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A parasite vector-host epidemic model for TSE propagation

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Summary

Background: Transmissible spongiform encephalopathies (TSEs) are a family of diseases that infect mammals. They are explained by cross-contamination through an unknown route or from infection of food contaminated with prion proteins (PrPs), natural proteins that take an infectious form contributing to the slow destruction of the animal brain. While the extreme resistance of PrPs to denaturation and proteolysis accounts for a route from the mouth to the brain, the possible role of another route of contamination is explored here. Many diseases are spread by vectors, as seen in plague, typhus, malaria, or dengue. The situation where PrPs would be transmitted by a vector and, from the characteristics of outbreaks, proposed hypotheses about the biological nature of such vectors are explored.

Material/Methods: The nontrivial situation where contamination by the vector prevents infection by making the host immune to further vector contamination was analyzed. To investigate the nature of a possible vector, the spread of a disease in a closed population of hosts and vectors where the number of hosts is constant and the vectors multiply in the host was modeled mathematically. In this model, the disease is caused by an infective agent and is spread by a vector, while direct host-to-host spread is not permitted.

Results: Concrete values of the parameters of the model were computed from simulation of the BSE outbreak in the UK as a possible example of the process.

Conclusions: Microbial vector-borne diseases might play an unexpected role in the spread of epidemics, warranting further exploration.

key words: **microsporidia • spores • contaminated pastures • polyxenous parasites • transmissible spongiform encephalopathies**

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BACKGROUND

An epidemic of bovine spongiform encephalopathy (BSE) spread through the UK during the nineteen eighties and nineties. This unfortunate event triggered a renewed interest in transmissible spongiform encephalopathies (TSEs), ubiquitous but poorly understood diseases that plague many mammal families, in particular herds of herbivorous animals [1]. After years of controversy, the ultimate cause of the disease has been attributed to an extremely active stable form of a normal host protein, named the prion protein (PrP), which reprograms the folding of a normal innocuous host protein into the pathogenic PrP form [2]. While the extreme resistance of a PrP to denaturation and proteolysis allows one to assume that it may travel directly through an oral route to the brain of animals [3–6], it appears important to explore further, unconventional routes for efficient contamination. Indeed, prion-mediated diseases have a complex pathway of transmission, which, despite an apparent consensus in the case of BSE (where it is admitted that the disease is spread through contaminated food), is far from fully understood. In particular, in the case of the related TSE scrapie, infection of animals could happen through contaminated pastures a long time after they have been out of use [7].

Because the hypothesis of contamination by food supplies was immediately accepted, to the best of our knowledge no experimental studies have been published so far that test for the possible existence of horizontal transmission of the disease (except as a result of contaminated fertilizer sludge [8] and an epidemiological model of BSE that explicitly discards horizontal transfer as a possible cause of the epidemic [9,10]). To explore the route of BSE transmission to sheep by the oral route, i.e. the likelihood that sheep were fed BSE-infected meat and bone meal, an ambitious project to create a BSE- and scrapie-resistant national sheep flock by selectively breeding for a genotype of sheep believed to be resistant to both diseases has been set up. This genotype has recently been shown to be susceptible to BSE by intracerebral inoculation, while it has been shown that a previous estimate of the risk of BSE transmission to sheep via the feed-borne route remains robust [11].

Recently, however, horizontal transmission was observed in a cohort of mule deer [12]. The fact that TSEs exist in many animal species, including wild animals, is an indication that the propagation of the disease is not entirely understood [13–15]. A matter of particular concern is the transmission not within, but between different species, since this might (and apparently did) reach humans. We think that, because of their very high socio-economical consequences, it is most important to explore all possible avenues, including unconventional ones, in order not to overlook an important pathway for the propagation of TSEs.

Many diseases are spread by vectors, as we can see with plague (spread by direct contamination, but usually by fleas), typhus (spread by lice), malaria, or dengue fever (the latter two spread by mosquitoes). In order to investigate the nature of a possible vector, we constructed a simplified model for the spread of a disease in a closed population of hosts and vectors where the number of hosts is constant (this can be assumed if the disease has a very slow course, as in the case of TSE). In this model, the disease is caused by an infective agent and is spread by a vector that can multiply in the host and be released, sometimes as an infected vector, while host-to-host direct spread of the agent is not permitted. Within this framework we explored the nontrivial situation where infection by the vector makes the host immune to further infection because the host has become immune to super-infection by the (possibly contaminated) vector (this would not be the case of insect vectors, for example). In this model it is important to notice that the host is not supposed to be become immune to the infective agent, but only to the vector. We give an approximate solution for the time-course of creating an infected population. As an illustration, while we do not assume that this has been the case, we see how this model could have been applied to the BSE outbreak in the United Kingdom and explore some of the broad outbreak patterns that would arise if this mode of transmission did indeed have some impact.

MATERIAL AND METHODS

Many fascinating models describe the spreading, oscillatory, stable, or chaotic behavior of infectious diseases [16–18]. Our purpose here is more modest. Exploration of a completely new hypothesis in the case of TSE disease transmission precludes the incorporation of all the minute details of the transmission process into the model. In addition, we do not go into the intricacies of the mathematical solutions of a new epidemiological model, but rather try to test with very crude hypotheses whether a new mode of transmission might account for surprising aspects of some epidemics. One of the reasons for our simplified approach is that the more parameters introduced, the easier it is to represent reality (this was the basis of the epicycle representation of the movement of planets in the Ptolemaic system). Conclusions from this model would help one to construct further refinements (some of which of some mathematical interest) if it comes out as plausible. We explored the simplified situation of a steady state where the host population is not supposed to change drastically and where the transmission vector can contaminate the host with the infective agent (it is a commensal, a parasite, or a pathogen) in a way that depends on the immune system of the host (namely, the host can become resistant to super-infection by a possibly contaminated vector after primary vector attack).

This model differs in several ways from the standard epidemiological model, the SIR (susceptible-infected-removed) epidemic model, for example [19,20]. The growth rate of the hosts is assumed negligible during the process. The contact between vectors carrying the infective agents and the host population determines the rate of spread of the disease. In the present model we assume a smooth, homogeneous contact probability, which is of course a very crude approximation but may give us general trends that should be explored in detail in further models if the model has an interesting outcome.

The hosts can exist in several different, mutually exclusive states: susceptible (S), infected (H^+), immunized (H^-) against the vectors, or removed (R). Note that we do not assume that the host, nor the vector, can be immune to the infective agent, as no conventional immunity against PrPs has been found [21], although some immune reactivity ($CD4^+$ T cells) against PrPs from a foreign source may exist [22].

The vector can propagate from a host to another (naïve) host. The vector is assumed to be able to multiply inside its host and be released into the environment in a resistant form, where it can contaminate other hosts, with a certain probability. The vector can be V^+ (carrying the infective agents) or V^- (does not carry the infective agents). When a host is infected by a contaminated vector, it will produce vectors at a constant rate (m per unit time), some of which, with a proportion λ, will be carrying the infective agents, while most will not carry the infective agents. When a vector carries the infective agents, it will carry it forever. When a susceptible host S encounters a vector V^+ before a vector V^-, it will be infected and becomes H^+. If it is infected, it will die or be removed from the population (and becomes R) after a period of time, say $1/\beta$ years. When a host encounters a vector V^- before a vector carrying the infective agents, it will be immunized (H^-) to the vectors and therefore cannot be infected by the infective agents (see Figure 1).

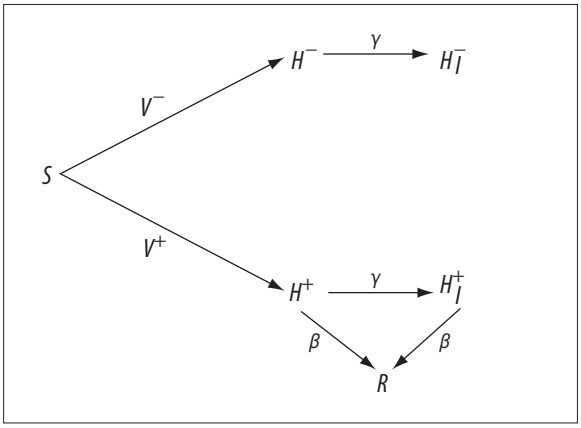

Figure 1. Host vector interaction: (**A**) host classes, H^-, H^+, H_I^+, H_I^-; (**B**) vector classes, V^-, V^+.

As mentioned before, we assume that the vector is able to multiply inside its host and shed vectors out of the host. However the multiplication of vectors inside the host should go through a peak and then decrease to zero as the host builds up its immune response. Therefore, the host should no longer shed vectors after a certain period of time, say $1/\gamma$ years. In order to take this assumption into account, we further introduced two classes of hosts, namely H_I^+ and H_I^-. We assume that a H^+ (H^-) will becomes H_I^+ (H_I^-), which can no longer shed any vectors after a mean period of $1/\gamma$ years. Like H^+, we also assume that H_I^+ will die or be removed from the population (and becomes R) after $1/\beta$ years. Finally, we assume that the vectors themselves have a mean lifetime of $1/r$ years.

A mathematical model

Base on the assumptions of the host-vector-pathogen model described in the last section, we shall construct a mathematical model in this section. The system dynamics of the host-vector-pathogen model is governed by a system of nonlinear ordinary differential equations. In our mathematical model we assume that the host population is constant and we divide it into the following six classes:

- S, susceptible, whose number at time t will be denoted by $S(t)$;
- H^+, infected hosts that are producing vectors, the number of H^+ at time t is denoted by $A(t)$;
- H_I^+, infected hosts that are no longer producing vectors, whose number at time t is $A_I(t)$;
- H^-, immunized hosts that are producing vectors, whose number is $B(t)$;
- H_I^-, immunized hosts that are no longer producing vectors, whose number is $B_I(t)$;
- R, removed hosts from the H^+ or H_I^+ classes, whose number is $R(t)$.

We also divide the vector population into two classes:

(i) infective (V^+) vectors (i.e. those carrying the pathogen), its number denoted by $X(t)$;
(ii) non-infective vectors (V^-) (i.e. those not carrying the pathogen), its number denoted by $Y(t)$.

Moreover, we shall make the following assumptions:

(i) When S and V^+ contact, S becomes H^+.
(ii) When S and V^- contact, S becomes H^-.
(iii) H^- produces V^- constantly at the rate of m units per unit time.
(iv) H^+ produces both V^+ and V^- constantly at the rates of $\lambda * m$ and $(1-\lambda) * m$ units per unit time respectively.
(v) H^+ and H^- will become H_{I+} and H_I^-, respectively, after a period of $1/\gamma$ years. Therefore, during the time interval between t and $t+dt$ there are $\gamma A(t)dt$ of H^+ becoming H_I^+ and $\gamma B(t)dt$ of H^- becoming H_I^-.
(vi) The vectors have a mean lifetime of $1/r$ years; hence during the time interval between t and $t+dt$, there are $rX(t)dt$ and $rY(t)dt$ vectors removed from class V^+ and V^-, respectively.

Suppose the spread of the disease starts at time $t=0$. Let the total constant population of the host be S_0; among them a proportion b_0 have been previously immunized against the vector. Let the initial number of infective vectors and non-infective vectors be x_0 and y_0, respectively. It follows that the number of susceptibles at time t is $S_0-A-A_I-B-B_I-R$. The contact chance between hosts and vectors will be assumed not to be dependent on whether the vector is infective or not (as this is a "hidden state" of the vector) and we shall denote the contact chance by α. Based on the above assumptions and applying the mass action principle, we can derive the following system of ordinary differential equations that governs the system dynamics of our host-vector-pathogen model:

$$dA/dt = a*X*(S_0 - A - A_I - B - B_I - R) - \beta*A - \gamma*A$$
$$dA_I/dt = \gamma*A - \beta*A_I$$
$$dB/dt = \alpha*Y*(S_0 - A - A_I - B - B_I - R) - \gamma*B$$
$$dB_I/dt = \gamma*B$$
$$dX/dt = m*\lambda*A - r*X$$
$$dY/dt = m*(B + (1-\lambda)A) - r*Y$$
$$dR/dt = \beta*A + \beta*A_I$$

Let us explain the terms that enter this epidemic model. The first equation describes the evolution of the number of H^+ infected hosts. We have already seen that $(S_0-A-A_I-B-B_I-R)$ is the number of susceptible hosts. According to assumption (i), when these hosts are in contact with V^+ vectors (of total number $X(t)$) they may become infected. During a small time interval dt the number of contacts between S and V^+ will be assumed to be directly proportional to both the number of S and V^+ (i.e. $X*(S_0 - A - A_I - B - B_I - R)$).

Table 1. Total population of cattle and calves in the UK (1000 head in June).

Year	1986	1987	1988	1989	1990	1991	1992	1993	1994
Total population	12648	12293	12008	12101	12192	12003	11924	11851	11954
Year	1995	1996	1997	1998	1999	2000	2001	2002	2003
Total population	11857	12040	11633	11519	11423	11133	10600	10343	10459

Table 2. Number of Cases of BSE reported in Great Britain.

Year	1986	1987	1988	1989	1990	1991	1992	1993	1994
Cases reported	0	442	2469	7137	14181	25032	36682	34370	23945
Year	1995	1996	1997	1998	1999	2000	2001	2002	2003
Cases reported	14302	8016	4312	3179	2274	1355	1113	1044	549

Thus the number of susceptibles that are infected, i.e. that go to class H^+ during the time interval dt, will be $\alpha^*X^*(S_0 - A - A_1 - B - B_1 - R)\,dt$, where α is some proportionality constant (which represents the probability for S and V^+ to meet and result in an infection during the time interval). In the absence of any other interaction, one would have $A(t+dt) - A(t) \sim \alpha^*X^*(S_0 - A - A_1 - B - B_1 - R)\,dt$ for small dt and hence $dA(t)/dt = \alpha^*X^*(S_0 - A - A_1 - B - B_1 - R)$.

We have thus explained the contribution of $\alpha^*X^*(S_0 - A - A_1 - B - B_1 - R)$ that appears with a positive sign in dA/dt. The same works for the term $\alpha^*Y^*(S_0 - A - A_1 - B - B_1 - R)$ in dB/dt (recall that B is the number of H^- hosts).

The last two terms in dA/dt result from hypothesis (v). For instance, during a time interval of dt, the number of H^- hosts (of which there are $A(t)$ at time t) becoming H_1^- is assumed to be $\gamma^*A(t)dt$ and therefore the contribution to $dA(t)/dt$ will be $-\gamma^*A(t)$. It can be shown that the constant γ is related to the mean time that an individual remains in class H^-; this builds on the standard remark that in the absence of any other interaction, equation $dA(t)/dt = -\gamma^*A(t)$ has the solution $A(t) = exp(-\gamma t)A(0)$ and the mean time that an individual spends in class H^- will be the integral of $A(t)$ from 0 to infinity divided by $A(0)$. The integral is easy to compute and it is in fact equal to $1/\gamma$.

We can check that the terms $\gamma^*A(t)$ and $\beta^*A(t)$ enter with positive signs in dA_1/dt dB_1/dt and dR/dt. The remaining equations can be derived by following precisely the same line of thought.

Note that in order to reduce the number of parameters that we need to estimate later, we have chosen certain consistent measuring units for the vectors so that the vector production rate is unity, i.e. $m=1$.

Modeling the spread of BSE in the UK

In this section we investigate whether it is possible to model the spread of BSE in the United Kingdom by using the proposed host-vector-pathogen model. We do not assume that this was the real cause of the epidemic, but we are trying to see whether epidemics with the same pattern might have been caused by the proposed scenario. As we have mentioned before, we assume in our model that an infected host has an incubation period for the disease, preventing it from being removed from the population long enough to be able to transmit the disease. The majority of cattle in the UK are slaughtered for consumption between 18 months and 2 years, and this may interfere with our assumption.

In order to apply our model to the study of the BSE data in the UK, we now make the further simplifying assumption that among those cattle which are going to be slaughtered for consumption, the proportion of those which are susceptible to infection is equal to the proportion of infected or immunized cattle in the whole population of cattle. In other words, if we let C be the total number of cattle in the UK at time t and D be the total number of infected or immunized cattle, c the total number of cattle which is going to be slaughtered at time t, and d the number of infected cattle. Then $D/C=d/c$. Now after slaughtering the cattle at time t, even though the population of cattle is decreased, this factor does not affect the proportion of uninfected and non-immunized cattle, which remains constant (indeed, this proportion is now $(D-d)/(C-c)$ but, since $D/C=d/c$, then $(D-d)/(C-c)=D/C$). Therefore, with this further assumption, which we believe is reasonable in the absence of a model for contamination, we can apply our model to the study of the spread of BSE in the UK.

Among others, the model is supposed to render the correct proportion of the infected population of cattle. The parameters that enter the model description will therefore be optimized to replicate the existing data. We used two sources to obtain the experimental data:

- The total population of cattle in the United Kingdom from the year 1986 to 2003, which is summarized in Table 1. These statistics were obtained from *http://statistics.defra.gov.uk/esg/publications/auk/2003/6-13.xls*. It is observed that the total population varies only slightly around 10–12,000,000.

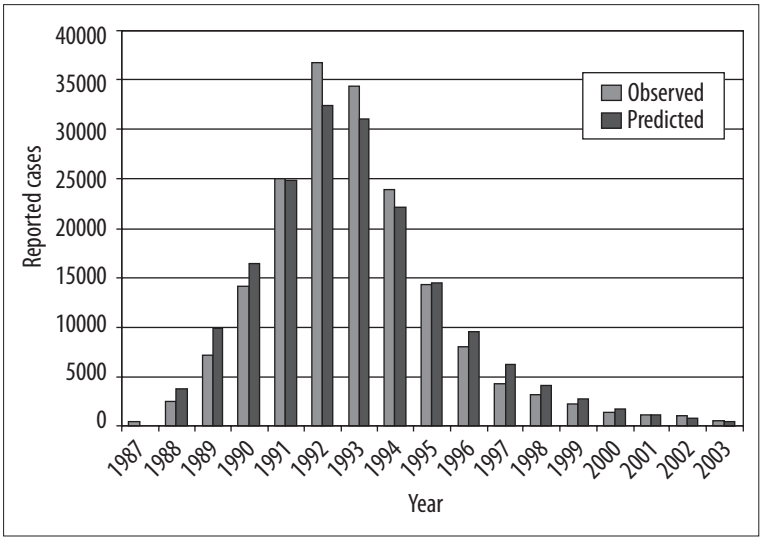

Figure 2. The fit result for λ=0.2 and r=0.3. The overall fit error is 2%. Parameters for this simulation are X(t=0)=0.05636% S_0, α=3.157/S_0, β=0.4232.

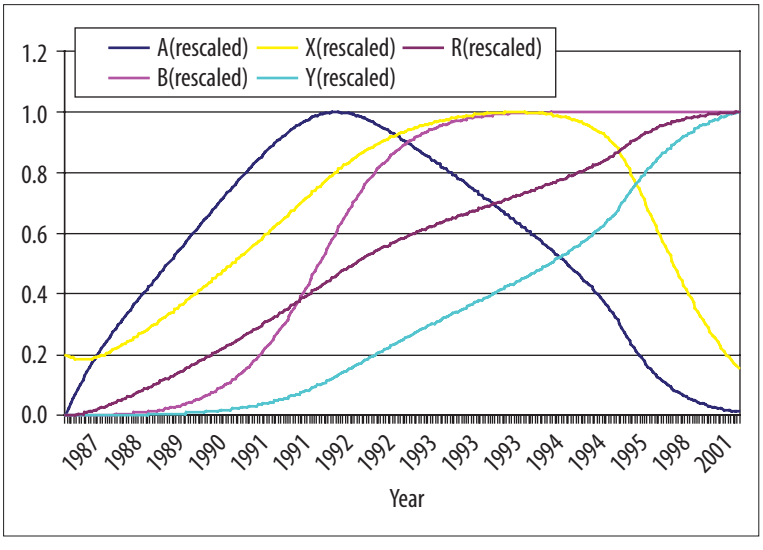

Figure 3. The time evolutions of the classes A, B, X, Y, and R during simulation with parameters in Figure 2. For graphical convenience, all data were rescaled, i.e. divided by their maximum values. These values are: A_{max}=0.667% * S_0, B_{max}=98.4% * S_0, X_{max}=0.284% * S_0, Y_{max}=317.3% * S_0, R_{max}=1.511% * S_0.

- The reported BSE cases in the United Kingdom from the year 1987 to 2003 given in Table 2. The statistics of the reported BSE cases in the United Kingdom can be obtained from *http://www.oie.int/eng/info/en_esbru.htm*. In the model we assume that the number of cases in 1986 is zero and that an unknown proportion of vectors carrying the infective agents started the spread of the disease.

The quality of the fit was explored using a variant of Nelder-Mead optimization algorithm [23]. The initial population was set to S_0=12,000,000. The variables that were optimized are: *X(t=0)*, the initial proportion of pathogen infected vectors, *Y(t=0)*, the initial proportion of pathogen-free vectors, *B(t=0)*, the initial proportion of immunized hosts, and the constants α, β, γ, and λ. Furthermore, the quality of the outcome was explored for different values of the parameters λ and r. It was surprising to notice that, without any additional requirement than the feedback from the data to fit, the optimization algorithm put by itself *Y(t=0)* and γ to zero. Putting *Y(t=0)* to zero means that initially only infected vectors are present. Setting γ to zero means that immunity to vectors is not necessary to explain the propagation, i.e. we can suppose that a host contaminated by vectors will produce vectors at all ulterior times (or, in other words, immunity to vector has a longer time scale than the phenomena under study). Note that γ=0 also implies that the class A_1 is always empty and further simplifies the fitting procedure.

With these search provisions, many solutions were found that are compatible with the data. We next explored the range of admissible λ and r values that compared favorably with the data. The following conclusions were obtained:

- The proportionality constant λ of infectious vectors (V^*) produced by an infected host (H^*) is found in the range 20–100%, i.e. greater than 20%.
- Good data fit is obtained for r values in the range 0–0.3. This implies that the vector lifetime ($1/r$) is at least 3.3 years.

As an example, we give below the fit found for two different scenarios: an infectious vector proportion of 20% with a vector lifetime of 3.3 years (Figures 2 and 3) and an infectious vector proportion of 25% with a vector lifetime of 4 years (Figures 4 and 5).

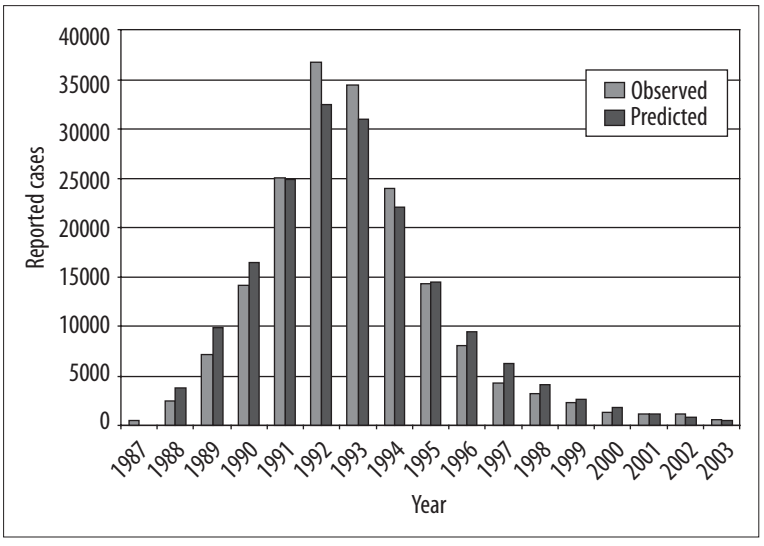

Figure 4. The fit results for λ=0.25 and r=0.25. The overall fit error is 0.6%. Parameters for this simulation are X(t=0)=0.03485% S_0, α=3.271/S_0, β=0.5256.

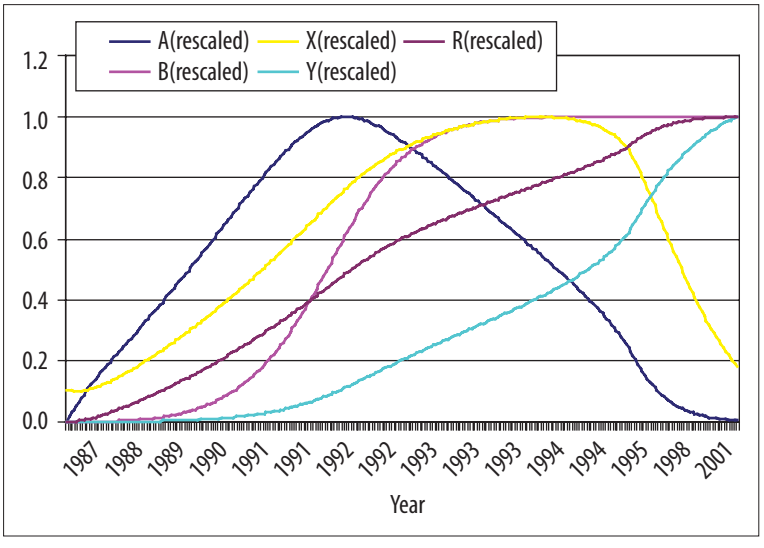

Figure 5. The time evolutions of the classes A, B, X, Y, and R during simulation with parameters in Figure 4. As in Figure 3, all data were divided by their maximum values which are A_{max}=0.603% * S_0, B_{max}=98.5% * S_0, X_{max}=0.331% * S_0, Y_{max}=370.0% * S_0, R_{max}=1.491% * S_0.

RESULTS

The present work aims at exploring the behavior of a population towards TSE if the prion protein was transmitted through some vector to which the hosts could become immune. In order to get a concrete idea of the parameters involved, we tried to simulate the situation of the BSE outbreak in the United Kingdom (but we do not claim that this was the actual cause of the epidemic). A set of simulations allowed us to propose upper and lower bounds for the proportion of susceptible and infected hosts. Four parameters are important for the time-course evolution of the system: the infection rate α, the mean time to immunization from vector $1/\gamma$ the proportion of infectious vectors (V^-) produced by an infected host (H^-) λ and the mean time to removal of an infected host (H^-) $1/\beta$.

Analysis of the corresponding parameters is revealing: the UK epidemic fit with the model for many alternatives which include the case of few initial vectors, all infected with the pathogen agent. The model predicts in the long run that, in the absence of prophylactic measures, 1.5% of the cattle population would have suffered from BSE, which is consistent with available data (after heavy culling of infected and non-infected animals, but if our hypothesis is taken into consideration, a simple change in exposure to the vector would have lead to a similar outcome).

One remarkable outcome of this model is that the behavior of the population is highly dependent on the distribution of the infected and non-infected vectors: for instance, in the situations in Figures 4 and 5, if we suppose that half of the initial infected vector population *X0* is actually not infected (i.e. $Y_0^{new}=X_0^{new}=X_0/2$), then the final size of the epidemic is reduced by 50%, from 1.5%S_0 to 0.7%S_0. Also relevant is the observation that if we keep the same population of infected vectors but put an equal population of non-infected vectors (i.e. $Y_0^{new}=X_0^{new}=X_0$), the epidemic size is reduced by 26% to 1.1%S_0; when the introduced non-infected vectors Y_0^{new} are such that the infected vectors represent λ=25% of all vectors, the decrease in epidemic size is even more spectacular, i.e. 60% to 0.6% S_0. This indicates that the apparition of an epidemic would be dependent on the vector infectivity and, as such, the dependence on the *total*

number of vectors will be nontrivial. Thus, provided that an external source of uncontaminated vectors can be identified, bringing them into the host environment will actually protect against the disease.

Discussion

One of the most puzzling features of the BSE epidemic in Europe is its highly nonrandom distribution: while it was clearly spreading as an epidemic in the UK, it was more like a collection of random cases in most other parts of Europe, although one could clearly observe foci of epidemic infection [24,25]. Within the frame of the present model, this is highly significant, since it is consistent with highly different patterns of spread of the disease, depending on the local presence of an elusive vector. Our model of prion transmission has also to take into account the mode of prion replication.

How do prions replicate if they carry no genetic material? The accepted model of prion replication is that an abnormal form, PrP Sc (Sc for "scrapie"), propagates itself by inducing a conformational change in the normal cellular form PrP C and/or by triggering its aggregation, perhaps using the mediation of an RNA molecule *in vivo* [26]. This happens intracellularly, at least during the initial stages of the progression of the disease. Then, if a vector were to be involved, it would need to have an intracellular stage in brain tissue. What would be the nature of a possible vector? Several apparently inconsistent features have to be reconciled: tropism for both the gut and the brain, access to the infective form of the PrP, and a long time stability of the infected vector. The latter property is consistent with spores. Access to the infective form of PrP indicated that the spores must be formed intracellularly. Also, an important feature which would account for the apparent breach of interspecies barriers would be that the vector is polyxenous. We have therefore to look for spore-forming, possibly polyxenous, intracellular parasites. One category of such ubiquitous parasites, often overlooked, is that of *Microsporidia* [27]. These mitochondria-less *Eukarya* develop intracellularly, make resistant spores, and usually have an oral route to the brain. They can infect almost all classes of animals (*Nosema bombycis* is the agent of pebrin, the infamous silk moth disease studied by Pasteur) and they can often cross species barriers [28]. We think, therefore, that the status of animal and human populations with respect to prevalence of *Microsporidia* infection warrants relevant epidemiological study. This is particularly important because the status of animal and human populations with respect to contamination by a given parasite may be variable: the model presented would then easily account for differences in patterns (epidemics or sporadic cases).

A final epidemiological observation brings weight to the importance of the vector hypothesis: there is usually a south-north gradient of (parasite) infection that may account for the difference between the spread of BSE in continental Europe as compared to that in the UK. As a case in point, *Toxoplasma gondii*, which is an important human parasite with a remarkable, although unsuspected, role in rodent behavior [29], infects British and French citizens in a very different way [30]. This parasite might well be a vector as well. Its resistance, however, is much less than that of the spores of *Microsporidia*.

Before concluding, we wish to emphasize that we are well aware that there may be several sources of contamination and we claim neither to have discovered the one and only cause of TSEs nor that direct contamination by infected PrPs does not happen. As a case in point, AIDS is propagated by very different routes, blood and sexual intercourse being the commonly admitted ones. This very fact prompted us to explore routes that would be alternative to the usually accepted oral food contamination route [31–33]. History shows that one should not forget indirect routes (e.g. "mal'aria" was caused by "bad air"). An intriguing coincidence exists in the time of appearance of BSE in the UK and the onset of the AIDS epidemic. It is known that *Microsporidia*, from a variety of origins, often infect AIDS patients [34]. One may wonder whether this might not have been an accessory fact leading to the weakening of interspecies barriers: the sudden availability of a pool of *Microsporidia* in a naïve context allowing simultaneous contamination of a variety of mammals with the creation of an infective variant in cattle. We hope that the conclusion of this study will trigger further investigations, because it has strong implications in terms of future healthcare and should prompt appropriate epidemiological research to see whether a parasite is not involved in the propagation of TSEs (as well as other viral or even bacterial diseases, see for example the case of *Plasmodium* as a possible vector for viruses [35]). If this is so, the policy of culling cattle might have been rather inadapted, while an approach involving vaccination against the vector would probably have been appropriate.

Conclusions

Unconventional diseases such as transmissible spongiform encephalopathies perhaps require unconventional exploration of their transmission properties. We have shown here that microbial vectors (in particular spore-forming ones) might play a role in such transmission. While the present study is very crude, involving assumptions about a smooth and continuous pattern of transmission, it will be interesting to explore further the situation where space is taken into account in addition to time. Discrete events might also have a definite influence on the real patterns of outbreaks. We hope that this study will trigger interest in exploring new avenues of the way diseases emerge or re-emerge.

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