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Epidemiology Of Brucellosis And Changing Trends In Control & Treatment

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Abstract

Background: Brucellosis is defined as the “zoonotic infection” of large animals, for instance, camels, cattle, goats and sheep. Brucella organisms can be infected by human by the oral route i.e. ingestion of contaminated foods or through percutaneous route i.e. during slaughtering animals. The presumed route of infection of this serious disease is by the airborne route. **Aim:** The predestined aim of this study was to determine the epidemiology of brucellosis and the changing trend regarding the control and treatment of this disease. **Methodology:** The secondary qualitative research method was used for the collection of data from the evidence based databases. The content analysis was carried out to determine the epidemiology of this disease and the changing trend in the control and treatment of the disease. **Results:** The results of the study revealed that epidemiology of the disease vary from region to region and for treatment a 6-week oral therapy with a combination of doxycycline and rifampin was effective and relapse was found among 10% of patients. Alternatively, fluoroquinolone plus doxycycline was found effective. Six weeks administration of doxycycline along with streptomycin for 3 weeks was also effective. Netilmicin or gentamicin can be used as a substitution of streptomycin. There is no available vaccine for the treatment of this infection among human. The control and prevention of the disease is possible by using preventive approaches. **Conclusion:** The epidemiology of Brucellosis varies in different part of the world. There is an increased changing trend in the treatment and control of infection and there is a crucial need for the advancement in these trends.

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INTRODUCTION

Brucellosis is defined as a zoonotic infection which is caused by the genus Brucella usually in the wild and domestic animals. This can occur in human if they consume the food which has contact with the infected animals or by the inhalation of the infectious aerosols due to bioterrorism or any accident. The brucellosis in the human has been described in detail by using the approach of military medicine¹. The comprehensive cases of the relapsing chronic febrile illness were discussed by G Cleghorn in 1751. He was British army surgeon stationed on Minorca, and he related this chronic illness with the disease which was described 2000 years earlier by Hippocrates².

After this description, three other British army surgeons during the 1800s who were working on Malt Island reported the similar observations regarding this disease. The clinical characteristics this infection was described in detail by JA Marston in 1861³. David Bruce isolated the causative organism of this disease in from the spleens of five patients who died due to this disease. He inserted this microorganism within the genus Micrococcus for

evaluation⁴. ML Hughes after 10 years coined the term “undulant fever,” and he published a detailed monograph based on pathological and clinical findings in 844 patients⁵.

In the same year, a Danish investigator B Bang named this organism as “bacillus of abortion,” as it was found in the fetuses and placentas of cattle that were suffering from the problem of contagious abortion⁶. AC Evans in 1917 recognized Bang’s organism had the identical characteristics to those that were described as the causative infectious agent of human brucellosis by Bruce. This organism is responsible for causing infection in cattle, ruminants, goats and sheep and may lead to abortion, genital infection and death of fetus^{7, 8}. The human who get infection accidentally due to the contact with the infectious animals or ingestion of infected dairy foods can develop several symptoms. Some of the usual symptoms that are associated with this infection are muscle pain, fever and malaise. The risk of the exposure to this disease during military deployment or international travel is increased due to the distribution of this infection worldwide⁹. The property of this disease is that it may become chronic and has the property to relapse even if the treatment of this disease is taken. This disease has been documented by various researchers so as to increase the awareness of the people regarding this infection¹⁰⁻¹³.

In the biotechnology industries and academic where there is an expansion of the biodefense research, the frequency of the laboratory accidents increases. The incidence of these accidents can be reduced by strict adherence of the lab people to good microbiology and laboratory techniques, proper engineering controls, and the use of the vaccination and personal protective equipment^{14, 15}. However, there is still no availability of the human brucellosis vaccine for laboratory workers. There is a serious concern regarding the military or war purpose of the *Brucella*. The reason for which this genus can be used as a biological warfare agent is that it can be easily transmitted by aerosol. This is a serious concern because if this agent is used as a warfare agent, it may lead to serious disasters that would be very difficult to be managed.

In 1942, the United States began to develop *Brucella suis* as a biological weapon against their enemies. The rationale for the development of this biological weapon is the maintenance of effective and long-term viability. This agent was placed into bombs field trials were carried out with the animal targets in 1944 and 1945. In the year 1969, the offensive *Brucella* program was terminated by the United States and all its biological weapon munitions were destroyed to completely eradicate this project. However the developed munitions developed were never utilized in combat but the research studies that were conducted under this offensive program increase the reinforcement of the concept that *Brucella* organisms is an effective warfare weapon that can be used against US troops¹⁶. The civilian populations even before the end of the attack of the anthrax were well aware about *brucella* as potential agent to target population. A model designed in 1997 regarding aerosol attack with *Brucella* on urban population estimated that approximately \$477.7 million economic loss was reported per 100,000 person’s exposed¹⁷. *Brucella* is one of the clinical representatives of the biological agents associated with zoonotic disease that are able to generate threat among the people as a terrorist weapon against agricultural or human targets¹⁸. A comprehensive and excellent review regarding, epidemiology, causes and control of brucellosis was published in the year 2005¹⁹.

Aim of the Paper

The predetermined aim of this paper was to determine the epidemiology of brucellosis worldwide and the changes that have occurred in the trends regarding the control and treatment of this disease.

Rationale of the Study

The reason for choosing this topic is that brucellosis is the major causative factor for various diseases among the domestic animals and human beings. The study of the prevalence data has revealed that this disease is prevalent in various regions of the world; however, the prevalence rate is different in different regions. Moreover, there is a prime requirement to develop effective treatment and control approaches for this disease to avoid serious health consequences. Therefore, this study has taken into consideration the epidemiology of this disease and the preventive and control methods along with the treatment approaches.

Materials and Methods

This study was based on the secondary qualitative research and data was collected from the evidence based databases. The relevant data regarding this disease was extracted from Pubmed, Cochrane, CINHALL, Ebcos etc. after the collection of the relevant data, the content analysis was carried out to find out the results related to epidemiology and control and treatment trend.

Results and Discussion

Epidemiology

It is evident from the above described that brucellosis is a prime source of disease in domesticated animals and humans. There is a great variance in the prevalence and evidence of the disease as the prevalence may vary from region to region. The brucellosis among bovine is caused mainly by *B. abortus* which is the most widely spread form of this disease (Tables 1-5). In humans, *B. melitensis* is responsible for causing ovine/caprine brucellosis. The geographical distribution of this disease is limited but this is a major problem of western Asia, Mediterranean region, and parts of America and Africa. The reemergence of the disease is the major problems that cause the failure of eradication of this disease²⁰. It is evident from the literature review that goats, sheep and their products are the major factor causing infection, in Israel, Saudi Arabia, some southern European countries, Kuwait, *B. melitensis* is the major associated. The reason is that the *B. abortus* vaccines do not have the capability to provide effective protection against *B. melitensis* infection, moreover, the use of the *B. melitensis* Rev.1. vaccine in cattle is not evaluated completely.

This is the major reason for increased prevalence of bovine *B. melitensis* infection in some countries of the world. Similar to this, another problem is also found prevalent in South American countries, for instance Colombia and Brazil, where *B. suis* biovar 1 is found in cattle²¹. In some other areas of the world, pigs are more frequent cause of human infection as compared to cattle. However, the true prevalence of brucellosis among human is still unknown. The incidence which is reported in endemic-disease usually varies from <0.01 to >200 per 100,000 population²². In some other areas of the world, for instance, Saudi Arabia, Kuwait, Peru there is high incidence of acute infections. On the other hand, in some brucellosis endemic areas low incidence is reported. This low incidence is due to the low levels of reporting and surveillance, however, the risk of this infection is influenced by some factors for instance, heat treatment of dairy products, food preparation, and direct contact with animals.

Table 1.**Table 2.**

Table 1. Brucellosis in animals, Europe, 1994					Table 2. Brucellosis in animals, Africa, 1994				
Country	Bovine (<i>B. abortus</i>)	Ovine/ caprine (<i>B. melitensis</i>)	Porcine (<i>B. suis</i>)	Ovine (<i>B. ovis</i>)	Country	Bovine (<i>B. abortus</i>)	Ovine/ caprine (<i>B. melitensis</i>)	Porcine (<i>B. suis</i>)	Ovine (<i>B. ovis</i>)
Albania	-	+	+	+	Algeria	+	?	ND	+
Belgium	+	-	-	-	Angola	?	?	?	?
Bulgaria	-	-	+	+	Botswana	+	ND	-	ND
Croatia	-	-	+	+	Cape Verde	?	?	?	+
Czech Republic	-	-	?	-	Central African Republic	++	ND	+	ND
France	+	++	?	+	Chad	++	?	?	ND
Germany	+	-	?	+	Congo	+	-	-	-
Greece	+	++	ND	ND	Côte d'Ivoire	+	-	-	+
Ireland	+	-	-	-	Egypt	+	+	ND	-
Italy	+	+	-	ND	Eritrea	+	?	ND	+
Latvia	-	-	+	-	Ghana	+	-	-	-
Lithuania	-	-	-	?	Guinea	+	ND	-	ND
Macedonia	+	+	-	-	Kenya	+	+	ND	ND
Malta	+	+	-	-	Libya	+	+	-	-
Poland	+	+	?	-	Mauritius	-	?	-	-
Portugal	+	+	-	+	Morocco	+	?	-	-
Romania	-	-	+	-	Mozambique	++	+	++	+
Russia	++	++	+	+	Namibia	+	-	-	?
Slovakia	-	-	ND	-	Niger	+	+	ND	+
Slovenia	-	-	-	+	Nigeria	++	+	+	ND
Spain	+	+	-	+	Seychelles	+	-	-	-
Ukraine	ND	ND	ND	ND	South Africa	++	+	-	+
Yugoslavia	+	+	+	-	Sudan	++	+	-	-
-	not present				Tanzania	+	ND	ND	ND
+	low sporadic incidence				Tunisia	+	++	-	-
++	high incidence				Zaire	+	ND	+	ND
?	presence uncertain				Zimbabwe	+	+	-	+
ND	no data				-	not present			
None of the four types of brucellosis is present in Austria, Denmark, Estonia, Finland, Hungary, Iceland, Luxembourg, Moldavia, Netherlands, Sweden, Switzerland, and the United Kingdom					+	low sporadic incidence			
Source for Tables 1-8: FAO-WHO-OIE Animal Health Yearbooks, 1994, 1995.					++	high incidence			
					?	presence uncertain			
					ND	no data			
					No data on any of the four types of brucellosis are available for Gambia, Mali, and Mauritania				

The major sources which are identified for this infection include the occupational contact to the infectious agent and increased consumption of food which is contaminated with infectious agents. On the other hand the major

reason for the transfer of the disease from one human to other is sexual transmission or tissue transplantation²³. Preventive measures for human brucellosis are directly dependent on the control measures of the disease in animals. In many industrialized countries, the eradication of the bovine disease is successful Table (6), however, the control programs are also used in most of the other countries.

B. melitensis infection is identified as most intractable but the success for this infection is limited Table (7). Few recent outbreaks of this disease which is caused by *B. suis biovar 4* is also reported to be persistent in the Arctic regions of Russia and North America and cause serious hazards to the health²⁴. *B. ovis* is not reported to cause overt disease among humans although it is frequently distributed in sheep. *B. canis* is rare agent which may cause serious clinical outcomes in humans, and this is more prevalent in the countries where dogs are more frequently kept as pet animals²⁵.

Table3.

Table4.

Table 3. Brucellosis in animals, Asia, 1994					Table 4. Brucellosis in animals, the Americas, 1994				
Country	Bovine (<i>B. abortus</i>)	Ovine/ caprine (<i>B. melitensis</i>)	Porcine (<i>B. suis</i>)	Ovine (<i>B. ovis</i>)	Country	Bovine (<i>B. abortus</i>)	Ovine/ caprine (<i>B. melitensis</i>)	Porcine (<i>B. suis</i>)	Ovine (<i>B. ovis</i>)
Afghanistan	+	+	ND	ND	Antigua/	?	-	-	-
Bangladesh	+	+	ND	ND	Barbuda	-	-	-	-
Bhutan	+	-	-	ND	Argentina	++	-	+	++
China	+	+	+	+	Belize	-	-	-	ND
Hong Kong	ND	ND	?	ND	Bolivia	++	+	+	ND
India	+	+	?+	-	Brazil	++	-	+	-
Indonesia	+	ND	+	+	Canada	-	-	-	+
Iran	+	+	-	-	Chile	++	-	-	+
Israel	-	+	-	-	Colombia	+	-	-	-
Iraq	+	+	ND	ND	Cuba	?	-	++	-
Jordan	-	++	-	-	Dominican	++	-	+	-
Korea (S)	++	-	?+	-	Republic	-	-	-	-
Kuwait	++	++	-	-	Ecuador	++	ND	ND	ND
Malaysia	+	-	?-	-	El Salvador	++	ND	+	ND
Mongolia	++	+	-	+	Guatemala	+	-	+	-
Myanmar	+	ND	+	ND	Haiti	+	-	-	-
Oman	++	ND	ND	ND	Honduras	?	-	++	-
Qatar	ND	ND	ND	ND	Jamaica	?+	-	-	-
Sri Lanka	++	+	-	+	Mexico	+	+	ND	-
Syria	+	ND	ND	ND	Nicaragua	++	ND	ND	ND
Thailand	+	-	+	-	Peru	++	ND	ND	++
Turkey	++	++	-	ND	Paraguay	+	ND	-	+
UAE	-	+	-	+	Uruguay	+	-	-	+
Yemen	+	+	-	-	United States	+	-	(+)	+
					Venezuela	++	-	++	?

-	not present	-	not present
+	low sporadic incidence	+	low sporadic incidence
++	high incidence	++	high incidence
?	presence uncertain	?	presence uncertain
ND	no data	ND	no data
None of the four types of brucellosis is present in Bahrain, Cyprus, Japan, Malaysia (Sabah), Philippines, or Singapore		None of the four types of brucellosis is present in Barbados, Falkland Islands, Surinam, or St. Kitts/Nevis	
No data for countries of the former Soviet Union or Qatar			

It is evident from the literature review that there is a lack of precise information regarding the prevalence of this disease, although the prevalence of *B. canis* has been recorded in Mexico, the United States, China, Japan, Argentina, Spain, and some other countries. The strains of the distinctive *Brucella* tentatively named *Brucella maris*, has been isolated from marine animals in the United States and the United Kingdom and this has extended the ecologic range of this genus and its scope to act as zoonosis^{26,27}. The incidents of the laboratory-acquired infection have suggested the pathogenicity associated with this agent. Moreover, the occupational contact of the person with infected cetaceans or seals can cause this infection.

Table5.

Country	Bovine (<i>B. abortus</i>)	Ovine/ caprine (<i>B. melitensis</i>)	Porcine (<i>B. suis</i>)	Ovine (<i>B. ovis</i>)
Australia	-	-	(+)	+
Cook Island	-	ND	-	ND
New Caledonia	-	-	-	-
New Zealand	-	-	-	++
Samoa	+	ND	ND	ND

++ high prevalence
 + present
 (+) limited presence
 - not present
 ND no data
 None of the four types of brucellosis is present in Vanuatu

Table6.

Region	Country	Year
EUROPE	Bulgaria	1958
	Croatia	1965
	Czech Republic	1964
	Denmark	1962
	Estonia	1961
	Finland	1960
	Hungary	1985
	Iceland	(never recorded)
	Latvia	1963
	Lithuania	1952
Luxembourg	1993	
Netherlands	1993	
Romania	1969	
Slovak Republic	1964	
Slovenia	1970	
Sweden	1957	
Switzerland	1963	
U.K.	1993	
AFRICA	Mauritius	1986
AMERICAS	Belize	1980
Canada	1989	
ASIA	Cyprus	1932
	Israel	1984
	Japan	1992
	N Korea	1959
Jordan	1992	
Papua New Guinea	1974	
Philippines	1989	
U.A.E.	1992	
OCEANIA	Australia	1989
	French Polynesia	1984
	New Zealand	1989
Vanuatu	1992	

Table7.

Region	Ovine/caprine (<i>B. melitensis</i>)	Porcine (<i>B. suis</i>)	Ovine (<i>B. ovis</i>)
Europe	Bulgaria	Denmark	Czech Rep.
	(1941)	(1951)	(1951)
	Croatia	Estonia	Germany
	(1991)	(1988)	(1986)
	Czech Rep.	Lithuania	Latvia
	(1951)	(1991)	(1989)
	Germany	Sweden	
	(1986)	(1957)	
	Switzerland		
	(1963)		
Africa	Ghana	None	Ghana
	(1993)		(1993)
Americas	Namibia		
	(1990)		
Americas	United States	Belize	Falkland Is.
	(1972)	(1985)	(1991)
	Chile	Honduras	
	(1987)	(1992)	
Asia	Colombia	Mexico	
	(1982)	(1991)	
Oceania	Cyprus	Singapore	Yemen
	(1993)	(1989)	(1989)
	Not present	None	None

Treatment

The literature review regarding the treatment of brucellae showed that in vitro use of oral antibiotics intravenous/intramuscular aminoglycosides can be used as the infectious agent is sensitive to these agents. In June 2005, standard procedures for in-vitro testing and the minimum inhibitory concentration breakpoints for Brucella were established (Table 8). These procedures and breakpoints mentioned in the meeting were published in September-October 2005 in the new CLSI (NCCLS) guidelines²⁸. Moreover, if the single drug was used for the treatment, the chances of relapse increased many folds. The treatment with regimen of orally administered doxycycline for 6 weeks at 200 mg per day, with the combination of 1 gram streptomycin administered intramuscularly per day for first 2 to 3 weeks is found to be an effective therapeutic approach in adults in most of the types of brucellosis²⁹.

However, it was clear from a randomized, double-blind study that the use of doxycycline plus rifampin or streptomycin is effective and use of 100 mg oral doxycycline for two times a day with oral rifampin (15 mg/kg body weight) once daily for 45 days has the equal therapeutic significance as were produced by the combination of classical doxycycline plus streptomycin and this also provided the evidence the patient had no symptoms of spondylitis³⁰. A 6-week oral regimen of 900 mg rifampin per day and 200 mg doxycycline per day should produce effective results in almost 100% of the patients and the relapse occur in less than 10% of the patients³¹.

Several other studies,³²⁻³⁴ had suggested that the combination of doxycycline and streptomycin was more successful and relapse is less frequent when using this combination therapy. Streptomycin is found to be an imperative part of the therapies associated with the treatment of the serious diseases, however there are some disadvantages associated with its use, i.e. limited availability and the requirement of the streptomycin for intramuscular injection. Netilmicin and Gentamicin are more readily available and can be administered intravenously and this is the reason that they have substituted the use streptomycin and their success is studied in few studies. The similar efficacy was found when the combination of the Fluoroquinolones with rifampin was used. Therefore, in the cases of doxycycline-rifampin interactions, this combination can be used as an alternative approach³⁵⁻³⁹.

Rifampin, doxycycline and streptomycin can be used for 6 weeks for the treatment of endocarditis however it is mandatory to replace the infected valves⁴⁰. However, in the cases where the patients do not represent valvular destruction or congestive heart or other problems, three antibiotics or their combination can be used for the therapeutic purpose 1) doxycycline or tetracycline (2) Rifampin, (3) trimethoprim/sulfamethoxazole or aminoglycoside, the use for 3 months would be highly effective⁴⁰. The patients who have spondylitis require treatment for 3 or more months. A combination of rifampin and trimethoprim/sulfamethoxazole is effective to get a response from central nervous system, but prolonged therapy can be required by the patient. The combination of the antibiotics latter described is also beneficial for the children who have age less than 8 years⁴¹.

“The Joint Food and Agriculture Organization–World Health Organization Expert Committee” have recommended the woman with this infection by using rifampin. The organisms in case of some biological problems may be resistant to these first-line antimicrobial agents. It is the prime duty of medical officers to obtain environmental and tissue samples for the bacteriological culture for the determination of the antibiotic susceptibility profile for brucellae so that the dose can be adjusted according to requirement.

TABLE 8
Brucellosis minimum inhibitory concentration breakpoint ranges

Antimicrobial	Minimum Inhibitory Concentration Range (mg/mL)
Azithromycin	0.25 – > 64
Chloramphenico	0.5 – 4
Ciprofloxacin	0.25 – 8
Streptomycin	1 – 16
Tetracycline	0.03 – 0.5
Doxycycline	< 0.015 – 1
Gentamicin	0.5 – 4
Rifampin	< 0.12 – 2
Levofloxacin	< 0.06 – 4
Trimethoprim	
Sulfamethoxazole	0.25 – 2

Data sources: (1) Patel J, Heine H. Personal communication from Clinical Laboratory Standards Institute (CLSI, formally known as National Committee for Clinical Laboratory Standards or NCCLS) June 2005 Guideline Meeting. (2) Patel J, et al. *J Clin Microbiol*. Publication pending .

Prophylaxis

The prevention of the brucellosis is made possible by using some approaches, for instance, the persons handling the animals should wear protective clothing and appropriate protective equipments while working with infected animals. The milk should be pasteurized and the cooking of the meat should be carried out properly. Appropriate biosafety levels 2 or 3 containment should be used by the laboratory analysts. The biosafety levels should be maintained at a level as maintained at the “US Army Medical Research Institute of Infectious Diseases, Fort Detrick, Md”. In case of the possible chances of exposure, chemoprophylaxis is not recommended in the case of endemic disease.

In the case of the any biological attack, the “M40 mask (ILC Dover, Frederica, Del)” should be used by the personnel to avoid the exposure to airborne brucellae because these organisms are not capable to penetrate the intact skin. The standard disinfectants can be used to decontaminate the clothes or equipments after moving away from the area of exposure in order to minimize the chances of the infection which are associated with conjunctival inoculation or accidental ingestion of viable organisms. In the case of accidental attack or biological attack, 3- to 6-week course of therapy with one of the medication described above should be used⁴².

Prevention

There are various preventive approaches for preventing the prevalence of Brucellosis in animals and humans and this is dependent on the control of the disease and infection in the host animals. The best preventive approach is the use of hygienic precautions as this approach is effective for limiting the exposure of the individual to the infection during their occupational activities. Moreover, the proper heating of the contaminated food and dairy products is effective preventive approach. In the past years, the use of vaccines in such infections was considered effective but now it is evident that vaccination has a limited role in the prevention of the prevalence of this infection. During the past years, live attenuated “*B. abortus* strains 19-BA and 104M” were used by the clinicians.

The phenolin soluble peptidoglycan vaccine and the polysaccharide protein vaccine were also used in the past years. All of these vaccines possess limited efficacy⁴³ and potentially serious reactogenicity were associated with the live vaccines. However, subunit vaccines are still used against brucellosis. The use of the live vaccines has been eliminated due to unacceptable reactions and actions in individuals who had previous exposure to *Brucella*. A combination of detoxified lipopolysaccharide- protein antigens and protein conjugate can be used as an effective approach, for instance, “*pur E* mutants” of “*B. melitensis*” is found to be effective and safe⁴⁴ some new vaccines were also evaluated by the researchers for example, *B. suis* strain 2 live vaccine given either parenterally or orally⁴⁵.⁴⁶ This vaccine has less affectivity as compared to the Rev.1. strain so as to prevent *B. melitensis* infection in goats and sheep and this was found to be ineffective against the infection caused by *B. ovis*. Strain 19 of *B. abortus* is found to be highly effective for the prevention of this serious infection. However, the use of the “RB51 strain” of *B. abortus* which is a live vaccine can be used for cattle⁴⁷.

The *rfb* mutants of *B. suis* and *B. melitensis* are also be used for the treatment but there is limited data regarding its safety for the prevention of infection. The other preventive approach that can be effective for the prevention of this infection is the educational program for the community and the increased level of awareness through community based learning is effective for the prevention of increasing trend of brucellosis. The similar results were found by the Karimy et al. who described the education as an empowerment for the population to avoid the increase of Brucellosis⁴⁸⁻⁵⁰.

Conclusion

The results of the recent study concluded that there is a variance in the epidemiology of the disease from region to region. In some areas this infectious disease is more prevalent while in some areas, there is low reporting or evidence data for prevalence. There are different drugs and their combination which are used for the treatment, for instance, it was found that 6-week oral therapy of combination of doxycycline and rifampin was effective and relapse was found in less than 10% of patients. Moreover, the use of the fluoroquinolone plus doxycycline was found to be effective. The literature review also illustrated that six weeks administration of doxycycline along with streptomycin for 3 weeks is of therapeutic importance. The literature review also demonstrated that Netilmicin or gentamicin can be used as a substitution of streptomycin. In addition, there is no available vaccine for the treatment of this infection among human. However, the control and prevention of the disease is possible by using preventive approaches. There is an increased changing trend in the treatment and control of infection and there is a crucial need for the advancement in these trends. Moreover, further advanced research based studies should be carried out in different regions of the world to understand the changing trends.

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