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QUANTITATIVE RISK ASSESSMENT ANALYSIS PROJECT

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1. INTRODUCTION

Echinococcus multilocularis (EM) is a significant public health concern due to its zoonotic nature and the severe health consequences it can cause (Woolsey and Miller, 2021). Human transmission occurs when individuals ingest live parasite eggs through close contact with the host, such as hand-to-mouth transmission or consuming contaminated food and water. Dogs, in particular, can transmit EM to humans directly through physical contact or indirectly through contact with contaminated faeces (Toews et al., 2021). Once the parasite enters the human body, it migrates to target organs, most notably the liver, where it develops into larvae, leading to a condition known as human alveolar echinococcosis (AE). The disease's initial stage is asymptomatic, and it can take 10 to 15 years before symptoms such as fatigue, weight loss, and abdominal pain appear (Woolsey and Miller, 2021, EFSA, 2023, Santa et al., 2021). If left untreated, AE can progress to liver failure, splenomegaly, portal hypertension, acidosis, and potentially result in death (Umhang et al., 2022, EFSA, 2023). Even with treatment, this infection can have severe health consequences, with an estimated global burden of about 666,434 disability-adjusted life-years (DALYs) annually (EFSA, 2023).

EM is primarily found in the Northern Hemisphere, with a wide distribution among various species, including red and Arctic foxes and dogs. Domestic dogs are particularly interesting due to their close association with humans (Woolsey and Miller, 2021, EFSA, 2023). The prevalence of EM varies across Europe, ranging from 0% in countries like Finland, Norway, and the United Kingdom to over 10% in Estonia, Germany, and France. Particularly in France, the initial outbreaks of EM were identified in the northeast in the 19th century. While this area continues to harbour the highest density of EM predominantly, during the 20th century, some outbreaks emerged in the central region. More recently, the presence of EM has also been reported in the eastern part of the country (Umhang et al., 2022).

Factors influencing this variability include geographical location, climate, local wildlife dynamics, and national regulations. The European Food Safety Authority and other organisations are actively working to combat EM through regulations and recommendations. The EU Pet Travel Scheme (PETS) is a key EU regulation that applies to the non-commercial movement of animals accompanied by their owners (EFSA, 2023, Wright, 2020). Since its implementation, pet travel has steadily increased, with approximately 300,000 dogs entering the UK annually (Norman et al., 2020, Wright, 2020). While the United Kingdom has not reported recent cases of EM, the risk of reintroduction is potentially due to increased human migration, international trade, climate change, and the importation of dogs from regions where the parasite is prevalent (Norman et al., 2020, Wright, 2020, Santa et al., 2021). To address this risk, the European Scientific Counsel Companion Animal Parasites (ESCCAP) UK & Ireland recommend four key steps when dealing with imported or travel-exposed pets in the UK: first, checking for ticks; second, recognising clinical signs relevant to diseases in visited countries or the country of origin for imported pets; third, conducting screening tests, four, treating dogs with praziquantel within 30 days of their return to the UK (Norman et al., 2020, Wright, 2020).

In this report, a quantitative risk assessment analysis was conducted to determine the risk of importing EM into Great Britain (GB) from dogs returning from a 2-week holiday in France. It is carried out a risk assessment focused on the influence of key parameters: the probability of a dog becoming infected whilst it is on holiday, the probability that dog owners do not treat their dogs prior to returning to GB and the probability that treatment time is outside the window period, considering that current regulation indicates that treatment must have been given between 24 to 120 hours before re-entering GB. Firstly, it is studied the uncertainties around this parameter. Then, the risk is predicted by calculating the annual risk, the expected number of years between EM being imported and the expected number of infected dogs per year. Finally, the sensitivity of AR to variations in these parameters and their potential impact on disease control measures is tested.

2. METHODS

Based on the literature related to this topic (Jones et al., 2004, Muñoz-Pérez et al., 2023), the risk of importing EM into GB is summarised in FiG. 1. The probability of a dog becoming infected whilst it is on holiday (PI), the probability that dog owners to do not treat their dogs prior to returning to GB (PNT) and the probability that treatment time is outside the 24–120-hour window (PTO) were estimated, and used to estimate the two components of this risk analysis: the annual probability of importing EM to GB (AR) and the expected number of infected dogs returning from holiday (EI).

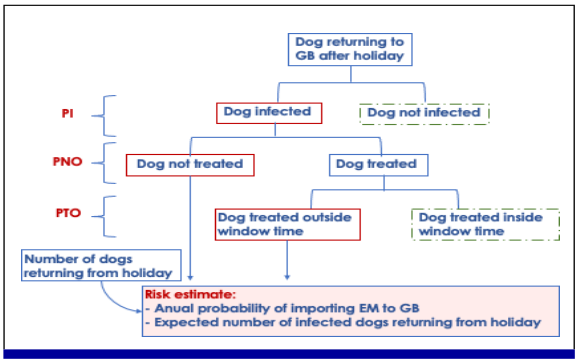

FIGURE 1. Route for the introduction of EM into G

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2.1 Estimating the probability of a dog becoming infected whilst it is on holiday (PI).

To estimate PI, it was used a mathematical model developed by researchers, as seen in (1):

$$p(t) = \frac{\beta(1-e^{-(\mu+\beta)t})}{\beta+\mu} \quad (1)$$

Where p(t) is the probability a dog becomes infected during t weeks of holiday, μ is the recovery rate with the value reported in the literature, and β is the infection pressure, an uncertain parameter, and data suggest that it can be between min=0.00001 max=0.0006, and a most likely value (m) of 0.000187. To model the uncertainty associated with the parameter β, random samples were generated from a PERT distribution, with min, max most likely values as suggested for the data, using Monte Carlo simulation, with 10,000 iterations. Then, the probability values p(t) were calculated for each of the 10,000 betas previously generated randomly and substituted into (1).

2.2 Studying the probability that dog owners to do not treat their dogs prior to returning to GB (PNT).

To evaluate the uncertainty associated with PNT, performed an analysis using Bayesian inference, with a conjugate analysis with the combination of a U~ (0, 0.3) for an unknown prior, where all the values are equally likely, and it is impossible to choose an unlike value greater than 1 or below 0. Considering the result of a 2010 survey, a Binomial ~ (200, 0.1) was defined as likelihood, assuming that there are two outcomes (to be treated or not treated), the number of dogs is fixed, and it is assuming that the risk of being treated in any one of the dogs is independent of the other one and have the same probability. Combining the prior and the likelihood, a Beta ~ (21, 181) was obtained as posterior. The number of successes (not treated dogs) is denoted as k.10, and the sample size as n.10. For the uniform distribution used as prior belief, was not considered all the range [U~0,1], as the values of k.10 and n.10 suggest a result concentrated on the left side of the x-axis. Then, it was considered the result of a second survey, applied in 2022. Also, Bayesian inference with a conjugate analysis and a sequential updating, was used. The posterior obtained before (based on the 2010 survey) was used as the new prior belief and was defined as Beta ~ (21,181). The likelihood was described as a Binomial ~ (26, 0.0385), considering the result from the 2022 survey. The posterior was defined by a beta distribution (alpha + k.22, beta + n.22 – k.22), where alpha and beta were categorised as the shape parameters in the posterior distribution for the analysis based on the 2010 survey (the new prior for this analysis); n.22 and k.22 were the sample size and the number of success (dogs not-treated) in the 2022 survey. As a result, a Beta ~ (22, 206) was obtained as posterior. For the binomial distribution, there were considered the same assumptions as before.

2.3 Studying probability that treatment time is outside the 24–120-hour window (PTO).

Contemplating that it is not only important that the dog be treated but also that the treatment be administered within the time window of 24-120 hours, the probability of compliance with this regulation was studied. Based on the provided data, and assuming that it is known that the treatment time before entry to GB follows a normal distribution and that the data provided includes random values, it was applied a parametric bootstrapping technique to characterise the uncertainty around the mean ($\bar{X}q$) and standard deviation (SD) of the treatment time before entry. A total of 10,000 repeatedly resampling data points from a normal distribution with the same parameters as the original dataset ($\bar{X}q$=71.56, SD=38.31) were performed. Then, it was obtained and stored the $\bar{X}q$ and SD for each of the 10,000 resampled datasets, which represent the uncertainty distribution for each statistical parameter, considering the previously mentioned distribution. Then, PTO was calculated using the cumulative distribution function (CDF) of the normal distribution with each of the 10,000 sets of $\bar{X}q$ and SD generated previously through bootstrapping, and evaluating for the range of interested (probability of 24h < PTO < 120h).

2.4 Determining the probability that any dog returning to GB after a two-week holiday is infected with EM.

To determine the probability that any dog returning to GB is infected with EM (P), a tree diagram was constructed (Fig. 2), concluding that P can be defined as:

$$P = PI\,)PNT + [PTO(1 - PNT)]2 \quad (2)$$

The uncertainties, previously calculated, around PI, PNT and PTO were taken into account in the calculation of P.

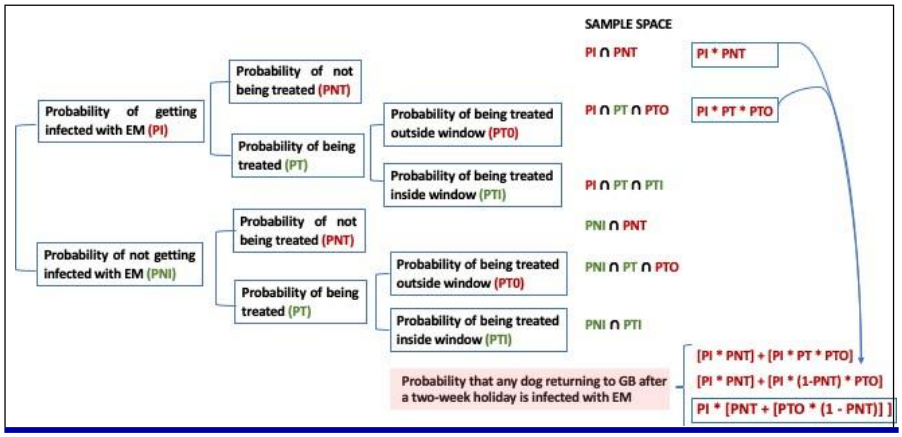

FIGURE 2. Tree Diagram: Probability that any dog returning GB is infected with EM

2.5 Estimating the components of this risk analysis: annual risk and expected number of infected dogs.

2.5.1 Annual risk of EM introduction into GB per 1000 dogs.

Assuming that each dog is independent of the rest and that they all have an equal probability of being infected (P) or not being infected (1-P), and therefore considering that the number of infected dogs will follow a binomial distribution, the probability of at least one dog returning infected with EM each year from a two-week holiday in France is defined as follows (Muñoz-Pérez et al., 2023, Jones et al., 2004):

$$ar = 1 - (1 - P)^N$$

where N is the number of dogs returning from vacation each year. Then, ar was estimated for each of the 10,000 values of P calculated in (2). In addition, the expected number of years that will pass between an imported infection case occurring was calculated using the reciprocal of ar.

2.5.2 Expected number of infected dogs returning from holiday.

The expected number of infected dogs per year (EI) was estimated through a second-order model using Monte-Carlo simulation. First, the uncertainty around P was considered, using the 10,000 values previously generated stored as a vector of probabilities. Next, the variability was modelled using a binomial distribution, considering each value of P (10,000 binomial distributions) and conducting 1,000 iterations for each. In the end, a matrix was obtained with 10,000 rows of binomial distributions per P and 1,000 columns of binomial distributions per iteration. The average expected number per row (per P) was calculated, resulting in 10,000 values for EI at the end of the process.

2.6 Exploring the effect of changing some of these parameters on the annual risk of disease introduction.

AR was evaluated considering three scenarios for parameter β, PTO, PNT and the number of dogs travelling for a two-week holiday to France, as summarised in Tab. 1.

TABLE 1. Variations of β, PTO, PNT to evaluate AR

	For β	For PNT	For PTO	For number of dogs
Baseline	rpert(10,000, 0.00001, 0.000187, 0.0006)	n=200 / k=20	= PTO	1,000
Below baseline	rpert(10,000, 0.00001, 0.000187, 0.0003)	n=200 / k=5	PTO/2	500
Above baseline	rpert(10,000, 0.00001, 0.0003, 0.0009)	n=200 / k=40	PTO*2	2,000

3. RESULTS

3.1 Uncertainty associated with PI.

The 10,000 values of the β parameter, randomly obtained in this simulation, have a median=0.00022, in the range 0.00001 to 0.00059, very close to what was suggested by the data (0.00001 to 0.0006). The 90% credible interval (90% CI) obtained allows us to affirm that there is a 90% chance that β will lie down between 0.00007 and 0.00038. The probability density curve (pdf) (Fig. 1) showed that the PERT distribution (with red dots) was reasonable to modulate the uncertainty around this parameter. Notice also that the curve is skewed to the left-hand side of the axis.

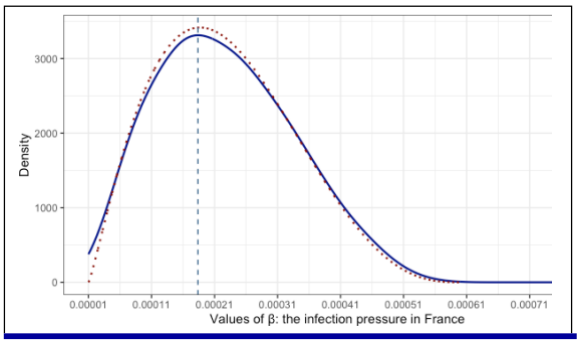

FIGURE 3. Uncertainty associated with β

The derived distribution that describes the uncertainty associated with PI, calculated as in (1), is skewed to the left (Fig. 4), as in β, with values from a min=0.00002 to a max=0.00106 and median=0.00040 (90% CI=0.00012, 0.00078).

3.2 Uncertainty associated with PNT.

The pdf of the posterior distribution Beta, based on the 2010 survey, is shown in Fig. 5, highlighted with the green line. The distribution's Xqand median are very close (Xq̄0.104, median=0.103), and it can be noticed graphically in the symmetry of the curve. The values obtained for these parameters are according to the result of the 2010 survey (p=0.1). There is a 90% chance that PNT will lie down between 0.071 and 0. 0.141 (90% CI=0. 0.071, 0. 0.141).

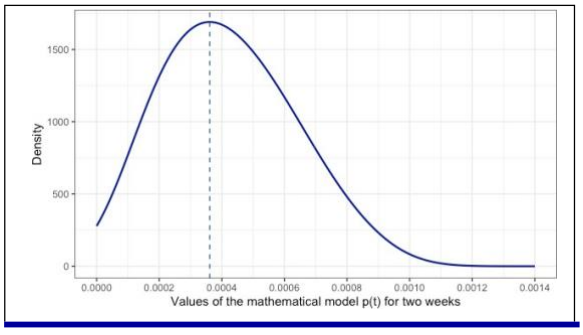

FIGURE 4. Uncertainty associated with p(t)

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After the updated with 2022 results the Xq and the median of this distribution obtained are very close (Xq=0.096, median=0.095), and this is graphically shown in the symmetry of the corresponding curve (Fig. 5). It can be observed clearly that the new 2022 survey did not change our posterior significantly. Also, the values of the Xq and median are closer to the 2010 posterior than to the likelihood derived from the 2022 survey (Xq =0.096 & median=0.095), though the 90%CI is slightly narrower than the previous obtained and suggesting that there is a 90% of chance that PNT will lie down between 0.067 (6.7%) and 0.130 (13%).

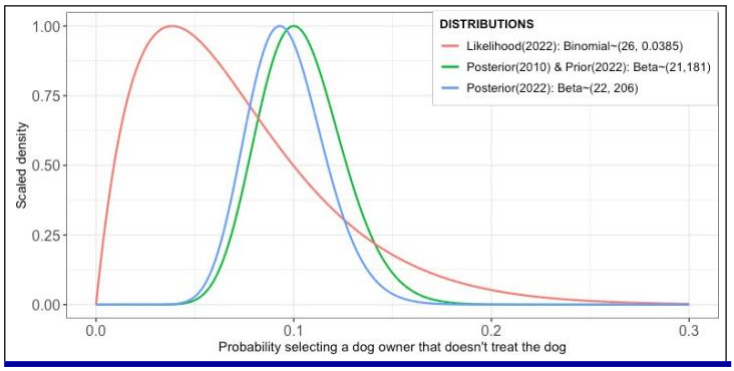

FIGURE 5. Prior (survey 2022), likelihood (survey 2022) and posterior (2010 & 2022) for PNT

The poor influence of the new survey in the resulting posterior is due to the small sample size of the 2022 survey compared to the 2010 survey (n=26 vs. 200, respectively). Therefore, the posterior is dominated by the prior information and not by the likelihood, as the prior comes from a larger and more robust sample.

3.3 Uncertainty associated with PTO.

The Xq of the means and SDs generated through the bootstrapping are very close to the Xq (71.56 vs 71.44 respectively) and the SD of the dataset provided (38.31 vs 37.83 respectively). The 90%CI obtained after the bootstrapping implies a 90% chance that the Xq of the treatment times lies below, between 58.88 h and 84.24 h, with an SD between 29.03 and 47.38 h (Tab. 2).

TABLE 2. Bootstrapping technique

Summary	Means	SDs
Mean	71.48	37.83
SDs	7.68	5.47
Lower 90% CI	58.90	29.08
Upper 90% CI	84.12	46.95

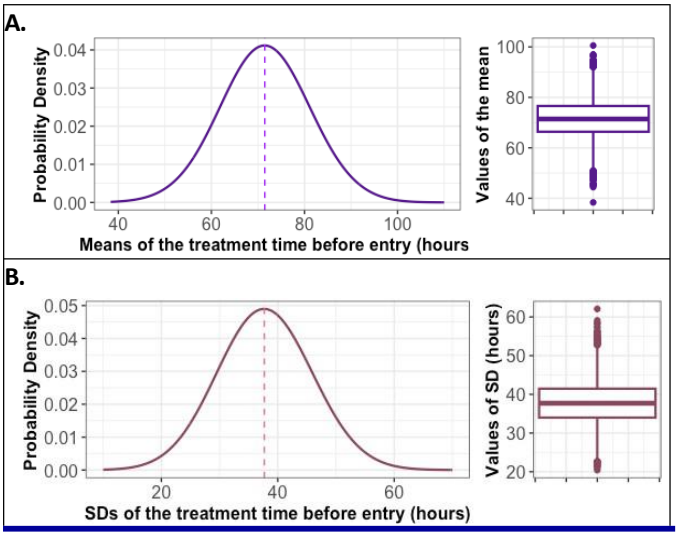

FIGURE 6. Bootstrapping technique: distribution for means (a) and SDs (b)

The values of SD (Tab. 2) for both parameters and the box size in the boxplots indicate that the data spread is not substantial. Outliers in both datasets can be appreciated in the boxplots.

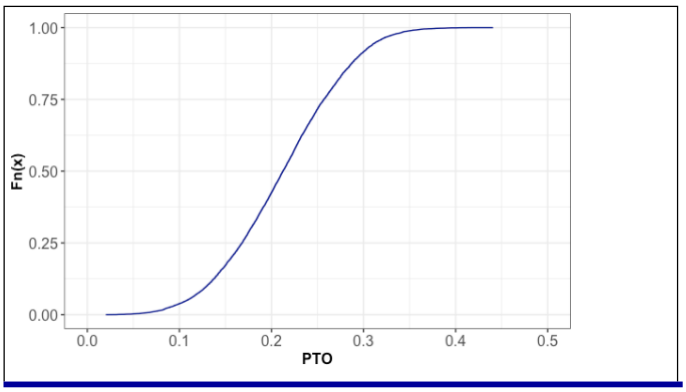

FIGURE 7. CDF of PNT

Regarding PTO, considering the results generated through the bootstrapping, a range from 0.02 to 0.44 was obtained, with a Xq=0.21. It is possible to statistically sustain, with a 90% chance, that this proportion will be found between 11% and 31% (90%CI=0.11, 0.31). These results can be observed in the CDF (Fig. 7).

3.4 Determining P.

P values are distributed from zero to 0.00043, with a Xq=0.00012 and median=0.00011. There is a 90% that this probability lies down between 0.00003 to 0.00024.

TABLE 3. Predicted risk: annual risk, expected number of years between EM being imported and expected number of infected dogs per year

Summary	Anual_Risk	Expected_Years	Expected_Infected
Minimum	0.00	2.87	0.01
Maximum	0.35	273.29	0.42
Mean	0.11	12.63	0.12
Median	0.11	9.42	0.11
Lower 90% CI	0.03	4.66	0.03
Upper 90% CI	0.21	30.96	0.24

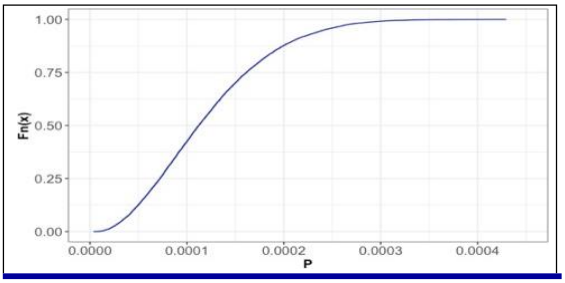

FIGURE 8. CDF of P

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3.5 Annual risk of EM introduction into GB per 1000 dogs.

The AR estimated ranges from 0.00 to 0.35, with a Xq and median=0.11. EI shows similar descriptive statistics (Tab. 3). The expected number of years between EM being imported has a wide range (from 2.87 to 273.29), but it is expected that every 12.63 years EM will be imported through dogs travelling to France in a 2-week holiday (4.66, 30.96 90% CI) (Fig. 9).

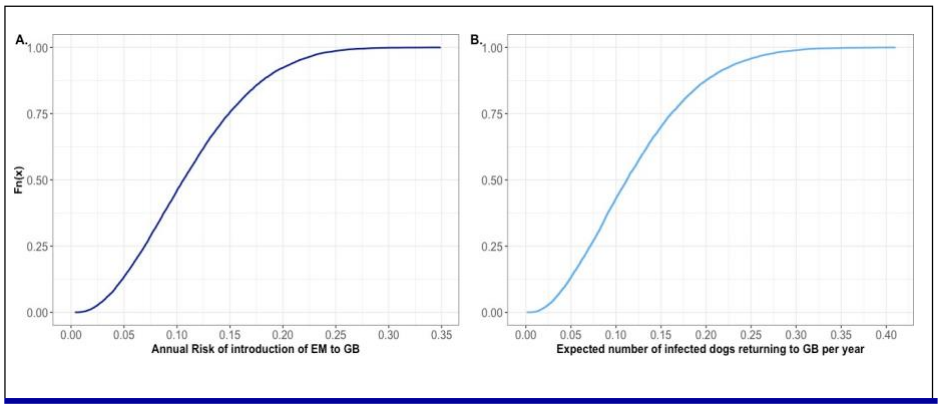

FIGURE 9. CDF of Annual Risk of introduction of EM (A) and the Expected number of infected dogs returning to GB per year (B)

3.6 Exploring the effect of changing some of these parameters on the annual risk of diseaseintroduction.

If the β range is reduced, with its max decreasing by 50%, AR decreases by 18%. However, increasing this max in the same proportion increases AR by 55%. Regarding PNT, a decrease (from 20 to 5) in non-compliance to the treatment rule, decreases AR by 18%, and an increase in non-compliance increases AR by 27%. Concerning treatment administration outside the 24–120-hour window, AR decreases by 27% if non-compliance is halved. However, if this non-compliance is duplicated, AR increases by 63%. As for the number of dogs, reducing its number to half the baseline decreases AR by 45%, and doubling their number increases AR by 91% (Tab 4. and Fig. 10).

TABLE 4. AR for different values of β, PNT, PTO and number of dogs

	Mean	90% CI
Baseline	0.11	0.03, 0.19
Changing β		
Below baseline	0.09	0.04, 0.13
Above baseline	0.17	0.05, 0.28
Changing PNT		
Below baseline (k=5)	0.09	0.02, 0.16
Above baseline (k=40)	0.14	0.04, 0.23
Changing PTO		
Below baseline (PTO/2)	0.08	0.02, 0,13
Above baseline (PTO*2)	0.18	0.05, 0.30
Changing number of dogs		
Below baseline (500)	0.06	0.02, 0.10
Above baseline (2000)	0.21	0.06, 0.34

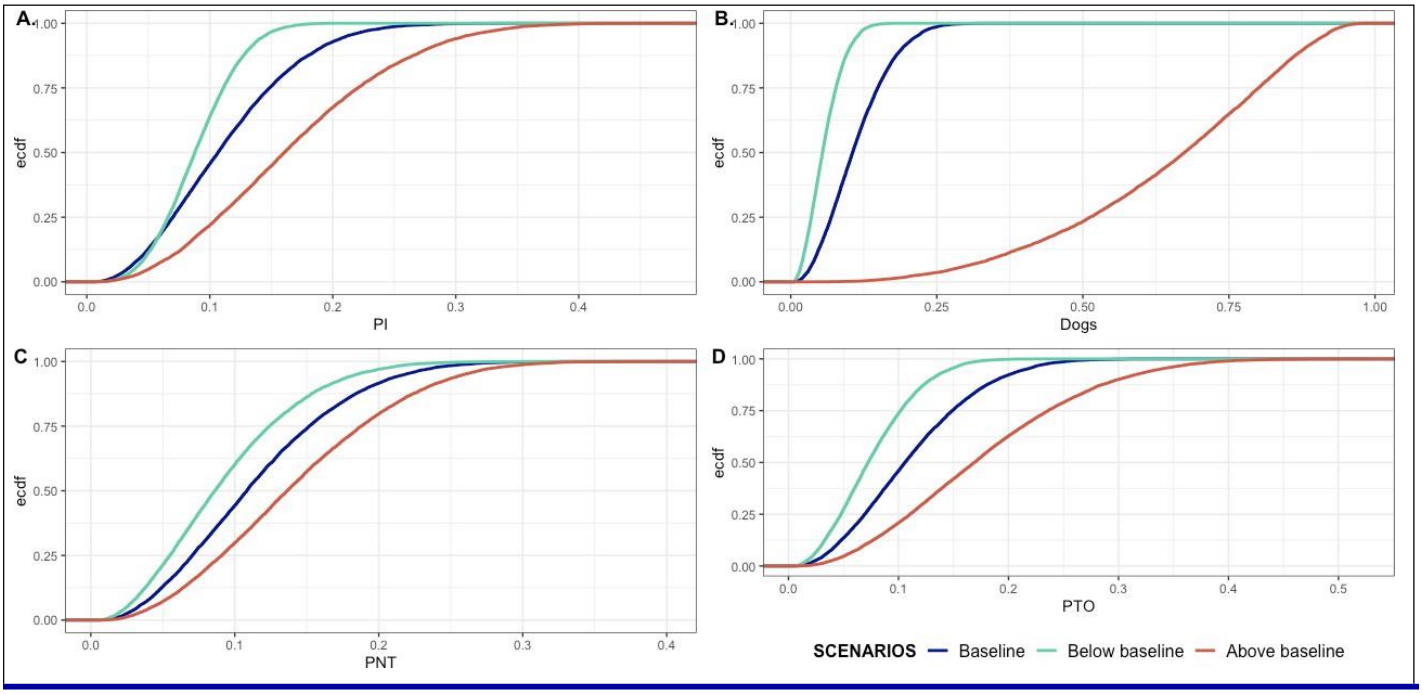

FIGURE 10. CDF of AR for different values of β (A), number of dogs means (B), PNT (C) and PTO (D)

4. DISCUSSION

After examining the uncertainties associated with and calculating the AR, EY and EI, and the influence of changes in the fluctuation of AR, several observations and implications arise. The study delves into the uncertainty associated with the β parameter, which is crucial for this risk assessment. Given that the min, max, and most likely β values are known, an attempt is made to model the uncertainty around β through a triangular distribution. However, even though the randomly generated values roughly follow the proposed distribution, this is not the case at the extremes. It is decided to switch to a PERT distribution, an alternative that uses the same three parameters but results in a smoother shape than the triangular distribution. It is considered a better approach in this case, but some work mention limitations of this distribution (MacCrimmon and Ryavec, 1964, Wehrspohn and Ernst, 2022). Also, it should be pondered that the β has a wide range (0.00001 to 0.0006) and it is considered that the wider range is highly influential in the wide range obtained for AI, EY and EI (AI: 0.00 to 0.35, EY: 2.87 to 273.29 and EI: 0.01 to 0.42). If a more precise parameter could be available from the outset, it would lead to obtaining more precise indicators at the end of the analysis.

The examination of PNT reveals that the posterior distribution modelled aligns well with the observed data from the 2010 survey about complaint rate. The introduction of data from a 2022 survey has a limited impact due to the smaller sample size, highlighting the significance of sample size in Bayesian inference.

The study employs bootstrapping to assess the uncertainty associated with PTO and obtain a proportion of treatment outside the recommended window within a well-defined range, allowing for robust estimation. However, the number of iterations was chosen aleatory, preferring the volume over efficiency, and it is considered that a better approach must be taken.

The predicted risk (P) is estimated considering all the uncertainties of its component (PI, PNT and PTO). The data indicates a relatively low X_q and median arithmetic value for P. However, these figures must be analysed in the epidemiological context of EM transmission, which exceeds the objectives of this report. Future studies should contextualise these figures and qualifier them based on the epidemiologic risks they imply.

The study explored the effects of changing various parameters on AR, shedding light on the sensitivity of the risk assessment model. It becomes evident that changes in parameters β, PNT, PTO, and the number of dogs can significantly impact AR. The magnitude of these impacts varies depending on the specific parameter under consideration. In general, the increase in the increase in the number of dogs, PTO and β have the main effect, in that order.

The study's findings have practical implications for risk assessment and decision-making in disease control. First, it underscores the importance of precise parameter estimation, as slight variations can significantly affect risk estimates. It highlights the value of data quality and sample size in constructing robust Bayesian models. The analysis also emphasises the sensitivity of AR to parameter variations. Decision-makers must be cognizant of the potential effects of parameter changes such as the number of dogs traveling, PNT and β when implementing disease control measures. The results suggest that interventions targeting these parameters could substantially reduce the annual risk of disease introduction.

However, it must be highlighted that despite its valuable insights, the study has limitations. It relies on specific assumptions, and the model's accuracy depends on the data's quality and representativeness. Furthermore, it is crucial to consider that the assumption of independence used for the application of the binomial distribution in the conjugate analysis may be violated. For example, if owners have several dogs, this assumption may not hold, and an alternative approach should be considered. Additionally, the study does not fully explore the effects of interactions between parameters, which could be a topic for future research.

5. CONCLUSION

In today's globalised world, the migration of parasites from their endemic regions to new areas is a reality. Once these microorganisms migrate to new geographical areas, they can impact community health, and have economic and biodiversity implications (Santa et al., 2021). The study of these migrations has progressed slowly compared to the research on other types of biological invasions, such as those involving animals or plants (Toews et al., 2021). Implementing preventive measures is essential to control these invasions and effectively address the challenges posed by our interconnected world (Santa et al., 2021). While the study's findings are specific to the case of EM in GB, the principles and methodologies discussed can be applied to a broader range of epidemiological assessments, serving as a valuable guide for policymakers seeking to mitigate disease risks. Further research in this area can continue to refine and enhance the accuracy of risk assessments as a powerful method for preventing and containing these threats.

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