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Letters to the Editor

Readers are encouraged to write letters to the editor concerning articles that have been published in Japanese Journal of Infectious Diseases.

Survey of Zoonoses in Extremadura, Spain

Dear Editor: In a previous issue of the Japanese Journal of Infectious Diseases, Asencio et al. carried out a study on the seroprevalence, and the risk factors associated with, 5 major zoonotic diseases namely brucellosis, echinococcosis, spotted fever, leishmaniasis, and toxoplasmosis, in the Spanish region of Extremadura (1). Despite their comprehensive study, and the limitations that the authors recognized in their paper, several further remarks should be taken into account.

In the introduction, authors stated that ''the actual prevalence of these diseases and their association with recognized risk factors remain unknown'', but their results showed the epidemiological situation in Extremadura region from 2002–2003. So how far are those conclusions easily extrapolated to the current situation in the same study area? The readers might be interested to know the real human population involved in the study over whom the results may be extrapolated. Census for estimations was taken in 1991. In the material and methods, several aspects may create confusion to readers; first, how were questionnaires carried out? It seems that patients were selected in health centers, but there is no comment regarding who completed the questionnaires (presumably, primary care clinicians). Moreover, there is a lack of information on the number of health centers that participated, and the number of questions included in the questionnaires. For example, after the selection of patients, how were they questioned? Were phone calls, written forms, or alternative methods used?

Additionally, more details should be given on the laboratory assays that were carried out; the name and/or references of the commercial kits used should be provided in order to facilitate further experiments by other investigators.

The main remarks are related to the risk factors analyzed. Several of them have no apparent link with the disease, e.g., ingestion of homemade sausages is related with hydatidosis, but it has never been identified as a risk factor (2), because the parasite life cycle is not known to include direct infections in humans due to meat or meat product consumption. It has instead been confirmed that the main risk factor is the ingestion of poorly washed vegetables, as may occur with *Toxoplasma gondii*. For this latter zoonotic agent, ingestion of undercooked lamb meat, contact with cats, or gardening, have been shown to be the most common exposure-related factors in Europe (3).

Additional findings need clarification; readers might be confused on what exactly ''independent risk factors'' means, or the way in which they were chosen; what is highlighted in table 2 with asterisks should be clarified; the population criteria for rural or urban distribution, and the reasons for dividing patients among 8 health areas, with limited spatial surface, if livestock farming, environmental conditions and culinary aspects might be similar, should be stated.

We strongly encourage that a similar survey should be carried out in order to update the current epidemiological situation in the Extremadura region of Spain. It is desirable that more accurate risks factors that are more specific for each disease should be taken into account. For example, the relationships between adequate washing of vegetables and fruits and *T. gondii* infection, implementation of the correct deworming plan for dogs and cats and *Echinococcus granulosus* infection, or education or socioeconomic status and *Brucella melitensis* and other zoonoses.

In conclusion, attention should be focused on the study of epidemiologically specific risk factors associated with each disease, and on obtaining up-to-date prevalence data.

Conflict of interest None to declare.

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In Reply: This letter is in reply to questions by Calero-Bernal and Delgado de las Cuevas.

Although we are aware that changes may have occurred in the epidemiology of the Spanish region studied, we believe that the current situation is not necessarily different, because only 12 years have elapsed. Furthermore, our data could serve as a reference to assess the actual changes in this time period (1). A total of 1,050,490 inhabitants were involved in the study, according to the National Statistical Institute (1,092,997 in 2015).

Patients were selected from health centers at the time of blood collection. An additional sample (10 mL in adults and 5 mL in children) was collected from those who had been sent for blood testing for any condition other than the diseases under study. Prior to blood sample collection, nurses informed all patients about the survey, and patients who agreed to participate were asked to complete a specific questionnaire at that time. If any data were missing, the patient was interviewed by telephone.

It is not possible to include ''all these data'' in an article because of the limitations of space. There were 36 participating health centers. They are listed in the accompanying table.

As previously stated, questionnaires were completed by the patients at the time of blood sample collection to ensure proper data collection. The variables included in the survey were as follows.

- Identification variables: name, age, date of birth, sex, place of residence, address, and telephone number.
- Personal and family history including diseases.
- Current and /or previous occupation and profession of head of household.
- Vaccines and drug treatment received.
- History of immunosuppressive disease and /or immunosuppressive therapy or corticosteroids in the prior 3 months (if the answer was affirmative to any of these, the patient was excluded from the study).
- Contact with animals: cattle (sheep, goats, cows), dogs, cats.
- Consumption of unpasteurized milk or dairy products (cheese and/or homemade butter), raw vegetables, homemade sausage, and/or undercooked meat (pork, wild boar).
- Field trips (hunting, fishing, etc.) and tick bites.

Antibodies to *Brucella sp*. were determined by slide agglutination by using Rose Bengal (Difco, Madrid, Spain). To confirm the results and determine the antibody titer, standard tube agglutination (Cromatest, Linear Chemicals, SL, Barcelona, Spain) was performed, with a threshold for a positive result set as a titer of 1:80. Antibody titers against hydatid disease, spotted fever, leishmaniasis, and toxoplasmosis were determined by commercial enzyme immunoassay techniques using an automated TECAN-IDT Minilyser-Genesis system (Innogenetics Diagnostics and Therapeutics, Barcelona, Spain):

- Hydatid disease, spotted fever, and leishmaniasis: Vircell IgG ELISA (Granada, Spain).
- Toxoplasmosis: Mercia Toxoplasma G EIA (Microgen Bioproducts, Surrey, the UK).

Health area	% Population	Samples per area	Number of health centers
Badajoz	22.82	80	8
Merida	14.20	50	5
Don Benito	13.79	50	5
Llerena	10.42	40	4
Caceres	17.75	60	6
Coria	4.82	20	2
Plasencia	11.25	40	4
Navalmoral de la Mata	4.91	20	2
Extremadura	100	360	36

The results published in our study identify the consumption of homemade sausage as a risk factor for hydatid disease. Assuming that the study design is accurate, we believe that our results are valid even though some are unexpected and will prompt further discussion. The assumption of a probable cross-infection had been previously proposed. Thus, some authors had claimed that indirect transfer of *Echinococcus granulosus* eggs in contaminated water and uncooked food might also cause human infection (2). In contrast, the work cited by Calero et al. did not include the consumption of any food, except for family-grown vegetables, as a possible risk factor for hydatid disease (3). Other studies could obviously confirm or refute our findings.

Two risk factors are independent when the value for one does not statistically affect the value of the other. The selection of independent risk factors is performed by multivariate analysis using logistic regression techniques. The population criterion for urban distribution is more than 10,000 inhabitants, according to the National Statistics Institute. We divided the patients into different areas because of the climatic differences of Extremadura. Therefore, farming and exploitation of resources in certain areas such as ''the Siberia extremeña'' in Badajoz (arid and dry area) and ''Valley of Jerte'' in Caceres (green area with cherry trees) are heterogeneous. Giving the results by health region, more information is provided to the reader and allows us to locate small endemic areas of zoonoses within the same population.

It would be very interesting to perform further studies to update the epidemiological situation in Extremadura, as Dr. Calero has suggested, and would enable us to compare our results. However, if consumption of homemade sausage is not included as a possible risk factor for hydatid disease, our findings would remain controversial and not purely anecdotal. We thank the authors for their helpful contributions to our study.

Conflict of interest None to declare.

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Economic Burden of Hepatitis in South Korea

Dear Editor: It is important to understand the relative economic burden of different diseases in order to make the best public health policy decisions. Therefore, we read with interest the recent paper by Shon et al. (1) who estimated the economic burden of hepatitis A, B, and C in South Korea. In their study, the population prevalence and mortality rates were estimated for each of these diseases over a 4-years study period, that is, 2008–2011. The mortality rates estimated in this study, expressed as the rate per 100,000 of the population, were over 10 times higher for hepatitis C virus (HCV) infection than for hepatitis B virus (HBV) infection. For example, mortality rate for HCV infection was 0.58 compared with 0.03 for HBV infection in 2011.

The prevalence of chronic HBV infection is considerably higher than that of HCV infection in South Korea. Furthermore, HBV was found to be associated with a majority of cirrhosis and hepatocellular carcinoma (HCC) cases in a large, single-center Korean cohort-based study (2), and the population-attributable fraction of HCC for HBV was estimated to be 68.1% (3). In contrast, Shon et al. reported higher mortality rates for HCV infection. Since the findings were unexpected, we reviewed the figures presented in the paper. We assumed that the absolute number of deaths (obtained from the Korean Statistical Information Service) were correct. Additionally, we assumed that the total number of cases of each disease (obtained from the Korean National Health Insurance Service) were correct. We obtained the total population number by back-calculation from the number of cases and population prevalence figures. Subsequently, we recalculated hepatitis B-related mortality rates (per 100,000) for each year and obtained the following numbers: 1.79 for 2008, 1.68 for 2009, 1.80 for 2010, and 1.73 for 2011. In contrast to the results published in the paper by Shon et al., we estimate that the mortality rates due to hepatitis B in South Korea were 3 to 5 times higher than those for hepatitis C.

We could not determine whether this correction of the mortality rate calculation for hepatitis B would have a significant impact on the indirect costs and calculated economic burden. However, if the authors agree with our revised mortality rate calculations, we suggest that they should confirm whether there is any impact on the estimations of the economic burden.

Additionally, our review of other figures revealed a discrepancy in the per capita total costs for hepatitis A in 2011. Our recalculation revealed a cost of 1.94, instead of 1.17 (thousands of US dollars), which is slightly higher than values reported for hepatitis B and C, and this brings it in line with the values determined for the prior 3 years for hepatitis A. Based on the original calculation showing hepatitis C accounted for the highest total per capita costs in 2011, the authors speculated that the relatively high cost of hepatitis C might be because of the higher cost of medicines used to treat that disease. However, if hepatitis A has the highest per capita cost, there might be other more important factors influencing the relative cost of the 3 diseases for each patient, which could be further investigated.

Conflict of interest HW, PM, and JE are employees of Sanofi R&D which is researching new treatments for viral hepatitis.

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In Reply: The critical comments of Watson et al. were very helpful. Accordingly, we again reviewed our manuscript. We found that the summing process of the values of each age group had errors, and some part of the paper required correction. In other words, the mortality rates for hepatitis B infection were 1.68, 1.59, 1.70, and 1.64 in 2008, 2009, 2010, and 2011, respectively. Additionally, the per capita cost due to hepatitis A infection in 2011 was found to be 1.93, rather than 1.17 thousand US dollars. Therefore, the mortality rates for hepatitis B infection was higher than those for hepatitis A and C infection during 2008–2011. However, the trend for mortality, including the increasing trend for hepatitis C infection-related mortality and steady trend for hepatitis B infection, did not change. In addition, the per capita cost for hepatitis A infection was higher than that for hepatitis B and C infection in 2011. In 2011, hepatitis A infection had the highest per capita cost, followed by hepatitis C and B infections. However, in 2010, hepatitis C infection had the highest per capita cost, followed by hepatitis A and B infections; hence, the per capita cost did not show a constant trend. Hepatitis A infection can result in severe diseases such as fulminant hepatic failure, especially in adults (1); this may explain the high per capita cost for hepatitis A infection. Table 3 also had an error in the exchange rate for the Korean won to US dollar, and this has been