fang Data, and Cochrane Library I electronically searched PubMed's material using MESH and the keywords "brucellosis," "Malta fever," and "brucella melitensis" with the assistance of trained medical librarians. For entries published after the database was launched before December 2016, "or" Brucella "and" symptoms "," sequelae "," morbidity "," mortality "," transmission method ", "Food origin" and "China", "India" (20,21). (20,21). The kind of study or publishing language is not constrained. Two researchers looked at the article's title and summary, author, year of publication, volume, and other information to find duplicate entries.

Statistical Analyses

The ratio of the number of reported cases with particular clinical symptoms to the total number of cases reported in each research is how I determined the event rate. To make forest plots, summarise complicated data, and provide 95 percent confidence intervals for each symptom ratio, use the R statistical programme (version 3.4.2, meta-analysis). In the hypothesis test, two-sided results below 0.05 are regarded as statistically significant.

Methodology

AREA OF STUDY: Brucellosis in India and global picture-Meta analysis.

Data Type: Basically I used secondary mode of data collection.

A. Collection of data from various journals.

B. There is a collection of some data from books.

There is a review of literatures and article from various online sources.

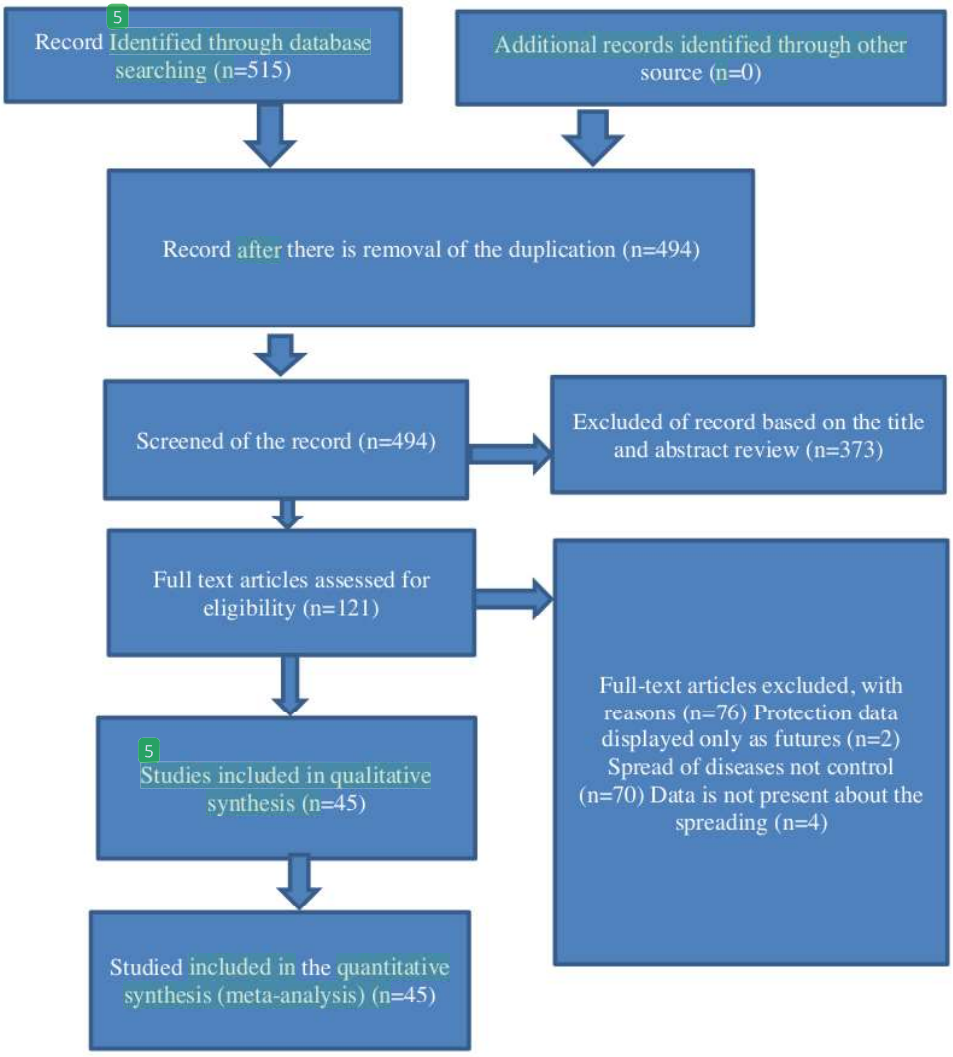
Research tool: Collection of secondary data from the report published in different articles.

Time frame-From August 2000 to Dec 2021.

Search engine: Pub med, Ind. Med, Google scholar.

Ethical clearance: Will be applied.

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Criteria).



Results

Key features of all studies included in the meta-analysis.

First author & ref. number	Year	Age category	Location	Cases	Available contact history data	Available laboratory data	Available blood culture data	Available misdiagnosis data
Wu et al. [14]	2012	All ages	Beijing	44	Yes	NA	NA	Yes
Tong et al. [17]	2013	All ages	Beijing	35	Yes	NA	NA	NA
Wang et al. [19]	2015	All ages	Gansu	61	Yes	Yes	NA	NA
Zhang et al. [21]	2012	All ages	Henan	21	Yes	Yes	Yes	NA
Li et al. [24]	2008	All ages	Heilongjia	165	Yes	Yes	Yes	NA
Liu and Zhang [25]	2016	All ages	Inner Mongolia	44	NA	NA	NA	NA
Sun et al. [30]	2010	All ages	Jilin	270	Yes	NA	NA	NA
W. Yang and F. Yang [35]	2015	All ages	Inner Mongolia	228	Yes	Yes	NA	Yes
Wang et al. [45]	2014	Children	Hebei	80	Yes	NA	NA	NA
Fan et al. [48]	2016	Children	Xinjiang	24	Yes	Yes	NA	NA
He [44]	2015	Children	Xinjiang	19	Yes	Yes	Yes	Yes
Liu et al. [52]	2016	Children	Heilongjiang	94	Yes	Yes	Yes	Yes

Zheng et al. [55]	2016	Adults	Guangdong	12	Yes	Yes	Yes	Yes
Ji et al. [59]	2006	Adults	Heilongjiang	30	NA	Yes	Yes	Yes
Yan et al. [54]	2016	Adult	Ningxia	31	NA	Yes	Yes	NA
Wu et al. [56]	2007	Adults	Shanxi	28	Yes	Yes	NA	NA
Zhang and Li [57]	2015	Adults	Shaanxi	35	Yes	Yes	Yes	NA
Wang[58]	2014	Adults	Tianjin	17	Yes	Yes	Yes	Yes
Zhou and Yang [59]	2014	Adults	Tianjin	18	Yes	Yes	Yes	NA
Xu et al. [60]	2007	Adults	Zhejiang	31	Yes	NA	NA	NA
Chen et al. [63]	2016	Adults	Xinjiang	74	Yes	Yes	NA	NA
Wang et al. [61]	2014	All ages	Liaoning	88	Yes	NA	NA	NA
Zhang and Wang [67]	2013	All ages	Ningxia	128	Yes	NA	NA	Yes
Feng and Deng [64]	2016	All ages	Shanxi	105	Yes	Yes	Yes	Yes
Zheng et al. [65]	2016	Adults	Guangdong	12	Yes	Yes	Yes	NA
M.Wang and L Wang [63]	2007	Adults	Jilin	26	Yes	Yes	NA	Yes

Bai and Duan [63]	2015	Children	Ningxia	48	Yes	Yes	Yes	Yes
Gao et al. [67]	2002	All ages	Gansu	182	Yes	NA	NA	NA

Contact history meta-analysis

Contact	*n*	Proportion [95% CI]
Contact history	54	0.794 [0.7651; 0.8240]
Digestive tract contact	31	0.115 [0.0844; 0.1567]
Unknown	43	0.167 [0.1347; 0.2077]

Meta-analysis of clinical symptoms of brucellosis by age group

Manifestation	Children		Age category Adults		All ages		All studies	
General	*n*	% [95% CI]	*n*	% [95% CI]	*n*	% [95% CI]	*n*	% [95% CI]
Fever	10	92 [87; 97]	17	99 [97; 100]	41	83 [80; 87]	68	87 [85; 90]
Fatigue	7	68 [56; 83]	14	64 [55; 74]	34	62 [57; 67]	55	63 [59; 67]
Chills	3	26 [8; 82]	5	53 [36; 79]	4	37 [33; 42]	12	43 [33; 55]
Sweats	8	60 [45; 79]	16	57 [48; 68]	39	54 [49; 59]	63	55 [51; 60]
Arthralgia	9	52 [43; 64]	17	61 [52; 70]	40	63 [59; 68]	66	62 [58; 65]
Headache	4	8 [3; 19]	10	29 [19; 42]	27	21 [18; 25]	41	21 [18; 25]
Muscle pain	2	31 [7; 100]	5	76 [60;	20	53 [47;	27	56 [51; 62]
Nausea/vomiting	6	27 [16; 43]	8	26 [15; 45]	17	25 [19; 34]	31	26 [21; 33]

Rash	3	13 [6; 29]		3	7 [3;9 19]		5	[3; 11]		15	7 [4; 11]	
Weight loss	0	-		4	26 [14;	5	32 [17;		9		29 [17; 48]	

				47]				61]				
Skin petechia	3	8 [4; 18]	2	18 [10; 32]	9		5 [3; 8]	14	7 [4; 10]			
Abdominal pain	2	6 [1; 31]	3	6 [3;3 14]			8 [4;8 16]		8 [5; 11]			
Chest pain	0	-	2	7 [3;1 17]			5 [3;3 10]		6 [3; 10]			
Cough	5	12 [8; 17]	4	19 [12; 29]	5		10 [8; 14]	14	12 [10; 15]			
Hepatomegaly	7	28 [18; 42]	7	23 [13; 40]	23		13 [10; 17]	37	16 [13; 20]			
Splenomegaly	7	35 [27; 45]	10	29 [22; 39]	23		21 [16; 27]	40	24 [20; 29]			
Lymphadenectasis	7	38 [25; 58]	7	32 [22; 48]	27		16 [12; 21]	41	19 [15; 25]			
Hepatitis	8	48 [34; 67]	15	60 [52; 69]	24		38 [30; 49]	47	45 [38; 54]			
Neurological	4	8 [4; 17]	3	8 [2; 36]	14		4 [2; 9]	21	5 [3; 10]			
Cardiac	3	19 [2; 100]	2	5 [1; 19]	12		9 [6; 14]	17	9 [6; 16]			
Hemophagocytic syndrome	0	-	0	-	4		6 [2;4 23]		6 [2; 23]			
Respiratory	5	26 [12; 57]	3	11 [6;8 20]			9 [4; 23]	16	13 [7; 21]			
Orchitis/epididymitis	1	67 [45; 100]	7	6 [3; 12]	34		9 [7; 12]	42	9 [7; 12]			
Osteoarthritis	2	16 [8; 35]	4	22 [9; 52]	11		23 [17; 31]	17	22 [17; 29]			

4

Meta-analysis of the incidence of laboratory tests

Laboratory	The number of articles	Proportion [95% CI]
Trombocytopenia	32	0.158 [0.1268; 0.1979]
Aleucocytosis	37	0.241 [0.1951; 0.2984
Leukocytosis	16	0.106 [0.0819; 0.1365]
Anemia	28	0.239 [0.1847; 0.3094]
Pancytopenia	6	0.132 [0.093; 0.187]

3

Demographic characteristic of seropositive and seronegative among the rural population in Nagpur district of Maharashtra state, India (*n*=382)

Characteristics	Seropositive individuals *n* [%] =7[1.83]	Seronegative individuals *n* [%]=375 [98.17]
Gender		
Male	6 [85.7]	294 [78.4]
Female	1 [14.3]	81 [21.6]
Marital status		
Married	7 [100]	345 [92]
Unmarried	0 [0]	30 [8]
Education level		
None	2 [28.6]	60 [16]
Primary	4 [57]	151 [40.3]
Secondary	1 [14.3]	141 [37.6]
Tertiary	0 [0]	23 [6]

VACCINES

Human vaccination There is no strong evidence supporting the use of levamisole or other immune system modulators like brucella vaccines or antigen preparations to treat brucellosis in people. Anti-inflammatory medications should be used with caution when treating local problems. There aren't many accessible safe and reliable vaccinations to protect against brucellosis in people. However, in the former Soviet Union and China, vaccination has been a significant factor in the prevention of the disease when combined with other interventions. In locations with severe infection, two live attenuated vaccine strains are frequently employed. The skin was cut to give the vaccination (epidermal route). Although the protection lasted up to a year, it was most potent five to six months after vaccination. Redness was a local response manifestation.

DIAGNOSIS

Suspicious diagnosis:

A suspicious diagnosis of brucellosis in humans can be made by the following tests:

a. Rose Bengal Test (RBT) for screening. Positive test b that must be confirmed by one of the confirmation tests.

b. Standard agglutination reaction (SAT).

Confirmation diagnosis

Confirmation diagnosis of brucellosis can be made by the following tests.

a. Isolation of Brucella species from clinical samples like blood.

b. An estimated laboratory diagnosis based on the detection of non-aggregated antibodies in addition to aggregated antibodies (RBT, SAT).

1. An IgG ELISA test.

2. Coombs IgG

The certification of PCR and new quick tests like immunochromatography is still required.

Patients with fever of unknown origin (FUO) who receive a negative result from a regular test are advised to obtain a bone marrow culture. Due to the Hook effect, serological testing for brucellosis may result in misleading negative results. (Deepak and others, 2003)

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Discussion

One of the most common zoonotic illnesses in the world is brucellosis. In China, there are more and more brucellosis patients every year. Shietal. According to a paper that examined the spatiotemporal distribution of human brucellosis in China from 1955 to 2014, the disease has returned since the mid-1990s, affecting areas from the north coast to the north grasslands. and demonstrated how it migrated to the southwest. Since 2004, brucellosis in regional China has increased economic losses and has turned into a public health issue.

In humans, brucellosis affects several organs and has a wide range of clinical symptoms that can range from mild to severe, making it simple to mistake it for another illness. I have. If the chronic phase appears as a result this study found that the main clinical symptoms of human brucellosis were fever, malaise, arthralgia, and myalgia.

The most common clinical syndromes in adult patients are fever, myalgia, arthralgia, and sweating.orchitis/ epididymitis. We also found that chills, headaches, and weight loss were less common in pediatric patients.

Brucella's multi-organ involvement is probably underestimated. The bones, central nervous system, and epididymis are the most commonly affected organs. The results of the current study were similar to those reported in other published articles. In the current study, the results show that hepatitis and osteoarthritis were more common complications. Serious complications such as central nervous system dysfunction, cardiovascular disease, respiratory symptoms, and hemophagocytic syndrome are also observed.

Epididymitis or epididymitis occurred in 9% of male patients. Brucellosis complications remain a major medical problem and must still be considered a serious public health problem in China.

The results of the study show a high rate of misdiagnosis, which occurred primarily in non-pastoral areas. Brucellosis is often misdiagnosed because of these symptoms, such as fever, back pain, cough, gastrointestinal symptoms, and blood abnormalities.

The majority of misdiagnosed patients were admitted to the Department of Rheumatology, Hematology, Orthopedics and Ventilation on their first visit. Brucella culture is the "gold standard" for diagnosing brucellosis. In this study, 87% of patients with brucellosis had a fever.

Blood cultures, however, only analysed 30 items, including 4681 instances, and 48 cases were discovered. Since Brucella melitensis is present in 3% of cases, it is possible that this is the primary cause of improper diagnosis and therapy. Therefore, it is essential to expand the idea of clinical diagnosis with a thorough medical history, do coagulation tests, and take blood cultures in order to effectively reduce the rate of misdiagnosis, especially in non-idyllic areas and places where the frequency of tuberculosis is high.

As quickly as feasible, patients with fever are present. The most prevalent laboratory abnormalities are vague, which makes brucellosis diagnosis difficult. Most people have blood cell counts that are normal. Leukocytosis was one of the prevalent abnormal laboratory tests in this study.

CONCLUSION

Brucellosis is kind of endemic disease in India. It is widespread in all livestock species and humans. Despite knowledge of the disease and its easy way of transmitting it, the disease has been ignored in terms of fighting it. India needs to make effective plans to control the disease, either through vaccination or through an easy-to-implement policy of removing infected animals from herds. Challenges remain because the country has diverse religious beliefs. With much higher prevalence observed in humans, effective strategies for controlling the disease require swift and rigorous action. Brucellosis places a significant cost on the human health system and restricts the economic development of people, communities, and nations, where such development is crucial to lowering the rate of poverty. Public policies that aim to reduce the socioeconomic effects of brucellosis on human and animal populations must be put into place immediately. Plans for mitigating related results should take into account both qualitative and quantitative effects. It entails interdisciplinary, team-based, or "one health" initiatives for managing livestock and wildlife species, as well as infrastructure development for disease monitoring and reporting in the veterinary and medical disciplines. I require a strategy.

According to a thorough assessment of the literature, brucellosis cases are often recorded from Kashmir, Karnataka, Maharashtra, Delhi, and Kerala. Field veterinarians in Delhi, Rajasthan, Uttarakhand, Kerala, and Himachal Pradesh reported much higher incidence rates. High incidence among butcher and slaughterhouse employees has been noted in Delhi. SAT was the sole diagnostic technique employed in the vast majority of trials (n = 9). For diagnosis, further tests such the RBPT, 2ME, ELISA, CFT, and Coombs test are also employed.

Only a small number of states, including Karnataka, Maharastra, Kerala, Tamirnadu, Jammu & Kashmir, Uttaracand, Himachal Pradesh, and Delhi, have done studies defining clearly defined study designs and methodologies. It has been noted that although prevalence has been reported in several places, there aren't any reliable measurements or reliable testing. Most instances have been documented with debilitating diseases such as joint pain, muscle pain, and low back pain have also been reported. Significant delays in proper diagnosis and treatment have been reported. This systematic review contributes to understanding the burden of brucellosis in India. The severe debilitating and chronic effects of brucellosis are highlighted. The current epidemiological scenario emphasizes the need for a repository of Brucella strains.

My molecular subtyping techniques, such as PFGE, MLST, and MLVA, can be used to

explore the polymorphisms of diverse strains. India has produced Brucella vaccines and entire genome sequencing of field strains; these research will aid in the advancement of the disease's molecular and serological detection. Clinical symptoms and exposure risks of the disease are better understood by well-planned epidemiological research from regions where data are lacking.

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