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Trends of Reported Human Cases of Brucellosis
Kingdom of Saudi Arabia, 2004 – 2012

By

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MASTER OF PUBLIC HEALTH

GLOBAL HEALTH

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Trends of Reported Human Cases of Brucellosis
Kingdom of Saudi Arabia, 2004 – 2012

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Dedication

For my father and my brother, Dakheel and Dr. Abdulsalam, who have always stood behind me, promoting my success, pushing me forward to achieve my dreams, and encouraging me to pursue my interests. I hope I have done you proud.

For all my brothers and sisters, who have believed in me and shared all my life's moments. You don't know the extent of my gratitude. All I can say is thank you.

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Abstract

Objectives: Human brucellosis is an important zoonotic disease and is especially concerning in the Kingdom of Saudi Arabia (KSA), where livestock importation is significant. We analyzed reported human brucellosis disease trends in KSA over time to help policymakers understand the magnitude of disease and guide the design of prevention and control measures.

Methods: Using data from the national registry of reported human brucellosis cases from the Infectious Disease Department (IDD) of the KSA Ministry of Health (MoH), we calculated the cumulative numbers by age group and month of year from 2004 – 2012. We also determined the trends of incidence rates (IRs), by gender and nationality from 2004 – 2012 and by region from 2007 – 2012. Population data came from the Ministry of Economy and Planning, Central Department of Statistics and Information.

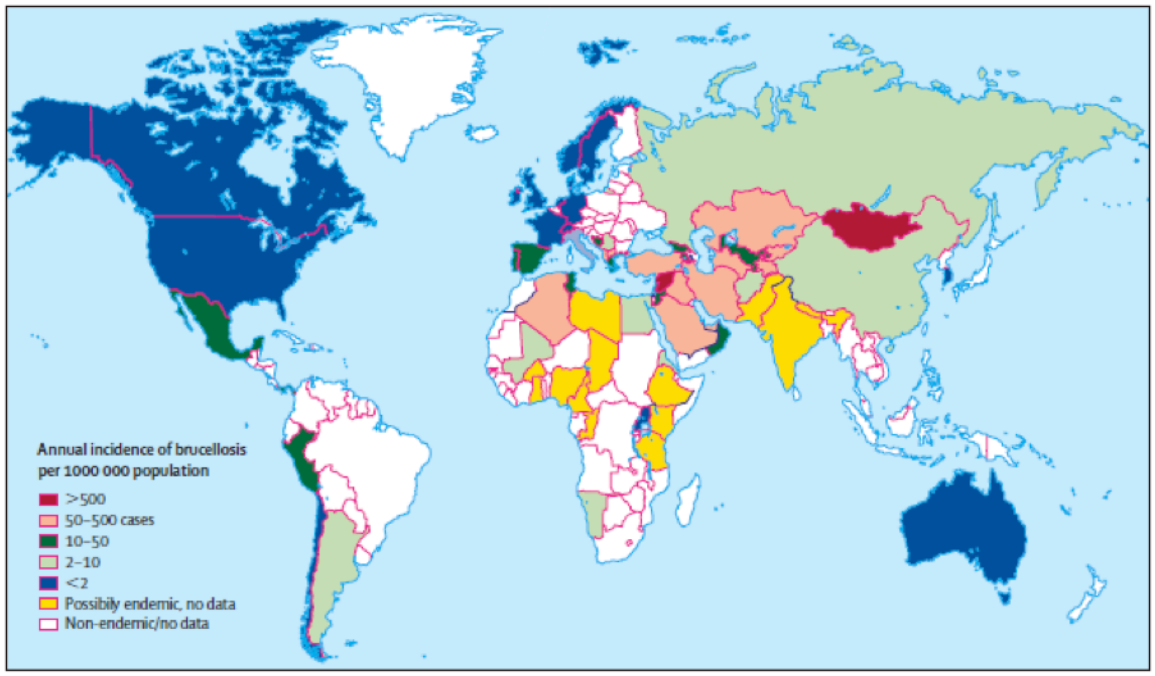
Results: There were 37, 477 reported human brucellosis cases from 2004 – 2012. Persons 15 – 44 years of age had greater cases (19,130) than any other age group. The IRs (per 100,000 population) significantly decreased from 22.9 in 2004 (95% CI=22.3, 23.5) to 12.5 in 2012 (95% CI=12.1, 13). Males had a significantly greater IR than females. Males had an IR of 23.4 (95% CI=22.6, 24.3) and females had an IR of 22.3 (21.4, 22.2) in 2004, while in 2012, males had an IR of 15 (14.5, 15.7) and females had an IR of 9.3 (8.8, 9.8). Most cases were reported during spring and summer seasons (from March to July). In 2012, there were 536 cases reported in May, while only 225 cases were reported in January. The IR of Saudi citizens was significantly greater than that of non-Saudis, but this difference shrank over time. Saudi citizens had an IR of 27.1 (95% CI=26.4, 28) and non-Saudis had an IR of 11.5 (10.7, 12.4) in 2004, while in 2012, Saudi citizens had an IR of 13.2 (95% CI=12.7, 13.7) and non-Saudis had an IR of 11.2 (95% CI =10.5, 11.9). From 2007 – 2012, the IRs of Al-Qassim, Aseer, and Hail were in the highest 25th percentile, while the IRs of Al-Jouf, Jazan, Makkah, and Al-Riyadh were in the lowest 25th percentile.

Conclusion: Young, male Saudi citizens living in highly endemic areas were at greatest risk of acquiring brucellosis. We recommend vaccinating susceptible animals against brucellosis, enforcing animal importation protocols, and increasing the public's awareness of preventive measures. Additionally, the MoH, along with other responsible parties such as the Ministry of Agriculture, should enhance and further develop the national brucellosis surveillance program.

Chapter 1: Introduction

Brucellosis is a major bacterial zoonotic infectious disease, meaning that infected animals are the source of human infection. This disease contributes to the global health burden. Annually, there are > 500,000 reported human brucellosis cases (1)(Figure 1). Since brucellosis affects humans and animals, it negatively impacts the economic, agricultural, and health sectors. Its effects are influenced by its worldwide distribution: it is rare in most industrialized countries and more common in developing ones. However, the threat exists that brucellosis's reach will extend globally, as countries' borders do not prevent diseases from spreading; countries like the Kingdom of Saudi Arabia (KSA), which hosts a myriad of travellers and imports much livestock, are especially at risk. Its emergence can be expected in any country that doesn't apply critical disease prevention protocols. In KSA, which represents a significant focus of human brucellosis, this disease still constitutes a major health problem.

Figure 1. World Incidence of Human Brucellosis, 2006 (1).



Brucellosis, also known Malta fever, undulant fever, or Mediterranean fever, is a systemic infectious disease that is transmitted to humans through the ingestion of raw or unpasteurized milk and cheese from animals infected with *Brucella* organisms. Brucellosis is frequently transmitted in laboratories. Infections usually occur when a laboratory technician accidently inhales the bacteria. Bacteria can be transmitted from animals to humans through ingestion, inhalation, or via injured skin or the mucous membrane. Sheep, cattle, camels, pigs, and dogs are the animals most commonly infected (2). Brucellosis can also be transmitted person-to-person by someone who has come into

contact with infected animals, but this is rare. Another person-to-person route is from infected mothers to their babies. Other less common transmission routes include the ingestion of the undercooked meat of infected animals and blood transfusions.

The *Brucella* group includes the species *B. abortus, B. suis, B. ovis, B. canis, B. neotomae*, and *B. melitensis,* the last being the one most responsible for human brucellosis (BP26). *B. abortus* and *B. suis* are also fairly common among human brucellosis cases. Recently, marine mammal species such as seals, porpoises, dolphins have been found to have *B. ceti* and *B. pinnipedialis*, which have been isolated from humans (3, 4). The gram-negative *coccobacilli* are intracellular bacteria that multiply inside immune cells, becoming a granulomatous infection. Though rarely fatal, brucellosis may lead to numerous systemic complications affecting the musculoskeletal, genitourinary, and nervous systems. Fever is the most common feature of brucellosis; other significant symptoms include joint pain, anorexia, malaise, weight loss, splenomegaly, and cardiomegaly. Like syphilis and tuberculosis, human brucellosis has a wide spectrum of clinical manifestations, and clinical diagnosis depends on the stage of disease. A blood culture test is the gold standard of diagnosis, and other imaging tests such as x-rays and computed tomography (CT) can be used to diagnose brucellosis' systemic complications (5).

KSA is a country that has undergone rapid modernization over the last 40 years. In the midst of this, some people continue to maintain their traditions. One of the main features of life in KSA is the combination of the modern and the traditional. Raising camels is an essential part of the history of KSA, and camel owners are proud of their herds and proud to take care of their dynasties. Also, they derive many benefits from camels, including the consumption of their milk and meat. Those who own and tend camels usually prefer to drink the milk when it is frothy and warm, directly after squeezing it from a mother, in its unpasteurized state. Passersby also commonly enjoy camel milk, preferring to get it directly from shepherds, at its most fresh. People who live in rural areas often raise sheep and goats and serve their unpasteurized milk to guests.

Generally, the nomadic lifestyle has decreased over the years, but people who carry on those traditions have retained a fondness for camels, goats, and sheep, and they believe that boiling an animal's milk takes away its taste and goodness. However, anyone who drinks unpasteurized milk is at risk of getting brucellosis, as *Brucella* organisms are concentrated in the milk of infected animals.

Brucellosis can be transmitted to people who are exposed to infected meat and products of infected animals. Ritual meat eating is a central part of Islamic practice and Saudi Arabian culture. KSA is the seat of Islam, home of the Two Holy Mosques, Haram Mosque and the Prophet's Mosque,

which are precious to every Muslim. Millions of pilgrims flock to these mosques to perform the Hajj rituals. Part of this ritual is the slaughter of goats, sheep, or other types of cattle. Muslims who are not doing Hajj also have cattle slaughtered as part of the observance of the Hajj Holy days. In 1998, 3.8 million animals were imported, including goats, sheep, camels, and, cows (6). In 2010, the total value of imported live animals and animal products was $2,702,316,709 (7). Last year during Hajj season, 3.2 million goats, sheep, camels, and other cattle filled the Saudi markets. Of those livestock, 75% were imported and 25% were raised locally (8).

Brucellosis is endemic in KSA and classified as a notifiable disease by the Saudi Ministry of Health (MoH). Local health departments must notify the Infectious Disease Department at the MoH when cases are suspected or confirmed. A blood culture test can detect the disease, and this is how 40 to 70% of the cases are diagnosed; others are mainly diagnosed with a standard agglutination test (9). Brucellosis cases present mainly with bouts of fever and musculoskeletal pain. Because of the non-specific manifestation of its presentation, brucellosis diagnosis is challenging, which likely leads to underestimation and underreporting of brucellosis cases (5). Endemicity varies across the regions of KSA: it is higher in rural areas, where people live in closer proximity to animals (10).

Epidemiologic statistics show significant differences in the distribution of brucellosis across the globe; in some countries brucellosis is rare, while in others, it greatly affects the status of population health. Generally, it is rare in industrialized countries and more common in developing countries. In the U.S. in 2002, the incidence was 100 cases, and in Australia, it was 40 cases (11, 12). In most South American countries, this disease is underreported and underestimated. About 40% of Latin Americans live in regions where brucellosis is endemic in the reservoir animals. In Ecuador, the cost of brucellosis is high; the annual economic loss to cattle producers is $5.5 million (13). The organism *b. abortus* is the most common circulating agent in Latin America. There are around 2000 new cases of human brucellosis annually in Mexico (14).

In recent years, the incidence has risen dramatically in China, especially in the province of Inner Mongolia, which is considered one of the main foci of human brucellosis globally. In 2010, the total number of cases reported in China was 33,772, and almost half of those (16,224) occurred in Inner Mongolia. The incidence was 2.56 per 100,000 (15).

In 2006, Syria had the highest incidence worldwide (Figure 1), with 1,603 cases per 100,000,persons followed by Mongolia (605.9 cases), Kyrgyzstan (362.2 cases), Iraq (287.4 cases), and Turkey (262.2 cases). In the Gulf region, Kuwait had 33 cases per 100,000 and the United Arab Emirates had 41 cases (1).

Worldwide, there has been a noticeable decrease in the incidence and prevalence of

brucellosis; still, it remains a public health concern for local and international health agencies. Most cases occur during the spring and summer seasons among those aged 20 – 45 (16).

KSA had the highest incidence of human brucellosis in the Middle East during the late 1990s, but the rate has decreased in recent years due to the implementation of regulations by the Saudi Ministry of Agriculture that make brucellosis vaccinations for cattle compulsory, the improved control of imported livestock, and the enhanced cooperation between veterinarians and the public health sector (10, 17). Even though its incidence has dropped, brucellosis is still considered endemic in KSA.

This study will explore the trends of human brucellosis in KSA over 9 years (2004 – 2012) across all of the regions, taking into account occurrences per month as well as the incidence by gender, age group, and nationality.

Chapter 2: Literature Review

Since the discovery of brucellosis, researchers have been devoted to studying the issues surrounding it: its epidemiology, mode of transmission, causes, and management. Brucellosis was discovered in the 1850s in Malta after the Crimean War; a medical team in the British army played an important role in its discovery. In Malta in 1851, Dr. Jeffery Marston described many cases with mysterious "undulant fever," a condition characterized by a rising and falling fever during the four to six weeks of the disease. In 1887, Dr. David Bruce (after whom brucellosis was named), Lady Bruce, and Dr. Guiseppe Scicluna recognized the shape of this micrococcus bacteria. Soon after, Maltese and British public health specialists recognized the bacteria causing this disease in serum and milk by applying and cultivating the bacteria in an agglutinin test to distinguish this disease from typhoid fever. The most renowned test was Zammit's test. Dr. Zammit, *et al.* showed that this zoonotic disease was transmitted through infected goat milk, and banning the use of goat milk was recommended in 1904. However, in Malta, milk pasteurization was not introduced until 1930, when production of cheap, sterile containers became possible. In 2005, after nearly a century, Malta was declared free of brucellosis (18).

In antiquity, according to University Museum of Chieti, Italy, the first case of brucellosis affecting the human skeletal system occurred during the Middle Bronze Age (2.3 – 2.5 million years ago). There were many cases of brucellosis during the era of the Roman Empire and the Middle Ages as well (20). Today, brucellosis is the most common zoonotic disease globally—although it has been eradicated in some countries. It is a notifiable disease and reported in at least 56 countries. Globally, 60% of emerging diseases are zoonotic in nature. Globalization and international travel systems, along with socioeconomic development, improved sanitation, and political support have played an important role in changing brucellosis trends in the past 25 years. Brucellosis has decreased in developed countries, and yet it has remained a significant imported disease, persisting in developing countries, especially those in the Mediterranean and Middle Eastern regions (19, 21).

Between 1993 and 2003, the number of brucellosis cases decreased dramatically in countries such as Portugal (from 1,166 to 139), Spain (from 2,842 to 642), Italy (from 1,120 to 631), France (from 127 to 33), and Jordan (from 750 to 159). Over this period, the number of cases increased dramatically in Syria (from 1,391 to 23,297), Turkey (from 6,795 to 14,572), Egypt (from 256 to 4,335), and Algeria (from 1,616 to 2,783 cases) (19).

Brucellosis is classified as an occupational disease because abattoirs, veterinarians, shepherds, and laboratory personnel who deal with brucellosis cases are at risk (19). As mentioned, the incidence rate of brucellosis varies among countries worldwide and within a single country's

regions. After reviewing 2,385 articles from 1990 to 2010 in a systemic review study, researchers found that the incidence rate per 100,000 in Iraq was 52.29 cases in rural areas and 268.81 cases in semi-rural areas. In Egypt, in two different rural areas, the incidence rates were 0.28 cases and 70 cases per 100,000 person-years. In KSA, the rate was 137.61 per 100,000 person-years. In contrast, the incidence rate in Greece was 4 cases in the western area and 32.49 cases in the central area, while in the U.S., the incidence rate ranged from 0.02 – 0.09 cases in different studies. In neighboring Mexico, the incidence rate was 25.69 cases (22).

In KSA, the history of reported cases of brucellosis can be traced back to 1956, when Saudi Aramco Health Center in the Eastern Province conducted a study of brucellosis among their employees that spanned to 2007. They found 39 sporadic cases from 1956 – 1982. During 1983 and 1984, when brucellosis was recognized as a major public health problem, there were 48 new cases reported. Younger men were at higher risk than older people because they traveled and were more exposed to infected animal milk and its products. Also, older women were at higher risk than younger ones because they would tend to the livestock while the younger women took care of their children during their childbearing years. The number of brucellosis cases increased over time; there were 65 cases in 1985 and 193 cases recorded in 1987, the highest number. In 1983, the incidence rate was 13 cases per 100,000 population. The rate started to rise in 1986, reaching 51.3 cases per 100,000, and it peaked in 1987 at 70 cases per 100,000 population. Improving statistical analysis techniques and hiring skilled personnel might be the reason behind the discovery of more cases (23, 24).

After 1987, there was a dramatic decrease in the incidence rate, which fell to 25 cases per 100,000 population in 1992 and dropped to <10 cases by the mid-1990s. Since that time, the incidence rate has fluctuated (24).

A study was conducted in 1997 to evaluate the prevalence of brucellosis in the Medina region of KSA. This cross-sectional, multistage survey study was done on 500 random households; a total of 3,917 participants were tested by the tube agglutinin test (TAT) and the 2-mercaptoethanol test (2ME) to detect both acute and chronic brucellosis. The prevalence was 2.6%, which is considered high. The researcher identified many factors that play an important role in the disease's prevalence, such as drinking raw and unpasteurized milk and coming into contact with animals (taking care of livestock, handling an animal's placenta membrane, and butchering raw meat) (25).

Brucellosis may have several potential adverse effects on pregnant women. The disease can induce spontaneous abortion, although this is more common in animals than humans due to the absence of erythritol in the human placenta and fetus. Also, the presence of anti-brucella activity in

human amniotic fluid decreases the likelihood of abortion. A study was conducted on 92 pregnant women infected with brucellosis in Saudi hospitals from 1983 to 1995. The study showed that the cumulative incidence was 1.3 cases per 1000 deliveries, and the incidence for spontaneous abortion in the first and second trimesters was 43%; intrauterine death in the last trimester was 2%. In fact, these figures reflect a high percentage of spontaneous abortion among pregnant women, and researchers recommended delivering immediate therapy with antimicrobial agents. Premature delivery, miscarriage, and intrauterine death cases have all been reported as consequences of having brucellosis during pregnancy, but the brucella organism's role in causing abortion is not more prominent than that of other bacteria (26-29).

Brucellosis is one of the most common laboratory-acquired infections in endemic and non-endemic countries: 2% of laboratory-associated infection outbreaks are attributed to brucellosis. The attack rate has ranged from 30 - 100%, depending on the source at the moment of exposure and the physical location of the workers (30). Out of 667 laboratory workers in Turkey, 38 (5.8%) had a history of laboratory-acquired brucellosis. Being male (odds ratio: 2.1; 95% CI = 1-4.5; $p = 0.042$) and working with the brucella bacteria (5.1; 95% CI = 2.3-11.6; $p < 0.001$) were found to be the main independent factors that increase the risk of laboratory-acquired brucellosis infection on multivariable scale (31).

In KSA, brucellosis was the top-ranked (22.5%) reportable communicable disease in National Guard communities in 1998. From 1991 to 2000, there were seven laboratory-acquired brucellosis infections reported among expatriate hospital employees: six of them were antimicrobial technologists and one was a pathologist. Although class II laboratory biosafety measures were applied, the brucellosis cases persisted among laboratory personnel because of the large number of infected specimens that they handled (17,500 annually) (32).

Within families, there could be a single source of infection: family members usually drink the same infected milk. By looking at the index case and its relation to members of one family, we may assume a relation between them. A study was done in KSA to show the relationship between an index case and the case's family members; the researchers did a serological screening of the family members of the index case and found that most of the index cases were young Saudi males (48%) with acute brucellosis. Serological evidence of brucellosis infection for all household members was identified in 13%. The source of infection for the index case and other family members was the ingestion of raw milk; 71% of all household members reported that they consume milk (33).

Since 1983, the animal infection rate has been tracked; it has exceeded 20% in sheep and goats. In Al-Madina region, the animals most responsible for brucellosis transmission in 1997 were goats, sheep, camels, and cows. Humans acquired the infection from animals most commonly through the handling of placenta membranes of infected animals, breeding infected ones, drinking raw or unpasteurized milk from an infected animal, milking infected animals, and dealing with infected animal products, such as raw meat (25).

Brucellosis is still affecting the economy and livestock of KSA due to its high prevalence in humans and livestock. In 1989, the overall prevalence in camels was only 8% (212 infected camels from 2,630 tested serum samples) (34).

Gap in the Literature

The history, epidemiology, modes of infection transmission, causes, diagnosis, and management of brucellosis have been studied in many scientific papers, as the previous review has shown. Worldwide, the incidence of brucellosis has decreased, especially in developed countries, but it remains a threat to people's health, their livestock, and the economy in most developing countries, especially Mongolia and those in South America, the Mediterranean, and the Middle East.

Because the incidence has fallen worldwide, the amount of literature covering it has also decreased. The last WHO report on brucellosis was published in 2006; in contrast, there was an abundance of literature before 2000. However, brucellosis is re-emerging as the most common zoonotic disease globally.

In KSA, considered one of the biggest importers of livestock, brucellosis remains a problem that challenges the public health, veterinarian, and agricultural departments. As seen above, this disease has been studied in most endemic regions in KSA, especially over the last century. Most studies present descriptive epidemiology features of this disease and its relation to the significant factors affecting incidence such as age, gender, occupation, and location. Also, within the academic literature, there have been systematic review studies showing the national incidence of brucellosis in KSA and other affected countries. However, for the most part, those studies have not examined brucellosis's significant variables concurrently—gender, distribution by age group, frequency by month, and distribution across regions. Although a few studies have looked at brucellosis throughout KSA, no study has shown the national incidence with the aforementioned variables.

In the present study, the trends of brucellosis will be explored in all regions of KSA over a 9-year period (2004 – 2012) taking into account the variables that play significant roles in the epidemiological features of human brucellosis: age group, gender, time of infection's occurrence, and nationality.

Chapter 3: Manuscript

Trends of Reported Human Cases of Brucellosis
Kingdom of Saudi Arabia, 2004 – 2012

By

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A. Introduction

Brucellosis is one of the major bacterial zoonotic infectious diseases, meaning that infected animals are the source of infection. This disease increases the burden on public health globally. Annually, there are more than 500,000 new brucellosis cases (1). Since brucellosis affects humans and animals, it negatively impacts the economic, agricultural, and health sectors. Its effects are influenced by its worldwide distribution: it is rare in most industrialized countries and more common in developing ones. However, the threat exists that brucellosis's reach will extend globally, as countries' borders no longer prevent diseases from spreading, especially in countries like KSA that host a myriad of travellers and import much livestock. Hence, its emergence can be expected in any country that doesn't apply critical disease prevention protocols. In KSA, which represents a significant focus of human brucellosis, this disease still constitutes a major health problem.

Brucellosis, also known Malta fever, undulant fever, or Mediterranean fever, is a systemic infectious disease that is transmitted to human through the ingestion of the unpasteurized or raw milk and cheese of animals infected with *Brucella* organisms (e.g., sheep, cattle, camels, pigs, and dogs) or with people who have come into contact with infected animals. Ingestion of undercooked meat of infected animals is an uncommon route of transmission. It is considered one of the most common laboratory infectious disease transmissions. Infections usually occur when a laboratory technician accidently inhales the bacteria (2).

KSA is a country that has undergone rapid modernization over the last 40 years. In the midst of this, some people continue to maintain their traditions. Combining the modern and the traditional is considered one of the main features of Saudi Arabian life. Raising camels is an essential part of the history of KSA, and camel owners are proud of having them and taking care of their dynasties. Also, they derive many benefits from camels, including the consumption of the milk and meat. Those who own and tend camels usually prefer to drink their milk when it is frothy and warm, directly after squeezing it from a mother, in its unpasteurized state. Passersby also commonly enjoy camel milk, preferring to get it directly from shepherds, at its most fresh. People who live in rural area often raise sheep and goats and serve their unpasteurized milk to guests.

KSA is the seat of Islam, home of the Two Holy Mosques, Haram Mosque and the Prophet's Mosque, which are precious to every Muslim. Millions of pilgrims flock to these mosques to perform the Hajj rituals. Part of this ritual is the slaughter of goats, sheep, or other types of cattle. Muslims who are not doing Hajj also have cattle slaughtered, as it is part of the observance of the Hajj Holy days. In 1998, the total number of livestock importation in this year only was 3.8 animals including goat, sheep, camel, and cows (6). In 2010, the total cost of live animals and animal products

importation was $2,702,316,709(7). Last year during Hajj season, 3.2 million goats, sheep, camels, and other cattle filled the Saudi markets. Of those livestock, 75% were imported and 25% were raised locally (8).

Brucellosis is endemic in KSA and classified as a notifiable disease by the Saudi MoH. Local health departments must notify the Infectious Disease Department of the MoH when cases are suspected or confirmed. A blood culture test can detect the disease, and this is how 40 to 70% of the cases are diagnosed; others are mainly diagnosed with a standard agglutination test (9). Brucellosis cases present mainly with bouts of fever and musculoskeletal pain. Because of the non-specific manifestation of its presentation, brucellosis diagnosis is challenging, which likely leads to underestimation and underreporting of brucellosis cases (5). Endemicity varies across the regions of KSA: it is higher in rural areas, where people live in closer proximity to animals (10).

Worldwide, there has been a noticeable decrease in the incidence and prevalence of brucellosis; still, it remains a public health concern for local and international health agencies. Most cases occur during the spring and summer seasons among those aged 20 – 45 (16).

KSA had the highest incidence of human brucellosis in the Middle East during the late 1990s, but the rate has decreased in recent years due to the implementation of regulations by the Saudi Ministry of Agriculture that make brucellosis vaccinations for cattle compulsory, the improved control of imported livestock, and the enhanced cooperation between veterinarians and the public health sector (10, 17). Even though its incidence has dropped, brucellosis is still considered endemic in KSA.

This study will explore the trends of human brucellosis in KSA over 9 years (2004 – 2012) across all of the regions, taking into account occurrences per month as well as the incidence by gender, age group, and nationality.

B. Methodology

Brucellosis data were collected from the Infectious Disease Department (IDD) at the KSA MoH, while population data were collected from the Saudi Central Department of Statistics and Information. The estimated population data by region were taken from Ministry of Finance because it was not available from the Saudi Central Department of Statistics and Information. The researcher is familiar with the process of reporting brucellosis data from its origin at peripheral health centers and hospitals to its destination at the IDD at the MoH. The information about this process was collected mainly from the IDD at King Fahd Hospital in Al-Madina City for the purpose of reporting qualification.

Brucellosis is a notifiable disease in KSA. According to the MoH, all brucellosis cases should be reported monthly—including number of cases, nationality, region, gender, and test result diagnosis—to the IDD. Every suspected case is investigated by using a standard agglutination test, culture (blood or bone marrow, CSF), ELISA, or other tests if they are available. Along with the laboratory results, every reported case form includes all patient identification and disease data: name, age, sex, occupation, nationality, and contact information; physician in charge; time of reporting; travel history; history of animal contact; state of the ingested milk; and previous attacks of brucellosis (35).

Although brucellosis trends have been studied in KSA among different regions, this research extended the boundaries of these studies and included brucellosis distribution and determination from 2004 to 2012 among the main regions of KSA, taking into account gender, nationality, and age groups. The distribution of brucellosis cases was studied by month as well.

Variables

Gender was defined as female and male; nationality was classified as Saudi and non-Saudi; age groups were identified as <1, 1-4, 5-14, 15-44, and > 45 years old; and frequency of cases was expressed in months. Population data were used from 2004 to 2012 according to gender, region, and nationality.

Statistical Analyses

Exploratory analyses were conducted to assess for missing and incomplete data followed by descriptive analyses for cases and the whole population. The incidence rate (IR) was calculated per 100,000 persons for the total population, region, and nationality, and when applicable by nationality and gender. IR was calculated using this formula: (number of cases/total specific population) * 100,000. Confidence interval (CI) was calculated using the Wilson approximation for a large population with the proportion/population ratio below <0.0002 (36). Microsoft Excel 2011 was used to translate and organize the data sets and for developing graphs and charts. SAS 9.3 (Cary, NC) was used for database concatenation, management and statistical analyses.

Ethics

This analysis was determined to be IRB-exempt because it is an analysis of secondary data and all data were de-identified prior to analysis. Prior to data collection, all portions of the study were reviewed by Emory University‘s Institutional Review Board and determined to meet the criteria for exemption.

C. Results

Brucellosis IR trends showed fluctuation over the period from 2004 – 2012, with a steady decrease in the IR from 2009. The highest IR of the total population rate was 22.9 (95% CI: 22.3, 23.5) in 2004 and the lowest was 12.5 (12.1, 13) in 2012 (Table 1). The total number of cases for the period was 37,477, with a low of 3,447 cases in 2008 and a high of 5,169 cases in 2004. The mean was 4,164.1 and the median was 3,997.

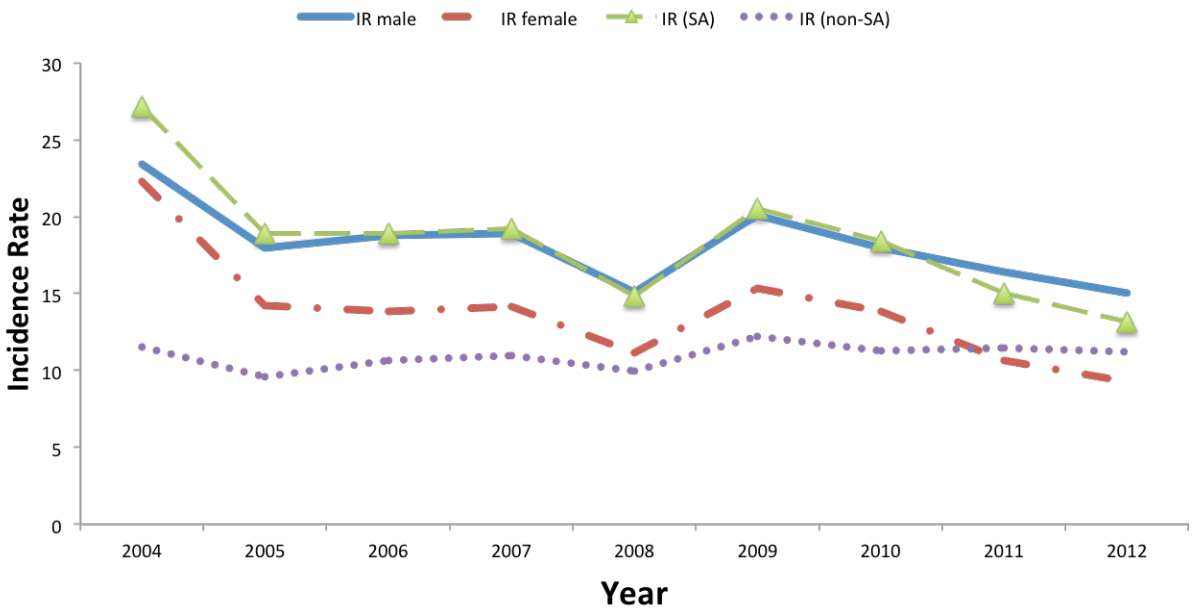
Table 1. Reported Cases and Incidence Rates of Human Brucellosis, by Year, Kingdom of Saudi Arabia, 2004 — 2012

Year	# Cases (IR°)	95% CI*
2004	5,169 (22.9)	22.3 – 23.5
2005	3,804 (16.3)	15.8 – 16.8
2006	3,997 (16.6)	16.1 – 17.1
2007	4,194 (16.8)	16.3 – 17.3
2008	3,447 (13.4)	12.9 – 13.8
2009	4,803 (18)	17.5 – 18.5
2010	4,460 (16.2)	15.7 – 16.7
2011	3,942 (13.9)	13.5 – 14.3
2012	3,661 (12.5)	12.1 – 13
Total	37,477	

°IR = incidence rate per 100,000 population
*CI = confidence interval

Over the total period of the study, the IRs among Saudi citizens were consistently higher than that among non-Saudis, but this difference shrank over time. Saudi citizens had an IR of 27.1 (95% CI=26.4, 28) and non-Saudis had an IR of 11.5 (10.7, 12.4) in 2004, while in 2012, Saudi citizens had an IR of 13.2 (95% CI=12.7, 13.7) and non-Saudis had an IR of 11.2 (95% CI =10.5, 11.9). There was an overall downward IR trend from 2004 to 2012 among Saudi citizens, with the exception of 2009, whereas among non-Saudis the IR remained stable. Males had a consistently higher IR than females, and the overall IRs from 2004 to 2012 fell for both males and females, with the exception of 2009. Males had an IR of 23.4 (95% CI=22.6, 24.3) and females had an IR of 22.3 (21.4, 22.2) in 2004, while in 2012 males had an IR of 15 (14.5, 15.7) and females had an IR of 9.3 (8.8, 9.8) in 2012 (Figure 2).

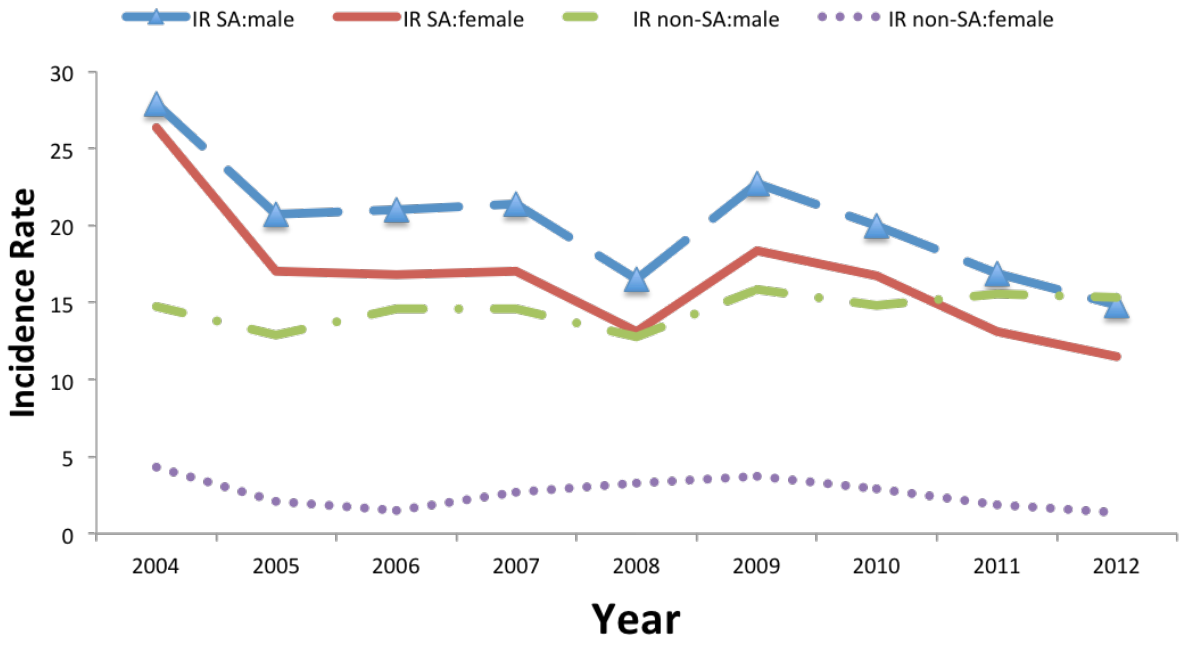
Figure 2. Incidence Rates° of Reported Cases of Human Brucellosis, by Gender and Nationality, Kingdom of Saudi Arabia, 2004 — 2012



° per 100,000 population

This trend was similarly reflected when gender was paired with nationality. There was a downward trend for male and female Saudi citizens, but the IR among non-Saudi males remained stable during the study period. Non-Saudi females consistently had the smallest IRs. Additionally, Saudi males had a steeper upward IR trend compared to others, with the exception of 2012, when it was almost the same as the trend for non-Saudi males. By and large, the IR among males was higher than among females across all of the study data. However, in 2004, the IR among Saudi females was higher than among non-Saudi males, and the difference between these two groups decreased over time until 2012, when males eclipsed females: the IR was 11.5 (10.8, 12.2) among Saudi females and 15.4 (14.4, 16.3) among non-Saudi males (Figure 3).

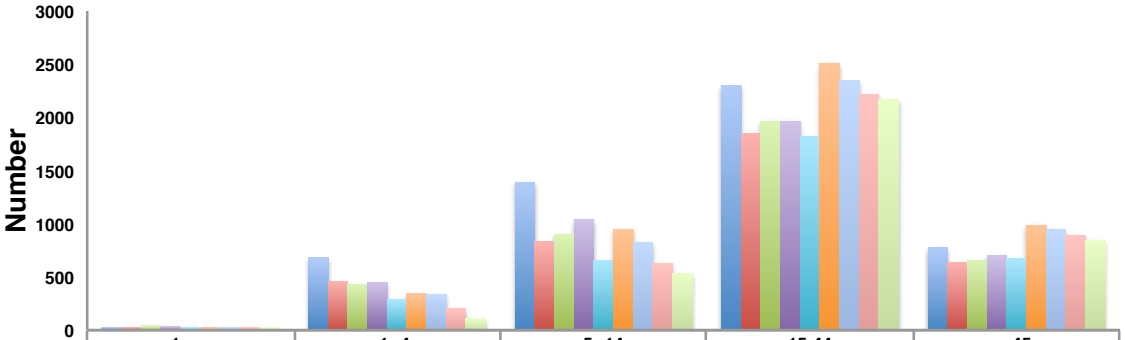
Figure 3. Incidence Rates° of Reported Cases of Human Brucellosis, by Saudi Gender and non-Saudi Gender, Kingdom of Saudi Arabia, 2004 — 2012



° per 100,000 population

By age group, those aged 15-44 had the highest prevalence, and those under 1 year had the lowest prevalence. Among those under 1 year old, the average number of cases was 27.8 and the median was 29, while among those aged 1 – 4 years old, the average was 406.6 cases and the median was 441. Among those aged 15 – 44 years old, the average was 2155.1 cases and the median was 2193, and among those over 45 years old, the average was 784.4 cases and the median was 779.5 (Figure 4).

Figure 4. Reported Cases of Human Brucellosis, by Age Category, Kingdom of Saudi Arabia, 2004 — 2012



	<1 year	1--4	5--14	15-44	>45
2004	29	680	1389	2297	774
2005	29	460	829	1846	640
2006	40	433	899	1966	659
2007	37	449	1043	1966	699
2008	17	287	651	1818	674
2009	14	345	948	2508	988
2010	17	334	824	2343	942
2011	10	202	623	2220	887
2012	20	106	528	2166	841
Total	213	3296	7734	19130	7104

Age Category

Most brucellosis cases were reported from March to August. In May, the month with the highest number of reported cases, there were 557 cases reported in 2004 and 536 cases in 2012. Across the study period, the average was 468.1 cases and the median was 486 cases. In contrast, November was the month with the lowest number of reported cases, with 236 cases in 2004 and 263 cases in 2012. Across the study period, the average was 247.7 cases and the median was 263 cases (Figure 5).

Figure 5. Reported Cases of Human Brucellosis, by Month of the Year, Kingdom of Saudi Arabia, 2004 — 2012

Year	January	February	March	April	May	June	July	August	September	October	November	December	Total
2004	380	383	494	556	557	447	603	410	447	307	236	349	5169
2005	187	346	459	374	321	464	355	303	284	227	179	305	3804
2006	260	304	449	410	393	430	429	315	352	192	265	198	3997
2007	243	300	411	412	486	521	344	389	350	225	276	237	4194
2008	189	311	418	415	487	386	9	323	196	229	277	207	3447
2009	270	360	463	622	537	555	552	359	224	334	272	255	4803
2010	289	355	349	579	462	439	434	320	382	325	247	279	4460
2011	337	306	448	459	434	452	306	203	273	251	214	259	3942
2012	225	274	347	425	536	313	266	255	272	243	263	242	3661
Total	2380	2939	3838	4252	4213	4007	3298	2877	2780	2333	2229	2331	37477

Across the total study period, the IR was higher in Al-Qassim, Aseer, Hail, Northern Borders, and Najran than in other regions. In 2007, the IR was 76.2 in Al-Qassim, 61.8 in Aseer, 43.7 in Hail, 37.2 in Northern Borders, and 32.2 in Najran. In 2012, the IR was 69.6 in Al-Qassim, 38.8 in Aseer, 32.7 in Hail, 34.5 in Northern Borders, and 22.4 in Najran. Although there was a relative decease in IR across the total period of study in the aforementioned regions, they still had the highest IR.

IRs were relatively low in Al-Jouf, Jazan, Tabouk, Makkah, and Al-Riyadh compared to other regions. In 2007, the IR was 2.1 in Al-Jouf, 9.6 in Jazan, 9.6 in Tabouk, 5.2 in Makkah, and 7.8 in Al-Riyadh, while in 2012, it was 3.8 in Al-Jouf, 4.2 in Jazan, 1.5 in Tabouk, 3 in Makkah, and 6.2 in Al-Riyadh (Figure 6).

Figure 6. Incidence Rates° of Reported Cases of Human Brucellosis, by Region, Kingdom of Saudi Arabia, 2004 — 2012

Year	Al-Riyadh	Makkah	Al-Madinah	Al-Qassim	Eastern Region	Aseer	Tabouk	Hail	Northern Borders	Jazan	Najran	Al-Jouf	Al-Baha
2007	7.8	5.2	7.6	76.1	16.5	61.8	9.6	43.7	37.2	9.6	32.2	2.1	16.3
2008	5.1	4.2	4.9	70.9	12.7	43.0	7.0	57.6	37.8	5.0	33.5	2.5	8.5
2009	8.1	6.6	7.9	94.6	18.6	55.5	4.8	67.2	38.4	6.2	48.1	2.9	15.6
2010	4.3	5.9	19.9	86.1	15.5	49.6	7.6	53.9	25.3	5.0	41.3	1.6	8.3
2011	5.3	3.7	12.7	61.6	13.5	44.0	7.3	62.5	25.2	3.5	38.1	2.8	5.8
2012	6.2	3.0	9.2	69.6	11.0	38.8	1.5	32.7	34.5	4.2	22.4	3.8	18.0

° per 100,000 population

D. Discussion

The results of this study show that brucellosis is a major health problem in KSA. From 2004 to 2012, the IR of brucellosis fell, but it was still higher than that of developed countries and most other developing countries. In KSA, males aged 15-44 who are Saudi citizens were at highest risk of acquiring this disease. They may be more likely to come into contact with infected animals, as they travel more than women do and have more opportunities to drink raw milk during the spring and summer seasons.

The western part of KSA has the fewest number of cases compared to other areas, and Al-Qassim in the central part has the greatest number of cases, followed by Aseer in the south and Hail and Northern Borders in the north. Brucellosis is not confined to any one region; in other words, when a region is endemic for brucellosis, the disease could easily spread to neighboring regions. Enforcing livestock importation protocols is highly recommended to decrease the brucellosis incidence rate among imported animals (17, 23). Regional variations could also be attributable to certain illness patterns. Entire families can be infected by a single source of infected milk, and young males often bring home fresh milk to their families.

Lifestyle differences among population subgroups can account for variable incidence rates of brucellosis. Generally, those infected with brucellosis have come into contact with infected animals or ingested unpasteurized or raw milk; also, laboratory workers are at risk when they deal with brucellosis samples, so it is considered an occupational disease.

The researcher found that brucellosis rates are higher among males than females. Young Saudi males usually have more opportunities to drink unpasteurized or raw milk than females. Males often go camping for days in the desert, and while doing so, enjoy fresh milk directly from shepherds. The fact that brucellosis is mainly an occupational disease (abattoirs and veterinarians) may be another reason why the prevalence is higher among males than females. The prevalence of brucellosis among those under age 14 is lower than among other groups, most likely because children come into contact with infected animals less often than adults.

There are limitations of the study. The IR of age groups could not be calculated because the population data by age group was not available. Brucellosis cases are reported at the regional level and not by cities or governorates; therefore, determining the major foci of brucellosis was not possible. The age spans of the groups were not equal, and the age span for adults was wide (15-44 years old). We were not able to specify which people in this age group were the most affected.

We used the best available estimated population data. However, there was some inconsistencies in the published records. The main official source is the Saudi Central Department

of Statistics and Information. Regional data was not publically available, so the researcher used that which was found through the Saudi Department of Finance. Although yearly population increases were not taken into account by the Ministry of Finance from 2004 to 2012, they were overestimated by the Saudi Central Department of Statistics and Information; this has a negligible effect on the yearly incidence rate (to the hundredth decimal place). The percentage difference in total population by gender across regions per year between Ministry of Finance and Saudi Central Department of Statistics and Information ranged from -5 to 0%. The population data of the Saudi Central Department of Statistics and Information was overestimated.

Other important variables that play a role in brucellosis or could confound other variables were not available for inclusion in our analysis. Data such as brucellosis prevalence among shepherds, abattoirs, and laboratory workers are not kept by the KSA MoH. Other information like urban or rural location, occupation, level of education, social status and income should be included as well. Behavioral variables such as the role of milk collection, contact with animals, and how laboratory workers deal with samples should be included in future studies. Also, an assessment of how well animal importation protocols have been applied should be included as well, especially in areas where high numbers of animals are imported annually, such as Makkah.

Chapter 4: Conclusion and Recommendations

Brucellosis still affects people's health in KSA and causes economic losses. Our recommendations point mainly toward decreasing the brucellosis IR until the disease is eventually eradicated. However, it is difficult to control in KSA, where there is substantial animal importation each year, especially during Hajj season, and where there are a high number of livestock owners living in rural areas who may not be aware of the risks attendant to their behaviors. In addition, there is a large amount of uncontrolled livestock movement across the neighboring countries' borders (23).

The main goal is to decrease brucellosis prevalence among humans and infection sources. Prevention measures should include:

1- Implementing a governmental surveillance program for brucellosis prevention that includes:
   a. Create a clearer case definition to capture all cases. This case definition should be more sensitive to make sure that health providers capture all suspected case of brucellosis.
   b. Organize the flow of reported data from health centers, laboratories, and the Infectious Disease Department at the MoH so that it is smooth and fast.
   c. Provide all health centers with the qualified laboratory personnel and equipment to capture all brucellosis samples.
   d. Take samples frequently from susceptible livestock, especially those in potentially epidemic areas.
2- Enforce animal importation protocols.
3- Enforce compulsory vaccination of all susceptible animals at veterinary clinics and agricultural offices.
4- Increase the level of education and awareness among people, especially people who are at risk, such as shepherds, abattoirs, and laboratory workers. Also, rural health centers should increase health awareness among people. The brucellosis cases were found most among uneducated people or those who had not completed secondary school(25).
5- Increase the biosafety level in laboratories to level 3, as laboratory workers are at risk. Brucellosis is considered one of the most common laboratory-acquired infections. Even the centers not located in potentially epidemic areas should increase their biosafety level because the personnel are usually not familiar with brucellosis samples and the disease's clinical manifestations (30, 37).

6- Motivate researchers to do more studies of brucellosis in KSA, as most of published papers have not covered the main distribution and determinant factors of brucellosis transmission in KSA in recent years. Also, the majority of published papers rely on the serology of the disease in humans and animals, which could lead to underestimation of brucellosis.

The One Health approach is a concept connecting human health to animals and the environment with the goal of building a healthy and safe environment for all; in other words, the health of humans is connected to the health of animals and the environment. Building collaborations between medical personnel, veterinarians, and other environmental disciplines is also one of the aims of the One Health approach, as well as the prevention of potential disease outbreaks. The vaccination of susceptible animal against brucellosis has resulted in a notable decline of brucellosis cases among humans and decreases in economic and livestock loss (38), but the disease still deserves attention and resources so that it can be fully eradicated.

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Appendix

Table 2. Reported Cases of Brucellosis Infection and Incidence rates, by Year and Gender, Kingdom of Saudi Arabia, 2004 — 2012

Year	Male		Female	
	# Cases (IR°)	95% CI*	# Cases (IR°)	95% CI*
2004	2925 (23.4)	22.6 – 24.3	2244 (22.3)	21.4 – 23.2
2005	2330 (18)	17.3 – 18.7	1474 (14.2)	13.5 - 15
2006	2521 (18.8)	18 – 19.5	1476 (13.8)	13.1 – 14.5
2007	2636 (18.9)	18.2 – 19.6	1558 (14.2)	13.5 – 14.9
2008	2187 (15.1)	14.5 – 15.8	1260 (11.1)	10.5 – 11.8
2009	3016 (20.1)	19.4 – 20.8	1787 (15.3)	14.6 – 16.1
2010	2802 (18)	17.3 – 18.7	1658 (13.8)	13.2 – 14.5
2011	2628 (16.4)	15.8 - 17	1314 (10.7)	10.1 11.2
2012	2488 (15)	14.5 – 15.6	1173 (9.3)	8.8 – 9.8
Total	23533		13944	

°IR = incidence rate per 100,000 population
*CI = confidence interval

Table 3. Reported Cases of Brucellosis Infection and Incidence rates, by Year and Nationality, Kingdom of Saudi Arabia, 2004 — 2012

Year	Saudi		Non-Saudi	
	# Cases (IR°)	95% CI*	# Cases (IR°)	95% CI*
2004	4463 (27.1)	26.4 – 27.9	706 (11.5)	10.7 – 12.4
2005	3183 (18.9)	18.2 – 19.6	621 (9.6)	8.9 – 10.4
2006	3268 (18.9)	18.3 – 19.6	729 (10.6)	9.9 – 11.4
2007	3397 (19.2)	18.6 – 19.9	797 (11)	10.3 – 11.8
2008	2685 (14.8)	14.3 – 15.4	762 (9.9)	9.3 – 10.7
2009	3809 (20.5)	19.9 -21.2	994 (12.2)	11.5 - 13
2010	3491 (18.4)	17.8 - 19	969 (11.3)	10.6 - 12
2011	2911 (15)	14.5 – 15.6	1031 (11.5)	10.8 – 12.2
2012	2613 (13.2)	12.7 – 13.7	1048 (11.2)	10.5 – 11.9
Total	29820		7657	

°IR = incidence rate per 100,000 population
*CI = confidence interval