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Bayesian space–time analysis of *Echinococcus multilocularis*-infections in foxes

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ABSTRACT

A total of 26,220 foxes that were hunted or found dead in Thuringia, Germany, between 1990 and 2009 were examined for infection with *Echinococcus multilocularis*, the causative agent of human alveolar echinococcosis, and 6853 animals were found infected. The available data on the foxes including the location (local community; district) and the date of hunting/death were analyzed using a hierarchical Bayesian space–time model. The distribution of the model parameters and their variability was estimated on the basis of the sample size, the number of cases per spatial unit and time interval, and an adjacency matrix of the municipalities using a Markov Chain Monte Carlo simulation technique to assess the spatial and temporal changes in the distribution of the parasite. The model used to evaluate the data is widely applicable and can be applied to analyse data sets with gaps and variable sample sizes per spatial and temporal unit. In the study area, the prevalence of *E. multilocularis* increased from 11.9% (95% confidence interval 9.9–14.0%) in 1990 to 42.0% (39.1–44.1%) in 2005. While the infection was present in foxes only in the north-western parts of Thuringia in 1990, it had spread over the entire state by 2004. These results demand increased vigilance for human alveolar echinococcosis in Thuringia.

1. Introduction

Alveolar echinococcosis is a rare human disease that ends often lethal if left untreated. It is caused by the larval stage of the cestode parasite, *Echinococcus multilocularis*. In central Europe, the main definitive host of *E. multilocularis* is the red fox (*Vulpes vulpes*), but occasionally the parasite is also found in dogs and cats (Eckert et al., 2000; Thiess et al., 2001; Romig et al., 2006). Raccoon dogs (*Nyctereutes procyonoides*), which invaded large territories in Europe in recent decades, represent a new definitive host, which is very susceptible to infection (Thiess et al., 2001; Kapel et al., 2006; Romig et al., 2006). To assess the risk for human infection, it is important to monitor the epidemiological situation of *E. multilocularis* in its definitive hosts in time and space.

The spatial and temporal analysis of wildlife diseases is particularly challenging, because the population size of the target species is usually unknown, random sampling of animals is often not possible, and the spatial boundaries of epidemiologic units may be artificially chosen and not relevant to disease spread (Staubach et al., 2002). Hunting foxes, the most important definitive host of *E. multilocularis* in Europe, is not a random selection. However, at least as far as the infection status of individual foxes with *E. multilocularis* is concerned, infected and uninfected animals should have nearly the same chance to enter a

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sample because the infection status of a fox cannot be determined by clinical signs, behaviour etc. by the hunter (Conraths et al., 2003). With respect to their spatial origin, samples of foxes obtained by hunting are usually heterogeneous and not randomly distributed because hunters select places where they shoot animals by following certain rules.

Moreover, random variation in the estimated prevalence per geographic unit is possible, so that the significance of spatial and temporal changes is difficult to assess. Data may be missing for several spatial or temporal units leading to increased uncertainty and different sample sizes may be available from the spatial units. The sample size in some spatial units or strata may even be too low to obtain reliable prevalence estimates (Staubach et al., 2002).

To overcome these constraints, a hierarchical Bayesian space–time model (Staubach et al., 2002) was used and the distribution of the model parameters and their variability estimated by using a Markov chain Monte Carlo (MCMC) simulation technique, on the basis of the sample size, number of cases per spatial unit and time interval, and the adjacency matrix of the municipalities respectively.

This model was used to analyse the distribution of *E. multilocularis* in foxes in Thuringia, Germany, in time and space.

2. Materials and Methods

2.1. Foxes and examination for E. multilocularis

A total of 26,220 foxes that were hunted or found dead in the state of Thuringia, Germany, between 1990 and 2009 were examined using an OIE/WHO standard protocol, the intestinal scraping technique (Deplazes and Eckert, 1996; Eckert et al., 2001). Data on the foxes including the date of hunting/death, location (local community; district) and the result of the examination for *E. multilocularis* were recorded (Tackmann et al., 1998) and exported into a data base (Microsoft Access) that could be linked to a geographical information system. Further data management and mapping was done in ArcGIS Arcview 9.3 (ESRI, Redlands, CA, USA). Thuringia is a German federal state with an area of 16,171 square kilometers and 2.29 million inhabitants. It is located in the central part of Germany (51°39′N 9°55′E; 50°8′N 12°36′E).

2.2. Statistical model

A hierarchical Bayesian space–time model was set up to analyse the data from the state of Thuringia from 1990 to 2009, and to test for significance of temporal and spatial effects in the study area. The model is an extension of an existing hierarchical model proposed for disease mapping (Staubach et al., 2002) with the addition of time effects. We used a Bernoulli observation model, i.e. we assumed that the number of cases x is binomially distributed in each spatial unit i at each time t.

$$x_{it} \sim \text{Bin}(n_{it}, \pi_{it}),$$

where n_{it} is the sample size and π_{it} the unknown prevalence. To split up the prevalence π_{it} in spatial and temporal components, it is modelled using a logistic link as:

$$\eta_{it} = \log\left(\frac{\pi_{it}}{1-\pi_{it}}\right) = \mu + \upsilon_i + \nu_i + \phi_t$$

where

- μ is an intercept, i.e., the average logit prevalence
- υ_i is a structured spatial effect in the area i, i.e., a spatial effect which assumes dependencies between areas
- ν_i is an unstructured random effect, taking into account the heterogeneity mainly based on the sample size per spatial unit
- ϕ_t is a temporal effect, as deviation from the average logit prevalence at the time t.

In Bayesian models, prior knowledge or assumptions about the effects are formulated as prior distributions. Here, the structured spatial effect υ_i is assumed to cover spatial dependencies. These can be described by a so-called Gaussian Markov Random field (GMRF), where for each area i a priori we expect the value of υ_i to be roughly around the average of the values of the neighbouring units. That is, we use a Gaussian distribution:

$$\upsilon_i \sim N\left(\frac{\upsilon_{\text{neigh}}}{k}, \frac{\sigma_\upsilon^2}{k}\right)$$

with $\upsilon_{\text{neigh}} = \sum_{j\in\partial i} \upsilon_j$, where ∂i is the set of neighbouring units of unit i, and k the number of neighbouring units of unit i. Only the first neighbours of each spatial unit were taken into account.

The unstructured random effects ν_i are a priori independently Gaussian distributed:

$$\nu_i \sim N(0, \sigma_\nu^2).$$

In units with no observation, ν_i is set to 0. For the temporal effect ϕ_t we assume a linear trend. This is done using a so-called random walk (RW) prior of second order, where the a priori expected value of ϕ_t is $2\phi_{t-1} - \phi_{t-2}$, i.e.,

$$\phi_t \sim N(2\phi_{t-1} - \phi_{t-2}, \sigma_\phi^2).$$

The Bayesian model is completed with Inverse Gamma priors for the unknown variance parameters, with the following hyper parameters:

$$\sigma_\upsilon^2 \sim \text{Inv-gamma}(1, 0.001)$$

$$\sigma_\nu^2 \sim \text{Inv-gamma}(1, 0.05)$$

and $\sigma_\phi^2 \sim \text{Inv-gamma}(1, 0.05)$.

The joint distribution of the full Bayesian model is analytically intractable. Therefore, a Markov Chain Monte Carlo (MCMC) algorithm was used in form of a combination of Metropolis–Hastings and Gibbs steps in order to estimate the posterior distribution of the model parameters on the basis of the sample size, the number of cases per spatial unit and time interval, and the adjacency matrix of the municipalities in a C++ program with Fortran code (Staubach et al., 2002; Schmid, 2004; Holmes and Held, 2006). After 1000