# Using the basic reproduction ratio to quantify transmission and identify data gaps for epizootic haemorrhagic disease, an emerging vector-borne disease in Europe

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**Abstract**

Epizootic haemorrhagic disease virus (EHDV) is an arbovirus transmitted by *Culicoides* biting midges that has recently emerged in Europe. In this paper, the basic reproduction ratio ($R_0$) was used to quantify the transmission of EHDV and its dependence on temperature for the most important livestock and wildlife hosts, cattle and deer, respectively. Using data from the published literature the parameters needed to calculate $R_0$ were estimated with Bayesian methods to incorporate uncertainty in the calculations. Sensitivity analysis, specifically the Sobol method, was used to determine the most influential parameters determining the magnitude of $R_0$ and, hence, to identify important data gaps. Results show that $R_0$ for EHDV depends on strain, with maximum $R_0$ varying from 0.7 to 2.5 in cattle and 1.3 to 4.3 in deer. The maximum $R_0$ occurred at temperatures between 22 and 25 °C, while the lowest temperature at which $R_0$ exceeded one was between 16 and 20 °C. The sensitivity analysis identified the threshold temperature for virus replication, the probability of transmission from host to vector and vector to host ratio as the most important parameters influencing $R_0$. Furthermore, there are only limited data on EHDV in European deer species and on transmission in wildlife and at the livestock/wildlife interface. These data gaps should be the focus of future research.

Keywords: transmission; *Culicoides*; cattle; deer; epizootic haemorrhagic disease virus; EHDV

## 1 Introduction

Epizootic haemorrhagic disease virus (EHDV) is an arbovirus of the genus *Orbivirus*, which also includes bluetongue virus (BTV) and African horse sickness virus (AHSV). It is transmitted by *Culicoides* biting midges and can infect a wide range of wild and domestic ruminants [1,2]. It causes epizootic haemorrhagic disease (EHD), which can be particularly severe disease in wild deer, especially white-tailed deer, while clinical signs tend to be milder in cattle [3]. Historically, outbreaks of EHD have been reported in North and South America, Africa, Asia and Australasia [2,4]. In 2022 the first outbreaks of EHD were reported in Europe, caused by a strain of EHDV serotype 8. These outbreaks were detected in Sicily and Sardinia in October 2022 and in southern Spain in November 2022, and probably occurred as a result of incursions from North Africa [5]. The virus subsequently spread through the Iberian Peninsula, reaching France in 2023 [6,7].

To date limited attention has been given to quantifying the transmission of EHDV. In particular, no studies have integrated the available data to assess transmission risk or to identify important data gaps. A useful approach for doing this is to calculate the basic reproduction ratio, $R_0$. This quantity is defined as the average number of secondary cases that arise from a single primary case in an otherwise susceptible population [8]. Because the introduction of an infectious disease can only result in an outbreak if $R_0>1$, this is a means of quantifying risk, such as has been done previously for BTV [9] and AHSV [10]. Furthermore, $R_0$ is a useful way of identifying host, virus, vector and environmental factors that influence transmission [11] and, hence, where there are important data gaps.

The approach taken in the present study was to use a previously published expression for $R_0$ for *Culicoides*-borne viruses [9,11] to identify parameters needed to calculate $R_0$ for EHDV.

Suitable experimental and field data were extracted from the published literature and used to estimate these parameters using Bayesian methods. Once posterior distributions for each parameter had been obtained, uncertainty analysis was used to calculate $R_0$ for EHDV. Sensitivity analysis, specifically the Sobol method [12,13], was then used to identify the most important parameters influencing the magnitude of $R_0$ and, hence, to identify important data gaps.

The focus was on the transmission of EHDV in cattle and deer, which are the principal livestock and wildlife host species, respectively [1,2]. Fewer data are available for other susceptible species, such as sheep and goats [1,2,14], so they were not considered. Furthermore, evidence from previous outbreaks suggests that these other species play only a limited role in epidemics of EHDV [15].

## 2 Methods

### *2.1 Basic reproduction ratio for EHDV*

The basic reproduction ratio, $R_0$, for *Culicoides*-borne viruses has been derived previously [9,11]. For a single host and vector, it is given by,

$$R_0 = \sqrt{\frac{ba}{\mu}\left(\frac{k\nu}{k\nu+\mu}\right)^k \times \frac{\beta m a}{r}}. \tag{1}$$

This expression for the basic reproduction ratio, (1), can be understood heuristically as follows. After a midge takes an infected blood meal, it must complete the extrinsic incubation period (EIP) before it becomes infections. Assuming that the duration of the EIP follows a gamma distribution with mean $1/\nu$ and variance $1/k\nu^2$ [16], the probability that the midge will survive the EIP is $(k\nu/(k\nu+\mu))^k$ where $\mu$ is the vector mortality rate. Once a midge has completed its EIP, it will remain infectious for the rest of its lifespan, which will be $1/\mu$ days

on average. During this period, it will bite susceptible hosts $a$ times per day (where $a$ is the reciprocal of the time interval between blood meals, assumed to be equal to the biting rate), a proportion, $b$, of which will result in a newly infected host. After a host becomes infected, it will remain infectious for the duration of viraemia, which lasts $1/r$ days on average. During this time the host will be bitten by susceptible midges on average $m \times a$ times per day (here $m=N/H$ is the vector to host ratio and $N$ and $H$ are the number of vectors and hosts, respectively) and a proportion, $\beta$, of these bites will result in a newly infected vector.

When there is substantial disease-associated mortality (as can be the case for EHDV infection in deer), the mean duration for which a host remains infectious ($1/r$) is replaced by a more complex expression. Assuming the duration of viremia follows a gamma distribution with mean $1/r$ and variance $1/nr^2$, the appropriate expression is $(1/d)\times(1-(nr/(nr+\mathrm{d}))^n)$ where $d$ is the disease-associated mortality rate [11].

### *2.2 Parameter estimation*

The parameters needed to calculate $R_0$ for EHDV in cattle and deer were estimated from previously published data on EHDV and its *Culicoides* vectors. If suitable data for EHDV were not available, data for bluetongue virus (BTV) were used instead. The data used for parameter estimation is available in the electronic supplementary material, dataset S1 and the code to implement the methods is available online [17].

#### *2.2.1 Probability of transmission from host to vector*

The probability of transmission from host to vector was estimated using data from oral infection studies using field-caught midges [18-20]. This provided the number of infected midges and the number of midges tested after feeding on a blood/virus mix via a membrane.

The species tested were *C. imicola* and *C. bolitinos* [18] or *C. obsoletus* and *C. scoticus* [19,20]. Thirteen studies were included: eight using one strain of each serotype of EHDV [18]; one using a strain of EHDV-6 [19]; and four using strains of EHDV-6 and EHDV-7 [20].

The probability of transmission from host to vector for each strain, $\beta_s$, was assumed to be drawn from a beta distribution with parameters $a_{HV}$ and $b_{HV}$ (i.e. $\beta_s \sim \text{Beta}(a_{HV}, b_{HV})$). The parameters ($a_{HV}$ and $b_{HV}$) were estimated in a Bayesian framework. The likelihood for the data is,

$$L = \prod_s \binom{N_s}{I_s} \beta_s^{I_s} (1-\beta_s)^{N_s - I_s}, \tag{2}$$

where $I_s$ is the number of infected midges, $N_s$ is the number of midges tested and $\beta_s$ is the probability of transmission from host to vector for strain $s$. Exponential priors with mean 100 were used for $a_{HV}$ and $b_{HV}$. The methods were implemented in OpenBUGS (version 3.2.3; https://www.mrc-bsu.cam.ac.uk/software/). Two chains of 120,000 iterations were run, with the first 20,000 iterations discarded to allow for burn-in. The chains were then thinned (by selecting every tenth iteration) to reduce autocorrelation. Convergence was checked visually and using the Gelman-Rubin statistic implemented in OpenBUGS.

### *2.2.2 Biting rate*

The biting rate was assumed to be equal to the reciprocal of the length of the gonotrophic cycle. Data on the reciprocal of the length of the gonotrophic cycle in field-caught *C. sonorensis* (electronic supplementary material, figure S1) were extracted from the bottom panel of figure 1 in [21] using WebPlotDigitiser (version 4.6; Automeris.io) [22].

The biting rate ($a$) depends on environmental temperature ($T$) and was assumed to be described by a Briere function [23], so that,

$$a(T) = \begin{cases} 0 & T < T_0 \\ a_0 T(T - T_0)\sqrt{T_1 - T} & T_0 \le T \le T_1 \\ 0 & T > T_1 \end{cases}, \tag{3}$$

where $a_0$ is a scale parameter and $T_0$ and $T_1$ are the minimum and maximum temperatures for biting, respectively. Parameters were estimated in a Bayesian framework, assuming a normal likelihood and exponential priors with mean 100 for all parameters. Because there are no data on the declining portion of equation (3) (see electronic supplementary material, figure S1), the maximum temperature for biting ($T_1$) was fixed at 42 °C (cf. [21]). The methods were implemented using OpenBUGS. Two chains of 50,000 iterations were run, after which the chains were thinned (by selecting every fifth iteration) to reduce autocorrelation. Convergence was checked visually and using the Gelman-Rubin statistic implemented in OpenBUGS.

### *2.2.3 Duration of viraemia in cattle*

Data used to estimate the duration of viraemia in cattle were: for two calves experimentally infected with EHDV-1 or EHDV-2 [24]; for 127 cattle naturally exposed to EHDV-2, 5, 7 or 8 [1]; for four calves experimentally infected with EHDV-7 [25]; for three calves experimentally infected with EHDV-7 [26]; and for four calves experimentally infected with EHDV-8 [14]. Because of the frequency of sampling in each study, the data were used to compute the minimum and maximum duration of viraemia based on the results of virus isolation for each animal.

The duration of viraemia was assumed to follow a gamma distribution with shape parameter $n_C$ and mean $1/r_C$. Parameters were estimated in a Bayesian framework. The likelihood for the data was given by

$$L = \prod_a \int_{t_{\min}^{(a)}}^{t_{\max}^{(a)}} f(u)\,\mathrm{d}u, \tag{4}$$

where $t_{\min}^{(a)}$ and $t_{\max}^{(a)}$ are the minimum and maximum duration of viraemia for animal $a$, respectively, and $f$ is the probability density function for the gamma distribution. Exponential priors with mean 100 were used for all parameters.

Samples from the joint posterior density were generated using an adaptive Metropolis scheme [27], modified so that the scaling factor was tuned during burn-in to ensure an acceptance rate of between 20% and 40% for more efficient sampling of the target distribution [28]. Two chains of 120,000 iterations were run, with the first 20,000 iterations discarded to allow for burn-in of the chains. Chains were subsequently thinned (by taking every 10th sample) to reduce autocorrelation. The adaptive Metropolis scheme was implemented in Matlab (version R2020b; The Mathworks Inc.). Convergence of the scheme was assessed visually and by examining the Gelman-Rubin statistic in the coda package [29] in R (version 4.4.0) [30].

For EHDV-2 and EHDV-5 there were sufficient data to explore whether parameters ($n_C$ and $1/r_C$) differed between strains. Four different models were compared (electronic supplementary material, table S1) in which: (i) the shape and mean were common to both strains; (ii) the shape parameter differed between strains and the mean was common; (iii) the shape parameter was common and the mean differed; or (iv) the shape parameter and mean differed between strains. Models were compared using the deviance information criterion (DIC) [31].

### *2.2.4 Duration of viraemia and disease-associated mortality rate in deer*

Data used to estimate the duration of viraemia and disease-associated mortality rate in deer were: for 16 white-tailed deer experimentally infected with EHDV-2 [32]; for six white-tailed deer experimentally infected with EHDV-7 [33]; and for five white-tailed deer experimentally infected with EHDV-6 [34].

The duration of viraemia in deer was assumed to follow a gamma distribution with shape parameter $n_D$ and mean $1/r_D$. Parameters were estimated in a Bayesian framework, as described in section 2.2.3. For deer which succumbed to disease or which were still viraemic at the end of the experiment, the duration of viraemia was right-censored (i.e. the maximum duration was set to $+\infty$).

Case fatality in deer ($f_D$) was estimated using the same approach as described in section 2.2.2, but replacing the probability of transmission from host to vector with the case fatality and the number of infected midges and number of midges tested with the number of deer succumbing to disease and the number of deer infected, respectively. The disease-associated mortality rate ($d_D$) can be calculated from the mean and shape for the duration of viraemia and the case fatality, using the following relationship,

$$d_D = n_D r_D \left( \frac{1}{(1-f_D)^{1/n_D}} - 1 \right). \tag{5}$$

(see [10] for derivation).

### *2.2.5 Extrinsic incubation period*

The temperature dependence of the EIP was estimated from data on the infection of colonised *C. sonorensis* with different strains of EHDV [35,36]. In the experiments, *C. sonorensis* were allowed to feed on a source of virus (either on a blood/virus mix via a membrane or on an infected deer; see electronic supplementary material, table S2) and then maintained at different constant temperatures. At certain times post feeding, individual midges were tested for the level of virus present (electronic supplementary material, figure S2). A titre >2.5 $\log_{10}$ $TCID_{50}$ [35] or >2.7 $\log_{10}$ $TCID_{50}$ [36] was used to define a midge with a fully disseminated infection (i.e. one that is infectious).

The EIP was assumed to follow a gamma distribution with temperature-dependent mean equal to $1/v(T)$ and variance equal to $1/kv(T)^2$, where $k$ is the shape parameter for the distribution and

$$v(T) = \begin{cases} 0 & T \le T_{\min} \\ \alpha(T - T_{\min}) & T > T_{\min} \end{cases} \tag{6}$$

is the reciprocal of the mean EIP [16]. Here $\alpha$ is the virus replication rate and $T_{\min}$ is the threshold temperature (°C) for replication. This model assumes that a midge completes it EIP once it has accumulated sufficient thermal time.

The probability that a midge has a disseminated infection when tested $t$ days after feeding when maintained at temperature $T$ is given by,

$$p_{tT} = \beta \int_0^t f(\tau; v(T), k)\, \mathrm{d}\tau, \tag{7}$$

where $\beta$ is the probability of transmission from host to vector, $f$ is the probability density function for the gamma distribution, $v(T)$ is the reciprocal of the mean EIP (given by equation (6)) and $k$ is the shape parameter. Differences in parameters ($\beta$, $T_{\min}$ and $\alpha$) amongst strains and feeding routes were incorporated by allowing them to differ amongst experiments. This

was incorporated by assuming hierarchical structure in the parameters such that they are drawn from higher-order distributions, so that

$$\begin{aligned} \beta &\sim \text{Beta}(a_\beta, b_\beta) \\ T_{\min} &\sim \text{Gamma}(a_T, b_T) \\ \alpha &\sim \text{Gamma}(a_\alpha, b_\alpha) \end{aligned} \tag{8}$$

where $a_i$ and $b_i$ are the distribution parameters for the higher-order beta or gamma distributions for parameter $i$. Nine different models were compared to explore which of the parameters differed with virus strain or feeding route (electronic supplementary material, table S3).

Parameters were estimated using Bayesian methods. In this case, the likelihood for the data is given by

$$L = \prod_t \prod_T p_{tT}^{I_{tT}} (1 - p_{tT})^{N_{tT} - I_{tT}}, \tag{9}$$

where $I_{tT}$ and $N_{tT}$ are the number of midges with a fully disseminated infection and the number of midges tested $t$ days after being given an infected blood meal when maintained at temperature $T$, respectively. Hierarchical priors were used for those parameters that differed amongst strains/feeding routes and exponential priors (with mean 100) were used for the higher-order parameters in the hierarchical distributions. If a parameter was common to all species, a uniform prior (with range [0,1]) was used for $\beta$ and an exponential prior (with mean 100) was used for $T_{\min}$ or $\alpha$. An exponential prior with mean 100 was used for the shape parameter ($k$).

Samples from the joint posterior density were generated using an adaptive Metropolis scheme as described in section 2.2.3. In this case, two chains of 600,000 iterations were run, with the

first 100,000 iterations discarded to allow burn-in of the chains. Each chain was subsequently thinned by taking every 50th iteration.

Models assessing whether the probability of transmission from host to vector, the threshold temperature for replication or the virus replication rate differed amongst strains and feeding routes were compared using the DIC.

#### *2.2.6 Vector mortality rate*

The vector mortality rate was estimated using data on the lifespan of field-caught *C. sonorensis* [37]. Data were extracted from figure 9 in [37] using WebPlotDigitiser (version 4.6; Automeris.io) [22]. The estimated lifespan was used to calculate the mortality rate (electronic supplementary material, figure S1) by assuming the mortality rate is equal to the reciprocal of the mean lifespan.

The mortality rate ($\mu$) depends on environmental temperature ($T$) and the relationship can be described by

$$\mu(T) = \mu_0 \exp(\mu_1 T), \tag{10}$$

where $\mu_0$ and $\mu_1$ are parameters. These parameters were estimated in a Bayesian framework, assuming a normal likelihood and exponential priors with mean 100. The methods were implemented using OpenBUGS. Two chains of 120,000 iterations were run, with the first 20,000 iterations discarded to allow for burn-in. The chains were then thinned (by selecting every tenth iteration) to reduce autocorrelation. Convergence was checked visually and using the Gelman-Rubin statistic implemented in OpenBUGS.

### ***2.3 Uncertainty and sensitivity analysis***

To calculate $R_0$ for EHDV in cattle or deer allowing for uncertainty in the underlying parameters, multiple sets of parameters were drawn at random from their joint posterior distributions and used to compute $R_0$ at environmental temperatures between 10 and 40 °C.

The sensitivity of $R_0$ to changes in each parameter was assessed using the Sobol method [12,13]. This is a variance-based global sensitivity analysis that estimates the influence of each parameter on the outputs of a model. In the context of the present study, the method quantifies the contribution of each parameter in table 1 individually and in interactions with other parameters to the total variance in $R_0$. In particular, the first-order sensitivity index for a parameter measures the main effects of that parameter for $R_0$ (i.e. without interactions), while the total sensitivity index measures the total effect of the that parameter (i.e. including all interactions with other parameters). When the index for a parameter is zero, $R_0$ does not depend on that parameter, while if it is equal to one, $R_0$ depends solely on that parameter.

The first-order and total sensitivity indices for the parameters were calculated for $R_0$ at different environmental temperatures using Monte Carlo methods [38]. Briefly, two random $N$ by $p$ matrices (where $N$ is the number of samples and $p$ the number of model inputs) were generated by sampling from the joint posterior distributions for the model parameters. The model (i.e. $R_0$) was then evaluated for each set of inputs in these matrices and for combinations of the two matrices, which allows calculation of the sensitivity indices for that input (see electronic supplementary material, text S1 for details). Because they are jointly distributed (and so not independent), some parameters were grouped together as model inputs: biting rate parameters ($a_0$, $T_0$); host parameters ($1/r$, $n$, $d$); EIP parameters ($\alpha$, $T_{\min}$, $k$); and vector mortality rate parameters ($\mu_0$, $\mu_1$). In addition, multiple replicates of the sensitivity analysis were run to check convergence of the indices.

The uncertainty and sensitivity analyses were implemented in Matlab (version R2020b; The Mathworks Inc.). The code used for the uncertainty and sensitivity analysis is available online [17].

# 3 Results

## *3.1 Parameter estimation*

### *3.1.1 Probability of transmission from host to vector*

The posterior medians (95% credible interval) for $a_{HV}$ and $b_{HV}$ were 1.36 (0.59, 2.85) and 47.8 (17.6, 104.7), respectively. This gives a median probability of transmission from host to vector ($\beta$) of 0.022 and a 95% range of ($1.6\times10^{-3}$, 0.088) (table 1).

### *3.1.2 Biting rate*

The posterior medians (95% credible interval) for the slope ($a_0$) and minimum temperature ($T_0$) were $1.4\times10^{-4}$ ($9.8\times10^{-5}$, $2.2\times10^{-4}$) and 6.93 (0.49, 14.32), respectively (table 1). The fitted function, (3), and data are shown in electronic supplementary material, figure S1.

### *3.1.3 Duration of viraemia in cattle*

When fitting the model to data for all strains combined the posterior medians (95% credible intervals) for the shape parameter ($n_C$) and the mean duration ($1/r_C$) were 1.09 (0.67, 1.66) and 6.61 (5.51, 7.86) days, respectively (table 1). When fitting to data for EHDV-2 and EHDV-5 only, there was evidence that the shape parameter ($n_C$) differed between the strains, but not the mean duration ($1/r_C$) (electronic supplementary material, table S1). In this case, the posterior medians (95% credible intervals) for $n_C$ were 1.37 (0.75, 2.34) and 0.22 (0.05,

0.98) for EHDV-2 and EHDV-5, respectively. The posterior median (95% credible interval) for $1/r_C$ was 7.06 (5.61, 8.66) days, which is similar to that obtained for all strains combined.

### *3.1.4 Duration of viraemia and disease-associated mortality rate in deer*

The posterior medians (95% credible intervals) for the shape parameter ($n_D$) and mean duration ($1/r_D$) were 5.19 (1.92, 11.94) and 27.17 (20.70, 45.42) days, respectively (table 1). When estimating the case fatality in deer ($f_D$) the posterior medians (95% credible interval) for $a_F$ and $b_F$ were 71.0 (10.4, 252.6) and 87.1 (11.5, 300.9), respectively. This gives a median case fatality of 0.45 and a 95% prediction range of (0.37, 0.53). Combining the estimates for the mean and shape parameter for the duration of viraemia and the case fatality using equation (5) yields a posterior median (95% credible interval) for the disease-associated mortality rate ($d_D$) of 0.023 (0.014, 0.034) (table 1).

### *3.1.5 Extrinsic incubation period*

The best-fitting model for the EIP was one in which the threshold temperature for replication ($T_{\min}$) and virus replication rate ($\alpha$) differed amongst strains, but not with feeding route (electronic supplementary material, table S3). This model adequately captured the data (electronic supplementary material, figure S2). The threshold temperature for replication ranged from 15.0 °C for EHDV-7 (Israel) to 19.5 °C for EHDV-1 (unknown) (table 1). The virus replication rate also varied amongst strains, ranging from 0.008 for EHDV-2 (USA) to 0.075 for EHDV-1 (unknown) (table 1).

Estimates for the probability of transmission from host to vector ($\beta$) using colony reared midges (as in the EIP studies) were markedly higher than when using field-caught midges (although of different species) (electronic supplementary material, table S4; cf. table 1). In

addition, the probability of transmission from host to vector was three times higher for membrane-fed midges compared with those fed on an infected deer (electronic supplementary material, table S4).

#### *3.1.6 Vector mortality rate*

The posterior medians (95% credible interval) for the mortality rate parameters ($\mu_0$ and $\mu_1$) were 0.012 (0.007, 0.019) and 0.15 (0.13, 0.17), respectively (table 1). The fitted function, (10), and data are shown in electronic supplementary material, figure S1.

### ***3.2 Basic reproduction ratio for EHDV***

The virus replication rate and the threshold temperature for virus replication varied significantly amongst EHDV strains, though there was no evidence for strain variation amongst any of the other model parameters. Accordingly, the basic reproduction ratio ($R_0$) was calculated separately for each of the four strains for which $\alpha$ and $T_{\min}$ were estimated.

For all four strains and both host species $R_0$ increased once the threshold temperature for virus replication was exceeded, reached a maximum level and then declined (figure 1). There is uncertainty relating to the maximum $R_0$, the temperature at which this occurs and the minimum temperature for $R_0$>1 (figure 1). However, there are discernible trends amongst the strains and between host species. Comparing strains, the highest maximum $R_0$ was for EHDV-1 (unknown) followed by EHDV-1 (USA) then EHDV-7 (Israel) and EHDV-2 (USA). The median maximum $R_0$ was between 0.7 and 2.5 in cattle and 1.3 and 4.3 in deer. In particular, that for EHDV-2 (USA) in cattle did not exceed the threshold at $R_0$=1. The median maximum $R_0$ occurred at temperatures between 22.3 and 25.1 °C, with the lowest temperature for EHDV-7 (Israel) and the highest for EHDV-1 (unknown). Finally, the

threshold at $R_0$=1 was exceeded at the lowest temperature (16.5 °C) for EHDV-7 (Israel) and at the highest temperature (19.9 °C) for EHDV-1 (unknown). These patterns were the same for both cattle and deer, but $R_0$ for all strains was higher in deer than in cattle.

### *3.3 Sensitivity analysis*

The first-order and total sensitivity indices for $R_0$ for EHDV in cattle and deer are shown in figure 2. The patterns in the sensitivity of $R_0$ to the underlying parameters were the same for cattle and deer. Both indices indicate that the sensitivity of $R_0$ to changes in underlying parameters depends on environmental temperature for all four strains. At lower temperatures (<18 °C) $R_0$ is sensitive only to the EIP parameters (and the threshold temperature for virus replication, $T_{min}$, in particular), and none of the others. However, at higher temperatures (>20 °C) $R_0$ is most sensitive to the probability of transmission from host to vector ($\beta$) and the vector to host ratio ($m$), with these two parameters contributing approximately equally. The remaining parameters (or groups of parameters) had very limited impact on $R_0$, either as main effects (all first-order indices <0.1) or when interactions with other parameters are also considered (all total indices <0.1).

## 4 Discussion

In this study the temperature-dependent basic reproduction ratio, $R_0$, for EHDV was calculated in cattle and deer populations, the most important livestock and wildlife hosts of this virus. The parameters needed to calculate $R_0$ were estimated from previously published data and their influence on predictions of $R_0$ were assessed by computing Sobol sensitivity indices. Any conclusions drawn from such uncertainty and sensitivity analyses are valid only over the parameter ranges considered. However, these ranges (and the corresponding distributions) were derived from the best available data on EHDV and its *Culicoides* vectors.

The only exception was the probability of transmission from vector to host, for which no data were available and was estimated based on BTV transmission to sheep instead.

Bearing these caveats in mind, the maximum $R_0$ for EHDV was between 0.7 and 2.5 in cattle and 1.3 and 4.3 in deer, depending on strain, and occurred at temperatures between 22 and 25 °C (figure 1). This indicates that some strains of EHDV could cause outbreaks (i.e. $R_0$>1) at temperatures relevant to much of Europe and so poses a risk to European cattle and deer. Furthermore, it is consistent with the observed spread of EHDV-8 following its introduction to southern Europe in 2022 and subsequent spread in 2023 [5-7].

The predicted values of $R_0$ for EHDV in cattle obtained in the present study are different to those for the two other *Culicoides*-borne viruses that affect cattle and that have previously spread widely in Europe: BTV and Schmallenberg virus (SBV) (figure 3). In particular, the magnitude of $R_0$ for EHDV (0.7-2.5) is much lower than for BTV (3.3) or SBV (4.5). Moreover, the minimum temperature for which $R_0$>1 is lower for BTV (14 °C) and SBV (13 °C) than for EHDV (18-20 °C), as is the temperature at which $R_0$ has its maximum (BTV: 21 °C; SBV: 21 °C; EHDV: 22-25 °C).

Although $R_0$ only considers spread at a local spatial scale, differences in the magnitude of $R_0$ amongst viruses would also be reflected in differences in their speed of spatial spread, with EHDV spreading more slowly that either BTV or SBV in the same region. The rate of spread has been estimated for epidemics of BTV serotype 1 in Andalusia in 2007 and in southwestern France in 2008 [39], both regions where there were outbreaks of EHDV-8 in 2022-2023. Corresponding estimates have yet to be published for EHDV-8 in either region, but comparison of maps showing spread in southwestern France suggest that the rate of

spread of EHDV-8 [6,7] was slower than for BTV-1 [39]. This is consistent with a lower $R_0$ for EHDV compared with BTV, but perhaps not one so low as predicted in the present study. For example, the difference in $R_0$ between BTV (3.3) and SBV (4.5) was sufficient to explain the considerably greater spread of SBV compared with BTV in northern Europe [11]. These differences in $R_0$ were a consequence of higher vector competence and faster replication within vectors at lower temperatures for SBV compared with BTV [11].

The magnitude of $R_0$ for EHDV was highly sensitive to both the probability of transmission from host to vector ($\beta$; i.e. vector competence) and the EIP parameters (figure 2). Vector competence has not yet been reported for EHDV-8 in any *Culicoides* species, though the virus has been detected in pools of *C. obsoletus/scoticus*, *C. imicola* and *C. punctatus* collected in Sardinia [40]. The minimum prevalence for *C. obsoletus/scoticus* (i.e. no. positive pools/total no. insects in the pools) was 0.11% (4/3542). This is comparable to the minimum prevalence for SBV (0.14%; 2/1440) [41] and higher than for BTV-8 (0.05%; 1/2200) [42]. This is likely indicative that vector competence for EHDV-8 is similar to that for SBV and higher than that for BTV-8. It would also indicate that the vector competence is likely to be at the higher end of the distribution estimated in the present study (table 1).

Experimental work to better quantify vector competence in European *Culicoides* species should be a priority, especially for the strain of EHDV-8 currently circulating in Europe. However, analysis in the present study indicates that the probability of a vector becoming infected depends not only on EHDV strain, but also on feeding route (feeding via membrane or on an infected animal), vector species and field-caught compared with colony midges (table 1; electronic supplementary material, table S4). Other experimental work has also shown a dependence of the probability of infection on viral titre in the blood meal on which

an insect fed [43-45]. Consequently, these factors should also be taken into account in the design any vector competence experiments.

The threshold temperature for virus replication ($T_{min}$) determines the temperature at which $R_0$ changes from zero to greater than zero and so constrains the transmission season for EHDV. The threshold temperatures (15-19 °C) estimated in the present study for four strains of EHDV are higher than estimated for BTV (11-14 °C) [16] or SBV (12 °C) [11]. This suggests that the transmission season could be shorter for EHDV compared with *Culicoides*-borne viruses that have previously spread in Europe, especially at more northerly latitudes. Moreover, the EIP parameters in general, and the threshold temperature in particular, are important for determining the magnitude of $R_0$ for EHDV at temperatures close to the threshold (figure 2). Accordingly, the EIP for EHDV-8 and its dependence on temperature, which has not been quantified, is an important data gap.

A third parameter to which $R_0$ for EHDV is sensitive is the vector to host ratio ($m$) (figure 2). The assumed variation in this parameter for cattle reflects for the most part farm-to-farm variation in midge population sizes (table 1). Although various *Culicoides* species are known to feed on deer [46,47], little else is known about their association with deer populations [48], including the relationship between abundance and deer population size. In the absence of this information, the vector to host ratio was assumed to follow the same distribution as for cattle. Similarly, the biting rate on deer was assumed to be the same as that for cattle. Better characterisation of the relationships between deer and *Culicoides* biting midges would allow a more robust assessment of the role of deer in the transmission of EHDV in Europe. Evidence from previous epidemics of BTV suggest that deer played an important role in maintaining the virus and vector populations in areas of southern Europe [48]. By contrast,

deer were less important in northern and central Europe, where they did not act as maintenance hosts for BTV [49].

For all four strains of EHDV considered in the present study $R_0$ was higher in deer than in cattle (figure 1), suggesting deer could play an important role in the transmission of EHDV. However, the parameters for deer used in the present study were estimated from data on white-tailed deer infected with strains of EHDV circulating in the USA. EHDV has been widely studied in white-tailed deer [2], reflecting the impact of EHD on populations of this species in endemic areas [3]. Only limited data are available on EHDV infection in European deer species [50,51]. These demonstrate that red, roe and fallow deer and muntjac are susceptible to EHDV infection and, in the case of red deer, can develop clinical disease, but are not sufficient to parameterise transmission models.

## 5 Conclusions

Results of the present study show that $R_0$ for EHDV depends on strain, but that $R_0$ exceeds one (and so can cause outbreaks) at temperatures relevant to much of Europe. Sensitivity analysis identified the probability of transmission from host to vector (i.e. vector competence), the threshold temperature for virus replication and the vector to host ratio as the most important parameters influencing $R_0$. In addition, there are only limited data on EHDV in European deer species and on *Culicoides* populations at the deer/livestock interface. These areas should be the focus of future research.

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**Data sharing**

No new data were generated by this work. The data extracted from the published literature and used to parameterise the model are provided in the electronic supplementary material, dataset S1. All code used to estimate parameters and implement the uncertainty and sensitivity analyses is available online [17].

**Ethics statement**

No ethical issues were raised by this work.

**Author contributions**

Conceptualization: SG. Formal analysis: SG. Methodology: SG. Software: SG. Writing - original draft: SG. Writing - review & editing: SG.

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**Table 1.** Parameters for the transmission of epizootic haemorrhagic disease virus (EHDV) in cattle and deer by *Culicoides* biting midges.

| description | | symbol | estimate* or function | comments |
|---|---|---|---|---|
| probability of transmission from vector to host | | $b$ | 0.80 (0.48, 0.97) | estimated by [10] from data on infection of sheep with bluetongue virus by *C. sonorensis* [52] |
| probability of transmission from host to vector | | $\beta$ | 0.022 ($1.6\times10^{-3}$, 0.088) | estimated in the present study |
| vector to host ratio (cattle) | | $m_C$ | 1425 (149, 5361) | estimated by fitting to bluetongue outbreak data for Great Britain [53]; reflects farm-to-farm variation in this parameter |
| vector to host ratio (deer) | | $m_D$ | 1425 (149, 5361) | assumed to be the same as for cattle |
| reciprocal of the time interval between blood meals | | $a$ | $a(T)=a_0T(T-T_0)(42-T)^{1/2}$ | depends on temperature; parameters ($a_0$ and $T_0$) estimated in the present study |
| | | $a_0$ | $1.4\times10^{-4}$ ($9.8\times10^{-5}$, $2.2\times10^{-4}$) | |
| | | $T_0$ | 6.93 (0.49, 14.32) | |
| duration of viraemia (cattle)† | mean | $1/r_C$ | 6.61 (5.51, 7.86) | estimated in the present study |
| | shape | $n_C$ | 1.09 (0.67, 1.66) | |
| disease-associated mortality rate (cattle) | | $d_C$ | 0 | mortality in cattle is typically low (<2%) [1,2] |
| duration of viraemia (deer)† | mean | $1/r_D$ | 27.17 (20.70, 45.42) | estimated in the present study |
| | shape | $n_D$ | 5.19 (1.92, 11.94) | |
| disease-associated mortality rate (deer) | | $d_D$ | 0.023 (0.014, 0.034) | |
| extrinsic incubation period (EIP)† | mean | $1/v$ | $v(T)=\alpha(T-T_{\min})$ | depends on temperature; parameters ($\alpha$, $T_{\min}$ and $k$) estimated in the present study for four strains of EHDV |
| | shape | $k$ | 2.94 (2.24, 3.94) | |
| virus replication rate | EHDV-1 (USA) | $\alpha$ | 0.017 (0.012, 0.025) | |
| | EHDV-2 (USA) | | 0.008 (0.005, 0.014) | |

| description | | symbol | estimate* or function | comments |
|---|---|---|---|---|
| | EHDV-7 (Israel) | | 0.015 (0.011, 0.019) | |
| | EHDV-1 (unknown)‡ | | 0.075 (0.058, 0.098) | |
| threshold temperature for virus replication | EHDV-1 (USA) | $T_{\min}$ | 16.72 (14.72, 17.87) | |
| | EHDV-2 (USA) | | 16.28 (14.30, 17.66) | |
| | EHDV-7 (Israel) | | 14.97 (12.51, 16.49) | |
| | EHDV-1 (unknown)‡ | | 19.46 (19.26, 19.61) | |
| vector mortality rate | | $\mu$ | $\mu(T)=\mu_0\exp(\mu_1 T)$ | depends on temperature; parameters ($\mu_0$ and $\mu_1$) estimated in the present study |
| | | $\mu_0$ | 0.012 (0.007, 0.019) | |
| | | $\mu_1$ | 0.15 (0.13, 0.17) | |

* posterior median (95% credible interval)

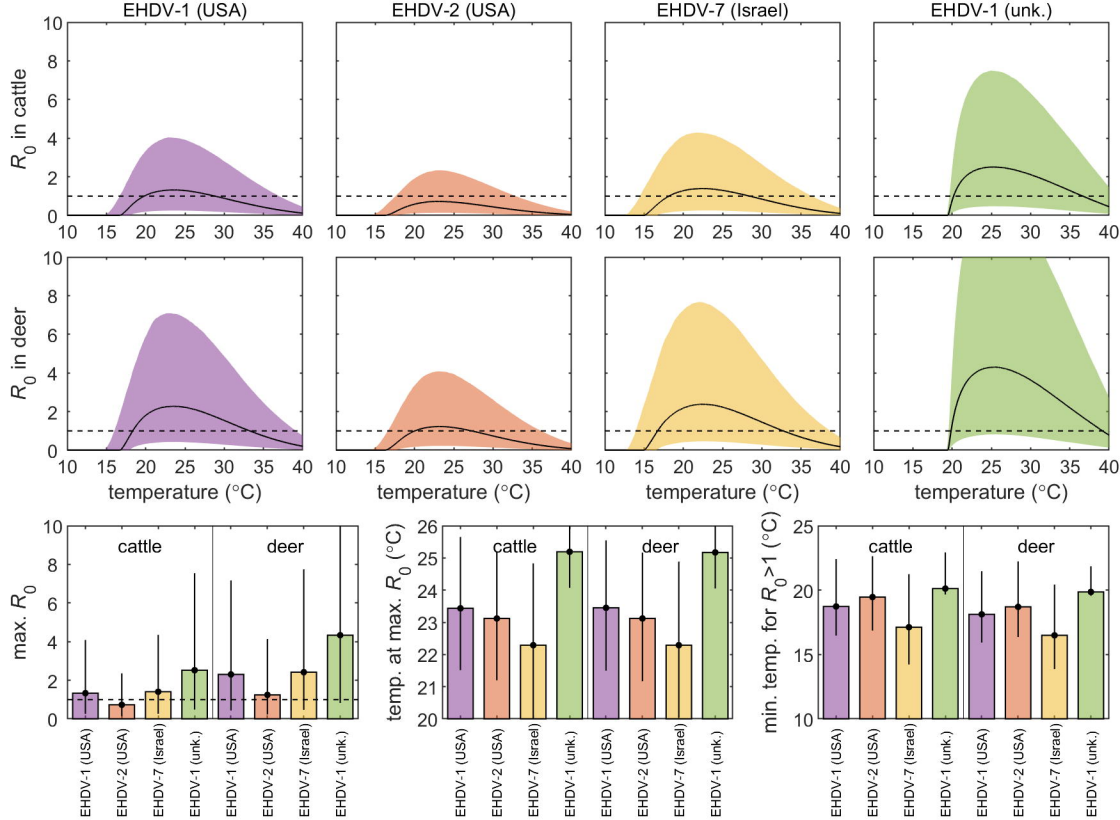
† the duration of viraemia in cattle and deer and the duration of the EIP are assumed to follow gamma distributions; the mean and shape parameterise the distribution

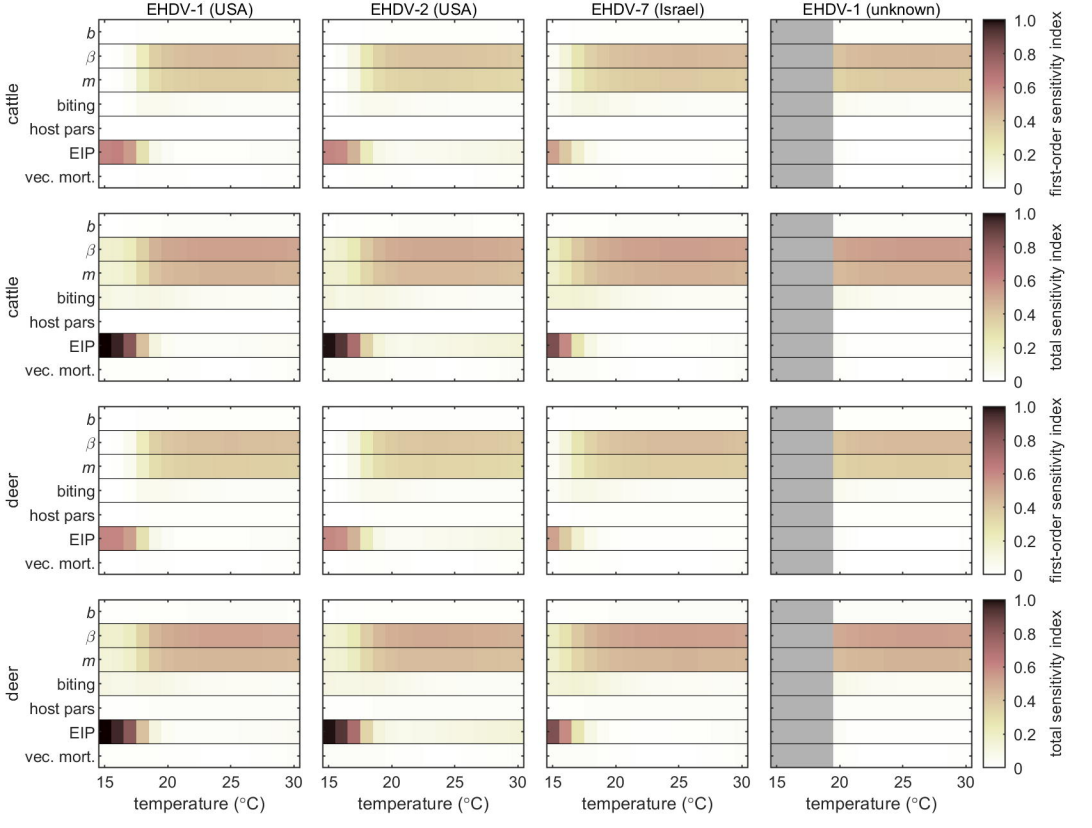
‡ the estimates for $\alpha$ and $T_{\min}$ for EHDV-1 (unknown) are similar to those derived previously using the same data [16]

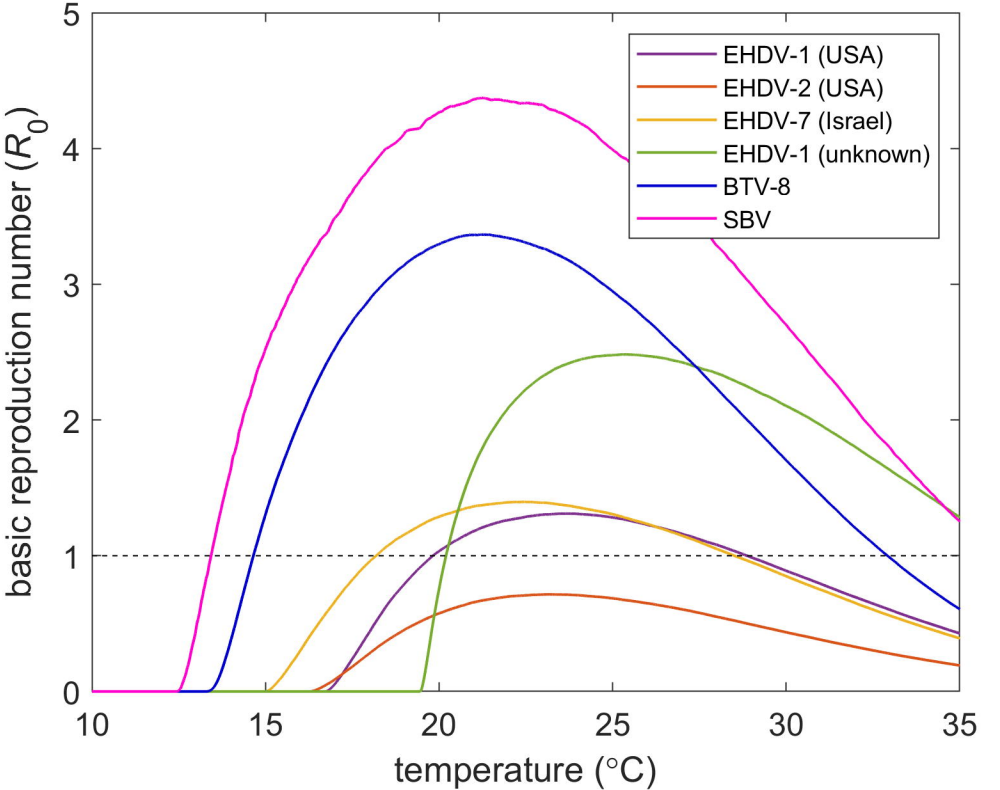
**Figure 1.** Basic reproduction ratio ($R_0$) and its dependence on temperature for four strains of epizootic haemorrhagic disease virus in cattle or deer. The top two rows show the median (black line) and 95% prediction interval (coloured shading) for $R_0$ as a function of environmental temperature for the strain. The bottom row shows the median (bar) and 95% prediction interval (error bars) for the maximum $R_0$, temperature at maximum $R_0$ and minimum temperature for $R_0$>1 for each strain. A black dashed line indicates the threshold at $R_0$=1. Results are based on 10000 samples drawn from the joint posterior distribution.

**Figure 2.** Sensitivity of the basic reproduction ratio, $R_0$, for transmission of four strains of epizootic haemorrhagic disease virus in cattle or deer to underlying parameters and how this varies with environmental temperature. Each plot shows the first-order or total Sobol sensitivity indices (indicated by the colour bar) for each parameter or group of parameters: probability of transmission from vector to host ($b$); probability of transmission from host to vector ($\beta$); vector to host ratio ($m$); biting rate parameters ($a_0$, $T_0$); host parameters ($1/r$, $n$, $d$); extrinsic incubation period (EIP) parameters ($\alpha$, $T_{\min}$, $k$); and vector mortality rate parameters ($\mu_0$, $\mu_1$). Results are the median of 10 replicates with 10000 samples drawn from the joint posterior distribution for each replicate.

**Figure 3.** Comparison of the basic reproduction ratio ($R_0$) in cattle for epizootic haemorrhagic disease virus (EHDV), bluetongue virus (BTV) and Schmallenberg virus (SBV). Each curve shows the posterior median for $R_0$ and its dependence on environmental temperature for a virus/strain: EHDV-1 (USA) (purple); EHDV-2 (USA) (orange); EHDV-7 (Israel) (yellow); EHDV-1 (unknown) (green); BTV-8 (northern Europe, 2006-2010) (blue); and SBV (northern Europe, 2011) (magenta).


EHDV-1 (USA)
EHDV-2 (USA)
EHDV-7 (Israel)
EHDV-1 (unk.)
$R_0$ in cattle
$R_0$ in deer
temperature (°C)
max. $R_0$
temp. at max. $R_0$ (°C)
min. temp. for $R_0$>1 (°C)
cattle
deer
EHDV-1 (USA)
EHDV-2 (USA)
EHDV-7 (Israel)
EHDV-1 (unk.)


EHDV-1 (USA)
EHDV-2 (USA)
EHDV-7 (Israel)
EHDV-1 (unknown)
cattle
deer
b
β
m
biting
host pars
EIP
vec. mort.
15
20
25
30
temperature (°C)
1.0
0.8
0.6
0.4
0.2
0
first-order sensitivity index
total sensitivity index


EHDV-1 (USA)
EHDV-2 (USA)
EHDV-7 (Israel)
EHDV-1 (unknown)
BTV-8
SBV
basic reproduction number ($R_0$)
temperature (°C)
0
1
2
3
4
5
10
15
20
25
30
35