Cystic Echinococcosis in the Province of Álava, North Spain: The Monetary Burden of a Disease No Longer under Surveillance

Hélène Carabin¹, Francisco J. Balsera-Rodrı́guez², José Rebollar-Sáenz², Christine T. Benner¹, Aitziber Benito³, Juan C. Fernández-Crespo⁴, David Carmena⁵

¹Department of Biostatistics and Epidemiology, College of Public Health, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, United States of America, ²Department of General Surgery, Section of Hepato-Biliopancreatic Surgery, Txagorritxu Hospital, Vitoria-Gasteiz, Spain, ³Health Promotion Section, Department of Health, Basque Government, Vitoria-Gasteiz, Spain, ⁴Laboratory of Public Health of Álava, Department of Health, Basque Government, Vitoria-Gasteiz, Spain, ⁵Parasitology Service, National Centre for Microbiology, Health Institute Carlos III, Majadahonda, Madrid, Spain

Abstract

Cystic echinococcosis (CE) is endemic in Spain but has been considered non-endemic in the province of Álava, Northern Spain, since 1997. However, Álava is surrounded by autonomous regions with some of the highest CE prevalence proportions in the nation, casting doubts about the current classification. The purpose of this study is to estimate the frequency of CE in humans and animals and to use this data to determine the societal cost incurred due to CE in the Álava population in 2005. We have identified epidemiological and clinical data from surveillance and hospital records, prevalence data in intermediate (sheep and cattle) host species from abattoir records, and economical data from national and regional official institutions. Direct costs (diagnosis, treatment, medical care in humans and condemnation of offal in livestock species) and indirect costs (productivity losses in humans and reduction in growth, fecundity and milk production in livestock) were modelled using the Latin hypercube method under five different scenarios reflecting different assumptions regarding the prevalence of asymptomatic cases and associated productivity losses in humans. A total of 13 human CE cases were reported in 2005. The median total cost (95% credible interval) of CE in humans and animals in Álava in 2005 was estimated to range between €61,864 (95%CI: €47,304–€76,590) and €360,466 (95%CI: €76,424–€752,469), with human-associated losses ranging from 57% to 93% of the total losses, depending on the scenario used. Our data provide evidence that CE is still very well present in Álava and incurs important cost to the province every year. We expect this information to prove valuable for public health agencies and policy-makers, as it seems advisable to reinstate appropriate surveillance and monitoring systems and to implement effective control measures that avoid the spread and reccurrence of the disease.

Introduction

Cystic echinococcosis (CE or hydatid disease) caused by the larval stage of the taeniid tapeworm Echinococcus granulosus is an important zoonotic disease with a worldwide distribution. Domestic transmission of the infection relies on dogs as definitive hosts and a range of livestock unglutate intermediate hosts, mainly sheep and cattle. The disease represents a serious human and animal health concern, causing important economic losses derived from the costs of medical treatment, morbidity, life impairment and fatalities in human cases and decreased productivity and viscera condemnation in livestock species [1–4]. Estimation of the CE monetary burden in humans and livestock quantifies the societal impact of the disease, which can aid policymakers in allocating financial and personnel resources. As such, these investigations should be an integral part of any decision regarding priorities for zoonoses control programs [4].

CE is considered endemic in Spain [5], but this classification varies from region to region. Attempts to effectively control the disease began in 1986 with a pilot program in the Autonomous Region (AR) of Navarre in collaboration with the Spanish Ministry of Health and the Mediterranean Zoonoses Control Centre. This initiative was soon after extended to the ARs of Aragon, Castile-La Mancha, La Rioja and Madrid [6], with some other ARs (Castile-León and Extremadura) developing independent control programs. Because of this concerted effort, there has been a marked reduction in the overall incidence rate of human CE and in the prevalence of animal CE over the past 20 years [7,8]. However, despite the program’s success, CE remains a serious health and economic problem in the North-eastern, Central and Western parts of the country [9]. The overall CE-associated economic losses in Spain were estimated to an average of €149 million (95% credible interval, CI: €22 to €394 million) for the year 2005, with human-associated costs constituting 89.1% of total losses [1]. Reporting of human CE is currently mandatory in nine of the 17 Spanish ARs. The Basque Country, to which Álava belongs, is part of the remaining eight ARs that were classified as non-endemic for CE in 1997 based on the initial success achieved after the implementation of control campaigns. This decision resulted in revoking an obligation to report new human CE cases, and
Author Summary

Historically, cystic echinococcosis (CE) is one of the most important zoonotic diseases in Spain. The initiation of a number of control campaigns in the second half of the 1980s has led to a substantial reduction of the number of CE infections both in humans and livestock species. As a consequence of this initial success, obligation to report human CE cases was revoked in 1997 in a number of Spanish autonomous regions that were consequently considered non-endemic for CE. This policy has not been translated to livestock species, where the identification of hydatid cysts and the reporting of prevalence data remain compulsory in all national slaughterhouses. We present here an estimation of the human and animal CE associated economic losses in the province of Álava, North Spain, for the year 2005. Obtained economic data corroborate the epidemiological findings and demonstrate that CE has important socio-economic consequences in Álava. Taking together, our data suggest that surveillance status of CE in Álava (and very likely in other Spanish regions currently classified as non-endemic areas) should be reassessed. The situation also indicates that more accurate and effective methods for detecting and reporting the disease at the regional and national level are greatly needed.

Materials and Methods

Ethical statement

Hospital medical records (HMR) used in this survey to gather clinical and socio-demographic data were anonymized prior to any review or analysis in order to preserve the identity of the affected patients. This study was been approved by the Research Ethics Committee of the Health Institute Carlos III.

Estimation of the annual incidence rate of human CE in Spain and Álava between 1982 and 2007

The official number of reported CE cases in the province of Álava between 1982 and 1996 and in Spain between 1982 and 2007 were obtained from the national epidemiological surveillance network [13]. Since reporting of CE cases in Álava was discontinued in 1997, we reviewed the HMRs of all patients who were diagnosed with CE in the two main hospitals of the province (Txagorrirria Hospital and Santiago Apóstol Hospital) from 1991 to 2007. In Álava, all patients suspected of having hydatid cysts (e.g. positive scrology) are referred to one of these hospitals for confirmation and treatment. The population sizes for 1982 to 2007 in Álava were taken from the Basque Statistics Institute [14]. The annual incidence rate (per 100,000 person-years) was estimated by dividing the total number of cases residing in Álava at the time of diagnosis by the estimated population size for that year, and then multiplying by 100,000. Socio-demographic (age group, gender, place of birth and residence at the moment of diagnosis, urban/rural environment) and clinical (methods of diagnosis, cyst type and location, complications presented, treatment adopted, follow-up, re-operations, re-infection, mortality rate) parameters were retrieved from the HMR of each individual CE case attended in the two hospitals between 1991 and 2007.

Estimation of the prevalence of CE among sheep and cattle slaughtered in Spain and the Basque Country between 1998 and 2006

The numbers of sheep and cattle found to have CE lesions at slaughter in the Basque country during the period 2000–2006 were provided by the Department of Health of the Basque Country. Equivalent figures at the national level between 1998 and 2006 were obtained from the Spanish reports on Trends and Sources of Zoonoses and Zoonotic Agents in Humans, Animals and Foodstuff submitted to the European Food Safety Authority [15]. Regional and national data do include home slaughtered animals infected with CE since by law, every killed animal destined to human consumption must be examined by a veterinarian.

Human epidemiological and clinical parameters for the 2005 economical valuation

Estimation of the frequency of treatment of diagnosed cases.

The frequency of different diagnosis and treatment received by the 13 CE cases diagnosed in 2005 was extracted from the HMR data of the two main hospitals in Álava described above (Table 1). Additional epidemiological parameters were obtained from the literature (Table 2). Eight patients were surgically- or chemotherapeutically treated, whereas five patients were left untreated under a watch-and-see policy. Recidival disease was documented in two of the treated patients: one was further subjected to chemotherapy and the remaining one left untreated. Overall, a single 91-years old female patient died in 2005 as a consequence of the infection.

Estimation of the frequency of undiagnosed cases.

Diagnosed CE cases are considered to be only the tip of the iceberg when it comes to estimating the monetary burden of CE, since undiagnosed and asymptomatic cases are believed to suffer productivity losses due to the disease [1–4,16]. Yet, no ultrasound surveys to detect CE have been conducted in Spain. Therefore, we used three different approaches to estimate the number of asymptomatic cases. In a first approach, it was assumed that there were no asymptomatic cases. For the two other approaches, we assumed that the prevalence of undiagnosed cases would be proportional to that estimated in the only two available studies linking CE ultrasound-based prevalences and the incidence rates of clinical cases seen in hospital in the same geographic region namely ultrasound surveys conducted in individuals of all ages from rural Uruguay (prevalence of 1.64%) [17] and children in
Turkey (prevalence of 0.24%) [18]. In these two studies(), the average annual clinical incidence rates based on hospital cases were 36.1 and between 2 and 3.4 cases per 100,000 person-years (average of 2.7 cases per 100,000 person-years), for ratios of undiagnosed cases to clinical cases seen in hospitals of 45.4 and 88.9, respectively. When applying these ratios to the incidence rate of clinical CE cases seen in hospitals in the province of Álava in 2005 (305,822 inhabitants; 4.25 cases per 100,000 person-years), we estimated the mean prevalence of undiagnosed or asymptomatic CE cases to be between 0.19% and 0.38%. Hence, in our

Table 1. Distribution of diagnostic tests and treatments received by diagnosed human CE cases in 2005 (13 cases) and for the period between 1991 and 2007 (154 cases) in the two major hospitals capturing all CE cases in Álava.

| Type of diagnosis and treatment (%) | 2005 | 1991–2007 |
|-----------------------------------|------|-----------|
| **Diagnosis**                      |      |           |
| Clinical<sup>a</sup>               | 7.7  | 10.5      |
| Serology                          | 23.1 | 15.7      |
| Chest X-ray                       | 15.4 | 5.2       |
| CT                                | 76.9 | 73.2      |
| Ultrasonography                   | 30.8 | 43.8      |
| MRI                               | 7.7  | 7.8       |
| No Data                           | 0.0  | 5.2       |
| **Treatment**                     |      |           |
| Chemotherapy                      | 15.4 | 11.8      |
| Surgery                           | 46.1 | 54.9      |
| Total exeresis                    | 23.1 | 20.2      |
| Partial exeresis                  | 7.7  | 28.1      |
| Not specified                     | 15.3 | 6.6       |
| None                              | 38.5 | 41.8      |
| No data                           | 0.0  | 0.6       |
| **Post-treatment recidives<sup>b</sup>** |     |           |
| Over 2 patients                   | 61.5 | 66.2      |
| Over 21 patients                  |      |           |
| Chemotherapy                      | 50.0 | 33.3      |
| Surgery                           | 0.0  | 57.1      |
| Combined                          | 0.0  | 4.8       |
| None                              | 50.0 | 4.8       |
| **Follow up**                     |      |           |
| Yes                               | 38.5 | 47.3      |
| Average (Months)                  | 13.5 | 37.2      |
| No                                | 61.5 | 46.7      |
| No data                           | 0.0  | 6.0       |
| **Mortality due to CE**           | 7.7  | 3.9       |
| **Length of hospital stay (Days)** | 18.4 | 10.4      |

<sup>a</sup>Diagnosis based on signs and symptoms of the disease.

<sup>b</sup>Treatment provided to those patients that experienced recrudescence of the disease after being chemotherapeutically- or surgically treated.

Table 2. Additional epidemiological parameters used to estimate the cost of medical treatment for cystic echinococcosis in Álava, 2005.

| Item                                      | Frequency | Distribution       | Reference |
|-------------------------------------------|-----------|--------------------|-----------|
| Duration of follow-up                     | 4.5 months| Uniform (3,6)      | [39]      |
| Number of follow-up visits to monitor drug response | 7.5       | Fixed              | [40]      |
| Albenzazole treatment dose (per day)      | 800 mg    | Fixed              | [39]      |

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second approach, we used a uniform distribution between the Uruguay estimate (0.19%) and the Turkey estimate (0.30%), while in our third approach we used a triangular distribution between 0% and the Turkey estimate (0.30%), with a mode at the Uruguay estimate (0.19%), to represent the frequency of undiagnosed cases and its uncertainty. The estimated total number of asymptomatic cases under each approach was assumed to follow the age-gender distribution of cases seen in the two reference hospitals between 1991 and 2006.

**Estimating the level of productivity lost to diagnosed and undiagnosed CE.** Seven out of the thirteen CE cases diagnosed in 2005 required hospitalization for diagnosis or treatment procedures. The length of stay of hospitalisation of each of the seven CE inpatients was extracted from the hospital medical charts and used to estimate the wage lost during hospitalization for CE patients. In addition, all diagnosed (inpatients and outpatients) and estimated undiagnosed CE cases were assumed to lose some percentage of their productive time to CE. Although a lower quality of life has been reported among asymptomatic cases of CE [16], the percentage of productivity loss for these cases is unknown. The only available estimate comes from an assumed use in a study aimed at estimating the monetary burden of CE in Uruguay, where asymptomatic cases were assumed to see a 2% decrease in their annual productivity [19]. Due to the very uncertain nature of this estimate, we modelled productivity losses using two distributions: a uniform distribution ranging from 0% to 4% and a general beta distribution with parameters 1 and 3 (average of 1%), and truncated between 0% and 4%. A third approach, using a triangular distribution with minimum and mode values of 0% and a maximum of 4% was explored but not presented. No losses associated with death were included in the analysis since the only death occurring in 2005 was a female whose age was over the life expectancy for Spanish women.

**Source of health provider and non-health provider costs**

To estimate the annual overall cost of human CE we included both health provider (direct) costs and non-health provider (indirect) costs. The health provider costs were obtained from the Txagorritxu Hospital financial department for the year 2008 and adjusted the values for 2005, accounting for inflation. Since the health system is public in Spain, the costs in all hospitals in Álava are similar. The cost of each diagnostic test, surgical intervention, and medical treatment reported to have been used for the CE cases treated in 2005 was obtained. Health provider cost estimates included separate calculations for surgical and non-surgical patients.

The non-health provider costs only included productivity losses during hospitalisation for inpatients and productivity losses due to the disease itself for all CE cases. No productivity losses were attributed to medical visits since no information was available on the duration of each visit, and that the work or activities lost during the visit could be completed when the patients returned to their work or home (for retired people). Average wages according to sex and age for the Basque Country, including average pensions for retired people, were obtained from the 2005 Wage Distribution Survey of the National Statistics Institute [20]. We assumed equivalent wages for the province of Álava. The itemised cost menu is presented in Table 3.

**Livestock epidemiological parameters**

Production animal species considered in the analyses included sheep and cattle. Goats and pigs were not considered because none were identified with CE-infection during the study period. Due to the lack of active abattoirs in Álava in 2005, most of the animals from this province were slaughtered somewhere else in the AR of the Basque Country. Therefore, CE infection prevalence proportions in sheep and cattle in Álava were assumed to be the same as those globally reported for the AR of the Basque Country. Final prevalence estimates excluded data from non-autochthonous CE cases (91.1% of infected sheep and 79.2% of cattle were raised and slaughtered in the AR of the Basque Country) [9]. The number of sheep and cattle infected in Álava was estimated by multiplying the prevalence of CE among autochthonous animals slaughtered in the AR of the Basque country by the total population of each species in Álava. Estimates for autochthonous livestock life expectancy and reproductive rates were provided by Carlos Marín Ruiz (Department of Livestock, Regional Government of Álava). Official figures for annual livestock meat and milk production were obtained from the Spanish Ministry of Agriculture, Food and Environment [21]. Data stratified by age (young lambs: <1.5 months; lambs: 1.5 months to 1 year; adult sheep: >1 year old; calves: <1 year old; young cattle: >1 and <2 year old; adult cattle: >2 year old) were included when available. Productivity losses associated with CE – including reduction in growth, reduction in milk production and decrease in fecundity – were estimated from the published literature available [7,22–25]. All productivity losses estimates were attributed a uniform distribution to reflect their uncertainty (Table 4). The costs of fecundity and growth losses were only estimated for meat animals up to 1 year for sheep (lamb) and 2 years for cattle (beef cattle). The animal epidemiological parameters used in this study are reported in Table 4.

**Estimation of livestock costs**

Direct costs (loss of revenue through offal condemnation) and indirect costs (reductions in growth, fecundity, and milk production) were the parameters we used to estimate the overall losses associated with bovine and ovine CE in Álava province in 2005. The itemised cost menu for animal losses is presented in Table 5.

**Offal condemnation (direct costs).** In the province of Álava, like the rest of Spain, identification of hydatid cysts at meat inspection leads to condemnation of infected offal. The distribution of liver, lung, and liver and lung lesions at slaughter was estimated at 5%–15%, 25%–35% and 50%–70% for sheep and 17.9%, 6.4% and 73.5% for cow, respectively, based on a study conducted in abattoirs in Romania [26]. The direct lost revenue for each CE-infected animal was estimated according to the average weight (see ref. [1]) and market value [27] of both liver and lung by species and age at slaughter. We calculated the direct costs by multiplying the lost earnings at abattoir per animal with the number of reported infected animals in each species group.

**Growth reduction.** A reduced carcass weight of CE infected animals at slaughter was assumed. We first estimated the difference in income from the sale of a healthy carcass and a CE-infected carcass (which will weigh less due to growth reduction) for each species. We calculated the net loss to the farmer per infected animal as the difference between the potential income and the reduced price of an unhealthy animal, accounting for the annual farmer investment for an individual sheep or cow projected to 2005 values [28]. We assumed that farmers would invest equally in a CE-infected or uninfected animals, but the CE infected animal would weigh less. For all species, the annual cost for CE-associated growth reduction was calculated from the product of the loss in net profit per infected animal and the number of infected animals identified at slaughter for each species.

**Milk production.** Estimates of total annual milk production and current CE prevalence in dairy species were used to estimate losses due to reduction in milk production. Based on published estimates of the average reduction in an infected animal’s annual milk yield that is attributable to CE, we calculated the potential
milk not produced due to infection in each species population. Total costs were calculated by multiplying annual loss of milk in an infected animal by the 2005 dairy market prices for each species. Decreased fecundity. Losses associated with unborn animals were limited to meat producing breeds in sheep and cattle. To simulate the birth rate in the absence of infection, we divided the total number of meat animals born per year by the sum of the number of not infected meat reproductive females and the number of infected meat reproductive females times the reduction in fecundity [24]. The number of meat animal born that would be born in the absence of infection was estimated by multiply the total number of reproductive meat females by the birth rate in the absence of infection. We estimated the total number of unborn animals by calculating the difference between the potential and actual births for each species.

Sensitivity analyses

We generated five different scenarios to assess the impact of undiagnosed or asymptomatic CE cases in the province of Álava and the annual productivity losses due to CE infection in humans given the variability of both parameters in the available literature [17,18] (Table 6). Scenario 1 includes wages lost during hospitalization for inpatients but excludes productivity losses and asymptomatic cases. Scenario 2 includes annual productivity losses (uniform distribution between 0% and 4% per year) and applied to both diagnosed cases and estimated number of asymptomatic cases based on a uniform distribution between the Turkey and Uruguay estimates [18]. Scenario 3 uses the same method except that a triangular distribution is applied to estimate the number of asymptomatic cases centred around the Uruguay estimate [17], with minimum prevalence set to zero and using the upper limit of the Turkey estimate as a maximum value [18]. Scenarios 4 and 5 use the same models to estimate the number of asymptomatic cases, but using a Beta distribution ascribed to the reduction in annual productivity.

For each scenario, 10,000 iterations were generated using Latin hypercube random sampling of the input parameter values and based on their assigned distributions. The 50th percentile of this

### Table 3. Age-gender stratified wages in the Basque Country in 2005 and costs of treatment and diagnostic test to treat CE patients in Álava, 2005.

| Economic Parameters | Value | Reference |
|---------------------|-------|-----------|
| **Average yearly wage (€)** | | |
| For males, by age group (years) | | |
| <25 | 16,508 | [20] |
| 25–34 | 20,872 | [20] |
| 35–44 | 23,343 | [20] |
| 45–54 | 31,100 | [20] |
| ≥55 | 29,482 | [20] |
| For females, by age group (years) | | |
| <25 | 12,309 | [20] |
| 25–34 | 16,873 | [20] |
| 35–44 | 19,253 | [20] |
| 45–54 | 21,570 | [20] |
| ≥55 | 21,138 | [20] |
| **Cost of diagnostic procedures and medical treatment/care (€ per case)** | | |
| Chest X-ray | 9.7–11.9 | Uniform distribution from Txagorritxu Hospital |
| CT | 98.6 | Txagorritxu Hospital |
| MRI | 222.7 | Txagorritxu Hospital |
| Ultrasonography | 38.5 | Txagorritxu Hospital |
| ECG | 6.3 | Txagorritxu Hospital |
| Standard analyses | 13.1 | Txagorritxu Hospital |
| Serology (hydatidosis) | 20.1 | Txagorritxu Hospital |
| Chemotherapy (Mbz/Albz) | 59.3 | Txagorritxu Hospital |
| Initial Outpatient medical visit | 103.2 | Txagorritxu Hospital |
| Follow-up outpatient medical visits | 52.03 | Txagorritxu Hospital |
| CBC count | 13.1 | Txagorritxu Hospital |
| **Cost of surgical procedures (€ per case)** | | |
| a | 2,832–3,776€ | Uniform distribution from Txagorritxu Hospital |

*This figure includes the cost of diagnosis, anesthesia, treatment of complications of surgery, post-operation follow-up, re-operations, medical care during hospitalization and hospitalization). CT, computed tomography; ECG, electrocardiogram. Mbz/Albz, mebendazole/albendazole; MRI, magnetic resonance imaging.

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Table 4. Epidemiological parameters used to estimate the economic losses associated with CE in livestock, Álava, 2005.

| Parameter                                                                 | Value       | Distribution | Range       | Unit       | Reference |
|----------------------------------------------------------------------------|-------------|--------------|-------------|------------|-----------|
| Total sheep population<sup>a</sup>                                         | 88,369      | Fixed        | NA          | Individuals| [27]      |
| Lambs<sup>a</sup>                                                          | 4,600       | Fixed        | NA          | Individuals| [27]      |
| Lambs for slaughter                                                        | 47,709      | Fixed        | NA          | Individuals| [27]      |
| Proportion of slaughtered lambs aged <1.5 months                           | 28          | Fixed        | NA          | % of slaughtered lambs | [27] |
| Adults for slaughter                                                       | 53          | Fixed        | NA          | Individuals| [27]      |
| Ewes producing milk<sup>a</sup>                                            | 28,691      | Fixed        | NA          | Individuals| [27]      |
| Ewes producing meat lamb<sup>a</sup>                                       | 29,019      | Fixed        | NA          | Individuals| [27]      |
| Adult nulliparous ewes<sup>a</sup>                                         | 23,871      | Fixed        | NA          | Individuals| [27]      |
| Males for reproduction                                                     | 2,187       | Fixed        | NA          | Individuals| [27]      |
| Prevalence of infection at inspection                                      | 1.76        | Fixed        | NA          | % of infected animals at slaughter | Calculated |
| Lambs                                                                      | 1.74        | Fixed        | NA          | % of infected animals at slaughter | Basque Government |
| Adults                                                                     | 1.79        | Fixed        | NA          | % of infected animals at slaughter | Basque Government |
| Proportion of infected sheep with lung cysts only                          | 10          | Uniform      | 5–10        | % infected sheep at slaughter | [26] |
| Proportion of infected sheep with liver cysts only                         | 30          | Uniform      | 25–35       | % infected sheep at slaughter | [26] |
| Proportion of infected sheep with lung and liver cysts                     | 60          | Uniform      | 50–70       | % infected sheep at slaughter | [26] |
| Average weight                                                             |             |              |             |            |           |
| Live lamb (<1.5 months)                                                    | 11          | Uniform      | 8–14        | Kg         | [20]      |
| Live lamb (1.5 months-1 year)                                              | 24          | Uniform      | 22–26       | Kg         | [20]      |
| Lamb liver                                                                 | 0.85        | Uniform      | 0.8–0.9     | Kg         | Extrapolated from [41,42] |
| Lamb lung                                                                  | 0.60        | Uniform      | 0.5–0.7     | Kg         | Extrapolated from [41,42] |
| Sheep liver                                                                | 1.00        | Uniform      | 0.9–1.1     | Kg         | Extrapolated from [43] |
| Sheep lung                                                                 | 0.70        | Uniform      | 0.6–0.8     | Kg         | Extrapolated from [43] |
| Mean lambing/year – meat sheep                                             | 1.5         | Fixed        | NA          | Lambs per ewe per year | See text   |
| Average milk yield of dairy sheep                                          | 165         | Uniform      | 160–170     | Kg per year | Extrapolated from [20] |
| Total cattle population<sup>b</sup>                                         | 40,196      | Fixed        | NA          | Individuals| [27]      |
| Calves (<1 yr. old) for slaughter                                          | 170         | Fixed        | NA          | Individuals| [27]      |
| Calves for milk replacement                                                | 1,923       | Fixed        | NA          | Individuals| Estimate  |
| Calves for beef cattle                                                     | 5,869       | Fixed        | NA          | Individuals| Estimate  |
| Calves for beef cattle reproduction                                        | 2,096       | Fixed        | NA          | Individuals| Estimate  |
| Beef cattle (>1 and <2 yr. old) for slaughter                              | 3,987       | Fixed        | NA          | Individuals| [27]      |
| Young animal for milk replacement                                          | 441         | Fixed        | NA          | Individuals| Estimate  |
| Young animals for beef cattle reproduction                                  | 236         | Fixed        | NA          | Individuals| Estimate  |
| Adults (>2 yr. old)<sup>a</sup>                                            | 25,382      | Fixed        | NA          | Individuals| [27]      |
| For slaughtering (cows)                                                    | 2,393       | Fixed        | NA          | Individuals| [27]      |
| For slaughtering (bulls)                                                   | 4,665       | Fixed        | NA          | Individuals| [27]      |
| For milk production                                                        | 6,915       | Fixed        | NA          | Individuals| [27]      |
| No. of cattle slaughtered/year                                              | 11,215      | Fixed        | NA          | Individuals| [27]      |
| Calves                                                                     | 170         | Fixed        | NA          | Individuals| [27]      |
| Beef cattle                                                                | 3987        | Fixed        | NA          | Individuals| [27]      |
| Adult cows                                                                 | 2393        | Fixed        | NA          | Individuals| [27]      |
| Bulls                                                                      | 4665        | Fixed        | NA          | Individuals| [27]      |
| No. of infected cattle slaughtered/year                                    | 304         | Fixed        | NA          | Individuals| Calculated |
| Prevalence of infection at inspection                                      | 2.71        | Fixed        | NA          | % of infected animals at slaughter | Basque Government |

<sup>a</sup> Calculated

<sup>b</sup> Extrapolated from [20]
Table 4. Cont.

| Parameter                                           | Value | Distribution | Range       | Unit  | Reference |
|-----------------------------------------------------|-------|--------------|-------------|-------|-----------|
| Proportion of infected cattle with lung lesions only| 17.9  | Fixed        | NA          | Percent| [26]      |
| Proportion of infected cattle with liver lesions only| 6.4   | Fixed        | NA          | Percent| [26]      |
| Proportion of infected cattle with lung and liver lesions| 73.5  | Fixed        | NA          | Percent| [26]      |
| Average weight                                      |       |              |             |       |           |
| Live calf                                           | 160.0 | Uniform      | 130–190 Kg  | Kg    | [20]      |
| Live young cattle                                    | 480.00| Uniform      | 460–500 Kg  | Kg    | [20]      |
| Calf liver                                          | 3.20  | Uniform      | 2.9–3.5 Kg  | Kg    | [44–46]   |
| Calf lung                                           | 3.75  | Uniform      | 3.5–4.0 Kg  | Kg    | [44–46]   |
| Young animal lung                                    | 5.09  |              |             |       |           |
| Young animal liver                                   | 5.25  |              |             |       |           |
| Cow liver                                           | 6.35  | Uniform      | 5.4–7.3 Kg  | Kg    | [44–46]   |
| Cow lung                                            | 6.15  | Uniform      | 5.2–7.1 Kg  | Kg    | [44–46]   |
| Mean calving/year – beef cow                        | 1.05  | Fixed        | NA          | Calves per cow per year | See text |
| Average milk yield of dairy cow                     | 7,064 | Fixed        | NA          | Kg per year | [27] |
| Productivity losses – all livestock                 |       |              |             |       |           |
| Decrease in fecundity                               | 5.5   | Uniform      | 0.0–11.0 % decrease per year | [24] |
| Decrease in carcass weight                          | 6.25  | Uniform      | 2.5–10.0 % decrease per year | [7,25] |
| Decrease in milk production                         | 2.5   | Uniform      | 0.0–5.0 % decrease per year | [7,25] |

*Census at 31 December 2005.
NA, not applicable.
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Table 5. Cost parameters used to estimate the economic losses associated with CE in sheep and cattle, Álava, 2005.

| Parameter                                           | Value | Reference |
|-----------------------------------------------------|-------|-----------|
| **Sheep**                                           |       |           |
| Average value                                       |       |           |
| Amount paid to farmer for young lamb live carcass (<1.5 months) (€ per 100 kg) | 404   | [27]      |
| Amount paid to farmer for lamb live carcass (>1.5 months) (€ per 100 kg) | 265   |           |
| Sheep liver (€ per kg)                               | 0.65  | [27]      |
| Sheep lung (€ per kg)                                | 0.09  | [27]      |
| Sheep’s milk at farm gate (€ per 100 L)              | 79.11 | [21]      |
| Farmer investment (€ per kg)                         | 1.59  | Extrapolated from [28] |
| **Cattle**                                          |       |           |
| Average value                                       |       |           |
| Amount paid to farmer for young calf live carcass (<1 year) (€ per 100 kg) | 379.95 | [27]      |
| Amount paid to farmer for beef cattle live carcass (1–2 year) (€ per 100 kg) | 335.09 | [27]      |
| Young live cow (€ per kg)                            | 1.76  | [21]      |
| Beef carcass (€ per kg)                              | 3.35  | Extrapolated from [27] |
| Cow liver (€ per kg)                                 | 0.85  | [27]      |
| Cow lung (€ per kg)                                  | 0.06  | [27]      |
| Cow’s milk at farm gate (€ per 100 L)                | 31.25 | [21]      |
| Farmer investment/kg (€ per kg)                      | 2.04  | Extrapolated from [28] |
doi:10.1371/journal.pntd.0003069.t005
A stepwise linear regression of the estimated costs against the input parameter values (i.e. the parameters with a distribution) was performed to assess the impact of each uncertain parameter on the overall cost estimate. The estimates from models with and without asymptomatic cases and the resulting figures illustrating the impact of input parameters were generated using @Risk Version 5.5.0 software (Palisades Corporation, Ithaca, New York, USA), running as an add-in to Microsoft Excel.

# Results

## Annual incidence rate of human cystic echinococcosis between 1982 and 2007 in Spain and Álava

Figure 1 shows available historical annual incidence rate of human CE in the province of Álava obtained from different sources, including revised HMR (1991–2007) and the official incidence of the disease (1991–1996) provided by the Compulsory Notifiable Diseases system (CND) of the national epidemiological surveillance network [13]. National official incidence rates (1982–2007) have also been included for reference [13]. Not surprisingly, HMR evidenced remarkably higher human CE rates than those reported by the CND, with an average 6-fold increase for the common period between 1991 and 1996. Similarly, a 4-fold increase was observed when the HMR figures were compared to the national official incidence rates for the period between 1997 and 2007.

## Socio-demographic characteristics of human CE cases treated in Álava between 1991 and 2007

One hundred and fifty-four (154) patients were diagnosed with human CE during 1991–2007 in the two main hospitals of the province of Álava (Table 7). The male/female ratio was 1.05 and the age of cases ranged from 13 to 91 years (mean: 61.5; SD: 17.8).

### Table 6. Sensitivity analyses and conditions used to estimate the economic losses associated with CE in humans and livestock (sheep and cattle), Álava, 2005.

| Scenario | Distribution of the proportion of undiagnosed cases | Distribution of productivity losses percent |
|----------|-----------------------------------------------------|-------------------------------------------|
| 1        | NA                                                 | NA                                       |
| 2        | Uniform(0.19,0.38)%                                 | Uniform (0,4%)                            |
| 3        | Triangular(0%,0.19%,0.38%)                          | Uniform (0,4%)                            |
| 4        | Uniform(0.19%,0.38%)                                | Beta General (1,3,0,0.04)                 |
| 5        | Triangular(0%,0.19%,0.38%)                          | Beta General (1,3,0,0.04)                 |

*Extrapolated from data obtained from reference [18] and [19], see text.

NA, not applicable.

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Figure 1. Annual incidence rate per 100,000 inhabitants of cystic echinococcosis in the province of Álava using hospital medical records (1991–2007), and the national surveillance system at the provincial (1982–1996) and national (1982–2007) levels. Legend: Full circles: Estimated annual incidence rate using the Álava Compulsory Notifiable Diseases system; Full squares: Estimated annual incidence rate using the National (Spain) Compulsory Notifiable Diseases system including data from all 17 Spanish autonomous regions (1982–1996) and the nine Spanish autonomous regions considered endemic after (1997–2007); Full triangles: Estimated annual incidence rate using the Hospital Medical Records from the two treating hospitals for CE in Álava. CND: Compulsory Notifiable Diseases system; HMR: Hospital Medical Records.

doi:10.1371/journal.pntd.0003069.g001
Only three subjects (1.9%) were of paediatric age (defined as ages from birth to 15 years of age), while patients over 60 years old accounted for 61.7% of cases. Most (57.8%) diagnosed cases were native to Álava. Only 4 individuals (2.6%) were born outside of Spain. The vast majority (144 cases, or 93.5%) of cases resided in the province at the moment of diagnosis, with 81.2% living in urban settlements in or around the capital Vitoria-Gasteiz. CE patients residing in rural areas were exclusively distributed alongside the eastern, southern, and western boundaries of the province bordering the ARs of Navarre, La Rioja, and Castile-León, respectively (Figure 2).

Comparison of the characteristics of the CE cases diagnosed in Álava in 2005 and between 1991 and 2007

Economic losses for CE in humans in 2005 were based on the 13 cases diagnosed at Txagorritxu Hospital (7 cases) and the Santiago Apóstol Hospital (6 cases). In order to demonstrate the representativeness of the data obtained from the HMR of these 13 patients, we carried out a direct comparison of the average figures of different clinical and epidemiological parameters in 2005 and those corresponding for the whole period 1991–2007. Compared variables included the type of method used to reach a diagnosis, the specific treatment (if any) followed, and also relevant socio-demographic parameters. As clearly shown in Table 1, Table 2, and Table 7, average figures obtained for the years 2005 are in close agreement with those for 1991–2007, demonstrating that the set of data we have used in our analyses did not have unexpected or out of range values and providing evidence of the robustness and accuracy of our results.

Prevalence of CE among sheep and cattle slaughtered in Spain and Álava between 1998 and 2005

CE prevalence in livestock species (sheep and cattle) for the period 1998–2006 in Spain and the Autonomous Region of the Basque Country were obtained from official sources. Both epidemiological series showed a sustained, declining trend with average ovine and bovine prevalence 2- and 4-fold higher in the Basque Country than in Spain, respectively (data not shown). In the AR of the Basque Country ovine and bovine infections were 2.4% and 6.1% in 2000 and 0.1% and 1.7% in 2006, respectively.

Economic losses in human and livestock cystic echinococcosis

The five scenarios run to estimate the total cost of CE in Álava for 2005 showed considerable variation, depending on assumptions made on the prevalence of asymptomatic cases and their associated productivity losses (Table 3 and Figure 3). When asymptomatic cases and productivity losses were excluded, the median cost was estimated at €61,864 (95%CI: €47,304–€76,590). All other scenarios had a lower credible interval.
superior to €61,000, but the lower whiskers (25th percentile minus 1.5 times the interquartile range) were similar among the models, with a value similar to the median under scenario 1 [see Figure 3]. Scenarios 2 and 3, where productivity losses were assumed to follow a uniform distribution between 0% and 4%, resulted in the largest and most uncertain estimates.

Total livestock losses were estimated at €26,425 (95%CI: €76,424–€752,462), with indirect costs representing 93% of the total costs. Compared to human monetary losses, livestock costs represented 43% of the total costs in scenario 1 whereas they represented only 7% of the total costs in scenario 2, where the total median cost was estimated at €360,466 (95%CI: €76,424–€752,462). Figure 4 shows that most of the variation in the total costs in scenario 1 could be attributed to animal productivity estimates. In scenarios 2–5, the total costs depended largely on the percentage of productivity losses (normalized regression coeffi-

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**Table 7. Human CE epidemiological parameters based on individual hospital clinical histories in Álava, 1991–2007.**

| Parameter                        | 2005  | 1991–2007 |
|----------------------------------|-------|-----------|
| Total no. of diagnosed cases     | 13    | 154       |
| in males, by age group, in years |       |           |
| 0–19                             | 0     | 1         |
| 20–29                            | 0     | 6         |
| 30–39                            | 0     | 8         |
| 40–49                            | 2     | 12        |
| 50–59                            | 2     | 18        |
| 60–69                            | 2     | 21        |
| 70–79                            | 0     | 8         |
| ≥80                              | 0     | 3         |
| Place of birth (%)               |       |           |
| A.s. Álava                       | 53.8  | 57.8      |
| Rest of the Basque Country       | 0.0   | 3.2       |
| Rest of Spain                    | 30.8  | 31.8      |
| Abroad                           | 0.0   | 2.6       |
| Gender (%)                       |       |           |
| Male                             | 46.2  | 51.3      |
| Female                           | 53.8  | 48.7      |
| Place of residence at diagnosis (%) |       |           |
| A.s. Álava                       | 100   | 93.5      |
| Place of birth (%)               |       |           |
| Rural                            | 30.8  | 18.8      |
| Urban                            | 69.2  | 81.2      |

Distributions have been indicated for those parameters used to estimate the human economic losses associated with CE in Álava, 2005. doi:10.1371/journal.pntd.0003069.t007
cients ranging from 0.82 in scenario 3 to 0.98 in scenario 4), followed by the estimated prevalence of asymptomatic cases in the population (normalized regression coefficients ranging from 0.43 in scenario 5 to 0.53 in scenario 3). The next parameter to contribute to the overall variation was the reduction in milk production with normalized regression coefficients of 0.03 in scenario 2 and 0.06 in scenario 5.

Discussion

This comprehensive assessment of human and animal CE in Álava demonstrates that CE remains a veterinary public health concern in this Spanish province. Active search of patients diagnosed with CE in HMR demonstrated that the incidence of the disease during the study period is 4- to 6-fold higher than the figures reported in official sources, both at regional and national levels. These results are in-line with recent reports that the CND system underestimates the true incidence of CE disease in Spain [9,29–31]. It should be noted that of the three paediatric patients identified one was born in Mauritania (a 13 years-old male), whereas the other two subjects (two females aged 13 and 14 years, respectively) were born and grew up in the province of Álava. Although acquisition of the infection in other regions/countries cannot be entirely ruled out (e.g. no records of travelling abroad were available), these two patients were almost certainly autochthonous cases. This finding, together with the previous detection of adult E. granulosus worms in both urban [10] and rural [11] dog populations, strongly suggests that an active transmission cycle of the parasite is being maintained in Álava. It has been recently reported that between 21–60% of CE cases from Spanish HMR correspond to immigrants from endemic countries [31,32]. This is not the case in Álava, where only 4 patients (2.6%) were born abroad (one in France, one in Portugal and two in Mauritania). Comparing the proportion of cases among immigrants is difficult, since immigrants in the AR of the Basque Country represent a low percentage of the total population compared to other Spanish ARs.

Regarding livestock CE, the prevalence of the infection in production animal species in the province of Álava was assumed identical to that of the AR of the Basque Country. This assumption is reasonable because i) no operational abattoirs were running in the province during 2005 ii) animals raised in Álava were almost exclusively slaughtered in abattoirs of the AR of the Basque Country, and iii) due to the small size of this AR, the environmental and biological characteristics and the livestock management techniques are homogeneous across the region. The trend of our CE prevalence data series is in agreement with those reported at national level showing slow but sustained reduction in animal infection and ultimately reaching a plateau [9]. This may suggest that CE infection has diminished during the transition from ‘attack phase’ to the ‘consolidation phase’ of the control programs implemented in Spain in the 1980’s. Consistent with the human incidence data, average ovine and bovine CE prevalence for the 2000–2004 period were 2- and 4-fold higher in the Basque Country than in Spain, respectively. In this regard, it is worth mentioning that CE bovine infection proportions in the Basque Country have increased from 1.5% in 2006 to 4.6% in 2007 and 4.1% in 2008 [12]. Whether this finding indicates a true re-emergence will require further investigation. Taking together our epidemiological data clearly indicate that both human and animal CE infection rates in the province of Álava/Basque Country are well above the national average figures.

The preferred way to capture both the human and agricultural effect of a zoonosis is to estimate its economic impact [33]. Indeed, to determine the economic burden of human and animal CE is recently identified by international experts as one of the key

Figure 3. Boxplot representing the estimated total costs of CE in Spain in 2005 under the five scenarios. Legend: Lower line of the box represents the 25th percentile value. Middle line of the box represents the median. High line of the box represents 1.5 the 75th percentile value. The upper whisker represents the 75th percentile plus 1.5 the interquartile range. The lower whisker represents the 25th percentile minus 1.5 the interquartile range. The dots over the high lines represent values that lie outside the lower and upper whisker values (outliers). doi:10.1371/journal.pntd.0003069.g003
Table 8. Median costs, in euros, associated with CE in humans and livestock (sheep and cattle), including and excluding asymptomatic or undiagnosed productivity losses in each scenario considered, Álava, 2005.

| Scenario | 1 | 2 | 3 | 4 | 5 | Median | 95% CI | Median | 95% CI | Median | 95% CI | Median | 95% CI | Median | 95% CI | Median | 95% CI |
|----------|---|---|---|---|---|--------|-------|--------|-------|--------|-------|--------|-------|--------|-------|--------|-------|
| **Human** | | | | | | | | | | | | | | | | | |
| Direct | 27,400 | 24,681–30,134 | 27,400 | 24,681–30,134 | 27,400 | 24,681–30,134 | 27,400 | 24,681–30,134 | 27,400 | 24,681–30,134 |
| Wage loss during hospitalization | 8,175 | 7,857–8,490 | 8,175 | 7,857–8,490 | 8,175 | 7,857–8,490 | 8,175 | 7,857–8,490 | 8,175 | 7,857–8,490 |
| Asymptomatic NI | NI | NI | 308,502 | 22,825–698,762 | 186,709 | 15,883–572,971 | 133,230 | 13,301–467,203 | 83,738 | 11,014–366,724 |
| Subtotal | 35,590 | 32,813–38,373 | 335,380 | 50,460–726,147 | 214,305 | 43,449–600,334 | 160,187 | 40,633–495,260 | 111,346 | 38,368–394,626 |
| **Direct** | 1,790 | 1,607–1,975 | 1,790 | 1,607–1,975 | 1,790 | 1,607–1,975 | 1,790 | 1,607–1,975 | 1,790 | 1,607–1,975 |
| Indirect | 24,502 | 10,071–38,857 | 24,502 | 10,071–38,857 | 24,502 | 10,071–38,857 | 24,502 | 10,071–38,857 | 24,502 | 10,071–38,857 |
| **Total** | 61,864 | 47,304–76,590 | 360,866 | 76,424–752,469 | 241,616 | 69,064–626,804 | 187,481 | 65,215–522,282 | 138,398 | 61,167–421,680 |

NI, not included.

doi:10.1371/journal.pntd.0003069.t008

In conclusion, our findings support the idea of an active transmission cycle of *E. granulosus* in the province of Álava primarily maintained between farm dogs acting as definitive host and mainly sheep as intermediate host species. This situation implies that domestic dogs have access to raw viscera of infected animals, most likely by the occasional feeding on carcasses abandoned in the fields. Parasite infection pressure research priorities in the study of echinococcosis [34]. The aid of computer-based models have been increasingly used in recent years to estimate the socioeconomic burden of CE globally [4] and in a number of endemic regions including Iran [3], Peru [2], Spain [1], the Tibetan plateau [16,35], and Tunisia [36]. In line with these studies, we present here data on the economic impact of human and animal CE infection in the province of Álava for 2005 based on a Latin Hypercube design. By representing the uncertainty inherently associated to input parameters, this analytical tool is particularly suited for estimating indirect costs where accurate epidemiological information is scarce. Our project design benefits from the incorporation of data at the regional level. For instance, we used the annual CE incidence based on an active search of hospital records rather than the official, potentially underreported figures provided by the national surveillance system. Similarly, CE prevalence proportions in sheep and cattle were obtained from regional abattoir records and appropriately adjusted to exclude non-autochthonous CE infections. In addition, we used stratified rates of human CE infection and average wages by age and gender. For livestock, we used age-stratified prevalence proportions where available.

Our estimates of the monetary burden associated with CE in the province of Álava in 2005 were between €0.06 and €0.36 million. These results reflect the range of variation observed between epidemiological scenarios where productivity losses associated to undiagnosed/asymptomatic infections were excluded, to a worse case situation in which the highest proportion of undiagnosed/asymptomatic CE were considered. All scenarios where asymptomatic cases were included depended largely on the estimated productivity losses and the prevalence of asymptomatic cases in the population. The costs associated with human cases represented from 83% to 94% of the total costs. These results are consistent with our previous estimates for Spain where asymptomatic cases represented 89.1% of the total cost in 2005 [1]. The upper and lower credible intervals of the “worst case scenario” (scenario 2) differed by a factor of ten. This large uncertainty calls for urgent need for more studies of the prevalence of asymptomatic cases in this region and for research on how asymptomatic CE may affect productivity in humans.

The economic burden associated with animal CE was also consistent with our previous estimates for Spain in 2005 [1]. Estimates associated with productivity losses contributed to the largest proportion of the total costs. This demonstrates, as with humans, the urgent need for studies to better estimate productivity losses associated with CE in livestock. In addition, our findings are in line with the fact that *E. granulosus* has been ranked second in the FAO/WHO list of foodborne parasites using a multi-criteria based approach reflecting the number and rank of computer-based models have been increasingly used in recent years to estimate the socioeconomic burden of CE globally [4] and in a number of endemic regions including Iran [3], Peru [2], Spain [1], the Tibetan plateau [16,35], and Tunisia [36]. In line with these studies, we present here data on the economic impact of human and animal CE infection in the province of Álava for 2005 based on a Latin Hypercube design. By representing the uncertainty inherently associated to input parameters, this analytical tool is particularly suited for estimating indirect costs where accurate epidemiological information is scarce. Our project design benefits from the incorporation of data at the regional level. For instance, we used the annual CE incidence based on an active search of hospital records rather than the official, potentially underreported figures provided by the national surveillance system. Similarly, CE prevalence proportions in sheep and cattle were obtained from regional abattoir records and appropriately adjusted to exclude non-autochthonous CE infections. In addition, we used stratified rates of human CE infection and average wages by age and gender. For livestock, we used age-stratified prevalence proportions where available.

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In conclusion, our findings support the idea of an active transmission cycle of *E. granulosus* in the province of Álava primarily maintained between farm dogs acting as definitive host and mainly sheep as intermediate host species. This situation implies that domestic dogs have access to raw viscera of infected animals, most likely by the occasional feeding on carcasses abandoned in the fields. Parasite infection pressure...
appears sufficient even to induce disease in humans, as demonstrated by the detection of two allegedly autochthonous cases. Documented human and animal CE infection rates are well above national averages, providing strong evidence that the disease is underreported in Spain. Moreover, CE has a significant economic burden in this area, particularly due to indirect costs associated to losses attributed to undiagnosed/asymptomatic cases in humans and reduced productivity in livestock species. The results of our analysis also suggest that public health agencies and policy-makers maintain and/or intensify the surveillance and monitoring systems currently in place in order to decrease the prevalence of *E. granulosus* in this area and to avoid the recrudescence of the infection. Ultrasound-based epidemiological surveys in Spanish regions endemic for CE would allow far more accurate estimations on the actual proportions of undiagnosed/asymptomatic human cases. In addition, molecular studies aiming to investigate the frequency of *Echinococcus* genotypes currently circulating in the province of Álava would be also useful to ascertain the transmission dynamics of the parasite.

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**Author Contributions**

Conceived and designed the experiments: DC HC. Performed the experiments: HC CTB FJBR JRS. Analyzed the data: HC CTB JRS DC. Contributed reagents/materials/analysis tools: FJBR JRS AB JCFC. Wrote the paper: DC HC.

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