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Risk factors for human brucellosis in Yemen: a case control study

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SUMMARY

Brucellosis is known to occur in Yemen but its epidemiology has not been extensively studied. The present investigation examined risk factors for human brucellosis in Yemen using a hospital-based case-control study. A total of 235 consecutive patients with brucellosis attending the Central Health Laboratory in Sana'a, Yemen, were matched in respect of age, sex, and place of residence, rural or urban, with 234 controls selected from individuals attending the Central Health Laboratory for unrelated health problems. Clinical information on patients and controls was supplemented with occupational and socio-economic data obtained by interview of cases and controls using a standard questionnaire.

After controlling for confounding factors significant risk factors for infection related to occupation as a farmer (OR 2·5 (95% CI 1·4–4·5, $P < 0{\cdot}0001$)), shepherd (OR 7·8 (95% CI 1·0–61, P 0·05)) or microbiologist (OR 24·5 (95% CI 2·9–204, P 0·003)); and drinking fresh milk (OR 2·0 (95% CI 1·3–4·3, P 0·001)) and laban (OR 22·7 (95% CI 1·7–4·2 $P < 0{\cdot}0001$)). Taking other milk products and offal were not risk factors. Socio-economic and educational factors were also independent risk factors. Occupational, food and socio-economic risk factors significantly confounded one another.

Yemen shares some but not all of the risk factors of neighbouring countries. The interrelation between the various factors is complex and studying any one in isolation may give a false impression of its public health significance. Control through education of the population to minimize exposure to, and contact with, animals and their milk and milk products and to boil milk before drinking it or using it to make buttermilk, would be difficult as these would represent such fundamental changes to established patterns of behaviour of this society. Ideally there would be a campaign to control the infection by animal vaccination but the costs and logistic difficulty would be great. Presently there is a clear need for doctors in Yemen to be made aware of the frequency of this infection, the means available for clinical and laboratory diagnosis and effective treatment, while strategies to control the disease in Yemen are formulated and field tested.

INTRODUCTION

Human and animal brucellosis is endemic world-wide with success in eradication in some European countries and the USA [1]. The incidence of human brucellosis in countries of the Arabian peninsula is high with reports of large numbers of cases from Saudi Arabia [2], Kuwait [3] and Oman [4]. Yemen has been neglected with regard to the study of brucellosis.

Brucellosis is a zoonosis with infection in man often

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resulting from ingestion of milk and milk products and, less often, contact with an environment contaminated by animal discharges. There are strong occupational predispositions to infection. All of these possible sources of infection are relevant in the Arabian Peninsula [2, 3, 5]. Risk factors for this infection are related to cultural and occupational factors and these cannot readily be extrapolated from one society to another.

Brucellosis of goats, sheep and humans has been reported in Yemen [1, 6, 7]. Many people in Yemen keep livestock in and around the family home with family members tending goats, sheep and sometimes cattle. They live in close proximity to their livestock which may be kept in the lower floor of the home, consume untreated milk and make laban (buttermilk) using unhygienic methods. Milk and laban are sold to the consumer directly or through groceries in cities and towns. Brucellosis is sufficiently common in Yemen that specific public health measures are needed to combat this debilitating disease but these measures may need to be targeted at specific routes of infection among defined groups.

Our aim was to study the range of factors which influence the occurrence of brucellosis in Sana'a, Yemen. Several studies in different countries have demonstrated individual risk factors but these may interrelate in a complex fashion. It is easy to get a very misleading impression of the public health importance of a particular risk factor studied in isolation. We therefore set out to investigate occupational, dietary, educational and socio-economic factors and examine their interactions.

METHODS

Patients and controls

All patients with brucellosis presenting to the Central Health Laboratory in Sana'a during the 2 years to February 1993 were included. All the five hospitals in Sana'a participated to ensure maximum case finding. A search was made for cases of brucellosis among patients with fever of undetermined origin and patients with the clinical diagnosis of possible brucellosis. In all 235 cases were identified. A case of brucellosis was defined by the presence of clinical symptoms of fever, fatigue, night sweats and myalgia together with either isolation of *Brucella melitensis* from blood culture, present in 16 patients corresponding to 7·9% of the cases, or positive brucella serology by the standard tube agglutination at a titre of $\geqslant 160$. The controls were selected from persons who were attending the Central Health Laboratory for a variety of clinical problems unrelated to either brucellosis or febrile illnossos; for example patients with helminthic infections or attending for routine blood tests before elective surgery. Every person had a probability of being selected as a control equal to that of every other person of the same sex and age range irrespective of residence. Frequency was matched at the rate of one control to each case.

The individual controls were defined as persons who were free of brucellosis and fever of undetermined origin. Cases and controls were matched for age, sex and place of residence.

Information on patients and controls was supplemented with data obtained by interview with study subjects or their parents using a standard questionnaire. This recorded 41 items of information on socio-economic status as well as questions on direct as well as indirect exposure to established risk factors for brucellosis. Cases and controls were asked to answer the questions at interviews conducted in hospital or the Central Health Laboratory.

There was a range of potential sources of bias. A pilot serological survey was undertaken to learn the prevalence of antibodies to brucella among asymptomatic healthy members of the study population; titres of $\geqslant 160$ were rare, found in 0·4% [8]. The agglutination titre seemed to discriminate clearly between those who had brucellosis and those free of the condition thus allowing these subjects who had relevant symptoms and signs to be included as cases. All patients attending the Central Health Laboratory satisfying the brucellosis case definition criteria were selected as cases. Consideration was given to the possible occurrence of brucellosis in the control group. The case notes of each potential control subject were reviewed and the individual excluded from the study if they gave a positive agglutination titre of $\geqslant 20$. The possibility of occult infection in the control group was therefore minimized. All cases and controls were interviewed in Arabic by one of us (HA Al-S) using the same questionnaire. To avoid differential questioning, questions were designed to be closed ended. To avoid 'leading line questioning' general questions were asked first and specific questions related to exposure later. All questions concerning exposure related to the previous 2 years.

Data was entered using Epi-Info version 6 [22] and analysed using the STATA statistical package (Stata-

Table 1. *Risks for brucellosis in Sana'a, Yemen, uncorrected and controlling for potential confounding factors*

	Cases	Controls	OR	OR Controlling for confounding (95% CI)*	Significance
Occupation					
Farmers	90	26	5·0	2·5 (1·4–4·5)	< 0·0001
Shepherds	14	1	14·7	7·8 (1·0–61)	0·049
Microbiologist	14	1	14·7	24·5 (2·9–204)	0·003
Abattoir worker	3	0	n/a		
Food					
Milk products	116	86	4·1	2·8 (1·8–4·3)	< 0·0001
Fresh milk	130	68	3·0	2·0 (1·3–4·3)	0·001
Laban	125	65	4·2	2·7 (1·7–4·2)	< 0·0001
Yoghurt	4	2	2·0	2·0 (0·4–11)	0·4
Soft cheese	20	12	0·6	0·6 (0·3–1·2)	0·1
Offal	26	22	1·2	1·2 (0·78–1·9)	0·4
Education					
Illiterate	102	58	2·3	2·5 (1·7–3·8)	< 0·0001
Primary	55	64	0·8	0·8 (0·6–1·3)	0·5
Secondary	45	72	0·5	0·5 (0·3–0·8)	0·004
University	29	42	0·6	0·5 (0·3–0·8)	0·015
Socio-economic indicators					
Low income	82	38	2·8	1·5 (0·9–2·5)	0·09
> 2 people/room	114	75	2·0	1·3 (0·9–2·0)	0·1
No TV/radio	21	3	7·5	2·0 (0·5–7·9)	0·3

Corp 1993). Uncorrected odds ratios were calculated for all risk factors. Biologically plausible confounding factors were tested using Mantel–Henzelt analysis and confounding was felt to be potentially significant if odd ratios shifted appreciably. Where two or more potential confounding factors were identified further analysis was performed with logistic regression models. In practice all dietary factors were tested with models including both occupation and education (as a proxy for socio-economic status), all occupational risks with models including dietary and socio-economic factors and so on. Further factors were included where they were thought potentially relevant. The 'corrected' odds ratios quoted are from logistic models including all factors where confounding or interaction were thought to be biologically plausible and which, when added to the model, led to any appreciable change in odds ratio.

RESULTS

A total of 235 cases and 234 controls were analysed: 132 cases and 125 controls were male. The age of the cases ranged from 1 to 85 years and for controls from 2 to 75 years. All cases and controls were Yemeni, 62·5% living in the city and 37·5% living in villages. 16·7% were without drainage systems, 64·7% used piped water and 32·3% used well or spring water. The socio-economic status of the families of both cases and controls was low. Approximately 84% had a family income of less than US$ 70 per month. There was no significant difference between the two groups for median age, income or marital status.

Potential risk factors are outlined in Table 1, giving odds ratios for brucellosis uncorrected and after controlling for important confounding factors. Important confounding occurred for many of these risk factors. Occupation, consumption of milk products, education and socio-economic factors are related in a complex fashion.

Both farmers and shepherds drink more fresh milk and more laban than other groups. Occupation and drinking milk and laban confound each other, part of the apparent risk of milk products is accounted for by having large numbers of farmers consuming them, and part of the apparent risk for farmers is probably accounted for by their high milk and milk product consumption. Socio-economic factors had had a small additional effect and the corrected odds ratios for milk products are reported for occupation and income as confounders and by occupation for milk products and income.

In the case of microbiologists, both veterinary and medical, income and education were confounding factors. The apparent risk for microbiologists increases markedly when education and income are controlled for. There is a clear gradation in risk according to education level which is independent of other socio-economic factors. Occupation and consumption of laban were confounders. An apparently greater risk in the university educated group compared to those who had only secondary school education reverses once laban consumption and the risk of being a microbiologist are controlled for. All measures of low socio-economic status were associated with increased risk of brucellosis, three examples are shown. Occupation and education were confounding factors and corrected odds ratios found after controlling for farming and educational level show this association becoming non-significant although the non-significant trend for lower socio-economic subjects to have brucellosis persists.

No significant association was found with places of residence, urban or rural, ownership of cattle and camels, animal slaughter or handling fresh meat.

DISCUSSION

Hospital-based case-control studies have limitations which are well known. An ideal study would be community-based but was not practical in this context. By careful selection of controls we hope these have been minimized without over-matching, but the usual problems of control selection should always be borne in mind.

This study was designed to identify the major risk factors for brucellosis in Yemen. This infection is associated with occupation and food and so is culturally very specific. Risk factors important in one society may not be so important in another. The majority of previous studies have reported crude risk or odds ratios to predispositions, but these are potentially inter-related in a complex way and actual risks may be either under or over estimated because of significant confounding. An attempt was made in this study to investigate and, if possible, control for these interactions.

Our study suggests that some, but not all, of the predispositions for brucellosis identified in other societies are important in the Yemen. Drinking fresh milk and laban are significant risk factors but there is no significant association with yoghurt and soft cheese consumption. This may be explained by the sensitivity of *Brucellae* to the low pH of yoghurt, while soft cheese in Yemen is commonly made from cow's milk which is a source with a very low prevalence of brucellosis [9]. These findings confirm the potential for heat treatment of milk for control of brucellosis in Yemen yet implementing this would be difficult because of the major change in deeply rooted, traditional practices required. It is generally believed that the boiling of goat or sheep milk 'spoils the taste and removes the goodness'.

Consuming uncooked or partially cooked animal products, such as raw caudate lobe of liver and spleen is common in the Arabian peninsula and has been suggested as a source of infection [2, 10]. However, despite the consumption of these items at time of animal slaughter in Yemen this was not associated with risk of infection. In contrast a number of uncontrolled studies [2, 10, 11] have noted a large proportion of cases, 29–83%, reporting recent consumption of raw liver or meat. We found no such association.

Brucellosis has long been recognized as an occupational disease [12–15]. Farmers and shepherds have frequent contact with animals that may have brucellosis and therefore show enhanced risk of infection. Workers in microbiology laboratories, medical and veterinary, were at high risk in our study, indicating the highly infectious nature of *Brucellae* [16]. Manipulation of culture on open benches, mouth pipetting and creating acrosols (17, 18) are some of the reasons for this risk. The importance of awareness of this risk among laboratory workers in endemic areas cannot be overemphasized and as a consequence appropriate training and provision of equipment such as safety cabinets are essential.

Skin penetration during butchering, skinning, evisceration and meat processing are all well recognized routes for transmission [10, 21] but no associations with these activities in this study, probably because slaughtering of animals in the home was a relatively infrequent event occurring only on very special occasions.

Educational level was correlated with risk of brucellosis and some of this effect was independent of other measured socio-economic factors, occupation and consumption of milk products. This study is not able to determine whether health education specifically, as a part of general education, protects or whether with education goes something else such as a change in behaviour related that itself reduces exposure. The apparently significant socio-economic gradient seems to be largely accounted for by identifiable occupational, food and educational risk factors.

This study demonstrates that risk factors cannot be looked at in isolation. Among our cases the most important confounding was between occupation and food consumption with farmers occupationally exposed and having easy access to unpasteurized milk, these significantly interact with each other. If risk factors are studied on their own it is easy to overestimate the potential impact of a public health measure, for example if the apparent risk of drinking milk were looked at on its own it is tempting to think that brucellosis in Yemen could be halved simply by having people boil their milk, whereas in fact much of the apparent risk of milk reflects concurrent occupational and socio-economic factors. Studies of brucellosis need to take account of these complex interactions.

Finally the data reported here indicate that there is no significant association between risk of contracting brucellosis and place of residence in contrast to Cooper's observations in Saudi Arabia [5] showing strong association with residence in rural villages. The differences found may relate to the setting of the present study in an urban centre drawing a proportion of the studied population from homes within the city while the cases seen at the Riyadh-Al Kharj programme drew its patients predominantly from rural villages.

Occupational risk factors, milk and milk products and educational level are all associated with increased risk of brucellosis in Yemen. Farming and consumption of fresh milk and laban are the most important of these but the various risk factors interrelate and cannot be taken in isolation. The extremely high risk for microbiologists requires prompt attention.

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