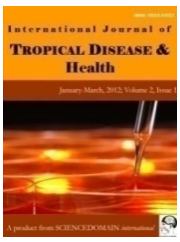

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Trends in the Epidemiology of Brucellosis in a Highly Afflicted Region in Egypt: A 16 Year Experience (1997-2012)

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Authors' contributions

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Original Research Article

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ABSTRACT

Background: Brucellosis is a serious re-emerging zoonosis which vastly afflicts human health and animal productivity. The reported incidence may under-represent the real burden of the disease that has drastically evolved during the past decade. Incomplete epidemiological data particularly from developing countries and remote areas reflects partly the lack of accurate disease diagnosis and under reporting. This necessitates the comprehensive review of past experiences and disease trends over time to tailor proper intervention and control strategies.

Aim: This hospital based study is an attempt to explain reasons beyond the evolution and alteration of brucellosis epidemiology in a highly burdened rural region in Egypt over 16 years (1997-2012).

Methods: All cases of human brucellosis admitted to Damanhour fever hospital from 1997 to 2012 were analyzed. During 2007, the study was complemented by a detailed patient evaluation and disease description. Data about animal brucellosis were reviewed from records in the veterinary sector.

Results: A total of 4371 [2609 (59.7%) males and 1762 (40.3%) females, median of age=31 years] brucellosis cases were reviewed during the study period. The annual

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occurrence among human has increased early in the decade and showed two peaks of incidence in 2002 and 2005-2006. On the other hand, animal brucellosis showed significant decline across decades thanks to enforcement of control measures. The disease was frequently presented by nonspecific constitutional symptoms and reticuloendothelial system involvement, yet sever complications were less encountered. All patients were treated according to the standard therapeutic guidelines and showed clinical improvement before discharge.

Conclusion: These results indicate that human and livestock brucellosis persisted in Northern Egypt across the study period albeit with a fluctuating incidence. The current situation necessitates more appropriate disease surveillance and improving the control and containment strategies in order to alleviate disease burden on both human and animal populations.

Keywords: Brucellosis; trend; epidemiology; burden; Egypt.

1. INTRODUCTION

Brucellosis is a re-emerging zoonosis occurring throughout the world particularly in the Middle-East and the Mediterranean region [1]. The disease is rare in industrialized countries thanks to the routine standardized screening of domestic and imported livestock, testing of abortions , animal vaccination and slaughtering of infected animals [2].

Despite the continuous progress in brucellosis control measures in many countries, it persists as a major public health problem of great economic impact. Moreover, frequent human infection results in prolonged aching, debility, incapacity for work, disabilities from osteoarticular complications and potential mortality usually from endocarditis [3], pneumonia or meningioencephalitis [4,5]. Eradication of brucellosis in animal reservoirs proportionally results in a significant decline in the disease incidence in humans.

The global annual occurrence of human brucellosis amounts to more than 500,000 cases [6, 7]. Egypt has high prevalence rates of *B. melitensis* infections in cattle, buffaloes, camels, sheep, and goats [8,9] yet it may account for 10% in high risk human population [10].

Brucellosis in animals was first reported In Egypt in 1939 [8]. The incidence in the recent years (1960s till 1980s) in cattle rated 38% with the importation of foreign Friesian breeds for the establishment of governmental farms with large numbers of animals (including also sheep and goats) concentrated on relatively small area of land. On the touch Tambesha farm in Menofia and Dulla El Baraka in El Sharkia Governorates. The later reported 71% positive and 14% suspicious cases that stood against the implementation of test and slaughter policy [8].

Consequently, a marked increase in the number of brucellosis infected patients in the recent past (24 cases in 1988 versus 1429 cases in 1998) has been recorded and warned occurrence of an epidemic [11].

The dramatic spread of zoonosis in Egypt may underlie contributions of negative socio-economic factors, together with increased livestock importation, unofficial animal movements and uncontrolled trade in agricultural products [8].However, this can reflect improved disease recognition as a common cause of acute febrile illness rather than a true increase in disease incidence.

A full description of the disease epidemiology and its implications is indispensable approach for intervention planning employing appropriate public health control measures to achieve disease eradication. Nevertheless, little reliable data on disease burden in Egypt are available so far.

This study provides base line epidemiological data to delineate challenges for brucellosis control in this identified area and provides a starting point for implementing targeted intervention measures.

2. METHODS

This hospital based study was conducted at to Damanhour fever hospital (DFH), El-Behira governorate. The hospital is a catchment area for nearby rural administrative districts of El-Beheira governorate including Damanhour, Hosh Issa, Abu Hummus, El Mahmoudiya, El Delengat, Etay El Barud, Abou El Matamir (Fig. 1). The other districts including Edko, KomHamadah, Kafr El Dawar, have their own fever hospitals. Municipalities like Wadi El Natrun, El Nubariyah, Shubrakhit, El Rahmaniyah and Rosetta are nearer to other governorates so that, for any case of fever, it is easier to be referred to the nearby fever hospital (Fig 1). El-Behira, like other governorate in the Nile delta, has a major agrarian population where the proportion to urban society reaches 24:1 [12]. Only cases with febrile illness arrive at fever hospitals where they are subjected to different serological and microbiological investigations to confirm the presumptive diagnosis (typhoid, brucellosis, leptospirosis, avian flu, hepatitis, meningitis, HIV, etc....). The annual rate of admission in DFH over the study period was 4000 in 1997 and reached 9000 fever cases in 2012. The proportion of brucellosis cases varied between 2-8%.

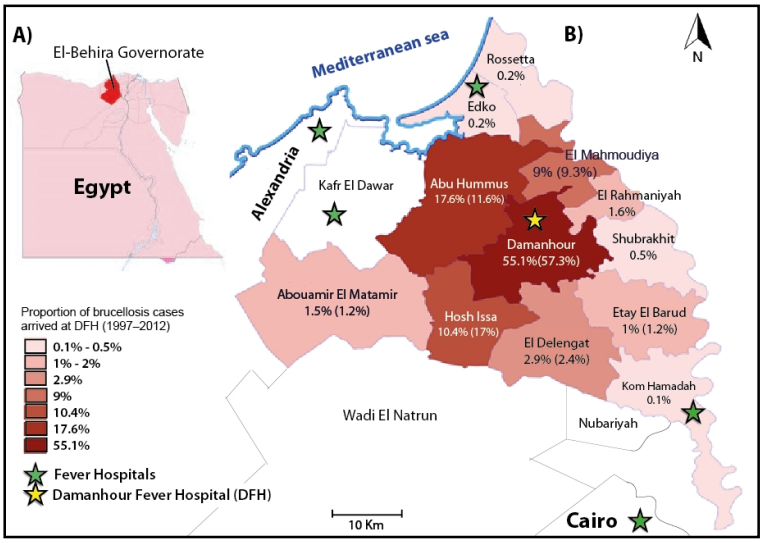

Fig. 1. Map A, shows the location of El-Behira governorate (red), East to Alexandria and North of the capital Cairo, Egypt. Map B shows El-Behira governorate grouped into 15 administrative districts. The map depicts the catchment area of DFH (yellow star) and displays the proportion of human brucellosis seropositives per district arrived at DFH between 1997 - 2012; numbers between brackets indicate proportions of 2007 cohort. The locations of other fever hospitals serving other districts are indicated by green stars.

Data were abstracted retrospectively from inpatient logbooks and hospital annual records over a 16 years period (1997-2012). The annual number of brucellosis cases was reviewed. Basic data included patient's age, gender, occupation, residence, complains, duration of illness prior to admission, titer of brucellosis agglutination test, treatment received, disease outcome and possible complications. During 2007, all admitted seropositives were interviewed using a standardized pre-designed questionnaire covering data about socio-demographic characteristics, clinical symptoms, disease onset, detailed current and past medical history, paying more attention to history of risky behaviors and exposures. Complete clinical evaluation was done for all enrolled cases during the study year to include complete chest, heart, abdomen, and musculoskeletal examination with a particular stress on potential brucellosis complications such as arthritis. Diagnosis of brucellosis was based on World Health Organization (WHO) case definition, i.e. the presence of symptoms such as recurrent fever, malaise, headache, profuse sweat, joint and bone aches, supported by a history of recent exposure to a probable source of infection. Suspicious cases were then subjected to confirmation by detection of *Brucella* IG antibodies (titer >1:160) using a standard serological test (Standard Tube Agglutination Test (SAT) for *B. abortus and B. mellitensis; (The commercial Stained Febrile Antigen of Plasmatec Laboratory Products Ltd*). Automated blood culture system (BACTEC 9240) was done for doubtful cases but not routinely. Other investigations such as erythrocyte sedimentation rate (ESR), complete blood picture (CBC) and urine analysis were also done.

Data about animal brucellosis between 1990 and 2012 was reviewed from records of El-Behira Directorate of Veterinary Medicine, sector of public health and zoonotic disease. However, complete data about disease incidence among different livestock species, animal vaccination, and compensation payments were only available for the years 2007-2012.Hospital based annual Incidence per 100,000 inhabitants in the settlements of the reported cases (catchment area of DFH) was calculated for each year to highlight any temporal changes in risk over the 16-year periods, using annualized population census estimates obtained from The Egyptian Central Agency for Public Mobilization and Statistics [12]. Socio demographic and clinical parameters were analyzed using SPSS 16 and the appropriate statistical tests (means, median, quartiles, percentages, relative risk, risk ratio, chi square test, ANOVA, and Pearson correlation coefficient). A p-value ≤ 0.05 was considered significant.

3. RESULTS

3.1 Disease Pattern Over 16 Years (1997-2012)

3.1.1 Animal brucellosis

The number of seropositive animals showed gradual increase early in the decade to reach a highest peak of occurrence in 1997. A corresponding increase in human brucellosis cases arriving at DFH was observed albeit with a much lower rate. Afterwards, animal brucellosis rate started to decline steadily meanwhile showed high occurrence peaks in 2002, 2005-2007 and 2010. This significant drop certainly reflects the impact of brucellosis control program that implement test-and slaughter policy, animal vaccination (a total of 100652 animals were vaccinated in the last 6 years using Rev1 and vac RBS1 for cattle and buffaloes and S19 for sheep and goats), (Supp. Figs. 1, 2), quarantine and farm disinfection, market control of milk and dairy products, and veterinary reporting of aborted animals [13].

Although numbers of cattle and buffaloes in the governorate were consistently higher, the percentages of infected and slaughtered animals were higher among goats and sheep (3-13% and 2-8% respectively), (Supp. Fig. 2).

Likewise, the number of human cases admitted to DFH started to increase remarkably in 2000, 2001 to show two peaks of incidence in 2002, and 2005-2006. Thereafter, a steady decline of human brucellosis ensued to reach 173 cases in 2012 (Fig. 2). More detailed information on the annual human brucellosis occurrence and the monthly distribution are shown in (Supp. Fig. 3).

The incidence per 100.000 was calculated, assuming that the number of tested animals in test-and slaughter brucellosis control program represent the animal population at risk. No significant correlation was found between the incidence per 100.000 among animals and that among human cases (Pearson coefficient (r= -0.2), 95% CI -0.62-0.31, r^2= 0.035, P= 0.48), (Supp. Fig. 4).

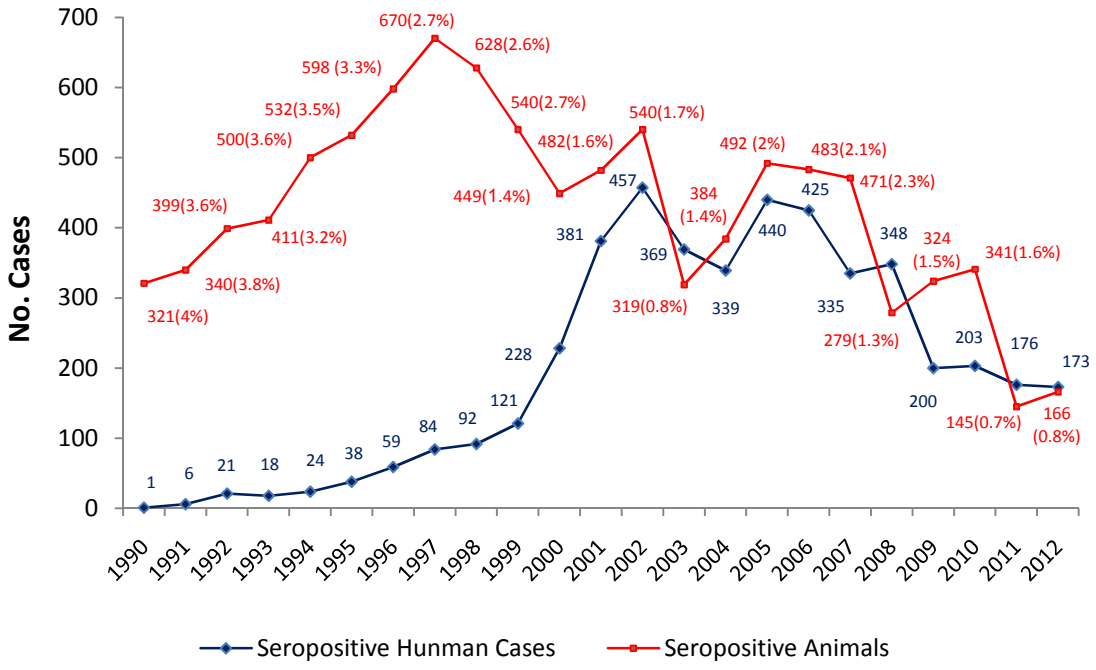

Fig. 2. Numbers of confirmed seropositive animals in El Behira governorate and numbers of confirmed seropositive human cases admitted to DFH over two decades (1990-2012). (numbers between brackets indicate percentage of infected animal of the totally tested).

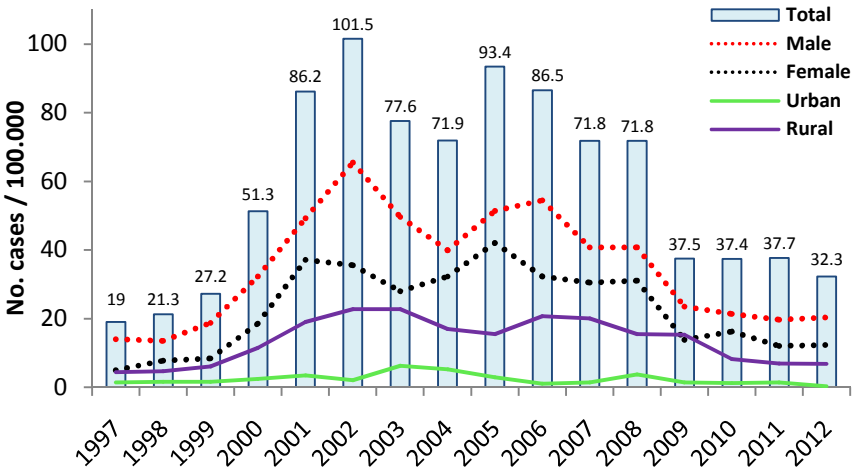

Fig. 3. Human brucellosis cases in DFH (1997-2012). Combination chart showing the hospital based annual incidence of human brucellosis cases per 100,000 populations (solid bars) and incidence among males versus females and among urban versus rural residents (line graphs)

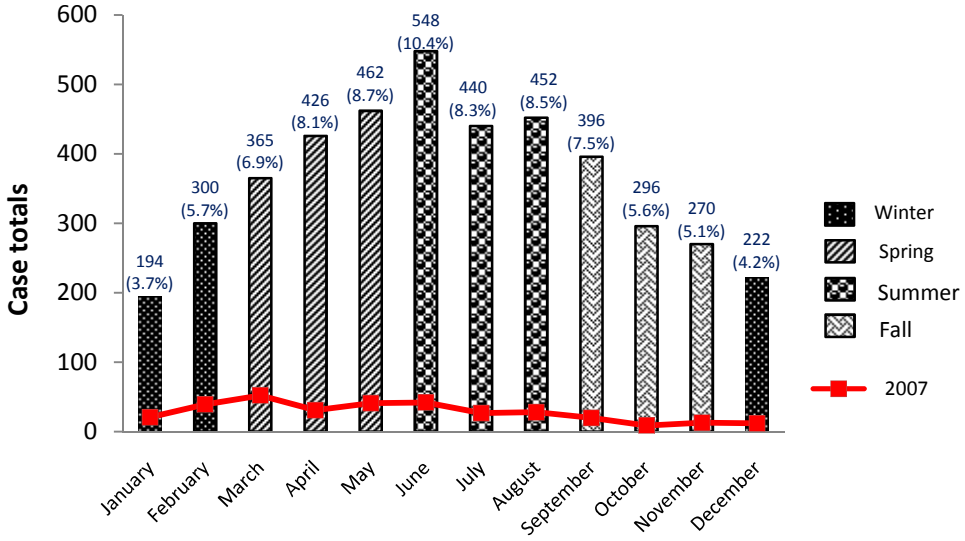

Fig. 4. Total number of human brucellosis cases admitted at DFH by month and season over the period 1997-2012. Winter months (n = 716) are shown in the graph by dotted black bars, spring months (n = 1,253) are displayed by the crosshatched bars, summer months (n = 1,440) are represented by sphered bars, and Fall months (n = 962) are displayed by the weaved bars. The pattern for the year 2007 is indicated by red color.

3.1.2 Human brucellosis

Over the 16 years period of the study (1997-2012), the total number of admitted human brucellosis cases in DFH was 4371, including 2609 (59.7%) males and 1762 (40.3%) females (M:F=1.5:1). Brucellosis was recognized in all age groups, (ages ranged between 1 and 95 years; Median=31, Q1=20, Q3=41 years). The middle age group (15-45 years) was the most frequently affected (64.5%) whereas those under 15 and over 45 constituted 13.7% and 21.8% respectively, a pattern which was consistent over the study period after adjusting the incidence rate per 100.000 population. Males were 4-6 times more affected across all age groups. Regarding the place of residence, a sustained and highly significant disease incidence (P< 0.001) prevailed in the rural areas (95.8%), while cases from urban settlement represented only 4.2% of the total, (Table 1, Fig. 3).

Over a ten years period (1997-2007), the locations of brucellosis cases were aggregated to seven municipal districts in El–Behira governorate with a widely varied rate of occurrence. The incidence was highest in Damanhour (55.1%), followed by Abu Hummus (17%), HoshIssa (10.4%), El Mahmoudiya (9%), El Delengat (2.9%), Abou El Matamir (1.5%) and Etay El Barud(1%). Thereafter, the catchment area of DFH was extended to receive cases from other municipalities; El Rahmaniyah (1.6%), Shubrakhit (0.5%), Edko and Rosseta (0.2% each) and KomHamadah (0.1%) (Fig. 1).

Brucellosis maintained its distinct seasonal characteristics by a significant variation in the temporal distribution during the entire observation period (P= 0.001). Proportion of admitted patients was highest late in spring (May; 462 (8.7%) cases) and across summer (a peak reached in June; 548 (10.4%), July; 440 (8.3%), and August; 452 (8.5%) cases). The fewest were registered during winter (December–January, 4%), (Fig. 4). Interestingly, in 2007, an unusual peak of disease occurrence was observed in March which accounted for 14.6% of the total reported cases during the year (Fig. 4).

The distribution of the reported brucellosis cases according to their occupation did differ significantly over the 16 years of the study, (P< 0.001). The number of cases observed among farmers together with housewives was consistently high (1407 (32.2%) and 1345 (30.8%) respectively) amounting collectively to about two thirds of the total reported cases. The unemployed or self-employed (manual workers and clerks) categories were equally represented (4.6%, 5.2% and 5.8%, respectively) among cases. Affected preschool children (2.6%) and students (17.2%) together comprised one fifth of all cases. During the last six years, the disease started to appear among professionals (1.2%); included were 4 laboratory technicians, military personnel (0.3%), and those dealing with animals or animal products (0.23%); shepherds, butchers, food handles and peddlers (Supp. Fig. 5).

Regarding the clinical features of the disease, brucellosis was presented by symptoms and signs that varied widely across decades. Fever, headache, night sweating, malaise and chills were the main constitutional symptoms encountered among 99.9%, 44.2%, 15.6%, 12.2 and 11.7% of the cases, respectively. Muscloskel et al. involvements were frequent and included arthralgia/arthritis (20.8%), low back pain/bone aches (20.7%), and myalgia (14.1%). Gastrointestinal manifestations in the form of vomiting (16.1%), diarrhea/constipation (9.4%) were reported by one fourth of the evaluated cases. Complication by chest infection was recorded among 207 (4.7%) and presented by dyspnea, cough, and wheezes. Focal genitourinary complications were more encountered among middle aged males that experienced epididymo-orchitis in 54 (1.2%) and cystitis/urethritis in 24 (0.5%) cases. Features of reticloendothelial compromise were not uncommon and

Table 1. Human brucellosis case admitted at DFH by age, gender and residence, 1997–2012

Year	Age group	Male				Female				Total	RR	Rural			Urban			RR	B/A[e]
		Popul.[a]	No.	%	I[b]	Popul.[a]	No.	%	I[b]		M/F[c]	Popul.[a]	Cases	I[b]	Popul.[a]	Cases	I[b]	U/R[d]	
1997	<15	352689	11	73.3	3.1	351281	4	27	1.1	4.2	2.7	1792089	78	4.4	425844	6	1	3.1	8.1
	15-45	535590	44	71	8.2	533452	18	29	3.4	11.6	2.4								
	>45	222905	6	85.7	2.7	222015	1	14	0.5	3.2	6								
	total	1111184	61		14	1106748	23		5	19	5								
1998	<15	359215	5	45.5	1.4	357781	6	55	1.7	3.1	0.8	1825247	85	4.7	433723	7	2	2.9	2
	15-45	545500	42	61.8	7.7	543322	26	38	4.8	12.5	1.6								
	>45	227029	10	76.9	4.4	226123	3	23	1.3	5.7	3.3								
	total	1131744	57		14	1127226	35		7.8	21.3	5.8								
1999	<15	365741	6	50	1.6	364281	6	50	1.6	3.2	1	1858405	114	6.1	441602	7	2	3.9	2.4
	15-45	555410	69	75	12	553193	23	25	4.2	16.6	3								
	>45	231153	11	64.7	4.8	230230	6	28	2.6	7.4	1.8								
	total	1152304	86		19	1147704	35		8.4	27.2	5.8								
2000	<15	372266	22	61.1	5.9	370780	14	39	3.8	9.7	1.6	1891564	217	12	449481	11	2	4.7	4.4
	15-45	565319	99	60.7	18	563063	64	39	11	28.5	1.5								
	>45	235278	21	72.4	8.9	234338	8	28	3.4	12.3	2.6								
	total	1172863	142		32	1168181	86		19	51.3	5.7								
2001	<15	378792	26	56.5	6.9	377280	20	44	5.3	12.2	1.3	1924722	365	19	457360	16	4	5.4	6.2
	15-45	575229	150	55.6	26	572933	120	44	21	47.1	1.2								
	>45	239402	39	60	16	238446	26	40	11	27.3	1.5								
	total	1193423	215		49	1188659	166		37	86.2	4								
2002	<15	385318	45	64.3	12	383780	25	36	6.5	18.2	1.8	1957880	447	23	465240	10	2	11	8.1
	15-45	585139	197	61.9	34	582804	121	38	21	54.7	1.6								
	>45	243526	49	71	20	242553	20	29	8.2	28.3	2.4								
	total	1213983	291		66	1209137	166		36	102	5.9								
2003	<15	391843	34	61.8	8.7	390279	21	38	5.4	14.1	1.6	1991038	339	17	473119	30	6	2.7	6.1
	15-45	595049	164	61	28	592673	105	39	18	45.6	1.6								
	>45	247651	33	73.3	13	246662	12	27	4.9	18.2	2.7								
	total	1234543	231		50	1229614	138		28	77.6	5.9								
2004	<15	398369	32	64	8	396779	18	36	4.5	12.5	1.8	2024197	314	16	480997	25	5	3	5.2
	15-45	604959	133	55.9	22	602544	105	44	17	39	1.3								
	>45	251774	25	49	9.9	250769	26	51	10	19.9	1								
	total	1255102	190		40	1250092	149		32	71.9	4								

2005	<15	404895	41	60.3	10	403278	27	40	6.7	16.8	1.5	2057355	426	21	488877	14	3	7.2	5.5
	15-45	614869	167	55.3	27	612414	135	45	22	49.2	1.2								
	>45	255898	36	51.4	14	254878	34	49	13	27.1	1.1								
	total	1275662	244		51	1270570	196		42	93.4	3.8								
2006	<15	411420	42	67.7	10	409778	20	32	4.9	15.1	2.1	2090513	420	20	496756	5	1	20	4.8
	15-45	624779	166	54.8	27	622284	137	45	22	48.6	1.2								
	>45	260023	46	76.7	18	258985	14	23	5.4	23.1	3.3								
	total	1296222	254		55	1291047	171		32	86.5	6.6								
2007	<15	416765	19	63.3	4.6	415101	11	37	2.6	7.2	1.7	2117670	328	16	503209	7	1	11	4.3
	15-45	632894	133	56.8	21	630368	101	43	16	37	1.3								
	>45	263401	40	56.3	15	262350	31	44	12	27.2	1.3								
	total	1313060	192		41	1307819	143		31	71.8	4.3								
2008	<15	424490	24	68.6	5.7	422796	11	31	2.6	8.3	2.2	2156923	329	15	512537	19	4	4.1	4.7
	15-45	644626	128	52.5	20	642053	116	48	18	37.9	1.1								
	>45	268283	41	59.4	15	267212	28	41	11	26.3	1.5								
	total	1337399	193		41	1332061	155		31	71.8	4.7								
2009	<15	459404	14	70	3	457569	6	30	1.3	4.3	2.3	2334325	192	8.2	554692	8	1	5.7	3.4
	15-45	697645	92	63.4	13	694860	53	37	7.6	20.8	1.7								
	>45	290349	21	60	7.2	289190	14	40	4.8	12	1.5								
	total	1447398	127		24	1441619	73		14	37.5	5.5								
2010	<15	469681	27	81.8	5.7	467806	6	18	1.3	7	4.5	2386550	196	8.2	567101	7	1	6.7	3.6
	15-45	713253	66	48.5	9.3	710406	70	52	9.9	19.2	0.9								
	>45	296845	19	55.9	6.4	295660	15	44	5.1	11.5	1.3								
	total	1479779	112		21	1473872	91		16	37.4	6.7								
2011	<15	481236	17	65.4	3.5	479315	9	35	1.9	5.4	1.9	2445263	168	6.9	581053	8	1	5	3.4
	15-45	730800	68	56.7	9.3	727883	52	43	7.1	16.4	1.3								
	>45	304148	21	70	6.9	302934	9	30	3	9.9	2.3								
	total	1516184	106		20	1510132	70		12	31.7	5.5								
2012	<15	494103	18	60	3.6	492130	12	40	2.4	6	1.5	2510639	171	6.8	596588	2	0	20	2.7
	15-45	750339	65	63.1	8.7	747343	38	37	5.1	13.8	1.7								
	>45	312279	25	62.5	8	311033	15	38	4.8	12.8	1.7								
	total	1556721	108		20	1550506	65		12	32.3	4.9								

[a] Population at risk in the settlement of brucellosis cases admitted at DFH.
[b]Hospital based annual incidence calculated per 100.000 inhabitants in the settlement of brucellosis seropositives admitted at DFH .
[c]Male to female relative risk (risk ration); [d]Rural to Urban relative risk (risk ration)
[e]Proportion of brucellosis case to the total febrile cases admitted at DFH

Included splenomegaly (4.8%), hepatitis and/or hepatomegaly (1%), elevated liver enzymes (0.8%) and jaundice (0.6%). In the series of 4371 patients, neurological findings were seen in only 16 (0.37%) cases and included psychiatric manifestations that affected mainly malesin middle age and 3(0.07%) cases of brucella meningitis. Out of 6 patients, 5 middle aged males were presented with erythematous popular skin lesions.

Brucellosis patients tended to wait few to several days before seeking medical advice. The duration of illness prior to examination day varied between 1 and 120 days (Mean±SD=11.6±9.5, median=10, Q1=6, Q3=14 days) and almost recorded to be less than 2 weeks in 77.7% of the patients, signifying the predominance of the acute form of the disease.

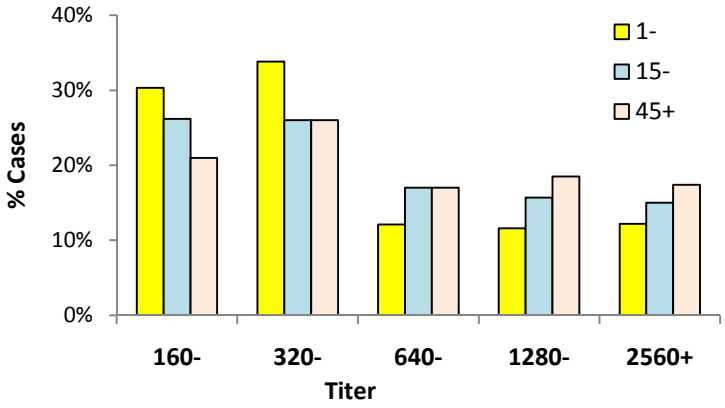

Fig. 5. Levels of serum brucella antibody titer among different age groups of brucellosis cases admitted at DFH over the period 1997–2012

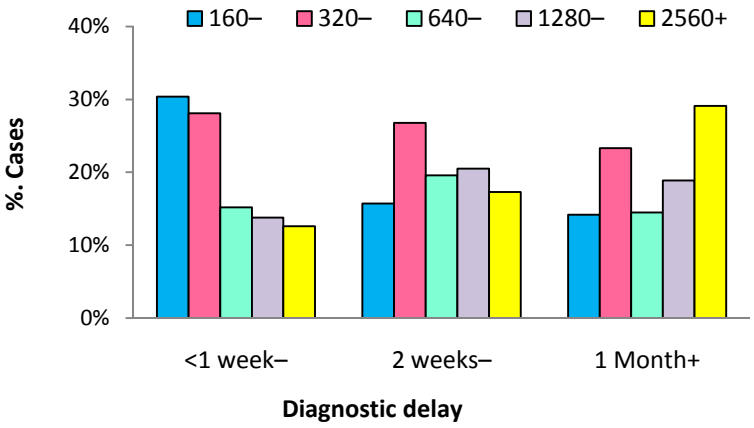

Fig. 6. Correlation between serum brucella antibody titer and the duration of illness prior to admission among different age groups of brucellosis cases admitted at DFH over the period 1997–2012

Brucella antibody titer varied significantly among seropositives over years (P< 0.001). The trend over the 16 years was fluctuating meanwhile showing a significant sharp rise in 2006 and 2007(ANOVA, F=8.4, P< 0.001). Titers lower than 1:640 were relatively much represented among younger age groups (below 40 years) and increased significantly with age (P< 0.001), (Fig. 5). Likewise, elevated titers correlated significantly (P< 0.001) with prolonged disease duration (Fig. 6).

The therapeutic regimen till 2010 was a combination of Streptomycin plus Doxycycline prescribed for adults (90%) and restricted the administration of Rifampicin plus Cotrimexazole for young children below ten (67%). In 2011, due to shortage of streptomycin ascribed to a temporary interruption in manufacturing, the product was replaced by rifampicin but re prescribed in 2012 (S. Fig. 6).The mean hospital stay was estimated to be 5 days (Mean±SD=5±2.4, median=5, Q1=3, Q3=6days). The patients are discharged while receiving their treatment meanwhile showing clinical improvement. No follow up is adopted and hence the response and relapse rates are not evaluated.

3.1.3 Pattern of Human brucellosis in 2007

The sociodemographic and epidemiological characteristic of the evaluated 2007 cohort did not vary widely compared with previous trends. Out of 335 cases, 192 (57.3%) were males and 143 (42.7%) were females with ages in the range 3–70 years (Mean±SD=33.4±14.9, median 31, Q1=22, Q3=45), almost residing in rural settlements (97.9%). The professional structure was likewise maintained.

Analysis of predisposing factors and risky behavior revealed a variety of hazardous exposures commonly associated with brucellosis (Table 2). Possible foodborne transmission via consumption of dairy products prepared from fresh unboiled milk, including Karish (village cheese), white cheese, Romy (hard cheese), and goat cheese was reported among 62.1%, 28.7%, 7.2%, and 6% of the cases, respectively. The majority of the evaluated cases (61.8%) used to drink boiled or pasteurized milk whereas raw milk and ice cream were consumed by a negligible number of patients (1.8% and 0.6%, respectively). No history of imperfectly cooked meat consumption was recorded. Direct contact with field or domestic animals was reported by almost half (47.8%) of the cases. This included handling animal during rearing (22.4%), cleaning (21.2%), home slaughtering (8.4%) or engagement in parturition (1.2%). Engaged patients in the listed risky activities were more likely to be farmers (43.1%) or housewives (42.5%) (Supp. Fig. 7). The coincidental occurrence of similar cases in the patient's household or residential area was reported by 9.3% and 2.4% of the cases, respectively.

The clinical aspect varied widely among the evaluated patients (Table 3). Three quarters of the patients were presented with fever of more than 38 C° (Mean±SD=38.3±0.9) for a duration greater than 2 days (Mean±SD=12.5±11.4, median=10, Q1=7, Q3=14). Other predominant symptoms and signs included headache (45%), low back pain (34%), toxic general look (33.4%), fatigue (27.5%), night sweating (27.2%), arthralgia and bone aches (25.1%), chills (15.5%), anorexia (7.8%), vomiting (1.5%) and diarrhea (0.6%).

On examination, 43 (12.8%) had tachycardia and equal proportions have experienced tachypnea (3.6%) and bradypnea (3.6%).

Table 2. Clinical features on admission among evaluated brucellosis cases in DFH, 1997-2012

Clinical Aspects^	Gender				Total		Age Group (years)					
	Male		Female				1-		15-		45+	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
None	3	43	4	57	7	0.16	0	0	7	100	0	0
Constitutional symptoms												
Fever	2606	60	1759	40	4365	99.9	559	14	2815	65	951	22
Headache	1164	60	768	40	1932	44.2	167	8.6	1308	68	457	24
Malaise	310	58	222	42	532	12.2	12	2.3	365	69	155	29
Night sweating	404	59	277	41	681	15.6	35	5.1	460	68	186	27
Chills	235	64	186	36	511	11.7	46	9	326	64	139	27
Muscloskeletal involvement												
Low back pain, bone aches	544	60	361	40	905	20.7	19	2.1	646	71	240	27
Arthralgia/Arthritis	524	58	387	43	911	20.8	22	2.4	630	69	259	28
Myalgia	354	57	263	43	617	14.1	16	2.6	443	72	158	26
GIT manifestations												
Diarrhea/Constipation	239	58	171	42	410	9.4	10	2.4	277	68	123	30
Vomiting	399	57	304	43	703	16.1	74	11	431	61	198	28
Cutaneous manifestations												
Rash	5	83	1	17	6	0.14	1	17	3	50	2	33
Genitourinary manifestations												
Cystitis/Urethritis	24	80	6	20	30	0.7	0	0	19	63	11	37
Epididymo-orchitis	54	100	0	0	54	1.2	0	0	38	70	16	30
Reticloendothelial system												
Splenomegaly	125	67	61	33	186	4.3	15	8	104	56	67	36
Elevated liver enzymes	27	77	8	23	35	0.8	0	0	9	26	26	74
Hepatitis/Hepatomegaly	22	51	21	49	43	1	7	16	21	49	15	35
Jaundice	19	83	4	17	23	0.6	0	0	2	8.7	21	91
Pulmonary involvement												
Bronchitis* (cough, dyspnea, wheezes)	128	61	82	39	210	4.8	31	15	120	57	59	28
CNS involvement												
Meningitis	2	67	1	33	3	0.07	0	0	1	33	2	67
Depression/psychiatric manifestations	10	77	3	23	13	0.3	1	7.7	9	69	3	23

^ More than one symptom and sign could be encountered

** One adult male(20 years) was presented with pneumonia in 2007*

Splenic enlargement was a frequent feature among 124 (37%) patients of which 22 (6.5%) had hepatosplenomegaly. Hepatomegaly alone and lymphadenopathy were seen in 31 (9.3%) and 4 (1.2%) of the evaluated cases, respectively. Pulmonary involvement was predominantly presented as bronchitis (22.1%) but less often as pneumonia (0.3%).

Table 3. Frequency of clinical manifestations and laboratory findings on admission among evaluated brucellosis cases in DFH, 2007

Signs & Symptoms^	2007	
	No=335	%
Fever		
<37.2 (No fever)	36	10.7
37.2–	52	15.5
38–	146	43.6
39–	78	23.3
40+	23	6.9
Mean±SD38.3±0.9		
Night sweating	31	9.3
Sweating	91	27.2
Arthralgia, bone aches	84	25.1
Headache	151	45.1
Fatigue	92	27.5
Anorexia	26	7.8
Chills	52	15.5
Vomiting	5	1.5
Diarrhea	2	0.6
Lower back Pain	114	34.0
Toxic general look	113	33.4
Loss of weight	2	0.6
Tachypnea[a]	12	3.6
Bradypnea	12	3.6
Tachycardia[b]	43	12.8
Bradycardia	12	3.0
Hypertension[c]	54	16.1
Lymphadenopathy	4	1.2
Hepatomegaly	31	9.3
Splenomegaly	124	37.0
Tender Abdomen	7	2.1
Bronchitis	74	22.1
Pneumonia	1	0.3
BMI		
Underweight <18.5	25	7.5
®Normal 18.5–	116	34.6
Overweight 25–	134	40.0
Obese 30+	60	17.9
Laboratory findings		
Elevated ESR	60	17.9
Pus cells in urine	60	17.9
Anemia (<10 g%)	126	37.7
Leucopenia with relative lymphocytosis	7	2.1
Leucopenia (<4000/cmm)	21	6.3
Leucocytosis (>11000/cmm)	17	5.1

^More than one symptom and sign could be encountered

[a]The normal respiratory rate is 22-34 cycle per minute in age group 0-6 years, and 18-30 in children aged > 6 years and 12-20 in adults. [b]The normal heart rate is 80-120 beat per minute in age group 0-3 years, and 75-110 in children aged 3-6 years, 60-90 in adolescents, 60-100 in adults. [c]The normal blood pressure is 90/70 in age 3—4 years, 100/70 in 4-6 years, 110/70, in 6-18 years & 120/80 in adults. ® Reference category [d]Normal ESR 3-13 mm/hr

Laboratory investigations revealed an elevated ESR in more than two thirds of the cases (69.2%) that was not significantly related to elevated titers (P= 0.77) or fever (P= 0.25). Although pyuria was significantly higher among females as compared to male patients (15 (4.3%) versus 11 (3.3%) respectively), (P< 0.046), its detection in the later may denote epididymo-orchitis as a common genitourinary complication of brucellosis in men. Regarding the hematological changes, 55.7% of the examined blood samples were of normal profile. However, anemia was observed in 37.7%, leukocytosis in 5.1% and Leucopenia in 8.4% (30% were with relative lymphocytosis) of the cases (Table 4).

The co-morbidities included hypertension (4.5%), diabetes (3.6%), and co-infection with Bilharziasis (12.5%) and/or fascioliasis (0.6%). A number of patients reported relevant past history of brucellosis (4.2%), typhoid (1.5%), arthralgia (3.9%), prolonged fever (3.3%), besides positive family history of brucellosis (0.9%) and Pyrexia of Unknown Origin (PUO) among (9.3%).

4. DISCUSSION

This hospital based studyis in an attempt to explain reasons beyond the evolution and persistence of brucellosis infection in a highly burdened rural region in north Egypt in recent decades. Except for the study year 2007, the presented data were reviewed from historical medical records that most likely represent an under estimation of the disease levels. Moreover, data were not available for individual cases to track the actual history of exposure and the presenting clinical picture. It was possible only to abstract annual and monthly occurrences by age, gender, occupation, residence, and still to aggregate little about the presenting symptoms and treatment received. These thus hampered a better comparison of deviations in disease trends and explaining the increased burden over the study decades.

Analyzing hospital based data are not representative of the general population and hence may introduce biases. In fact, individuals in rural areas particularly those with low socio-economic standard may not have access or able to afford health care and medication costs. Moreover, cases presented to the private sector are not notified and thereby resulted in underreporting. Over the period 1997-2012, the total number of reported brucellosis cases in DFH was 4371 with a mean hospital based annual incidence of 58/100.000 inhabitants in the settlements of the reported cases (catchment area of DFH). This was consistent with previous records [7] and estimates reported by Jennings *et al*., in El Fayoum governorate (2002-2003) [14]. Meanwhile, it was much higher than incidence per 100.000 inhabitants reported in many other countries in the Middle East and the Mediterranean region [6,7,15]. A striking higher incidence amounting to 160/100.000 was reported in Syria in 2004. However, the actual disease incidence reported in the present study might be 3-5 times under estimated considering the misdiagnosis, reluctance of the patients in seeking medical advice, purchase of self-medications, and the failure of disease notification [7,14,16-19].

This study did not adequately define the disease burden among animals, since no records for animal statistics are available. Instead, the percentage of infected animals among the totally tested per year was estimated. The later does not necessarily reflect the total numbers of animals in the governorate since a considerable number of animals are being raised in households precluding an effort to draw out a true disease incidence. This may explain why human brucellosis was not related to seroprevalence among livestock in concordance with a survey conducted in 2007 in two Egyptian villages [20]. This relation was however, emphasized very recently by Bonfoh and co-workers who stated that in

Kyrgyzstan, 1% increase in the seroprevalences of sheep and small ruminant, increased human seroprevalence by 0.97 and 0.83%, respectively [21].

Intersect oral cooperation with the veterinary sector is therefore needed to provide necessary information on disease incidence among animals to better correlate with human brucellosis.

Two peaks of incidence of human brucellosis were described in 2002, and 2005-2006. This may denote the occurrence of epidemics that were controlled afterwards. In fact, the first peak was attributed to the reluctance of livestock owners to follow regular veterinary examination and quarantine of the infected farm animals. In the next year, the government adopted national disease control initiatives guided by FAO/ WHO/ OIE guidelines for Middle Eastern countries to extend animal health insurance coverage that ensured animal treatment, vaccination, regular surveillance, and healthy slaughter of infected livestock (test-and-slaughter policy) [13,22,23]. In case of slaughtering infected animals, generous compensation payment was granted (total compensations paid reached100.000 US dollars per year) besides allowing the livestock owners to release the meat in the market after condemning the offal. The situation was aggravated during 2005-2006 following a wide importation of infected herds of cattle from endemic areas in Sudan and Ethiopia as a part of a national food and security program.

Particular age predominance is not a feature of brucellosis rather than being strongly related to occupational exposure and risky behaviors. Age specific incidence clustering among middle ages (65% for age group 15-45 year-olds), in accordance with recent studies [14,18], was an obvious theme over years. Those under 15 were quite represented among cases probably due to their frequent consumption of contaminated milk and milk products or suggest their involvement in farming and flock management activities or accompanying their parents for helping on farms [16,24] since only 3% of this age group have cited their true occupation as farmers.

Infection among preschool children is necessarily linked to children feeding on infected animal milk and dairy products or their presence in a potentially contaminated environment.

The occurrence in adults was almost more frequent in males as in females although the male to female ratio was decreasing over years (2.6:1in 1997 versus 1.7:1 in 2012). In fact, men in rural communities tend to take more responsibilities in dealing with animals and engagement in farming. However, our results indicate that by time, more women are being engaged in agricultural and animal raising activities due to economic strains. Increased risk among children and women could also reflect difficult enforcement of hygienic measures for controlling unrestricted practices followed in commercializing and distributing milk and dairy products in endemic countries [25,26]. Consistent data were obtained in Saudi Arabia [27], Greece [28], Turkey [16], and Azerbaijan [29], while in Germany males were equally represented as females [30].

No shift of brucellosis from rural into urban communities has been demonstrated, thus the disease was persistently higher in rural areas where the agrarian population is generally in close contact with potentially infected farm animals, handle raw ruminant products, or use dried animal dung as fertilizers. Further risks are confounded by transhumance grazing, cattle mingling with mobile sheep and goat flocks, unrestricted animal movement and trade, poor farm hygiene, together with deficient health care infrastructure [26].

The seasonal influence on brucellosis incidence is usually demonstrated in temperate zones rather than tropical and subtropical regions where animal breeding extends throughout the year [26]. However, the temporal distribution of human brucellosis in Egypt over one and half decades demonstrated distinct seasonality in the monthly occurrence. It is noteworthy that the monthly occurrence may have been skewed since the diagnostic delay may extend up to a period of 4 month due to patients not immediately seeking medical advices. Farmers can delay their health care seeking because they are needed to harvest during cropping periods in the country. The incidence increased from May to August where it reached the highest peak in June. Meanwhile, the lowest occurrence was shown in winter. This marked seasonal variation with most cases occurring in spring and summer may coincide with the peak period for parturition or abortion among ruminants, and hence the highest level of exposure for those in direct contact with animals or handling animal products [25,26,29,31]. Interestingly, the pattern in 2007 depicted a striking change where the peak occurrence was recorded late in winter and decreased thereafter. This clustering may underlie a larger disease outbreak in the local livestock population. Similar findings related to brucellosis seasonality were recently described [16,17,27-30].

Farmers and housewives were equally and highly represented most likely due to their frequent engagement in farming, husbandry work, slaughtering, parturition, together with the frequent consumption of contaminated food. Certain occupations entailing direct contact with animals as for shepherds, and butchers are highly associated with increased risk of acquiring brucellosis infection particularly in developed countries [26,32,33]. However, such occupations were described only later in the second study decade.

Interestingly, brucellosis was recognized for the first time in this study in Egypt among military soldiers. This category was found to acquire infection during travel to endemic area [34]. Nevertheless, in the present study hazardous food consumption is incriminated for infection in the military.

With exception of farmers, the exposure risk was mainly non occupational and this was in full accordance with the findings in other epidemiological studies in turkey [16,35], Greece [28] and Saudi Arabia [27].

Foodborne transmission is an important source for contracting brucellosis in most human populations [25,36]. In Egypt, some commercially available dairy products such as white cheese are produced from unpasteurized milk by addition of rennet usually manufactured in non-licensed local factories and thus go with no surveillance. This type of cheese together with the homemade Karish cheese that were the most frequently consumed among the study population, concentrate large number of the organism and hence transmits the disease unless stored at cold temperature for at least six months before consumption (26). Consistent with other studies conducted earlier in Egypt [14,18], drinking unboiled fresh milk is uncommon practice owing to awareness of its hazards. Nevertheless, others traditionally have the concept that consuming raw milk is healthier and boosts immunity. Hard cheeses like Romy cheese that was less commonly consumed in the present study, is prepared by lactic and propionic acid fermentation and therefore harbours a minor risk [26]. In a recent case control study conducted in Alexandria-Egypt, Meky and co-workers scored ice cream purchased from street vendors as the most significant source of infection [18]. In Macedonia, 23.4% of brucellosis infections were found to be acquired through the alimentary tract. Studies conducted in Turkey [16,37,38] and Saudi Arabia [27], reported high percentage, 63%-95%), and 71.6%, respectively, of raw milk and dairy product consumption among their study populations.

The coincidental occurrence of similar cases in the patients' households or neighborhood reported in the present study could involve sharing the aforementioned risk factors rather than person to person transmission. In fact, in rural areas neighbours usually assist each other in executing different home activities or farm duties, assist in animal parturition, and share food stuffs particularly milk and homemade dairy products. John and co-workers stated in their epidemiological study conducted recently in Tanzania that the risk of contracting brucellosis increases the closer the households are [32].

Concerning the clinical picture of the disease, the period between presumed infection and the onset of overt disease varied between few days to 4 months. Typical form of acute brucellosis was presented with leading symptoms such as fever, headache, chills, malaise, night sweating, arthralgia and bone aches. The frequency of the symptoms decreased with the prolonged disease duration. Buzgan et al., reported a mean diagnostic delay of 1-6 month in 50% of the studied brucellosis cases albeit with a mean of 6 days in the remaining half [16]. Likewise, constitutional symptoms lasted more than 4 months among populations in central Greece with a mean diagnostic delay of 2.5 month [30]. These variations most likely reflect differences in various population characteristics, their practices, habits, traditions and occupation.

Persons in endemic areas and at high occupational risk frequently acquire subclinical infections and hence manifest mild symptoms unlike those encountering the disease occasionally [28].

Data on disease complications from hospital records in the first study decade (1997-2006) were not available. However, complications of brucellosis were common among the evaluated cases in 2007 and thereafter. Reticuloendothelial system involvements such as lymphadenopathy, splenomegaly, hepatomegaly, hepatitis, disturbed liver functions, and jaundice were documented to be as a consequence of bacterial sequestration and multiplication in monocytes and macrophages of the lymphatic organs [26,39]. Nevertheless, hepatic or splenic enlargement may be sequelaes of the co-morbid Bilharziasis observed in 12.5% of the evaluated cases in 2007. Hepatic involvement in the form of hepatitis was reported as frequent as 3% [38], 24% (16) and 40% with mild elevation of liver enzymes. Hematological involvement was recognized as anemia, leukocytosis and leucopenia with or without relative lymphocytosis. The presence of the later is an evidence for better adaptive humoral and cellular immunity involving the production of specific B- and T- (cytotoxic and helper) lymphocytes [26].

In accordance with previous records [16,37-39], the presence of pyuria among males assumes focal epididymo-orchitis whereas in females, pyuria may not be solely ascribed to brucellosis since urethritis and cystitis caused by other pyogenic bacteria are common urogenital manifestation in women [40].

Pulmonary involvement was frequently encountered among cases as bronchitis and only one case developed pneumonia, although pneumonia was reported to complicate up to 16% of brucellosis cases (15). Chest infection due to brucellosis occurs mostly through airborne inhalation of the organism contaminating abattoirs, animal yards and farm environments (15, 26) or if animals are kept in household [41].

Brucellosis rarely involves the gastrointestinal tract and causes ileitis or colitis (26). However, vomiting, diarrhea and constipation were frequent symptoms experienced by one fourth of the studied patients. The incidence of mucocutaneous manifestations,

cardiovascular involvement by endocarditis and CNS complication by meningo-encephalitis was frequently reported in the literature [4,15,16,30,33,35,37,38]. These complications were observed among our study population but not in other recent studies conducted in Egypt [14,18].

Despite being rare [42], psychiatric manifestations namely depression and personality disorders were better described among 13 cases of the 2008-2012 cohort. These patients were referred to the fever hospital for investigating a state of PUO and unexpectedly the neurological symptoms showed dramatic response to the conventional brucellosis treatment. This mean that quite a number of neurobrocellosis is overlooked and hence should be considered for differential diagnosis of neurological signs in endemic areas [42].

Titers ≥ 1:160 IU of brucella agglutinins were considered significant in our study. Nevertheless, brucellosis can't be excluded with titers below the cutoff value for patients in endemic areas. This highlights the need for bacterial or molecular isolations at the genus level to confirm the diagnosis [5,46]. Moreover, false negative SAT could occur early in the disease, or in the presence of blocking antibodies as well as in chronic and complicating infections [43,44]. The significant rise of mean brucella antibody titer late in the decade together with the presentation of elevated titers among older age groups (≥ 45 years) suggest the evolution of the antibody curves in patients who had previously acquired brucellosis during their life or having a relapsed infection [45]. In fact, the antibody levels in patients with previous history of contracting brucellosis remain elevated for a longer time, as a result of the sensitized memory cells of the immune system that respond vigorously upon repeated encounters of the microbe. On the other hand, low titers observed among younger ages may reflect recent and primary infection where longer time is required to stimulate naïve lymphocyte clones [44,45], or correlates with shorter clinical course, since sick children are brought to medical attention earlier than adults. The predominance of high fever and elevated ESR among the study population is an evidence for a good inflammatory and immune response against brucella evasion [46].

5. CONCLUSION AND RECOMMENDATIONS

Despite the effective and enforced control measures, brucellosis persists as a public health problem in Northern Egypt threatening both human and animal. This necessitates revision and adequate implementation of control strategy adopted for animals. Adequate follow up of human cases for at least 6 month should be conducted as a step in patient management to track relapses and complications. The private sector is encouraged to notify any suspected case of brucellosis and to emphasize record keeping to better delineating disease epidemiology.

The present work recorded sero-epidemiological variations in human and livestock brucellosis; however, the data obtained do not link definitive disease risk attributed to animal contact, food consumption or occupational exposure as required for better evaluation of the potential impact of different prevention and control strategies. Accordingly, more reliable study design will be helpful in the assessment of attributable risks related to different exposures.

The frequent exposures associated with well-defined risk factors enforces the need for extensive and sustained multidisciplinary efforts to emphasize food safety, educate people regarding potential food, farming and animal related exposures or risk factors and the importance of prudent animal vaccination, and personal and occupational hygiene. Further

and more extended multicenter studies and active surveillance programs coupling both humans and animals evaluations thus integrating efforts from the veterinary sector are needed for better recognition of the disease dynamics in Egypt and tracing further morbidity and mortality. This should integrate geospatial analytical techniques employing the geographic information system (GIS) mapping and mathematical modeling to identify potential areas burdened with high disease levels.

CONSENT

During the study period (1997-2012), data were abstracted retrospectively from inpatient logbooks and hospital annual records over a 16 years period. No human subjects work was undertaken in this stage, however strict anonymity of patients' data was considered. Concerning the study year 2007, an informed written assent was provided by all participants (parents or caregivers provided oral consent on behalf of children and minor participants) after explaining the aim and concerns of the study. The Data collection questionnaire forms were coded, respecting confidentiality and anonymity.

ETHICAL APPROVAL

The present study and the protocol adopted for data collection were approved by both the institutional research review board and Ethics Committee of the High institute of public Health affiliated to Alexandria University - Egypt.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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