"How it spreads"

Modelling of a vector-borne disease

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1 INTRODUCTION

Starting August 2006 a major disease epidemic of Bluetongue (BTV-8) was diagnosed in North-West Europe, affecting The Netherlands, Belgium, Germany, Luxemburg and the North of France. The BTV-8 virus is a non-contagious viral disease affecting domestic and wild ruminants. BTV-8 is spread by midges. BTV-8 is a so-called OIE[1]-listed disease, saying that it is one of the diseases that are considered to be the most infectious and economically damaging diseases for commercially reared livestock (Burrell, 2002).

Although BTV-8 is not harmful for humans and can be overcome by ruminants, the consequences of the disease for farmers and their herds can be significant. The morbidity rate of the herds that are infected by the disease were as high as 100% of the herd, the mortality rate ranged from 2-30% but were also as high as 70% in the 2006-2008 epidemic(OIE, 2008). This is devastating for a farmers business.

The government response to counter the BTV-8 epidemic was for most European countries to set up a mandatory vaccination program, however the Netherlands and the UK opted for a voluntary vaccination campaign. With both the mandatory and the voluntary vaccination campaign the disease epidemic was eradicated (Elbers et al., 2010). The debate of using a voluntary campaign or a mandatory one is still ongoing. This has to do with the effectiveness and the efficiency of both programs, especially if a new epidemic resembling the BTV-8 epidemic would appear. The effectiveness is supposed to be higher in a mandatory campaign since every farm will be vaccinated by the authority of the government, in a mandatory campaign the government can only be a facilitator and cannot force farms to vaccinate which could lead to a lower count of farms that would be vaccinated. The efficiency of a voluntary campaign is supposed to be higher than in a mandatory one. This could have to do with public spending and the fast distribution of a vaccine (Sok et al., 2014).

The subject of a study of Jaap Sok is to assess whether voluntary approaches for intervention would be appropriate to use if a disease epidemic with similar characteristics to the BTV-8 epidemic appear. Besides that it is expected that voluntary approaches are more efficient and/or (cost) effective than a mandatory campaign, things like bad experiences with previous contaminated vaccines play a role (e.g. Barkema et al., 2001) .

For his research Jaap Sok and Caspar Snijders created an agent-based model in a course (INF-50806) at Wageningen University. This was based on the reasoned action approach (Fishbein and Ajzen, 2010). With this theory the vaccination behaviour of farmers is studied in an agent based model.This theory states that a given behaviour can be predicted by measuring one's intention towards that behaviour; the intention is a proxy for behaviours. The intention in turn is a function of three constructs: one's attitude towards that behaviours, the perceived norms one has and the perceived behavioural control (Sok & Snijders, 2014).

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[1] Stands for Office International des Epizooties, better known by its English acronym World Organisation for Animal Health.
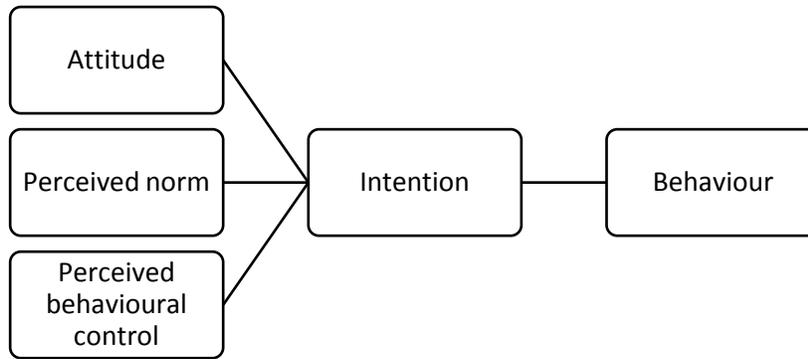
Graphical illustration of the different construct underlying the intention (Sok and Snijders, 2014 based on theory of Fishbein and Ajzen, 2010)

The above graphical illustration of the different constructs underlying the intention to perform a behaviours was the basis of the farmers behaviour in the model created. Attitude was the attitude towards the behaviour, the perceived norm was the belief whether most people would perform the behaviour and the perceived behavioural control was the persons own perceived ability to perform the behaviour. The behaviour studied is the farmers intention to vaccinate his/her herd. With these three constructs the researchers try to simulate the vaccination behaviour of farmers, when faced with a thread of a disease epidemic.

This model was created to see if a disease epidemic would appear and a voluntary vaccination campaign was in place, if this program could be effective enough to eradicate the disease.
Although this model was sufficient to model the farmers' behaviour, there were caveats on the modelling of the spread of the disease epidemic. The spread of the disease was modelled very simplistically with a range in which midges can move a certain radius.
 In order to model the actual vaccination of the farms veterinarians were included which would visit farmers and vaccinate herds of farmers whom had decided to vaccinate.

The BTV-8 disease epidemic was eradicated in the Netherlands by a massive government campaign which stimulated farmers to vaccinate, whilst it was voluntary in nature. Farmers could decide for themselves to vaccinate or not. If a new disease epidemic emerged similar to the BTV-8 virus, the farmers' behaviours and intention to vaccinate could be of great importance in order to eradicate the disease epidemic.

Instead of creating a whole new agent based model this thesis will focus on an agent based model simulating the outbreak of the BTV-8 epidemic and improvement of the pre-existing model. The main problem with the pre-existing model was the epidemiology. The latter was inadequately modelled as it was not based on any data and was of big influence in the simulation outcomes. In the sensitivity analysis conducted on the model, the range of the midges that spread the disease was the most influential in the outcome of the simulations. To be able to simulate the farmers' behaviour more conveniently, the disease epidemic should be modelled more precisely as it forms the basis of the agent based model. Also further improvements could be made in the farmers' behaviour whilst the use of theory could be more simplistically modelled.

2 MATERIALS AND METHODS

In order to get a good view of the problem of the models epidemiology, a meeting was arranged with experts in the field of epidemiology. With their expertise they saw what was wrong with the model in the first place and recommended additions to the model and parts that were not necessary or obsolete. With the recommendations of the experts a literature study was done to study what should be added to the model.

2.1 MEETING WITH EXPERTS AT THE CENTRAL VETERINARY INSTITUTE

A meeting was conducted with 3 experts of the Central Veterinary Institute (CVI) Armin Elbers, Egil Fischer and Jantien Backer in order to establish the most important aspects of the virus that could be useful for improving the existing model.

The model of Sok and Snijders was shown and the experts made clear that the model was from an epidemiology standpoint not correct. The spread from the epidemic was modelled with midges that had ranges in which they could move and infect farms in that way. However midges are only of influence on the spread of the disease at the micro level of the epidemic, meaning that midges primarily spread the disease on the farms itself and in farms that are in a close range to those farms. The bigger influence of the spread was the transport of animals. The model was thus too much focused on the micro level of the spread of the disease instead of the macro level, the macro level of the spread of the disease is the most important aspect in their professional opinion.

The model also didn't include more stages of infection, which plays a big part in the spread of the disease and could be of influence in the outcomes of the simulations. These stages are the susceptible stage, the latent stage, the infected stage and the recovered/immune stage.

To susceptible stage means that a farm is susceptible for infection by an infected farm or midge. The latent stage means that a farm is infected by another farm but is not yet infectious and therefore cannot infect other farms. The infected stage is the stage that a farm will go into after the latent stage of a certain amount of days has ended, the farm is now infectious and can infect other farms. The recovered/immune stage is the stage a farm goes in after it gets infected and the herd is healed from the disease by itself or the farm is vaccinated, in both cases the farm cannot become infected anymore. The experts therefore recommended the paper of Koeijer et al.2011, which contains all the information needed to further improve the model.

Besides giving the recommendation of the paper one of the experts modelled a preliminary model which contained the code to model the spread correctly.

2.2 LITERATURE STUDY

To model the spread of the BTV-8 virus theories have to be implemented in the model to make the model more realistic in the spread of the disease. In an agent based model emergence is of big importance as well as randomness. The theories that have been selected to implement in the model

support this. In the literature study much of the literature was outside of the scope of the thesis itself, whilst the focus is on theories that can be implemented in an agent based model as well as the timeframe of the thesis deeper studies in the disease were not needed and therefore not included in the paper. The theory selected for the model are the spatial transmission kernel and the indicator for the spread of a disease R0 was selected.

The spatial transmission kernel describes and estimates the spread of the disease between farms in relationship with the distance of an infected farm to a susceptible farm. The spatial transmission kernel is the theory that will determine the spread of the disease.

The R0 is a basic reproductive number which tells how many farms can be infected by an infected farm in a fully susceptible population. The R0 can be used to validate the model.

2.2.1   Spatial transmission kernel

The spatial transmission kernel is a function that is described as a transmission rate λ (r) over distance (r) (de Koeijer et al., 2011). The transmission rate of the disease encompasses all factors that determine the spread of the disease e.g. transport. The spatial transmission kernel is used whilst it has been used in other research to estimate the spread of the BTV-8 virus with the help of real data. This means that using the kernel the model can represent the spread of the BTV-8 virus.

The function of the transmission kernel is :

$$\lambda (r) = \frac{\lambda_0}{1+(\frac{r}{r_0})^\alpha}$$

In this function r represents the inter-farm distance, λ_0 the initial rate of transmission and r_0 the scaling distance. Via the power of α the total range of global (α<2), intermediate (2<α<3) and local kernels (α>3) could be matched (Boender et al., 2007). For global kernels the transmission is not limited to certain regions, because average transmission distance, i.e. the first moment, is infinite. For intermediate kernels the transmission could be regional depending on the actual location of farms in a country, because the average transmission distance in one dimension exists, while the average transmission distance in two dimensions, i.e. the second moment, is infinite. For local kernels the transmission is regional, because the average transmission distance in two dimensions exists.

The use of the spatial transmission kernel in the model is usefull, whilst the spread of the epidemic of 2006 cannot be reproduced because of the lack of data. Therefore an estimation is the closest one can get to the real epidemic.

 With the transmission kernel a transmission probability can be computed. The formula of the transmission probability is as follows:

$$p(r\ T) = 1 - \exp(-\lambda(r)T)$$

This equation describes the transmission probability for an infectious period T and an inter-herd distance r.

The transmission probability is the probability that an infected and infectious farm will infect another farm dependent on the inter-herd distance and the time that the infected farm is infected.

2.2.2 R0

R0 estimates the number secondary infections by one infected farm in the early stages of an epidemic. When R0>1 the disease can become an epidemic whilst 1 farm can at least infect 1 other farm, however if the R0<1 the disease is not able to cause an epidemic.

The R0 of the BTV-8 virus is known to be 4(de koeijer et al, 2011) and therefore the R0 can be used to validate the model .
The equation of the R0 is :

$$R = 2\pi \int_0^\infty \rho_i(r)p(r)rdr$$

Where ρ_i the farm density and p (r) is the transmission probability. (Boender et al. 2007….) This formula works with the transmission kernel. The density of farms will have an impact on the R0 while infection is able to spread easier.

2.3 AGENT BASED MODEL

The agent based model that is used in this thesis is in a big part still the same model as the one built by Sok and Snijders, 2014. The model parameters for the reasoned action approach are not changed also the veterinarian parameters are not changed. This thesis is solely focussed on the epidemiology of the BTV-8 virus and thus if more information is needed, we refer to the unpublished data of the model of Snijder and Sok,2014.

To get a good representation of the spread of the disease epidemic, the model of Sok and Snijders,2014 was inadequate, therefore the whole section of the spread of the disease had to be removed from the model and be replaced.

The changes made on the model will now be described in detail.

2.3.1 Added stages of the disease

In the initial model farms had in relation with the disease 3 stages: susceptible, infected and immune. This was for the spread of the disease a big influence, because with instant infected and infectious farms the disease would spread faster and was not a good representation of the actual spread of the disease and the symptoms of the disease itself.

An animal when infected with the BTV-8 virus has different stages it will go through. When an animal is not infected and not immune the animal is in the susceptible stage (S). When infected, the animal will first be infected but not infectious, which is the latent stage (E). When infected and infectious, the animal is in the infected stage (I) (Boender et al.,2011) After a certain number of days the animal will be recovered and immune of the disease(R). The other way to get immune is when an animal is in the susceptible stage and is vaccinated by a veterinarian, when vaccinated it takes a number of days before the animal is immune. The time period to get immune by vaccination is modelled as 1 time period opposed to the slider that controls the period that a farm is infected.

2.3.2 Kernel function in the model

The disease epidemic in the model of Sok and Snijders,2014 was modelled with agents which represented the midges, which are the actual vectors that spread the disease. This was according to the

experts not a good representation of reality. Whilst midges are the actual agents that spread the disease, the spread of the disease is in reality influenced by other factors than by midges flying from farm to farm. Therefore the kernel function introduced in the literature study is implemented in the model.

Because the kernel function contains every factor of the disease, the midges are not in the model anymore. The kernel function is determined by distance and probability a farm will become infected. Therefore the kernel function is a function and process addressed to farms instead of a stand-alone agent.

In the model the transmission probability is used, an infected farm will look for susceptible farms and will see how much distance they are apart. This distance is used in the formula and a probability will calculated. To determine if a farm will get infected the susceptible farm gets a randomly assigned number between 0 and 1 and will calculate if this number is bigger of smaller than the probability. If the number is smaller the farm will get latent, if not the farm will stay susceptible.

2.3.3   R0

For the validation of the model R0 is introduced. This is shown in a counter. With the formula in the literature study the average reproduction number is calculated for the farms that are infected. The outcome of the formula is then the reproduction number for the area that is simulated which can be validated by the reproduction number of real data.

2.3.4   Farm density

For a good representation of reality the amount of farms is modelled as farm density instead of a number of farms determined by the controller of the model. With the farm density different kinds of regions and different kinds of animal farms can be simulated based on actual data.

2.3.5   Model parameters

The parameters of the changes in the model mostly exist out of the parameters of the kernel function. The $\lambda 0$ can be adjusted by a slider, at default settings it is 1000×10^{-6} whilst this is the initial rate of transmission of the BTV-8 epidemic of the Netherlands, the default settings are set to simulate the BTV-8 virus of the Netherlands.

The $r0$ which is the scaling distance can be adjusted by a slider, the default setting is 3.9.

The total range of the kernel can also be adjusted, in default settings it is 2 which is an intermediate kernel.

The period a farm is infected and infectious before it will recover can also be adjusted by a slider. This is 120 in default settings whilst this is the period the model will run and therefore simulates the whole season the disease will be likely to spread. (de koeijer et al, 2011)

The farm density can be adjusted by a slider, this is always a number between 0 and 1 which represents the amount of farms per square kilometre. The default setting is 0.24.

The number of ticks in default settings is 120 whilst this represents 4 months which is the length of the season that the midges will be active and infect farms.

3   RESULTS/VALIDATION

To determine whether the improved model is more valid than the old model an analysis has been done, in which there were hundred repetitions of a full simulation. This means the model ran 100 times, with those 100 runs the mean and standard deviation were computed of the number of farms that were infected. Next to the mean and standard deviation also the R0 was computed, this will determine if the model is valid or not.

Two configurations of the model were tested, the model <u>with</u> vaccination and the model <u>without</u> vaccination. Testing the model with vaccination is to compare it with the old model and if the model is improved. The model without vaccination was tested in order to test the model only for validation.

3.1.1   Comparison

In the following graphs the mean and standard deviation of the new model as well as from the old model is shown. The new model ran for 120 ticks whilst this is approximately the number of days the midges are active and the disease will spread. The graph of the old model however runs till 180 ticks, this should be taken into account when comparing the graphs of the models.

When comparing the two graphs of the new model, the average amount of farms at the end of the 120 ticks is far less than the amount of ticks for the old model. For the model with vaccination this is 8 and for the model without vaccination this is 17 compared to the 84 farms that are infected in the old model. The standard deviation of the new models also seems lower than for the old model, however the standard deviation is biggest at the end of the runs of the model. This means that the model still has quite a big uncertainty.

 To see if the model is more valid the R0 is computed for both the new models.

	mean R0	stdev active R
with vaccination	2,93	0,569816993
without vaccination	4,24	0,76

The table above shows that the R0 of BTV-8 is around 4 which the model without vaccination is the same, this model is focused only on the epidemic. The model with vaccination has a R0 of 2,93. This can mean that the model is not as valid as the model without vaccination but can also mean that the reproduction number can be lowered with the use of vaccination.

For the comparison of the validity of the new model and the old model the R0 is not calculated for the old model, however the findings show that the new model is valid and the old model does not by far resemble the outcomes of the new model which could mean that the old model is not valid and the new model is.

Graph 1

Graph 2

OLD MODEL

Number of farms infected vs *Ticks*
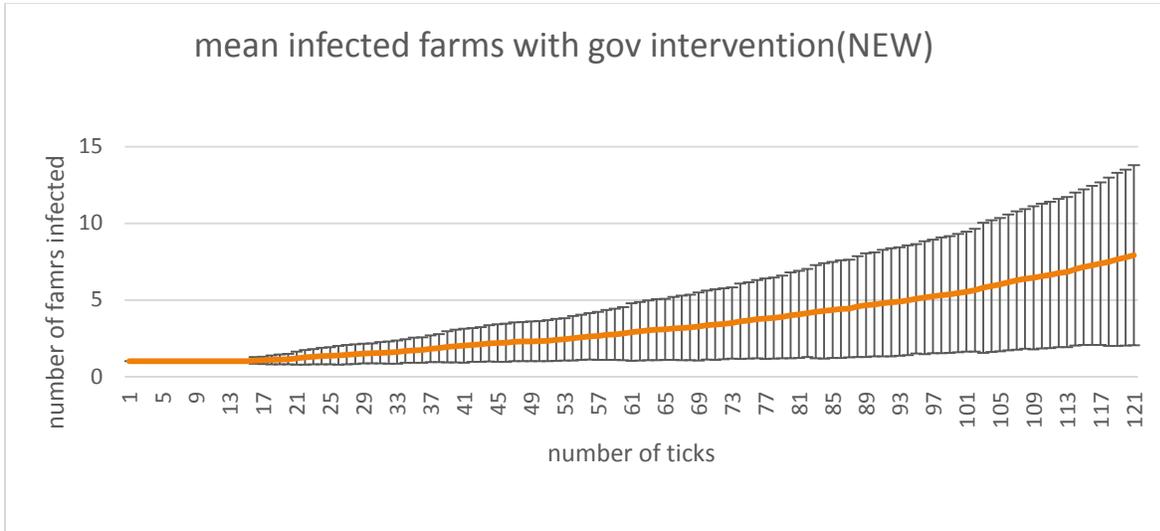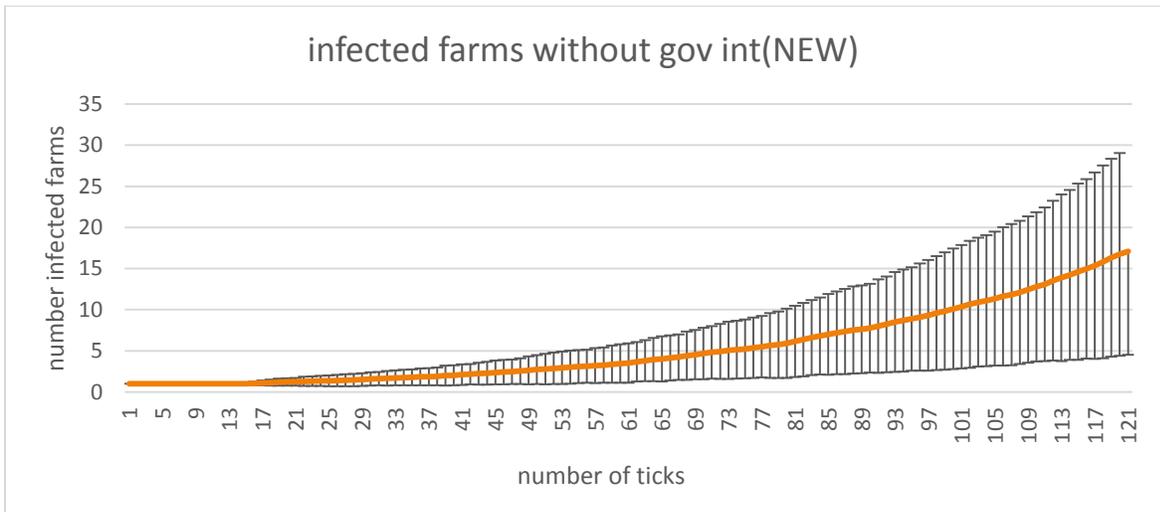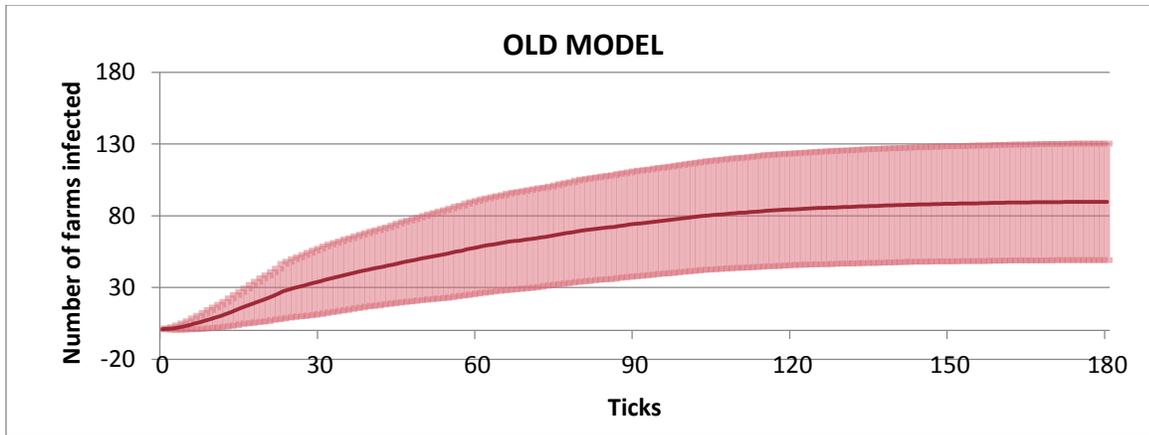
Graph 3

4 CONCLUSION

To model the spread of the BTV-8 virus to represent reality, a spatial transmission kernel has to be used. This will ensure that the model can be used to test other theories and behaviours of agents and there will be no question to the validity of the epidemiology of the model. In an agent based model the spatial transmission kernel connects the epidemiology and behaviour of farmers. An agent based model will be able to represent an outbreak of a disease and can then be used to further investigate agent behaviour. If the validity of the old model and the new model is compared it is clear that the old model was far from valid and the new model approaches the R0 of the BTV-8 virus. With the R0 from the model close to the R0 of reality the model can be seen as valid and although the old model is not tested with R0 the spread is far from close to the spread of the new model which can mean that the old model is not valid at all.

5 DISCUSSION

The model constructed in this thesis did not undergo an extensive sensitivity analysis, which could be useful for further research whilst it may show the weak points of the model of the factors that influence the spread of the disease the most.

With this model the validity of the old model is improved, however some points could make the model more realistic.
This model only simulates one vector season, whilst the epidemic of BTV-8 lasted for 2 years. This could have impacts on the farmers behaviour and on the spread of the disease. The farms for are in this model randomly appointed a place in the grid of the model, however in reality farms will be clustered together in some places and in other places like urban areas farms will be absent. This might have an impact on

the spread of the disease.

Also the instantaneous knowledge of an infected or latent farm by the rest of the farms can be unrealistic. It might happen that a farm will not be willing to report the infection and therefore other farms will not be up to date with the disease.

The purpose of this research was solely focussed to construct a model in which the epidemiology of BTV-8 is modelled correct and can be validated. This means that this model as it now stands will help with the exploration of new theories. This model can however be a basis to explore new theories.

Famers will have in this model a network of farms in a certain range in order to see the perceived norm. This could however be modelled with random network, whilst farmers might know other farmers that live far away and will be influenced by them more than by farms close by.

There are also different regions with their own culture, in the model now the culture isn't present. But the behaviour and the perceived norm of farmers in the north of the Netherland and the south of Netherlands could differ. If different regions with different cultures could be modelled, different approaches to get the farmer to vaccinate could be explored.

6 LITERATURE

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