

EPIDEMIOLOGICAL AND PUBLIC HEALTH ASPECTS OF BRUCELLOSIS IN THE REPUBLIC OF MACEDONIA

Donev D.,¹ Karadzovski Z.,² Kasapinov B.,² Lazarevik V.¹

¹*Institute of Social Medicine, Faculty of Medicine, Skopje, R. Macedonia*

²*Institute of Public Health, Skopje, R. Macedonia*

Abstract: *Aim:* To analyze and present epidemiological patterns of human brucellosis cases and the main factors for the appearance and spread of *B. melitensis* infection among animals and humans in R. Macedonia in the period from 1980 to 2009.

Methods: Retrospective study based on the epidemiological reports and official data on brucellosis cases from the Institute for Public Health in Skopje and other institutions from the health and veterinary sectors in R. Macedonia, and a review of the relevant literature.

Results: From 1980 until December 2009, a total of 11,451 brucellosis cases were reported in R. Macedonia, with a mean annual incidence rate of 18.9/100,000. The highest morbidity rate during this period was recorded in 1992 (922 cases and an incidence rate of 47.6/100,000), and the lowest one in 1983 (12 cases and an incidence rate of 0.6/100,000).

From the total number of cases reported in R. Macedonia from 1980 to 2009, 66.2% were males and 33.8% were females. Only 7.2% of patients were under the age of 10, and the most of the patients were from the age group 20–39 (31.9%). Seasonal characteristics of the disease were expressed with the highest occurrence in May (15.9%), June (16.3%) and July (15.1%). Within the total number of 3,284 brucellosis cases in the period 2001–2009, 2320 (70.6%) were from rural settlements and 964 (29.4%) from urban areas. 385 of all cases of brucellosis (8.4%) reported in the period 1998–2009 were from the ranks of professional staff.

Conclusion: Brucellosis was, currently is and will be a significant disease problem and concern in R. Macedonia which should be approached in a more comprehensive and organized way in the coming years. There is a need to establish intersectoral collaboration by joint efforts of all relevant factors in the prevention and

eradication of brucellosis, as well as collaboration between all countries in the SEE region.

Key words: Brucellosis, zoonoses, epidemiology, prevention/control programme, Republic of Macedonia.

Introduction

Brucellosis is the most widespread zoonosis in the world and the infection is almost invariably transmitted to people by direct or indirect contact with infected animals or their products. The annual occurrence of human brucellosis in the world is more than 500,000 cases [1, 2]. The most commonly affected animals are cows (*B. abortus*), sheep and goats (*B. melitensis*), pigs (*B. suis*), and some other domestic animals. Some wild animals might also be affected by this zoonosis, but these are rarely implicated as sources of human disease. Brucellosis has been virtually eliminated from the majority of the developed countries, but it is still endemic in Africa, the Middle East, Central and Southeast Asia, Central and South America and in most of the Southern European countries. In Europe, brucellosis affects mainly the Mediterranean countries, where it is one of the most frequent zoonoses with high incidence rates in spite of the measures undertaken to prevent and control the disease [2–6]. The reported annual incidence rate of human brucellosis in the endemic-disease areas in the world varies widely, from < 0.01 to > 200 cases per 100,000 population [5]. The annual incidence rate per 100,000 population in 2005 in Syria was 160.3, Mongolia 60.6, Turkey 26.2, Saudi Arabia 21.4 [1, 2].

Estimates of the prevalence of animal and human brucellosis are not available for many countries of the world. The low incidence rate reported in known brucellosis-endemic countries of Africa and Asia may reflect the absence or the low levels of surveillance and reporting systems [2, 3, 5–7].

Brucellosis in humans is known as "undulant fever" or "Mediterranean fever", "Malta fever" or "Bangs disease" [3, 8]. It is a systemic infection and may present in many atypical forms, from mild to severe acute infections in about half of the cases. Symptoms include recurring fever, headache, arthralgia and muscle aches, anorexia and weight loss, constipation, secondary anaemia, nervous system signs, night sweating and orchitis [3–5, 8–12]. The disease in humans may last for three months and mortality is low. In animals, the primary sign of infection in females is abortion and in males epididymitis and orchitis and diagnosis can only be confirmed by laboratory tests that may even confirm latent infections [3, 8, 13].

Bacteria from *Brucella* species can survive for a long time, up to a few months, in both hot and cold environments, particularly in moist conditions.

Pastures and animal accommodation on farms may remain contaminated for prolonged period, with survival of the pathogen for months, up to a year or probably longer. However, the organisms are very sensitive to direct sunlight, and can be destroyed by pasteurization or cooking [10, 11, 13].

The principal routes of infection for humans is foodborne transmission via ingestion of contaminated unpasteurized milk or dairy products (fresh cheese) and occupational or environmental direct exposure (infected calves, placentas, amniotic fluids and other secretions and excrements of infected animals, either by contact with skin cuts and abrasions, conjunctival contamination or via inhalation of infectious aerosols [3, 4, 8–10, 14]. It takes from 5 to 90 days (usually 14 days) from infection to the first sudden severe symptoms of the disease [13, 15].

Huge economic losses from *B. melitensis* infection in livestock and humans arise due to long-term hospital treatment, cost of drugs and loss of work or income due to illness of infected people. This mostly requires regulatory and enforcing policies involving costly implementation of the brucellosis control and eradication programmes: serology tests for animal check-ups, vaccine cost and compensation paid to the farmers for slaughter of infected animals are some of the factors emphasizing the importance of this zoonosis as an economic and public health concern of each affected country [4, 16, 17]. Unless treated promptly, the infection persists and progresses to a chronic incapacitating disease with severe complications.

Public health aspects of brucellosis in R. Macedonia

Brucellosis is a significant public health challenge and socio-economic problem in many countries in the world, especially in the Mediterranean region and in R. Macedonia as well. The incidence of brucellosis caused by *Brucella melitensis* is very high, and affects primarily sheep and goats. Brucellosis remains a major cause of morbidity throughout the world, particularly for the poorest segment of the human populations and in medically underserved regions. This zoonosis plays a significant role in the national economy and the public health of many developing countries, especially in the countries of the Mediterranean region [6, 18].

Human brucellosis is found to have a significant presence and a correlation between the level of *B. melitensis* infection in small ruminants and the number of infections in humans. This is the case in rural/nomadic communities in R. Macedonia where people live in close occupational contact with animals and consume raw milk and fresh cheese, and poorly cleaned or partly cooked offals (liver) from such animals. Aerosol and hand-to-mouth transmission may

occur in abattoirs or laboratories. Control of the disease in animals is a prerequisite to reducing its burden on public health [1, 4, 6, 16]. Some negative political and socio-economic forces that have fuelled regional conflicts and wars or reduced vigilance in control programmes, together with international travel of people and trade in agricultural products, have resulted in a resurgence and worsening of the situation with brucellosis in some developing countries, including new countries established in early 1990s after the breaking apart of the former Yugoslavia [1, 2].

The Republic of Macedonia represents an endemic area where brucellosis prevails as a dominant zoonosis with high morbidity and huge economic losses. *B. melitensis* infection has been a severe public health and socio-economic problem in R. Macedonia for more than 30 years. Infection prevails among sheep and goats with huge economic losses due to abortion, premature birth of weak offspring and decreased provision of meat and milk production, as well as lost trade opportunities [1, 16]. Brucellosis in humans is also a big health and social problem in R. Macedonia because of high morbidity, long-lasting hospital and expensive antibiotic treatment, chronicity and incapacity for work, relapses and complications. In addition, the costs of serologic testing of livestock and compensation to farmers for slaughtered seropositive animals are very high, on average about 1.5 million Euros per year within the period 1999–2009 according to the official data from the Veterinary Directorate in Skopje, R. Macedonia [19, 20].

Aim. The aim of the study is to analyze available data and present the frequency and distribution of brucellosis in humans in R. Macedonia in the period 1980–2009 by gender, age, place of residence, profession, and seasonal distribution of the brucellosis cases. In addition, the study intends to review the most important factors of the appearance and spread, and the approaches for control and eradication of *B. melitensis* infection in animals and humans in R. Macedonia.

Methods

Various data and reports on the illness of brucellosis in humans from the Institute of Public Health, Skopje, and other institutions were used in the study, including official reports on contagious diseases, terrain investigation and epidemiological surveys, monthly and annual reports from the regional centres of public health, departments of infectious diseases within general hospitals, other health institutions and some data from the Veterinary Directorate of R. Macedonia.

A patient suspected to be suffering from brucellosis, according to the WHO case definition and evidence in support of the diagnosis, besides a history of recent exposure to a known or probable source of *Brucella* spp. and the most common clinical symptoms, was put under investigation for confirmation of diagnosis by bacteriological and serological tests, and demonstrated a positive reaction (standard agglutination – Wright test and Rose Bengal plate test used as orientation method, and other tests as confirmatory methods, i.e. complement fixation test – CFT, enzyme-linked immunosorbent assay – ELISA, Coombs' test or fluorescent antibody test) [3, 5, 7, 11–14, 21, 22]. Bacteria isolation and typing of *Brucella* spp. from blood and other tissues in acute human brucellosis cases is the most accurate method for a definitive diagnosis. However, this type of confirmation carries a biohazard risk posed by culture and had not been performed routinely for all hospitalized cases in R. Macedonia since no adequate laboratories existed (Biosafety Level III) [6]. The collected data came from persons in whom brucellosis was confirmed by an immunologic/serologic test. The study is focused on the epidemiological situation of human brucellosis cases without an analysis of the animal brucellosis and epizootiological situation in R. Macedonia.

Data were organized and analyzed by demographic and epidemiological variables and appropriate statistical calculations and evaluations were made supported by review of the relevant literature. The incidence rate was calculated in a ratio of 1 : 100,000 inhabitants.

Results

In the period 1980–2009, the total number of reported human brucellosis cases in R. Macedonia was 11,451 (Mean = 381.7; Standard Deviation = 245.1). Up to 1980, brucellosis in R. Macedonia was a very rare disease with just 45 registered cases in the period from 1945 to 1979 [6]. The first outbreak of brucellosis was registered in 1980, with a total number of 112 cases, 104 of them in the municipality of Bitola [23]. According to the data from National Institute of Public Health, Skopje, the number of settlements in which brucellosis cases were registered was 150 in 1993 and 120 in 2009, with the lowest number of 111 in 2000 and the highest number of 158 settlements in 2008. The number of cases occurring annually and by months in R. Macedonia is shown in the Table 1.

Table 1 – Табела 1

Reported brucellosis cases, by months and years, in R. Macedonia, 1980–2009

*Пријавени случаи на бруцелоза, по месеци и години, во Р. Македонија,
1980–2009*

Year	Appearance of the reported brucellosis cases by months												Total
	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	
1980	4	8	10	21	24	8	6	6		4		11	102
1981	8	2	21	19	25	17	12	8	6	1	1	2	122
1982				2	7	6	4	5	3	1	7	1	36
1983	1	1	2		5	1	1	1					12
1984					2	3	7	12	2	3			29
1985	2		2	15	8	8	3	12	4	5	1	5	65
1986	1		1	5	5	11	14	10	14	5	3	5	74
1987			3	11	55	69	48	14	23	7	6	6	242
1988	4	4	8	24	26	48	28	7	8	8	5	2	172
1989	3	8	16	34	53	65	37	58	39	18	9	6	346
1990	12	16	37	68	110	116	122	66	46	32	9	12	646
1991	16	26	55	80	124	100	73	84	79	40	26	25	728
1992	27	34	65	133	161	136	119	90	66	38	34	19	922
1993	14	29	47	82	56	97	95	61	35	21	19	9	565
1994	11	12	46	90	97	104	104	42	42	25	22	8	603
1995	12	15	45	90	119	109	145	87	66	28	17	19	752
1996	14	10	69	99	100	77	58	50	32	25	16	15	565
1997	12	13	35	94	143	127	131	84	34	38	39	23	773
1998	17	22	39	47	73	91	93	61	40	17	20	11	531
1999	9	17	31	72	65	65	58	54	38	21	19	11	460
2000	7	18	23	44	62	89	50	54	44	16	13	2	422
2001	6	11	35	48	54	58	105	35	15	23	14	10	414
2002	7	14	18	29	54	95	81	38	32	19	11	7	405
2003	13	24	24	37	68	52	48	36	40	20	12	4	378
2004	8	7	26	32	45	48	33	30	25	16	12	15	297
2005	11	17	34	41	55	46	42	19	22	11	18	7	323
2006	6	11	32	44	61	41	31	26	24	14	12	7	309
2007	11	11	37	37	66	60	54	32	18	24	22	9	381
2008	15	25	33	62	63	78	82	49	35	22	13	13	490
2009	12	21	28	32	37	40	40	16	29	12	9	11	287
Total	263	376	822	1,392	1,823	1,865	1,724	1,147	861	514	389	275	11,451

Source: Institute of Public Health – Skopje, R. Macedonia

In 1980 112 cases of human brucellosis were registered in R. Macedonia. Since 1987, and especially since 1990, the number of cases has started to increase remarkably. The highest number of human brucellosis cases in R. Macedonia (922 cases) and the highest rate of incidence (45.3/100,000) were

reported in 1992 (Figure 1). Two small municipalities were the most affected: the municipality of Radovis with 271 reported cases in 1991 and a morbidity rate of 890/100,000, and the municipality of Valandovo with 87 cases and a morbidity rate of 780/100,000.

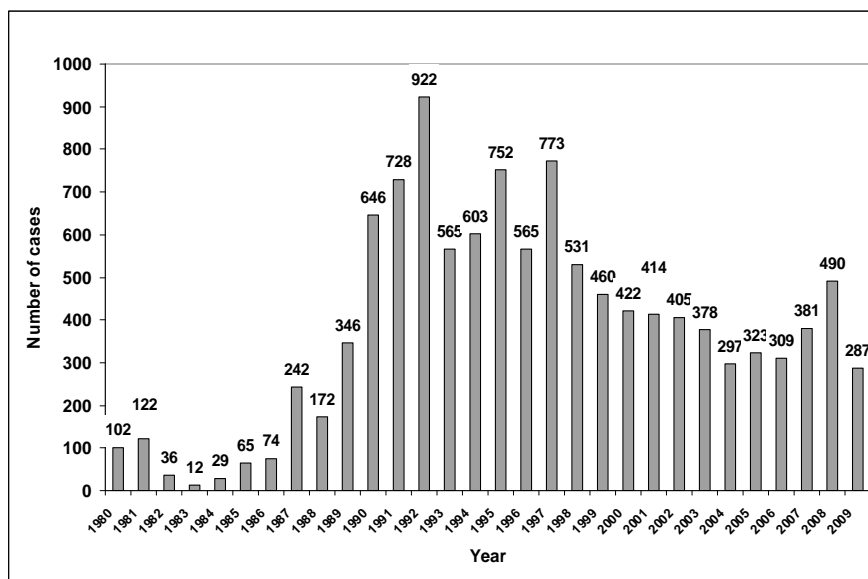


Figure 1 – Reported brucellosis cases in R. Macedonia, 1980–2009

Слика 1 – Пријавени случаи на бруцелоза во Р. Македонија, 1980–2009

During the entire observed period of 30 years, the mean annual incidence rate in R. Macedonia was 18.9 per 100,000 inhabitants. The highest mean annual rates of incidence were recorded in the municipality of Radovis (262.7/100,000) and Valandovo (133.2/100,000) (Table 2).

Most of the brucellosis cases were recorded in the following municipalities: Radovis, Skopje, Prilep, Strumica, Tetovo, etc. (Figure 2).

Besides the epidemic form of brucellosis occurrence, individual (sporadic) cases were recorded in many other municipalities in R. Macedonia, which means that almost the whole territory of the country was an endemic and contaminated area. Only in two municipalities (Delcevo and D. Hisar) were brucellosis cases not recorded.

Table 2 – Табела 2

*Brucellosis incidence rates in the most affected municipalities
in R. Macedonia, 1980–2009*

*Стајанки на инциденца на бруцелозата во најмногу погодениите општини
во Р. Македонија, 1980–2009*

Municipality	Number of cases 1980–2009	Population (Census 2002)	Incidence rate per 100.000 population	
			Cumulative rate (1980–2009)	Mean annual rate
Bitola	488	95,385	511.6	17.,1
Kicevo	171	30,138	567.4	18.9
Veles	690	55,108	1,252.1	41.7
Gevgelija	285	22,988	1,239.8	41.3
Kavadarci	448	38,741	1,156.4	38.5
Kumanovo	493	105,484	467.4	15.6
Ohrid	253	55,749	453.8	15.1
Prilep	986	76,768	1,284.4	42.8
Strumica	858	54,676	1,569.2	52.3
Valandovo	475	11,890	3,995.0	133.2
Tetovo	831	86,580	959.8	32.0
Stip	529	47,796	1,106.8	36.9
Skopje	1,532	506,928	302.2	10.1
Struga	229	63,376	361.3	12.0
Radovis	2,226	28,244	7,881.3	262.7
R. Macedonia	11,451	2,022,547	566,2	18.9

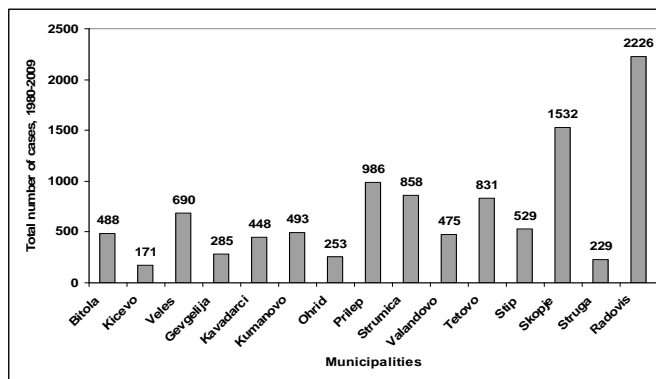


Figure 2 – Municipalities in R. Macedonia with the highest number of brucellosis cases, 1980–2009

Слика 2 – Општини во Р. Македонија со најголем број заболени од бруцелоза, 1980–2009

Human brucellosis cases in R. Macedonia were recognized in both sexes and all age categories. The number of the male patients was 7,579 (66.2% of all

cases) and females 3,872 (33.8%), whereas the male-to-female ratio was calculated as 1.96 : 1, indicating that men acquired *Brucella* spp. infection about twice as often as women (Table 3).

Table 3 – Табела 3

Reported brucellosis cases by age and gender in R. Macedonia, 1980–2009
Пријавени случаи на бруцелоза според возраст и пол во Р. Македонија, 1980–2009

Age groups	Brucellosis cases				Incidence rate/100,000
	Male	Female	All	%	
0–6	267	201	468	4.1	259.9
7–9	230	126	356	3.1	414.5
10–14	509	279	788	6.9	491.5
15–19	747	296	1043	9.2	630.5
20–29	1,325	563	1888	16.5	598.6
30–39	1,204	562	1766	15.4	592.4
40–49	1,105	548	1653	14.4	570.8
50–59	1,033	602	1635	14.3	733.2
60 +	1,159	695	1854	16.1	608.4
Total	7,579	3,872	11,451	100.0	566.2

Source: Institute of Public Health, Skopje, R. Macedonia

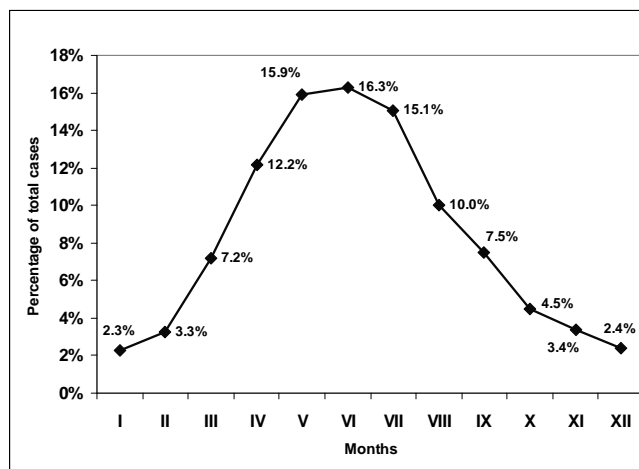


Figure 3 – Seasonal distribution of brucellosis cases ($n = 11,451$) in R. Macedonia, 1980–2009
 Слика 3 – Сезонска дистрибуција на заболеније од бруцелоза во Р. Македонија, 1980–2009

The mean age of the patients was 37.8 years. Only 7.2% of patients were under the age of 10, and most of the patients were at the age of 20–29 (16.5%), and of 30–39 (15.4%), as well as over 60 years of age (16.1%) (Table 3).

Brucellosis is maintaining its characteristics of a seasonal disease by a significant seasonal distribution of brucellosis cases in R. Macedonia. The monthly distribution of cases in the 30-year period is presented in Table 1. The largest number of patients was registered in the period from April to August (69.4%), with a peak reached in June (16.3%) (Figure 3).

In general, brucellosis in R. Macedonia is maintaining its characteristics of an occupational disease, which might be concluded indirectly from the structure of the reported human brucellosis cases by place of residence in the period 2001–2009 (Figure 4).

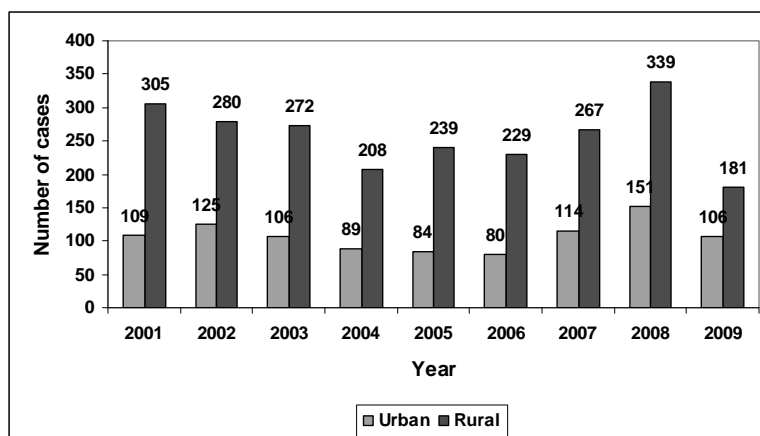


Figure 4 – Reported brucellosis cases in R. Macedonia by place of residence, 2001–2009

Слика 4 – Пријавени случаи на бруцелоза според место на живеење во Р. Македонија, 2001–2009

During the entire period observed, the prevailing numbers of patients are from the rural areas where the main route of transmission of the infection to humans is expected to be through contact with infected animals and animal products, as well as via ingestion of contaminated unpasteurized milk and dairy products [6]. Of the total number of 3,284 brucellosis cases in the period 2001–2009, 2,320 (70.6%) were from rural settlements and 964 (29.4%) from urban areas.

Distribution of the brucellosis cases, reported in R. Macedonia from 1998–2009, by profession is presented in Table 4.

Table 4 – Табела 4

Reported brucellosis cases by profession in R. Macedonia, 1998–2009
Пријавени случаи на бруцелоза според професија
во Р. Македонија, 1998–2009

Profession	Number of brucellosis cases			% of total
	Male	Female	Total	
Unemployed and self-employed	1481	264	1745	37.9
Householder/ housewife of farmer family	3	706	709	15.4
Pupil, 7-18, (farmer family)	427	185	612	13.3
Retired	414	124	538	11.7
Worker	318	45	363	7.9
Child, 0-6 (farmer family)	124	92	216	4.7
Sheep/Goat Farmer	148	29	177	3.8
Shepherd	75	1	76	1.7
Stockbreeder	36	0	36	0.8
Veterinarian	35	0	35	0.8
Slaughterhouse worker/ Butcher	24	0	24	0.5
Veterinary laboratory technician	18	2	20	0.4
Nurse	1	7	8	0.2
Student (farmer family)	6	1	7	0.2
Physician	2	4	6	0.1
Paramedic	1	2	3	0.1
Other	22	5	27	0.6
Total	3,135	1,467	4,602	100.0

Source: Institute of Public Health, Skopje, R. Macedonia

In the period 1998–2009 a total number of 4,602 brucellosis cases were reported in R. Macedonia. The number of brucellosis cases in the category of unemployed and self-employed was very high, 1,745 in total (37.9%), and together with the category householder/housewife, 709 (15.4%), retired, 538 (11.7%), and workers, 363 (7.9%), comprises almost three fourths (72.9%) of the brucellosis cases in the observed period in R. Macedonia. It is not possible to make a clear distinction of those cases by place of residence because some of them, from the smaller urban proportion, officially declare a town as their place of residence but during the spring and summer period live in rural and mountain areas and work with the agricultural and livestock breeding activities. Children from 0–6 and pupils from 7–19 years of age all together comprise almost one fifth of the cases (18%), most of them from rural areas and farmers' families

with the predominant route of transmission of infection being consumption of raw milk. According to professional categories, exposure to infected animals or animal products or infective materials in hospitals and laboratories most directly accounts for the transmission of the disease. Such is the case with sheep/goat farmers, shepherds, stockbreeders, veterinarians and veterinary laboratory technicians, as well as nurses, doctors and paramedics, who account for 385, or 8.4% of the total number of brucellosis cases reported in R. Macedonia from 1998 to 2009.

Discussion

In the period 1980–2009, the total number of reported human brucellosis cases in R. Macedonia was 11,451, with a mean annual incidence rate of 18.9 per 100,000. The real number of human brucellosis cases in R. Macedonia is probably much higher, due to the high proportion of undiagnosed, misreported and unreported cases.

Compared to other countries, the total number of reported human brucellosis cases in R. Macedonia is much higher than in many countries in SEE and the Mediterranean region. The main reason for the increase of brucellosis cases in R. Macedonia in the early 1990s was probably the military conflict and the breaking apart of the former Yugoslavia, which led to population and animal migration and uncontrolled trade in food. Due to the war between some of the former republics in Yugoslavia, and political instability and economic crisis in R. Macedonia, veterinary control of imported livestock was not adequately performed. Inadequate implementation of measures against epizootic disease in affected municipalities contributed to the faster spread of this zoonosis to the remaining parts of R. Macedonia [6].

The number of human brucellosis cases in R. Macedonia in 2004 (297) was higher compared to some other countries in the Balkans and Europe: Serbia reported only 39 cases, Bosnia and Herzegovina 83, France 25, Germany 32 and Greece 223. But certain countries in the Mediterranean region reported a higher number: Spain 596, Italy 631, Turkey 18,264 and Syria 29,580 [24]. Bulgaria, from 2005 to 2007, reported 105 cases [25], and approximately 100–200 cases occur in the U.S. each year [5, 9].

In Greece, in the period from 1993 to 2000 there had been an increase in the reported cases from 112 to 548 (1.1 to 5.0 per 100,000), whereas after the year 2000, a remarkable decrease in the number of reported cases was observed because of vaccination against animal brucellosis and health education efforts in the late 1990s [21, 26]. Between 2000 and 2007, the mean annual incidence rate in Greece was 2.9/100,000. The annual incidence rate shows a decreasing tendency, from 5 in 2000 to 2.1 in 2004 and 1.9/100,000 in 2007 [15]. In certain rural areas of Greece recent studies reported an annual human brucellosis inci-

dence of 17.3–1,110 per 100,000 population [27–29]. This is much above the numbers for whole country which indicates that the control of the disease in some rural areas in Greece is weak. This implies that brucellosis in Greece still represents a great concern, too.

Most of the brucellosis patients in R. Macedonia are in the age categories from 20 to 49 and above 60, and almost twice as more often in males as in females (male-to-female ratio of 1.96 : 1). The higher frequency of *Brucella* spp. infection in men can probably be attributed to their occupations, since in rural areas, men deal more often than women with animal husbandry, which increases exposure to *Brucella* organisms and less diligent personal hygiene [1]. Epidemiological studies of human brucellosis conducted in some other countries have shown similar results. Thus, the grouping of patients into the working population category is typical of areas where brucellosis is associated with occupational exposure. In Central Greece, the largest number of cases included men between 30–50 years [21], while in Germany a clustering of patients based on their age was not observed [30]. In countries or areas where *B. melitensis* is prevalent, the practices followed in marketing and distributing sheep and goat milk products in particular make the enforcement of hygienic measures very difficult. In those countries and areas the whole population is at risk and many cases occur in women and children [3]. In Northern Saudi Arabia the male-to-female ratio reported recently was 1.7 : 1, chiefly in individuals 13–40 years of age [1]. In Germany, from 1995 to 2005, a total number of 290 brucellosis cases was reported and both sexes were almost equally represented among the patients (54% male vs. 46% female) [30], but in Central Greece the human brucellosis male-to-female ratio was 2.99 : 1, indicating that men acquired *Brucella* spp. infection about three times more often than women [21].

Brucellosis, in general, is much more common during summer than the winter months, as is the case in R. Macedonia. The incidence of human brucellosis in R. Macedonia increased from March to June when it reached the highest peak. Then it started and continued to decrease from June to September and October, reaching the lowest level in the winter period, from November to February. In Germany, the largest number of cases was recorded in August and September [30]. In Central Greece, two peaks were recorded: one in March and another in May [21]. In countries with temperate or cold climates there is a marked seasonal variation in the incidence of acute brucellosis, with most cases occurring in spring and summer. This coincides with the peak period for abortions and parturition among farm animals, and hence the highest level of occupational exposure of those attending the animals and consuming their raw milk [3]. In R. Macedonia, the seasonal distribution of brucellosis cases coincides with abortions and parturition among sheep and goats, most often from April to June, when the farmers and their family members are in direct contact with aborting ewes as the most significant factor for contracting brucellosis because

of occupational exposure and ingestion of contaminated food products. Certain occupations are associated with a high risk of infection with brucellosis. These include farmers, farm labourers, shepherds and their family members who help them with the animals, workers in slaughterhouses and meat processing plants in endemic areas, veterinarians and other health professionals at risk through direct contact with infected animals or through exposure to a heavily contaminated environment. Laboratory workers involved in culturing *Brucella* spp. are at particular risk [3, 31]. Foodborne transmission is usually the main source of brucellosis for urban populations. In any case, ingestion of raw milk or dairy products prepared from unheated milk is the main source of infection for most populations, transferring brucellosis from an occupational disease to a foodborne disease [3, 5, 6, 8]. Epidemiological survey data showed that 34.3% of patients in R. Macedonia in the period 1980-2001 were infected by direct contact with infected animals, 23.4% through the alimentary tract, while 42.3% may have contracted in both ways [6]. Most of the urban population in R. Macedonia is not at potential risk of acquiring brucellosis because all dairy products available in the commercial market network are produced from pasteurized milk.

According to place of residence, only 20.5% of patients were from urban areas and 79.5% from rural settlements where the population is generally in close contact with animals potentially infected by brucellosis, or handles raw animal products such as milk, meat (offals), etc. or consumes raw milk or homemade dairy products from unheated milk, a common nutritional habit in some rural communities in R. Macedonia [6, 32]. In most of the rural areas in R. Macedonia there is a traditional belief among the population that consuming raw sheep's and goat's milk is very healthy and increases immunity, especially in children. Because of this a brucellosis prevention health educational programme is necessary for high risk groups and the entire population, especially in the affected rural communities in R. Macedonia.

*Veterinary and health policy in dealing with the problem
of brucellosis in R. Macedonia*

Uncontrolled trade and migration of animals is the main way of spreading brucellosis. The introduction of an infected animal into an uninfected herd results in a rapid spread of infection among the animals, by direct contact, possible sexual transmission, and environmental contamination following abortion [3]. Control of animal movement and trade is the main means of prevention and control of brucellosis spreading. Animals should be individually identified by brand, tattoo or ear-tag, and unauthorized sale or movement of animals from an infected area to other areas should be forbidden [1, 33, 34].

Up until 1988, due to the official policy of the health authorities in R. Macedonia, brucellosis disease data were not disclosed, which hampered the efficiency and success of the control and eradication programme. The current action programme for the eradication of brucellosis contains veterinary and medical measures including: a) systematic examination of all domestic animals; b) control of animal movement and trade; c) health care and health promotion activities [6]. The Macedonian Government implemented a "test and slaughter" strategy for more than two decades as the main approach to control and eradication of the disease in animals. Since 1992 the number of brucellosis cases shows an almost constant slow decline, from 565 in 1992 to 490 in 2008 (Figure 1). The control and eradication strategy was strengthened in 2008 by mass vaccination with Rev 1 live strain vaccine of all sexually mature animals in herds of sheep and goats with a high group prevalence. It was followed by vaccination of young replacements in affected herds, test and slaughter programmes of adult animals identified as infected where the level of disease had been reduced and stabilized at a very low level, with adequate economic compensation to farmers for slaughtered animals [19, 20]. Although the period of two years is very short for a reliable evaluation of the animal vaccination impact on human brucellosis, there is an obvious decrease in the number of brucellosis cases, from 490 in 2008 to 287 in 2009 (Figure 1).

In the area of veterinary policy, progress has been made in R. Macedonia by adopting legislation on control systems in the internal food market and for imports, identification and registration of the movements of sheep and goats, and implementation of control measures [35–40]. In 2009, the allocation for veterinary expenditure on measures for animal health and veterinary public health was 4.43 million Euros. The capacity of the laboratories of the Faculty of Veterinary Medicine, Veterinary Services at both central and local levels and of veterinary inspectors has been improved, but is still not satisfactory [19, 20, 35].

*Main directions and activities in brucellosis prevention,
control and eradication*

The fight against zoonoses begins by eliminating the pathogen at its animal source. This fact provides the Veterinary Services, veterinarians, farmers, managers of wildlife and the OIE with a leading role at both the national and international level. The quality of the Veterinary Services and appropriate diagnostic laboratories on the basis of adopted OIE standards, appropriate veterinary legislation and animal health policies are an essential prerequisite for efficient control and eradication of brucellosis, as well as having an impact on poverty reduction and food safety [41–44].

The surveillance and reporting systems should include domestic animals and wildlife disease control methods, including the use of vaccination under

certain circumstances, with a relevant corresponding human continuum [11, 22, 26, 42, 45, 46].

Ensuring safe food is paramount for the protection of human health and for enhancement of the quality of life. Risk based programmes should aim at preventing or decreasing the transmission of zoonoses, including brucellosis, through adequate policy frameworks, prevention and control measures, and education, to prevent and control the spread of all zoonoses and foodborne diseases [35, 38, 47].

Pasteurization of milk and sanitary or herd surveillance, with animal vaccination and culling techniques for infected animals and herds of sheep, goats, cattle and other animals for brucellosis have considerably reduced the incidence of outbreaks in many developed countries (New Zealand, Sweden, the U.K. and France have earned the designation brucellosis free). Agricultural efforts and investments in brucellosis control and eradication programmes are worth many millions of dollars [1, 25].

Vaccination by Rev 1 live strain vaccine of all sexually mature animals in herds of sheep and goats with a high group prevalence or vaccination of young replacements, test and slaughter programmes of adult animals identified as infected when the level of disease has been reduced and stabilized at a very low level, with adequate economic compensation to farmers, as well as control of animal movement, are essential parts of the brucellosis control and eradication strategies.

Cooperation between Veterinary Services and the Public Health Services is necessary in control of zoonotic diseases, including brucellosis, by suitable budgetary allocations for disease prevention and support for the activities of established national joint multidisciplinary committees, aimed at permanent intersectoral consultation and cooperation [39, 48].

Regional collaboration among SEE and Mediterranean countries is necessary for efficient control and eradication of brucellosis in this region [49].

FAO, OIE and WHO, through coordinated actions, intend to develop a standard "peer review" evaluation process of national and regional brucellosis control and eradication programmes. Country specific programmes might be submitted to FAO for review and be a subject of modifications at the country level [16].

Limitations of the study

Most of the data about the brucellosis cases within the observed period from 1980 to 2009 are not available for individual cases but only as aggregated data by year, month, gender and age groups, especially during the socialist period in former Yugoslavia up to 1990 when the presence of brucellosis in R.

Macedonia was kept secret for a long time and that was one of the reasons for lack of data and inefficient prevention and control of brucellosis. Aggregate data on brucellosis cases is an objective limitation for additional statistical analysis.

Conclusion

Based on the dimensions and consequences of the disease problem, it is obvious that brucellosis was, currently is, and will be a significant concern and public health priority in R. Macedonia. The disease should be approached in a more comprehensive and organized way in the coming years. Besides general and occupational hygiene measures from veterinarians and cattlemen, education of all personnel involved is essential, as well as the adoption of appropriate control and eradication programmes. Cooperation between the Veterinary Services and Public Health Services, together with farmers, is essential for efficient implementation of the brucellosis control and eradication strategies. It is necessary to carry out careful herd management and control of animal movement within R. Macedonia and with and between neighbouring countries, and implementing basic biosecurity measures. Continuous surveillance and reporting are necessary to monitor the presence/absence of brucellosis and the efficacy of control programmes. There is a need to establish or strengthen intersectoral cooperation by the joint efforts of all the relevant factors in support of primary health care approaches, animal production, food safety and consumer education in the prevention and eradication of brucellosis. Prompt diagnosis and appropriate treatment and health care of diseased persons are very important. Collaboration between all countries in the SEE region and beyond is necessary, with technical and financial support of appropriate brucellosis control and eradication programmes from the European Commission, FAO and other international organizations, that will include all countries in the region, regardless of the magnitude of the brucellosis incidence.

REFERENCES

1. Rust R., Worrel TE. Brucellosis. Available at: <http://www.emedicine.com/neuro/topic42.htm> Accessed: 20.06.2009.
2. Pappas G., Papadimitriou P., Akritidis N., Christou L., Tsianos EV. (2006): The new global map of human brucellosis; *Lancet Infect Dis*;6:91–9. Available from: <http://www.thelancet.com/journals/laninf/article/PIIS1473-3099%2806%2970382-6/fulltext> Accessed: April 4, 2010.
3. Corbel MJ. (2006): Brucellosis in humans and animals. WHO, FAO, OIE, Geneva. Available from: <http://www.who.int/csr/resources/publications/Brucellosis.pdf> Accessed: Jan 31, 2010.

4. FAO Animal Production and Health Division. Animal health disease cards – Brucellosis Ovine/Carpine. Available from:
<http://www.fao.org/ag/againfo/subjects/en/health/diseases-cards/brucellosi-ov.html>
Accessed: March 5, 2010.

5. Harrison's Practice. Brucellosis. Available from:
<http://www.harrisonspractice.com/practice/ub/view/Harrisons%20Practice/141056/all/Brucellosis>
Accessed: December 26, 2009.

6. Taleski V., Zerva L., Kantardjiev T., Cvetnic Z., Erski-Biljic M., Nikolovski B., *et al.* (2002): An overview of the epidemiology and epizootology of brucellosis in selected countries of Central and Southeast Europe. *Vet Microbiol*; 90: 147–55.

7. OIE. Manual of Diagnostic Tests and Vaccines for Terrestrial Animals 2009. Available from: http://www.oie.int/eng/normes/mmanual/A_summry.htm Accessed: March 5, 2010.

8. Centers for Disease Control and Prevention – Office of Communication. Facts about brucellosis. Available at:
http://www.wrongdiagnosis.com/artic/facts_about_brucellosis_cdc_oc.htm Accessed: Dec 16, 2009.

9. Hutch P. Brucellosis – Symptoms and causes of brucellosis. Available from:
<http://www.articlesphere.com/Article/Brucellosis---Symptoms-and-Causes-of-Brucellosis/138346> Accessed: 20.06.2009.

10. Health Protection Agency. Brucellosis. Available from:
<http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/Brucellosis/> Accessed: December 26, 2009.

11. Health Protection Agency. Guidelines for action in the event of a deliberate release: Brucellosis. Available from:
http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1194947355003 Accessed: 25.10.2009.

12. Bax HI., Van Veelen M-LC., Gyssens IC., Rietveld AP. (2007): Brucellosis, an uncommon and frequently delayed diagnosis. *The Netherlands Journal of Medicine*; 65(9): 352–5. Available from: <http://www.njmonline.nl/njm/getpdf.php?t=a&id=10000225> Accessed: April 4, 2010.

13. Ministry of Foreign Trade and Economic Relations Veterinary Office of Bosnia and Herzegovina. Brucellosis. Available from:
<http://www.vet.gov.ba/?q=en/node/857> Accessed: 25.10.2009.

14. Vassalos CM., Economou V., Vassalou E., Papadopoulou C. (2009): Brucellosis in humans: why is it so elusive? *Reviews in Medical Microbiology*; 20(4): 63–73. Available from:
http://journals.lww.com/revmedmicrobiol/Abstract/2009/10000/Brucellosis_in_humans__why_is_it_so_elusive_.1.aspx Accessed: April 12, 2010.

15. Vorou R., Gkolfinopoulou K., Dougas G., Mellou K., Pierrousakos IN., Papadimitriou T. (2008): Local brucellosis outbreak on Thassos, Greece: a preliminary report. *Eurosurveillance*; 13 (25) :pii=18910. Available from:

<http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=18910> Accessed: April 4, 2010.

16. FAO. 2010. *Brucella melitensis in Eurasia and the Middle East* FAO Animal Production and Health Proceedings. No. 10. Rome. Available from: <http://www.fao.org/docrep/012/i1402e/i1402e00.htm> Accessed: May 5, 2010.

17. Bernard Vallat. Improving animal health worldwide is a priority. Available from: URL: http://www.oie.int/eng/Edito/en_edito_juil07.htm Accessed: January 23, 2010.

18. World Health Organization. Veterinary public health (VPH). Available from: <http://www.who.int/zoonoses/vph/en/> Accessed: January 31, 2010.

19. Ministry of Agriculture, Forestry and Water Economy of R. Macedonia. (2009): Reimbursement for the slaughtered livestock. [In Macedonian]. Daily Newspaper *Vreme*, Dec 29, 2009:12.

20. Ministry of Agriculture, Forestry and Water Economy of R. Macedonia – Veterinary Directorate. (2010): Reimbursement for the slaughtered livestock from brucellosis and tuberculosis started out. [In Macedonian]. Daily Newspaper *Vreme*, Jan 4, 2010: 22.

21. Minas M., Minas A., Gourgoulianis K., Stournara A. (2007): Epidemiological and clinical aspects of human brucellosis in Central Greece. *Jpn. J Infect Dis*; 60: 362–6. Available from: <http://www.nih.go.jp/JJID/60/362.pdf> Accessed: April 12, 2010.

22. Robinson A. Guidelines for coordinated human and animal brucellosis surveillance. FAO animal production and health paper 156. Food and Agriculture Organization of the United Nations, Rome 2003. Available from: <http://www.fao.org/docrep/006/y4723e/y4723e00.HTM> Accessed: April 12, 2010.

23. National Institute of Public Health, Skopje. (2010): Report on implementation of the Programme on examining of appearance, prevention and control of brucellosis in humans in the Republic of Macedonia in 2009. [In Macedonian]. National Institute of Public Health–Skopje.

24. OIE. Annual disease status of brucellosis by regions and by countries. Available from: <http://www.oie.int/hs2/report.asp> Accessed: May 15, 2010.

25. Russo G., Pasquali P., Nenova R., Alexandrov T., Ralchev S., Vullo V., *et al.* (2009): Reemergence of Human and Animal Brucellosis, Bulgaria. *Emerging Infectious Diseases*; 15(2): 314–6. Available from: <http://www.cdc.gov/eid/content/15/2/314.htm> Accessed: April 12, 2010.

26. Jelastopulu E., Bikas C., Petropoulos C., Leotsinidis M. (2008): Incidence of human brucellosis in a rural area in Western Greece after the implementation of a vaccination programme against animal brucellosis. *BMC Public Health*; 8: 241–6. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18637172> Accessed: 25.10.2009.

27. Hadjichristodoulou Ch., Soteriades E., Goutsiana G. (1999): Surveillance of brucellosis in a rural area of Greece: Application of the Computerized Mapping Programme. *Eur J Epidemiol*; 15: 277–83.

28. Hadjichristodoulou Ch., Papatheodorou Ch., Soteriades E., Panagakos G., Kastiris I., Gotuziana G., *et al.* (1999): Epidemiological study of brucellosis in eight Greek villages using a Computerised Mapping Programme. *Eur J Epidemiol*; 15: 671–80.
29. Bikas C., Jelastopulu E., Leotsinidis M., Kondakis X. (2003): Epidemiology of human brucellosis in a rural area of North-Western Peloponnese in Greece. *Eur J Epidemiol*; 18: 267–74.
30. Dahouk SA., Neubauer H., Hensel A., *et al.* (2007): Changing Epidemiology of Human Brucellosis, Germany, 1962–2005. *Emerging Infectious Diseases*; 13(12): 1895–900. Available from: http://www.medscape.com/viewarticle/568520_3 Accessed: April 12, 2010.
31. Yoo SJ., Choi YS., Lim HS., Lee K., Park MY., Chu C., Kang YA. (2009): Seroprevalence and Risk Factors of Brucellosis among Slaughterhouse Workers in Korea. *J Prev Med Public Health*. 2009; 42(4): 237–42. Available from: <http://synapse.koreamed.org/DOIx.php?id=10.3961/jpmph.2009.42.4.237> Accessed: April 12, 2010.
32. Ministry of Health of R. Macedonia. (2010): National program for exploring the appearance, spreading, prevention and eradication of human brucellosis in the Republic of Macedonia. *Official Gazette of RM*, No. 20/10.
33. OIE. Terrestrial Animal Health Code 2008. Available from: http://www.oie.int/eng/normes/MCODE/en_chapitre_1.1.1.htm Accessed: March 5, 2010.
34. OIE. Terrestrial Animal Health Code 2009. Available from: http://www.oie.int/eng/normes/Mcode/en_sommaire.htm Accessed: March 5, 2010.
35. Commission of the European Communities. Progress Report 2009 – FYR Macedonia – Chapter 12: Food safety, veterinary and phytosanitary policy. Available from: <http://www.nrc.nl/redactie/Europa/voortgangsrapporten2009/macedonie.pdf> URL: Accessed: Jan 24, 2010.
36. Ministry of Agriculture, Forestry and Water Economy of R. Macedonia. (1998): Veterinary Health Protection Law. [In Macedonian]. *Official Gazette of RM* No. 28/98.
37. Ministry of Agriculture, Forestry and Water Economy of R. Macedonia. (2004): Law on identification and registration of animals. [In Macedonian]. *Official Gazette of RM* No. 69/04.
38. Ministry of Agriculture, Forestry and Water Economy of R. Macedonia. (2002): Law on security of food and products and materials becoming in contact with food. [In Macedonian]. *Official Gazette of RM* No. 54/02.
39. Government of the Republic of Macedonia. (2004): Law on Protection of the Population Against Communicable Diseases. [In Macedonian]. *Official Gazette of RM* No. 66/2004. Available from: http://tsf.undp.org.mk/comp_includes/webdata/documents/ZAKON%20ZA%20ZASTITA%20NA%20NASELENIETO%20OD%20ZARAZNI%20BOLESTI.pdf Accessed: 25.05.2009.

40. Commission of the EU Communities. (2009): Enlargement Strategy and Main Challenges 2009–2010 FYR Macedonia 2009 Progress Report. SEC 1335/3, Brussels, 14.10.2009.
41. Bernard Vallat. Prevention, detection and monitoring of animal diseases, including those harmful to humans: veterinary services are the keystone of the global system. Available from: URL: http://www.oie.int/eng/Edito/en_edito_mars06.htm Accessed: January 23, 2010.
42. Bernard Vallat. Emerging and re-emerging zoonoses. Available from: http://www.oie.int/eng/Edito/en_edito_nov04.htm Accessed: January 23, 2010.
43. Bernard Vallat. Veterinary legislation is the foundation of any efficient animal health policy. Available from: http://www.oie.int/eng/Edito/en_edito_nov09.htm Accessed: January 23, 2010.
44. OIE. The OIE's Reference Laboratories and Collaborative Centres: the core of its scientific excellence. Available from: www.oie.int/eng/Edito/en_lastedito.htm Accessed: 22.04.2010.
45. Food and Agriculture Organization of the United Nations, World Organization for Animal Health (Office International des Épizooties), World Health Organization. (2006): Global Early Warning and Response System for Major Animal Diseases Including Zoonoses (GLEWS). Available from: http://www.oie.int/fr/OIE/accords/GLEWS_Tripartite-Finalversion010206.pdf Accessed: January 23, 2010.
46. WAHID Interface. OIE World Animal Health Information Database (WAHID) Database. Available from: URL: <http://www.oie.int/wahis/public.php?page=home> Accessed: January 23, 2010.
47. FAO Animal Production and Health Division. Veterinary Public Health and Feed and Food Safety (VPH). Available from: <http://www.fao.org/ag/againfo/programmes/en/A6.html> Accessed: March 5, 2010.
48. Bernard Vallat. One World, One Health. Available from: URL: http://www.oie.int/eng/Edito/en_edito_apr09.htm Accessed: January 23, 2010.
49. Epi South Network for Communicable Diseases Control in SEE and Mediterranean Countries. Framework of collaboration on epidemiological issues across the countries of the Mediterranean and the Balkans. Available from: http://www.episouth.org/relevant_links_docs.html Accessed: 22.04.2010.

Резиме

ЭПИДЕМИОЛОШКИ И ЈАВНО-ЗДРАВСТВЕНИ АСПЕКТИ НА БРУЦЕЛОЗАТА ВО РЕПУБЛИКА МАКЕДОНИЈА

Донев Д.,¹ Карацовски Ж.,² Касапинов Б.,² Лазаревиќ В.¹

¹Институт за социјална медицина,

Медицински факултет, Скопје, Р. Македонија
² Институт за јавно здравје, Скопје, Р. Македонија

Цел: Да се анализира и прикаже епидемиолошкиот модел на хуманата бруцелоза и главните фактори за појавата и ширењето на инфекцијата со *B. Melitensis* меѓу животните и луѓето во Р. Македонија во периодот 1980–2009.

Методи: Ретроспективна студија базирана на епидемиолошки извештаи и официјални податоци за случаите на бруцелоза од Институтот за јавно здравје во Скопје и други институции од здравствениот и ветеринарниот сектор во Р. Македонија, како и преглед на релевантната литература.

Резултати: Од 1980 година до декември 2009 година во Р. Македонија биле пријавени вкупно 11,451 случај на бруцелоза, со просечна годишна стапка на инциденца од 18,9/100.000. Во овој период, највисока стапка на заболување од бруцелоза е забележана во 1992 година (922 случаи со стапка на инциденца од 47,6/100.000) додека најниска стапка е регистрирана во 1983 година (12 случаи и стапка на инциденца од 0,6/100.000).

Од вкупниот број на пријавени случаи во Р. Македонија во периодот 1980–2009, 66,2% биле лица од машки пол и 33,8% биле лица од женски пол. Само 7,2% од пациентите биле на возраст под 10 години, додека најголемиот број од заболените биле на возраст меѓу 20 и 39 години (31,9%). Сезонските карактеристики на заболувањето се прикажани со најголема појава во месеците мај (15,9%), јуни (16,3%) и јули (15,1%). Од вкупно 3.284 случаи на бруцелоза во периодот 2001–2009 година, 2.320 (70,6%) биле од руралните области, додека 964 (29,4%) биле од урбаните средини. Од професионалниот кадар, 385 лица, или 8,4% од сите пријавени во периодот 1998–2009, заболеле од бруцелоза по контактен пат.

Заклучок: Бруцелозата беше, е и ќе биде значаен проблем во Р. Македонија на кој во наредните години треба да се пристапи со посеопфатен и организиран начин. Постои потреба да се воспостави интерсекторска соработка со заеднички напори на сите релевантни фактори во превенцијата и ерадикацијата на бруцелозата како и соработка меѓу сите земји од регионот на ЈИЕ.

Клучни зборови: Бруцелоза, зоонози, епидемиологија, програма за превенција/контрола, Република Македонија (FYRM).

Corresponding Author:

Doncho Donev, MD, PhD, Professor
Institute of Social Medicine
Faculty of Medicine, Ss Cyril and Methodius University
MKD-1000, Skopje, Republic of Macedonia

Phone: +389 2 3298580; Fax: +389 2 3298582

E-mail: dmdonev@gmail.com