Using the basic reproduction number to assess the risk of transmission of lumpy skin disease virus by biting insects

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Short running title: R_0 for LSDV

Summary

In recent years, lumpy skin disease virus (LSDV) has emerged as a major threat to cattle outside Africa, where it is endemic. Although evidence suggests that LSDV is transmitted by the bites of blood sucking arthropods, few studies have assessed the risk of transmission posed by particular vector species. Here this risk is assessed by calculating the basic reproduction number (R_0) for transmission of LSDV by five species of biting insect: the stable fly, *Stomoxys calcitrans*, the biting midge, *Culicoides nubeculosus*, and three mosquito species, *Aedes aegypti*, *Anopheles stephensi* and *Culex quinquefasciatus*. Parameters relating to mechanical transmission of LSDV were estimated using new analyses of previously-published data from transmission experiments, while vector life history parameters were derived from the published literature. Uncertainty and sensitivity analyses were used to compute R_0 for each species and to identify those parameters which influence its magnitude. Results suggest that *S. calcitrans* is likely to be the most efficient at transmitting LSDV, with *Ae. aegypti* also an efficient vector. By contrast, *C. nubeculosus*, *An. stephensi*, and *Cx. quinquefasciatus* are likely to be inefficient vectors of LSDV. However, there is considerable uncertainty associated with the estimates of R_0, reflecting uncertainty in most of the constituent parameters. Sensitivity analysis suggests that future experimental work should focus on estimating the probability of transmission from insect to bovine and on the virus inactivation rate in insects.

Keywords: cattle; epidemiology; transmission model; Bayesian methods; uncertainty analysis; sensitivity analysis

1 Introduction

Lumpy skin disease (LSD) is an important transboundary disease of cattle and is caused by lumpy skin disease virus (LSDV). Historically, LSD outbreaks have largely been confined to Africa (EFSA Panel on Animal Health and Welfare, 2015), where the disease contributes to rural poverty and food insecurity (Tuppurainen & Oura, 2012; Molla, de Jong, Gari & Frankena, 2017). In recent years, however, LSDV has emerged as a major threat to cattle outside of Africa. In 2012 it spread to the Middle East, through Israel and the Lebanon, reaching Turkey in 2013 (Alkhamis & VanderWaal, 2016). In 2015, the first cases of LSD were reported in Greece (Tasioudi et al., 2016) and the virus subsequently spread to much of the Balkans (Mercier et al., 2018).

Evidence from the field and from experiments indicates that transmission of LSDV by most direct and indirect routes is inefficient (Weiss, 1968; Carn & Kitching, 1995). The principal transmission route for LSDV is believed to be via the bites of blood sucking arthropods (Tuppurainen & Oura, 2012; EFSA Panel on Animal Health and Welfare, 2015). This has been shown experimentally for *Aedes aegypti* mosquitos (Chihota, Rennie, Kitching & Mellor, 2001) and for *Rhipicephalus appendiculatus* male ticks (Tuppurainen et al., 2013). The stable fly, *Stomoxys calcitrans*, has been incriminated as a potential vector in Israel by comparing its seasonal abundance with the seasonality of LSD cases (Kahana-Sutin, Klement, Lensky & Gottlieb, 2017) and because of its ability to transmit the closely related capripox virus between sheep and goats (Kitching & Mellor, 1986; Mellor, Kitching & Wilkinson, 1987). The potential for the biting midge, *Culicoides nubeculosus*, and two other mosquito species, *Culex quinquefasciatus* and *Anopheles stephensi*, to transmit LSDV has also been assessed, though for these three species attempts at transmission were unsuccessful (Chihota, Rennie, Kitching & Mellor, 2003).

In this study, the risk of transmission of LSDV posed by different insect species is explored by estimating the basic reproduction number for five species of biting insect (*S. calcitrans*, *C. nubeculosus*, *Ae. aegypti*, *An. stephensi* and *Cx. quinquefasciatus*). These species were selected as their potential role in LSDV transmission has been investigated previously (Chihota, Rennie, Kitching & Mellor, 2001, 2003) and they represent insect species (or at least genera) that are relevant to Europe. The basic reproduction number, denoted by R_0, is the "average number of secondary cases arising from the introduction of a single infected individual into an otherwise susceptible population" (Diekmann & Heesterbeek, 2000). An outbreak can occur only if $R_0>1$ and, consequently, R_0 provides a means to assess the risk posed by each vector species.

Using a transmission model, an expression for R_0 is derived that shows how it relates to the underlying transmission processes in insect vectors and cattle. These constituent parameters are then estimated using data from the published literature. In particular, data from transmission experiments involving the five putative vector species (Chihota, Rennie, Kitching & Mellor, 2001, 2003) are re-analysed using Bayesian methods to quantify the uncertainty in parameters relating to mechanical transmission. In addition, the latent and infectious periods for LSDV are estimated from the outcome of challenge experiments (Tuppurainen, Venter & Coetzer, 2005; Babiuk et al., 2008), again using Bayesian methods. Finally, uncertainty and sensitivity analyses are used to calculate R_0 and to determine which of the constituent parameters has the greatest influence on its magnitude.

2 Materials and methods

2.1 Basic reproduction number for LSDV

For an infection transmitted mechanically by biting insects the basic reproduction number can be written as,

$$R_0 = \sqrt{\frac{ba}{(\gamma+\mu)} \times \frac{\beta m a}{r_I}}. \quad (1)$$

A full mathematical derivation of this expression for R_0, including the transmission model on which it is based, is presented in the supporting information (Text S1). However, the expression, (1), can be understood heuristically as follows. After it feeds on an infected animal, an insect remains infected (and infectious) until the virus becomes inactivated or it dies, a period which lasts on average $1/(\gamma+\mu)$ days, where γ is the virus inactivation rate and μ is the vector mortality rate. During this time it will bite susceptible cattle a times per day (where a is the reciprocal of the time interval between blood meals) and a proportion, b, of these bites (i.e. the probability of transmission from insect to bovine) will result in a newly infected host. Once infected, a bovine will remain infectious for the duration of its infectious period, which lasts $1/r_I$ days on average. During this time the host will be bitten by susceptible insects 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), a proportion, β, of which will result in a newly infected vector (i.e. the probability of transmission from bovine to insect).

2.2 Mechanical transmission of LSDV by insects

Data on mechanical transmission of lumpy skin disease virus to cattle by five species of biting insect (*S. calcitrans*, *C. nubeculosus*, *Ae. aegypti*, *An. stephensi* and *Cx. quinquefasciatus*) were extracted from the published literature (Chihota, Rennie, Kitching & Mellor, 2001, 2003). This provided the number of positive insects (i.e. those for which viral DNA was detected; virus isolation was only carried out for a small number of pooled samples) and the number of insects tested after feeding on a LSDV-infected bovine (*S.*

111 *calcitrans*, *C. nubeculosus* or *Ae. aegypti*) or a blood-virus mix via a membrane (*An.*
112 *stephensi* and *Cx. quinquefasciatus*) at each day post feeding (Table S1). It also provided
113 information on whether or not transmission occurred when batches of insects that had
114 previously fed on an infected animal or received an infected blood meal were allowed to
115 refeed on a naïve bovine (Table S1).
116
117 These data were used to estimate the virus inactivation rate (γ), the probability of
118 transmission from bovine to insect (β) and the probability of transmission from insect to
119 bovine (b) for each species. Parameters were estimated in a Bayesian framework to facilitate
120 the incorporation of uncertainty in estimates of R_0. The likelihood for the data is given by,

121
$$L(\gamma,\beta,b)=\prod_i \binom{N_i}{Y_i} p_i^{Y_i}(1-p_i)^{N_i-Y_i}\times \prod_j q_j^{I_j}(1-q_j)^{1-I_j}, \quad (2)$$

122 where Y_i and N_i are the number of positive insects and number of insects tested at t_i days post
123 feeding, respectively, and I_j is a variable indicating whether (I_j=1) or not (I_j=0) transmission
124 occurred when insects were allowed to refeed on naïve animal j at t_j days post initial feed. In
125 equation (2),

126
$$p_i=\beta\exp(-\gamma t_i), \quad (3)$$

127 is the probability that an insect is positive at t_i days post feeding and,

128
$$q_j=1-(1-b\beta\exp(-\gamma t_j))^{n_j}, \quad (4)$$

129 is the probability that transmission occurred from infected insects to bovine j at t_j days post
130 initial feed. The probability, (3), is the probability that an insect became infected (β)
131 multiplied by the probability that it was still infected when tested ($\exp(-\gamma t_i)$). The probability,
132 (4), is the probability that at least one insect (out of the n_j feeding) transmitted LSDV, where
133 the probability that an individual insect will transmit LSDV is the product of the probabilities

that it became infected (β), that it was still infected when refeeding occurred ($\exp(-\gamma t_j)$) and that it subsequently transmitted LSDV to the animal during refeeding (b). Non-informative priors were assumed for all three parameters: exponential with mean 100 for γ and uniform with range (0,1) for b and β.

Samples from the joint posterior density were generated using an adaptive Metropolis scheme (Haario, Saksman & Tamminen, 2001), 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 (Andrieu & Thoms, 2008). Two chains of 50,000 iterations were run, with the preceding 10,000 iterations discarded to allow for burn-in of the chain. The chains were then thinned (taking every fifth sample) to reduce autocorrelation amongst the samples. The adaptive Metropolis scheme was implemented in Matlab (version R2018a; The Mathworks Inc.). Convergence of the scheme was assessed visually and by examining the Gelman-Rubin statistic provided in the coda package (Plummer, Best, Cowles & Vines, 2006) in R (R Core Team, 2018).

2.3 Latent and infectious periods for LSDV in cattle

The mean infectious period ($1/r_I$) for LSDV in cattle was estimated using data from experimental infections (Tuppurainen, Venter & Coetzer, 2005; Babiuk et al., 2008). Three proxy measures of infectiousness were considered: detection of viral DNA in blood by PCR; detection of virus in blood by virus isolation (VI) in cell culture; and detection of virus (by transmission electron microscopy) or viral DNA (by PCR) in skin lesions. For each animal, the minimum infectious period was calculated as the time between the first positive and last positive samples, while the maximum infectious period was calculated as the time between

158 the last negative and first subsequent negative sample for each measure (i.e. accounting for
159 sampling frequency) (Table S2).
160
161 Although it is not needed for the calculation of R_0 (see equation (1)), the mean latent period
162 was also estimated for each proxy measure using data from experimental infections of cattle
163 (Chihota, Rennie, Kitching & Mellor, 2001; Tuppurainen, Venter & Coetzer, 2005; Babiuk et
164 al., 2008). In this case, the shortest latent period was the time of the last negative sample and
165 the longest latent period was the time of the first positive sample for each measure (i.e.
166 detection of viral DNA in blood, detection of virus in blood and appearance of skin lesions)
167 (Table S2).
168
169 The infectious period was assumed to follow a gamma distribution with mean duration $1/r_I$
170 and shape parameter n_I, while the latent period was assumed to follow a gamma distribution
171 with mean duration $1/r_E$ and shape parameter n_E (see Text S1). Parameters (i.e. mean and
172 shape parameter) for each proxy measure were estimated using Bayesian methods, with the
173 likelihood given by,

174 $$L(r_i, n_i) = \prod_j \int_{t_{\min}^{(j)}}^{t_{\max}^{(j)}} f(\tau)\, \mathrm{d}\tau, \qquad (5)$$

175 where $t_{\min}$ and $t_{\max}$ are the minimum and maximum infectious period (i=I) or latent period
176 (i=E) for an animal, respectively, and f is the probability density function for the gamma
177 distribution. Non-informative priors (exponential with mean 100) were assumed for both the
178 mean and the shape parameter.
179
180 Samples from the joint posterior distribution were generated using a random walk
181 Metropolis-Hastings algorithm (Andrieu & Thoms, 2008), with each parameter updated in

182 turn. Two chains of 20,000 iterations were run, with the preceding 5,000 iterations discarded
183 to allow for burn-in of the chain. The chains were then thinned (taking every other sample) to
184 reduce autocorrelation amongst the samples. The Metropolis-Hastings scheme was
185 implemented in Matlab (version R2018a; The Mathworks Inc.). Convergence of the scheme
186 was assessed visually and by examining the Gelman-Rubin statistic provided in the coda
187 package (Plummer, Best, Cowles & Vines, 2006) in R (R Core Team, 2018).
188

189 ### *2.4 Vector life history parameters*

190 Life history parameters, specifically the reciprocal of the time interval between blood meals
191 (a), the vector to host ratio (m) and the vector mortality rate (μ), were estimated for *S.*
192 *calcitrans*, *C. nubeculosus*, *Ae. aegypti*, *An. stephensi* and *Cx. quinquefasciatus*. For each
193 parameter, plausible ranges were derived from the published literature (Table 1), so they
194 could be incorporated in the uncertainty and sensitivity analysis.
195

196 ### *2.5 Uncertainty and sensitivity analyses*

197 Replicated Latin hypercube sampling (LHS) was used to explore the parameters influencing
198 the basic reproduction number, R_0 for each insect species and proxy measure of
199 infectiousness (Blower & Dowlatabadi, 1994; Luz, Codeco, Massad & Struichner, 2003;
200 Gubbins et al., 2008). Parameters were sampled either from their marginal posterior
201 distributions (b, β, γ and $1/r_I$) or uniformly from plausible ranges (a, m and μ). The LHS
202 results were used to compute the median and 95% prediction interval for R_0. The sensitivity
203 of R_0 to changes in each parameter was assessed by calculating the partial rank correlation
204 coefficients (PRCCs). The uncertainty and sensitivity analyses were implemented in Matlab
205 (version R2018a; The Mathworks Inc.).
206

3 Results

3.1 Mechanical transmission of LSDV by insects

The model, (3), adequately captured the data for all five species of biting insect, with the observed number of positive insects lying within the 95% credible intervals for the posterior predictive distribution (Figure 1). Although there is uncertainty associated with all the parameters related to mechanical transmission, there are still clear differences amongst the species (Figure 2). The virus inactivation rate is lowest for *Ae. aegypti* (0.08 day^{-1}), intermediate for *An. stephensi* (0.2 day^{-1}) and *Cx. quinquefasciatus* (0.3 day^{-1}) and highest for *S. calcitrans* (1.6 day^{-1}) and *C. nubeculosus* (71.4 day^{-1}) (Table 2). The probability of transmission from bovine to insect is highest for the three mosquito species, lower for *S. calcitrans* and lowest for *C. nubeculosus* (Table 2; Figure 2).

There is considerable uncertainty in the estimates for the probability of transmission from insect to bovine for all five insect species (Figure 2; Table 2). The posterior mode was non-zero only for *Ae. aegypti*, though the probability of transmission from insect to bovine could not be precisely estimated for this species (Figure 2). The posterior median for the probability of transmission from insect to bovine was low for *An. stephensi* (0.03) and *Cx. quinquefasciatus* (0.04), though the upper 95% credible limit for both species is an order of magnitude higher (Figure 2; Table 2). Finally, the probability of transmission from insect to bovine could not be reliably estimated for either *S. calcitrans* or *C. nubeculosus* (Figure 2; Figure S1). This is, in part, because the number of insects refeeding when attempting transmission to cattle was not reported for these species (Chihota, Rennie, Kitching & Mellor, 2003). For *C. nubeculosus*, the posterior distribution for the probability of transmission from insect to bovine was identical to the prior distribution (Figure S1), regardless of assumptions made about the numbers of insects that refed (either 1, 5, 10, 20, 50 or 100). For *S. calcitrans*

232 the posterior mass for the probability of transmission from insect to bovine was shifted
233 towards zero if a larger number of insects was assumed to refeed, though the 95% credible
234 interval remained large (Figure S1). For both species, estimates for the virus inactivation rate
235 and probability of transmission from bovine to insect were not affected by the number of
236 insects assumed to refeed (Figure S1). In the uncertainty and sensitivity analyses for these
237 species, the posterior distributions for parameters related to mechanical transmission (b, β and
238 γ) were those obtained when 100 insects were assumed to refeed, as this provides the most
239 conservative assessment of the risk they pose.
240

241 ### *3.2 Latent and infectious periods for LSDV in cattle*

242 The mean infectious period depends on the proxy measure used to determine when an animal
243 is infectious (Table 3). It is shortest when based on virus isolation from blood (8.8 days),
244 intermediate when based on detection of viral DNA in blood (16.3 days) and longest when
245 based on detection of virus or viral DNA in skin lesions (23.1 days). The mean latent period
246 also depends on the proxy measure used to determine when an animal is infectious. It was
247 estimated to be 5.8 days for blood (PCR), 8.1 days for blood (VI) and 7.3 days for skin
248 lesions (Table 3).
249

250 ### *3.3 Uncertainty and sensitivity analyses*

251 The basic reproduction number for LSDV was highest for transmission by *S. calcitrans*,
252 intermediate for *Ae. aegypti*, low for *C. nubeculosus* and *An. stephensi* and lowest *Cx.*
253 *quinquefasciatus* (Figure 3; Table 4). Indeed, the median R_0 for *Cx. quinquefasciatus* was
254 below the threshold for an outbreak to occur (i.e. R_0=1). The magnitude of R_0 depended on
255 the proxy measure of infectiousness used (through its influence on the duration of
256 infectiousness), with higher values when based on detection of virus or viral DNA in skin

lesions, intermediate when based on detection of viral DNA in blood and lowest when based on detection of virus in blood (Figure 3; Table 4).

The sensitivity of R_0 to changes in its constituent parameters differed amongst the insect species, though some patterns emerge (Figure 4). For all species, the strongest correlations were with the probability of transmission from insect to bovine (b; PRCC>0.66), the biting rate (a; PRCC>0.75, except for *Ae. aegypti*), the vector to host ratio (m; PRCC>0.58) and the virus inactivation rate (γ; PRCC<-0.47, except *An. stephensi* and *Cx. quinquefasciatus*). For the three mosquito species, there was also correlation with the vector mortality rate (μ; PRCC<-0.45), but this was not the case for the other dipteran species (PRCC≈0). The probability of transmission from bovine to insect (β) and the mean infectious period ($1/r_I$) were also positively correlated with R_0 (PRCC=0.3-0.4 and PRCC=0.2-0.5, respectively). These patterns are independent of the proxy measure of infectiousness used (Figure 4).

4 Discussion

The results of the uncertainty analysis for the basic reproduction number (Figure 3; Table 4) suggest that *S. calcitrans* is likely to be the most efficient vector of LSDV (out of the five species considered in the present study), with *Ae. aegypti* also an efficient vector of the virus. By contrast, *C. nubeculosus*, *An. stephensi* and *Cx. quinquefasciatus* are likely to be inefficient as vectors of LSDV.

These conclusions would potentially be different if the risk posed by each species was assessed on the outcome of the transmission experiments alone (Table 2). While the experimental outcome suggests *Ae. aegypti* might be an efficient vector, it could be concluded that *S. calcitrans* is likely to be a poor vector given the very short duration of

282 infection (<1 day) and the comparatively low probabilities of transmission from bovine to
283 insect or insect to bovine for this species. By contrast, the results of the transmission
284 experiments suggest that *Cx. quinquefasciatus* could be a more efficient vector than it is
285 based on the estimates for R_0, because of the relatively long duration of infection and the high
286 probability of transmission from bovine to insect. This highlights the importance of
287 considering all factors associated with transmission, including vector life history, when
288 assessing the risk of transmission for each species. For both *S. calcitrans* and *Cx.*
289 *quinquefasciatus* the main reason for the difference in conclusions between transmission
290 experiments and R_0 is the time interval between blood meals, which is shorter than the
291 duration of infection for *S. calcitrans*, but longer than the duration of infection for *Cx.*
292 *quinquefasciatus* (Tables 1 & 2).
293
294 A certain amount of care should be taken in interpreting these results, however, because there
295 is substantial uncertainty associated with the estimates of R_0 for all five species, but
296 especially for *S. calcitrans* and *C. nubeculosus*. One of the major sources of uncertainty is the
297 probability of transmission from insect to bovine (Figure 2; Table 2). Although transmission
298 to naïve cattle was attempted (Chihota, Rennie, Kitching & Mellor, 2003), it was done at
299 times when *S. calcitrans* and *C. nubeculosus* were unlikely to still be infectious (see Figure 1;
300 refeeding was at 1-3 days post infection for *S. calcitrans* and 3-5 days post infection for *C.*
301 *nubeculosus*). Consequently, there is little information in the data to estimate this parameter,
302 which is reflected in the posterior distributions being almost the same as the prior
303 distributions, especially in the case of *C. nubeculosus* (Figure 2; Figure S1). Yet the
304 probability of transmission from insect to bovine was identified as one of the parameters to
305 which the basic reproduction number is most sensitive for all five vector species considered
306 (Figure 4).

307

308 The influence of the virus inactivation rate and vector mortality rate on R_0 differed amongst
309 the species (Figure 4). The duration of infection (i.e. the reciprocal of the virus inactivation
310 rate) for *C. nubeculosus* or *S. calcitrans* is much shorter than the lifespan of an insect and,
311 consequently, only the virus inactivation rate is important for determining the magnitude of
312 R_0. By contrast, the duration of infection and insect lifespan are comparable for *Ae. aegypti*,
313 *An. stephensi* and *Cx. quinquefasciatus*, so that both of these parameters have an influence on
314 the basic reproduction number.

315

316 As with all uncertainty and sensitivity analyses, the conclusions drawn from them are valid
317 only over the parameter ranges considered. For parameters related to mechanical
318 transmission, these ranges were estimated from the available data on the outcome of
319 transmission experiments (Chihota, Rennie, Kitching & Mellor, 2001, 2003) and so represent
320 the best current estimates. Given the uncertainty in these parameters (which reflects the small
321 numbers of animals and insects tested at each time point in the studies; Table S1), a focus of
322 future experimental work should be to more precisely measure parameters related to
323 mechanical transmission and, in particular, the probability of transmission from insect to
324 bovine and the virus inactivation rate.

325

326 All three vector life history parameters were identified as influencing the magnitude of R_0
327 (Figure 4). Plausible ranges for these parameters were drawn from the published literature
328 (Table 1). Wherever possible, ranges were derived using data relating to the species
329 themselves. If suitable data were not available, however, ranges were derived using data for
330 related species. In addition, the vector life parameters were assumed to be constant, but they
331 will depend on environmental factors, including temperature and rainfall. Consequently, the

basic reproduction number, and so the risk of transmission, is unlikely to be constant over space or time, but will vary both geographically and seasonally.

This study considered the potential of five species of biting insects to transmit LSDV. This was primarily because their ability to transmit LSDV had been assessed experimentally for each of the species. However, the present analysis did not consider the effect of vector feeding preferences on their potential role in transmission. The stable fly, *S. calcitrans*, is one of the most damaging arthropod pests of cattle worldwide, both through its impact on production (Taylor, Moon & Mark, 2012) and its ability to transmit a number of pathogens (Baldacchino et al., 2013). Consequently, this species' feeding preferences are unlikely to affect its efficiency as a vector of LSDV. Similarly, *C. nubeculosus* and other *Culicoides* species for which *C. nubeculosus* can be considered a model are livestock-associated (Lassen, Nielsen & Kristensen, 2012; Purse, Carpenter, Venter, Bellis & Mullens, 2015), suggesting host preference will not reduce their efficiency as a vector of LSDV. By contrast, *Ae. aegypti* feeds primarily on humans (Reiter, 2010), potentially limiting its role in the transmission of LSDV, despite its apparent efficiency as a vector. However, there are other *Aedes* species (for example, *Ae. cinereus* or *Ae. vexans*), which display a preference for feeding on cattle (Hayes, Tempelis, Hess & Reeves, 1973; Magnarelli, 1977) and for which *Ae. aegypti* could act as a model vector species. Many *Anopheles* species, including those in the Maculipennis subgroup, which is of most relevance to Europe (Sinka et al., 2010; ECDC, 2019), are described as zoophilic (Sinka et al., 2010). Accordingly, host preference is unlikely to limit their ability to transmit LSDV. Finally, host preference in *Cx. quinquefasciatus* varies according to environmental conditions and geographical area, though it does feed on mammals (Hayes, Tempelis, Hess & Reeves, 1973; Molaei, Huang & Andreadis, 2012; Janssen et al., 2015). However, any preference for non-bovine hosts in this species (or other

357 *Culex* species for which it is a suitable model) will only further reduce its importance in the
358 transmission of LSDV.
359
360 The magnitude of the basic reproduction number depends on the proxy measure used for
361 infectiousness (Figure 3). Viral titres in blood can be low and detection of virus intermittent
362 (Tuppurainen, Venter & Coetzer, 2005; Babiuk et al., 2008), suggesting this may not be the
363 best proxy measure. By contrast, skin nodules have high titres of virus (Babiuk et al., 2008)
364 and insects which feed on nodules become infected (Chihota, Rennie, Kitching & Mellor,
365 2001, 2003), indicating that this may be a reasonable proxy measure. This could be tested
366 experimentally by feeding insects on areas with and without lesions of clinically-affected
367 cattle and on infected, but subclinical cattle and relating viral titres in skin and blood to the
368 probability of insects becoming infected.
369
370 The expression for the basic reproduction number presented in equation (1) assumes there is
371 negligible disease-associated mortality in cattle (see Text S1). Reported mortality for LSD
372 outbreaks in the Balkans was very low, with the median within-herd mortality being zero in
373 all affected countries (EFSA, 2017). In endemic settings, mortality is generally low (1-3%)
374 (Tuppurainen & Oura, 2012; Molla, Frankena & de Jong, 2017), but it may sometimes reach
375 40% (Tuppurainen & Oura, 2012). If disease-associated mortality (up to 40%) is included in
376 the computation of R_0, it does not greatly affect the conclusions of the present study regarding
377 either the magnitude of R_0 for each vector species or the sensitivity of R_0 to changes in its
378 constituent parameters (see Text S2).
379

380 Two previous studies have estimated the basic reproduction number for LSDV using
381 outbreak data. In the first, Magori-Cohen et al. (2012)[1] estimated R_0 to be around 4 for an
382 outbreak in a large dairy herd in Israel in 2006, where *S. calcitrans* was likely to be the
383 principal vector species (Kahana-Sutin, Klement, Lensky & Gottlieb, 2017). Because of the
384 control measures implemented on the farm (removal of cattle showing generalised disease on
385 the day of detection), this implicitly assumed an infectious period of around one day. If a
386 mean infectious period of 23 days is used instead (i.e. the maximum estimated in the present
387 study; Table 3), the corresponding value for R_0 is around 19, which is similar to the median
388 estimate for transmission by *S. calcitrans* obtained in the present study (Figure 3; Table 4).
389 By contrast, the second study estimated R_0 to be around 1.1 for outbreaks in eight cattle herds
390 in Ethiopia in 2014-2015, using viraemia as a proxy for infectiousness (Molla, Frankena & de
391 Jong, 2017). This is substantially lower than the ranges estimated for either *S. calcitrans* or
392 *Ae. aegypti*, but is consistent with those for *C. nubeculosus*, *An. stephensi* or *Cx.*
393 *quinquefasciatus* (Figure 3; Table 4). However, the vector species involved in transmission of
394 LSDV in Ethiopia are not known (Molla, de Jong & Frankena, 2017).
395
396 In this paper, the risk of transmission of LSDV was assessed for five species of biting insect
397 using the basic reproduction number. The results suggest that *S. calcitrans* and *Ae. aegypti*
398 are likely to be efficient vectors (i.e. R_0 is substantially above one), while *C. nubeculosus*, *An.*
399 *stephensi* and *Cx. quinquefasciatus* are likely to be inefficient vectors (i.e. R_0 is close to or
400 below one). However, there is considerable uncertainty associated with the estimates of R_0
401 for LSDV and future work should focus in particular on estimating the probability of
402 transmission from insect to bovine and the virus inactivation rate. Finally, using the basic
403 reproduction number has demonstrated that any assessment of the risk posed by an insect

[1] Because of differences in model formulation, the value of R_0 presented by Magori-Cohen et al. (2012) is the square of R_0 in the current paper. Here the square root transformed values are presented.

404 vector needs to consider all factors which influence its ability to transmit the virus, including

405 life history parameters.

406

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Conflict of interest

None to declare.

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Table 1. Life history parameters for five putative insect vectors of lumpy skin disease virus.

parameter	symbol	range	comments	references
Stomoxys calcitrans				
biting rate (day^{-1})	a	0.33-6	time interval between blood meals ($1/a$) of 4-72 hours	Salem et al. (2013); Baldacchino et al. (2013)
vector to host ratio	m	30-145	-	Kunz & Monty (1976); Jacquiet et al. (2014)
mortality rate (day^{-1})	μ	0.04-0.11	median lifespan ($1/\mu$) of 9-26 days	Salem et al. (2013); Skovgård & Nachman (2017)
Culicoides nubeculosus				
biting rate (day^{-1})	a	0-0.4	based on duration of gonotrophic cycle	Birley & Boorman (1982); Braverman et al. (1985); Mullens et al. (2004)
vector to host ratio	m	0-5000	based on a maximum host biting rate ($m \times a$) of 2500 bites per host per day	Gerry et al. (2001)
mortality rate (day^{-1})	μ	0.1-0.5	based on proportion of females surviving gonotrophic cycle	Birley & Boorman (1982); Braverman et al. (1985)
Aedes aegypti				
biting rate (day^{-1})	a	0.18-0.23	-	Scott et al. (2000); Liu-Helmersson et al. (2014)
vector to host ratio	m	0-80	modelled ratio of *Aedes* to cattle	Gachohi et al. (2016)
mortality rate (day^{-1})	μ	0.07-0.2	lifespan of 5-15 days estimated using a modelling analysis of 50 mark-release-recapture field studies	Brady et al. (2013)
Anopheles stephensi				
biting rate (day^{-1})	a	0.25-0.5	time interval between blood meals ($1/a$) of 2-4 days	Killeen et al. (2000); Charlwood et al. (2016)
vector to host ratio	m	0.6-60	based on a host biting rate ($m \times a$) of around 2 to 120 bites per host per day	Killeen et al. (2000); Ryan et al. (2017)
mortality rate (day^{-1})	μ	0.02-0.38	daily survival probability ($\exp(-\mu)$) of 0.68-0.98	Kiszewski et al. (2004)

parameter	symbol	range	comments	references
Culex quinquefasciatus				
biting rate (day^{-1})	a	0.08-0.25	time interval between blood meals ($1/a$) of 4-12 days	Griffith & Turner (1996); Reisen et al. (2006)
vector to host ratio	m	0-80	modelled ratio of *Culex* to cattle	Gachohi et al. (2016)
mortality rate (day^{-1})	μ	0.07-0.84	-	Gad et al. (1989); Jones et al. (2012)

Table 2. Parameters for mechanical transmission of lumpy skin disease virus for five species of biting insect.

species	virus inactivation rate (γ; day^{-1})		mean duration of infection ($1/\gamma$; days)		probability of transmission from bovine to insect (β)		probability of transmission from insect to bovine (b)	
	estimate†	95% CI‡	estimate	95% CI	estimate	95% CI	estimate	95% CI
S. calcitrans§	1.71	(0.80, 3.34)	0.58	(0.30, 1.26)	0.46	(0.23, 0.71)	0.07	(0.002, 0.64)
C. nubeculosus§	71.16	(4.65, 390.0)	0.01	(0.003, 0.22)	0.27	(0.09, 0.54)	0.50	(0.03, 0.98)
Ae. aegypti	0.09	(0.01, 0.19)	11.23	(5.19, 79.11)	0.90	(0.64, 0.99)	0.48	(0.04, 0.97)
An. stephensi	0.24	(0.10, 0.42)	4.08	(2.38, 9.64)	0.61	(0.36, 0.83)	0.03	(0.001, 0.16)
Cx. quinquefasciatus	0.34	(0.17, 0.55)	2.96	(1.81, 5.74)	0.72	(0.47, 0.91)	0.04	(0.002, 0.28)

† posterior median

‡ CI: credible interval

§ estimates are shown for the analysis assuming 100 insects refed when attempting transmission to cattle

Table 3. Parameters for latent and infectious periods for lumpy skin disease virus in cattle.

proxy measure	shape parameter		mean (days)	
	estimate†	95% CI‡	estimate†	95% CI‡
latent period (days)				
skin lesions	25.4	(4.8, 82.7)	7.3	(5.9, 9.7)
blood (PCR)	3.4	(1.6, 6.4)	5.8	(4.4, 7.8)
blood (VI)	5.7	(1.8, 13.6)	8.1	(5.9, 12.1)
infectious period (days)				
skin lesions	10.4	(2.1, 36.1)	23.1	(16.4, 36.2)
blood (PCR)	3.1	(1.1, 7.1)	16.3	(11.4, 25.4)
blood (VI)	2.6	(0.7, 6.7)	8.8	(5.5, 17.8)

† posterior median

‡ CI: credible interval

Table 4. Basic reproduction number† (R_0) for lumpy skin disease virus (LSDV) for five species of biting insect.

species	proxy measure of infectiousness		
	skin lesions	blood (PCR)	blood (VI)
S. calcitrans‡	15.5 (1.4, 81.9)	13.1 (1.2, 70.8)	9.7 (0.9, 51.7)
C. nubeculosus‡	1.8 (0.06, 13.5)	1.5 (0.05, 11.3)	1.1 (0.04, 8.8)
Ae. aegypti	7.4 (1.3, 17.6)	6.3 (1.1, 14.5)	4.6 (0.8, 11.2)
An. stephensi	1.6 (0.2, 6.0)	1.4 (0.2, 5.0)	1.0 (0.1, 3.9)
Cx. quinquefasciatus	0.8 (0.09, 3.5)	0.7 (0.08, 2.8)	0.5 (0.06, 2.2)

† median (95% prediction interval) based on replicated Latin hypercube sampling

‡ estimates are shown for the analysis assuming 100 insects refed when attempting transmission to cattle

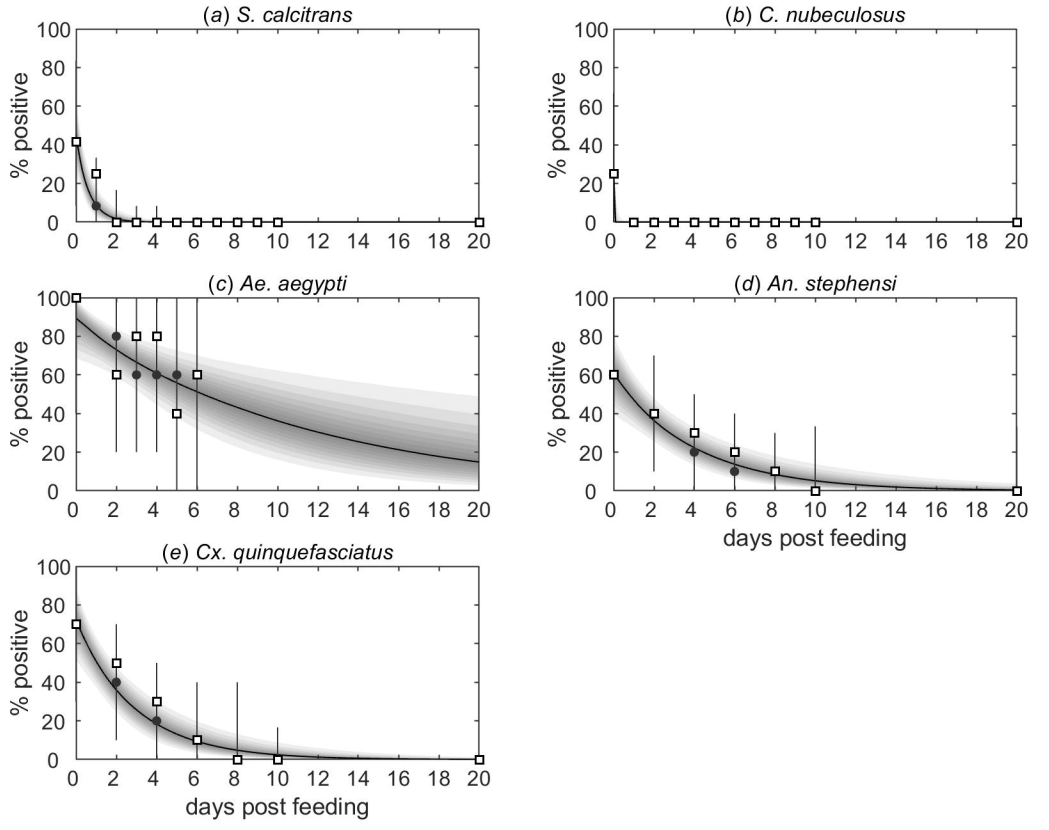
Figure 1. Proportion of biting insects positive for viral DNA after feeding on a bovine infected with lumpy skin disease virus. Results are shown for five species of biting insect: (*a*) *Stomoxys calcitrans*; (*b*) *Culicoides nubeculosus*; (*c*) *Aedes aegypti*; (*d*) *Anopheles stephensi*; and (*e*) *Culex quinquefasciatus*. Each plot shows the observed proportion of infected insects (open squares), the expected proportion of infected insects (black line: posterior median; shading: percentiles of the posterior distribution in 5% bands from 5% to 95%) and the posterior predictive distribution for the proportion of infected insects (grey circles: median; grey error bars: 95% prediction intervals).

Figure 2. Parameters for mechanical transmission of lumpy skin disease virus by five species of biting insect: (*a*) virus inactivation rate (γ; day^{-1}); (*b*) probability of transmission from bovine to insect (β; Pr(B to I)); and (*c*) probability of transmission from insect to bovine (*b*; Pr(I to B)). Each plot shows the median (black circle), 25th and 75th percentiles (black line) and density (shape) for the marginal posterior distribution. Results shown for *S. calcitrans* and *C. nubeculosus* assume 100 insects refed when attempting transmission to cattle.

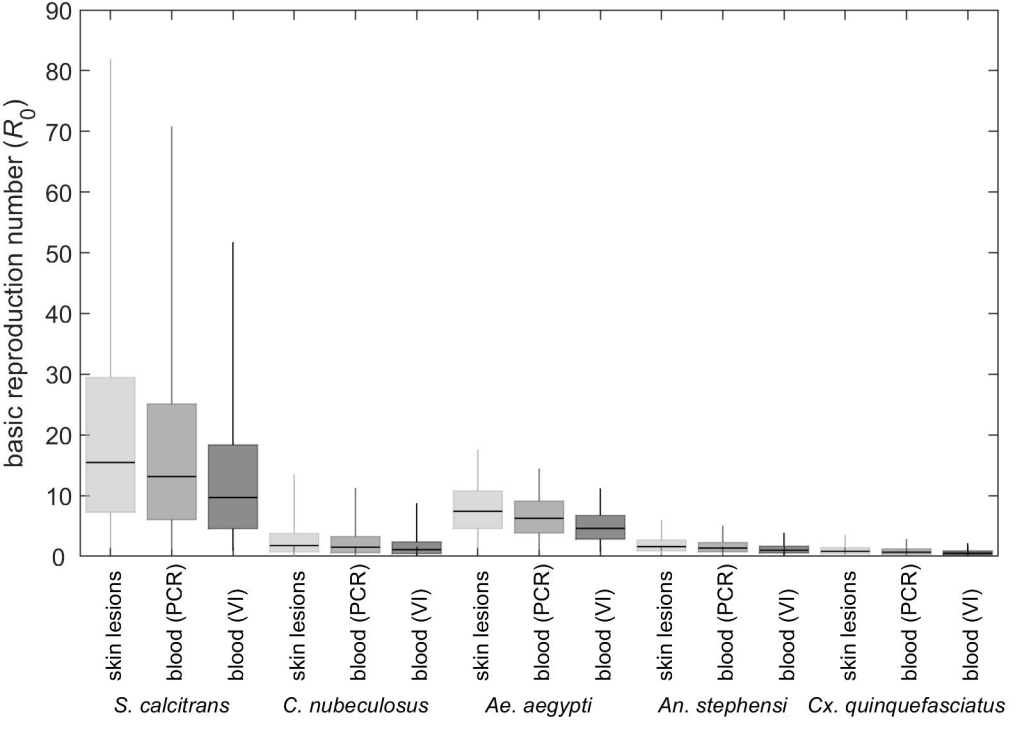
Figure 3. Basic reproduction number (R_0) for lumpy skin disease virus (LSDV) when transmitted by *Stomoxys calcitrans*, *Culicoides nubeculosus*, *Aedes aegypti*, *Anopheles stephensi* or *Culex quinquefasciatus*. The estimated values for R_0 are shown for three proxy measures of infectiousness: detection of virus or viral DNA in skin lesions (light grey); detection of viral DNA in blood (mid grey); or detection of virus in blood (dark grey). Box and whisker plots show the median (black horizontal line), interquartile range (coloured box) and 95% range (whiskers) based on replicated Latin hypercube sampling (100 replicates with the range for each parameter subdivided into 100 steps). Results shown for *S. calcitrans* and

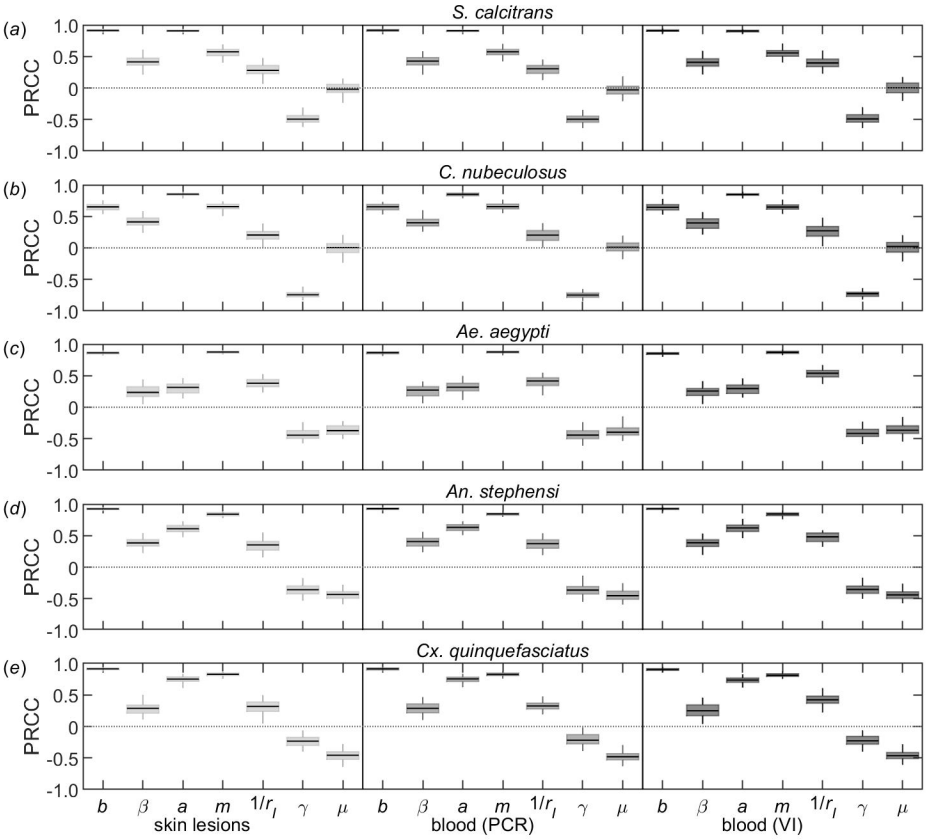
C. nubeculosus used the posterior distributions assuming 100 insects refed when attempting transmission to cattle.

Figure 4. Sensitivity analysis of the basic reproduction number (R_0) for lumpy skin disease virus (LSDV) when transmitted by: (*a*) *Stomoxys calcitrans*; (*b*) *Culicoides nubeculosus*; (*c*) *Aedes aegypti*; (*d*) *Anopheles stephensi*; or (*e*) *Culex quinquefasciatus*. Plots show the partial rank correlation coefficients (PRCC) for each parameter when the estimated values for R_0 are calculated using three proxy measures of infectiousness: detection of virus or viral DNA in skin lesions (light grey); detection of viral DNA in blood (mid grey); or detection of virus in blood (dark grey). Box and whisker plots show the median (black horizontal line), interquartile range (coloured box) and 95% range (whiskers) for the PRCCs based on replicated Latin hypercube sampling (100 replicates with the range for each parameter subdivided into 100 steps). Results shown for *S. calcitrans* and *C. nubeculosus* used the posterior distributions assuming 100 insects refed when attempting transmission to cattle.


(a) S. calcitrans
(b) C. nubeculosus
(c) Ae. aegypti
(d) An. stephensi
(e) Cx. quinquefasciatus
% positive
days post feeding

(a)
inactivation rate
10^3
10^2
10^1
10^0
10^{-1}
10^{-2}
(b)
Pr(B to I)
1.0
0.8
0.6
0.4
0.2
0
(c)
Pr(I to B)
1.0
0.8
0.6
0.4
0.2
0
S. calcitrans
C. nubeculosus
Ae. aegypti
An. stephensi
Cx. quinquefasciatus


basic reproduction number (R_0)
0
10
20
30
40
50
60
70
80
90
skin lesions
blood (PCR)
blood (VI)
skin lesions
blood (PCR)
blood (VI)
skin lesions
blood (PCR)
blood (VI)
skin lesions
blood (PCR)
blood (VI)
skin lesions
blood (PCR)
blood (VI)
S. calcitrans
C. nubeculosus
Ae. aegypti
An. stephensi
Cx. quinquefasciatus


(a)
S. calcitrans
(b)
C. nubeculosus
(c)
Ae. aegypti
(d)
An. stephensi
(e)
Cx. quinquefasciatus
PRCC
1.0
0.5
0
-0.5
-1.0
b β a m 1/r_I γ μ
skin lesions
blood (PCR)
blood (VI)