Brucellosis a possible link to Increased Stillbirths: A Population based Study from Malta, 1919-1954

Lianne Tripp¹, Larry A. Sawchuk¹, and Mahinda Samarakoon¹

¹University of Toronto Scarborough

April 30, 2024

Abstract

This study is novel in that it quantitatively examines the impact of human brucellosis, an endemic zoonotic disease in Malta from 1919 until 1954, and the impact on reproductive loss through stillbirths. Based on regression analysis, brucellosis had a statistically significant effect (t = 2.8986, p = 0.0039) on stillbirth rate for males, but the effect of brucellosis on stillbirths is not statistically significant for females (p = 0.9103). This paper points to the importance of brucellosis, one of the most common zoonotic diseases, as having implications for health burden in women and fetuses in the contemporary context; this relationship has been largely ignored in the literature.

Introduction

The reemergence of brucellosis in Central Asia and the Middle East (Godfroid, et al., 2005; Seleem, Boyle, & Sriranganathan, 2009; Pappas, Papadimitriou, Akritidis, Christou & Tsianos, 2013) is a large part because of its changing epidemiology (Dahouk et al., 2007); the role of animal husbandry tradition; and a culture of raw milk consumption. These factors are also major reasons for the continued persistence in many countries around the world (Zhong et al., 2013; Wallach, 1997).

One health implication of human brucellosis (Brucella melitensis; the most common and virulent species of human brucellosis), one of the most widespread zoonotic diseases in the world, is the potential role of the bacteria in inducing fetal loss. The etiology of abortions and stillbirths are complex and can be attributed to either non-infectious causes (e.g., congenital anomalies, placental insufficiency, placental abruption and asphyxia), or to infectious agents (Goldenberg & Thompson, 2003). Approximately 9 to 15 percent of stillbirths are caused by infectious diseases and in particular, infections during early pregnancy (Gibbs, 2002). Economic factors can influence the role of infectious diseases and stillbirths. In middle- and low-income countries 50 percent or more of stillbirths can be attributed to infections, whereas, in high income countries, only 10 to 25 percent of maternal or fetal infections can account for stillbirths (Goldenberg & Thompson, 2003; Goldenberg, McClure, Saleem & Reddy, 2010). Specific infectious agents linked to stillbirths include syphilis, malaria, toxoplasmosis, parvovirus B-19, chorioamnionitis, and Listeria monocytogenes. Less definitive links to stillbirths include the genital mycoplasmas, Chlamydia trachomatis, HIV, and group B streptococci. and others (Gibbs, 2002; Goldenberg & Thompson, 2003).

It has been well documented that animal strains of brucellosis cause abortions of fetuses and ‘reproductive failure,’ in cows, dogs, goats, horses, pigs, sheep and even camels. (Lopes, Nicolino, & Haddad, 2010; Ocholi, Kwaga, Ajobi & Bale, 2005; Samartino, & Enright, 1993) B. Melitensis can be transmitted to humans only from goats or sheep, through consumption of unpasteurized milk and cheese; through close contact with animals (i.e. hunting, milking, or caring for sick veterinarians); through meat processing and meat consumption; or through inhalation or airborne of the pathogen. Rarely, the bacteria can be transmitted from person-to-person either via sexual contact or airborne transmission.
The study of the link between human \textit{B. melitensis} and the termination of births in humans is a topic that has received a dearth of attention. Few studies have examined relationship of human stillbirths and \textit{B. melitensis} , especially at the cohort or population level (for exceptions see: Gulsun, Aslan, Satici, & Gul, 2011, and Rujeni, & Mbanzamihigo, 2014). Others are case reports of stillbirth and abortions that are limited in scope and sample size (Karcaaltincaba, Sencan, Kandemir, Guvendag-Guyen, & Yalvac, 2010; Goldenberg et al., 2010; Mosayebi, Movahedian, Ghayomi, & Kazemi, 2005). These studies, however, point to the strong possibility that brucellosis is a risk for adverse health outcome to the human fetus.

In this paper we explore the relationship between human \textit{B. melitensis} and stillbirths specifically in the civil population of Malta during the period 1919 to 1954. The Maltese islands present a rare opportunity for a population-based inquiry into the potential adverse effects of brucellosis on fertility through fetal loss. The advantages of the study site include the following population-based attributes: First, brucellosis (a.k.a. Malta or Mediterranean Fever) was a notifiable disease since the early 20\textsuperscript{th} century and it remained endemic throughout the study period. Second, monthly statistics of births and stillbirths by sex were published since 1900. Third, pregnant women were at continuous and at high exposure to brucellosis because of high fertility rates owing to their adherence to strict Catholic precepts (Tripp & Sawchuk, 2015; 2017). Finally, throughout the study period, the health care infra-structure was rudimentary along with little available pre-natal care for expectant mothers putting the vast majority of women at risk for fetal loss (Savona Ventura & Grech, 1985; Seers, 1957; Tripp & Sawchuk, 2015).

Material and Methods

Yearly notifications of brucellosis were extracted from the Annual Health Reports on the Health of the Maltese islands. A comprehensive description of the reporting of brucellosis can be found in Tripp and Sawchuk (2015). Age and sex notification was only available for the sister smaller island of Gozo from the Health Office in Gozo, the records for Malta were unfortunately destroyed.

Monthly numbers of births and stillbirths by sex from April 1919 to June 1954 were drawn from the Maltese Gazette that was published under the auspices of the Medical Officer of Health. These records are housed at the National Archives of Malta (NAM), and The National Archives in Kew, England. Data on brucellosis cases was published in the monthly Gazette reports under the heading of ‘Return of cases of infectious diseases reported by month and location.’ The few missing values were estimated by linear interpolation (Moritz, 2016).

Beyond reporting the basic undulant fever rates, the primary goal was to investigate the relationship between the number of brucellosis cases and the proportion of stillbirths. Multiple regression was used to model a relationship between a dependent variable and one or more independent variables. These models assume the error terms to be independent. This assumption is frequently violated when applied to time series data. A model that allows correlated errors, is the regression model with integrated autoregressive moving average (ARIMA) errors. Consequently, in order to study the relationship between the number of brucellosis cases and the proportion of stillbirths, we used a regression model that allows auto correlated errors and has an ARIMA process. Ethical approval was not required for this study human subjects were not included in the study and the data was aggregated information that did not reveal any personnel identifiers. The graphs were created in Statistica (Statsoft, 2011) and the regression model was completed in R statistical software.

For the regression model, we used a logit transformation on the proportion of stillbirths, in particular the logarithms of the odds of stillbirths (i.e. \( \log \left( \frac{p}{1-p} \right) \)), where \( p \) denotes the proportion of stillbirths as the dependent variable, and time and brucellosis are the explanatory variables.

The data showed significant autocorrelations and cross correlations at many lags indicating serial correlations in the time series (see Figure 1). or each sex, we first fitted a logistic regression model with the logit of the stillbirth rate as the dependent variable and the time, month, and the number of brucellosis cases as the independent variables. The models were tested for multicollinearity, based on variance inflation factors (VIF). They are all well below 10, the usual critical value, indicating no serious multicollinearity exist between
independent variables. We then fitted the best suited ARIMA models for the resulting residuals (Hyndman & Khandakar, 2008), which were used as the process generating the errors of the regression models (Shumway, Stoffer, & Stoffer, 2000; Stoffer, 2016). The residual plots for the models fitted indicate no serious violations of the assumptions. The residuals of the white ARIMA processes for errors appear to be approximately white noise having an approximate normal distribution. The residuals of the white ARIMA processes for errors appear to be approximately white noise having an approximate normal distribution. In other words, the number of stillbirths and undulant fever taken at different months were random in nature taking on an approximate normal distribution.

Figure 1. Time series plots of logit transformed stillbirth prevalence for males and females, and for the independent variable of undulant fever cases

Results

Undulant fever was endemic to the islands with periodic outbreaks of major epidemics (see Figure 2). Since there was no significant difference in the mean number of cases between Malta and Gozo, the brucellosis numbers for the two islands were pooled. The mean number of undulant fever cases was 3.611 per 1000 living over the study period.

Figure 2. Undulant fever cases in the Maltese Islands: 1919-1954.
Figure 3, shows the breakdown of cases of brucellosis by age and sex in Gozo and presumably, reflective of that in Malta. The group most at risk of the disease were males (N = 961) with the most cases occurring in the age band of 20 to 24 years of age (see Figure 2). The peak age group for females (N = 684) were 15 to 19 years of age, and stayed elevated throughout the reproductive years. 69.36 percent of cases in males occurred in those aged 15 to 49 years. For females 71.22 percent of cases occurred in women aged 15 to 49 years.

Figure 3. Undulant fever cases by sex in Gozo from 1919 to 1940.
The regression model showed that brucellosis had a statistically significant effect \((t = 2.8986, p = 0.0039)\) on stillbirth rate for males, but the effect of brucellosis on stillbirths is not statistically significant for females \((p = 0.9103)\).

Discussion

Historically, the pattern of milk consumption in Malta was the drinking of fresh unpasteurized goat milk of local origin. The goat was considered to be a household feature of Maltese culture and daily life (Tripp & Sawchuk, 2015). Much like the rest of the Mediterranean, Malta lacked refrigeration; the high concentration of the population and short distances between villages and towns, and the poverty of grazing land, made the goat an ideal candidate for distributing milk on customers’ doorsteps (Azzopardi, 2012). The belief system was based on conviction that boiling milk: (1) ruined the quality and flavour of milk; (2) was considered superfluous by the people because it was known that the Maltese goat did not suffer naturally from tuberculosis which the precautions of boiling had been advocated abroad; but now great emphasis was laid on this simple yet effective measure; (3) having the goat milked at the door meant that contamination or adulteration of the milk is not possible, (4) distrust with scientific findings with ‘the general public has yet to be convinced that an apparently normal beverage drawn straight from the familiar goat can be productive of a deadly fever’. Finally, (5) the request by authorities to boil their milk was simply unobtainable given that the poor could simply did not have the means to boil milk (Tripp & Sawchuk, 2015).

As the Gozo notification records show both sexes were likely to contract undulant fever during their reproductive period. The fact that adults were more likely to fall ill with the disease is not surprising, considering that children and in particular infants were not encouraged to drink milk (Ganado, 1937). Consequently, milk consumption of fresh goat milk could have a potential impact on fetal loss through stillbirths.

The main finding of this study on the Malta as a whole is that there was a significant increased risk of male stillbirths associated with undulant fever after controlling for seasonality associated with birthing and undulant fever. Generally, the literature on sex-based differences in human stillbirths indicates that male stillbirths are more common than female stillbirths (Stinson, 1985).

Our study shows that the male fetus is significantly more vulnerable under an insult from brucellosis than a female fetus. Given the nature of this study we are unable to address this issue other than in broad terms. A review by Clifton (2010) may offer a plausible explanation as his review of the literature has found that mothers under adverse environmental conditions or events initiate different coping strategies according to the sex of the fetus. Female fetal growth was reduced while in contrast, the male fetus continues to grow normally which can ultimately result in preterm delivery and stillbirth.

Conclusion

While our results on this zoonotic disease are confined to historic Malta, the fact that brucellosis continues to be a health and economic burden in other countries suggests that other researchers should study the relationship of brucellosis and stillbirths in the modern context.

Acknowledgements

We thank Dr. Charles Farrugia of the National Archives of Malta for his generosity in granting us access to the Malta Government records, in particular, the Government Health reports. We are grateful to Joseph Borg from the Archives Section of the Health Office in Victoria, Gozo for allowing us to access the notification records.

References


