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EPIDEMIOLOGICAL STUDY OF HUMAN BRUCELLOSIS IN THE KINGDOM OF SAUDI ARABIA; PRE- AND DURING COVID-19 PANDEMIC

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Abstract: Brucellosis is one of the most reported zoonotic diseases that affects human health with subsequent economic losses. Brucellosis is an endemic disease in countries in many regions such as the Kingdom of Saudi Arabia (KSA) in the Middle East. On 30 Jan 2020, the Director-General of the World Health Organisation (WHO) declared the novel coronavirus outbreak (later named COVID-19) a public health emergency of international concern. In KSA, on 2 March 2020, the first case of COVID-19 was confirmed. To contain the disease outbreak, partial and full suspension of public activities/curfew started in March and April. In this study, characterization of brucellosis in KSA from 2013-2019 (pre-pandemic), the year 2020 (pandemic control interventions'" year), and the year 2021is presented. Incidence data were obtained from the Ministry of Health's (MoH) records for laboratory-confirmed cases. Extracted incidence data were analysed according to the nationality of the patients (Saudi and non-Saudi), gender (male and female), age, health regions (20 throughout KSA), and months. From 2013-2019, there were 28073 (mean; 4010) cases of human brucellosis reported. In 2020 and 2021, there were 2372 and 2400 cases of brucellosis reported, respectively. The decrease in 2021, which continued after easing PCI restrictions, is worth noting. This represents a decrease of 59.15% of reported cases compared to incidence means for the period 2013-2019. Compared to other studies, misdiagnosis, delayed diagnosis, patients not seeking medical examination, and dedicating much of the health sector for COVID-19 patients are likely reasons for brucellosis reporting reduction. However, and due to lack of additional necessary data, it is not possible currently to conclude that PCI have (or have not) influenced reducing brucellosis in KSA. Additionally, and in comparison, to reported regional and global incidence rates of the disease, reported rates from 2013-2019 in KSA are likely to be underreported.

Key words: brucellosis; incidence; epidemiology; Saudi Arabia; COVID-19 pandemic

Introduction

Worldwide, in human, it is estimated that *Brucella* spp. cause 832000 cases (range: 338000-19500000) of brucellosis every year (1). Brucellosis is one of the most reported zoonotic diseases in Northern Africa, the Middle East, Central, and Southern America, Southern Mediterranean countries, and Central and South Asia. Incidences of more than 100 cases/100000 persons-year have been reported in many Middle Eastern countries (2, 3). Globally, brucellosis infections in livestock and human are caused by *Brucella abortus* (infecting cattle), *Brucella melitensis* (infecting small ruminants), and *Brucella suis* (infecting swine) (4).

In livestock, brucellosis is a highly contagious disease resulting in the transmission of infection to other species. The infection can occur through contact with aborted foetuses and its liquid and membranes (5). Brucellosis infection in human can be contracted via the consumption of raw milk and its products, aerosols inhalation, and direct contact with infected animals/discharges. Consumption of undercooked meat, breastfeeding,

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and sexual contact are less common routes of infection (6).

Acute brucellosis is characterized by undulant fever, sweating, fatigue, weakness, headache, rash, and myalgia with recovery in less than 60 days, and may precede to a milder sub-acute phase lasting 2 months to a year. Brucellosis can be in chronic form with symptoms that may include recurrent fever, fatigue, arthritis, spondylitis, and endocarditis (6, 7).

In brucellosis endemic regions, the disease has direct and indirect effects on animals farming and humans. Visible direct effects on animals include reduced milk production, reduce weight, veterinary care, and losses due to culling (8). Invisible effects include reduced fertility and transmission of disease to offspring and other animals. Indirect effects are related to trade losses, vaccination campaigns, and control programs. (9).

On human, and in addition to physical pain and emotional suffering, direct effects include health care costs and non-health care costs (e.g., accommodation and transportation). Indirect effects are on individuals (e.g., loss of productivity due to premature death, fertility complications, loss of workdays), and on population (decrease in workforce ability and decrease in food security) (9).

The novel coronavirus, which originated in Wuhan, China was declared a Public Health Emergency of International Concern by WHO on January 30th, 2020. The virus, which was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected almost 48 million people by the 1st week of November 2020. The pandemic caused by the virus (named COVID-19 pandemic) resulted in about 634 million confirmed cases and 6.594 million deaths by mid-November 2022. (10). Symptoms in patients with COVID-19 include influenza-like symptoms, headache, dry mouth, fatigue, and sore throat. Although that asymptomatic state has been reported for 20 % of individual infected with virus, up to 18% can develop severe disease needing intensive medical care (11).

For countries to contain the spread of the pandemic, WHO has recommended strategic response and control pillars. Detailed description of the application of the WHO's recommendations in KSA has been reviewed elsewhere (12). Measures taken to control and prevent additional COVID-19 infections in KSA included suspension of social gatherings (in prayer, in schools/colleges, malls/restaurants, and wedding/parties) and travel within, to and from the Kingdom. It also included mandatory mask waring and vaccination. Other social activities that bring people and animals (camel) to place of activity (festival, races) were also suspended.

The Kingdom of Saudi Arabia (KSA) is the largest country in the Middle East with 2 million square kilometres. As of 2017, the population of KSA is estimated at 32.55 million of which 37.3% are non-Saudis (13). In 2016, KSA imported food products, animals, and vegetables valued at $ 19.48 billion representing 15% of total imports. Food animals and poultry are estimated to be 13849779 and 53139159, respectively. In 2017, 7173776 local and 4888494 imported food animals were slaughtered for meat consumption (13). The demands for red meat and fishery products due to population growth are increasing yearly.

Human brucellosis is a notifiable disease in KSA. This descriptive epidemiological study was carried out to analyse human brucellosis trends in the country from 2013-2019 (pre-COVID-19 pandemic) and during the pandemic.

Materials and methods

Incidence data source

Brucellosis-related incidence data were obtained from the Ministry of Health's records (MoH) for the period 2013 to 2020 (14).

Incidence data according to nationality (Saudi and non-Saudi), gender (male, female), age (< 1, 1-4, 5-14, 15-44, and ≥ 45 years old), months, and health provinces were extracted, grouped, and analysed. Data analysis was based on five-year population averages of 21.12, 11.06, 18.36, and 13.83 million, Saudi, non-Saudi, male, and female, respectively.

Case definition

Only laboratory-confirmed cases and reported as "brucellosis" were considered in this study.

Health provinces information

The population data for health provinces in KSA were obtained records of the General Authority

for Statistics (13**)**. Riyadh, Jeddah, the Eastern, Makkah, and Medinah are the largest provinces in KSA with 63% of the Kingdom's total population. Makkah, Medinah, and Jeddah are in western KSA where Riyadh is in the central.

Literature search

The databases (PubMed, ScienceDirect, SpringerLink, and Google Scholar) were searched in September 2022, for brucellosis- related data for the period 1997 to 2022.

The search was performed to obtain articles that contain the terms Saudi Arabia and *Brucella* or brucellosis; prevalence, incidence, in articles' title and/or abstract.

Additional search was performed for "brucellosis", "human brucellosis" and "coronavirus", "COVID-19" for the period from April 30, 2020, to September. 30, 2022.

Statistical Analysis

Statistical analysis was perform using SPSS software version 20. In addition to analysing data to calculate means, percentages, and incidence rate, the two-tailed t-test was performed to test if there is statistical significance (at p-value: <0.05) differences in incidences according to nationality, gender, and age.

Results

In KSA, during 2013-2019, there were total reported cases of 28073 of human brucellosis. This represents average incidence rates (I.R) over 7 years period of 12.83 per 100000 people (Table 1) of the disease in the general population. The I.R for 2020 and 2021, were 7.59 and 7.68 per 100000 people, respectively. From 2013-2019, there were fluctuations in brucellosis incidences recording the highest numbers in 2018. A sharp drop of reported incidences was observed by 59% in 2020 and 2021.

Nationality and Gender

According to the nationality of patients, I.R for brucellosis was 11.97 for Saudi patients and 11.78 for non-Saudi patients (p-value: 0.0159) (Table 1).

Among male and female population, I.R for brucellosis was 16.78 and 6.71, respectively (p-value; 0.00001). Generally, brucellosis affected Saudi males (mean; 1663) and non-Saudi males (mean; 1419) more than Saudi females (mean; 857) and non-Saudi females (mean;70) (p-value; 0.00001) (Table 1).

Health Provinces

Total cases, means, I.R for brucellosis in KSA 2013-2019, and reported cases in 2020 and 2021 by health provinces are shown in table 2. For brucellosis, the highest I.R were 91.1, 62.19, and 58.38 in Northern border, Najran, and Bishah, respectively. It is worth noting that Riyadh, Jeddah, the Eastern, Makkah, and Medinah are the largest provinces representing 63% of KSA's population.

Table 1: Total human brucellosis cases, mean, and incidence rate according to nationality, gender, and age group in KSA

	2013	2014	2015	2016	2017	2018	2019	Mean	I.R	*P*-value	**2020**	2021
MALE	2318	2372	2583	3217	3598	4218	3271	**3082**	16.78	<.00001	**1847**	1795
FEMALE	946	738	650	845	1094	1237	986	**928**	6.71		**525**	605
Saudi	2186	1983	1783	2314	2802	3759	2870	**2528**	11.97	<.00159	**1432**	1811
Non-Saudi	1078	1177	1450	1748	1890	1696	1387	**1489**	11.78		**940**	589
Saudi male	1338	1243	1184	1539	1780	2615	1946	**1663**		<.000922	**945**	1234
Saudi female	848	690	599	775	1022	1144	924	**857**			**487**	577
Non-Saudi male	980	1129	1399	1678	1818	1603	1325	**1419**		<.00001	**902**	561
Non-Saudi female	98	48	51	70	72	93	62	**70**			**38**	28
<15	504	387	366	428	541	785	750	**537**	5.97	<.00001	**296**	377
≥15	2760	2723	2867	3634	4151	4670	3507	**3473**	15.6		**2076**	2023

Table 2: Reported human brucellosis cases by health regions, means of 2013-2019, and incidence rates (I.R) in KSA

Health region	Reported	Mean	2020	2021	I.R
Riyadh	2552	364	366	504	4.63
Makkah	1090	155	134	308	7.18
Jeddah	1063	151	128	158	3.48
Taif	2499	357	301	318	28.13
Medinah	1525	218	114	202	10.69
Qassim	4081	583	234	186	42.06
Eastern	1943	277	233	154	8.99
Ahsa	342	49	23	20	4.07
HafrBaten	1193	170	72	39	38.82
Aseer	1898	271	64	61	15.32
Bishah	1504	214	141	100	**58.38**
Tabouk	636	91	29	42	10.18
Hail	1411	201	219	120	29.68
Northern border	2296	328	52	32	**91.1**
Jazan	175	25	7	9	1.66
Najran	2486	355	188	87	**62.19**
Baha	819	117	20	10	25.16
Jouf	308	44	34	37	13.25
Qurayat	187	27	2	0	16.28
Qunfatha	66	9	11	12	3.09

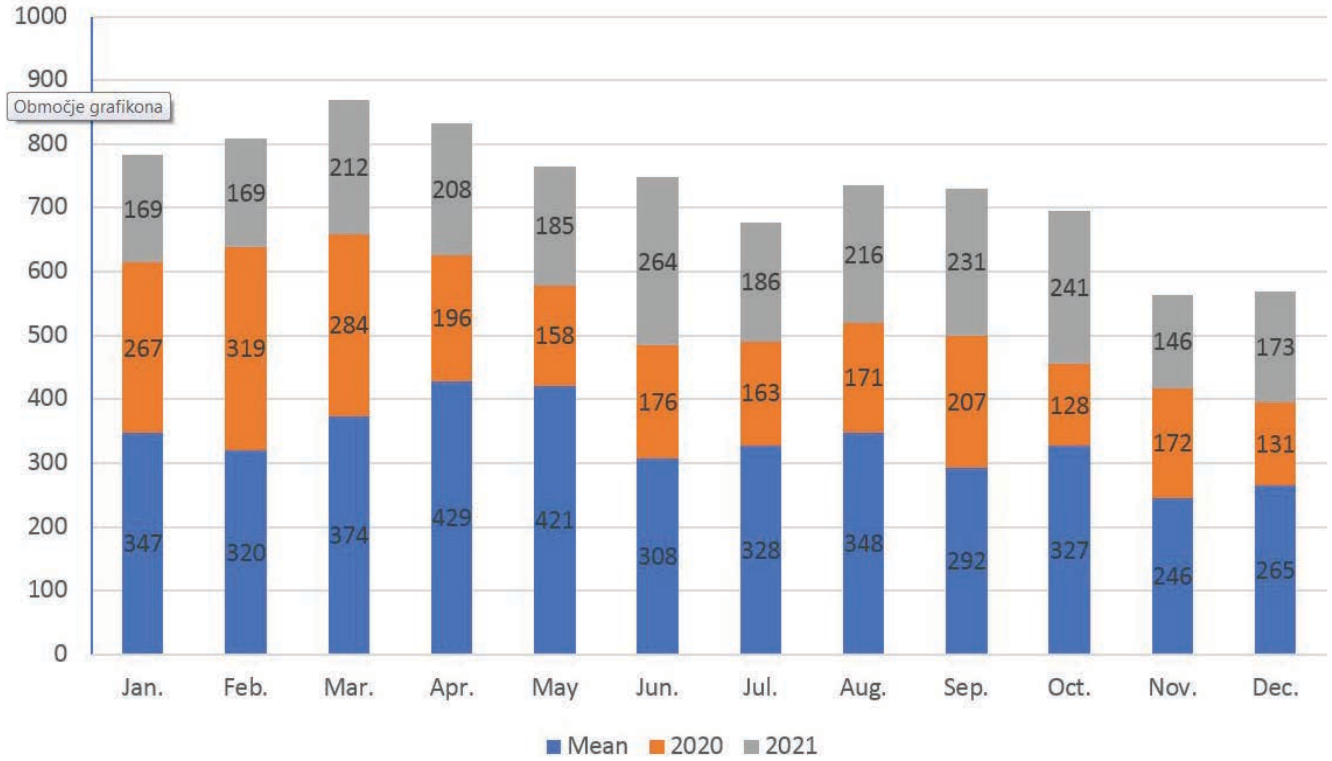

Figure 1: Means of monthly human brucellosis from 2013-2019 and reported cases in 2020 and 2021 in KSA

Age

Total reported cases according to age in 2013-2021, means and I.R (for 2013-2019) are shown in table 1. For children < 15 and population ≥ 15, I.R for brucellosis were 5.97 and 15.6 (p-value: 0.00001), respectively.

Seasonality

Means of monthly brucellosis incidence for 2013-2021 in KSA are shown in figure 1. The highest incidences for brucellosis were reported in March, April, and May with fluctuation in other month's incidences. The hottest months in 2013-2019 in KSA with average high temperatures over 40 c were June, July, and August. The average temperatures recorded were 24.7, 36.9, 40.9, 29 C for Jan-Mar., Apr.-Jun., Jul.-Sept., and Oct.-Dec. yearly quarters, respectively (13).

Literature search

A large brucellosis seroprevalence study covering different regions of KSA reported prevalence of 20%, 18.3%, 14.6%, 14%, and 11.6% in the northern, southern, central (15), eastern and western regions, respectively (16). Other studies showed a high prevalence in the northern (17, 18) and southern regions (19, 20, 21, 22). Active brucellosis cases ranged from 2.3-9.8% in seropositive patients (15, 21, 23). The estimated national brucellosis seroprevalence in KSA is 15% (15).

For effect of COVID-19 on diagnosis and reporting of human brucellosis incidence, few studies have been reported (24, 25). However, none of these studies had the necessary data to statistically conclude that COVID-19 control measures reduced the incidence of brucellosis.

Discussion

Sporadic cases were reported in KSA from 1956 to 1970 (26). With economic growth in the late 1970s, high numbers of cattle and sheep farms were established accompanied with the increase of animals import. The veterinary care at that time was not advanced to carry out required testing of imported animals and on the farms. This led to an increase in brucellosis in KSA (27). Serological testing for revealed that high numbers of the imported animal during Hajj season were infected (28). In 1980s, an increasing pattern of patients diagnosed with brucellosis was reported in main hospitals throughout KSA (29). This pattern was concurrent with an increase in brucellosis in farm animals. Unregulated animal imports, the spread of animal farms, raw milk consumption were the main factors contributing to this increase (30, 31). In 1999, a report about brucellosis in the Middle East ranked KSA as the highest country in the region affected by human brucellosis (32).

Regions most affected by brucellosis include the Middle East, the Mediterranean, Central Asia, Latin America and sub-Saharan African nations (2, 33). In Saudi Arabia, brucellosis is considered an endemic illness, whereas consumption of unpasteurized milk products is considered a risk factor (34).

In this study, total reported brucellosis cases were 28073 for the period 2013-2019 (Saudi; 58.9%, non-Saudi; 41.1%) and I.R was 12.83. The male (69.9 %): female (30.1%) ratio was 2.32:1. Most of the animals' farms' labour, veterinarians, and abattoirs workers in KSA are males. Males were generally affected by the disease more than females. This might be explained by the nature of brucellosis as an occupational disease and that males represent most workers dealing with animals (33). However, 30.1%% of the cases were among females. In KSA, in rural areas, female also participate in animal husbandry practices and may be exposed to contact with infected animals. Drinking of raw milk is another potential risk factor in such areas (33).

Among age groups, 15.46% of brucellosis cases were reported for < 15 years old population, and 84.54% for ≥ 15 years old. Infections in children might be as a sequence of contact with infected animals and consumption of raw milk in rural areas of KSA (33). This observation is similar to the reported prevalence in age groups in other studies where the disease affect > 15 years old population. (35, 36, 37).

Geographically, and within KSA, brucellosis I.R were higher in three health regions in the northern, central, and southern regions characterized by the presence of high animals farming projects and tribal population involvement in animals' husbandry. Demographic, occupational, and socioeconomic factors contribute to brucellosis incidence variations even within the same country (32). In KSA, disease's

full epidemiological and populations at risk may not receive the required characterization especially in small rural areas (33).

Consistent with other studies (17,18, 36), there were seasonal fluctuations in brucellosis incidence in KSA with an increase from February to May. During these months, there is an increasing pattern in birth in sheep and goat herds in the country.

Through a literature search, brucellosis seroprevalence in KSA is 15% (15). Brucellosis reported prevalence in neighbouring countries were 8% in Jordan (37), 6.7% in Yemen (39), 12% (40) and 24.8% in Kuwait (41).

Although brucellosis causes economic losses in livestock and adverse and prolonged health effects on human, the disease in patients is not easily recognised. The disease in human is characterised by non-typical influenza-like symptoms, fever, sweating, and fatigue (6, 7). Interestingly, such non-typical symptoms are observed in patients with COVID-19. Due to such symptoms similarity and pressure of time and resources dedication to COVID-19 patients, cases of brucellosis being initially diagnosed as COVID-19 have been reported (23, 24). Therefore, the decrease in disease reporting, during the pandemic might be attributed to misdiagnosis situations.

Brucellosis in human can develop a chronic form accompanied by recurrent fevers, arthritis, neuropathies, and myocarditis (23, 24). Delayed diagnosis and subsequent timely treatment may result in the proceeding into chronic brucellosis.

Brucellosis diagnosis was delayed by up to 52 days (42). Patients' education, income, insufficient diagnostic capability, and age of patients are factors leading to delay of diagnosis (43). These factors are thought be more complicated during COVID-19 pandemic. This is due toa added pressure on health systems and patients not seeking medical assistance because of contracting the viral infection. Therefore, reported incidence of brucellosis may not accounted for underreporting due to delayed and/or misdiagnosed.

In brucellosis endemic developing countries, national passive surveillance data, which rely on laboratory confirmation and clinical definition, may underestimate the disease true health burden. Underestimations by up to 18 folds have been reported (2, 44). The situation of underestimation extends to developed countries where disease cases are misdiagnosed, mismanaged, or not included in the official system database (33).

To estimate a disease incidence in a country or a region, numerical values (multiplier) are synthesized to construct a surveillance pyramid. The values are assigned for asymptomatic infection, not patients not seeking medical care, underdiagnosis, and underreporting. The accuracy of obtained values depends in part on the availability of laboratory infrastructures, trained personnel, and on data supplied by authorities investigating the disease in question. To estimate a disease 's incidence, and where a country-specific's multiplier is not available, it is possible to apply multiplier of neighbouring country or of the region to calculate a more accurate disease incidence (42,43).

A systematic review of disease frequency study (33) reported wide variations in brucellosis incidence in the Eastern Mediterranean Region (EMR) region including KSA with a reported incidence of 100 and 134/100,000 (3, 32). Another data synthesis study (1) estimating the burden of brucellosis among other 21 diseases at the regional and global level reported brucellosis median rate of 33/100,000 people (range: 10-187) and 6 (range: 2-132) as estimations for the EMR and globally, respectively. To estimate brucellosis incidence in EMR including KSA and some neighbouring countries, and to account for underreporting, a mean of 5.4 (range: 1.6-15.4) was used.

The disability-adjusted life years (DALY) metric measures the burden of disease (BoD) in a population. It accounts for not only premature mortality but also disability caused by a specific disease or injury. DALY, which is a time-based indicator, measures years of life lost because of premature mortality combined with years of life lost because of time lived suffering from the disease (45). Attempting to measure DALY for brucellosis in KSA based on the reported incidence rates will result in measurement (3.69 DALY/100000 people) which is well below regional (median 23 DALY/100000 people) values for the disease (1).

Conclusions

During 2020, and toward 2022, reported incidences of human brucellosis in KSA were 59% compared to means of 2013-2019. To statistically describe the reduction, there is a need for more incidence data for at least the coming year of 2022 and 2023. In KSA, brucellosis prevention measures

as in countries where the disease is endemic shall focus on disease eradication and prevention in livestock and human. Diagnosing, treatment/culling, and vaccinating animals help in reducing the spread of disease. Local authorities in KSA will need to collaborate with academic institutes to plan and co-supervise prevention campaigns and carry out research to accurately estimate the disease' burden throughout the country.

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