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Survey on Therapeutic Protocols of Human Brucellosis Prescribed By Urban and Rural Physicians and Persistence Risk Factors in the Governorate of Biskra, Algeria

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Received: 10 August 2017

Revised: 10 January 2018

Accepted: 17 January 2018

ABSTRACT

This cross sectional descriptive survey aimed to have a general idea about several therapeutic approaches of rural and urban physicians to confront human brucellosis in the governorate of Biskra (Algeria). This study was realized in 2010 and integrated 71 practitioners from private and governmental physicians. Questionnaires were distributed to physicians in urban or rural municipalities after concise face to face interviews. The studied qualitative variables were ; (to recover/to relapse, therapeutic success /failure, professional address municipality, prescribed antibiotics, type of antimicrobial resistance, causes of ruptures in the therapeutic protocol). While the quantitative variables were (professional experience period, prescribed therapy period, percentage of relapse to brucellosis after therapy). Results showed that ten antimicrobial substances were even used with dominance to doxycycline, gentamycin and rifampicin. Period of antibiotherapy goes from 10 days to one year. Percentage of relapse to brucellosis after treatment was 10-30% according to 56.33% of responders. To confront relapses, 25.35 % of physicians redo treatment using the same antibiotics, versus 50.70% who start again treatment using other antibiotics. Also, it had been revealed that rural physicians are well-informed about brucellosis symptoms. Successful therapy of brucellosis requires continuous training of concerned physicians and well equipped microbiology laboratories in proximity to endemic areas.

Keyword: Survey; physicians; Human brucellosis therapy; brucellosis persistence; Algeria

INTRODUCTION

In Algeria, despite control/eradication programs, brucellosis is endemic and remains a major public health problem [1]. The reemergence of brucellosis in some parts of the world is mainly the result of, the lack of vulgarization, non-respect of therapeutic protocols, excessive confidence after temporary eradication of some outbreaks, the insidious character of *Brucella* and the lack of accuracy of some used diagnostic

methods [2]. The essential element in the treatment of all forms of human brucellosis is the administration of effective antibiotics for an adequate length of time. A variety of antimicrobial drugs have activity in vitro against *Brucella* species; however, the results of routine susceptibility tests do not always correlate with clinical efficacy [3].

The optimal treatment for brucellosis remains an unsolved medical puzzle, owing to the

propensity of the infection for relapses, the universal failure of monotherapy and the absence of multiethnic, randomised trials evaluating possible new regimens for the disease [4]. The choice of regimen and duration of antimicrobial therapy should be based on whether focal disease is present or there are underlying conditions that contraindicate certain antibiotics (e.g. pregnant patients or children under 8 years old) [5]. Several antibiotics including tetracycline, doxycycline, rifampin, trimethoprim sulfamethoxazole, ciprofloxacin, and aminoglycosides have been used for treatment of brucellosis. Owing to the high incidence of relapse after monotherapy with any one antibiotic, the combination of at least 2 drugs is recommended [6]. The aim of this present study is to have an overview on the approaches applied by both of rural and urban physicians to cure human brucellosis and its persistence risk factors after therapy.

MATERIALS AND METHODS

Study area

The governorate of Biskra is located in Southeast of Algeria, on about 420 km from the capital Algiers, it occupies an area of 21 509.80 km². It is located between 4 ° 15 'and 6 ° 45' East longitude and between 35 ° 15 'and 33 ° 30' North latitude. Its altitude varies between 29 and 1600 m compared to the level of the Mediterranean [7]. It comprises 12 districts and 33 municipalities, with a population estimated in 2008 to 772 746 inhabitants. The governorate of Biskra is dominated by a Mediterranean climate with a semi-arid variant characterized by a dry and cold winter and a dry and hot summer [8]. It is a large palm trees and pastoral area with a special vocation of small ruminants breeding (sheep, goats), essentially, in extensive breeding system [9]. Currently the governorate of Biskra includes about 260 cattle farmers [10]. According to [11], there are 4995 bovine heads, 942 900 sheep heads, 293 000 goat heads and 5000 camel heads. In fact, this governorate has experienced a remarkable increasing of the number of brucellic human patients for two decades (e.g.; 431 human cases in 2009; [12]). Sheep and goat brucellosis are the most implicated, looking for the large numbers of small ruminants flocks reared in the form of nomadic and semi-nomadic systems.

Study background

During the 1990s, the Algerian authorities applied a screening/slaughter/compensation strategy for brucellic animals (cattle, sheep, goats). Then, in 2006, the Ministry of Agriculture and Rural Development of Algeria decided to engage in the vaccination of small ruminants against ovine and caprine brucellosis via the *Rev 1* vaccine in the governorates with high rates of *Brucella* infection. The governorate of Biskra is among the regions that have benefited from this favor. Despite all these measures, the disease persisted after that with considerable rates in the human population of this governorate [13, 14]. From this background, among several supposed hypotheses, one assumed that the persistence of human brucellosis, is due to a relative influence of the diagnostic or therapeutic approaches carried out by the treating physicians engendering ; incomplete or discontinuing treatment protocols, erroneous therapy or relapse cases.

Sampling

Initially, some data were collected concerning statistics, geographic distribution and current addresses of private physicians located in the governorate of Biskra, from the Directorate of Health and Population Services [15]. The survey included 71 private and governmental practitioner physicians, representing thus 33 % of whole concerned physicians by our subject through the governorate, just before the end of 2009 (n=215) [15].

Questionnaire conception

Questionnaire was composed of 31 questions, destined to practitioner physicians who could be in close contact with brucellic patients in urban or rural regions. A part of items targeted the knowledge of human brucellosis incidence and therapeutic protocols even prescribed to fight it. According to Schwartz recommendations [16], the studied qualitative variables are dichotomist (to recover/to relapse, therapeutic success /failure), or polychotomist (professional address municipality, prescribed antibiotics, type of antimicrobial resistance, causes of ruptures in the therapeutic protocol). The quantitative variables are measurable (professional experience period, prescribed therapy period, percentage of relapse to brucellosis after therapy).

Conducting the survey

The survey was realized between January and May, 2010. An initial plan of visits has been established in advance. In general, if the physician was available and had a time vacuum, an interview was conducted with him for a period not exceeding 30 minutes on average. Otherwise, the questionnaire was left at home to be recuperated later.

Results statistical presentation

As soon as the aim of this study was descriptive, only Microsoft Excel xp., 2007 was used to determine descriptive histograms and tables.

RESULTS

Physicians participating in this survey act as private (n = 49) and governmental (n = 22). The major part of responders was general physicians (n= 59), while others were specialist (n=12) (Table 1).

Table 1: Distribution of surveyed physicians' specialties:

Speciality	Responders (n)	Speciality	Responders
Internal medicine	03	Pediatrics	01
Rheumatology	02	Epidemiology	01
Infectiology	02	Clinical biology	01
Radiology	01	Orthopedy	01

Wholly, 12 municipalities were included, 35 responders were considered as rural practitioners while 36 as urban ones (Table 2).

Totally, responders have a professional experience going from 2 to 34 years.

Table 2: Distribution of surveyed physicians' professional addresses municipalities

Municipality	Biskra	Sidi Okba	Kantara	Sidi Khaled	Leghrous	Ourlal
Responders (n)	35	08	01	06	01	02
Municipality	Tolga	Ouled Djellal	Doucen	Z.El Oued	K.Sidi Nadji	Mzirâa
Responders (n)	05	03	01	07	01	01

Concerning the antibiotherapy often recommended, ten antimicrobial substances were mentioned. 23.94% of doctors declared that they prescribe rifampicin with doxycycline, whereas 22.53% prefer to associate gentamycin with

doxycycline, versus 15.49% whom combine these three antibiotics (rifampicin, doxycycline, gentamycin), the rest of physicians have other choices (Table 3).

Table 3: Frequently prescribed antimicrobial agents to confront brucellosis

Prescribed antimicrobial agents	Responders (n)
Never received brucellic human cases	07
Doxycycline + Rifampicin	17
Doxycycline + Gentamycin	16
Doxycycline + Gentamycin + Rifampicin	11
Gentamycin + Tetracycline	02
Gentamycin + Rifampicin	02
Tetracycline + Streptomycin	02
Amoxicillin only	02
Gentamycin only	02
Doxycycline only	02
Rifampicin only	01
Tetracycline only	01
Gentamycin + Doxycycline + Tetracycline	01
Doxycycline + Sulfamide	01
Tetracycline + Sulfamide	01
Vibramycin only	01
Chloramphenicol only	01
Quinolone only	01

The most frequently cited antibiotics are in descending order; doxycycline (n = 48), gentamycin (n = 34), rifampicin (n = 31) and tetracyclines (n = 07) (Fig. 1).

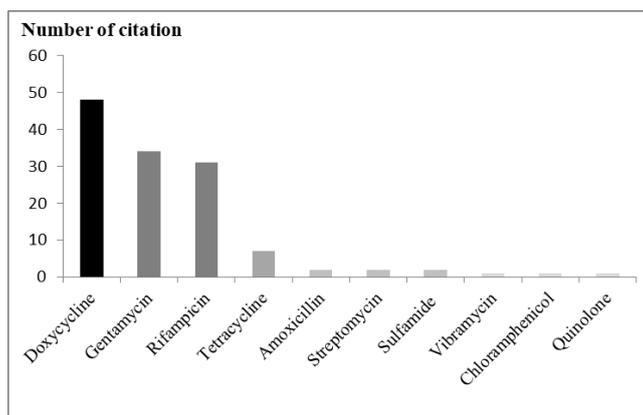


Fig. 1 : Descendant classification of prescribed antibiotics during brucellosis treatment according to non-cumulative number of citation

The most frequently cited periods of antibiotherapy against brucellosis are in descending order according to citation frequencies; 45 days, 2 months, 1 month, 42 days, 45 days to one year, and 10 days only (Table 4).

Table 4 : Frequently prescribed antibiotherapy periods

Prescribed antibiotherapy periods	Responders (n)
Never received brucellic human cases	07
45 days	19
2 months	18
1 month	12
42 days	08
From 45 days to one year (according to to <i>Brucellae</i> complications)	06
10 days	01

The approximate percentage of patients relapsing to brucellosis after receiving the necessary treatment would be 10-30 % according to 56.33 % (n = 40) of responders, while 31% (n = 22) do not make a census of brucellosis relapses cases (Table 5).

Table 5 : Approximate percentages of brucellosis relapses after treatment

Brucellosis relapse percentages	Responders (n)
Never received brucellic human cases	07
No idea (lack of registration)	15
10 %	20
20 %	14
30 %	06
≥ 40 %	06
00 %	02
01%	01

In order to confront relapses, 25.35 % of physicians redo treatment using the same antibiotics, compared with 50.70% who start again treatment after changing antibiotics, while 14.08 % prefer to refer relapsing patients to governmental health services (Table 6).

Table 6 : Prescribed measures in case of brucellosis relapses

Prescribed measures in case of brucellosis relapses	Responders (n)
Never received brucellic human cases	07
Start again treatment using other antibiotics	36
Redo treatment using the same antibiotics	18
Refer relapsing patients to governmental health services	10

The mostly probable causes of human brucellosis persistence during after therapy would be ; a native antimicrobial resistance according to 14.08% of physicians, a focal localization of *Brucellae* making them inaccessible to antibiotics according to 47.89 % of responders, while only 1.41 % of physicians attributed this therapeutic failure to recontamination (Table 7).

Table 7: Major cited causes of brucellosis persistence during/after therapy

Major causes of brucellosis persistence during/after therapy	Responders (n)
No idea	26
Focal brucellosis	34
Native antimicrobial resistance	10
Recontamination	01

Among the whole surveyed physicians, 76.05 % have no idea about antibiotics that became inactive against *Brucellae* during/after a treatment protocol. While, according to 23.95 % of responders, cases of antimicrobial resistance appeared, mainly, in descending order according to citation frequencies, to ; gentamycin, doxycycline and rifampicin (Table 8).

Table 8 : Major cited antibiotics being inactive against *Brucellae* during/after therapy

Antibiotics being inactive against <i>Brucellae</i> during/after treatment	Responders (n)
No idea	54
Gentamycin	06
Doxycycline	05
Rifampicin	03
Terramycine	01
Vibramycin	01
Aminosides	01

In the case of suspected antimicrobial resistance, 15.49% of physicians declared they changed antibiotics, compared to 2.82% who preferred to increase the dosage without changing antibiotics, while 5.63% chosen to refer their patients to governmental health services (Table 9).

Table 9 : Prescribed procedures in case of suspected antimicrobial resistance of *Brucellae*

Prescribed procedures in case of suspected antimicrobial resistance of <i>Brucellae</i>	Responders (n)
No idea	54
Change inefficient antibiotics	11
Refer patients to governmental health services	04
Increase the dosage without changing antibiotics	02

Within all surveyed physicians; (n = 32) considered the cause "d" as the primary origin of not continuing brucellosis treatment. Then comes in second place the cause "c" (n = 11), followed by the causes "e" and "f" in equal position (n = 9). Subsequently, come the causes "a" (n = 7) and the cause "b" (n=3) (Fig. 2). The cause "e" was cited by 22.2 % (n = 8) of rural physicians, versus 2.82 % (n = 1) of urban ones.

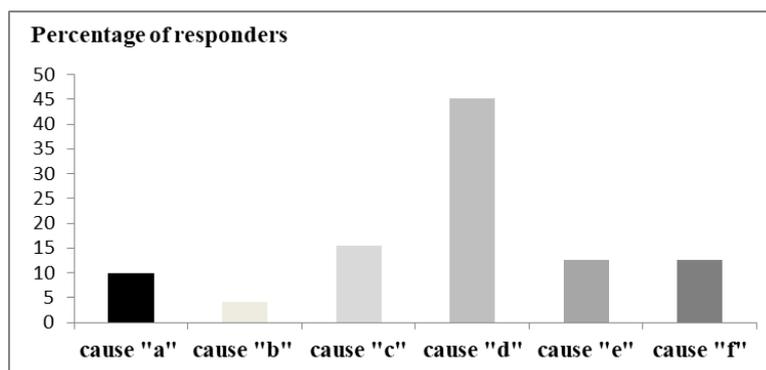


Fig. 2 : Non-cumulative distribution of main causes percentages of not continuing brucellosis therapy

- a. No idea
- b. Rupture of needed antibiotics on the pharmaceutical market
- c. Patients avoid painful and repeated injections (gentamicin)
- d. Some patients believe that they are totally cured once the fever disappears
- e. Difficulties to move to hospital to receive injections (rural or transhumant mode, long distances)
- f. Intermittent interruptions of therapeutic protocol by forgetting or omission

DISCUSSION

During this investigation it was noted that general practitioner physicians, especially those belonging to the governmental sector, are more in contact with brucellic patients than specialist physicians. In addition, it had revealed that rural physicians are more experienced and educated about brucellosis clinical aspects. This may be due to the high frequency of brucellic human cases in the rural environment, often in association to being in promiscuity with infected animals without taking prophylactic measures. Generally, specialist physicians are implicated when complications of disease occur. According to W.H.O [3], osteo-articular complications of brucellosis are common, occurring in up to 40% of cases in some series of patients. Some manifestations, such as sacroiliitis, endocarditis, epididymalorchitis, nervous disorders, and liver involvement, are frequently observed [3, 17].

Regarding the associated antibiotics and the periods recommended during brucellosis treatment protocols, the great majority of questioned physicians respect, relatively, the international recommendations [3], but without taking into consideration the long-term follow-up of the efficiency and the possible relapses with the chosen therapeutic protocols. In fact, there are worldwide controversial recommendations about brucellosis therapeutic regimen. WHO Expert Committee in 1986 [3], reported that the use of rifampicin is active in

vitro against *Brucella* species, and it recommended, in order to provide a completely oral regimen to treat brucellosis, the combination of doxycycline (200 mg/day orally) plus rifampicin (600–900 mg/day orally) for six weeks. This regimen has generally been found to be of similar efficacy to doxycycline plus streptomycin for patients with uncomplicated brucellosis. According to Solera et al [18], the combination of doxycycline for 45 days and gentamicin for 7 days is an effective and well-tolerated therapy for brucellosis. This combination is relatively inexpensive; gentamicin can be given intramuscularly once daily, and it is suited to outpatient therapy. The combination also appears promising for the treatment of brucellosis in patients with focal disease such as sacroiliitis and peripheral arthritis. During the same study, the relapse rates obtained with doxycycline treatment for 30 days appear to be higher than those obtained with doxycycline treatment for 45 days. Colmenero, et al [19] suggest that rifampicin induces a decrease in plasma doxycycline in patients receiving combination therapy of these two antibiotics and claim that the best combination of antibiotics to treat brucellosis, would be that of doxycycline with streptomycin. Whereas, Solera, et al [20], have proved experimentally that the best association for acute forms is ; doxycycline with streptomycin. In a recent study realized by Jia et al [17],

combination of doxycycline plus rifampicin for 12 weeks was an effective regimen for patients without complications. The 3-drug regimen (doxycycline +rifampicin + levofloxacin) for 12 weeks was recommended for those with complications. There were 6 patients died (1.02 %) with overall relapse rate of 5.98 %.

Pregnant women and nursing mothers pose special problems with regard to the selection of appropriate drugs. All drugs cross the placenta in varying degrees, thus exposing the fetus to potential adverse drug effects. Tetracyclines are contraindicated in pregnancy owing to the potential for permanent staining of fetal dentition, and the susceptibility of pregnant women to drug-induced fatty necrosis of the liver and pancreatitis [3]. In pregnancy, the W.H.O recommends rifampicin as the first line and the mainstay of treatment. In this case, a second drug (as an aminoglycoside, co-trimoxazole, or erythromycin) should be added to potentiate the bactericidal effect and decrease recurrence [21].

For brucellosis in neonates and children less than 8 years of age, tetracyclines are contraindicated because of the potential for permanent staining of deciduous teeth and inhibition of bone growth. Doxycycline binds less to calcium than other tetracyclines, and may pose less of a risk [3]. According to Alshaalan et al [22], a common combination for children yielding successful results is as follows: rifampicin and trimethoprim/sulfamethoxazole, for children below 8 years of age. Doxycycline and trimethoprim / sulfamethoxazole, or rifampicin for children older than 8 years of age. This combination has been shown to have the highest success rate and should be used in children above 8 years to avoid the staining of the teeth in younger children.

As regards to therapeutic duration, it is very important to note that during this study, the possible lack of the main antibiotics effective against *Brucellae* from pharmaceutical market in some regions influenced directly the efficiency and the duration of the therapeutic protocol recommended by treating physicians. Several authors recommend continuing the treatment, even after total disappearance of the symptoms, in order to avoid relapses, and affirm that a therapeutic protocol whose duration is less than 6 weeks is generally ineffective. In a study realized by Solera et al [23], and after a 30 days treatment with oral doxycycline, combined with

a single intramuscular injection of gentamycin, the percentage of relapses was very high (22.9%). Other authors emphasize the long-term toxicity of antibiotics, particularly tetracyclines and gentamycin, especially in children [24].

Usually, relapse occurs in 5 % to 30 % of patients [5]. Also, even if some patients are apparently cured, their organisms may remain infected, and as a consequence of a lack of effective and sensitive diagnostic tools, these patients often go unnoticed [25, 26]. Human patients with asymptomatic infection had low antibody titres and different contact patterns. Awareness of asymptomatic infection is important for early diagnosis of brucellosis and prevention of chronic infection [27].

During this present study 14.08 % of treating physicians prefer to refer relapsing patients to the governmental health services. They prefer to do not take risks that would be due to possible complications in the patient, and then decide to discharge their responsibilities. With reference to brucellosis relapses risk factors, according to a study realized by Alavi et al [28] it is proved that aging, gender, chronic infection and lymphopenia are risk factors for relapsing brucellosis. Also, in a recent study realized in Iran, Nematollahi et al [29] report that female sex, older age, and winter months were found to be significant determinants of recurrent human brucellosis. Since, it is very difficult to differentiate reinfection from relapse in the region of study with a high rate of repeating exposure to brucella antigens in men due to their occupational status and behaviors, Alavi et al [28], think that sex is not a real risk factor. *Brucellae* organisms are able to survive and even multiply within cells of mononuclear system, thus explaining the tendency of the disease to relapse [30]. Hagherizadeh et al [31] report that chronic and relapsed brucellosis are associated with diminished values in interleukin-12. Nevertheless, due to the high repetition rate of occupational exposure to *Brucella* antigens, the differentiation between reinfection and relapse in regions endemic for human brucellosis is a cumbersome task [29].

For this present study, even if the attitude of abusing the therapeutic protocol is difficult to prove in a palpable way, as soon as it constitutes a personal secret of the patient, experienced physicians can feel it through the controversial statements of their patients. In fact, the

prescription of gentamycin for a period of 21 days is not enough practical in rural areas, since transport is often deficient and distances are very long between dwellings and health services. To solve this problem, Dagan and Einhorn [32], suggest a short and effective program of treatment for brucellosis, while prescribing gentamycin in intramuscular way once a day, combined with doxycycline or co-trimoxazole for a short time, for adults or for children. In the case of nomadic and semi-nomadic life style, as it is in our study area, it is preferable to prescribe complete orally drugs protocols.

Jia et al [17] report that the fever in all the patients was removed very quickly once the patients took the drugs of doxycycline plus rifampicin. The fever was disappeared 2 or 14 days after taking antibiotics with the most (85.2%) back to normal in one week, authors suggest that it may be important for the doctors to make prescription in remote endemic areas, where diagnostic facility is poor; doctor may give doxycycline and rifampicin to these patients with fever before identification of pathogen.

Concerning brucellosis contamination risk factors, in Algeria, the distribution of human brucellosis was observed to be predominant in the steppe region compared to other regions. The high density of small ruminant population in these areas has been associated with the high number of cases. Sex-wise analysis showed a male predominance possibly because professionally, men are more within the health sector compared to women. Contrarily, women are more exposed than men when it has to do with contamination through food origin. Traditionally, this can be attributed to the fact that women handle the food items domestically than men [33]. It is primordial to take in consideration that all these *Brucellae* cause human disease: *B. melitensis*, *B. suis*, *B. abortus* and *B. canis* in descending order of pathogenicity. Also, the *Brucellae* are somewhat host-specific but cross-species infections occur, especially with *B. melitensis* [34, 35, 3, 36]. Remarkably, in Algeria the major efforts are concentrated on small ruminants and cattle brucellosis, but not dogs brucellosis, especially that the majority of visited municipalities, during this survey, are rural and pastoral areas including important flocks of small ruminants with the obligatory presence of many guard dogs. It is important to notify that number of

guard dogs, seems to be more important in nomadic transhumant life style rather than sedentary one. Also, there remains a risk for reemergence and spillback of brucellosis from wild host reservoirs [37], despite reliable human infections are quite rare [3]. Actually, there are no complete published data about brucellosis or other infectious diseases in wild fauna on the Algerian territory. The presence of wild boar species in near proximity to farms crops and reared domestic animals, would be considered as an significant risk factor of contamination and persistence of brucellosis. Studies in this field are hampered by the lack of logistic means, sponsor funds and research national programs. Prophylaxis should focus on vulgarization of nomadic populations and highlight the importance of the full respect of treatment periods [2]. Relating to this present study, it is necessary to consider the existence of a nomadic system of small ruminant breeding as an important brucellosis risk factor. In fact, in rural areas, the risk of developing brucellosis is attributed to unsafe animal handling, to the close contact with goats and sheep, keeping cattle, cattle vaccination and consumption of unpasteurized raw milk [38, 39, 40]. In study area, as several other parts of Algeria, consumers believe that she-camel milk has medicinal values only when it is drunk in raw status without heat treatment [41, 42]. Camels infected with *B. melitensis* shed the organisms in milk and in some countries this is a serious public health problem [3]. Clinical signs of brucellosis in camels appear to be very rare [3, 43]. Thus, contamination or recontamination risks by *Brucellae* from one infected she-camel milk, are very high. Also, in a study realized in Algeria by Khardjaj et al [44], it was suggested that stray dogs may play a role in the transmission of *Brucellae* to the domesticated animals and humans. The dogs were thought to be infected with *Brucellae* as a result of eating aborted materials originating from cattle and goats. It is evident that dogs are more frequent in rural areas, in a close contact with ruminant herds. This risk factor is very important especially that a recent study achieved by Khaldi et al [45] showed that the seroprevalence of cattle and sheep brucellosis from 2002 to 2014 remains remarkably high despite the vaccination program in Algeria. Contrary to some traditional views, *B. melitensis* remains

fully virulent for man after infecting cattle. The bovine infection presents a particularly serious problem because of the large volume of infected milk that can be produced by an individual animal [3].

The diagnosis of human brucellosis cannot be made solely on clinical grounds due to the wide variety of clinical manifestations of this disease, and it is essential to perform bacteriological and serological tests. However, all physicians dealing with a febrile patient living in an endemic area or recently travelled to a country where brucellosis is endemic ("travel-associated disease") must be aware of the possibility that the patient could be infected with *Brucella*. For this reason, correct clinical history taking is essential to orientate the diagnosis, and the need for some very basic questions (profession, food ingested, contact with animals and travel to endemic areas) must be emphasized. Moreover, a rapid screening test must be performed [3]. The Rose Bengal plate test can be used as a sensitive rapid screening test but the results should be confirmed by bacteriological and other serological tests [3, 46, 17]. The major problem in the case of human brucellosis therapy in Algeria is that treating physicians are obliged to go directly to antibiotic therapy as soon as the serological tests have proved positivity (SAT, RBT), whereas neglecting the degrees of sensitivity and specificity of these tests in the epidemiological situation of the country. W.H.O [3], reports that the sensitivity of RBT is over 99 %, but it can give false positive reactions with sera from patients infected with *Yersinia enterocolitica* 0 : 9 or other cross reactive organisms and from healthy individuals that have had contact with *S-Brucella* without developing disease. Moreover, in Algeria, except certain research structures, we observe the inability of laboratories belonging to hospitals to carry out bacterial cultures of *Brucella*, that had always hampered the identification of the *Brucella* species and consequently the practice of the antibiogram, and thus the detection of possibly resistant strains to one or more usual antibiotics. For reasons already mentioned, the identification of antimicrobial resistant strain seems to be very difficult in practice. In addition, according to W.H.O [3], brucellosis can be insidious and may present in many atypical forms. In many patients the symptoms are mild and, therefore, the diagnosis may not be even

considered. Indeed it should be noted that even in severe infections differential diagnosis can still be difficult.

For epidemiological surveillance of brucellosis, human cases may be a useful indicator of the presence of disease in animal populations and may be the only source of information for surveillance [3]. Also, monitoring of human brucellosis will provide a reliable indication of the success of animal prophylaxis; it will measure the effectiveness of mass vaccination in animals [47].

Veterinarians should be made aware on the importance of their role in the detection of zoonoses and vulgarization of both of breeders and consumers, while insisting on ensuring their personal safety when handling animals, biological samples or vaccine [2]. W.H.O [3], recommends ; the capture or shooting and serological examination of feral or wild-life species in contact with domestic animals, supported by isolation and identification of the organisms; also, an intersectoral collaboration by a close interaction between the medical authorities concerned with public health authorities on the one hand and the veterinary authorities on the other. This collaboration is only the first step in establishing an effective control program.

CONCLUSION

This present study showed that chosen approaches by urban and rural doctors during the treatment of human brucellosis in the governorate of Biskra, are relatively in conformity with international recommendations. As well, it revealed that rural physicians are more knowledgeable about the clinical diagnosis of brucellosis than their urban congeners. However, several conditions must be guaranteed to ensure the success of both of diagnostic and therapeutic approaches against brucellosis, among others ; ongoing and up-to-date training of practitioner physicians in brucellosis endemic areas ; building trust between patients and treating physicians to avoid false declarations ; insisting on the proper fully registration of observed clinical signs and treatment protocols ; a good accompaniment of brucellic patients until complete coverage. At the same time, microbiology laboratories should be equipped with more efficient, modern and reliable diagnostic tools (eg.; E.L.I.S.A, P.C.R) and be

able to cultivate and isolate different *Brucella* strains.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this paper.

ACKNOWLEDGMENTS

Author acknowledges all physicians participating in this survey and the administrator staff of Directorate of Health and Population Services (D.S.P) in the governorate of Biskra for facilitating this study.

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Cite this article as:

Mammeri Adel. Survey on Therapeutic Protocols of Human Brucellosis Prescribed By Urban and Rural Physicians and Persistence Risk Factors in the Governorate of Biskra, Algeria. *J Pharm Chem Biol Sci* 2017; 5(4):437-448.