

ORIGINAL RESEARCH

## Burden And Determinants Of Human Brucellosis In Patients With PUO (Pyrexia Of Unknown Origin) In A Tertiary Care Hospital In Jammu

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### ABSTRACT

**Background:** Brucellosis is endemic in many parts of the world including India and the disease is also the one of the important causes of PUO(Pyrexia of Unknown Origin).The population exposed to infected or contaminated animal and animal products are at a greater risk .The present study was conducted with an aim to determine the prevalence of Human Brucellosis in PUO cases among occupationally exposed individuals.

**Method:** In the present hospital based cross-sectional study which was conducted in a tertiary care medical teaching institute in northern India. A total of n=369 samples of serum from PUO cases were collected and tested for Human Brucellosis by RBPT, STAT, iELISA.

**Result:** Overall seropositivity in our study by different tests was found to be 0.5%, 0.8%, and 1.6% by RBPT,STAT and iELISA respectively.

**Conclusion:** Highest seropositivity was found to be in Nomads (36.3%) followed by Farmers (27.2%).With respect to the symptoms generalized aches (90.8%) was most common followed by anorexia(64.4%).Also in our study of all the serum samples collected 20.3% gave history of consumption of Gau Mutra of which 2.6% of the samples were found to be seropositive. However inspite of the low prevalence of Human Brucellosis, clinicians must keep the index of suspicion high of the possibility of a patient suffering from Brucellosis while encountering a case of PUO and it is adisable to elicit a history of certain occupation and risk factor for Brucellosis in patients with PUO.

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### INTRODUCTION

*Humanity has but three great enemies: fever, famine and war; of these by far the greatest, by far the most terrible, is fever. William Osler*

Fever -The most common indication for people to visit a health facility, yet most challenging. Fever which often occurs in response to infection, inflammation and trauma. The cases of fever where initial investigation fails to detect the cause, and is associated with diagnostic uncertainty and complicated management encompasses a large group called as PUO (Pyrexia of Unknown Origin).

**Petersdorf and Beeson** originally defined PUO in 1961 as:

- (1) A patient with fever higher than 38.3°C (101°F) on several occasions usually interpreted as at least three.
- (2) Illness of more than 3 weeks duration and
- (3) No diagnosis made after 1 week of inpatient investigation.

Brucellosis is the one of the most important yet under rated cause of PUO so investigators chose less stringent definition of PUO as proposed by some authors which defined PUO as 3 outpatient visits and/or 3 days in-patient stay (**Durack DT et al, 1991**) (**De Kleijn EMH et al, 2000**).

Brucellosis seems to fulfil all the conditions laid above and history of brucellosis dates back to 1886 when David Bruce a British army surgeon named a cocco-bacillus as 'micrococcous melitensis' isolated from the spleen of man who died of malta fever (**Bruce, S.D., 1887**).

Brucellosis is an endemic zoonotic disease which spreads invariably by direct or indirect contact with infected animals or their products.

**Animal rearing populations, slaughterhouse workers, laboratory workers, Veterinarians** etc are at higher risk and affects age groups and of both sexes. It is endemic in most of the production animals in India with seroprevalence of 9.3% in cattle (**Dhand NK et al, 2005**) (**Kollannur JD et al, 2007**) and 16.4% in buffalo populations (**Aulakh HK et al, 2008**). Recent studies in India demonstrate that brucellosis in livestock populations results in a median loss of US\$ 3.43 billion, with more than 95% of the losses occurring in the cattle and buffalo industry (**Dhand NK et al, 2015**).

On the other hand outbreaks continue to occur world wide. One such happened in Lanzhou was first uncovered in November 2019 (<https://www.usnews.com/news/top-news/articles/2020-11-06/explainer-how-thousands-in-china-got-infected-by-brucellosis-in-one-single-outbreak>).

The various means of transfer of brucellosis to humans include person- to-person transmission, infection from contaminated environment, occupational exposure from infected animals (**Panjarathinam Ret al, 1986**) (**Sharma VD et al, 1979**) (**Appannanavar SB et al, 2012**) (**Agasthya AS et al, 2007**) (**Yohannes M et al, 2011**) and food borne transmission.

The main symptom of Brucellosis is fever with unknown origin making its diagnosis very difficult. With an incubation period of 2-3 weeks, human brucellosis is known for presenting with varied manifestations like fever, arthralgias, sweat, fatigue, malaise, anorexia, weight loss, headache and back pain (**Dames S, et al, 2005**).

There is paucity of data about brucellosis in Jammu. A study done by **Kotwal et al** has shown seroprevalence of 4.96% (9.91% by RBPT, 9.91% by mRBPT, 9.09% by STAT, and 16.52% by I-ELISA) in humans in Jammu.

Educating and making people aware about the disease will yield fruitful results and will pay a long way in halting the spread of disease.

In view of the above, it is apparent that brucellosis commonly occurs yet it remains neglected as is not considered as an important differential diagnose in patients presenting with fever or PUO.

Also the population of J&K is closely involved in rearing animals from where infection can spread to humans. Therefore, it was thought pertinent to mount a study to evaluate the burden and determinants of Brucellosis among patients admitted as PUO. The study aims to establish the burden by using more accurate methods of diagnosis and help the outreach project on Zoonotic disorders to formulate strategies for mitigation of Human Brucellosis.

- 1) To study the seroprevalence and determinants of Human Brucellosis in patients admitted with PUO (Pyrexia of unknown origin) in tertiary care hospital in North India.

The present hospital based cross sectional study was conducted in a tertiary care Medical teaching institution in North India in collaboration with **Sher e Kashmir University of Agriculture Science and Technology** under **Outreach, Programme For Zoonotic Diseases**. The study population consisted of all the indoor patients and outdoor patients diagnosed with PUO and Fever from 1<sup>st</sup> November 2019 to 30<sup>th</sup> November 2020. All adult patients who attended Medicine OPD or were admitted in wards of Medicine with chief complains of Fever and Fever of unknown origin and who gave consent for participation were considered eligible for study. In order to reach the required sample the patients were enrolled on all days except Sundays. On each of these days, the investigator made a list of all the patients admitted/labelled with the diagnosis of fever and PUO in out-patient department of medicine. A sample size of 600 patients was calculated for the study to estimate the prevalence of brucellosis within 2.5% of estimated 10% in and around Jammu. (Based on estimates by **Sharma et al** seroprevalance of human brucellosis in and around Jammu using different serological tests), alpha= 0.05 and power of study being 80 % and non-response rate of 10%.

The study commenced after seeking approval from Institutional Ethics Committee GMC, Jammu.

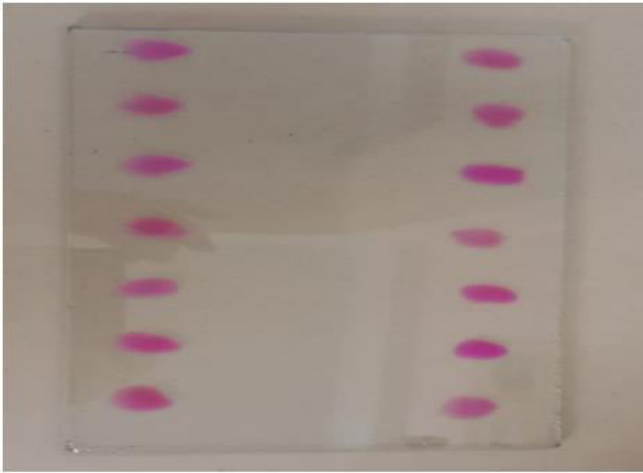
Operational definition of PUO given by **Durack DT, Street AC** was used for selection of the potential participants for study. Accordingly, any patient having unexplained fever and been seen in OPD on atleast 3 occasions and Patient admitted for duration in hospital which is less than 3 days were chosen for the study.

The eligible participants were briefed about the purpose of the study, and after their willingness to participate were subjected to detailed history as per proforma annexed (**Annexure 1**). Every patient was followed on day to day basis till the patient was discharged from hospital or an outcome was assigned to the patient. The questionnaire used in the study aimed at collection of information on socio-demographic information of the participants, clinical presentation and information about various environmental risk factors vis-à-vis brucellosis.

After collection of the information, 5 ml of blood was collected under all aseptic conditions. The blood sample was immediately centrifuged in the department of Microbiology, GMC Jammu and aliquots were prepared which were proper labelled. A unique ID was assigned to every sample. The samples were stored in deep freezer and transported under recommended temperature conditions to SKAUST- Jammu for analysis

The blood sample was subjected to Rose Bengal Plate Agglutination Test (RBPT), Serum Tube Agglutination Test (STAT) and PCR. RBPT, STAT were performed immediately whereas, ELISA was done after desired sample of 90 patients was achieved.

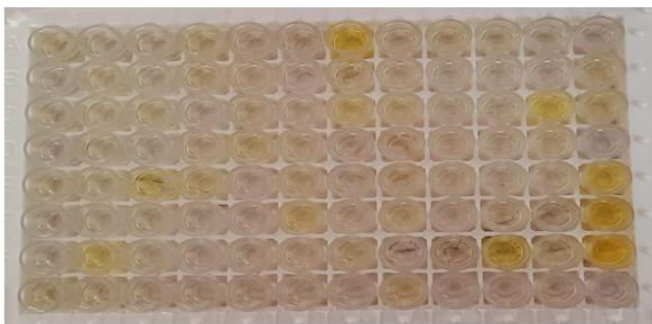
Initially, the study was planned to be conducted in GMC Jammu but due to COVID-19 Pandemic and declaration of GMC-Jammu as the dedicated COVID-19 hospital, blood samples from CHC R.S Pura, CHC Bishnah and CHC Sohanjana were collected in order to achieve desired sample size. Initially all samples were collected GMC Jammu (from 1 Nov. 2019 to 17 March 2020). Despite collecting samples from additional sites under intimation to Directorate of Health Services, IECGMC Jammu and Board of Studies, a sample size of 369 could be achieved against the proposed 600.



**Figure 1: An image of RBPT test**



**Figure 2: An image of STAT Test**



**Figure 3: An image of ELISA Plate**

**Table 1: Socio-Demographic Characteristics of the Cases of Fever and PUO Studied (N=369)**

Socio demographic characteristics	No.	Percentage (%)
<b>Gender</b>		
Male	261	70.7
Female	108	29.3
<b>Age( in years)*</b>		
10-≤19	8	2.2
20-≤29	103	27.9

30-≤39	114	30.8
40-≤49	63	17.1
50-≤59	53	14.4
60-≤69	17	4.6
70-≤79	7	1.9
80 and above	4	1.1
<b>Religion</b>		
Hindu	306	83.0
Muslim	57	15.0
Sikh	6	2.0
<b>Occupation</b>		
Govt. Job	83	22.5
Housewife	77	20.9
Pvt. Job	62	16.8
Student	50	13.6
Farmer	39	10.6
Nomad	26	7.0
Labourer	26	7.0
Others**	6	1.6

\*Youngest patient age was 12 years.

\*Oldest patient age was 85 years.

\*\*Defence personal, Carpenters.

Mean age male=37.63 ± 12.7 years male.

Mean age female=39.14 ± 13.08 years female.

Table 1 depicts socio demographic details of the patients with PUO and Fever. Males outnumbered the females with male: female ratio of (2.8:1). 3/4<sup>th</sup> of the study participants were between the age group of 20 – 49 years. Only 2.2% of the sample studied was < 20 years and 3% were older than 70 years. 1/4<sup>th</sup> of the participants in the study were government employee followed by homemaker and private jobs employee (20.9 and 16.8). 7% were nomads and 8% were engaged in manual works.

**Table 2: Distribution of environmental factors according to the food consumed, drinking water, animal owned, involvement in tending/rearing of animals and utilization of veterinary services in cases of Fever and PUO STUDIED (N=369)**

Environmental Factors		n(369)	Percentage(%)
(a)	<b>Consumption of milk</b>		
	Consumption of Raw Milk	217	58.9
	Consumption of Raw milk and undercooked Meat	142	38.5
	Others	10	2.6
	<b>Consumption of drinking water</b>		
	Consumption from piped water	184	49.9
	Consumption from piped water and public tap.	68	18.4
	Consumption from piped water, public tap , and open well	66	17.8
	Consumption from piped water and open well.	35	9.5
	Others	16	9.5

(b)	<b>Animal owned</b>		
	Cattle	256	69.4
	Others	34	9.2
	None	79	21.4
	<b>Tending/Rearing</b>		
	Cattle	201	54.5
	Assisted in animal birth	95	25.8
	Others	36	9.7
(c)	<b>Veterinary Services and Vaccination</b>		
	Cattle Vaccination	41	
	Veterinary services	133	
	Total	174	

As evident from the table 2a raw milk was consumed by majority of cases presenting with fever and PUO followed by consumers of raw milk and undercooked meat. As far as the consumption of drinking water is concerned nearly ½ of the participants consumed water from piped sources and 10% of the participants consumed water from open wells. It also shows that nearly 7 in 10 participants gave history of animal ownership particularly cattle and 9.2% domesticated animals were goat sheep and hens. 1/5<sup>th</sup> of the participants gave no history of ownership of animals. Half of the cases were directly engaged in tending/ caring of owned animals. Out of all the studied cases of fever and PUO 78.5% owned animals. 60% of the animals' owners availed Veterinary services and vaccination for their livestock.

**Table 3: Gender wise, age wise and occupation wise distribution of the clinical symptoms in the cases of PUO and Fever\* in study (n=369)**

	<b>GENDER</b>	<b>SYMPTOMS</b>						
(a)		<b>NIGHT SWEATS</b>	<b>FATIGUE</b>	<b>ANOREXIA</b>	<b>WEIGHT LOSS</b>	<b>HEADACHE</b>	<b>ARTHRALGIA</b>	<b>GENERALIZED ACHING</b>
	<b>MALE</b>	14(5.4)	79(30.3)	166(63.6)	33(12.6)	39(19.9)	87(33.30)	245(93.9)
	<b>FEMALE</b>	6(5.6)	38(35.2)	72(66.7)	22(20.4)	12(11.1)	34(31.5)	90(83.3)
(b)	<b>AGE (IN YEARS)</b>							
	<b>10 YR - 29 YR</b>	6(30)	36(30.7)	68(28.4)	16(29)	18(35.2)	39(32.2)	101(30)
	<b>30 YR - 59 YR</b>	13(65)	71(60.5)	154(64.6)	35(63.6)	24(46.9)	69(56.9)	208(62)
	<b>60 YR AND ABOVE</b>	1(5)	10(8.4)	16(6.6)	4(7.2)	9(17.6)	13(10.6)	26(7.5)
(c)	<b>OCCUPATION</b>							

GOVERNMENT JOB	2(2.4)	28(33.7)	56(67.5)	6(7.2)	7(8.4)	25(30.1)	79(95.2)
PRIVATE JOB	1(1.6)	17(27.4)	40(64.5)	8(12.9)	7(11.3)	14(22.6)	58(93.5)
HOMEMAKER	6(7.8)	22(28.6)	49(63.6)	18(23.4)	11(14.3)	26(33.8)	62(80.5)
NOMAD	0(0)	12(46.2)	21(80.8)	2(7.7)	2(7.7)	8(30.8)	26(100)
FARMER	6(15.4)	14(35.9)	22(56.4)	9(23.1)	8(20.5)	17(43.6)	34(87.2)
STUDENT	3(6)	19(38)	30(60)	5(10)	10(20)	20(40)	45(90)
LABOURER	1(3.8)	5(19.2)	15(57.7)	5(19.2)	5(19.2)	10(38.5)	26(100)
CARPENTER	1(50)	0(0)	2(100)	2(100)	1(50)	1(50)	2(100)

\*Fever>38.5°C

\*\* Multiple responses

\*\*\* Percentages do not add up to 100 due to multiple responses.

As evident from Fever, headache, arthralgia and generalized aching were predominantly present in males (70%, 15%, 33% and 94% respectively) whereas fatigue, anorexia and weight loss (35%, 67% and 20% respectively) showed female predominance. The symptom of night sweats showed almost equal distribution. Age wise distribution of clinical symptoms in the study participants showed that Anorexia and Generalized aches was the most common symptom reported in all age groups with minor variation. Occupation wise distribution of clinical symptoms in the cases of Fever and PUO. Night sweats were more commonly reported in carpenters. Fatigue, Generalized aches and anorexia showed almost uniform distribution through different occupations. Only anorexia and generalized aches was seen among Defense Personnel's.

**Table 4: Gender wise, age wise and occupation wise test positivity for brucellosis in study of Fever and PUO (n=369)**

<b>GENDER</b>	<b>ELISA</b>	<b>RBPT</b>	<b>STAT</b>
MALE	5(1.9)	3(1.14)	2(0.76)
FEMALE	1(0.9)	0(0)	0(0)
<b>AGE(IN YEARS)</b>			
10YR-29YR	2(33.3)	1(33.3)	0(0)
30YR-59YR	2(33.3)	1(33.3)	2(100)
60YR AND ABOVE	2(33.3)	1(33.3)	0(0)
<b>OCCUPATION</b>			
PRIVATE JOB	0(0)	0(0)	1(1.1)
NOMAD	2(7.6)	1(3.8)	1(3.8)
FARMER	2(5.1)	1(2.5)	0(0)
STUDENT	1(2)	1(2)	0(0)

LABOURER	1(3.8)	0(0)	0(0)
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Tables 4 shows the sero positivity with respect to Gender, Age and occupation for brucellosis. Table 4a shows the test wise positivity with different serological tests and an overall sero prevalence of 2.9%. Males outnumbered the females. More than ½ of the participants were of age groups of 20-49 years who were diagnosed by different serological tests employed in study. Table 4d depicts that the majority of the participants who were diagnosed with brucellosis were either nomads or were engaged in Farming.

**Table 5: Gender wise and age wise distribution for consumption of Gau Mautra in cases of Fever and PUO (n-369)**

AGE IN YEARS	CONSUMPTION OF GAU MUTRA					
	GENDER					
	MALE(n=51)		FEMALE(n=24)		TOTAL	
	n	%	N	%	N	%
10YR-29YR						
30YR-59YR	16	31.37	7	29.66	23	30.66
60YR AND ABOVE	33	64.70	17	70.83	50	66.66

Table 5 depicts that 20.3% (n=75) of the cases with fever and PUO give history of consumption of Cow's urine. Both males and females between 30-59 years (64.70 and 70.83% respectively) had the maximum consumption of gau mautra, whereas minimum consumption is reported in age groups of 60 and above of both the genders.

**Table 6: Brucellosis positive, in cases who consumed cow's milk (Gau Mautra)**

Characteristic	ELISA		STAT	
	No=6 Positive	Percentage (%)	No=2 Positive	Percentage (%)
Consumption of cow urine/ Gau Mautra	1	16.7	1	50.0

Table 6 depicts the results of the ELISA and STAT employed in the participants who consumed Gau mautra. ELISA and STAT were positive in only 1 case each respectively whereas RBPT was not positive in any of the cases who consumed Gau Mautra.

## DISCUSSION AND RESULTS

Seen through the prism of "Ecology of Medical Care" (LA Green *et al*, 2001) it is evidently clear that fever and fever of unknown origin ranks among important clinical entities around which health care is organized across a variety of health care settings including primary care. There are more than 200 causes ascribed, some common, some uncommon. Some causes remain obscure and undocumented because of the reasons stated above. Brucellosis is one such condition that defines such a scenario. Since brucellosis organism is susceptible to other antibiotics widely used in clinical practice, it is not known how many patients get cured of the illness while the intention to treat is not brucellosis but something else. (Vassalos, C.M., Economou, V., Vassalou, E. and Papadopoulou, C., 2009).

Prevalence surveys which are generally simple to conduct for assessing the magnitude of other maladies seem difficult for diseases like brucellosis. One of the biggest barriers is availability of appropriate diagnostic modalities in secondary and tertiary care facilities.



Early in the course of present investigation, we realized that it will be difficult to assemble the patients as per the case definition of PUO as understood routinely in clinical practice i.e., the definition of classic PUO or FUO as described by **Beeson in 1961**. Similarly, we were forced to effect more changes in our plan due to COVID 19. How far these changes have affected our prevalence estimates is difficult to quantify. However, it could be safely assumed that our prevalence estimates are lower than expected. The precision of the estimates made is also low as evident by wide confidence intervals.

The overall seroprevalence of Brucellosis in our study was 2.98% with the seropositivity of 0.5%, 0.8% and 1.6% by RBPT, STAT and iELISA respectively. In our study the STAT titres above 1:160 were considered diagnostic. However the areas where it is endemic, titres above 1:320 make the test more specific. (**Mantur, B.G. and Amarnath, S.K., 2008**). Several authors have reported prevalence of human *brucellosis in India ranging from 0.8% by Kadri et al*, 3.3% by **Handa et al**, 6.8% by **Sen et al** and 26.6% by **Yohannes M and Gill JP among cases of PUO**.

The age group 20-29 years was most commonly affected by brucellosis followed by 40-59 years. Least affected age groups were between 30-39 and 60-69 years. Our findings are in agreement with other authors (**Yohanes M, Gill JP and Mangalngi M et al**). The results however differed from the study results of **Sharma HK et al** who reported highest prevalence in the age group of >20-35 years Males were more commonly affected than females with sero positivity of 3.83% & 0.92% respectively. Less sero positivity among females can be attributed to small sample size in our study. However studies conducted by other researchers have also observed male predominance (**TN Mohanty etal, Fadhil AL et al**).

Brucellosis as a disease has assumed importance as more than 70% of Indian population is rural and there is constant threat of exposure from infected animals (**Park, K 2009 Banarsidas**). Therefore the presence of brucellosis is bound to be found in farmers, nomads, veterinarians and other occupationally exposed groups. Our study also reiterated these findings as among the different occupation groups included in our study, highest sero positivity was seen in nomads (36.3%) followed by farmers (27.2%).

Clinically brucellosis mostly presents with fever, headache, anorexia, generalized aches, arthralgias etc. In our study among the seropositive cases generalized aches (90.8%) was the most common symptom followed by anorexia (64.4%). The clinical results in our study are almost in agreement to studies conducted by V Jane Megid, Luis Antonio Mathias and Carlos A. Robles. In another study conducted by **Kochar et al 2007 and Mantur et al 2007** most common reported symptoms' were fever, fatigue, malaise, chills, sweats, headaches, myalgia, arthralgia, and weight loss. Only one seropositive case presented with complains of night sweats in our study which was similar to the findings of study by **Mantur, B.G et al 2007**.

In our study we tried to find out the relation between Brucellosis and consumption of cow urine (Gou Mutra). Though we could not find any similar study in literature, in our study out of 20.3% of the cases who gave history of consumption of cow's urine 2.6% of samples were found to be sero positive.

Conventional diagnostic methods were present since many years (**Samaha, H., Al-Rowaily, M., Khoudair, R.M. and Ashour, H.M., 2008**). In recent years emphasis was laid for the development of better serological tests with better sensitivity and specificity however, the serological tests differ in detection of various immunoglobulins' (Ig) due to varying sensitivity to different *brucella* infection, type, and purity of antigen besides variation in duration of incubation period during which test remains either positive or negative. To overcome these issues, new techniques have been developed such as ELISA which is regarded as gold standard test to detect bovine brucellosis, STAT and RBPT are traditional serological tests for detection of brucellosis in humans and animals(**Samaha, H., Al-**

**Rowaily, M., Khoudair, R.M. and Ashour, H.M., 2008).** However it was found each test was associated with certain disadvantages (**K Nielsen, 2002**).

In our study we compared ELISA, STAT and RBPT in diagnosis of brucellosis and ELISA was observed to be better diagnostic test over RBPT and STAT. Higher sero positivity was found among men as compared to females. Out of 10 seropositive males, 05 were sero positive by ELISA, 03 and 02 with STAT and RBPT respectively. Only 01 female was found seropositive by ELISA test. This was in accordance with 98.6% prevalence in males as compared to 1.03% in females by ELISA (**Agasthya, A.S., Isloor, S. and Prabhudas, K., 2007**). It has been opined that genus-specific PCR can also help to avoid false-negative results in the patients infected with unknown species and biovars (**Handa, R., Singh, S., Singh, N. and Wali, J.P., 1998**). We could not do PCR for our study samples as the kits were not available.

Similar studies conducted in Karnataka by other authors have (**Agasthya, A.S., Isloor, S. and Prabhudas, K., 2007, Mangalgi, S.S., Sajjan, A.G. and Mohite, S.T., 2012**). reported higher seropostivity rates than our study 2.26%, 2.26%, 19.69% by RBPT, SAT and Indirect ELISA, 4.79%, 4.41% and 4.41% among PUO cases by RBPT, SAT and 2ME. In another study of Brucellosis in PUO patients serum samples tested, 4.25%, 3.54%, 6.02% and 4.96% samples were positive by RBPT, SAT, indirect ELISA and IgG ELISA, respectively (**Pathak, A.D., et al., 2014**). In past few studies at limited scale have been conducted (**M Rashid et al, 2008**), but not many studies that involves human beings or animals have been performed on large scale in Jammu region.

In spite of the assertions made above, the present study indicates that the problem of brucellosis might not be as acute as expected. We had expected the prevalence to be higher among some sections of the population directly dealing with cattle rearing and in farming communities. Changes in the sampling methodology and our inability to study desired sample size has resulted in underestimation of the problem while throwing up estimates which are imprecise as well. However, in spite of low prevalence clinicians need to keep the index of suspicion high of the possibility of a patient suffering from brucellosis while encountering a patient of fever/PUO. It is also advisable to elicit history of certain occupations and risk factors for brucellosis in patients with PUO.

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