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Abstract

Epidemiological models in animal health are commonly used as decision-support tools to understand the impact of various control actions on infection spread in susceptible populations. Different models contain different assumptions and parameterizations, and policy decisions might be improved by considering outputs from multiple models. However, a transparent decision-support framework to integrate outputs from multiple models is nascent in epidemiology. Ensemble modelling and structured decision-making integrate the outputs of multiple models, compare policy actions and support policy decision-making. We briefly review the epidemiological application of ensemble modelling and structured decision-making and illustrate the potential of these methods using foot and mouth disease (FMD) models. In case study one, we apply structured decision-making to compare five possible control actions across three FMD models and show which control actions and outbreak costs are robustly supported and which are impacted by model uncertainty. In case study two, we develop a methodology for weighting the outputs of different models and show how different weighting schemes may impact the choice of control action. Using these case studies, we broadly illustrate the potential of ensemble modelling and structured decision-making in epidemiology to provide better information for decision-making and outline necessary development of these methods for their further application.

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6 decision-support framework to integrate outputs from multiple models is nascent in

7 epidemiology. Ensemble modelling and structured decision-making integrate the outputs of

8 multiple models, compare policy actions and support policy decision-making. We briefly review

9 the epidemiological application of ensemble modelling and structured decision-making and

10 illustrate the potential of these methods using foot and mouth disease (FMD) models. In case

11 study one, we apply structured decision-making to compare five possible control actions across

12 three FMD models and show which control actions and outbreak costs are robustly supported

13 and which are impacted by model uncertainty.   In case study two, we develop a methodology for

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15 impact the choice of control action. Using these case studies, we broadly illustrate the potential

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20 Key Words: ensemble modelling, structured decision-making, policy, disease management, foot

21 and mouth disease

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Introduction

Transboundary livestock diseases can have devastating animal-health and economic impacts because such diseases are highly contagious, with the potential for rapid spread across geographic boundaries. Government agencies and livestock industries worldwide continue to develop and refine their policy and management actions in the face of such threats (e.g. Keeling et al., 2003; Schoenbaum and Disney, 2003; Tildesley et al., 2006; Willeberg et al., 2011; Yoon et al., 2006). Similar challenges exist more broadly in animal and human health, for example malaria (Murray et al., 2014), tuberculosis (Suen et al., 2014), and dengue fever (Wilder-Smith and Macary, 2014; Shaman et al., 2016). Decision-making when managing transboundary livestock diseases is complex; it must balance trade-offs amongst competing objectives, limited resources, and uncertainty in disease risk (Taylor, 2003). A variety of tools that incorporate data from empirical studies, previous outbreaks, and expert opinion are used to support science-based decision-making (Green and Medley, 2002; Woolhouse, 2003; Keeling, 2005), particularly for diseases such as foot and mouth disease (FMD) in non-endemic countries. Many tools used to understand the potential for infection spread and the effect of response actions on that spread inherently require an underlying predictive model of disease transmission (Kao, 2002; Woolhouse, 2003; Keeling, 2005; Garner and Hamilton, 2011; Mansley et al., 2011; Willeberg et al., 2011).

Given the complexity of disease ecosystems, it is difficult to describe all aspects of disease processes accurately within one model. Choices must be made regarding what to include and what to omit, how to implement specific processes, and how to parameterize them. Thus, model outputs upon which policy decisions are based differ owing to different modelling approaches, assumptions, and parameter estimates (Green and Medley, 2002). These model differences are

47   often justifiable. Different models may produce similar or quite different outputs that can all be

48   considered plausible, where plausibility is often supported either from first principles and

49   parameterization from known literature values in the absence of observed outbreak data or by the

50   match between model outputs and the characteristics of observed outbreaks, when they are

51   available. Variability among models is valuable because it captures uncertainty in the system

52   and outbreak scenario, but reconciling variability can be difficult (Green and Medley, 2002;

53   Keeling, 2005). Many fields, including weather forecasting, climate-change science, and

54   medical science, use a diverse portfolio of models to indicate to decision-makers the amount of

55   uncertainty in possible outcomes (Mangiameli et al., 2004; Palmer et al., 2004; Araujo and New,

56   2007). Thus, justified model diversity should be harnessed to produce cohesive policy

57   recommendations from models, but this requires a method to incorporate potentially disparate

58   outputs objectively from an ensemble of model outputs.

59   The idea of integrating model outputs to achieve a transparent decision-support

60   framework has a relatively long history in weather forecasting (Sanders, 1963; Gneiting and

61   Raftery, 2005 ;), hydrology (Cloke and Pappenberger, 2009; Velázquez et al., 2010), and

62   climate-change modelling (Orsolini and Doblas-Reyes, 2003; Benestad, 2004; Palmer et al.,

63   2004; Tebaldi and Knutti, 2007; Chandler, 2013). In medical sciences, multi-model approaches

64   are used to assist physicians in making a medical diagnosis (Mangiameli et al., 2004; West et al.,

65   2005). Examples of integrated approaches within the ecological literature are increasing (Niu et

66   al., 2014) and include particle-filtering (Doucet et al., 2001) and Bayesian (Lindström et al.,

67   2015) approaches to integrate multiple parameterizations of a single model; another approach is

68   using integrated climate-change data to describe future environmental variables used as inputs

69   into ecological models (Araujo and New, 2007; Barbet-Massin et al., 2009; Coetzee et al., 2009;

70   Thuiller et al., 2009; Maiorano et al., 2011). The latter approach has been applied in

71   epidemiology where integrated climate projections were used to generate future environmental

72   variables that drive predictions of disease incidence (Palmer et al., 2004; Thomson et al., 2006;

73   Guis et al., 2012). To date, however, multiple model approaches have been applied only to a

74   limited extent in public health (Thomson et al., 2006; Shaman et al., 2016) and in agriculture

75   (Catelaube and Terres, 2005). Recent work suggests a way forward for multi-model, decision-

76   support frameworks in epidemiology and animal health. This work focuses on ensemble

77   modelling (Ward et al., 2007; Shaman and Karspeck, 2012; Lindström et al., 2015; Shaman et

78   al., 2016) and structured decision-making (Shea et al., 2014; Probert et al., 2016), although

79   available methods, at the time of writing, are at a preliminary stage.

80   **Ensemble modelling (EM)** combines model outputs to produce collectively a depiction of

81   future states including uncertainty from several potential sources. Single-model ensembles use a

82   single model structure but allow for different starting conditions and parameterizations whose

83   outputs are combined to produce probability distributions of modelled outcomes (Tebaldi and

84   Knutti, 2007). The mean of the probability distribution is the expected outcome, and credible

85   intervals quantify uncertainty in the outcome. Two different single-model EM methods have

86   been developed and applied in an epidemiological context to seasonal influenza (Shaman and

87   Karspeck, 2012) and FMD (Lindström et al., 2015). Multi-model ensembles incorporate outputs

88   from a set of structurally different models, referred to as an ensemble, that can incorporate

89   different underlying processes and contribute to the uncertainty estimate (Tebaldi and Knutti,

90   2007). These methods are in development for epidemiology (e.g. Shaman et al., 2016), but we

91   later present a preliminary case study addressing this methodological gap.

92   **Structured decision-making (SDM)** is a framework for analysing decisions by breaking

93   them into component parts (Clemen, 1997). In doing so, the key impediments to making a

94   decision are identified and effort can be focused on reducing uncertainty about relevant

95   components. The goal is to identify the decision that mathematically maximizes (or minimizes)

96   the specified objectives. By using a multi-model ensemble approach to SDM, uncertainty about

97   underlying mechanisms and parameters may be incorporated in the decision process. SDM

98   focuses on uncovering consensus as well as tradeoffs between underlying

99   mechanisms/parameters (represented by different models) and choice of objectives. Hence,

100   SDM is a method that uses the component parts of decision-making to organize or partition

101   uncertainty across models and objectives into a format in which major sources of uncertainty can

102   be identified and addressed. It has been used to facilitate decision-making in diverse fields such

103   as organizational learning, the use and management of natural resources, adaptive management

104   for pest control or biodiversity (Argyris and Schön, 1978; Hollings, 1978; Walters, 1986; Lee,

105   1993; Shea and Management, 1998; Parma, 1999; Shea et al., 2002; Williams et al., 2007;

106   Williams, 2011; Keith et al., 2011; Williams et al., 2011) and recently in animal health (Probert

107   et al., 2016).

108   Methodological development integrating EM and SDM is needed to create human- and

109   animal-health decision-support frameworks that integrate multiple model results (Karemer et al.,

110   2016; Lessler et al., 2016). A few studies have shown multiple model outputs side-by-side

111   (Murray et al., 2012; Smith et al., 2012; Probert et al., 2016) or have truly integrated outputs

112   from multiple parameterizations of a single model (Shaman and Karspeck, 2012; Lindström et

113   al., 2015). However, these approaches are not well-established and methods are lacking to deal

114   with integration of multiple, policy-informative simulation models with complex model

115   structure.

116   Our goal in this paper is to illustrate the potential of a combined multi-model EM and SDM

117   approach and encourage further work in this area. We present two illustrative case studies; one

118   highlighting the implementation of multi-model EM for an SDM scenario using a mock FMD

119   outbreak simulated in Cumbria, UK, and one focusing on how to incorporate models with

120   varying levels and types of plausibility into ensemble results by weighting the contribution of

121   different models in an objective fashion using a mock FMD outbreak simulated in The Midlands

122   and Wales, UK. We use an ensemble of FMD models that have been developed by a number of

123   FMD-free countries that are engaged in preparedness planning (Ferguson et al., 2001; Keeling et

124   al., 2001; Morris et al., 2001; Garner and Beckett, 2005; Harvey et al., 2007; Stevenson et al.,

125   2013) because of the large economic losses associated with previous outbreaks. We first briefly

126   describe the situation with FMD modelling. We then apply EM and SDM approaches to illustrate

127   how they can be used to integrate the outputs from multiple models and inform policy and

128   outbreak management in the two case studies. However, we stress that our goal is not to provide

129   specific recommendations with respect to FMD and that our results should not be taken as a

130   broad policy recommendation. Instead our goal is to illustrate how EM and SDM approaches

131   could be more broadly applicable to both human- and animal-disease preparedness planning and

132   response. We focus on FMD models because this is where our expertise lies and because it is an

133   important transboundary livestock disease with appropriate existing model results that were

134   available to us. In conclusion, we discuss the logistics of a fuller integration of EM and SDM

135   and the potential benefits to disease response and preparedness planning.

136

137   **Foot and mouth disease models**

138   We focus here on stochastic, spatially-explicit simulations of FMD, which comprise the

139   majority of models used to inform FMD policy in the last decade, e.g. AusSpread (Garner and

140   Beckett, 2005; Beckett and Garner, 2007), the Central Veterinary Institute model (CVI, Backer

141   et al., 2012), Exodis FMD (DEFRA, 2005), InterSpread Plus (Morris et al., 2001; Stevenson et

142   al., 2013), the North American Animal Disease Spread Model (NAADSM, Harvey et al., 2007),

143   and the Warwick model (Keeling et al., 2001; Tildesley et al., 2006). While each of these models

144   simulates the spread of disease between geographical locations where groups of animals are

145   managed as a single unit (i.e. farms), they differ in the way infection and disease transmission is

146   implemented. Many of these models incorporate multiple, specific pathways of transmission and

147   are generally designed to reflect the environment, production and marketing systems of the

148   source country for the model. Transmission pathways of infectious diseases mostly depend on

149   the biology of the disease and are similar within different countries. However, these models also

150   have built in flexibility that means they can be reparameterized or restructured and thus many of

151   them can and have been used for other countries or diseases. Examples of transmission

152   mechanisms include livestock shipments, feed truck deliveries, wind borne movement and fence

153   line contact. These models are often parameterized from empirical data collected during the

154   course of FMD outbreaks in other countries, survey data and expert opinion. Models of this type

155   include AusSpread, InterSpread Plus, and NAADSM. Other livestock disease models, such as

156   CVI and Warwick, use phenomenological spatial kernels to represent a convolution of specific

157   transmission pathways where the spatial kernel describes the neighbourhood of influence of an

158   infectious location and the risk of disease transmission generally decreases as a function of

159   distance from the focus of infection. The risk of infection is therefore based upon the location,

160   size and species composition of each premises as well as the distance between them. The

161   parameters of the spatial kernel can be estimated based upon historical data (Keeling et al., 2001,

162   Hayama et al., 2013). Exodis-FMD uses a mixture of spatial kernels and specific transmission

163   pathways. In the interest of brevity, we do not describe further details of the models, but present

164   a summary (Table 1) and rely on this summary, their policy relevance and peer-reviewed status

165   as sufficient justification of the models since the work proposed here does not depend directly on

166   the exact details of the models.

167   Within the context of FMD (and we suspect for other disease systems as well) the lack of a

168   decision-support framework for integrating model outputs means that often a single model is

169   used by analysts and policy makers or when multiple models are used their integration is

170   informal. Although these informal integrations are generally regarded as appropriate, decision-

171   making could be improved by more formal methods and transparency in how multiple model

172   outputs are combined through EM and SDM.

173   The first steps of a multi-model approach were begun as part of the "QUADS" series of

174   comparison studies (Dubé et al., 2006; Roche et al., 2014, Roche et al., 2015) in which results

175   were compared for standardized scenarios across a suite of FMD models (AusSpread, CVI,

176   Exodis FMD, InterSpread Plus, and NAADSM). The QUADS studies found that model results

177   were similar across many--but not all-- of the scenarios considered; the QUADS studies also

178   improved the understanding of individual models by highlighting the importance of model

179   assumptions that generated outputs that differed from the rest of the model suite. This type of

180   comparison was critical because it provides a logical starting point for fuller integration of

181   outputs, e.g. EM and SDM. To illustrate EM and SDM, we focus on the models used in the

182   QUADS studies plus one additional model (Warwick).

183

Case study one: Structured decision-making

Uncertainty in model outputs given a particular control action is sometimes of more

interest than the predicted number of infected locations or epidemic duration (Yoon et al., 2006).

The ensemble of model outputs encapsulates this uncertainty about the spatiotemporal dynamics

of infection spread, which may be a limiting step in the decision process. SDM assists decision-

making by incorporating this uncertainty while mathematically determining optimal management

decisions given specified objectives (Shea et al., 2014). The first step in an SDM approach is to

formalize the objectives, i.e. the fundamental goals that managers are trying to achieve through

their actions. The objectives, e.g. minimizing loss of livestock, minimizing epidemic duration,

minimizing economic costs, then provide a common measure by which to evaluate control

actions implemented in each model in the ensemble.

For relatively simple decision-analysis problems, the objectives can be evaluated by

generating a simulation experiment to project the outcome of all possible combinations of

control actions and models under consideration. Because our goal is to provide a perspective on

the use of SDM in epidemiology, we direct readers interested in more detailed methods to

Probert et al. (2016). In this case study, we focus on three FMD models where the needed

outputs were available to us: AusSpread, NAADSM, and Warwick (Table 2). Within the case

studies, we anonymize model names because our focus is on ensemble methods and not model

comparison. We illustrate SDM with a simple simulation experiment for a landscape consistent

with Cumbria, UK (details in Appendix A) that determines the mathematically optimal decision

for a given objective among five possible control actions in response to an FMD outbreak: 1)

culling of infected premises (IPs) only; 2) culling of IPs and those that have been identified as at

206 risk because they have had contact with IPs (contact tracing); 3) culling of all farms within 3 km

207 of IPs in addition to IP culling; 4) vaccination of all farms within 3 km of IPs in addition to IP

208 culling; and 5) vaccination of all farms within 10 km of IPs in addition to IP culling. The model

209 outputs depend strongly on multiple factors specific to the scenario investigated here, such as

210 underlying farm demography, the level of efficiency in the implementation of control strategies

211 and constraints on control resources. Hence, policy recommendations from the case study are

212 specific to this scenario.

213   The output of each simulation was summarized with respect to three measures of the

214 outbreak: 1) the economic cost (see description in Appendix A) in terms of the re-imbursement

215 payments to producers for culled animals only, assuming that vaccinated animals are not

216 subsequently culled owing to vaccination (vaccinate-to-live); 2) the economic cost in terms of

217 the re-imbursement payments to producers for culled and vaccinated animals (i.e. assuming that

218 vaccinated animals will also be subsequently culled owing to vaccination); and 3) the duration of

219 the epidemic from the first detected case to the last animal culled or vaccinated, which would

220 reflect the economic costs associated with the disruption of trade due to export bans. Particularly

221 with respect to the vaccinate-to-live strategies, we highlight that these strategies have a number

222 of other impacts (e.g. on animal movement, trading bans and animal welfare) that are not

223 specifically captured in the outbreak measures used.   The outcome of each control action was

224 simulated within the three models and the optimal action was taken as that which minimized the

225 outbreak duration (Table 2) or economic cost (Table 3). See Appendix A for details of the

226 simulations.

227   Here, all three FMD models predict the lowest mean cost due to livestock culled if a 10-

228 km ring vaccination action was applied – thus, although each model predicts different numbers

229   of cattle culled (Figure 1), the decision that minimizes that outcome is robust to model

230   uncertainty. In contrast, if the objective was to minimize the duration of the outbreak – i.e.

231   because of the larger economic costs of trade restrictions – the three models in the ensemble

232   made differing predictions of the best control action: both models 1 and 2 recommended a 3-km

233   culling ring, whereas model 3 recommended a 10-km vaccination ring (Table 2). This highlights

234   that the important distinction is whether the transmission dynamics are more likely to behave like

235   those of models 1 and 2 or like model 3, but distinguishing between models 1 and 2 would not

236   affect the decision about the action to take. In the absence of empirical evidence supporting one

237   model over another, policy-makers might set the initial policy as that which minimizes the

238   expected objective with respect to model uncertainty; here, 3-km ring culling is the preferred

239   option if the three models are given equal weight. If there is support for unequal weighting of

240   projection models, this can easily be incorporated into the proposed framework by taking a

241   weighted average of projected outcomes (i.e. an expectation relative to a probability model with

242   unequal weights on projection models) (McDonald-Madden et al., 2010; Shea et al., 2014).

243   There are many ways to arrive at unequal weights for projection models, ranging from goodness-

244   of-fit to historical or contemporary surveillance data to expert opinion (McDonald-Madden et al.,

245   2010; Shea et al., 2014). We present a novel approach to assessing model weights below.

246   Model uncertainty need not be the only factor limiting decision-making (Probert et al.,

247   2016). The mathematically optimal decision is a consequence of interactions between the

248   underlying model dynamics and the management objective. Table 3 illustrates the dependency

249   of the least costly control action, with outcomes averaged over the three FMD models, for two

250   different management objectives (i.e. measures of epidemic outcome). Clearly, when

251   vaccination has a low cost (i.e. compensation is only required for infected and not for vaccinated

252   animals – vaccinate-to-live) an aggressive vaccination approach is favoured in all models.

253   However, if producers must be compensated for vaccinated animals (vaccinate-to-die), then

254   limited culling minimizes costs. Vaccination may incur additional costs not considered here,

255   such as longer trade bans (Paarlberg et al., 2008; Anonymous, 2014) and, as seen above, more

256   aggressive ring culling results in the shortest outbreaks, when averaged across all models (Table

257   2). Thus, by taking an ensemble approach, we can highlight consensus recommendations and the

258   sensitivity of model output to the formulation of objectives that might have been confounded

259   with model choice in a single model analysis (Probert et al., 2016). Total economic costs are

260   arguably a more complete, and perhaps preferable, objective. However, their calculation

261   requires a sophisticated economic analysis taking into account decisions made by trading

262   partners that may itself have significant uncertainty. The specification of a full economic model

263   for outbreak costs is beyond the scope of the current analysis, but we address the dependence of

264   the analysis on alternative objectives in the General Discussion.

265

266   **Case study two: Model weighting**

267   In case study one, the contribution of each model was equally weighted and its influence

268   spread uniformly (see also Murray et al., 2012; Smith et al., 2012). Here, we illustrate the

269   application of the Bayesian Reliability Ensemble Average (BREA) method (Tebaldi et al., 2005)

270   to epidemiology, which can take into account multiple influences on model weights (see

271   Appendix B and Lindström et al., 2015 for technical details). The original BREA method

272   estimates model weights based on agreement with observed data (bias criterion) and consensus

273   between models (convergence criterion), which down-weights outliers. In the original climate

274   change application of BREA (Tebaldi et al., 2005), the main quantity of interest was the

275 estimated current and future mean temperature. The framework was set up to allow for

276 correlation between current and future temperature estimates, so that, for example, a model that

277 under-predicts current mean temperatures might also do so for future mean temperatures. The

278 BREA climate change example is analogous to the epidemiological problem where instead of

279 current and future mean temperatures we substitute an outbreak quantity under the implemented

280 control strategy and an alternative control strategy that a policy maker would like to compare

281 (Lindström et al., 2015). This approach is easily expandable to consider multiple outbreaks and

282 multiple, alternative control actions in epidemiological applications.

283   A major advantage is that BREA produces easily interpretable probability distributions for

284 outbreak quantities (e.g., size, duration, economic costs) under two or more different control

285 actions. The BREA framework promotes straightforward communication of uncertainty in

286 outcomes and the effect of control actions rather than just the most likely outcome (Wade, 2000)

287 or an equally-weighted, average outcome (as in Case Study 1). The BREA method is also

288 technically appealing because it can be used for applications where relatively small amounts of

289 data are available and model fitting-to-data is not required (Lindström et al., 2015). The

290 weightings in the BREA method can be based on summary statistics (e.g. number of infected

291 premises, outbreak duration, economic costs), which allows integration of models for which

292 outputs are not necessarily of the same format (e.g. temporal or spatial scale). Thus, we

293 anticipate that the BREA method will be broadly applicable in veterinary epidemiology.

294   Our case study incorporated simulations from a QUADS scenario outbreak consistent with

295 the Midlands counties and Wales in the UK performed with five models: NAADSM, AusSpread,

296 CVI, Exodis FMD, InterSpread Plus, and we further added the Warwick model to the ensemble.

297 We used outbreak duration as the quantity of interest and focused on comparison of two control

298   actions from the QUADS studies (Roche et al., 2014; 2015): IP culling (scenario S0 in the

299   QUADS studies: stamping out) and IP culling plus suppressive, prospective vaccination within

300   one km around IPs (scenario V6 in the QUADS studies). See Appendix B for more details on the

301   simulations. The original QUADS studies were based on standardized scenarios for model

302   comparison as opposed to actual outbreak data. Thus, we were unable to implement the bias

303   criterion aspect of estimated weights for this case study. Instead, we focus on comparison

304   between equal-weighting as in Case Study 1 and weighting using the convergence criterion to

305   down-weight outliers. We discuss the role of the bias criterion in estimating weights in the

306   General Discussion below.

307   Figure 2 shows the mean individual-model outputs as well as the marginal posterior

308   probabilities (probability distributions) of outbreak duration under the two considered weighting

309   schemes: equal-weighting and weighting based on the convergence criterion (see Appendix B

310   and Lindström et al., 2015 for technical details). Depending on the weighting scheme, the

311   expected outbreak duration (posterior mean and 95% central credibility interval) is reduced by

312   44.5 [-4.2, 104.3] or 32.8 [0.2, 88.2] days when vaccination is implemented with equal-

313   weighting and convergence-weighting respectively. When implementing the convergence

314   criterion for weighting, the distributions are shifted towards the centre of the ensemble compared

315   to equal-weighting. This formally down-weights outliers, providing a more conservative estimate

316   of the reduction in duration with vaccination, which here indicates a positive effect of

317   vaccination in the Midlands counties and Wales scenario. However, the probability distributions

318   corresponding to either weighting scheme are wide, with estimated reduction ranging from little

319   (or no) effect to several months. This stems from the discrepancy among the model predictions,

320   and demonstrates the hazard of relying on a single model to inform policy.

321　　　As the number of outbreaks and control actions considered increases, the complexity of

322　　estimating convergence-weighting increases and would be extremely difficult to justify without a

323　　BREA-like approach. Returning to an issue raised in the Introduction, the assumption in this

324　　case study is that the weighting of models differs based on their similarity with other models.

325　　Models with lower weights in this context are not eliminated from the ensemble (instead they are

326　　down-weighted); and incorporating some influence of these models on the integrated predictions

327　　is justified given that their similarity (convergence) with other models in this case study differs

328　　under different control actions (e.g. in Figure 2 the green and cyan models are outliers under

329　　different control scenarios). Similarly if we had been able to include the bias-weighting in this

330　　case study, models would be further weighted with respect to their predictions of observed

331　　outbreak statistics (see Lindstrom et al., 2015 for a single-model example with both bias- and

332　　convergence-weighting).

333　　**General Discussion**

334　　　Given the differences among modelling approaches, they sometimes appear to be in

335　　competition with one another (Kao, 2002; Woolhouse, 2003; Keeling, 2005; Garner and

336　　Hamilton, 2011). We suspect this competition largely comes from limited funding and

337　　constraints on how much model uncertainty can currently be incorporated into policy

338　　recommendations so that often a single model informs policy. However, model differences can

339　　be important characterizations of different risks in an outbreak, and uncertainty in these risks

340　　should be propagated to the evaluation of alternative actions. There is also growing interest in

341　　collaboration among different modelling teams (Dubé et al., 2007; Gloster et. al., 2010; Sanson

342　　et al., 2011) that serves to enhance emergency preparedness and builds confidence in model

343　　results. Ensemble approaches provide a way to use models representing different assumptions in

344 a complementary framework, thus emphasizing the potential for models to be mutually

345 informative while propagating uncertainty in epidemic processes to the evaluation of actions.

346 Case Study 1 using SDM, and Case Study 2 using BREA produce qualitatively similar

347 results: that the addition of ring vaccination with a relatively smaller radius results in shorter

348 outbreaks (~30 days shorter) in expectation; but, the BREA analysis highlights that strong

349 variation in outcomes within and between model projections results in very weak evidence that

350 this intervention will differ from simple IP culling. However, our goal is not to recommend

351 particular control actions for FMD, but to illustrate how control recommendations can be

352 integrated across multiple models and objectives. Model predictions of the effectiveness of

353 control will be highly dependent upon logistical capacities and it is therefore important to stress

354 that the control strategies predicted to be optimal in this analysis according to the SDM approach

355 may change as culling and vaccination capacities are varied. This phenomenon has been

356 investigated in detail elsewhere for the Warwick model (Tildesley et al. 2006).

357 SDM, as illustrated in Case Study 1, focuses on the issues associated with the choice of

358 objective and the potential for tradeoffs when multiple objectives are considered. One obvious

359 choice of objective is total economic costs, as is reducing the risk of adverse events (Gerber et

360 al., 2007). In the 2001 UK FMD outbreak, implementation of specific control actions was

361 influenced by several factors throughout the epidemic, including the availability of resources, the

362 perceived likelihood of spread and public perception of the impact of interventions (Andersen

363 2002). Hence, objectives associated with animal welfare (e.g. number of animals impacted),

364 maintenance of culturally important lifestyles (e.g. number of family farms impacted),

365 environmental damage (e.g. arising from the burial or burning of carcasses) and crisis fatigue

366 (e.g. duration of the control period) may better reflect the objectives of the many stakeholders in

367 this decision. Exact specification of these objectives may only be possible with retrospective

368 analysis in which data on direct outbreak costs as well as trade and additional other impacts are

369 available. In response situations and for more open-ended preparedness planning scenarios,

370 information on costs not directly associated with control actions can be difficult to specify. In

371 these situations, direct measurements of the outbreak such as the number of animals infected, the

372 number of premises infected and outbreak duration along with associated costs of these actions

373 may be all that is available. Thus, there are multiple objectives that may be desirable to consider

374 and understanding how tradeoffs among them interact with model uncertainty is the goal of SDM

375 and of benefit in decision-making.

376　　　　In contrast to SDM, BREA focuses on how to integrate multiple weighting schemes.

377 Bias-weighting has been used for several single-model ensembles (Murray et al., 2012; Shaman

378 and Karspeck, 2012; Lindström et al., 2015), and the next steps are to implement these

379 methodologies for the type of multi-model ensembles illustrated in Case Study 2. Bias-

380 weighting, based on the match of model predictions to observed data, is clearly an important way

381 to incorporate the plausibility of models into an integrated policy recommendation. However, it

382 should not be the sole consideration in all circumstances. Our experience is that models often

383 perform differently in different situations, and there is no single best model in terms of prediction

384 accuracy in all settings. Thus when considering alternative future control actions, i.e. for which

385 observed data are unavailable, weighting based on bias relative to past observations alone may

386 unnecessarily down-weight models that are more plausible for alternative control actions.

387 Convergence-weighting, based on the match of model predictions to each other, is a

388 complementary approach. The assumption here is that models that incorporate appropriate

389 mechanisms, for example because they are based on established first principles, should behave

390   similarly. The incorporation of both bias- and convergence-weighting captures the tradeoff

391   between bias and precision in ensemble forecasts or predictions and would be our recommended

392   approach. Because BREA methods are Bayesian, expert opinion in the form of priors can also

393   be included (Kuhnert et al., 2010).

394   While EM and SDM methods individually facilitate the incorporation of multiple models

395   into decision-making, we advocate the development of methodologies that combine both

396   approaches by combining multiple objectives and weighting schemes. This is feasible within the

397   BREA framework and methods development is underway to expand the BREA framework with

398   bias- and convergence-weighting to multiple summary statistics. Multiple summary statistics are

399   often correlated, and this must be appropriately taken into account. However, different summary

400   statistics have different information content if not fully correlated. Thus, using a combination of

401   summary statistics will further improve predictions (as more information can be used) while

402   more fully incorporating tradeoffs among objectives and multiple weighting schemes. This

403   overall framework is highly flexible and can be applied in both preparedness and response

404   settings with potential expansion to address questions beyond alternative controls. Analogous

405   with climate change in which the goal is to capture current and future climate characteristics,

406   BREA could use current outbreak data to predict future outbreak characteristics, such as final

407   size and duration for proposed response scenarios. Further, this overall framework can be

408   extended to allow for adaptive decision-making; i.e. as with model weights in EM, real-time

409   observation may result in increased support for a subset of models within the ensemble and thus

410   decisions might be made with greater weight on the outputs of that subset (Williams et al., 2007;

411   Williams, 2011; Williams et al., 2011). As a given outbreak progresses, observations may

412   increasingly support the predictions of one model over the others, setting the stage for an

413   adaptive management approach (Williams et al., 2007; Williams et al., 2011; Williams, 2011;

414   Shea et al., 2014) that shifts from the initial action that is robust to model uncertainty, to an

415   action that is conditionally optimal for the best supported model.

416   There are many potential benefits to a combined EM and SDM approach simply in terms

417   of the integration across models and objectives for more straightforward policy

418   recommendations. Additionally, ensemble methods have improved prediction over single

419   models in other areas of science (Palmer, et al., 2004; Gneiting and Raferty, 2005; Velazquez et

420   al., 2010; Niu, et al. 2014**)**. Our experience has been that the primary hurdles to integrating

421   multiple models are not technical but logistical. Choice of plausible models to include in the

422   ensemble is key as an ensemble of poor models can only produce poor predictions. The

423   individual models are complicated, so organizing collaboration among modeling groups or

424   training individuals to work across multiple models is both critical and challenging. For many

425   transboundary animal diseases, including FMD, the data are international and confidential in

426   nature and often government owned. Thus, negotiating international access and agreements for

427   data sharing with modeling groups is also a challenge. A final challenge is developing an

428   appropriate pipeline that works across different models for implementing standardized scenarios

429   and standardized outputs of individual models for use in the ensemble model. We find that a

430   formal feedback stage including all individual modeling groups is key to resolving differences in

431   interpretation of implementation (scenarios and parameters) because the models generally work

432   differently. Such a pipeline is important for improving the efficiency with which ensemble

433   results are produced. Once ensemble results are confirmed, straightforward visualizations of

434   results can be produced for decision-makers that illustrate the benefit of reducing modeling

435   uncertainty given outbreak measures of interest (such as Tables 2 and 3) and that illustrate the

436   relative benefit of different control actions while integrating across models and incorporating our

437   uncertainty in predictions (such as Figure 2). Our experience has been that both modeling

438   groups and data owners are fundamentally interested in collaboration and quickly see the

439   benefits of EM and SDM approaches, but patience and persistence are needed to successfully

440   develop the type of consortium needed to implement this framework.

441

442   **Conclusions**

443   Because an integrated EM and SDM framework will evaluate the outcomes of all models in an

444   ensemble across multiple objectives, they are useful to highlight control actions that are robust to

445   existing model uncertainty, identify the key differences among models in the ensemble that must

446   be clarified to resolve uncertainty in the best action, and illustrate trade-offs among the

447   objectives of management. Although we were motivated here by our experience with FMD

448   models, the proposed framework is broadly applicable to most, if not all, transboundary animal

449   diseases. Full development of this framework will take time, but it is a good investment because

450   of the role of models in policy and the complexity of integrating outputs from multiple models.

451   Clearly, there is a need to more strongly engage policy makers in development and use of more

452   science-based processes to integrate model recommendations both to inform policy and to

453   overcome constraints such as data collection and data sharing. Although many challenges exist

454   to the development of ensemble approaches for models of livestock and other diseases, their

455   successful application in weather forecasting and other predictive sciences provide strong

456   evidence for the importance of pursuing similar approaches in disease modelling.

457

467

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Appendix A - Methods for Case 1: Structured decision-making

675

676   For each of the 15 combinations of five control actions and three models (AusSpread,

677   NAADSM, and the Warwick model), we generated 100 stochastic simulations of an FMD

678   outbreak on a simulated landscape of 8000 farms. Farm sizes, composition (proportions sheep

679   and cattle), and spatial distribution were chosen to be consistent with the Cumbria region of the

680   UK. We chose the Cumbria region because of its relevance for the 2001 UK FMD outbreak, and

681   because the models used in this example were already parameterized for an FMD outbreak in

682   this region. During the UK 2001 outbreak, Cumbria was severely affected, with between 20 and

683   30 farms reporting infection per day at the peak of the outbreak and animals on up to 150 farms

684   being pre-emptively culled in an attempt to control the outbreak. This resulted in a maximum of

685   48,000 animals being culled per day in Cumbria alone. Vaccination was not used in 2001 for a

686   number of reasons, not least of which was that there was insufficient capacity at the time to carry

687   out a sustained vaccination campaign (Andersen 2002). Since 2001, vaccination has been

688   considered as part of the UK FMD contingency plan, with DEFRA estimating that at most

689   35,000 animals could be vaccinated per day nationwide during a future FMD epidemic

690   (Tildesley et al. 2006). In this paper we are considering a localised outbreak in Cumbria from a

691   single source and with this in mind we assume a conservative daily culling capacity of 50 farms

692   per day and a maximum vaccination capacity of 10,000 animals per day. Our objective in this

693   section of the paper is to explore the effectiveness of structured decision making in determining

694   the effectiveness of control, and it would be naïve to assume that the optimal strategy will be

695   consistent as capacities are increased.

696   For all simulations we assumed an initial period of undetected spread for 10 days prior to

697   the first detected case. Parameterizations for NAADSM and AusSpread were based on those

698   described in Sanson et al. (2011). The parameterization used in the Warwick model was as in

699   (Tildesley et al., 2008). The reimbursement costs to farmers were calculated as 1000£ per cattle

700   and 100£ per sheep and are based upon estimates of market prices of cattle and sheep in the UK

701   during the 2001 outbreak.

702

703   **Appendix B - Methods for Case 2: Determining ensemble weights**

704   *Application of Bayesian Reliable Ensemble Average Method to Epidemiology*

705   We here describe the BREA method used in Case study 2. For a fuller exposition on BREA

706   methods in epidemiology including both bias and convergence criteria, we refer readers to

707   Lindström et al. (2015).

708   One of the key aspects of the BREA method is that weights, expressed as a precision

709   parameter λ_i, are estimated jointly with the parameters of interest. In the original climate-change

710   application of the BREA method (Tebaldi et al., 2005), the main quantity of interest was the

711   estimated current and future mean temperature, denoted μ and $\hat{I}_{\_}$ respectively. The relationship

712   between these quantities (included in the analysis as random variables) and simulated current and

713   future mean temperatures (denoted X_i and Y_i, respectively) for each model i was given by

714
$$X_i \sim \text{Normal}\left(\mu, \lambda_i^{-1}\right)$$
$$Y_i \sim \text{Normal}\left(\nu + \beta\left(X_i - \mu\right), \left(\theta\lambda_i\right)^{-1}\right)$$
(0.1)

715   The parameter β is included to allow for correlation between current and future temperature

716   estimates, so that, for example, a model that under-predicts current mean temperatures might also

717   do so for future mean temperatures. Further, θ is included to allow for different levels of

718   discrepancy between projections of current and future temperatures, e.g. model simulation

719   outputs may be more similar for current than for future temperature projections.

720   The BREA climate-change example is analogous to the epidemiological problem where,

721   instead of current and future mean temperatures, we substituted an outbreak summary statistic

722   (e.g., number of culled animals, number of vaccine doses administered, outbreak duration) under

723   two different control actions. For equal-weighting of models, we estimated a single precision

724   parameter $\hat{\lambda}$, common for all models, i.e. $\lambda_1 = \lambda_2 = \ldots \lambda_n = \hat{\lambda}$, and for weights based on the

725   convergence criterion we estimated λ_i for each model i. For the latter we also implemented a

726   hierarchical approach similar to Smith et al. (2009) with $\lambda_i \sim Gamma\left(k_\lambda, {}^{k_\lambda}/_{m_\lambda}\right)$ that estimates

727   hyperparameters k_λ (shape) and m_λ (mean) of λ in the analysis (Lindström et al., 2015). This

728   corresponds to the assumption that the models in the ensemble come from a population of

729   possible models, and the outbreak quantities of interest for this population are estimated. This

730   approach reduces the sensitivity to which models are included or excluded in the analysis (Smith

731   et al., 2009). Defining the gamma distribution by m_λ allows us to specify a prior for a

732   hyperparameter that corresponds to $\hat{\lambda}$ in the equal-weighting analysis.

733   The method proposed by Tebaldi et al. (2005) also includes observed mean temperature, X_0,

734   in the analysis as $X_0 \sim \text{Normal}\left(\mu, \lambda_0^{-1}\right)$ where λ_0 is the precision of natural variability in

735   temperature. In climate modelling, it is reasonable that λ_0 is known, and it might also be the case

736   for some data-rich diseases that variability in outbreak size or duration is known. However, in

737   other cases such as FMD, natural variability in outbreak summary statistics is unknown. Thus,

738   we included $\lambda_0 \sim Gamma\,(a_\tau, b_\tau)$ as an estimated parameter for the natural variability in the

739   outbreak summary statistic in the epidemiological application of BREA (Lindström et al., 2015).

740   The stochastic simulations used for projection provided a mean simulated summary statistic, but

741   also a range of the summary statistic. In the absence of a sufficient number of observed

742   outbreaks to quantify λ_0, we estimated λ_0 based on variability in the simulated projections via the

743   hierarchical parameters, a_τ, b_τ.

744   Because the BREA method is a Bayesian approach, priors need to be specified for all

745   random variables. Where possible, we implement the same, vague priors as used by Tebaldi et al.

746   (Tebaldi et al., 2005) and specified $P(\mu) = P(\nu) = P(\theta) \propto 1$ and $P(\beta) = Gamma(a_\beta, b_\beta)$, i.e. a

747   gamma distribution with shape a_β and rate b_β, with $a_\beta = b_\beta = 0.001$. For the analysis of equal

748   weights, we implemented the prior $P(\hat{\lambda}) = Gamma(a_{\hat{\lambda}}, b_{\hat{\lambda}})$, with $a_{\hat{\lambda}} = b_{\hat{\lambda}} = 0.001$. For the model

749   with different weights, we implemented a hierarchical model, similar to Smith et al. (Smith et al.,

750   2009), and specified $\lambda_i \sim Gamma(k_\lambda, {}^{k_\lambda}/m_\lambda)$, i.e. a gamma distribution with shape k_β and mean

751   m_λ. By using this parameterization, we may express the prior on m_λ, which is the corresponding

752   parameter to $\hat{\lambda}$ in the equal-weight analysis. Thus, by using $P(m_\lambda) = Gamma(a_m, b_m)$ for $a_m =$

753     $b_m = 0.001$, we may ensure that potential differences observed between the two weighting

754   schemes are not the result of different priors. We also specified $P(k_\lambda) = Gamma(a_k, b_k)$ for a_k

755     $= b_k = 0.001$, thus allowing for a wide range of shapes of the hierarchical distribution.

756   Because duration is inherently positive, we specify our model on the log-scale to fit with the

757   assumptions of Eq. 0.1. That is, X_i and Y_i are interpreted as the mean log-duration, and μ and ν

758   are the corresponding ensemble quantities. In Figure 2, we present the marginal distribution of

759   these quantities, i.e. integrating over all other parameters in Eq 0.1, including model weights λ_i.

760   However, for transparency we transform all quantities and parameter estimates back to the

761   original scale (rather than the log-transformed duration) with days as unit. As such, our results

762   are presented for the geometrical mean duration.

763   *Simulations*

764   Case study 2 focuses on a mock outbreak of FMD in a subpopulation of farms from the

765   UK, consisting of the Midlands counties and Wales. AusSpread, the CVI model, Exodis FMD,

766   InterSpread Plus, and NAADSM had already simulated outbreaks as part of the QUADS studies

767   (Roche et al., 2014; 2015). We simulated the Warwick model for the same initial conditions,

768   underlying demography, and control measures as the QUADS studies scenarios (as given in

769   Roche et al., 2015). Table B1 summarizes the simulation data of the models used in the BREA

770   analysis for Case Study 2.

771   Vaccinations included all species and were assumed to start 14 days after first detection.

772   Simulations started after the silent-spread phase, thus excluding transmission via animal

773   shipments, and all models, scenarios, and replicates were seeded with the same 20 infected

774   farms, of which one was detected. Further details on the assumptions can be found in Roche et

775   al. (2014; 2015).

1   Table 1. Summary of FMD model properties. All models are stochastic, spatially explicit, state–

2   transition models. IP: infected premises, DC: dangerous contact, CP: contiguous premises.

3

4   Table 2. Mean predicted duration (days) of outbreak for each model and control action. Shading

5   indicates the action resulting in the shortest predicted outbreak duration for each model.

6   Numbers in parentheses indicate the 10th and 90th quantiles of the distribution of outcomes. The

7   "average" row gives results for an equally weighted mixture of the distributions resulting from

8   each model.

9

10   Table 3. Model-averaged predicted cost for each objective (rows) and control action (columns).

11   Predicted costs are given in millions of pounds (£). Numbers in parentheses indicate the 10th and

12   90th quantiles of an equally-weighted mixture distribution of the outcomes of the three models.

13   Shading indicates the action with lowest mean cost for each objective.

14

15   Table B1. Underlying data for Figure 2. Expected outbreak duration (log-transformed) under

16   control actions with infectious premises culling (X) and with vaccination in addition (Y).

17

18   Figure 1. The distribution of predicted cattle culled for 100 realizations of each combination of

19   model (rows) and control action (columns).

20

21   Figure 2. The expected predicted outbreak duration in days under control actions with infectious

22   premises culling (A) and with vaccination in addition (B) and the difference from using

23   vaccination (C). Coloured, dashed lines indicate the mean projection of each individual model,

24   consistently coloured across the three panels. The marginal posterior probabilities of the

25   ensemble analysis with equal weights (black lines) and convergence weighting (grey lines) are

26   indicated and were calculated as described in Appendix B.

27

Figure 1. The distribution of predicted cattle culled for 100 realizations of each combination of control action (rows) and model (columns).
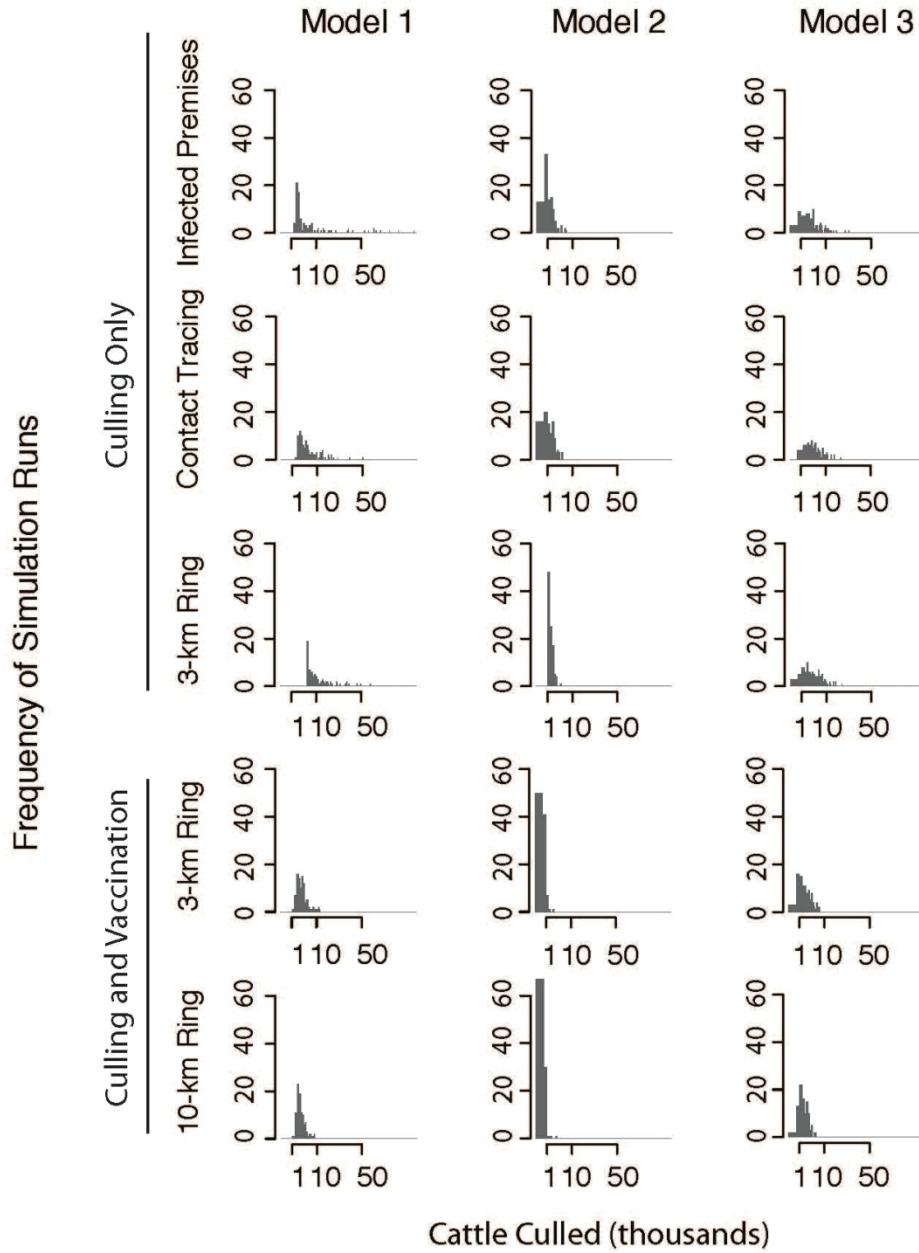
Figure 2. The expected predicted outbreak duration in days under control actions with infectious premises culling (A) and with vaccination in addition (B) and the difference from using vaccination (C). Coloured, dashed lines indicate the mean projection of each individual model, consistently coloured across the three panels. The marginal posterior probabilities of the ensemble analysis with equal weights (black lines) and convergence weighting (grey lines) are indicated and were calculated as described in Appendix B.
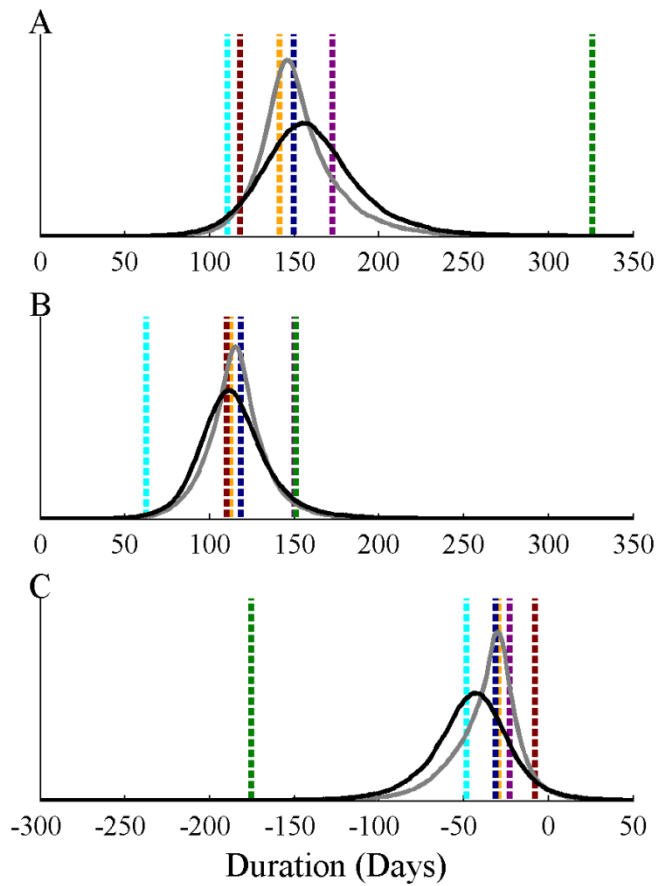
Table 1. Summary of FMD model properties. All models are stochastic, spatially explicit, state–transition models. IP: infected premises, DC: dangerous contact, CP: contiguous premises.

model	transmission via	control measures	references
AusSpread	Specific pathways	Quarantine, movement ban by zone or entire region, forward & backward tracing, IP, DC, and/or CP culls, vaccination, surveillance	Garner and Beckett, 2005; Beckett and Garner, 2007
CVI	Spatial kernel	Regulating transports, DC tracing, IP culls, ring culling, ring vaccination	Backer et al., 2012
Exodis-FMD	Mix of spatial kernel and specific pathways	Movement ban, protection & surveillance zones, culling of IP, DC, and/or contiguous, ring culling, welfare culling and vaccination, implemented by county.	DEFRA, 2005
InterSpread Plus	Specific pathways	Quarantine, movement ban by zone or entire region, forward & backward tracing, IP, DC and/or CP culls, vaccination, surveillance	Morris et al., 2001; Martinez-Lopez et al., 2009a; 2009b; Yoon et al., 2006; Stevenson et al., 2013

NAADSM	Specific pathways	Movement ban by entire region, forward tracing, IP, DC, and/or CP culls, vaccination, surveillance	Harvey et al., 2007
Warwick	Spatial kernel	Movement bans, IP, DC, and/or CP culls, vaccination	Keeling et al., 2001; Tildesley et al., 2006

Table 2. Mean predicted duration (days) of outbreak for each model and control action. Shading indicates the action resulting in the shortest predicted outbreak duration for each model. Numbers in parentheses indicate the 10th and 90th quantiles of the distribution of outcomes. The "average" row gives results for an equally weighted mixture of the distributions resulting from each model.

	culling only			culling and vaccination	
	infected premises[1]	contact tracing[2]	3-km ring culling[3]	3-km vaccination[4]	10-km vaccination[5]
Mean predicted duration (days):					
Model 1	151 (39, 396)	98 (37, 182)	42 (23, 74)	69 (38, 101)	69 (34, 110)
Model 2	135 (59, 245)	137 (52, 243)	17 (11, 27)	116 (48, 213)	110 (45 ,205)
Model 3	65 (27, 107)	42 (27, 56)	69 (29, 111)	43 (23, 64)	38 (24, 49)
average	117 (36, 222)	92 (33, 187)	43 (13, 93)	76 (30, 159)	72 (29 ,128)

[1] culling of infected premises only

[2] culling of infected premises and those identified as dangerous contacts

[3] culling in a 3-km ring around infected premises, including infected premises

[4] vaccination in a 3-km ring around infected premises and culling of infected premises

[5] vaccination in a 10-km ring around infected premises and culling of infected premises

Table 3. Model-averaged predicted cost for each objective (rows) and control action (columns). Predicted costs are given in millions of pounds (**£**). Numbers in parentheses indicate the 10th and 90th quantiles of an equally weighted mixture distribution of the outcomes of the three models. Shading indicates the action with lowest mean predicted cost for each objective.

objective	culling only			culling and vaccination	
	infected premises[1]	contact tracing[2]	3-km ring culling[3]	3-km vaccination[4]	10-km vaccination[5]

Predicted costs in millions of pounds (**£**)

objective	infected premises[1]	contact tracing[2]	3-km ring culling[3]	3-km vaccination[4]	10-km vaccination[5]
vaccinate-to-live	11.0 (2, 19)	8.8 (2, 18)	10.6 (3, 20)	5.1 (2, 9)	4.5 (2, 8)
vaccinate-to-die	11.0 (2 ,19)	8.8 (2, 18)	10.6 (3, 20)	23.8 (7, 44)	90.3 (22, 156)

[1] culling of infected premises only

[2] culling of infected premises and those identified as dangerous contacts

[3] culling in a 3-km ring around infected premises, including infected premises

[4] vaccination in a 3-km ring around infected premises and culling of infected premises

[5] vaccination in a 10-km ring around infected premises and culling of infected premises

Table B1. Underlying data for Figure 2. Expected outbreak duration (log-transformed) under control actions with infectious premises culling (X) and with vaccination in addition (Y).

Model	1	2	3	4	5	6
X	5.0097	5.7874	4.7045	4.9517	5.1512	4.7702
Y	4.7761	5.0168	4.3199	4.7196	5.0105	4.7035

1   Title: Ensemble Modelling and Structured Decision-making to Support Emergency Disease

2   Management

3

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