Risk of Transmission of Leptospirosis from Infected Cattle to Dairy Workers in Southern Israel

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Abstract

Background: Leptospirosis is a zoonotic disease that occurs worldwide, found predominantly in agricultural workers, port workers and dairy workers.

Objective: To investigate the risk of disease transmission to dairy workers following an outbreak in 1999 of *Leptospirosis hardjo* in the dairy herds of two kibbutzim in southern Israel.

Methods: A seroepidemiologic survey of all the dairy workers from these two kibbutzim was conducted, including individual interview and examination. Data were collected on the presence of clinical symptoms of leptospirosis during the previous month. One month later the medical personnel on the two kibbutzim were contacted in order to determine if any worker had subsequently developed clinical signs or symptoms of leptospirosis. All dairy workers had blood drawn for serology. Those workers whose initial serology had been borderline for leptospirosis had a repeated serology test between 2 and 4 weeks later. Doxycycline was given prophylactically to all dairy workers on one kibbutz only.

Results: Either with or without chemoprophylaxis, no dairy workers exposed to herds infected with *Leptospira hardjo* showed evidence of seroconversion or disease. This indicated a low risk of transmission of this serovar from cows to dairy workers.

Conclusion: Since human illness with leptospirae can cause illness associated with significant morbidity, we recommend that physicians make an informed decision regarding doxycycline prophylaxis for dairy workers exposed to cattle herds infected with *Leptospira hardjo.*

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Leptospirosis is a zoonotic disease known to occur in Israel and has occasionally been found among agricultural workers, port workers and dairy workers [1–4]. We report on an epidemiologic and serologic investigation of dairy workers who were exposed to a dairy herd infected with *Leptospira hardjo* in the Negev, a desert region in the south of Israel. Human infection with *Leptospira hardjo* has been reported to be associated with moderate to severe fever, intense headache, generalized aches and pains, marked lethargy, anorexia and generalized lymphadenopathy. Some patients also have splenomegaly and/or hepatomegaly. The illness with this serovar has been reported to last for 5–30 days. [4] In Australia, 43.1% of agricultural workers infected with *Leptospira hardjo* had symptoms severe enough to require hospitalization [5].

The incubation period for leptospirosis is 1–2 weeks (mean 10 days). The course of illness is classically biphasic. The first phase, termed the septicemic phase, lasts 4–7 days and is often characterized by the abrupt onset of high fever, headache, intense muscle tenderness, gastroenteritis and conjunctivitis. The second phase, the immune phase, can last for a month or longer. Skin rash, meningitis, liver or kidney involvement, acalculous cholecystitis and myocarditis may occur at this stage. Icteric leptospirosis (Weil's disease) is a more fulminant form of the disease than the anicteric form and is often without the biphasic course. In the pre-intensive care era, mortality rates of up to 40% were reported. The proportion of leptospiral infections that are asymptomatic or subclinical is not known. Ninety percent or more of all patients have an acute self-limited illness without jaundice and the prognosis is excellent. The remaining 10%, with jaundice, may be seriously ill. The case-fatality rate reported to the Centers for Disease Control in the United States in the period 1965–1974 was 7.7% [6].

Several different serotypes of leptospirosis have been identified as the cause of morbidity in Israel. *Leptospira ballum* was found among agricultural workers of the Sharon coastal plain, presumably due to contact with wet soil contaminated by the urine of infected rodents [1], while *Leptospira canicola* was identified in workers in pigsties in the north of the country [2]. *L. icterohaemorrhagiae*, the most virulent form of *Leptospira*, was found in port workers in Haifa [3], and *L. hardjo was* detected in dairy workers in the north of the country [4]. Thus, all the published reports on leptospirosis in Israel are from the center or north of the county. Leptospirae are known to be organisms that rapidly lose their infectivity under hot, dry conditions [7]. Presumably, the weather conditions in the north of the country provide a better environment for the spread of Leptospirae than does the hot, dry climate of the south (the Negev desert).

In 1999, the Regional Ministry of Health received a report of an outbreak of spontaneous abortions due to *L. hardjo* among cattle in a dairy herd of a kibbutz (communal agricultural settlement) in the Negev. All the dairy workers on the kibbutz were interviewed about clinical symptoms and work history and had blood samples taken for serology. We present the results of the seroepidemiologic survey of the dairy workers, the implications for the transmission of *Leptospira* and recommendations for prevention.

Materials and Methods

In September 1999, the District Veterinary Officer of the Negev reported an outbreak of *Leptospira hardjo* among cattle in a dairy herd on a kibbutz (Kibbutz A). Clinical manifestations in the cattle included an increased rate of spontaneous abortions. This was associated with positive serology. Among six cows that had recently had spontaneous abortions, five tested positive for *L. hardjo* with titers ranging from 1:100 to 1:200, indicating that the herd was currently infected.

A herd of cattle on a nearby kibbutz (Kibbutz B) was also tested prior to sale, although the dairy herd had no clinical manifestations of leptospirosis. Three of the seven cows tested had positive serology for *L. hardjo*, indicating past infection. In order to prevent further abortions among the cattle on Kibbutz A and to allow the movement of cattle from Kibbutz B, it was decided to vaccinate all adult cattle as well as heifers that were to be bred within 1 or 2 months on Kibbutz A and Kibbutz B.

All the kibbutz members, hired help and volunteers who worked in the cowsheds of the two kibbutzim were identified by the head dairy workers, based on the posted work schedule. Thirty dairy workers were identified on Kibbutz A and 22 on Kibbutz B. The workers were invited to the kibbutz clinic where each was individually interviewed. Data were collected on the presence or absence of clinical symptoms of leptospirosis during the previous month (fever, chills, headache, myalgia, weakness and/or lethargy), the presence or absence of chronic illness, the duration and frequency of work with the dairy herd, and basic demographic data. Workers with current symptoms underwent a physical examination directed towards signs of leptospirosis (hepatosplenomegaly, jaundice). All had blood drawn for serology. All those who currently worked with the dairy herd on Kibbutz A, in which there was both clinical and serologic evidence of activity of *L. hadjo* among the cows, were given doxycycline prophylactically at a dose of 200 mg, one dose weekly for 2 weeks. Dairy workers on Kibbutz B, where there was serologic evidence only of past infection among the dairy herd cows, were not prescribed prophylactic medication. Any worker whose initial serology was borderline for leptospirosis had repeat serology performed after an interval of 2–4 weeks.

Serologic testing was performed at the National Reference Laboratory for Leptospirosis by the following serologic procedure: Sera were examined by the microscopic agglutination test as described by Wolff [8]. The sera were diluted in saline to which 0.4% formalin was added. Leptospiral antigen was taken from 7 day old cultures grown in EMJH medium (Difco, USA). Antigens and sera dilutions were brought together in equal amounts and allowed to react overnight at room temperature. Clumping of 5% or more of the leptospirae constituted a positive reaction. Twenty-two reference serovars of living spirochetes were used with 20 pathogenic (*L. interrogans)* and two non-pathogenic *(L. biflexa)* serovars. A laboratory-confirmed case was defined as a fourfold increase in antibody titer or single titer of 1:200.

The medical staffs of the clinics serving the workers were contacted one month later to determine if any dairy worker had subsequently developed clinical symptoms of leptospirosis.

Results

On Kibbutz A, the mean age of the 30 dairy workers was 32.9 years (range 16–49 years) of whom 24 were men and 6 were women. The mean duration of work in the dairy herd was 5.4 years (range 1 month to 30 years). On Kibbutz B, the mean age of the 22 dairy workers was 29.3 years (range 13–44 years); 17 were men and 5 were women. The mean duration of work in the dairy herd was 2.0 years (range 1 month to 8 years).

Seven workers on Kibbutz A and one worker on Kibbutz B reported symptoms consistent with leptospirosis. All eight symptomatic workers reported headache, weakness and fatigue, while only one worker complained of fever and three others complained of upper respiratory symptoms (cough and rhinitis). All of the eight symptomatic workers had negative serology for leptospirosis.

One asymptomatic worker from Kibbutz A had an initial serology that was borderline with a titer for *L. hardjo* of 1:25. Repeat serology showed no rise in titer. This was a worker from Thailand who also showed borderline elevations of titer to a number of other serotypes of *Leptospira* (*Leptospira sejroc* M-84 1:50, *L. sejreo bratis* 1:50, *L. szwajizak* 1:50*)*. Repeat serology showed no rise in titer to these other serotypes. Three other asymptomatic workers (two from Kibbutz A and one from Kibbutz B) showed borderline elevations of titer to serotypes other than *hardjo: L. patoc*, *L. andamana*, *L. cynoperi canalzone*, *L. sejreo bratis* and *L. canicola* ATCC 23470, with no rise in titer on repeat examination 14 days later. No workers had clinical evidence of the development of clinical symptoms of leptospirosis during follow-up.

Discussion

Leptospirosis is a zoonotic disease that occurs worldwide but is most common in temperate or tropical climates. It is an occupational hazard for people who work outdoors or with animals, such as farmers, sewer workers, veterinarians, port workers, dairy farmers, and military personnel [9]. Disease is usually transmitted by contact of abraded skin or mucous membranes with water or moist materials contaminated with the urine of infected animals, but it may occasionally be transmitted by the inhalation of contaminated aerosols or the ingestion of contaminated foods [10]. Dairy workers are directly exposed to the urine of cattle and potentially contaminated by aerosols as they spray the udders of cows with water during their milking. One asymptomatic dairy worker had a weak serologic reaction to *Leptospira hardjo* (1:25) with no rise in titer on repeat serologic examination. This weak serologic reaction can be explained by past infection in his country of origin (Thailand) or cross-reaction with other diseases such as legionellosis, hepatitis or autoimmune diseases. No other dairy workers had a positive serologic reaction to *L. hardjo.*

None of the dairy workers exposed to the dairy herd infected with *L. hardjo* on Kibbutz A developed symptoms of disease, nor did any demonstrate seroconversion. This may be due to the fact that all the exposed workers received doxycycline prophylaxis as soon as the outbreak was identified in the infected herd. Recent field studies with volunteers demonstrated that 200 mg of doxycycline administered weekly was effective in the prevention of leptospirosis [11–15].

In a randomized, double-blind, placebo-controlled field trial of U.S. military personnel in the Republic of Panama, doxycycline prophylaxis was shown to be 95% ($P < 0.001$) effective in preventing disease by various serovars of leptospirae: *L. hebdomadis*, *L. pyrogenes*, *L. shermani*, *L. grippotyphosa*, *L. batavial. tarrasovi*, *L. djasima*, and *L. cynopteri*. Doxycycline (200 mg) or placebo was administered orally on a weekly basis and at the completion of training to 940 volunteers from two U.S. Army units deployed in Panama for approximately 3 weeks of jungle training. An attack rate of 4.2% in the placebo group, as compared with 0.2% in the doxycycline group demonstrated the value of doxycycline as a prophylactic drug against leptospirosis. [12]. Another randomized controlled clinical trial on North Andaman Island also showed the efficacy of doxycycline prophylaxis in the prevention of infection and clinical disease due to leptospirae during the outbreak period. A sample population of 782 people randomized into two groups was given doxycycline 200 mg/week or placebo. Infection rates were calculated in the two groups based on the serologic results. A statistically significant difference was observed in the clinical disease attack rates (3.11 vs. 6.82%) between the study group and the control group, but no difference was observed in infection rates. The results of the study indicate that doxycycline prophylaxis did not protect against infection as measured by seroconversions in an endemic area, but it did reduce morbidity and mortality during outbreaks [13]. Another double-blind, randomized, placebo-controlled pilot study found a protective effective of doxycycline for confirmed leptospirosis cases (relative risk 2.3) and seroconversion (RR 2.0) after high exposure to potentially contaminated water in Sao Paulo, Brazil. The association was not statistically significant because of the small number of individuals in this study [14].

It should be noted that dairy workers on the neighboring kibbutz B – who had presumably been exposed to *Leptospira hardjo* in the past since that herd had serologic evidence of past infection – also had no evidence of seroconversion or disease, although they had not received chemoprophylaxis. With or without chemoprophylaxis, no dairy workers exposed to either of the two herds infected with *L. hardjo* showed evidence of seroconversion or disease, indicating a low risk of transmission of this serovar from cows to dairy workers under these circumstances. We have no data on the extent and duration of shedding of *L. hardjo* by the cattle that were infected, nor do we know which dairy workers were actually exposed and for how long. Therefore, this study does not allow us to draw any firm conclusions regarding the risk of transmission of *L. hardjo* from infected dairy cows to dairy workers.

The physician in the community should take several factors into account when formulating a considered judgment as to whether or not to prescribe doxycycline prophylaxis for dairy workers exposed to a dairy herd infected with *Leptopira hardjo*. On the one hand, controlled clinical trials have proven the effectiveness of doxycycline prophylaxis in preventing seroconversion and illness among people exposed to other serovars of *Leptospira* (*L. hebdomadis*, *L. pyrogenes*, *L. shermani*, *L. grippotyphosa*, *L. bataviae*, *L. tarrasovi*, *L. djasima*, *L. cynopteri*). On the other hand, no controlled clinical trials have been conducted on the effectiveness of antibiotic prophylaxis among people exposed to the specific serovar of *L. hardjo*. An additional consideration is the long period during which cattle infected with *L. hardjo* may continue to shed infective organisms, even while receiving antibiotic treatment. Since they may continue to shed *Leptospira* for up to 6 months [15], the physician must consider the potential (unproven) benefits of doxycycline prophylaxis versus the potential adverse effects of long-term prophylaxis (potential side effects and emergence of drug resistance).

It is equally important to intervene at the route of transmission. Appropriate intervention in dairy herds infected with *Leptospira hardjo* includes: vaccination of dairy herds; isolation of infected animals and if necessary their slaughter; treatment of infected animals with antibiotics to control leptospiral shedding; disinfection of contaminated areas; and herd management (avoidance of communal pastures, purchasing from certified *Leptospira*-free stock). In addition, in order to prevent transmission of other *Leptospira* serovars, rodent control is essential. Appropriate protection of dairy workers is also necessary, such as wearing protective clothing (boots, gloves, spectacles, aprons, masks), washing off possible urine splashes or contaminated dirt, and cleaning wounds and applying water-proof dressing.

Since the 1999 outbreak of *Leptospirosis hardjo*, there have been two additional reports of activity of *L. hardjo* among dairy herds in the Negev. The treating physicians did not prescribe doxycycline prophylaxsis for the dairy workers, but other preventive measures were instituted. To date, none of the workers has developed clinical signs or symptoms of leptospirosis, indicating the low potential for transmission of *L. hardjo* from cattle to people in the hot dry climate of the southern part of Israel. Over the last 15 years, several epidemiologic characteristics of leptospirosis among humans in Israel have changed: namely, the attack rate, the affected population, and the dominant pathogenic serogroups [16]. The main change in the pattern of the disease in Israel has been the decline of occupational-agricultural related disease and the persistence of foci in large cities [16]. However, there is still a risk of exposure to *Leptospira* among dairy workers, mostly in the northern part of Israel. It is therefore important for physicians in Israel to be aware of the continued activity of *Leptospira* species in Israel, and of the need to make an informed decision about antibiotic prophylaxis among patients exposed to this bacterium.

RR = relative risk

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