UNIVERSITE BRETAGNE LOIRE

Oniris
ÉCOLE NATIONALE VÉTÉRINAIRE, AGROALIMENTAIRE ET DE L'ALIMENTATION
SANTÉ ET ALIMENTATION AU CŒUR DE LA VIE

Thèse de Doctorat

** (instructions page en annexe)*

Racem BEN ROMDHANE

Mémoire présenté en vue de l'obtention du
grade de Docteur d'Oniris - École Nationale Vétérinaire Agroalimentaire et de l'Alimentation Nantes-Atlantique
sous le sceau de l'Université Bretagne Loire

École doctorale : Ecologie, géosciences, agronomie alimentaire (EGAAL)

Discipline :
Spécialité : Épidémiologie, évaluation des risques
Unité de recherche : UMR 1300 BIOEPAR – ONIRIS / INRA

Soutenue le 08 Décembre 2017
Thèse N° :

Assessment of the effectiveness of bovine paratuberculosis control strategies: genetic selection or reduction of exposure in herds

JURY

Rapporteurs :	**Benoît DURAND**, Directeur de recherche, ANSES - France **Javier GUITIAN**, Professor, RVC - United Kingdom
Examinateurs :	**Maarten WEBER,** Senior researcher, GD Animal Health Service - The Netherlands **Carole MORENO-ROMIEUX**, Directrice de recherche, INRA - France
Invité(s) :	**Simon John MORE,** Professor, UCD - Ireland
Directeur de Thèse :	**Pauline EZANNO**, Directrice de recherche, INRA - France
Co-directeur de Thèse :	**Christine FOURICHON**, Maitre de conférence, ONIRIS / INRA - France

Résumé

La paratuberculose a un impact important sur la santé animale, l'économie agricole et la productivité du bétail (Beaudeau et al., 2007; McAloon et al., 2016; Richardson et More, 2009). Ott et al. (1999) ont estimé qu'aux États-Unis, la paratuberculose induit une perte de 200 à 250 millions de dollars par an. Les programmes de lutte contre la paratuberculose visent à limiter la propagation des *Mycobacterium avium paratuberculosis* (Map). Deux mesures principales sont mises en œuvre (Benedictus et al. 2000; Domenech et al., 2006; Lu et al., 2008): (i) mesures hygiéniques visant à diminuer la transmission de Map et (ii) mesures de test et de réforme qui visent à éliminer le plus tôt possible les animaux infectés pouvant disséminé la maladie dans le troupeau.

Cependant, les systèmes de lutte actuels ne semblent pas suffisamment efficaces pour contrôler de manière significative la paratuberculose dans les troupeaux infectés. L'efficacité des mesures d'hygiène dépend fortement de la gestion et des pratiques de l'exploitation (Marcé et al., 2011a), qui peuvent varier, dans une même région, d'une ferme à l'autre. Par conséquent, il devient difficile de définir un programme de contrôle unique, efficace et réalisable. En outre, ces mesures exigent des efforts de la part des agriculteurs pour une gestion très stricte de l'exposition des animaux en élevage.

Les tests de diagnostic ante mortem pour la paratuberculose consistent en: (i) culture fécale, (ii) détection des parties de Map par PCR et (iii) dosage immunologique (principalement tests ELISA et interféron gamma)(Collins et coll., 2005; Eirin et coll., 2015; McDonald et coll., 1999; Nielsen, 2008; Scott et coll., 2006; Singh, 2014). D'autre part, seuls 2% des animaux infectés présentent des signes cliniques. A cause de l'évolution longue et lente de la maladie, seule une faible proportion d'animaux infectés peut être détectée par les tests diagnostiques. Ces tests ont une faible sensibilité dans les premiers stades de l'infection. Kalis et al. (2004) ont montré que dans 90 troupeaux fermés sans antécédents de paratuberculose, après 9 séries de cultures fécales regroupées, seulement 39% des troupeaux étaient non infectés par Map et étaient négatifs à la culture. Ce résultat illustre la difficulté d'identifier avec précision l'infection dans les troupeaux.

La dynamique de la paratuberculose dans un troupeau est influencée par les structures de contact, entre les animaux sensibles et infectés (Marcé et al. 2011). Certaines pratiques de gestion des troupeaux susceptibles d'augmenter la transmission de la paratuberculose pourraient limiter l'efficacité des stratégies de lutte contre la maladie. L'évaluation de l'influence des pratiques d'élevage sur la diffusion de Map et l'efficacité des mesures de lutte contre la paratuberculose sont importants pour concevoir des mesures de contrôle adaptées aux spécificités de conduite des troupeaux (C. Rossiter et Burhans, 1996).

La sélection d'animaux résistants à la paratuberculose est une mesure prometteuse pour améliorer la lutte contre la maladie (Koets et al., 2010). Des études expérimentales et des observations sur le terrain des réactions de l'hôte à l'exposition à Map ont mis en évidence la variabilité de la sensibilité, de l'évolution de la maladie, de la sévérité des lésions et de l'excrétion chez les bovins (Mortier et al., 2011, 2014, 2015; Whitlock et al., 2000). En

considérant que la résistance à la paratuberculose, définie par une réponse négative aux tests ELISA chez les vaches exposées naturellement à Map et nées dans des troupeaux infectés, Hickey et al. (2003) ont montré que la résistance à la paratuberculose est héréditaire. Ce résultat a été confirmé par d'autres études utilisant différentes définitions de la résistance des bovins à la paratuberculose.

Plusieurs gènes et parties du génome ont été associés à la résistance individuelle à la paratuberculose (Alfano et coll., 2014 ; Auriol C. Purdie et coll., 2011; Vázquez et coll., 2014; Zare et coll., 2014a). Ces découvertes sur l'héritabilité et la génomique suggèrent que la résistance à la paratuberculose pourrait être sélectionnée chez les bovins. Néanmoins, les mécanismes et les gènes responsables d'une telle résistance restent mal connus. On peut facilement imaginer que la résistance à la paratuberculose, en tant que phénomène biologique, est l'expression résultante de plusieurs gènes codant pour différents caractères phénotypiques.

L'objectif de cette thèse était d'évaluer l'efficacité des stratégies de lutte contre la paratuberculose bovine en utilisant la sélection génétique ou la diminution de l'exposition des veaux.

Pour répondre à cet objectif, une synthèse bibliographique préalable a été nécessaire pour l’identification de traits phénotypiques de la résistance des bovins, en réponse à l’exposition a Map, potentiellement sélectionnables par voie génétique et l’estimation de leur variation chez les animaux. En effet, en ce qui concerne l'exposition à Map, une variabilité de la réponse de l'hôte a été décrite dans des études observationnelles et expérimentales (Davies et al., 2009, Mitchell et al., 2015). Dans les troupeaux où des animaux de même âge ont une exposition similaire à Map, la plupart des vaches infectées ne présentent aucun signe clinique et présentent une excrétion faible et intermittente de Map, tandis que certaines montrent une progression rapide vers un état de perte de poids élevée avec des signes cliniques probables. Les études expérimentales avec épreuve des animaux avec différentes doses infectieuses par voie per os et intraveineuse ont permis de noter que certains animaux ont présenté des signes cliniques, tandis que d'autres n’ont présenté aucun signe visible d'infection (Mortier et al., 2014). Dans le même sens, Mortier et al. (2015) ont noté que chez les animaux âgés de plus de 1 an soumis à une épreuve expérimentale avec la même dose de Map, seuls 42% d'entre eux étaient positifs à l'ELISA. Les schémas et les quantités d’excrétion varient beaucoup chez les animaux infectés (Crossley et al., 2005; Grandjean, 2013; Laurin, 2015; Whittington et al., 2000). Certains animaux perdent peu de bactéries dans les fèces alors que d’autres en perdent beaucoup (Mortier et al., 2014). Ces résultats suggèrent que les facteurs individuels de l'hôte contribuent à augmenter ou à limiter la propagation de Map dans les troupeaux infectés.

Cette héritabilité de la résistance à la paratuberculose a été estimée par plusieurs auteurs. Elle varie de 0,01 à 0,23 (Behr et Collins, 2010 ; Kirkpatrick et Shook, 2011 ; Küpper et coll., 2012 ; van Hulzen et coll., 2011; Y. Zare et coll., 2014). Ces études supposaient que la réponse à l'exposition à Map était un trait phénotypique binaire : résistant vs sensible. La résistance était principalement définie comme la réponse positive à un test de dépistage ou la présence de signes cliniques visibles de la maladie.

En ce qui concerne la complexité du mécanisme de résistance à la paratuberculose, un phénotype intermédiaire des réponses à l'exposition à Map pourrait facilement être supposé. Les études d'estimation de l'héritabilité sous représentent les réponses intermédiaires à l'exposition à Map. Par conséquent, l'héritabilité réelle de la résistance des bovins à l'exposition à Map devrait être supérieure à 0,23.

Pour tester les effets des différentes mesures de contrôle nous avons adopté une approche de modélisation. Nous avons commencé par l'identification des traits phénotypiques de la résistance bovine influençant la dynamique de la maladie dans un troupeau laitier ; ensuite nous avons évalué l'influence des spécificités du système d'exploitation et des prévalences des troupeaux sur l'efficacité des mesures conventionnelles de lutte contre la paratuberculose et enfin nous avons évalué l'efficacité de la sélection génomique pour la résistance à la paratuberculose afin de contrôler la maladie.

Traits phénotypiques de la résistance à améliorer chez les bovins pour contrôler la dynamique de la paratuberculose dans un troupeau laitier : une approche de modélisation

La résistance des bovins à la paratuberculose s'est avérée héréditaire, ce qui suggère que la sélection génétique pourrait améliorer le contrôle de la maladie. Pour identifier les caractères phénotypiques caractérisant l'évolution individuelle de l'infection influençant la diffusion de Map dans un troupeau de vaches laitières, nous avons utilisé un modèle mécanistique stochastique. La résistance consistait à prévenir l'infection et à faire face à l'infection. L'effet de la variation (seule et combinée) de quatorze caractères phénotypiques caractérisant l'évolution de l'infection a été évalué. Quatre sorties de modèles 25 ans après l'introduction de Map dans un troupeau naïf ont été calculés : i) incidence cumulée, ii) persistance de l'infection et iii) prévalence des animaux infectés et iv) affectés. Une analyse en grappes a permis d'identifier les phénotypes influents de la résistance du bétail. Une ANOVA a quantifié la contribution des traits à la variance de sortie du modèle.

Quatre traits phénotypiques ont fortement influencé la propagation de Map: i) la diminution de la sensibilité avec l'âge (la plus efficace), ii) la quantité de Map excrété dans les fèces par les émetteurs élevés, iii) la durée de la période d'incubation et iv) la dose infectieuse requise. L'interaction entre ces quatre traits phénotypiques a contribué à plus de 12% de la variance des sorties du model étudiées. Ceci témoigne de la valeur ajoutée attendue en sélectionnant plusieurs traits de résistance des bovins à la paratuberculose simultanément. La combinaison de variations des 4 traits phénotypiques les plus influents sur la dynamique de transmission de la maladie ont permis de réduire l'incidence cumulé a moins d'un animal nouvellement infecté par an. Cette situation de moins d'un animal nouvellement infecté par an peut être supposé comme une situation où la maladie est sous contrôle. Sur les 625 combinaisons de variation de traits phénotypiques étudiés 537 ont permis de réduire l'incidence cumulé sur les

25 ans de simulation de 617 animaux nouvellement infecte à moins des 25 animaux nouvellement infectés (Figure 1).

Les futures stratégies de sélection génétique pour le contrôle de la paratuberculose devront viser à améliorer simultanément les 4 traits phénotypiques identifiés comme les plus influents sur la dynamique de transmission de la maladie.

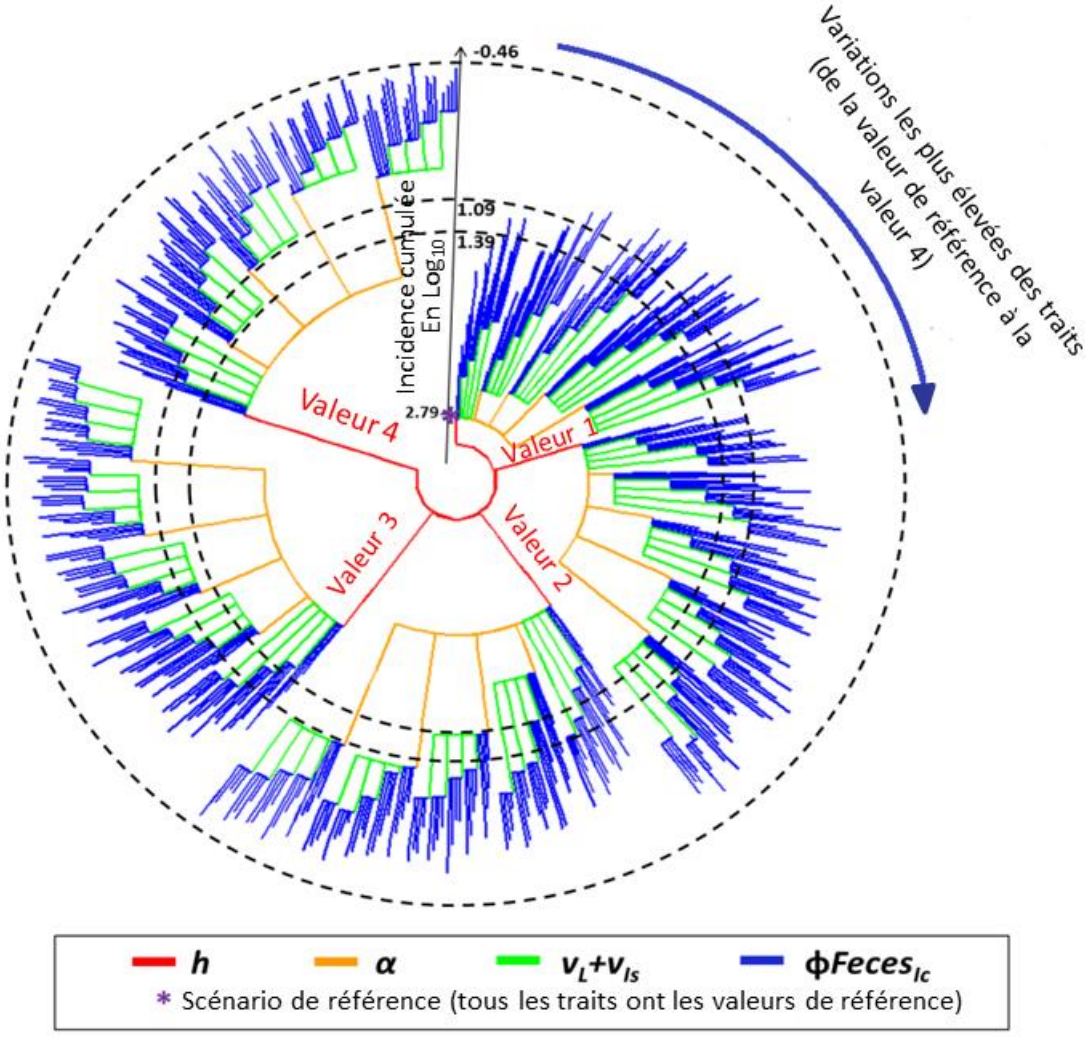

Figure 1: *Effet des variations combinées des quatre caractères phénotypiques les plus influents sur l'incidence cumulative. L'incidence cumulative a été calculée 25 ans après l'introduction initiale de la carte. Le cercle en pointillé externe correspond à l'incidence cumulée la plus faible (0,35 animaux nouvellement infectés) obtenue parmi les scénarios testés (log_{10} (0,35) = −0,46), les cercles en pointillés internes correspondent à des seuils de 25 (log_{10} (25) = 1,39) et 12 (log_{10} (12) = 1,09) animaux nouvellement infectés. L'astérisque correspond à l'incidence cumulée (log_{10} (617) = 2,79) pour le scénario avec les valeurs actuelles des caractères phénotypiques. h: diminution de la sensibilité avec l'âge, α: augmentation de la dose infectieuse requise, vL + vIs: augmentation de la durée avant une excrétion élevée ou un état cliniquement affecté, ϕFecesIc: diminution de la quantité de bactéries excrétées par les animaux élevés. Chaque feuille est un scénario avec des branches représentant des variations des quatre traits. Les scénarios sont présentés en augmentant le niveau de variation de chaque trait successivement (h, α, vL + vIs et ϕFecesI).*

Influence des systèmes agricoles sur les mesures conventionnelles de lutte contre la paratuberculose

Pour évaluer l'influence du système d'élevage sur la dynamique et le contrôle de la paratuberculose au sein d'un troupeau laitier, nous avons comparé la propagation de Map et l'efficacité des mesures actuelles de lutte contre la paratuberculose dans deux systèmes d'élevage de bovins laitiers: français occidental et irlandais. Ces systèmes d'élevage présentent des différences au regard des structures de contact entre les animaux, des taux de renouvellement, des stratégies de naissance, des périodes de pâturage et des races de bovins.

L'implémentation de certaines stratégies de maitrise de la paratuberculose requière une représentation individuelle des animaux du troupeau. Pour cela un model précédemment publié (Marcé et al. 2011 ; Beaunée et al. 2015) avec une représentation individu centré des animaux (Camanès et al. in prep) a été utilisé dans cette étude. Nous nous somme intéressé à différentes situation initiale au regard de la prévalence de la paratuberculose dans les troupeaux : des troupeaux modérément infecté (entre 0 et 7% de prévalence) et des troupeaux fortement infectés (plus de 7% jusqu'à 21% de prévalence). L'évaluation de la dynamique de transmission de la maladie a été suivie sur 25 ans de simulation. Des scenarios avec implémentation de stratégies de maitrise, avec différents efforts par mesure de maitrise, ont été comparé au scenario de référence, sans implémentation de mesure de maitrise (Figure 2).

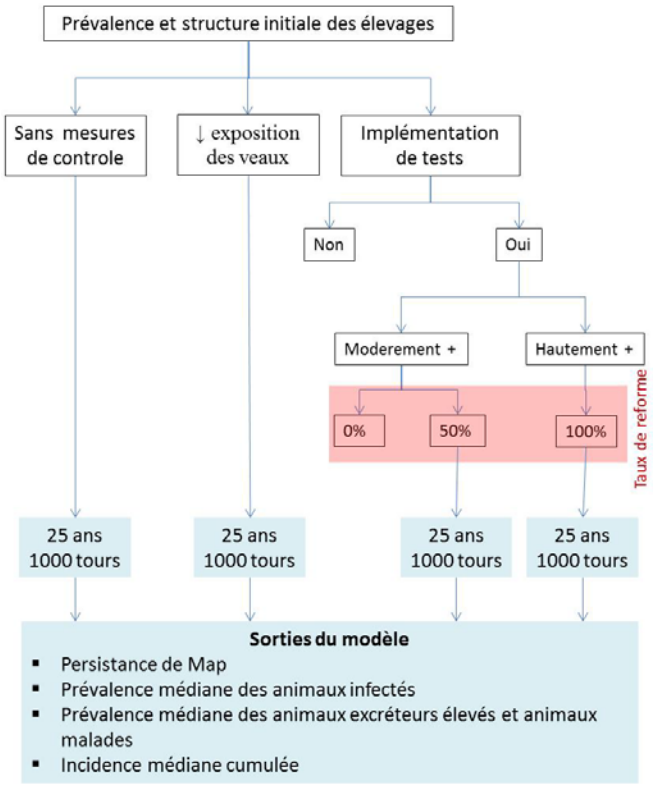

Figure 2: les options des mesures de contrôle investiguées

Les résultats de cette étude ont montré que la propagation de Map était largement influencée par les pratiques agricoles. L'efficacité des mesures de contrôle, même si on les examinait avec leurs variations relatives, était plus élevée sous les conditions agricoles irlandaises que françaises. Cette différence était due à la prévalence initiale dans le troupeau avec un impact contrasté entre la France et l'Irlande. L'influence de la prévalence initiale du troupeau sur l'efficacité des mesures de contrôle a été notée par Kudahl et al. La capacité à bien contrôler la paratuberculose à l'aide des mesures de contrôle actuelles doit tenir compte de la gestion, de la structure et des spécificités du statut d'infection du troupeau ciblé.

L'introduction d'une génisse infectée dans un troupeau irlandais naïf a produit environ 20% de la prévalence réelle du troupeau lorsqu'aucune mesure de contrôle n'a été mise en œuvre. Ce résultat est proche de la prévalence réelle au niveau animal estimée par McAloon et al 2016 allant de 0,9% à 14,5% mais il est supérieur à celui estimé par Good et al en 2015 (2,59-2,9%). la persistance de la maladie dans les conditions d'élevage irlandaises a été estimée à 12,2%. Notre résultat était inférieur à la prévalence au niveau du troupeau irlandais estimée entre 24,6 et 39,3%.

L'efficacité des mesures de lutte a été accrue quand on augmente les efforts de lutte à la fois pour le système agricole irlandais et français et pour les troupeaux fortement et faiblement infectés. La stratégie de lutte combinant la diminution de l'exposition des veaux à Map et le test et l’élimination de 100% des animaux hautement positifs et 50% des animaux modérément positifs était la stratégie la plus efficace indépendamment du système agricole ou de la prévalence initiale au sein du troupeau (figure 3). Cette constatation suggère que cette mesure pourrait être adaptée dans les troupeaux français et irlandais avec les attentes les plus élevées concernant son efficacité sur la lutte contre la paratuberculose.

Toutes les stratégies de contrôle testées étaient plus efficaces chez les troupeaux modérément infectés que chez ceux très infectés en France. L'efficacité d'une même mesure de contrôle était différente en ce qui concerne le statut initial du troupeau en matière de paratuberculose dans les deux systèmes de production. Les mesures de contrôle testées ont été plus efficaces dans les troupeaux irlandais que français. Ces résultats suggèrent que les attentes concernant l'efficacité des mesures de lutte contre la paratuberculose doivent tenir compte des spécificités du système d'exploitation et du statut du troupeau en ce qui concerne la prévalence de la maladie.

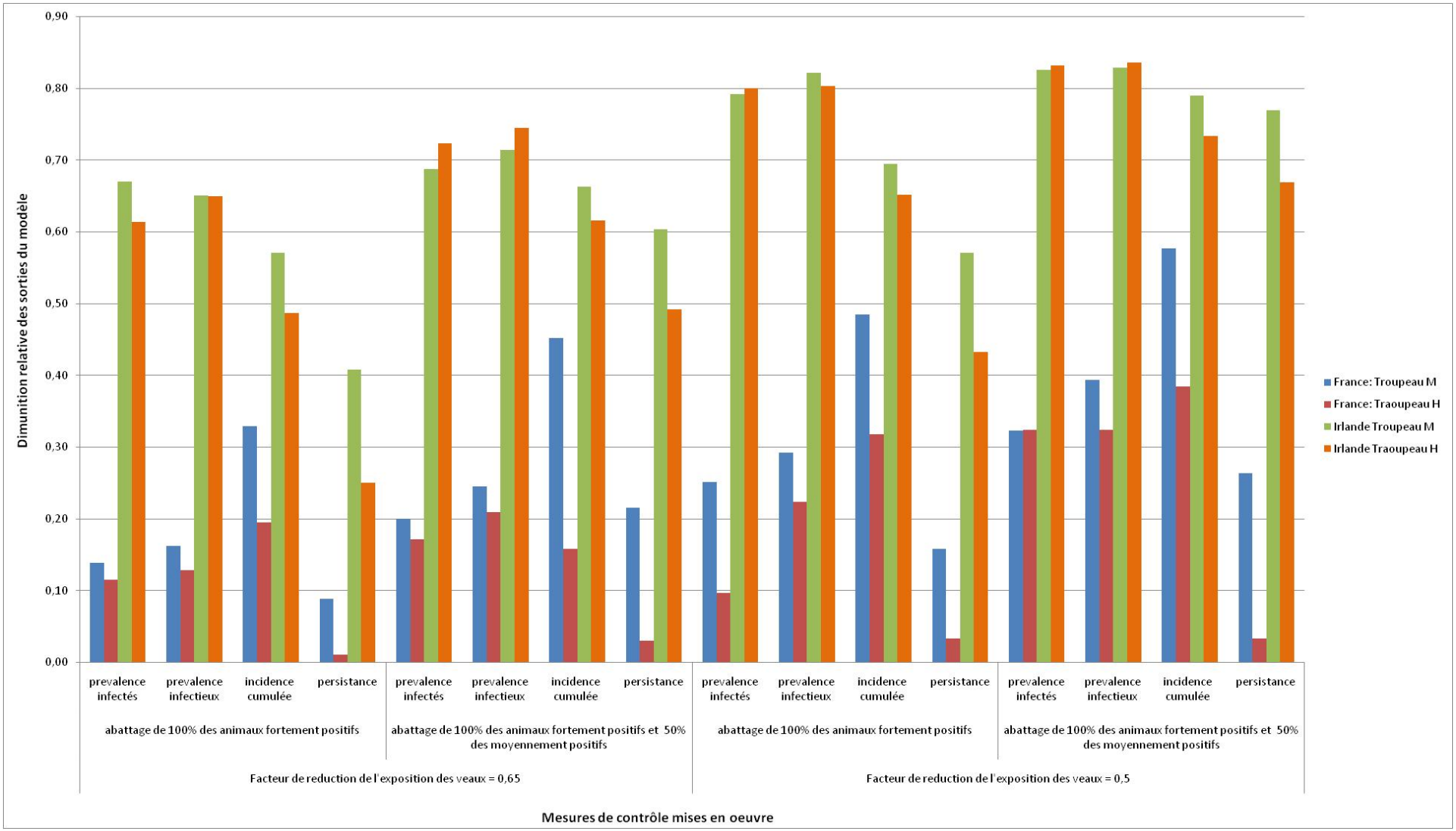

Figure 3: *Diminution relative des résultats des quatre modèles lors de la mise en œuvre de mesures de combinaison dans un troupeau modérément (M) ou fortement (H) infecté en Irlande et en France*

Efficacité de la sélection génomique de la résistance des bovins à l'exposition à Map

Nous avons développé un modèle de sélection génomique qui représente la sélection simultanée des quatre caractères phénotypiques de résistance à la paratuberculose bovine précédemment identifiés comme fortement influant sur la dynamique de transmission de la maladie. Nous nous sommes intéressé à une sélection de taureaux, car elle présentait le meilleur rapport coût-efficacité sur l'amélioration génétique au sein d'une population par rapport à la sélection de mères ou de mères et de pères. L'évolution des traits phénotypiques sélectionnés a été suivie à chaque génération d'animaux (figure 4). un pas de temps de génération (remplacement de la population entière par des animaux plus résistants) a été adopté.

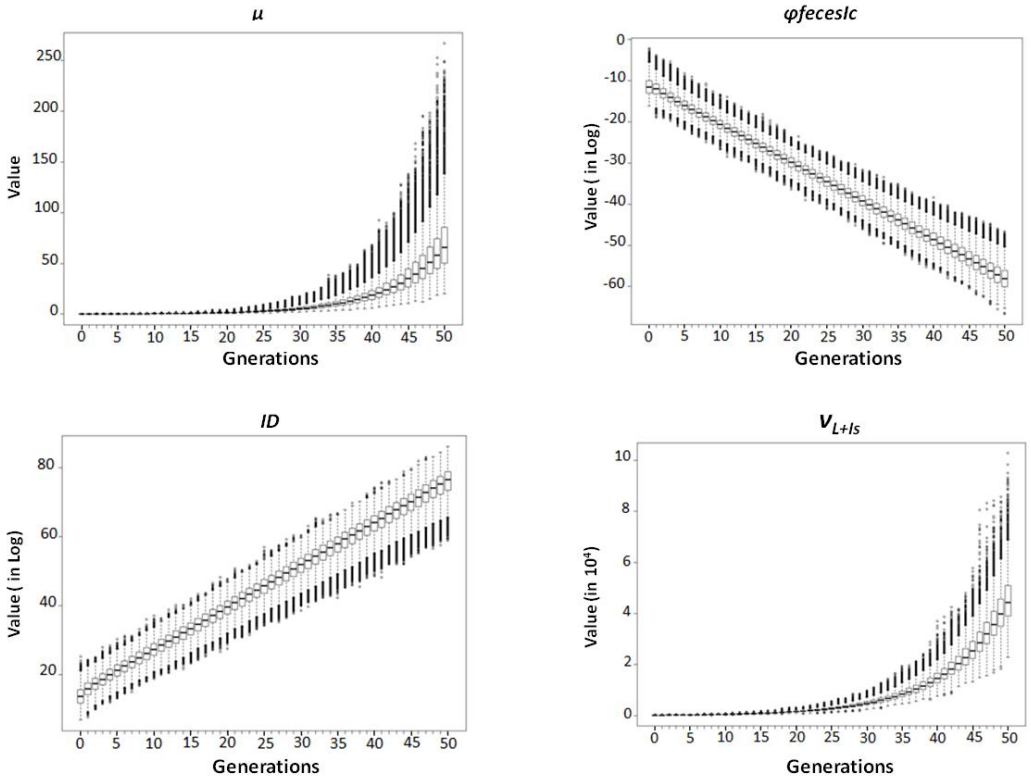

Figure 4: Evolution des quatre caractéristiques phénotypiques sélectionnées de la résistance à la paratuberculose sur 50 générations de sélection: le scénario le plus optimiste

En supposant une indépendance de la sélection des différents traits phénotypique, les valeurs des quatre caractères sélectionnés permettant un bon contrôle de la paratuberculose (valeurs identifiés en chapitre 3) pouvaient être atteintes entre 8 et 13 générations. La première combinaison de variation des quatre caractères sélectionnés permettant un bon contrôle de la paratuberculose à l'échelle du troupeau a été atteinte à la 3ème et à la 4ème génération de sélection (9 et 12 ans) en mettant en œuvre respectivement les scénarios de sélection optimiste et réaliste. Les dernières combinaisons ont été atteintes à la 13éme et 38éme génération, respectivement dans les plus optimistes et les plus réalistes.

Acknowledgements / Remerciements

To jury members, for their presence, for accepting to assess this work and for their challenging questions

For my supervisors,

A Pauline, merci pour ta présence, pour m'avoir appris qu'est-ce que c'est l'organisation. Merci pour l'accompagnement et de m'avoir aidé à développer mes compétences de modélisateur statisticien.

A Christine, merci pour ton encadrement, ta pédagogie, ta présence même parfois à des heures tardives pour m'appuyer dans mes travaux, pour vos conseils et pour m'avoir permis de passer du stade veto au stade chercheur.

To Simon, thank you for your supervision. Thanks for welcoming me in Ireland, It was a great pleasure to work with you,to learn a lot from you and to feel like I was a member of your group. Thank you very much.

A Didier Boichard pour m'avoir permis de bien comprendre la génétique chez les bovins et pour sa contribution à la réussite de ce travail. Merci.

Ames parents, qui ont dû parfois gérer mon stress et qui m'ont toujours poussé à toujours aller plus loin.

A ma mère qui m'a très jeune, baigné dans le secteur vétérinaire et dans l'épidémiologie et qui a été quelques fois tard pour que je ne lâche pas et aussi pour me dire de dormir.

A mon père qui m'a appuyé dans mes choix, qui m'a rendu çà possible et très confortable et qui m'a poussé à aller plus loin.

A ma petite sœur, qui aurait voulu être là. Qui m'a beaucoup encouragé, elle était là pour me dire qu'on ne dit pas ça comme ça en anglais. Je lui souhaite toutes les bonnes choses du monde

A ma grande sœur, Nadine, qui a été là dans les bons et les mauvais moments par lesquels je suis passé.

A Julie et aurélie qui ont été très présentes à mes côtés tout au long de cette aventure.

Amon oncle et ma tante, qui ont fait que je ne me sente jamais loin de chez moi, qui ont fait que je sois bien entouré pendant cette thèse et pour les grandes discussions sur comment passer d'une loi normale à une loi log normale et ces statistiques qui étaient assez compliquées

Ames cousins et cousines, ma tata cool, ma tata adulte, ma tata sérieuse, Chiheb, Karim, Sara, Gilles qui m'ont appuyé tout au long de ce travail, m'ont chalengé pour aller plus loin, m'ont encouragé dans cette démarche de thèse.

A mes collègues du groupe 2, merci pour la bonne humeur, le soutient et l'appui stratégique de la part de Erwan, Michel et yann. Merci à Sandie pour son appuie et pour m'avoir appris beaucoup de bonne pratiques de programmation.

A mes anciens collègues du groupe 4, pour les patientes discussions de modélisation et de la vie en général.

Pour ceux qui m'ont appuyé pour que ce travail soit finalisé : Guillaume, Gaël et Philippe qui a dû des fois rester très tard pour m'aider à finir mon model.

To CVERA staff who nicely welcomed me in Ireland and made my stay in Ireland rich and comfortable. Thanks for your contribution to the success of this work. Special thanks to Daniel and Jamie.

À tous ceux qui ont contribuer à l'aboutissement de ce travail.

Table of Contents

List of figures

Chapter 1

Chapter 3.

Chapter 4.

Chapter 5

List of tables

Chapter 1

Chapter 3

Chaper4 :

Chaper5 :

Chapter 1: General introduction

1. Introduction

Animal milk and meat are important sources of protein to human. These nutriments are in a large part provided by cattle. The demand on these products is in continuous progress in the last years. In Europe, the annual consumption increased by 7.7% for meat, from 53.2 to 57.4 million tonnes, between 2003 and 2013(FAO, 2017). In the same period, this increase was higher at the world level. The average annual consumptions showed an increase of 26.3% in meat (from 239.5MT to 302.4MT) and 32.2% in milk (from 307.6MT to 407.8MT). In addition, Human population is also in continuous progress. In 2017, the UN estimated human population to 7.5 billion people and estimated that in 2100 the population will increase by about 48% to reach 11.2 billion people (UN, 2017). To feed this people especially with animal proteins, the animal productivity must increase.

Consumer demands on food quality changed regarding recent social concerns for animal health and welfare. In developed countries, animal production aim to provide a better produced human feed through environment friendly productions. Such productions need to limit animal treatments against diseases by using the healthiest animals (Phocas et al., 2017; Tixier-Boichard et al., 2015).

Animal productions are also important issues for climate changes (Napolitano et al., 2013). In fact, animal production contributes to up to 15% of the annual CO_2equivalent production. In bovines, 2.8kg of CO2 equivalent are emitted per Kg of fat an protein corrected milk and 46.2 kg of Co2 equivalent are emitted per kg of carcass weight in beef(Napolitano et al., 2013).Hence, optimization of livestock productions and productivity are needed.

Several diseases in animals cause losses in productivity and should be controlled to reach a sufficient, healthy and Eco responsible animal productions. In developed countries, most of the epizootic diseases have been controlled or eradicated. Therefore, the economic and sanitary importance of enzootic diseases is much higher. Paratuberculosis is one of these diseases with an important impact on animal health, farm economy and livestock productivity (Beaudeau et al., 2007; Conor G. McAloon et al., 2016; Richardson and More, 2009).

2. Bovine paratuberculosis: generalities about the disease

Bovine paratuberculosis, also called Johne's disease (JD), is a bacterial disease caused by *Mycobacterium avium* subsp p*aratuberculosis* (Map). It mainly affects domestic ruminants but the infection was also described in wild ruminants (Behr and Collins, 2010). JD causes a chronical intestinal inflammatory disease. Bovine paratuberculosis is worldwide distributed (figure 1).Calves are known to be the most susceptible to infection which mainly occurs by ingesting Map (Behr and Collins, 2010). Infected calves shed the bacteria for a short period of time, denoted here as the transiently infectious state. Then, infected animals show barely detectable shedding of Map (latent state). When exposed to a stress (like calving) or naturally, latent animals restart shedding bacteria moderately but still have no clinical signs of the disease. Infection potentially leads to a high shedding state with likely clinical signs.

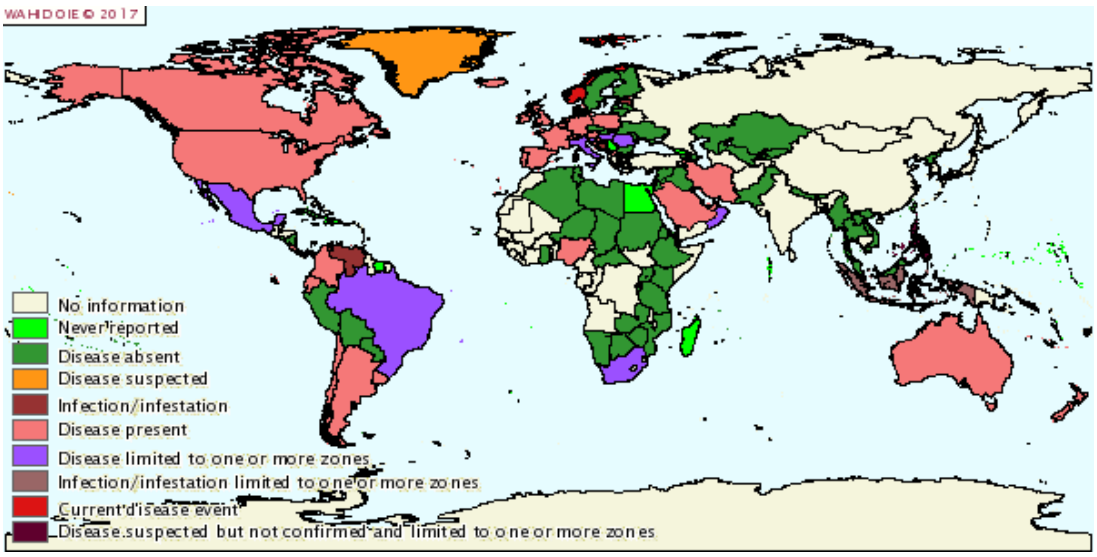

Figure 1: Distribution of paratuberculosis around the word during the second semester of 2016 (OIE-WAHIS, 2017)

Infectious animals shed bacteria through different routes (figure 2): (i) in faeces (ii) in milk and colostrum, and (iii) in utero. This evolution could take several years and up to10 years can occur between animal exposure and the first detection of the infection (Matthews, 1947; Mitchell and Medley, 2012; Nielsen, 2008; Stewart et al., 2007; van Roermund et al., 2007).

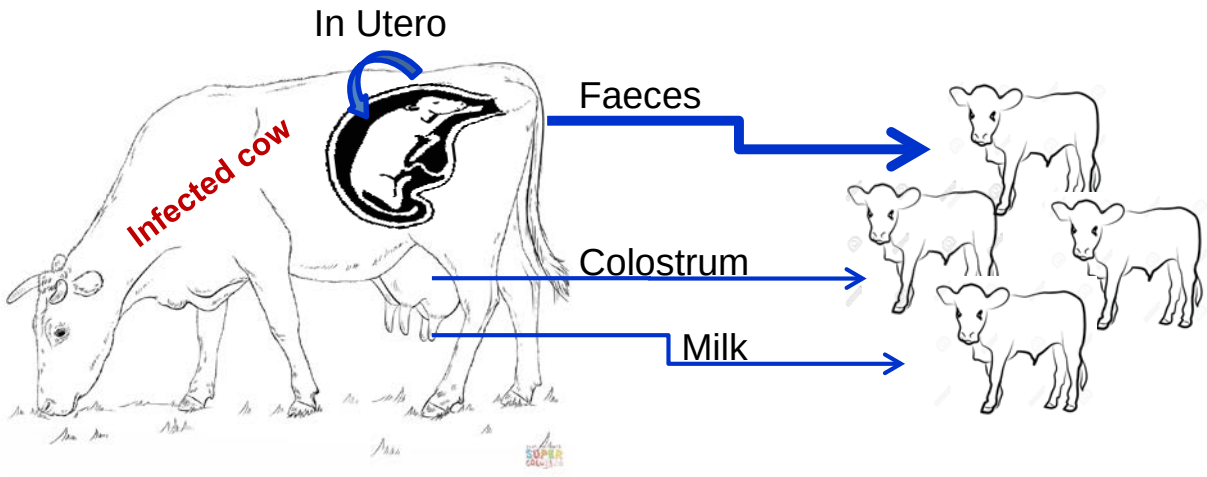

Figure 2.:paratuberculosis transmission routes

In developed countries, estimated herd prevalence in dairy herds can range from 30 to up to 50% (reviewed in Behr and Collins (2010), see figure 3). In dairy production, paratuberculosis causes important productivity and economic losses due to (Beaudeau et al., 2007; Garcia and Shalloo, 2015; Ott et al., 1999): a decrease in milk production, important emaciation, a decrease in fertility, an increase in culling, and the cost of treatment of concomitant diseases. Ott et al., (1999) estimated that in USA paratuberculosis induces a loss of 200 to 250 million dollars per year.

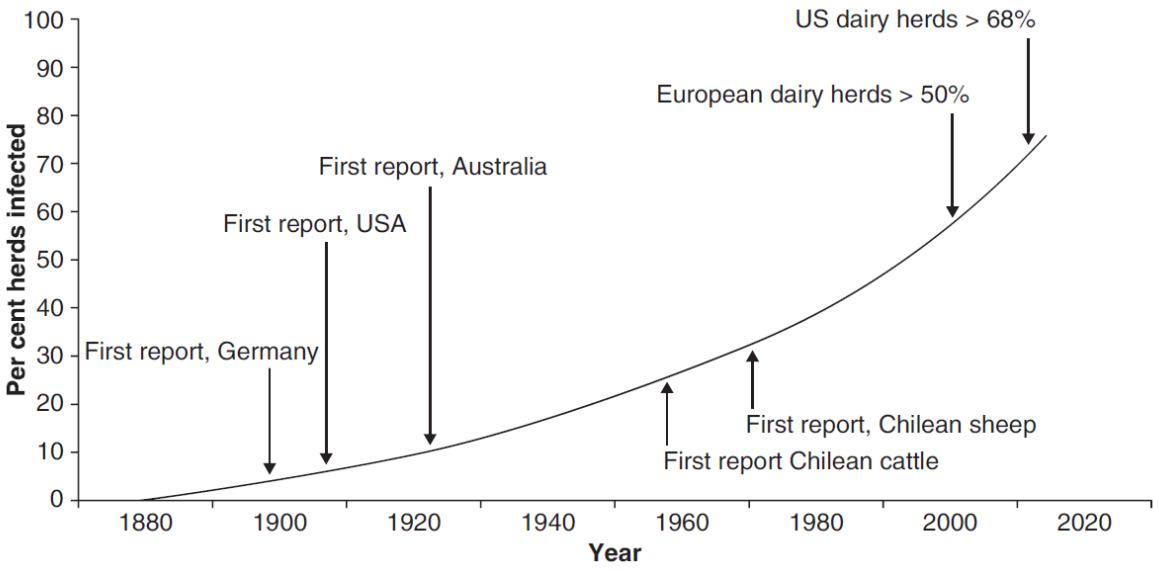

Figure 3: Theoretical global epidemic curve for herd-level paratuberculosis in dairy cattle (Behr and Collins, 2010)

3. Current control strategies and their limits

Regarding the clinical manifestation of paratuberculosis at the animal scale and the subsequent losses in productivity induced, paratuberculosis needs to be controlled. In Europe, control programs are mainly managed by stakeholders or local farmer groups but not funded by governments to avoid an unfair competition between European countries (Behr and Collins, 2010).

Paratuberculosis control programs aspire to limit Map spread. Two main measures are implemented(Benedictus et al., 2000; Domenech et al., 2006; Lu et al., 2008): (i) hygienic measures that aim to decrease the transmission of Map, and (ii) test and cull measures that aim to remove as early as possible infected animals that are likely to shed bacteria in the herd. Hygienic measures consist in limiting the exposure of susceptible animals (mostly calves) to farm environment contaminated by infectious animals (mostly adults). Therefore, calves have to be physically separated from dams and other adults, at the first hours of life. Test and cull measures consist in the early identification of infected animals to be culled, using diagnostic tests.

However, current control schemes seem not effective enough to significantly control paratuberculosis in infected herds. The effectiveness of hygienic measures strongly depends on farm management and practices(Marcé et al., 2011a), which may vary in Europe from farm to farm within a region. Therefore, it becomes difficult to define a unique effective and feasible control program. In addition, these measures request efforts from farmers and the exposure management should be very strict to be effective. Test and cull measures are based on the ability, using diagnostic tests, to early identify infected animals. Ante mortem diagnostic tests for paratuberculosis consist in(Collins et al., 2005; Eirin et al., 2015; McDonald et al., 1999; Nielsen, 2008; Scott et al., 2006; Singh, 2014): (i) culture methods mainly represented by the faecal culture, (ii) detection of Map parts using PCR, and (iii) immunological assay (mainly ELISA tests and interferon gamma). These tests have a low sensitivity in the early stages of the infection (table 1). In addition, only 2% of the infected animals show clinical signs. Regarding the long and slow evolution of the disease, only a small proportion of infected animals can be detected by these tests. Kalis et al.(2004) showed that in 90 closed herds assumed to be paratuberculosis free (with no history

of paratuberculosis), after 9 rounds of pooled faecal culture, only 39% of the herds were found to be non-infected by Map and were culture negative to all the test rounds. This result illustrates the difficulty to accurately identify the infection within herds.

Table 1: Sensitivity of the different paratuberculosis diagnostic methods

Diagnostic test	Sensitivity in early stages of infection	Sensitivity in late stages of infection	references
faecal culture	23% - 64%	70-88%	(Nielsen and Toft, 2009; Collins et al., 2005b)
PCR	4%	76%	(Scott et al., 2006)
ELISA	7-81%	67%-94%	(Collins et al., 2005b; Sockett et al., 1992; Nielsen and Toft, 2009)
Interferon gamma	34-85%	75-85%	(Huda et al., 2004)

Another control measure is vaccination (Bastida and Juste, 2011). First introduced In 1926 by Vallee and Rinjard, several vaccines then were developed and commercialised(Behr and Collins, 2010). The main evidenced benefits from the different available vaccines are a decrease in susceptibility, a delay of the clinical manifestation of the disease, and a decrease in clinical sign severity and shedding. The economic interest of vaccination was evidenced using modelling studies (Groenendaal et al., 2015). However, regarding the recent use of these vaccines, we still need more time to clearly conclude on the effectiveness and potential negative effects of a large vaccination program. In addition, the commercialised vaccines showed cross reaction with bovine tuberculosis (bTB) diagnostic tests (Pérez de Val et al., 2012). Developed countries implement active programs to eradicate the disease and almost all of them are TB free. Then, the use of vaccination against paratuberculosis is not relevant for keeping their bTB sanitary status. The lack of effectiveness of the different control measures suggests reflexions about innovative control measures to enhance the control of paratuberculosis.

Herd management practices could influence paratuberculosis control within herds. Paratuberculosis dynamics is influenced by herd contact structures between susceptible and infected animals (Marcé et al., 2011). Separation between calves and dams, animals exchange are known to play a major role in Map spared within and between herds (Beaunée et al., 2015; Doré et al., 2012; C. Marcé et al., 2011). Herd management practices increasing paratuberculosis transmission could limit the effectiveness of control strategies of the disease. The influence of the farming practices on Map spread and paratuberculosis control measures have to be assessed in order to design specific control measure adapted to the farming specificities(C. a Rossiter and Burhans, 1996).

4. Selecting for resistance to paratuberculosis: an innovative control measure

Selecting paratuberculosis resistant animals is a promising measure to enhance disease control(Koets et al., 2010). Experimental studies and field observations of host responses to Map exposure evidenced variability in susceptibility, disease evolution, lesion severities, and shedding among cattle(Mortier et al., 2011, 2014, 2015; Whitlock et al., 2000). Considering the resistance to paratuberculosis to be a negative answer to ELISA tests in cows naturally exposed to Map and born in herds where some congeners are found as infected, Hickey et al. (2003)evidenced that the resistance to paratuberculosis is heritable. This result was confirmed by other studies using different definitions of cattle resistance to paratuberculosis. The heritability of cattle resistance to paratuberculosis was estimated to range from 0.01 to 0.23 (Behr and Collins, 2010; Kirkpatrick and Shook, 2011; Küpper et al., 2012; van Hulzen et al., 2011; Zare et al., 2014). In recent years, genome exploration was enhanced by the large use of PCR in bovine. Several genes and genome parts were associated with the individual resistance to paratuberculosis(Alfano et al., 2014; Auriol C. Purdie et al., 2011; Vázquez et al., 2014; Zare et al., 2014a). These findings on heritability and genomics suggest that resistance to paratuberculosis could be selected in cattle. Nevertheless, mechanisms and the subsequent genes responsible of such a resistance remain barely known. In biology, a given phenotype could be considered as the combined expression of several phenotypic traits. We can easily imagine that resistance to paratuberculosis, as a biological phenomenon, is the resulting expression of several

genes coding for different phenotypic traits. The resistance to paratuberculosis needs to be more investigated to better identify associated phenotypes, understand how Map would spread in herds made of resistant animals, and guide the potential future genetic selection programs.

5. Why modeling pathogen spread in host population?

Epidemiological models mainly aim to better understand disease mechanisms and predict the effect of human intervention on disease dynamics (Diekmann and Heesterbeek, 2000; Keeling and Rohani, 2008). Epidemiological disease modelling was initially introduced in 1760, by Daniel Bernouli. Then, other epidemiological models were developed to investigate human and animal diseases enhanced by the development of informatics tools.

Mathematical equations are used to formally represent the dynamics of complex biological systems. Models can represent the evolution and dynamics of a disease at within host, herd, or regional levels. Two formalisms can be used: stochastic and deterministic(Daley et al., 2001; Pouillot et al., 2004). Deterministic models assume that processes happen at a given rate at each time step. Everything is determined the initial condition setting and parameter values, the model then, predicting only single trajectory. This approach is simpler and easier to use than the stochastic one. Stochastic models assume that at each time step processes have a given probability to occur. They are used to represent rare processes or small populations. They allow representing the potential extinction of the disease. Regarding the slow evolution of paratuberculosis and the relatively small herd sizes in Europe, stochastic models are the most appropriate to represent Map spread in European farms(Behr and Collins, 2010; Keeling and Rohani, 2008).

Individual based models (IBM) explicitly account for each animal. Such models allow a close follow-up of the disease dynamics among individuals but need a good knowledge and quantification of the different mechanisms involved in transmission and infection course. Alternatively, compartment-based models (CBM) consider animals of the same health state and age as similar and belonging to the same group. Compartmental-based model offer better calculation performances than IBM. The latter are needed necessary when individual characteristics and interventions targeting specific animals are studied.

Regarding the long evolution of paratuberculosis, the lack of knowledge about genetic component behind resistance to paratuberculosis, and the long time and expensive cost of observational studies on genetics, modelling seems to be the most appropriate approach to study the genetic selection of resistant cattle to paratuberculosis. The first model of bovine paratuberculosis dynamics was published by Collins and Morgan (1991). In the decade years, several working groups show a high interest in paratuberculosis modelling and 12 out of the 21 existing models have been published. Three of the published models are analytical and didn't explicitly represent the infection course of the disease (Ezanno et al., 2005; Conor G McAloon et al., 2016; van Roermund et al., 2002). Only three models are individual based allowing to account for individual differences in animals (Al-Mamun et al., 2016; Kudahl et al., 2007; Robins et al., 2015a). all Recent models account for demographic processes and integrating most up to date knowledge about the infection course(Al-Mamun et al., 2016; Cho et al., 2011; Lu et al., 2010; Clara Marcé et al., 2011; Robins et al., 2015b). Five of the published models account for the possible infection of adult animals (Al-Mamun et al., 2016; Lu et al., 2010; Magombedze et al., 2014; Mitchell et al., 2008; Robins et al., 2015b). the explicit representation of herd environment was taken into account in (Humphry et al., 2006; Clara Marcé et al., 2011). Marcé et al 2011 represented the heterogeneity of Map shedding through the different transmission routes between animals. only one regional model of paratuberculosis spread was identified in literature (G. Beaunée et al., 2015). The genetic variability of animals resistance was taken into account in one model that investigate the effectiveness of genetic selection of resistant animals to paratuberculosis on control of the disease in the herd (van Hulzen et al., 2014).

A unique modelling paper investigated the interest of a genetic selection of more resistant cattle to paratuberculosis as a measure to eradicate the disease within an infected herd(van Hulzen et al., 2014). In this study, three traits of bovine resistance to paratuberculosis were considered: (i) length of the susceptibility period, (ii) level of the susceptibility to infection (expressed as the dose of Map required resulting in infection), and (iii) duration of the latency period. The genetic selection of each of the considered phenotypes was based on dam and/or sires selection. Dam selection was represented by selecting the test negative cows. Sire selection consisted in selecting 80% sires producing the most resistant calves regarding their breeding value. The authors

focused on the time needed to eradicate the disease (less than 5% test positive adults) when selecting for a trait or another one at a time. They ranked the selected traits from most to less effective as: shorten the susceptibility period, decreased the susceptibility, and increased the latent period. Depending on the selected trait and parent, the time needed to eradicate the disease ranges from 147 to 702 years. This result suggests that a control program only based on genetic selection would take hundreds of years to control paratuberculosis. Further investigations are needed to explore the interest of selecting more phenotypic traits of resistance to paratuberculosis one by one or simultaneously. In Addition, Beaunée et al., (2015)clearly evidenced an added value when combining several control measures. Therefore, it is expected to be more relevant for future paratuberculosis control programs based on genetic selection phenotypic traits of resistance to combine them with current control measures. The genetic selection of dams and sires based on observed phenotypes, as it was the case in (van Hulzen et al., 2014), results in a relatively slow evolution of the selected traits. In genetic selection approach, selected phenotypic traits need to be observed in a candidate animal for selection or its relatives. Then the genetic value of this animal could be estimated. Another selection approach could be through genomic selection. This approach is based on the estimation of a candidate animal for selection using its genetic composition (genes and genome markers) and the link between genetic components and the selected phenotypic trait. Therefore, the genetic value could be estimated earlier through genomic selection that genetic selection approach. Genomic selection approach is expected to offer higher and quicker evolution of the selected traits (Boichard et al., 2016).

6. Objective and main steps of the thesis

The main objective of my PhD was to assess the efficacy of bovine paratuberculosis control strategies using genetic selection or livestock exposure in dairy herds. To reach this objective, the outline of the PhD project gathered in figure 4 was adopted.

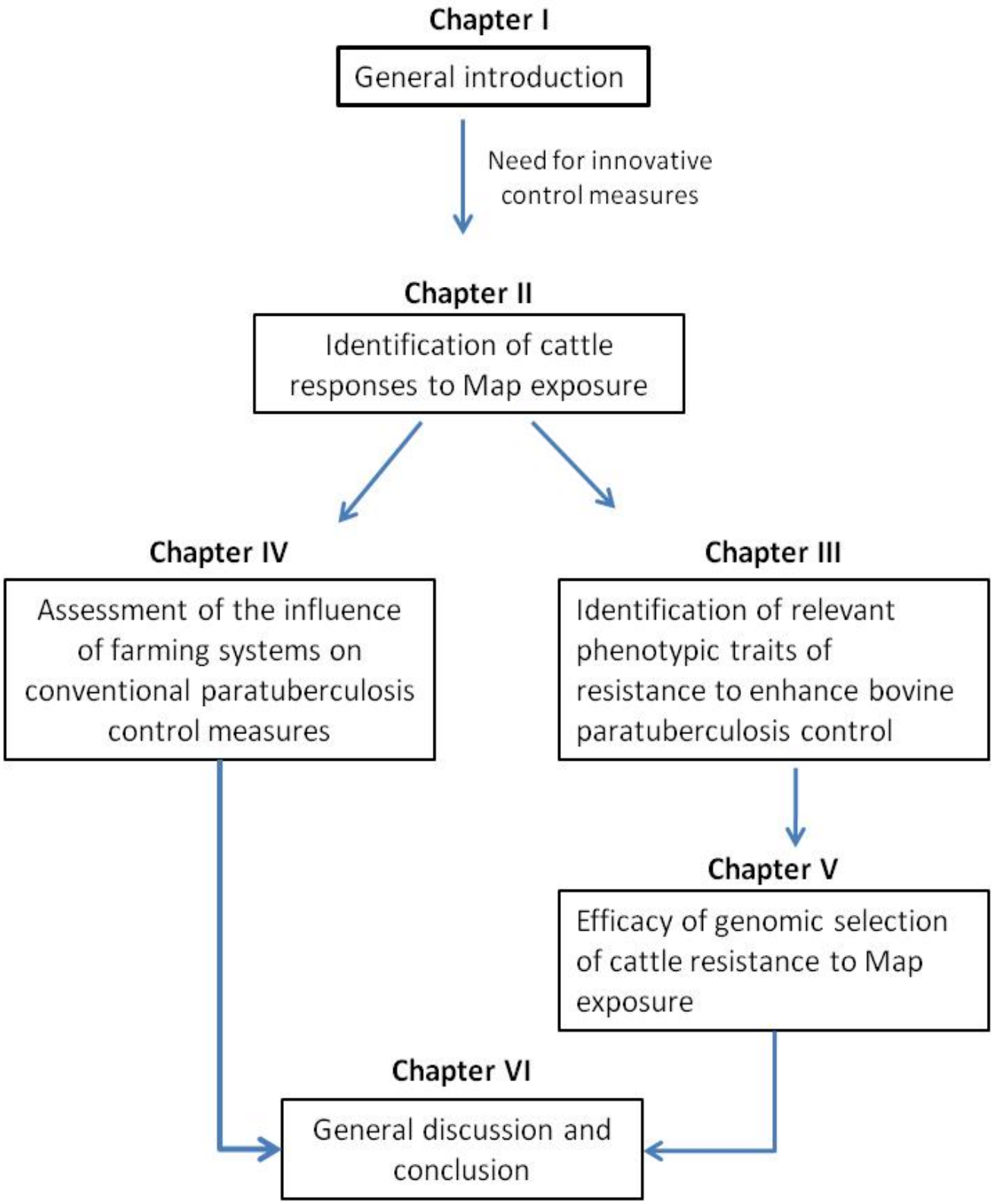

Figure 4: Scientific strategy of the PhD project

After this general introduction highlighting the limits of current paratuberculosis control measures and the need for innovative ones to enhance the disease control, five sections were developed in order to reach this thesis objective.

In chapter II, focusing on the literature, we identified phenotypic traits that could be targeted by potential genetic selection for resistance to paratuberculosis. The aim was to define phenotypic traits of cattle responses to Map exposure and the ranges of variations of this responses among cattle that are naturally present in animals to be assumed as potentially selectable.

In chapter III, we assessed the influence of varying these identified phenotypic traits of resistance to paratuberculosis on Map spread dynamics within a dairy herd. Assuming a successful selection has already achieved to improve one or more traits, we monitored Map spread indicators in a closed naïve herd at 25 years after introduction of an infectious animal. Traits most influencing the disease dynamics were identified. We described combination of variations of these traits that allowed a good control of paratuberculosis.

Previous studies highlighted that farm management influence the effectiveness of paratuberculosis dynamics. Therefore, the objective of chapter IV was to assess the influence of the farming system on the effectiveness of realistic control strategies. We compared the effectiveness of these control strategies two different dairy cattle farming systems: the western French and the Irish.

In chapter V, we developed a genomic selection model of resistant animals to paratuberculosis. We assumed a possible selection of the phenotypic traits identified as influencing within herd Map spread. The objective was to investigate the time needed to reach a sufficient variation in traits of resistance to paratuberculosis to allow a good control of the disease using a sire selection approach.

Finally, findings from this work were discussed in chapter VI with regards to current knowledge about the genetic resistance to paratuberculosis and existing control programs. Perspectives about more effective paratuberculosis control programs were proposed in chapter VII.

Chapter 2: Variability in cattle responses to Map exposure

1. Tolerance and resistance to infectious disease

To fight infection hosts mainly implement two mechanisms: resistance and tolerance. The study of such mechanisms and their impact on animal health is recent and limited to parasitology (Bishop, 2012; Kutzer and Armitage, 2016). (Bishop, 2012) defined resistance as the ability of a host to control the pathogen life cycle, while (Best et al., 2008) defined resistance as the ability of an host to reduce the risk of infection or to shorten the period to clear infection. Resistance can be divided into: (i) quantitative resistance, the ability of an organism to reduce the pathogen load (Graham et al., 2011; Råberg et al., 2009; Schmid-Hempel, 2011), and (ii) qualitative resistance, the ability to decrease the probability of infection if exposed to a given dose of pathogens(de Roode and Lefèvre, 2012; Restif and Koella, 2004).On the other hand, tolerance was defined as the net impact of a given level of infection on animal performances (Bishop, 2012). In ecology, it is defined as the ability of an organism, once infected, to limit the negative fitness effects of a given pathogen load (Best et al., 2008; Råberg et al., 2007).

There is a large variability among individual animal responses to infectious diseases. This variability was evidenced for different animal diseases in several host species in livestock (reviewed in Bishop et al., 2007; Bishop and Woolliams, 2014; Davies et al., 2009). This large variability in responses to disease exposure is known to decrease disease spread and severity of epidemic in infectious disease. The existence of genetic component driving the animal resistance to disease was evidenced species (Axford et al., 2000; Berry et al., 2011; Bishop and Woolliams, 2014). For example, in cattle for respiratory diseases(Glass et al., 2012; Snowder et al., 2006, 2005), foot and mouth disease(Glass, 2004), bovine tuberculosis (Allen et al., 2010; Bermingham et al., 2011, 2009),mastitis(Rupp and Boichard, 2003) and paratuberculosis(Kirkpatrick and Shook, 2011; Pinedo et al., 2007; Purdie et al., 2011).Such variability in cattle was noticed within and between breeds (Morris, 2006).The effectiveness of potential genetic selection for resistance to control animal disease was evidenced for parasitological and bacterial diseases (Axford et al., 2000; Bishop and Stear, 2003; Kadowaki et al., 2012). Moreover, Genetic selection for disease resistance would be a great opportunity to decrease use of chemical treatments in animals (Phocas et al., 2017; Tixier-Boichard et al., 2015).

2. Variability in cattle responses to Map exposure

As regards exposure to Map, a variability in host response was described in observational and experimental studies (Davies et al., 2009). Observational studies in naturally infected cattle animals focused on the evolution of the infection course (Mitchell et al., 2015). In herds where animals of the same age are assumed to have a similar exposure to Map, most of the infected cows do not show clinical signs and have a low and intermittent shedding of Map, while some others show a rapid progression to a high shedding state with likely clinical signs. In addition, this variability in cattle response to Map exposure also has been described in experimental study papers where protocol and environment are fully controlled. These studies assessed the effect of challenging animals with different infectious doses (from 10^3to10^{12}) and through per-os and intravenous routes. Calves of the same age challenged with the same dose of Map show various clinical, immunological, and shedding responses. As on the field, some animals show clinical signs , while others have no visible sign of infection (Mortier et al., 2014). A wide range of severity in specific paratuberculosis lesions can be observed from only histological lesions to macroscopic lesions and clinical signs (Mortier et al., 2011).Mortier et al. (2015) noticed that in animals older than 1 year experimentally challenged with same dose of Map only 42% of them were ELISA positive. The shedding patterns and quantities largely vary among infectious animals (Crossley et al., 2005; Grandjean, 2013; Laurin, 2015; Whittington et al., 2000).Some animals shed intermittently few bacteria in faeces when others shed continuously a high amount of bacteria (Mortier et al., 2014). These findings suggest that individual host factors contribute to increase or limit Map spread in dairy herds.

The response to Map exposure was evidenced to be heritable in cattle. Recent studies focused on resistance to paratuberculosis as expressed by negative ELISA test, negative faecal culture, or no clinical signs. They estimated an heritability of resistance to paratuberculosis ranging from 0.01 to 0.23 (Behr and Collins, 2010; Kirkpatrick and Shook, 2011; Küpper et al., 2012; van Hulzen et al., 2011; Y. Zare et al., 2014). These studies assumed the response to map exposure to be a binary phenotypic trait: resistant vs susceptible. Resistance was mainly defined as a positive answer to a positive test or presence of visible clinical signs of the disease. Regarding the complexity of paratuberculosis resistance mechanism, intermediate phenotypic of

responses to Map exposure could easily be assumed. The heritability estimating studies under represent the intermediate responses to Map exposure. Therefore, the real heritability of bovine resistance to Map exposure is expected to be higher than 0.23.

In addition, the large use of sequencing tools in recent years allowed identifying genes or genome markers associated with paratuberculosis resistance and tolerance (as reviewed in Purdie et al., 2011). The identified genomic components were associated to resistance of cattle to paratuberculosis as expressed by a negative response to ELISA test, negative faecal culture or no clinical signs in animals with proven exposure to Map(Alpay et al., 2014; Berry et al., 2010; Yalda Zare et al., 2014b). The genetic components associated to cattle resistance to paratuberculosis are known to play a role in immunological mechanisms such as preventing bacterial growth within cells (Purdie et al., 2011; Ruiz-Larrañaga et al., 2007; Singh et al., 2013), pathogen recognition (Koets et al., 2010; Purdie et al., 2011; Singh et al., 2013), and fighting infection(Purdie et al., 2011; Singh et al., 2013).

As far as we know, for now resistance to paratuberculosis was investigated as a binary phenotype: positive or negative to diagnostic tests, with or without clinical signs of the disease. Considered phenotypes are relatively easy to observe in the field. Nevertheless, they are the result of combined effects of several traits (and subsequent genes) of paratuberculosis resistance. Even if the role of these candidate genes has been studies, it is not currently possible to associate them to specific phenotypic traits involved in paratuberculosis resistance or tolerance.

3. Phenotypic traits of resistance and tolerance to paratuberculosis

The concepts of Resistance and tolerance can be adapted to bovine paratuberculosis infection. Resistance can be defined as the ability of an animal to prevent infection when exposed to a given dose of Map, while tolerance can be defined as the ability of an infected animal to cope with infection. Therefore, resistant animal would have a lower probability to be infected when exposed to a given dose of Map, thus need a

higher dose of bacteria to be infected, and would potentially show a faster decay in susceptibility with age, thus become no longer susceptible at an earlier age. On the other hand, tolerant animal would, once infected, delay the apparition of clinical signs by showing a longer latency or incubation period, and as a result have shorter periods of high shedding. Such an animal would potentially also have lower shedding level, and present a lower chance to infect its fetus in utero. Tolerance to paratuberculosis is expressed all-over the infections course. Magombedze et al. (2016), Klinkenberg and Koets (2015), Subharat et al. (2012), and Rodrick, (1996) highlighted that the variability of impact of host infection by Map on clinical state, shedding, and transmission is potentially associated to the variability of the immune responses induced to fight infection.

3.1. Phenotypic traits of resistance to paratuberculosis

First, resistant animals are less susceptible when exposed to a given dose of Map. This could be due to a shorten susceptibility period and a higher susceptibility decay with age. Indeed, calves are known to be the most susceptible animals to paratuberculosis(Behr and Collins, 2010) and a decrease in susceptibility with age has been demonstrated (R. Mortier et al., 2013; Windsor and Whittington, 2010) . It has been evidenced that calves remain susceptible to infection by Map mostly until 1 year of age (reviewed inBegg and Whittington, 2008; Hines et al., 2007) and recently (Mortier et al., 2011). Mortier et al., (2013; 2014) experimentally challenged animals from 3 age groups with contrasted infectious doses. These studies evidenced an age dependent susceptibility to infection: proportion of infected animals, lesion severity, and immune response intensity for animals exposed to the same infectious dose was lower in older animals than in young ones. However, Beard et al., (2001) challenged young calves, from 1 to 5 days old, with a high infectious dose (108- 109 bacteria) and noticed that out of 12 calves, the infection was not detectable in faecal culture of 7 calves. This result suggests that calves could be resistant to infection even in their first week of life. In the other hand, Larsen et al. Larsen et al., (1975)challenged trough oral route four adult bovine from 5 to 11 years and noticed that map is detectable in 66% of tissue culture from these animals,highlighting the possible infection of adult animals by Map. A recent study in naturally infected cows confirmed this finding (Pradhan et

al., 2011). However, natural infection of adults has been rarely observed and was only described in naïve animals following sudden exposure to a highly contaminated environment(Pradhan et al., 2011; J.D. Rankin, 1962).

Second, as a result of the previous point, resistant animals require an increased infectious dose to be infected. As far as we know this has not been well described. This trait is difficult to assess in naturally infected animals. Experimental infection studies mainly aim to produce a successful infection of the animals. Therefore, relatively high doses of bacteria are used in published experimental challenges. However, such studies could be used to quantify the variation among animals as regards the minimum dose of map needed to infect them. The doses of Map used in experimental assays were expressed in colony forming unit (CFU). The infectious doses used in experimental challenges of calves by Map range from 10^3 and 10^{12}.Stabel et al., (2009), challenged calves in the two first days of life with up to 10^{12}CFU of Map and noticed that some animals have no detectable infection. This finding suggests that even young calves, known to be very susceptible to paratuberculosis, may require up to 10^{12} bacteria to express a successful infection.

3.2. Phenotypic traits of tolerance to paratuberculosis

First, as shedding is positively associated to the immune response of the infected animal (Magombedze et al., 2016; Rodrick, 1996), more tolerant animals are expected to shed fewer bacteria through all of the transmission routes at each stage of the disease evolution. Only few studies quantified the amount of bacteria shed through the different transmission routes. In faeces, moderate shedders shed from 10^4 to 10^{15} CFU of Map per Kg of faeces, when clinical or high shedding animals shed from 10^8 to 10^{15} CFU of Map per Kg of Faeces (Jørgensen, 1982; C. A. Rossiter and Burhans, 1996; Whittington et al., 2000).

In the early stage of the infection, when newly infected calves are transiently shedders, van Roermund et al., (2007) noticed that animals shed from $6X10^4$ to $6X10^5$ CFU of Map per Kg of faeces. Moderate shedders show from 0 to $2x10^{10}$ CFU of Map per Kg of Milk or colostrum and high shedders shed from 700 to $2x10^{10}$ CFU of Map per Kg of milk or colostrum (Giese and Ahrens, 2000; Magnusson et al., 2006; Stabel et al.,

2014; Sweeney et al., 1992; Vissers et al., 2006). These observations suggest that tolerant animals can have no evidence of shedding in milk or colostrum when they are in a moderate shedding state, and as low as 700 CFU of Map per Kg of milk or colostrum when they are high shedders or clinically affected.

Second, as more tolerant animals have a better immune response and better control the infection, and as Map shedding level is related to the immune response, more tolerant animals may avoid or shorten the period of shedding. However the duration of the different shedding states are not well described in the literature. (Rienske Ar R Mortier et al., 2014)evidenced that experimentally infected animals transiently shed for a period as short as 1 to 5 days. Then shedding can barely be observed due to the quality of available diagnostic tests (Behr and Collins, 2010; Collins et al., 2005; Nielsen and Toft, 2009). This period corresponds to the incubation period. When tagged as clinically affected or high shedding, animals are rapidly culled. Therefore, estimation of the natural duration of this period can be found in the literature.

More interestingly, more tolerant animals are expected to have longer incubation period, delaying the onset of clinical signs and high shedding. The clear estimation of the paratuberculosis incubation period duration is not well documented in the literature due to the long evolution of the disease and the difficulty to clearly identify infected animals before lesions occur. However, this incubation period is commonly described to vary from 1 to 10 years (Behr and Collins, 2010), and most often ranging from 2 to 5 years (Chiodini et al., 1984; Espejo et al., 2012; Riemann and Abbas, 1983; WHITTINGTON and Sergeant, 2001). Most tolerant animals may therefore end their productive lifetime before entering a high shedding stage, thus barely contributing to Map spread.

Finally, more tolerant animals are expected to transmit less infection to their foetus during pregnancy. Such an in-utero transmission of paratuberculosis has been evidenced as reviewed in (Benedictus et al., 2008; Yayo Ayele et al., 2001). Only few studies estimated the probability of in-utero transmission. Doyle, (1958)detected Map in 9 (37.5%) foetuses and 13 (54.2%) foetus membranes out of 24 from clinically affected cows. Seitz et al., (1989)found 9 culture positive foetuses out of 24 from culture positive cows suggesting a 26.4% probability of in-utero transmission. Sweeney et al., (1992) noticed a probability of 17.85% in heavy shedding dam, and 0% in low

shedding ones. Only Whittington et al. (2009) classified dams with regards to their clinical state. This study estimated that the probability of in-utero transmission ranges from 0.06 to 0.15 in sub-clinical animals, and from 0.2 to 0.7 in clinically affected animals. However, clear evidence was made that even in infected dams the transmission probability can be as low as 0%, supporting the assumption that most tolerant animals may prevent in-utero transmission.

Chapter 3: Which phenotypic traits of resistance should be improved in cattle to control paratuberculosis dynamics in a dairy herd: a modelling approach

Racem BEN ROMDHANE*[1], Gaël BEAUNEE[2], Guillaume CAMANES[1], Raphael GUATTEO[1], Christine FOURICHON[1], Pauline EZANNO[1]

Vet. Res.

Published online 10 October 2017

1- *BIOEPAR, INRA, ONIRIS, 44307 Nantes, France*

2- *MAIAGE, INRA, 78352 Jouy-en-Josas, France*

Abstract

Paratuberculosis is a worldwide disease causing production losses in dairy cattle herds. Variability of cattle response to exposure to *Mycobacterium avium* subsp. *Paratuberculosis*(Map) has been highlighted. Such individual variability could influence Map spread at larger scale. Cattle resistance to paratuberculosis has been shown to be heritable, suggesting genetic selection could enhance disease control. Our objective was to identify which phenotypic traits characterising the individual course of infection influence Map spread in a dairy cattle herd. We used a stochastic mechanistic model. Resistance consisted in the ability to prevent infection and the ability to cope with infection. We assessed the effect of varying (alone and combined) fourteen phenotypic traits characterising the infection course. We calculated four model outputs 25 years after Map introduction in a naïve herd: cumulative incidence, infection persistence, and prevalence of infected and affected animals. A cluster analysis identified influential phenotypes of cattle resistance. An ANOVA quantified the contribution of traits to model output variance. Four phenotypic traits strongly influenced Map spread: the decay in susceptibility with age (the most effective), the quantity of Map shed in faeces by high shedders, the incubation period duration, and the required infectious dose. Interactions contributed up to 12% of output variance, highlighting the expected added-value of improving several traits simultaneously. Combinations of the four most influential traits decreased incidence to less than one newly infected animal per year in most scenarios. Future genetic selection should aim at improving simultaneously the most influential traits to reduce Map spread in cattle populations.

1. Introduction

Bovine paratuberculosis or Johne's disease (JD) is a bacterial infection caused by *Mycobacterium avium* subsp. *paratuberculosis* (Map). It mainly affects domestic ruminants. Paratuberculosis has a worldwide distribution with a high prevalence, herd prevalence being around 50% in Europe (Nielsen and Toft, 2009). The progressive evolution of the infection leads to a chronic diarrhoea, an emaciation and death. This infection is responsible for significant weight losses, a decrease in milk production, an increase in mortality, and the early culling of infected animals, inducing economic

losses (Whittington and Windsor, 2009). Infectious animals shed bacteria in their faeces, milk, and colostrum. Susceptible animals are infected by ingesting Map or in utero. Calves are known to be the age group most susceptible to infection (Mortier et al., 2011).

Individual response to a given exposure to Map differs among animals. Within-herd prevalence is usually low, with 2.8 to 27% of infected animals(Good et al., 2009; Raizman et al., 2011). Field observations have reported substantial variation in individual response to Map exposure: among birth cohorts, which are assumed to have been similarly exposed to Map, some are later shown to be infected/infectious, while others remain not infected/infectious. In addition, the following observations have been made following experimental infection of similar aged calves with similar infectious dose of Map: (1) a wide range of paratuberculosis lesion severity have subsequently been observed (Mortier et al., 2011), (2) different quantities of Map are shed in their faeces (Rienske Ar R Mortier et al., 2014), and (3) different antibody responses have been detected, suggesting a variable duration of the latency period (being the period between infection and later detection by direct or indirect tests) (Mortier et al., 2015). The duration of the incubation period (which is defined as the period between infection and clinical signs) varied greatly between animals, ranging from 4 months to 15 years (MATTHEWS, 1947; Mitchell and Medley, 2012; Nielsen, 2008; Stewart et al., 2007; van Roermund et al., 2007). The amount of bacteria shed by infectious cattle is also highly variable, some being high shedders, while others are low shedders. Both intermittent and continuous shedding has been observed.

Individual resistance to paratuberculosis is assumed to be highly variable among, and expresses as different courses of infection. The phenotype of cattle resistance to paratuberculosis can be divided into (1) the ability to prevent infection and (2) the ability to cope with infection. This resistance in response to Map exposure involves different mechanisms and individual characters. Each of these characters will be denoted thereafter as phenotypic traits, a phenotype being defined by combined phenotypic traits. At the population scale, the distribution of phenotypic traits among individuals will influence the level of herd immunity, and therefore impair Map spread.

Strategies to control Map spread within dairy cattle herds usually consist in two main actions: hygiene improvement to reduce environmental and food contamination by

Map, and a test-and-cull strategy to identify and remove infected animals. These control measures are not sufficient to control Map spread at herd and regional scales (Bastida and Juste, 2011; G. Beaunée et al., 2015; Ezanno et al., 2005). Vaccines against paratuberculosis have also been developed. Available vaccines decrease shedding of Map by infectious animals and decrease clinical signs of the disease (Bastida and Juste, 2011; Kalis et al., 2001). However, they do not prevent the infection of susceptible animals. In addition, most licensed vaccines show a cross reaction with tuberculosis diagnostic tests (Behr and Collins, 2010). Therefore, the use of vaccination is restricted in many countries.

The observed variability of the individual response to Map exposure could support the development of innovative control measures applied at population scale if the most resistant animals can be selected. Several studies demonstrated a heritability of resistance to paratuberculosis in cattle ranging from 0.01 to 0.23 (Behr and Collins, 2010; Kirkpatrick and Shook, 2011; Küpper et al., 2012; van Hulzen et al., 2011; Y. Zare et al., 2014). Recent studies highlighted an association between genetic markers and the course of Map infection (Alpay et al., 2014; Kirkpatrick et al., 2011; Purdie et al., 2011; van Hulzen et al., 2012; Zanella et al., 2011). Other genome markers were associated with Map shedding in faeces, presence of Map in several tissues, and sero-positivity, in animals from comparable herds regarding paratuberculosis infection and of the same age group. Therefore, these animals were assumed to have been exposed in a similar way (Alpay et al., 2014; Neibergs et al., 2010; Settles et al., 2009). This highlights the potential to select for cattle more resistant to paratuberculosis. However, there are still gaps of knowledge concerning the phenotypic traits of resistance that would be the most relevant to improvements in the control of Map spread at population scale.

Modelling is the most appropriate approach to investigate the dynamics of complex systems such as within-herd Map transmission. Observational and experimental studies are both difficult to implement and expensive regarding the long evolution of paratuberculosis. In addition, a modelling approach allows us to overpass the lack of knowledge on genetic resistance of cattle to paratuberculosis by assuming improved phenotypic traits as if they were already selected for. Simulations then provide information on how such modifications of phenotypic traits would influence Map spread. Only one recent study investigated the potential effectiveness of hypothetical

genetic selection as a strategy to control paratuberculosis at herd scale (van Hulzen et al., 2014). The authors assessed the effect of varying three phenotypic traits of resistance: (1) length of the susceptibility period, (2) level of the susceptibility to infection (expressed as the dose of Map required resulting in infection), and (3) duration of the latency period. Each tested phenotypic trait has been tested one-at-a-time and ranked by the time required to reach eradication. Modelling predictions showed that, when only genetic selection is implemented, eradication takes hundreds of years. However, this study did not investigate the potential progress in disease control when combining variations in several traits. In addition, other traits also could influence Map spread including intensity of shedding by infectious animals, in utero transmission, and progress of the infection course through different infection stages.

Our objective was to identify which phenotypic traits of resistance to paratuberculosis have the strongest influence on Map spread within a dairy cattle herd. The purpose was to identify ranges of phenotypic trait variations and trait combinations that limit Map spread in the herd. We assessed three categories of phenotypic traits both one-at-a-time and in combination, including: infection susceptibility, delays in the infection course, and shedding levels.

2. Materials and methods

2.1. Overall study design and model choice

A modelling approach was used to predict the effect of varying phenotypic traits of resistance to paratuberculosis on Map spread in a dairy cattle herd. We compared a situation where phenotypic traits were set at current observed levels with situations reached after a successful hypothetical genetic selection of more resistant animals in response to Map exposure. For each change of a trait, the resistance level was simulated as constant over time assuming that this average level had been reached in the population after a (not modelled) selection period. Several scenarios were simulated where one or several phenotypic traits were varied. The scenarios were compared regarding Map spread in the herd.

Several models have been published that represent Map spread within a dairy cattle herd (reviewed in (Marcé et al., 2010), and more recently (Al-Mamun et al., 2016; Koets and Gröhn, 2015; Lu et al., 2010; C. Marcé et al., 2011; Clara Marcé et al., 2011;

Martcheva et al., 2015; Robins et al., 2015a; Smith et al., 2015; van Hulzen et al., 2014)). We selected a stochastic compartmental model that offers an up-to-date description of Map spread within a dairy cattle herd. This model takes into account all of the major processes involved (according to the most recent literature) and allowed us to represent phenotypic traits of resistance corresponding to all of our hypotheses of interest. This model adequately combines demographical and infection dynamics, and accounts for herd structure, all these processes having been shown to highly influence Map spread (Clara Marcé et al., 2011). The chosen model is mechanistic: each step and mechanism of the infection course is represented by a model parameter. This allowed us to simulate changes in phenotypic traits of resistance by minimal changes in the model.

2.2. Main features of the model

The within-herd transmission model and the corresponding equations are fully described in Marcé et al. (Clara Marcé et al., 2011) and Beaunée et al. (G. Beaunée et al., 2015).And a detailed description of the model is presented in additional file 1.

The main modelling assumptions are the following: the herd population dynamics reflects the one of a typical western Europe Holstein herd with 5 age groups (unweaned calves, weaned calves, young heifers, bred heifers, and cows), a high renewal rate of cows (one third per year), and no males kept in the herd. The within-herd contact structure varies seasonally between housing and pasturing periods. The infection dynamics is represented by successive health states (Figure 1): animals initially susceptible (state *S*) are assumed to be no longer susceptible (state *R*) after a susceptibility period of duration *u*. Susceptibility decreases with age, assuming an exponential decay coefficient *h*. The possible infection of adults is neglected as it rarely occurs (it has only been demonstrated in adults following sudden exposure to a highly contaminated environment (Pradhan et al., 2011)). Infection can occur when a susceptible animal is in contact with a sufficient infectious dose per animal α (explicit indirect transmission),and then becomes transiently infectious (state *T*) for an average duration v_T. Then, infected animals enter a latent state (state *L),* during which shedding is neglected. After this latent period of average duration v_L, they become moderate shedders (state *Is*). For some animals, the evolution of the infection leads to a persistently high shedding and most of the animals are likely to have reduced milk yield

or clinical signs called here high shedding and clinically affected state (*Ic*) after an average duration v_{Is} in the moderate shedding state. Animals are assumed to be culled on average 6 months after entering *Ic* state.

Susceptible animals can be infected through five transmission routes (Clara Marcé et al., 2011): (1) contact with bacteria present in the general environment of the farm contaminated by all shedders, (2) contact with bacteria present in the local environment of calves contaminated by shedding calves, (3) in utero transmission from infected cows to their foetus, and (4) ingestion of contaminated milk or (5) colostrum from infectious cows.

2.3. Phenotypic traits of resistance to paratuberculosis

In this study we assessed the effect of varying 14 phenotypic traits of resistances to paratuberculosis and combination of them on Map transmission in the herd. Each of the tested scenarios corresponds to a variation, or combinations in variation, in one or more phenotypic trait of resistance to paratuberculosis.

The phenotype of cattle resistance to paratuberculosis is classically divided into (1) resistance to infection defined as the ability to prevent infection when exposed to a given dose of Map, and (2) tolerance to infection defined as the ability to cope with infection when infected (Råberg et al., 2007; Schneider and Ayres, 2008). On the one hand, animals are considered to be resistant (ability to prevent infection) if they show a decrease in susceptibility to infection, if they are no longer susceptible at a younger age, if they need to be exposed to a higher dose of Map to be infected, or if they show a faster decrease in susceptibility with age than less resistant animals. On the other hand, animals are considered tolerant(ability to cope with infection once infected) if they show longer latency and incubation periods, and a lower shedding level when infectious than less tolerant animals. In addition, fœtuses of the latter may have a lower chance to be infected in-utero.

We accounted for all of the potential mechanisms involved in an increased resistance to paratuberculosis because we assumed they could all contribute to Map spread at herd scale (Figure 1). The ability to remain non-infected was composed of four components: (1) a shorter susceptibility period for calves, (2) a faster decrease in age-related susceptibility, and (3) a higher infectious dose of Map needed to be infected

after birth. The ability to cope with infection was represented by a longer latency period before the onset of moderate shedding, a longer incubation period before high shedding and clinical signs, a decrease in the amount of Map shed through the different transmission routes and a decrease in the probability of in-utero transmission. Overall, we studied 14 parameters coding for the identified phenotypic traits of resistance to paratuberculosis (Table 1).

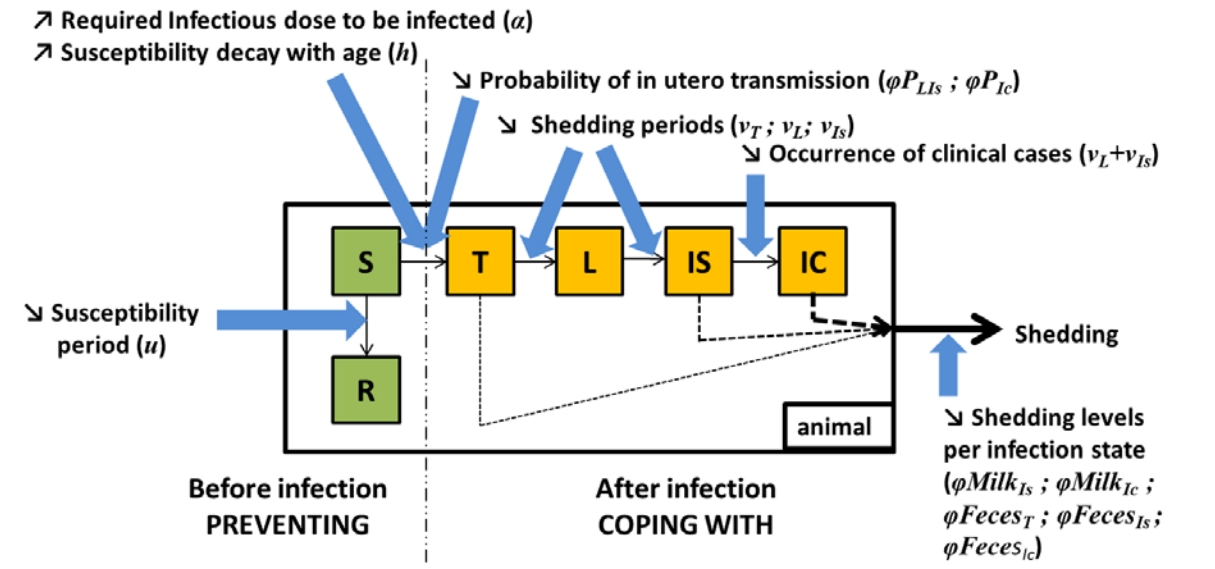

Figure 1: Paratuberculosis infection course and phenotypic traits of interest to reduce Map spread at herd scale: in bracket: the corresponding parameters coding for them in the model. Boxes: disease states, S: susceptible, R: no longer susceptible, T: transiently infectious, L: latent, Is: moderate shedder, Ic: high shedder or clinically affected animals. Green compartments: non infected states, orange compartments: infected states, dashed arrows: shedding, solid arrows: transitions between states, blue (large) arrows: changes in individual phenotypic traits that could limit Map spread at herd scale.

Based on the literature, we defined a realistic variation of resistance levels to simulate within observed values for the investigated traits. The reference value was the worst one. Changes were simulated from reference to the most favourable value observed value, indeed, calves susceptibility can sharply reduce, and animals are no longer susceptible, as soon as their first week of life (Sweeney et al., 1992; Whitlock and Buergelt, 1996) Some susceptible animals have been shown to need a dose of bacteria as high as 10^{12} to become infected (Giese and Ahrens, 2000). After a transient

shedding period, infected animals can have a barely detectable level of shedding for about four years (208 weeks) (Mitchell and Medley, 2012). Infected animals can show clinical signs of the disease up to more than nine years after infection (468 weeks). Concerning the probability of transmission of Map in utero from infected dam to its foetus and the quantities of bacteria shed through different routes, only partial information was available. Hence, we chose to test for extreme values by assuming that animals can stop shedding completely with no further in utero transmission of the infection. Nevertheless, it has been shown that high shedders and clinically affected animals can shed as few as 10^8 bacteria/kg of faeces, which corresponds to $1/100^{th}$ of the reference value that we have assumed in our model (C. a Rossiter and Burhans, 1996; Whittington et al., 2000).

2.4. Initial conditions and model outputs

Map spread was initiated by the introduction of a moderate shedding cow into a fully naïve herd of 260 animals. We assumed that herd renewal is mainly driven by internal demographic processes (no further introduction), which is typical of Western Europe farming systems. Map spread was predicted over 25 years. To obtain accurate outputs from the stochastic model, we ran 500 repetitions for each of the tested scenario. A scenario represented one phenotype of interest. Each phenotype was defined by a set of values of 14 parameters.

Four model outputs described Map spread within a herd (Table 2). All outputs were calculated at the end of the simulation, t = 25 years after Map introduction. The first output was the cumulative incidence calculated as the mean cumulative number of newly infected animals over the 25 years of simulation. The second output was the infection persistence defined as the proportion of runs where the infection persisted until 25 years after Map introduction, i.e. where there was at least one infected animal of state *T, L, Is*,or*Ic*, or bacteria in the environment. The third output was the prevalence of infected animals calculated as the median prevalence of infected animals in the population 25 years after Map introduction for runs where the infection persisted. Finally, the fourth output was the prevalence of affected animals calculated as the median prevalence of high shedding and clinically affected animals in the population 25 years after Map introduction for runs where the infection persisted. Outputs related

to prevalence were calculated only if Map persistence was higher than 6% (30 runs out of 500) in order to provide a sufficient number of runs to estimate medians.

2.5. Simulation protocol and output analysis

First, we performed a univariate simulation study: each of the traits of interest was varied one-at-a-time, assuming they varied independently (Table 1). Second, we performed a multivariate simulation study: combinations of phenotypic traits were studied to test for a potential enhanced effect of simultaneously improving several phenotypic traits simultaneously. The R programming language (R Core Team, 2016) was used for data analyses. Results obtained in the univariate simulation study revealed that some parameters — when analysed one-at-a-time — did not influence model outputs. Instead of keeping numerous parameters or removing some of them expected not to be influential, we grouped in this second step non-influential parameters when they are untangled in the same trait or when involved in a given transmission route. This decrease in the number of considered parameters without losing information eased the interpretation of the multivariate simulation study results. Ranges of variation of phenotypic traits were represented by five possible values per trait (including the reference value) combined in the multivariate simulation study using a complete factorial design, leading to 390 625 scenarios (Table 1). Five levels of variation per trait appeared to be a good compromise between parameter space exploration and number of scenarios to investigate interactions. A complete factorial design was required to assess all interaction orders.

Table 1: Parameters coding for the phenotypic traits of resistance: definition and values

Parameters	Definition	Reference value	Univariate simulations: [min-Max]	Multivariate simulations: tested values #1	#2	#3	#4	Source
u	Susceptibility period duration	52 weeks	[1 – 52]	-				(HAGAN, 1938; J D Rankin, 1962;
h	Decay in susceptibilitywith age	0.1	[0.1 – 1]	0.2	0.3	0.4	0.5	(Windsor and Whittington, 2010)
α	Required infectious dose to be infected	10^6 bacteria	[10^6– 10^{12}]	1.5×10^6	2×10^6	2.5×10^6	3×10^6	(Begg and Whittington, 2008)
v_L	Duration of latent state	52 weeks	[52 – 208]	-				(Mitchell and Medley, 2012: Nielsen, 2008)
$v_L + v_{Is}$	Duration before high shedding and clinically affected state	156 weeks	[156 – 468]	234	312	390	468	(MATTHEWS, 1947; Mitchell and Medley, 2012; Nielsen, 2008)
v_T *with* $v_T + v_L$= constant	Duration of transiently infectiousstate with constant duration before moderate shedding state	vT = 25 weeks (vT + vL = 77)	[1 – 25]	-				(Mitchell and Medley, 2012; Nielsen, 2008; Stewart et al., 2007; van Roermund et al., 2007)
v_{Is} *with* $v_L + v_{Is}$ = constant	Duration of moderate shedding state with constant duration before high shedding or clinically affected state	vIs = 104 weeks (vL + vIs = 156	[60 – 104]	95	86	77	68	(MATTHEWS, 1947; Mitchell and Medley, 2012; Nielsen, 2008; Stewart et al., 2007; van Roermund et al.
$\varphi Milk_X$	Factor of decrease of Map shed in milk by animals in health state X							
$\varphi Milk_{Is}$	moderate shedding state (*Is*)	100%	[0 – 100]	50%	10%	5%	0%	(Sweeney et al.,
$\varphi Milk_{Ic}$	high shedding and clinically affected	100%	[0 - 100]					(Giese and
$\varphi Feces_X$	Factor of decrease of Map shed in faeces by animals in health state X							
$\varphi Feces_T$	transient state (*T*)	100%	[0 – 100]	50%	10%	5%	0%	(van Roermund et al., 2007)
$\varphi Feces_{Is}$	moderate shedding state (*Is*)	100%	[0 – 100]					(C. a Rossiter and Burhans, 1996)
$\varphi Feces_{Ic}$	high shedding or clinically affected state	100%	[0 – 100]	66%	50%	40%	33%	(Jørgensen, 1982; Whittington et al.,
φP_X	Factor of decrease of probability of in utero transmission for cows in health state X							(Benedictus et al., 2008; Whittington
φP_{LIs}	latent and moderate shedding states	100%	[0 – 100]	50%	10%	5%	0%	
φP_{Ic}	high shedding or clinically affected state	100%	[0 – 100]					

We performed a cluster analysis of the multivariate scenarios based on two of our model outputs. Scenarios were grouped to minimise outputs variability within a cluster and maximise this variability among clusters. The aim was to identify and characterize groups of scenarios. We build clusters using the two model outputs available on all model repetitions of each scenario: cumulative incidence and infection persistence 25 years after Map introduction, after they were standardized into variables of comparable scales. To define the appropriate number of clusters, we studied the sum of squared distances between each scenario and the centroid of its corresponding cluster(called the sum of squared error or the within-group sum-of-squares)for different number of clusters(Everitt and Hothorn, 2010; MacQueen, 1967; Thinsungnoen et al., 2015). Clusters were built using k-means clustering method (*kmeans* function from R package "*FactoMineR*" (Husson et al., 2016)). A descriptive analysis was performed to characterize clusters for phenotypic traits using *catdes* function ("*FactoMineR*" package (Husson et al., 2016)). This step aimed to identify if tested variations in phenotypic traits are uniformly distributed in regards of cluster or if some values are over represented in a given cluster. Besides, we performed an ANOVA to quantify the contribution of each trait to the variance of each of the four model outputs. Each trait contribution to the model output variance (κ) was calculated as:

$$\kappa = principal\ effect\ of\ the\ trait + \sum_{i=1}^{i=m} \frac{i^{th}\ order\ interaction\ effect\ involving\ the\ trait}{i+1},$$

With i the interaction order and *m* the highest interaction order in which the trait was involved. A second ANOVA was performed on the influential phenotypic traits to quantify contribution of each trait (principal effect) and each combination of them (interaction) to the variance of each of the four model outputs. Factors (individual traits or combinations of traits) were influential if they contributed to more than 5% of the variance of at least one of the four model outputs.

In order to identify the most effective combinations of variation in phenotypic traits to decrease Map spread, we used the cumulative incidence output as an indicator of a successful Map control at herd scale. For each combination, the cumulative incidence was plotted and visually described (Figure 6). In addition, we chose two thresholds to evidence the most effective combinations with emphasis on the ones with the lowest variations in parameters (Figures6 and 7): (1) 25 newly infected animals over the 25 years of simulation, interpreting such a level of one newly infected animal per year as

an infection under control, and (2) half this threshold, i.e. 12 newly infected animals over the 25 years of simulation.

3. Results

In the univariate simulation study the variation of six phenotypic traits influenced at least one model output resulting in decrease in Map spread (Figure 2): a shorter susceptibility period (u), an increase in the decay in susceptibility with age (h), an increase in the required infectious dose (α), a longer latent state (v_L), a delayed occurrence of the high shedding or clinically affected state (v_L+v_{Is}), and a decrease in the quantity of Map shed in faeces by high shedders or clinically affected animals ($\varphi Feces_{Ic}$).

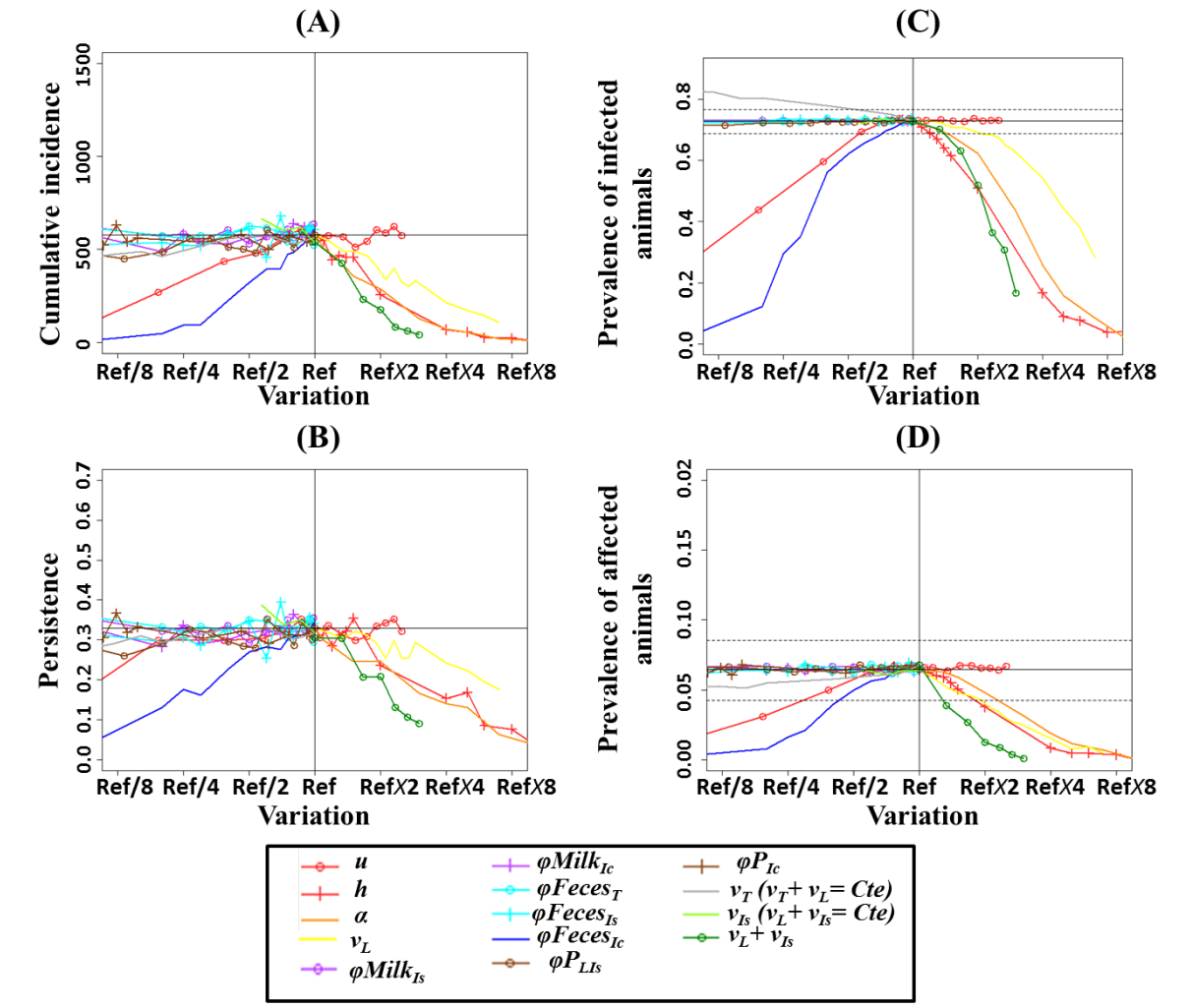

Figure 2: Changes in model outputs resulting from univariate variations of phenotypic traits of resistance to paratuberculosis. A: cumulativeincidence, B: persistence, C: prevalence of infected animals, D: prevalence of high shedders and affected animals at the end of simulations (25 years). "Ref" corresponding to the reference value of the phenotypic trait. See Table 1 for parameter definitions and tested values, Table 2 for output definitions. Vertical and horizontal solid lines give reference values, dotted lines give associated 5th and 95th percentiles.

Eight of the traits investigated in the univariate simulation study did not influence Map spread dynamics. These traits were: a shorter transiently infectious state when assuming a constant duration before the moderate shedding state (v_T with v_T+v_L= *constant*), a shorter latent state when assuming a constant duration before the high shedding and clinically affected state (v_{Is} with v_L+v_{Is}= *constant*), a decrease in the quantity of Map shed in milk by moderate shedders ($\varphi Milk_{Is}$) and high shedders and clinically affected animals ($\varphi Milk_{Ic}$), a decrease in the quantity of Map shed by

transiently infectious animals ($\varphi Feces_T$), and by moderate shedders ($\varphi Feces_{Is}$), and a decrease in the probability of in utero transmission by latent infectious animals and moderate shedders (φP_{LIs}), and by high shedders and clinically affected animals (φP_{Ic}).

We chose traits to be included in the multivariate simulation study in light of these results, noting that it was not possible to evaluate interactions among traits could have been evaluated with such a univariate analysis. Among traits highlighted as influential, we kept all except *u* that was redundant with *h*. Among other traits, we kept v_{Is} (assuming $v_L+v_{Is}= constant$) and we grouped traits related to Map shedding in milk and colostrum ($\varphi Milk$), to in utero transmission (φP), and to Map shedding in faeces by transiently infectious animals and moderate shedders ($\varphi Feces_{TIs}$).

The cluster analysis of multivariate scenarios identified seven groups of scenarios from current (A; assumed as the worst) to the best control of Map spread (G; Figures 3A and B). This analysis highlighted three distinct dynamics (Figure 3): clusters A and B represented low control with a decrease in cumulative incidence, a slight decrease in infection persistence, and an almost as high prevalence of infected animals. Clusters C, D, and E represented a good control with a low cumulative incidence, persistence and prevalence of infected animals, but with the occurrence of high shedders and clinically affected animals. Clusters F and G represented complete control with a very low cumulative incidence and persistence. Up to 80% of the scenarios were in these most favourable clusters F and G (Figure 3A).

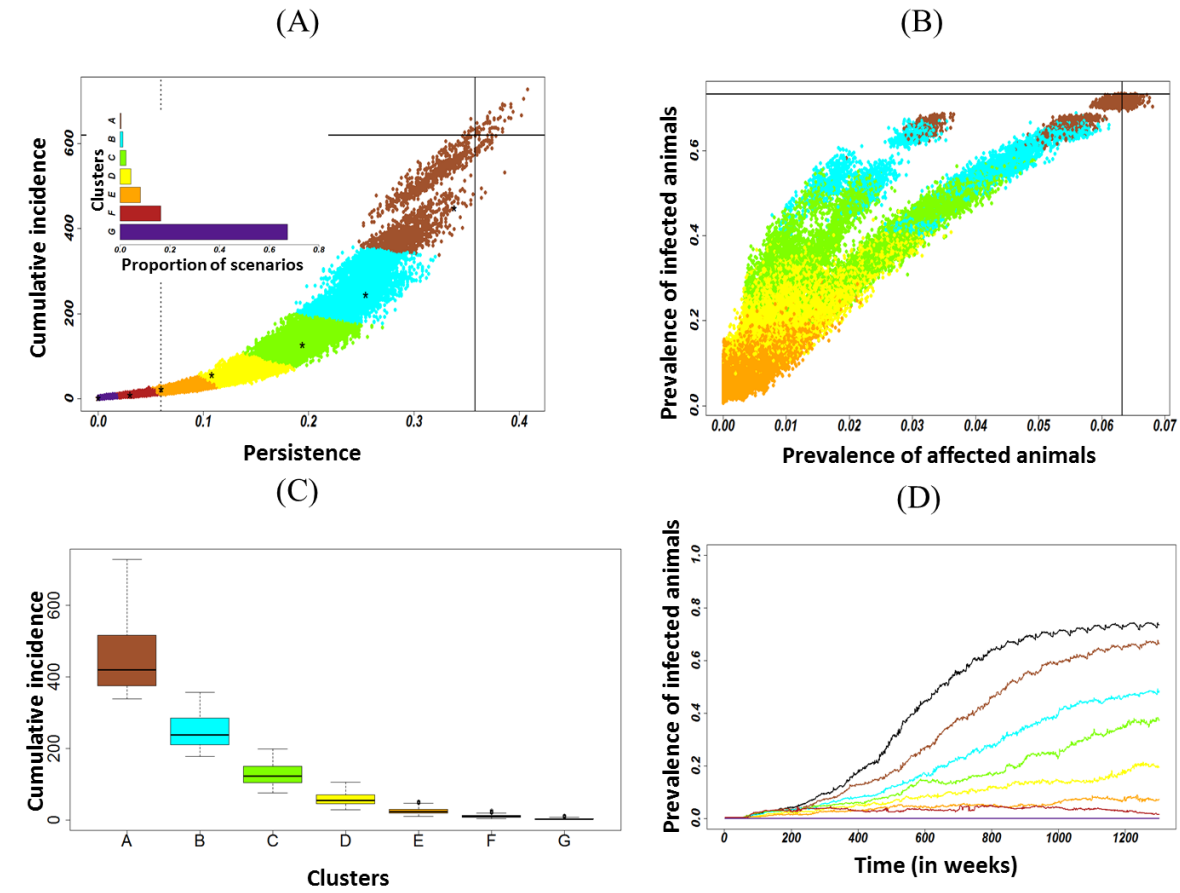

Figure 3: Model outputs 25 years after initial Map introduction for all of the multivariate scenarios: scenarios were clustered by cumulative incidence and persistence. A: cumulative incidence and persistence per scenario and proportion of scenarios per cluster; B: prevalence of infected animals and of affected animals per scenario where persistence was higher than 6%; C: boxplots of the cumulative incidence for each cluster; D: evolution over time of the prevalence of infected animals for the centroids of the seven clusters (A–G). Solid lines show output reference values, the dashed line represents the threshold of 30 runs where infection persists, asterisks indicate centroids of clusters. Total number of scenarios is 380 625.

The descriptive analysis (Figure 4) of clusters showed that the dynamics toward the most favourable clusters was mainly driven by four out of the eight traits: increasing the decay in susceptibility with age (h), lengthening the incubation period (v_L+v_{ls}), decreasing the quantity of Map shed in faeces by high shedders or clinically affected animals ($\varphi Feces_{lc}$), and increasing the required infectious dose (α). The ANOVA (Figure 5) evidenced that these four phenotypic traits contributed most to the variance of model outputs, and allowed us to rank phenotypic traits from the most to the less

influential. The increase in the decay in susceptibility with age (*h*) contributed the most to the variance of the four model outputs, while a decrease in the quantity of Map shed in faeces by high shedders and clinically affected animals ($\varphi Feces_{Ic}$), a longer incubation period (v_L+v_{Is}), and an increase in the required infectious dose (α) led to almost equivalent contributions to model output variances.

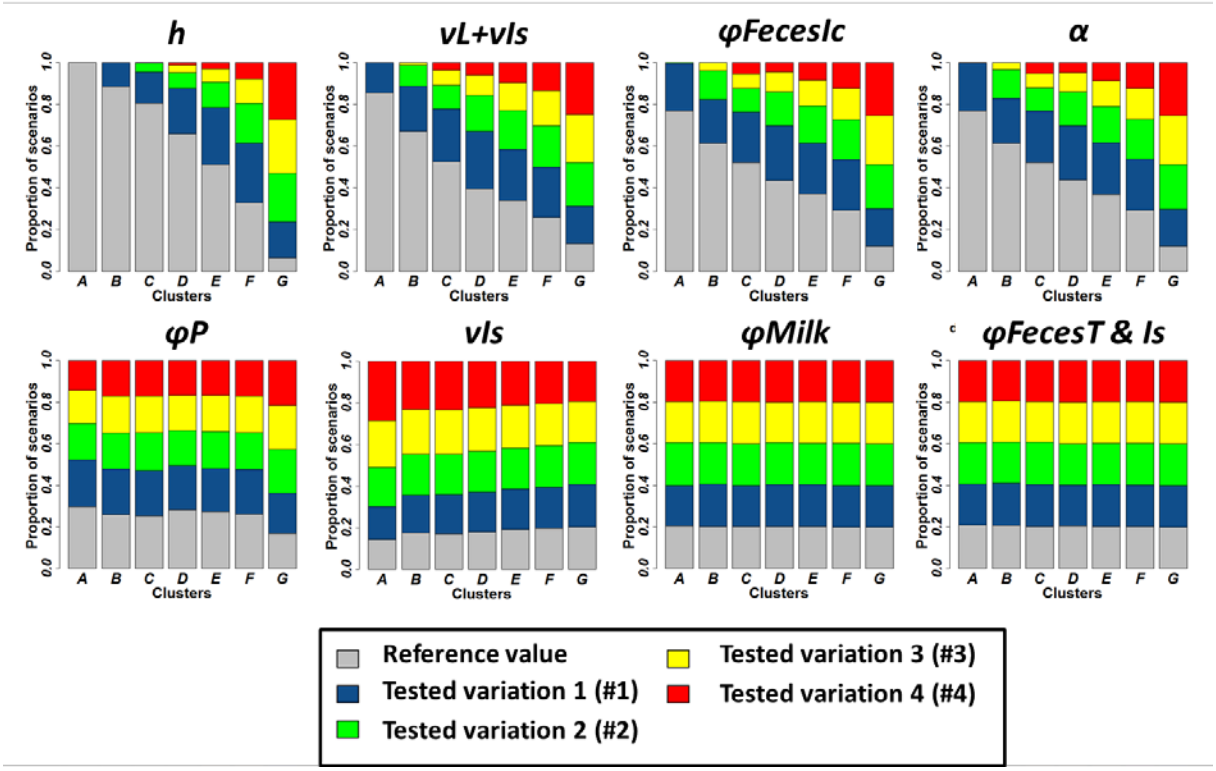

Figure 4: Distribution of scenarios among tested values for each phenotypic trait per cluster (A–G).See Table 1 for parameter definitions and values, and Figure 3 for cluster definition.

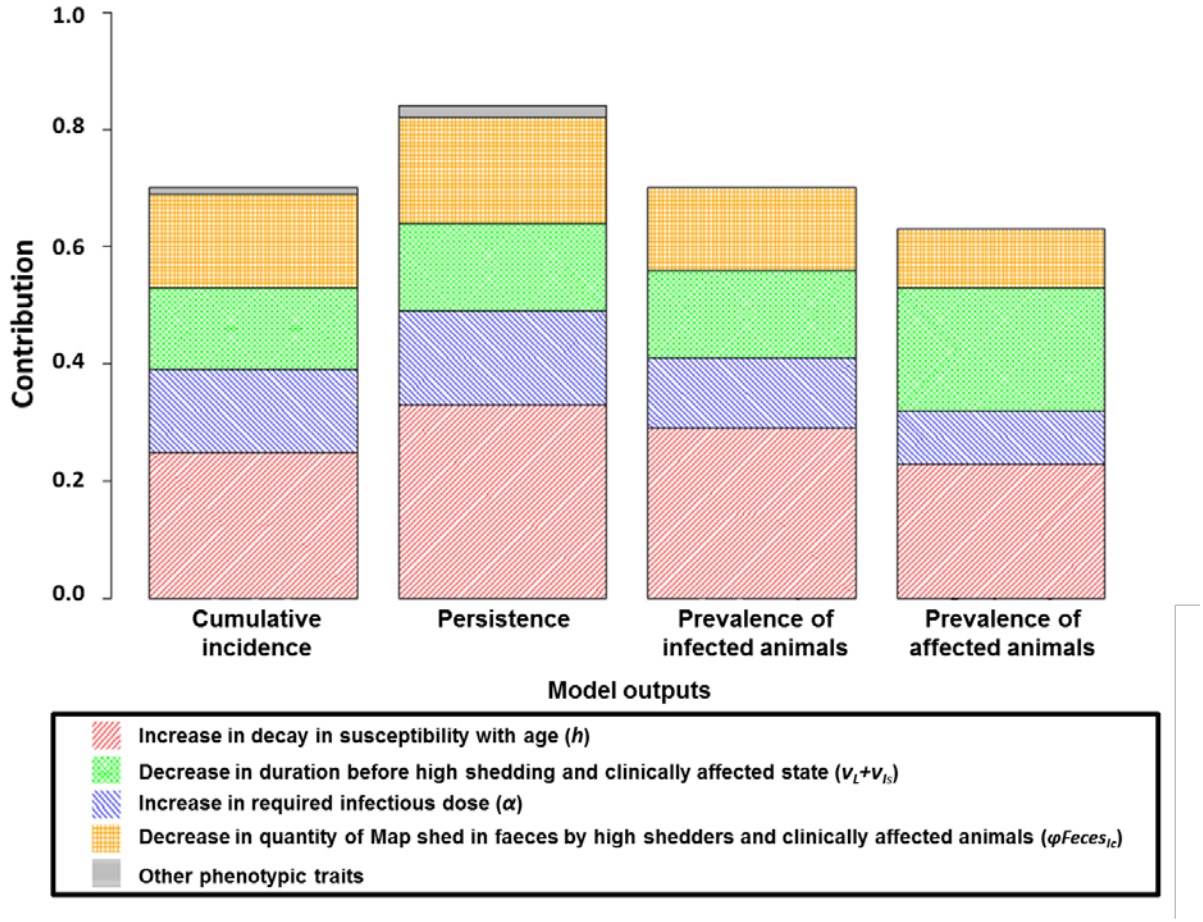

Figure 5: Total contribution of phenotypic traits to model output variance. Contribution includes the principal effect of a given factor and interaction effects in which this factor was involved divided by the number of factors involved.

Combined variations of phenotypic traits of resistance contributed to decrease Map spread dynamics. Interactions among traits showed contributions to model output variance ranging from 0.007% to up to 12% (Table 2). The interaction between increased decay in susceptibility with age (*h*) and a lengthened incubation period (v_L+v_{ls}) contributed to 12% of the variance of the prevalence of affected animals, and was also the most contributing interaction for other model outputs. In addition, *h* was involved in all of the contributing interactions, thus having both the highest principal and interaction effects.

Table 2: Contribution of the four most influential phenotypic traits to the model output variance. Contribution was estimated from the ANOVA. In bold, values above 5%

	Parameters	Cumulativeincidence	Persistence	Prevalence of infected animals	Prevalence of affected animals
Principal effect	h	**0.25**	**0.34**	**0.30**	**0.22**
	vL + vIs	**0.16**	**0.16**	**0.18**	**0.22**
	φFecesIc	**0.14**	**0.17**	**0.14**	**0.09**
	α	**0.13**	**0.17**	**0.12**	**0.08**
First order	h:vL + vIs	**0.07**	**0.05**	**0.09**	**0.12**
	h:φFecesIc	**0.06**	0.04	**0.06**	0.03
	h:α	**0.06**	0.04	**0.05**	0.03
	vL + vIs:φFecesIc	0.03	0.02	0.03	0.04
	α:vL + vIs	0.03	0.02	0.03	0.03
Second order	h:α:vL + vIs	0.03	2×10^{-3}	0.02	0.03
	h:vL + vIs:φFecesIc	0.03	10^{-3}	0.02	0.03
	α:φFecesIc	0.02	0.02	0.01	6×10^{-3}
	h:α:φFecesIc	0.02	2×10^{-4}	5×10^{-3}	10^{-3}
	α:vL + vIs:φFecesIc	8×10^{-3}	3×10^{-4}	2×10^{-3}	4×10^{-3}
Third	h:α:vL + vIs:φFecesIc	3×10^{-3}	3×10^{-3}	4×10^{-4}	7×10^{-5}
	Residuals	0.31	0.15	0.27	0.38

The combined variation in the four most influential phenotypic traits of resistance to paratuberculosis decreased the collative incidence to less than 1 newly infected animal over 25 years of simulation when set at their highest tested level. Over the 625 scenarios combining variations of the four most influential phenotypic traits, 537 scenarios resulted in decrease the cumulative incidence from 617 newly infected animals when phenotypic traits were set to their current values to 25 newly infected animals over the 25 years of simulation, and 473 scenarios allowed a cumulative incidence to be reached of 12 newly infected animals over the 25 years of simulation

(Figure 6). Fourteen of the tested scenarios allowed to achieve a good control of the disease dynamics in the herd (less than 25 newly infected animals over the 25 years of simulation) with one of the four most influential traits at its reference value and the other trait at value 1or value 2 (Figure 7).Some of the tested scenarios allowed to decrease the cumulative incidence to 25 newly infected animals over the 25 years of simulation or less were based on moderate variations of phenotypic traits (Figure 7). For example, a combined variation of the four most influential traits at their first tested level (#1) led to a cumulative incidence of 19 newly infected animals. On the other hand, improving a single trait, even a five-fold increase in the decay in susceptibility with age (#4), the most influential trait, was not sufficient to reach accumulative incidence of 25newly infected animals or less over the 25 years of simulations. Interesting examples of combined moderate variations of traits allowing decreasing the cumulative incidence were highlighted. First, halving the decay in susceptibility with age (h) (#2) together with a 50% increase in duration before entering the high shedding and clinically affected state (V_L+V_{ls})(#1), and a 34% decrease in the quantity of bacteria shed by high shedders or clinically affected animals($\phi FecesIc$)(#1) results in threshold being reached of 23 newly infected animals over the 25 years of simulation. Second, tripled three-fold increase in the decay in susceptibility with age (h) (#2) combined with a doubling of the required infectious dose (α) (#2), and a 34% decrease in the quantity of bacteria shed by high shedders or clinically affected animals($\phi Feces_{Ic}$) (#1) resulted in a cumulative incidence of 13 newly infected animals.

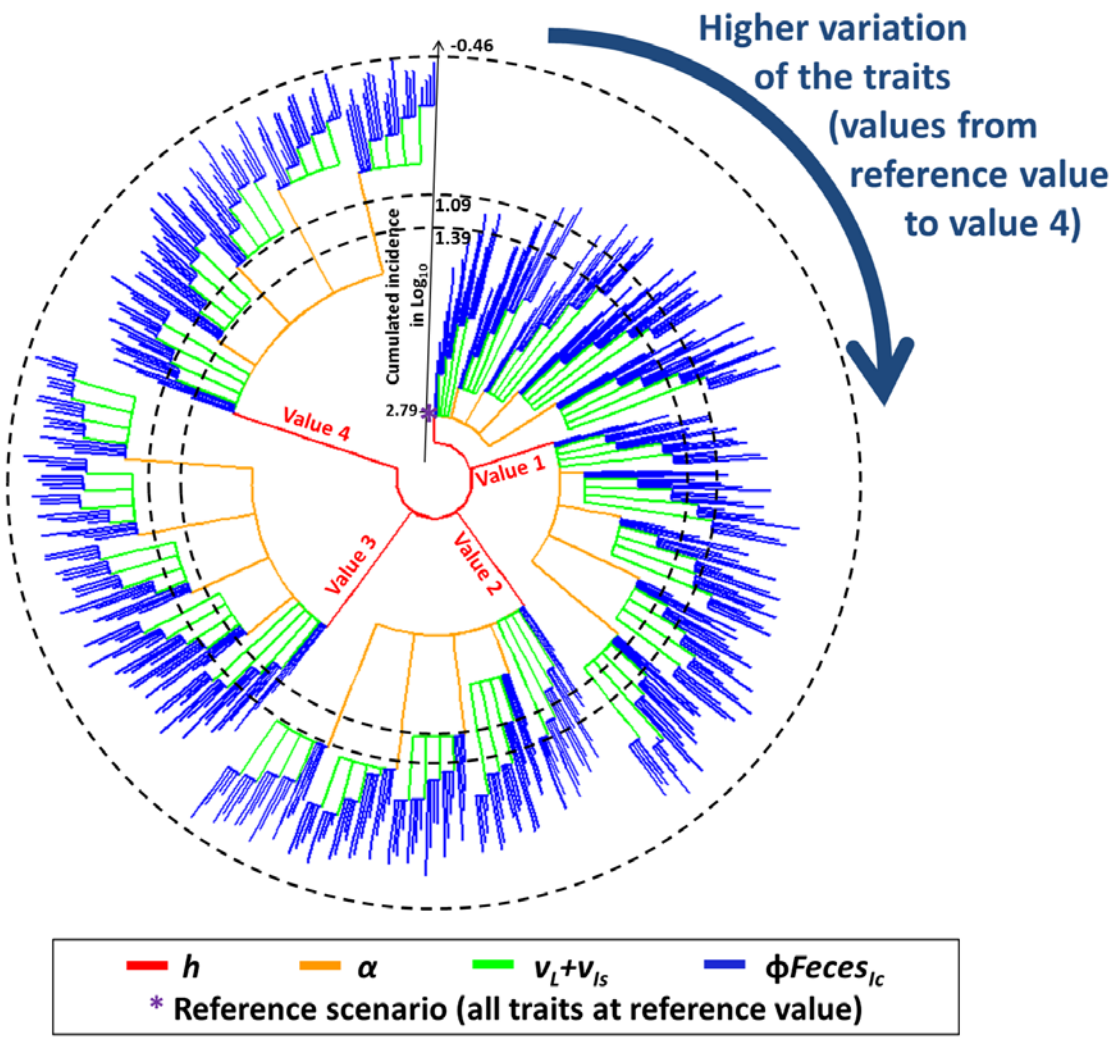

Figure 6: Effect of combined variations of the four most influential phenotypic traits on cumulative incidence. Cumulative incidence was calculated 25 years after initial Map introduction. The external dashed circle corresponds to the lowest cumulative incidence (0.35 newly infected animals) obtained among tested scenarios ($\log_{10}(0.35) = -0.46$), the internal dashed circles correspond to thresholds of 25 ($\log_{10}(25) = 1.39$) and 12 ($\log_{10}(12) = 1.09$) newly infected animals. Asterisk corresponds to the cumulative incidence ($\log_{10}(617) = 2.79$) for the scenario with current values of phenotypic traits. *h*: decay in susceptibility with age, *α*: increased required infectious dose, v_L+v_{Is}: increased duration before high shedding or clinically affected state, $\phi Feces_{Ic}$: decreased quantity of bacteria shed by high shedders or clinically affected animals. Each leaf is one scenario with branches representing variations of the four traits. Scenarios are presented by increasing level of variation in each trait successively (*h*, *α*, v_L+v_{Is}, and, $\phi Feces_I$). Tested values are given in Table 1.

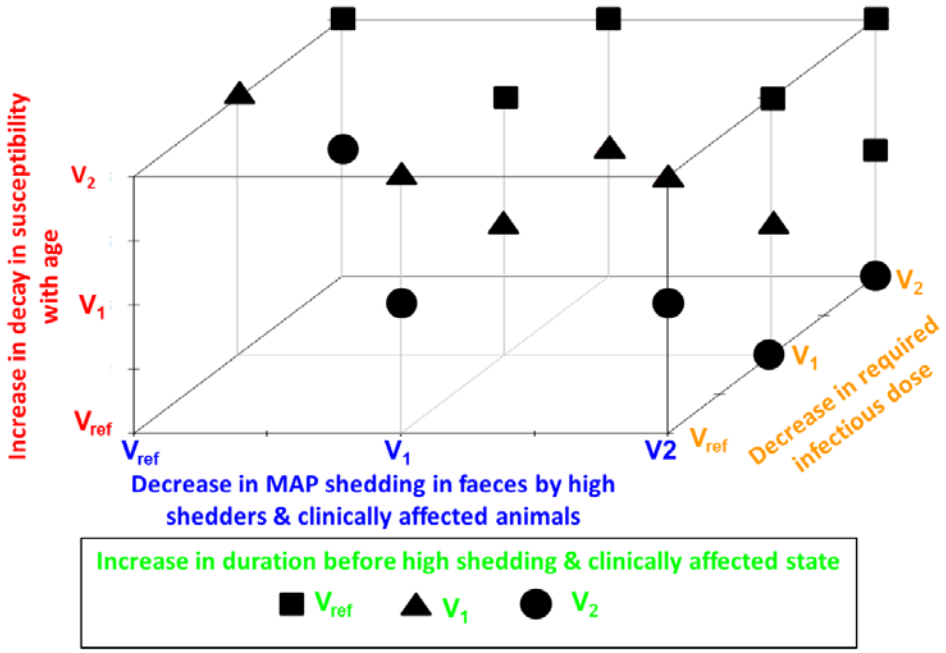

Figure 7: threshold of variation in influential parameters and combinations necessary to reach a low cumulative incidence. Squares, triangles and dots represent the threshold value for the parameter "duration before high shedding and clinically affected state" needed to reach the cumulative incidence < 25 over 25 years of simulation at the given value of the three other influential parameters (required infectious dose, Map shedding in faeces by high shedders and clinically affected animals, and decay in susceptibility). The 10 empty positions corresponds to combinations in variations where "duration before high shedding and clinically affected state" have to be more than doubled (> V2) to have a low cumulative incidence (< 25). Combinations represented here account only for threshold of variations below V2. Tested values (Vref, V1, and V2) are given in Table 1.

4. Discussion

Variations of four of 14 phenotypic traits strongly reduced Map spread within a dairy cattle herd: the decay in susceptibility with age, this being the most influential trait, the quantity of Map shed in faeces by high shedders and clinically affected animals, the duration of the incubation period, and the required infectious dose. Combining these phenotypic traits was the sole way to effectively control Map spread at the herd scale. Most tested combinations of these influential phenotypic traits allowed the cumulative incidence to be reduced to less than 25 newly infected animals over the 25 years of simulation, which was interpreted here as an infection under control. Interestingly, such a low level of cumulative incidence could not be reached when varying a single phenotypic trait.

The increase in the decay in susceptibility with age is largely related to a shorter susceptibility period. We also highlighted the required infectious dose as an influential phenotypic trait .Our results concerning these traits are in agreement with van Hulzen et al. (van Hulzen et al., 2014), who in a theoretical study also identified that an earlier resistance acquisition would be crucial when it comes to control paratuberculosis using genetic selection. However, there is nowadays no available knowledge to implement a genetic selection on these traits. These traits are not easily measurable in field conditions.

A decrease in the quantity of Map shed in faeces by high shedders and clinically affected animals, which was also identified as an influential phenotypic trait, might be achieved thanks to genetic selection. Currently, it has been shown that genetic markers could be associated with the occurrence of shedding versus no shedding at all by animals in infected herds (Kirkpatrick et al., 2011; Settles et al., 2009; Yalda Zare et al., 2014a). More precise knowledge is needed concerning our ability to select cattle that will shed less Map in faeces while in their last stage of infection.

While van Hulzen et al. [28] identified the increase in duration of the latency period as an effective phenotypic trait in controlling paratuberculosis through genetic selection, we highlighted that an increase in this latency period (this being the period between infection and the occurrence of a moderate detectable shedding) without delaying the

start of the high shedding or clinically affected state did not influence Map spread dynamics in the herd. We have shown that it will be more interesting to lengthen the incubation period, as this delays the occurrence of the high shedding or clinically affected state.

Phenotypic traits identified as influencing Map spread dynamics at the herd scale also are related to control measures currently implemented in infected herds in the field (Bastida and Juste, 2011). Therefore, a valuable interaction can be expected between routine control plans and innovative control through genetic selection.

The variation of several other traits did not influence Map spread dynamics: decrease in duration of transiently infectious state with a constant duration before moderate shedding state, decrease in quantity of Map shed in milk and colostrum irrespective of the animal infection state, decrease in quantity of Map shed in faeces by transiently infectious animals and moderate shedders, and decrease in probability of in-utero transmission irrespective of animal infection state. A decrease in duration of moderate shedding state (from 104 weeks to 60 weeks) did not influence Map spread dynamics. The range of variation modelled for this trait was lower than for other traits due to limitations inherent to the compartmental model. Nevertheless, as no effect was evidenced with a reduction of one third of that duration, we assumed that this trait was not highly influential over the simulated range.

The four traits identified as influential are well described in the literature therefore we can assume that their tested ranges of variation were realistic. We assumed extreme ranges of variation for traits for which information was missing. The other traits assessed were not influential even with such extreme, non-realistic, variations. Using a different set of variation in the investigated traits is not expected to change our conclusions concerning which traits influence Map spread within dairy cattle herds.

As our objective was to assess Map spread in herds in which phenotypic traits would have been improved, we did not account for the long time needed (van Hulzen et al., 2014) to reach such targeted levels of phenotypic traits by a potential genetic selection. On the one hand, recent studies identified several genetic markers associated with resistance (reviewed in (McSpadden et al., 2013; Pauciullo et al., 2015)), but genes and mechanisms responsible for the tested phenotypic traits are still unknown. Further genetic studies of resistance of cattle to paratuberculosis are required, especially to

identify genes and mechanisms involved in these relevant phenotypic traits to allow potential future selection of more resistant cattle. In addition, diagnostic tests currently available in the field do not allow identifying animals having the phenotypic traits identified here. Concerning future genetic selection, tests more sensitive during the early stage of the infection would be needed to distinguish infected animals from others and to better quantify the individual duration of incubation periods. On the other hand, there is a risk of a negative association between phenotypic traits of resistance to paratuberculosis and other traits of economic importance. For example, it has been shown that genetic markers associated with susceptibility to paratuberculosis could be associated to lactation persistence (Carvajal et al., 2013).

Our model represents a typical Western Europe farming system for dairy cattle herds. Demographic processes have been shown to highly influence the disease dynamics (Clara Marcé et al., 2011), and therefore, different farming systems could change the influence of the studied phenotypic traits on Map spread dynamics in the herd. We assumed a closed herd without introduction of animals from other herds. Animal exchanges between herds could reintroduce Map in free herds and thus influence disease dynamics. However, it is not expected to modify our conclusions as regards the identification of crucial phenotypic traits to better manage infected herds. Indeed, a single Map introduction can lead to infection persistence in 40% of the cases under current situation as regards phenotypic traits (Clara Marcé et al., 2011), with a huge cumulative incidence reached after 25 years if no control is applied. Animal movements are not expected to modify significantly this finding. However, the occurrence of animal movements might increase the cumulative incidence under controlled situations with improved traits.

This study highlighted four phenotypic traits of resistance of cattle to paratuberculosis influencing Map spread within a dairy herd: decay in susceptibility with age, quantity of Map shed in faeces by high shedders and clinically affected animals, duration of the incubation period, and required infectious dose. A combination of these traits strongly contributes to limit Map spread. Further genetic study should aim at better identifying cattle genes involved in these traits in order to allow their potential selection.

Chapter 4: Influence of farming systems on conventional paratuberculosis control measures

1. Introduction

Current control strategies are mainly based on two groups of measures: hygienic measures and test and cull. Hygienic measures consist in reducing exposure of susceptible animals to the bacteria by separating calves from older animals potentially shedding the bacteria. This measure is difficult to implement and maintain in herds. Test-and-cull control consists in the use of diagnostic tests to identify infected and / or shedding animals in order to cull them. Identification of infected animals is mainly limited by the characteristics of the avaible diagnostic tests. In fact sensitivity of the available tests, when defined as the ability of a test to effectively detect infected animals, is about 30%. In highly infected herds, the ability to cull a large number of positive animals is limited by the need to maintain economic stability of the farm.

Marcé et al. (2011) noticed that paratuberculosis dynamics within a dairy herd is influenced by contact structure between dams and calves. Regarding the variability in disease dynamics with regards to the contact structure between animals, other farming practices and herd specificities could influence Map spread. Dynamics of Paratuberculosis, as a transmittable disease, is expected to be influenced by the number of susceptible animals present in the herd. Proportion of susceptible animals in the herd is conditioned by the renewal rate. The replacement of animals in european dairy herds is mainly internal. Births within European herds are the major source of susceptible animals introduction. A large proportion of susceptible animals may be present during calving season in grouped calving herds. The different breeds used in European dairy production could show variable shedding of Map and influence the paratuberculosis transmission within herd. In this work, a farming system was assumed to be defined by a combination of different management specificities (culling rate, birth strategies, and grazing period), contact structures between animals, and cattle breeds. The farming system specificities expected to influence Map spread within herd.

The effectiveness of paratuberculosis control strategies is expected to be influenced by the farming systems where they are implemented. (Rossiter and Burhans, 1996) suggested that the limited adoption and success of conventional control recommendations could be explained by the fact that these recommendations don’t

take into account the unique specificities of individual farms. Regarding the different disease dynamics among the different farming systems, there could be interactions between the farming system, the herd statues with regards to paratuberculosis and the implemented control strategies. The effectiveness of genetic selection and conventional control measures on Map spread control could be improved or limited by the targeted herd specificities.

Farming systems are different even in geographically close herds. For example the contact structures, the birth strategies, the grazing period and the cattle breeds are different between western France and Ireland. It is relevant to compare paratuberculosis dynamics and to assess the effectiveness of such geographically close herds assuming that similar paratuberculosis strain are present in these two regions.

Modelling seems to be the appropriate approach to study the effectiveness of effectiveness of paratuberculosis control measures regarding the long time and cost of such study in the field. a unique model that explicitly representing the Irish farming system have been identified in published literature (Moorepark model by Shalloo et al., 2004) allowing to predict Irish herds productivity. Only one Bayesian model interesting on paratuberculosis in Irish farming conditions was published (McAloon et al., 2016). This model did not explicitly account for the farming system specificities. A French model for paratuberculosis dynamics was developed by Marcé et al., (2010)and (Beaunée et al., 2015). This model accounts for the most up to date knowledge about the disease. As a mechanistic model, it could be extended to different farming system with only slight changes.

The objective of this study was to assess the influence of the farming system on the paratuberculosis dynamics and control within a dairy herd. We compared the Map spread and effectiveness of current paratuberculosis control measures in two dairy cattle farming systems: western French and Irish ones.

2. Material and methods

2.1. The used models

We adapted an already published and well-studied stochastic and mechanistic model of Map spread within a dairy cattle herd, taking into account the specificities of the French dairy cattle farming system. This model is fully described in (Marcé et al. 2011; Beaunée et al. 2015) and in section III (additional file 1). As we aim here to assess the effect of implementing various control strategies including some targeting specific animals, we needed to clearly represent each animal present in the farm. Therefore, the existing compartmental model was adapted into an individual-based model (Camanès et al., in prep). All the mechanisms and processes of the compartmental model were kept. The model was then adapted to represent a typical Irish dairy cattle herd and associated farm management specificities.

2.2 The French and Irish farming systems

Even if France and Ireland are geographically close, the farming systems present some key differences. The French farming representation and calibration was mainly based on experts' opinions(Animal Health Services in Brittany GDS-Bretagne and scientific experts in farming systems from BIOEPAR research unit). The values of the parameters coding for the Irish farming system were estimated using the national database and European reports. Experts' opinions from Teagasc and AHI (Animal health Ireland) enabled us to develop a conceptual representation of the Irish farming system and to confirm and complete the model parameters coding for demographic processes estimated using statistics from the 2016th records of AMI (Animal Movement and Identification) database.

Conceptual differences were observed between the two farming systems. On the one hand, In Ireland, up 85% of the dairy herds are spring grouped calving herds with a large proportion (up to 85%) of births occurring from January to April (AMI, 2016).

Using AMI 2016 data, a weekly calving probability calendar was calculated. Calves are weaned at 11 weeks old. The weaned calves start grazing immediately after weaning. During the grazing period the calves share the cow pasture. Even if there is a physical separation between calves and cows, an indirect exchange of bacteria between their respective environments is possible. On the other hand, in France, calving occurs all over the year. Calves are weaned at 10 weeks old. Once weaned, calves are housed inside farm building for 16 weeks before entering the grazing pasture at 26 weeks old. In France, calves and young heifers share the same pasture when cows are grazing in a different pasture. The cattle breed in Ireland (mainly Frierson) has a smaller conformation and a lower milk yield than the French breed (mainly Holstein). Therefore, Irish cattle were assumed to shed less amount of Map through faeces and milk routes.

In both dairy cattle farming systems, renewal is mainly internal using heifers born in the farm. Herd size, maximum length of production life, and reproduction rates of animals are very similar for the two countries. We assumed that a similar number of animals are bought per herd per year in the French and the Irish farming system. Therefore, animal movements were not taken into account explicitly. The farming management specificities were conceptually represented in figure 1.

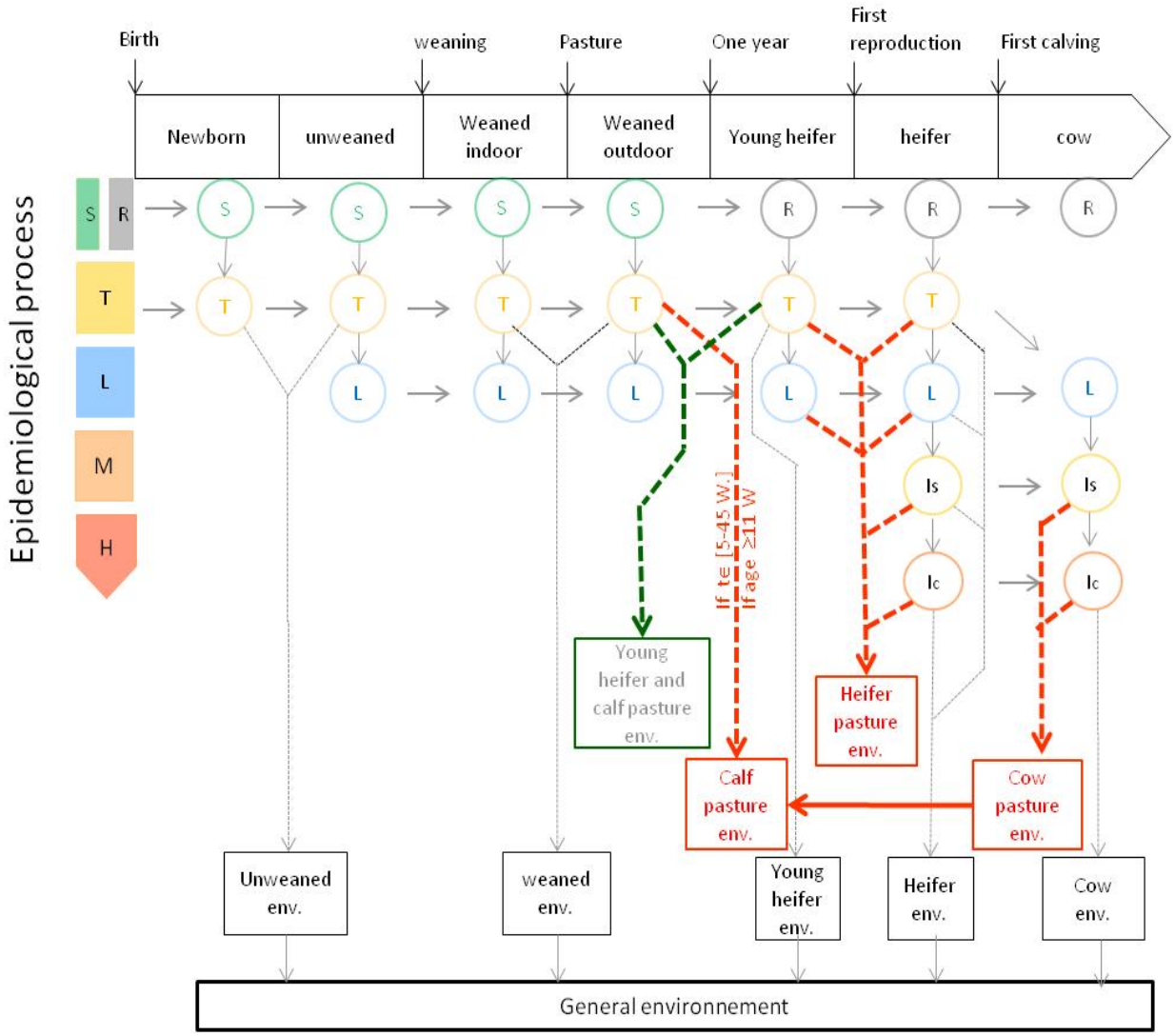

Figure 1: Conceptual representation of the Irish (orange) and French (green) model of paratuberculosis transmission and herd management. Letters corresponds to the different health states: susceptible (S), no more susceptible (R), transiently infectious (I_T), latently infected (I_L), moderately shedding (I_M), and high shedding and clinically affected (I_H). Plain arrows represent transitions between health states; dashed arrows represent animal contribution to their local environment (inside and outside of the building) and Map exchanges between environments; env.=environment.

Table 1: Parameters coding for herd management as used in the Irish and French models of Map spread within a dairy cattle herd.

Parameter	Irish context	French context	Unit	Definition	Ref
sexRatio	0.5	0.5	-	Sex ratio	1;2
σB	0.06	0.07	anim/wk	Death rate of calves at birth	1
σm	0; 0; 0.206; 0,206; 0.206;		anim/wk	Rate of selling for male calves (0 to 5 wk old)	2
σC1	0.018	0.015	anim/wk	Death rate of female calves (wks 1 & 2)(0.0-1.0)	1
σC2	0.0025	0.0035	anim/wk	Death rate of female calves (3 wk to weaning)	1
σC3	0.00024	0.00019	anim/wk	Death rate of heifers (from weaning to 1st AI)	1
σAi	0.0038; 0.0038; 0.004; 0.005; 0.0086	0.0056; 0.0051; 0.0066; 0.0066; 0.0184	Anim/wk	Annual rate of cow parity at 1, 2, 3, 4 et >5 calving	1
W	11	10	Week	Age at weaning	2
AgeHeifer	65	91	Week	Age at first Articial insemination	2
AgeGrazing	11	26	Week	Age at first grazing	2
y	52	52	week	Age at entering young heifer group (no more susceptible)	2
cal	104	130	week	Age at first calving	1;2
cci	53	56.3	week	Calving to calvinginterval	1;2
NbStageLact	5	5	year	Max number of milking years	2
b	5	5	L/day	Qty of colostrum given to a calf (3 first days of life)	
d	7	7	L/day	Qty of milk given to a calf (after 3 days old)	
prop	85	85	Pourcent of all cows	proportion of milkingcows	2;3
ε	15	25	L/d/anim	Qty of colostrum or milk produced	3;4
f1	0.4	0.5	Kg/day	Qty of faeces produced by an unweaned calf	1;2
f2	4.1	5.5	Kg/day	Qty of faeces produced by a weaned calf	1;2
fY	7.5	10	Kg/day	Qty of faeces produced by a heifer	1;2
fA	22.5	30	Kg/day	Qty of faeces produced by a cow	1;2
Graz	[5-45]	[14 - 46]	-	Grazing period (1 = first month of the year)	2
Kc	82	82	Animal	number max of adult cows	1;2

References used for the Irish context:

1: AIM database 2016; 2: expert opinion; 3: ICBF dairy calving statistics 2016; 4: IFA 2015 & milk market observatory 2015.

Anim/wk:animal per week ;L/day: litter per day; L/d/anim: litter per day and per animal; Kg/day: kilogram per day.

2.3 Initial conditions

First, we were interested in Map infection dynamics within a dairy cattle herd in the two farming systems. We assumed a unique introduction of an infected heifer into a fully naive herd.

Second, to assess the effectiveness of various control strategies, we assumed that the herd was initially infected. Based on experts' opinions both in Ireland and France, we assumed two initial herd statuses in terms of true prevalence of infection in cows: moderately infected herds (M) from 0 to 7%, and highly infected herds (H) from 7% to 21% of infected adults. Preliminary simulations were made to reach these targeted prevalences. A moderately shedding heifer was introduced into a naive herd and the infection dynamics was monitored over 15 years of simulations and 5000 stochastic repetitions. For each step time among all the runs, the prevalence and the corresponding herd structure as regards animal ages and health states were reached. One thousand initial herd composition representing the prevalence for each of the initial herd statuses (A or B respectively moderately or highly infected herd) were randomly picked from the generated data. One thousand stochastic repetitions were performed for simulated scenario. The simulation protocol adopted to generate initial condition is summarised in figure 2.

2.4 Simulation protocol and output analysis

We focused on four model outputs to compare the infection dynamics: Map persistence, the mean cumulated incidence, the median prevalence of infected animals, and the median prevalence of high shedding and clinically affected animals. The two latter were calculated on runs were the disease persisted. The four outputs were monitored at each time step among simulated scenarios. For each simulated scenario, 1000 stochastic runs were performed in order to have accurate outputs. The whole simulation scheme is presented in figure 3.

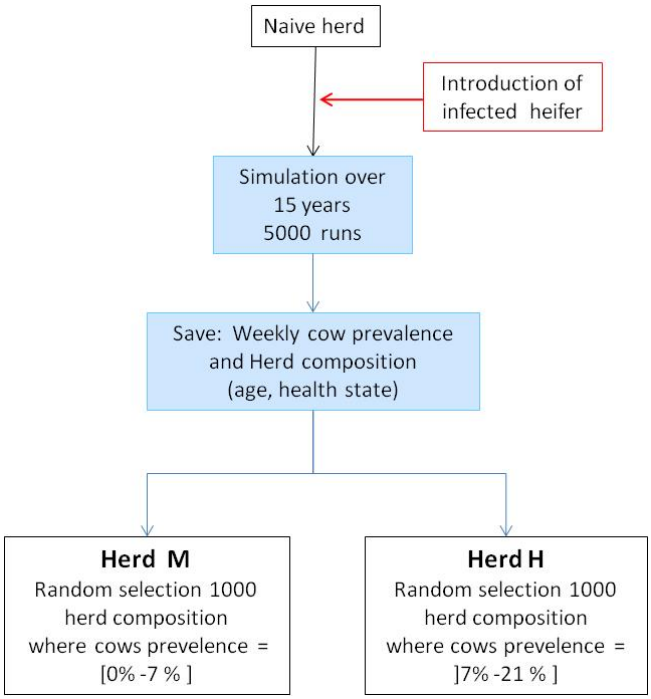

Figure 2: Simulation protocol to generate initial conditions for herds with moderate (M) or high (H) prevalence

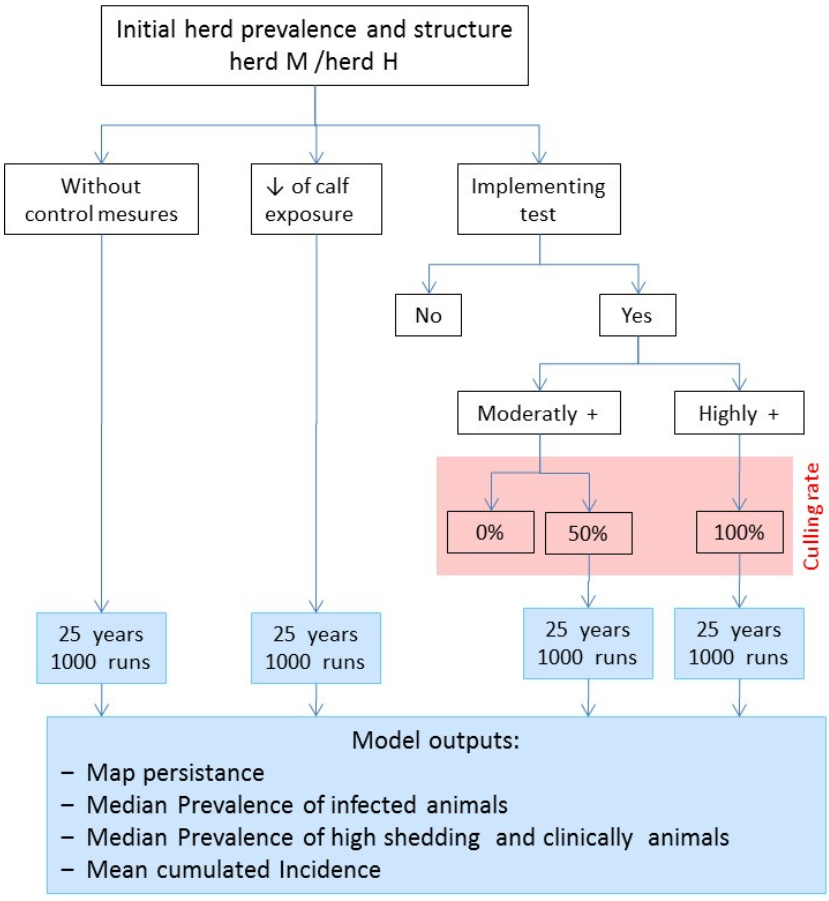

Figure 3: Possible options of control measures investigated. Moderately +: moderately positive answer to diagnostic test, and highly +: highly positive answer to diagnostic test.

In addition to a reference scenario without any control measures, we studied the effectiveness of implementing different control strategies. The purpose was to assess the influence of the farming system on the effectiveness of the control strategies. Two measures were tested: (i) the reduction of calf exposure to the general environment, and (ii) test-and-cull. We assumed that diagnostic tests could provide 3 responses: (i) negative for non-infected or false negative infected animals, (ii) moderately positive for true positive moderately shedding animals, and (iii) highly positive for high shedding and clinically affected animals. Test-and-cull measures were driven by three parameters: (i) the test frequency, (ii) the delay before culling positive animals, and (iii) the proportion of positive animals culled. A complete factorial design was used to test for all of the combinations of control measures. Each scenario was defined by a combination of control measures and initial herd prevalence. The tested control measures and their corresponding values are listed in table 2.

Table2: initial herd prevalence, control measures, and their corresponding tested values

Parameters	**Value(s)**
Initial prevalence within the herd	
Moderate prevalence (M)	$M \in [0, 0.07]$
High prevalence (H)	$H \in]0.07, 0.21]$
Factor of calves exposure reduction: decrease in unweaned and weaned calvesexposure to the general environment when inside the building (in % of present Map)	100; 65; 50
Test frequency (in weeks)	No test-and-cull; 104; 52
If implementing diagnostic tests	
Culling delay of animals detected as	
moderately positive	26 weeks
highly positive	13 weeks
Culling proportion (in %) of animals detected as	
moderately positive	0; 50
highly positive	100

First, we interested in a no control scenario assumed to be the reference one. We compared Map infection dynamics in a naïve herd where a moderately shedding heifer was introduced and monitored the four previously described model outputs for 25 years without implementing any control strategies in both countries. The purpose was to describe the influence of the farming system on Map spread. Then, we assessed the influence of the farming system on the effectiveness of control options through variations in the four model outputs representing Map infection dynamics after 25 years of control. We focused on the relative variations of the four model outputs:

$$Absolute\ variation$$
$$= value\ of\ output\ in\ no\ control\ scenario - value\ of\ output\ in\ control\ scenario$$

$$Relative\ variation\ = \frac{absolute\ variation}{value\ of\ the\ output\ in\ the\ no\ control\ scenario}$$

We compared the influence of the farming system and initial prevalence in the herd on the effectiveness of the implemented control measure as expressed by the corresponding absolute and relative variations of the four previously defined model outputs.

3. Results

Map spread was lower in the Irish farming system than in French one (figure 4). At 25 years after the introduction of a moderately shedding heifer in a naïve French herd, the median prevalence of infected animals, the median prevalence of high shedding and clinically affected animals, the persistence and the mean cumulated incidence reached respectively 0.92, 0.46, 0.31, and 369.32. In an Irish herd, the same initial conditions produced a 0.2 prevalence of infected animals, up to 0.11 as prevalence of high shedding and clinically affected animals, persistence of less than 0.13 ,and up 49 newly infected animals as cumulated incidence (figure 5).

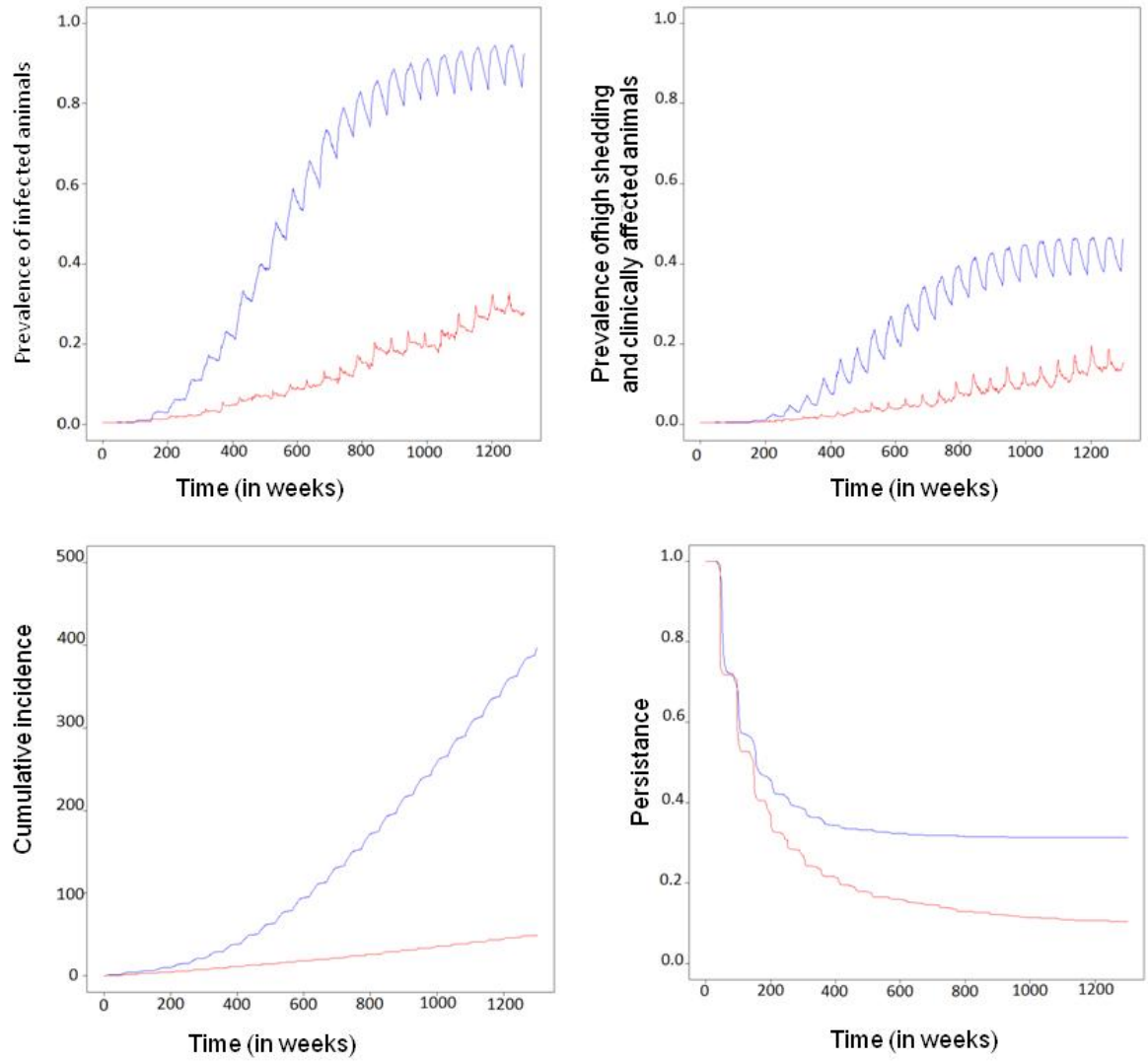

Figure 4: Paratuberculosis dynamics in two west European farming systems: the French (blue) and the Irish (red). The disease dynamics was monitored 1300 weeks (25 years) after initial introduction of a moderately shedding animal in a naïve herds and without any control measure.

The control measures were more effective in the Irish herd than in the French herd for all of the tested control measures, irrespective of the initial prevalence herd (M or H) (Figure 6, 7 and 8). For example, decreasing by 35% calf exposure to Map present in the environment in a moderately infected French herd (initial prevalence at A level) allowed to decrease by 5-22% only the prevalence of infected animals, the prevalence of high shedding and clinically affected animals, and the persistence at 25 years after the implementation of the control measure. Whereas, in an Irish herd a 30-73% decrease was achieved.

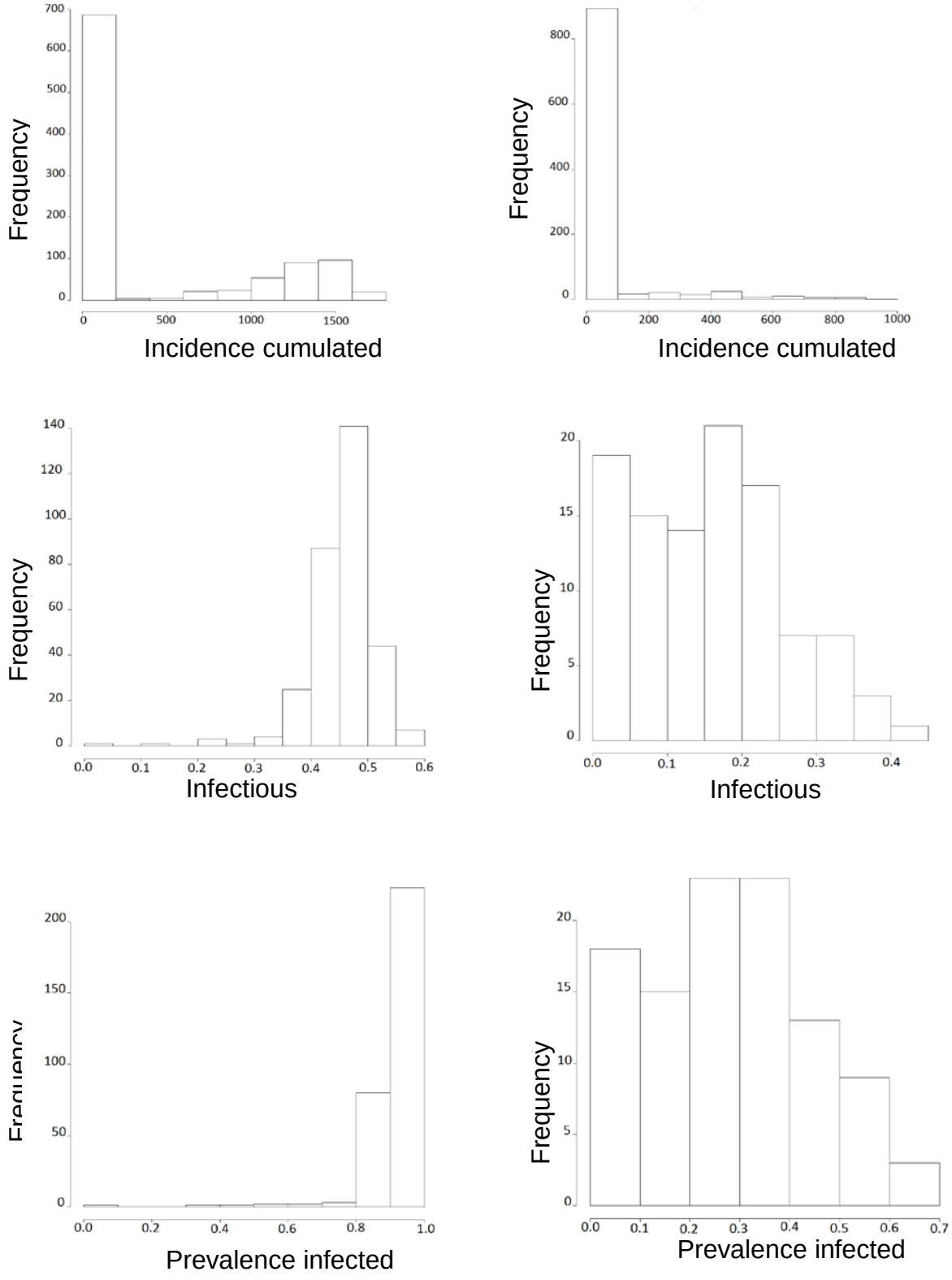

Figure 5: distribution of three of the model outputs at 25 years after the introduction of Map in the herd in the Irish (right) and the French (left) farming systems.

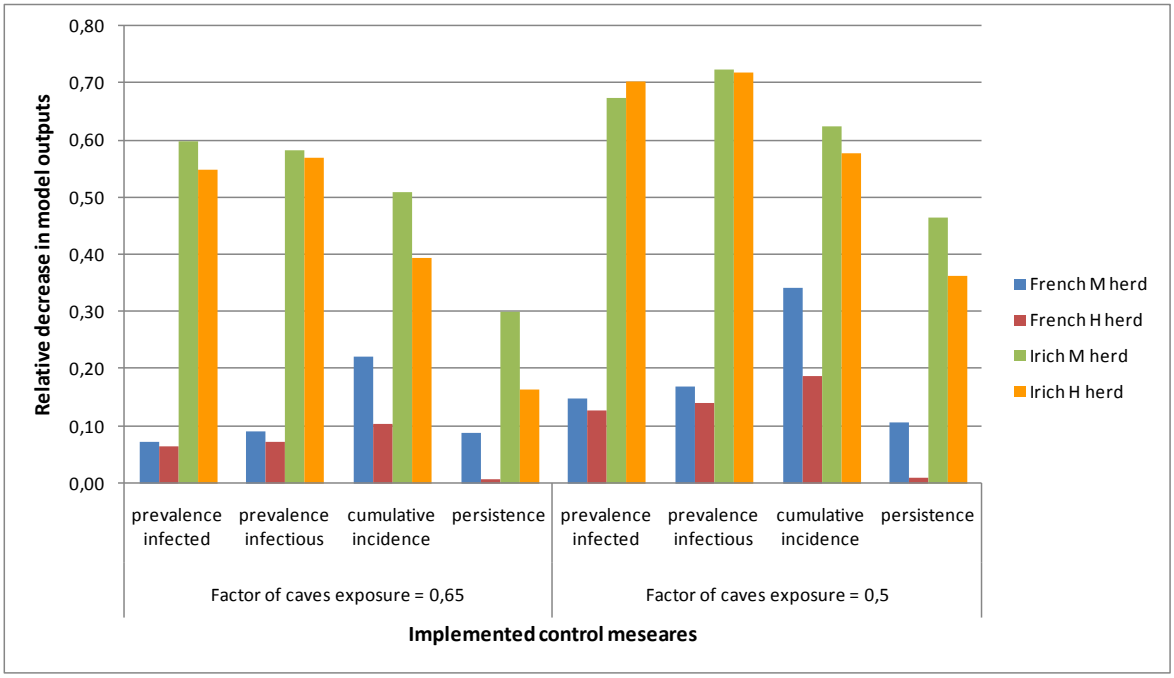

Figure 6: Relative decrease in the four model outputs when implementing a decrease in calf exposure to Map present in the environment in a moderately (M) or a highly (H) infected herd both in Ireland and in France

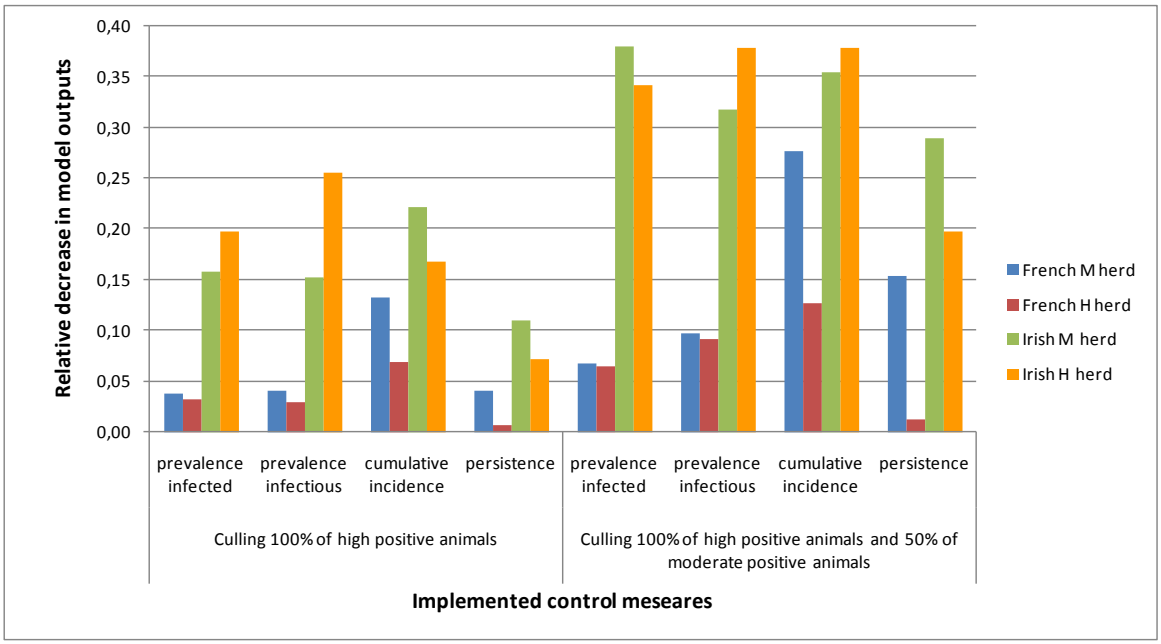

Figure 7: Relative decrease in the four model outputs when implementing an every year test and cull measure in a moderately (M) or a highly (H) infected herd both in Ireland and in France

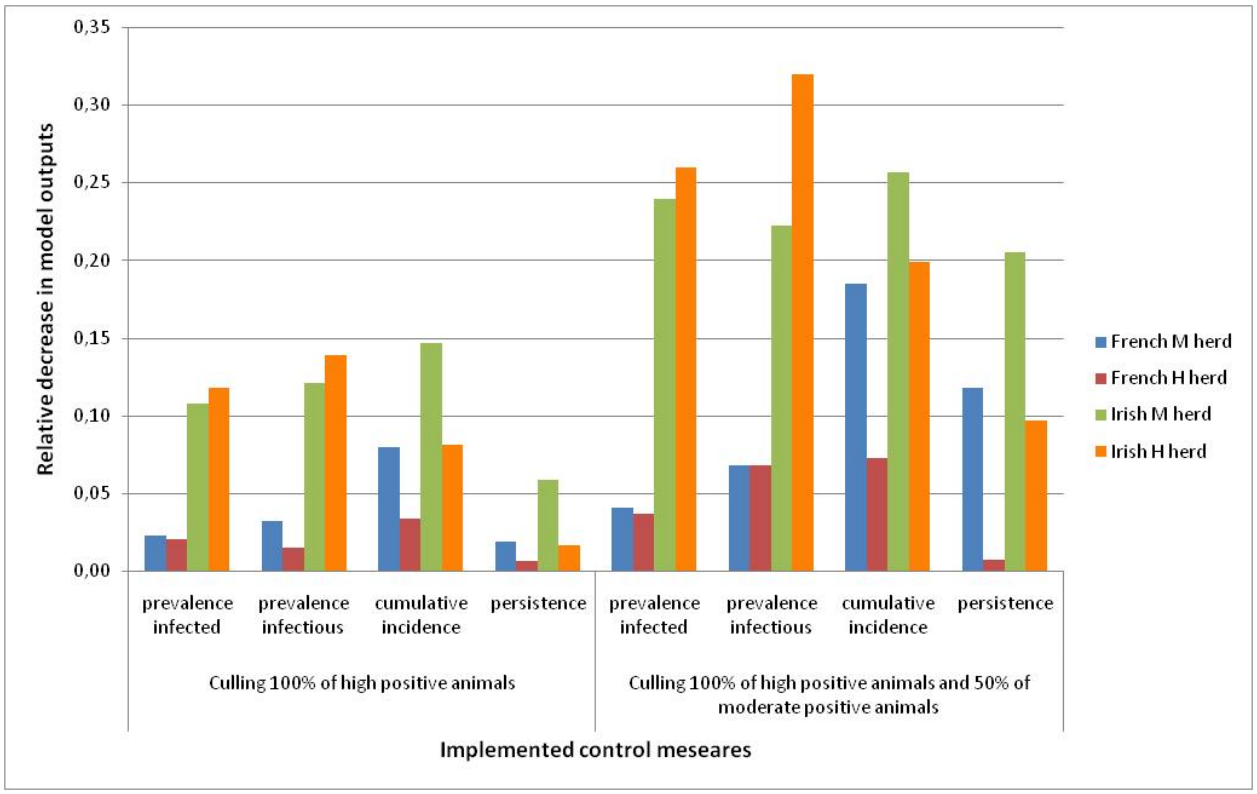

Figure 8: Relative decrease in the four model outputs when implementing an every 2 years test and cull measure in a moderately (M) or a highly (H) infected herd both in Ireland and in France

The efficacy of tested control measures was different regarding the initial herd prevalence and the farming system (figure 6, 7 and 8). In France, it was higher in a moderately infected herd than in a highly infected one. The opposite, the same control measure showed a higher effectiveness in controlling the disease in a highly infected herd than in a moderately infected one in Irish. For example, culling only highly infected animals within 13 weeks after detection using an annual testing strategy allowed decrease in the prevalence of infected animals, the prevalence of high shedding and clinically affected animals, and the persistence at 25 years after the implementation of the test and cull measure in France by 4 to 13%% in a moderately

infected herd and less than 7% in a highly infected herd. The same control measure implemented in Ireland allowed decrease of outputs by 11 to 21% in a moderately infected herd against 16 to up to 25% in a highly infected herd.

As expected, we confirmed that in both farming systems, effectiveness of control measures is positively correlated to the increasing efforts in implemented measures. The most effective control strategy combined the decrease in calves exposure by 50% (factor of calves exposure = 50%) and the culling of all highly positive animals and 50% of the moderately positive ones (figure 9). This measure allowed to decrease all model outputs by 4% to 58% and 68% to 83% respectively in French herd and Irish herd. The most effective control strategy was the same irrespective to the farming system and initial within herd prevalence in the herd where it was implemented.

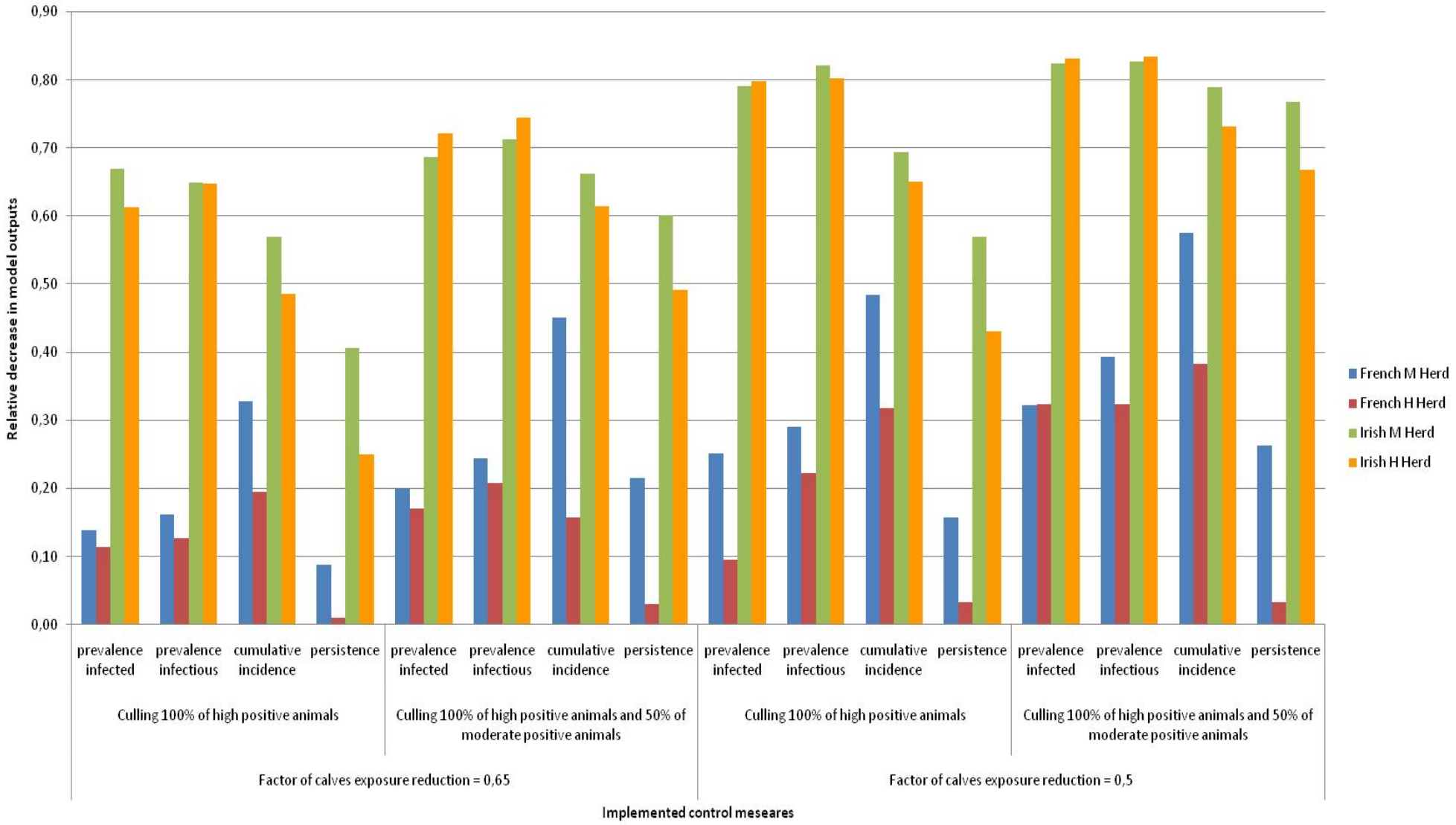

Figure 9: Relative decrease in the four model outputs when implementing combining measures in moderately (M) or a highly (H) infected herd both in Ireland and in France

4. Discussion

We highlighted that paratuberculosis dynamics within herd is influenced by the farming system. Differences in contact structures, renewal rates, birth strategies and cattle breeds induced a lower spread of Map in Irish herds than in western French ones. The herd structure was evidenced by (Marcé et al., 2011) to influence paratuberculosis dynamics. Further investigations are needed to quantify the effect of each of the farming systems specificities on Map spread within herd.

We noticed that the efficacy of paratuberculosis control measures is influenced by the initial prevalence and the farming system in herds where they are implemented. all the tested control strategies were more effective in moderately infected than in highly infected herds in France. The efficacy of a same control measure was different with regards to the initial herd status regarding paratuberculosis in both farming systems. The influence of the initial herd prevalence on the control measures effectiveness was described by (Kudahl et al., 2008).The tested control measures were more effective in Irish than in French herds. These findings suggest that the expectations about paratuberculosis control measures efficacy have to take into account the farming system specificities and the herd status with regards to the prevalence of the disease. A sensitivity analysis would allow to quantify the influence of the farming system specificities and the initial herd prevalence on the model outputs. Identifying factors influencing the most the disease dynamics and the efficacy of conventional control measure is expected to allow extending these findings to other farming systems.

The developed Irish model was calibrated using data from AMI database statistics and experts opinion. This calibration makes the model realistic. The model has to be validated by comparing the model outputs to field paratuberculosis data. However, the prevalence estimated by this model was similar to findings from Good et al. (2009) that estimate true within herd prevalence to range from 0.9 to 14% in Irish dairy herds.

In both French and Irish model we assumed that there was no introduction of animals from outside the herd. (Beaunée et al., 2015)evidenced that animal introducing only three animals per year induce a 50% probability of introducing Map in Britany. Accounting for the possible introduction of animal from other herds in our models

(French and Irish) would increase the disease dynamics but is not expected to affect our findings about the influence of the farming systems and initial herd prevalence on Map spread and control measures efficacy.

The effectiveness of the control measures was increased by increasing the control effort for both Irish and French farming system and both highly and moderately infected herds. The control strategy combining decrease in calves exposure to Map and test and cull of 100% of highly positive animals and 50% of moderately positive animals, was the most effective strategy irrespective to the farming system or the initial prevalence within the herd where it was implemented. This finding suggests that this measure could be adapted in the French and Irish herds with the highest expectation regarding its effectiveness on paratuberculosis control. Further assessment of the influence of other farming systems on the effectiveness of control strategies are needed to investigate if the highest effective control measure is the same in any farming system and within herd prevalence

Chapter 5: Efficacy of genomic selection of cattle resistance to Map exposure

1. Introduction

Genomic selection of resistant animals in response to Map exposure is questioned as an innovative and complementary control measure to decrease Map prevalence in infected herds and prevent its spread in free herds. First, current control strategies of paratuberculosis in dairy herds mainly aim to limit the exposure of susceptible animals and to decrease the contamination level of the herd environment. These measures are difficult to implement in the field and are not effective enough to reach a good control of the disease. In addition, the farming system influences the effectiveness of these control strategies (see section IV). Therefore, they have to be adapted with regards to farm and territorial specificities, leading to complexify the collective level of disease management. Having complementary control options becomes crucial. Second, genetic studies evidenced the existence of a heritable resistance to paratuberculosis in cattle, suggesting a potential interest of selecting for paratuberculosis resistance as an innovative control measure. We studied (see section III) the influence of varying phenotypic traits of resistance to paratuberculosis on Map spread. We highlighted that Map spread dynamics within a dairy herd is strongly influenced by variation in 4 phenotypic traits:(i) decay in susceptibility with age (μ), (ii) quantity of Map shed in faeces by high shedders and clinically affected animals ($\varphi fecesIc$), (iii) duration of the incubation period (V_{L+Is}),and (iv)required infectious dose to be infected (ID)and that a good control of paratuberculosis could be achieved by combined variations of these four traits (Ben Romdhane et al., 2017).

Two approaches are mainly used to achieve long term changes in selection of phenotypic traits in the domestic ruminant populations: genetic selection and genomic selection. On the one hand, genetic selection estimates the breeding value of an animal based on its own phenotype or the phenotypes of its relatives. On the other hand, in genomic selection, the breeding value of an animal is estimated using its genome. Based on a reference population, an association between genome parts and the targeted phenotype is established. Then, knowing the genome of a given animal, the identified association is used to estimate its breeding value.

The genetic progress from selection depends on four parameters: the genetic variability of the selected phenotypic traits, the selection intensity, the accuracy of

genomic evaluation, and the generation interval (Boichard et al., 2016). The last three parameters are influenced by the selection approach adopted. The genetic selection approach needs to observe and measure the phenotype of an animal or its relatives to estimate its breeding value. As a result, this approach has a long generation interval in ruminants, which in addition is increased for rare and barely observable phenotypes such as disease resistance (Bishop and Woolliams, 2014). In genomic selection the breeding value can be estimated as soon as the animal is genotyped. This genome mapping can be made in the early days of life or even before birth. Therefore, the generation interval becomes very short. As much the use of genomic tools for genetic selection of productivity phenotypes in cattle will increase, as much the cost of such tools will decrease. Therefore, more animals are expected to be genotyped in future years. The number of genotyped animals that could be candidate for selection and integrated in the reference population directly influences both the selection intensity and the accuracy of genomic evaluation of the selected phenotype. Increasing the number of selection candidates will allow to increase the selection intensity. As more animals will be genotyped, knowing their phenotypes will increase the accuracy of the genomic evaluation and improve the identification of genes responsible for the targeted phenotype. Therefore, genomic selection is expected to provide a better genetic gain than other selection approaches and this gain is expected to increase among years of selection (Boichard et al., 2016).

Concerning more specifically PTB, using genetic selection as a single measure has been shown to require hundreds of years to improve resistance at a population level. For example, Van hulzen et al (2014) evidenced that from 147 to 702 years are needed to eradicate PTB from an infected dairy herd using genetic selection targeting a single trait of resistance among 3 possible ones. To decrease the time needed to control paratuberculosis, other selection approaches have to be assessed such as targeting alternative phenotypic traits, targeting several traits simultaneously, and using genomic selection involving both bulls and dams to shorten selection time needed to control the disease. Furthermore, current genomic studies identified quantitative trait loci (QTL) associated with resistance to paratuberculosis in cattle(Sanchez et al., 2016). QTL are sections of the genome responsible for a part of the phenotype. The paratuberculosis resistance was associated to binary and summarized traits: answer to a diagnostic test, shedding, or presence of clinical signs of infection (Alpay et al., 2014; Kirkpatrick

et al., 2011; Purdie et al., 2011; Sanchez et al., 2016; van Hulzen et al., 2012; Zanella et al., 2011). Nevertheless, current knowledge does not allow to establish a quantitative link between the identified QTL and the phenotypic traits behind the bovine resistance to paratuberculosis. In addition the time needed to control PTB at herd scale using genomic selection is not known.

Genomic selection could be performed in both dam and sires. Using genetic selection,van Hulzen et al. (2014) highlighted, in a modelling study that the time needed to eradicate paratuberculosis using dam selection ranges from 379 to 702 years. In their study, sire selection eradicated the disease faster than the latter (from 147 to 223 years). For genomic selection, equivalent findings are expected on the effectiveness of selection for resistant animals on paratuberculosis control but with faster phenotypic progress. The simultaneous selection on dam and sire could also be envisaged, fastening even more the selection.

Our objective in this section was to assess the time needed to achieve a good control of paratuberculosis at herd scale using only genomic selection. We focused on the influence of parameters associated to selection, notably heritability (h^2), index precision, and the sire index evolution among generations of selection. Accounting for genetic variance of selected phenotypic traits from literature, we assumed selection is able to improve the phenotypic traits identified previously as key parameters in PTB control at herd scale (section III).

2. Materials and methods

2.1 The genomic selection model

We developed a genomic selection model that represents the simultaneous selection of the four previously cited phenotypic traits of resistance to bovine paratuberculosis. We focused in a first attempt on sire selection as it was evidenced to have the best cost-efficacy result on genetic improvement within a population comparing to dam only or simultaneous dam and sire selection. The evolution of the traits was monitored per trait at each generation of animals.

2.2 First round of selection

We assumed a population of 1000 sires was available for reproduction. Sire breeding value was defined using breeding indexes. Each year, 10 animals were randomly picked from 5% of the sire population presenting the best breeding indexes and were used for reproduction in the herd. The initial distribution of sire breeding indexes was randomly generated:

$$Index \sim N(0, R^2);\ \text{with} R^2 \text{the breeding index precision.} \qquad (1)$$

For each new born, a bull was picked from these 10 elite sires. A composite genetic value ($GV_{composite}$) of the latter was calculatedas:

$$GV_{composite} = index\ + \mathcal{N}(0{,}1 - R^2) \qquad (2)$$

The composite genetic value was then decomposed into genetic values for each trait targeted by the selection:

$$GV_{trait_i} = GV_{composite} \times \alpha_{trait\ i} + \mathcal{N}(0{,}1 - {\alpha_{trait\ i}}^2) \qquad (3)$$

We assumed a correlation (GV_{trait_i}) between the composite genetic value and the genetic value for phenotypic trait i. On the one hand, the decay in susceptibility with age, the duration of the incubation period, and the required infectious dose to be infected increase for more resistant animals. Therefore, we accounted for a positive correlation between their genetic values and the composite genetic value. On the other hand, the more an animal is resistant to paratuberculosis the less it sheds bacteria in the faeces. Therefore, a negative correlation between the composite genetic value and the genetic value for the amount of bacteria shed in faeces by a high shedder and clinically affected animal was assumed.

We assumed a herd of 100 cows which is representative of western European dairy herds. The genetic value of dams for each trait of resistance to paratuberculosis was calculated from randomly generated composite genetic values ($GV^{Dam}_{composite}$) using equation (3).

$$GV^{Dam}_{composite} \sim \mathcal{N}(0{,}1) \qquad (4)$$

The genetic value of a calf for trait i was calculated from his dam and sire genetic values for the same trait:

$$GV_{trait_i}^{calf} = \frac{GV_{trait_i}^{sire} + GV_{trait_i}^{dam}}{2} + meiosis\ random\ events \quad (5)$$

With: $meiosis\ random\ events \sim \mathcal{N}\left(0, \frac{1}{2} genetic\ variation\ of\ trait\ i\right) \quad (6)$

And $genetic\ variation\ of\ trait\ i\ = h^2 \times phenotypic\ variance\ of\ trait\ i \quad (7)$

The genetic variance of trait i depends on the heritability (h^2) and the phenotypic variance of the trait. For each trait of resistance to paratuberculosis, the literature was explored to define its distribution among animals (detailed in section II). The minimum, maximum, and most likely values were used to build a theoretical beta pert distribution for each trait. Then, the generated distributions were approximated by log normal distributions. The variance of the log normal distribution of trait $i$was used to calculate the genetic variance for this trait. The distributions of values and the phenotypic variance for each trait are summarised in table 1.

The calf genetic information for trait i was grouped in an “Abstract” genetic value ($Abstract\ GV_{traiti}$):

$$Abstract\ GV_{trait_i} = GV_{trait}^{calf} + residual\ genetic\ value\ of\ trait_i \quad (8)$$

With

$$the\ residual\ genetic\ value\ of\ trait_i = \mathcal{N}(0, (1 - h^2 \times\ phenotypic\ variance\ of\ trait_i) \quad (9)$$

Table 1: Distribution and variance of the selected phenotypic traits of resistance to paratuberculosis

Phenotypic trait	Minimum and maximum value	Most likely value	Parameters distribution [Min ; Mode ; Max]	Parameters of the Log normal distribution	reference
φfecesIc (quantity of Map shed in faeces by a high shedder and clinicallyaffected animal) (expressed in % of the quantity of Map shed in a kg of faeces by a non-resistant animal)	Quantity of bacteria shed by a high shedder and clinically affected animal = $[10^8 ; 10^{15}]$ → *φfecesIc*= $[10^{-7}; 1]$	Quantity of bacteria shed by a high shedder and clinically affected animal = 10^{10} → *φfecesIc*=10^{-5}	$[10^8;10^{10};10^{15}]$ → *φfecesIc*= $[10^{-7} ;10^{-5} ;1]$	μ=2.322 σ=1.210	(1) (2)
ID (required infectious dose of Map in CFU)	$[10^3 ;10^{12}]$	10^6	$[10^3 ;10^6 ;10^{12}]$	μ=25.347 σ=1.209	(3) (4)
μ *(coefficient of exponential susceptibility decay with age)*	Susceptibility period (in weeks) : [12 ;520] →μ : [0.04 ; 0.5]	52 weeks →μ = 0.1	[0.04; 0.1; 0.5]	μ=1.974 σ=0.502	(3) (4)
v_{L+Is} (duration of period before high shedding and clinically affected state)	[52 ; 520]	156	[52; 155;520]	μ=5.204 σ=0.436	(1) (2)

(1) Whittington et al. 2000; (2) Jørgensen 1982) ; (3) Begg and Whittington 2008; (4) Windsor and Whittington 2010)

The abstract genetic values are normally distributed. The limit of the 99% confidence interval of the abstract genetic values for trait *i* at time t_0 range between A_0 and B_0, with A_0<B_0. A fictive population of 100,000 animals was generated previous to simulations to define A_0 and B_0. We assumed a log normal distribution for the selected traits. Regarding the rare and limited description of the phenotypic traits in literature, we assumed that the limits of values in traits previously identified correspond to the limits of a 99% confidence interval for a given trait. The distribution of each phenotypic trait value in the current population (t_0) was defined by its lower limit value I_0, its higher limit value J_0, and its most likely value K_0. A function F was defined to calculate the phenotypic value knowing the abstract genetic value (x) of trait *i*:

$$\text{phenotypic value}_{trait_i} = F(x) = I_0^{\left(\frac{B_0-x}{B_0-A_0}\right)} \times J_0^{\left(\frac{x-A_0}{B_0-A_0}\right)} \quad (10)$$

$$F(A_0) = I_0 (11)$$

I_0= lower limit value of the 99% confidence interval of a phenotypic trait at t_0

$$F(B_0) = J_0 (12)$$

J_0= higher limit value of the 99% confidence interval of a phenotypic trait at t_0

$$F\left(\frac{A_0+B_0}{2}\right) = \sqrt{I_0 \times J_0} (13)$$

If K_0 is different from $\sqrt{I_0 \times J_0}$, (when the most likely value of a phenotypic trait identified in the literature is different from the mode of log normal distribution of these phenotypic trait values predicted using function *F),* a correction factor (Δ) was applied. The objective was to obtain:

$$K'_0 = F\left(\frac{A_0+B_0}{2}\right) = \sqrt{I'_0 \times J'_0} (14)$$

With:

$$K'_0 = K_0 + \Delta; \quad I'_0 = I_0 + \Delta \quad ; J'_0 = J_0 + \Delta \quad (15)$$

$$\Delta = \frac{K_0^2 - I \times J}{I + J - 2.K} \quad (16)$$

$$F(x) = \left[(I_0 + \Delta)^{\left(\frac{B_0-x}{B_0-A_0}\right)} \times (I_0 + \Delta)^{\left(\frac{x-A_0}{B_0-A_0}\right)}\right] - \Delta \quad (17)$$

2.3 Next rounds of selection

Each time step in our model corresponded to the full replacement of the population of dams by the next generation time step. All calves born at time *t* were assumed to become dams at time *t+1*. Accounting for an annual replacement rate of about 33% in herds, this time step corresponded to about 3 years. At each time t a population of 1,000 normally distributed sire indexes was generated the sire index progressed from time t to time+1 assuming 3 years of annual sire index improvement.

$$Sire\ index\ at\ time\ t \sim \mathcal{N}(t \times 3 \times \theta, R^2); (18)$$

With θ the annual sire index improvement factor.

At each time t, ten of the 5% elite sires with regards to indexes were retained for reproduction. Phenotypic trait values were then calculated for each newborn calf. The minimum and maximum values of the abstract genetic values and phenotype values at time *t-1*were used to define a new function (F_t) to calculate the phenotypic value for each trait at time t. The whole selection scheme and the steps to calculate the phenotypic trait value of an animal knowing his dam and sire are summarized in figure 1.

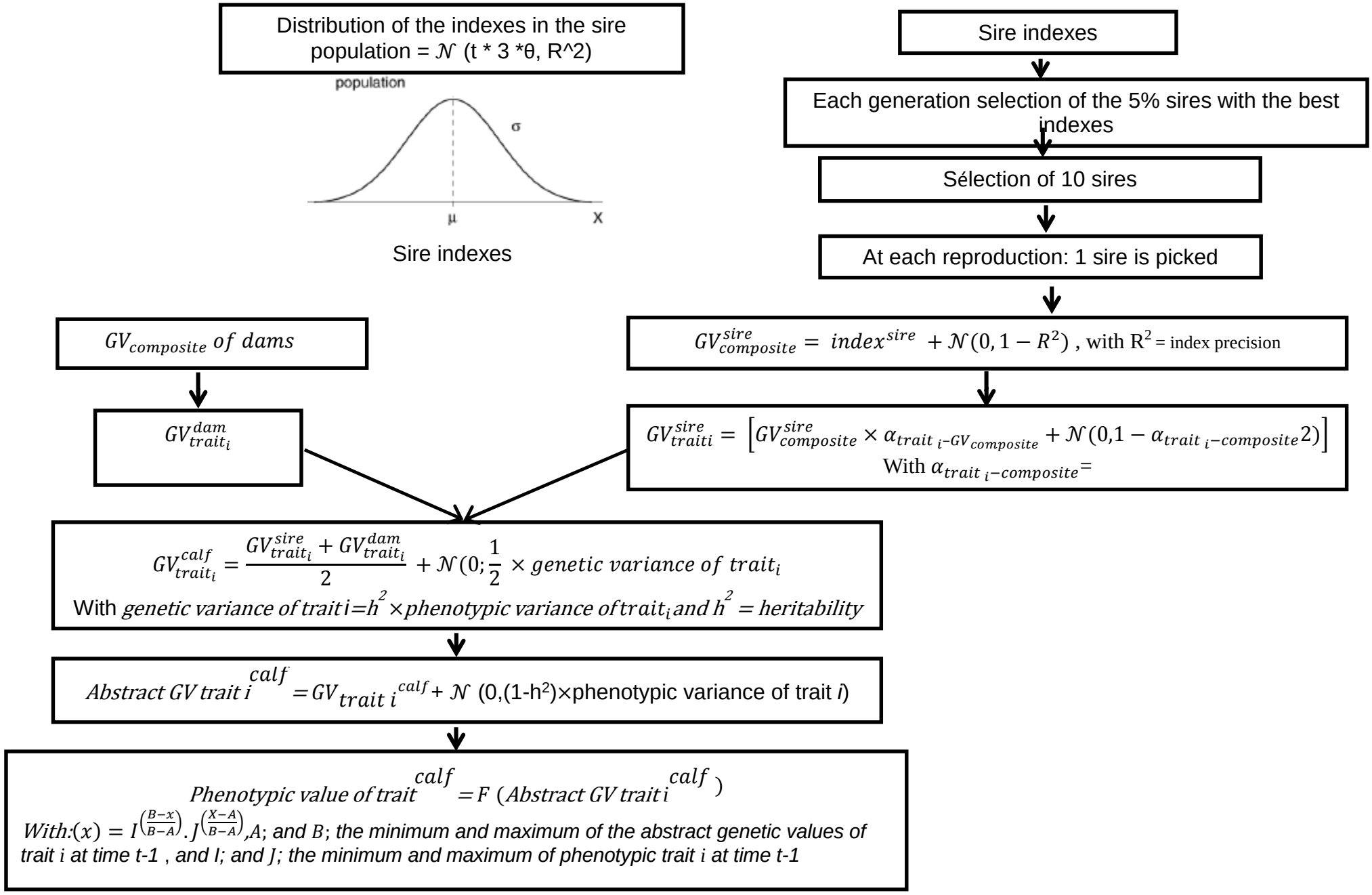

Figure 1: Conceptual scheme of the genomic selection model for paratuberculosis resistance

2.4. Simulation protocol and output analysis

Based on expert's opinion(D. BOICHARD, INRA), we selected a set of 2 or 3 values for the different parameters of our genomic selection model of resistant bovines to paratuberculosis inspired from existing selections schemes in bovine for production traits (Table 2). Each simulated scenarios was run 500 times in order to obtain accurate values of each selected trait median (similar median value with higher number of runs, results not shown).

The evolution of each phenotypic trait value in the dams was monitored over 50 generations of genomic selection (equivalent to 150 years). A visual analysis of the selected trait distributions was used to describe their evolution. We interested in the worst, most realistic, and most optimistic scenarios of selection with regards to the parameters of the genomic selection model.

Ben Romdhane et al. (2017) identified 537combinations of variations in the four traits influencing map spread which was found to ensure that less than 25 newly infected animals would be produced over 25 years of simulation if an infected animal was introduced in a naïve herd. These combinations are assumed to represent a good control of the situation as regards paratuberculosis spread and impact. As an indicator of the genomic selection effectiveness, we assessed more particularly the time needed to achieve a good control of paratuberculosis at herd scale. We focused on medians of the traits in the herd among the simulated generations of selection looking at predicted time steps at which one of the good control combinations was reached.

We assessed the influence of uncertainty about values of the genomic selection model parameters performing a sensitivity analysis of the model. This analysis accounted for variations in the all parameters of the genomic selection model in a complete factorial design. This analysis was performed using an ANOVA. The purpose was to quantify the influence of the model parameters relative to the genomic selection on the variance of the selected phenotypic trait medians at 50 generations of genomic selection.

Table 2: set of genomic selection parameters investigated (from expert's opinion)

Parameters	Definition	Studied values
θ	Sire index evolution factor	0† ; 0.1* ; 0.2‡
h^2	Heritability	0.25†* ; 0.5‡
R^2	Index precision	0.4† *; 0.6‡
$\alpha_{trait\ i}$	Correlation factor between the trait I and the composite genetic value (GVc)	
α_h	Susceptibility decay with age (μ)	0.5†* ; 0.8‡
α_{di}	The required infectious dose to be infected (DI)	0.5† *; 0.8‡
α_{vLIs}	The period before high shedding and clinically affected state (v_{L+Is})	0.5†* ; 0.8‡
$\alpha_{\varphi feces}$	Quantity of Map shed in faeces by high shedders and clinically affected animals ($\varphi_{fecesIc}$)	- 0.5†* ;- 0.8‡

(†): values used in the worst scenario;
(*) : values used in the most realistic scenario;
(‡): values used in the most optimistic scenario

3. Results

In the worst scenario, we noticed a slight evolution of the four selected traits during the first 3 generations of selection. Then, there was evolution of the four selected phenotypic traits in the herd population (figure 2).

In the most realistic scenario (Figure 3), an exponential evolution of the median of each of the selected traits was observed (linear increase of all log transformed outputs, not shown for $\varphi fecesIc$ and v_{L+Is}). The medians of the decay in susceptibility with age (μ), the quantity of Map shed in faeces by high shedders and clinically affected animals ($\varphi fecesIc$), the duration of the incubation period (v_{L+Is}), and the required infectious dose to be infected (*ID*) varied respectively from 0.1, 10^{-5}, 156, and 10^6 in the initial population (herd scale) to 0.83, 7.5 x10^{-12}, 946.92, and 3.5x10^{14}at the 50th generation of selection.

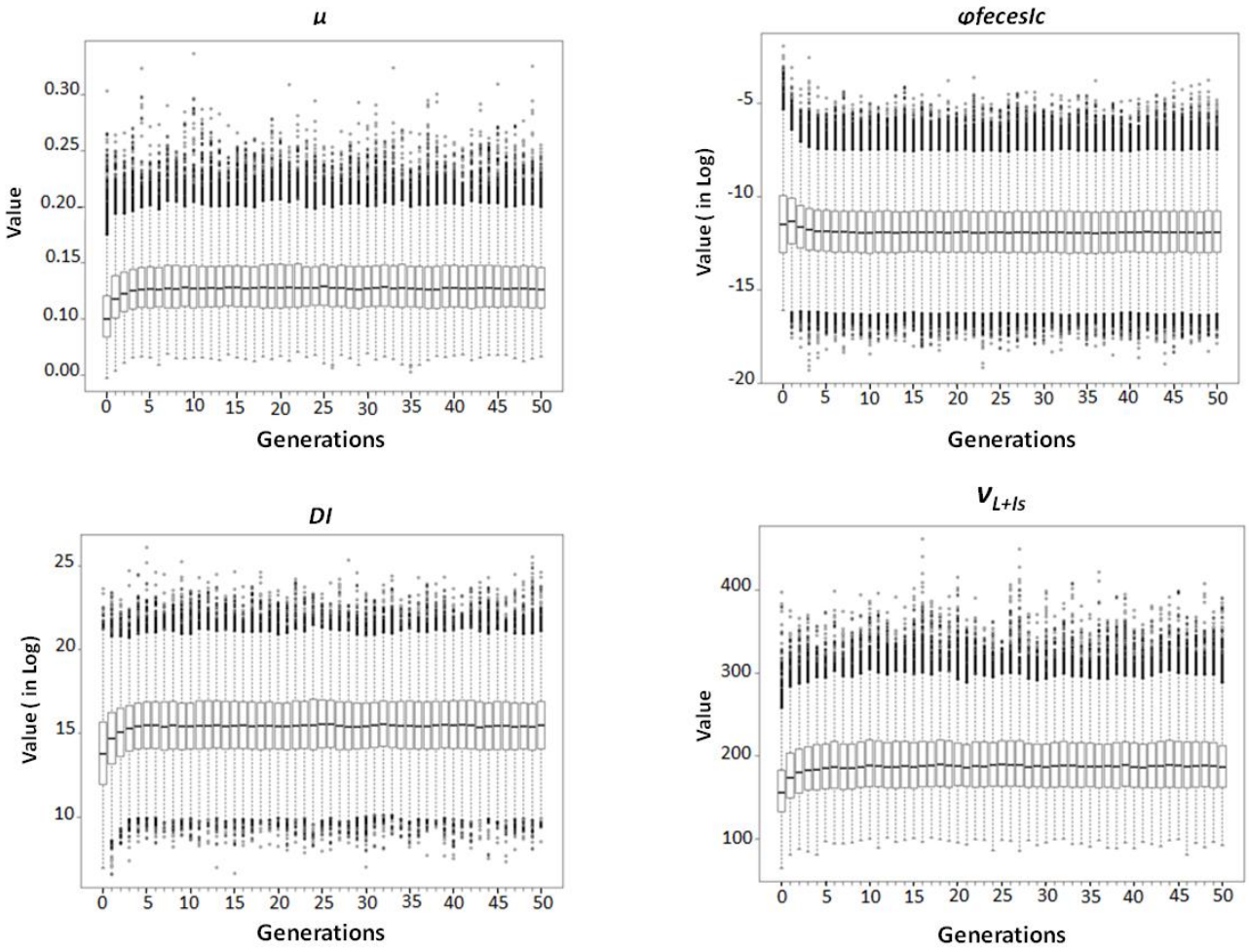

Figure 2: Evolution of the four selected phenotypic traits of resistance to paratuberculosis over 50 generations of selection: the worst scenario

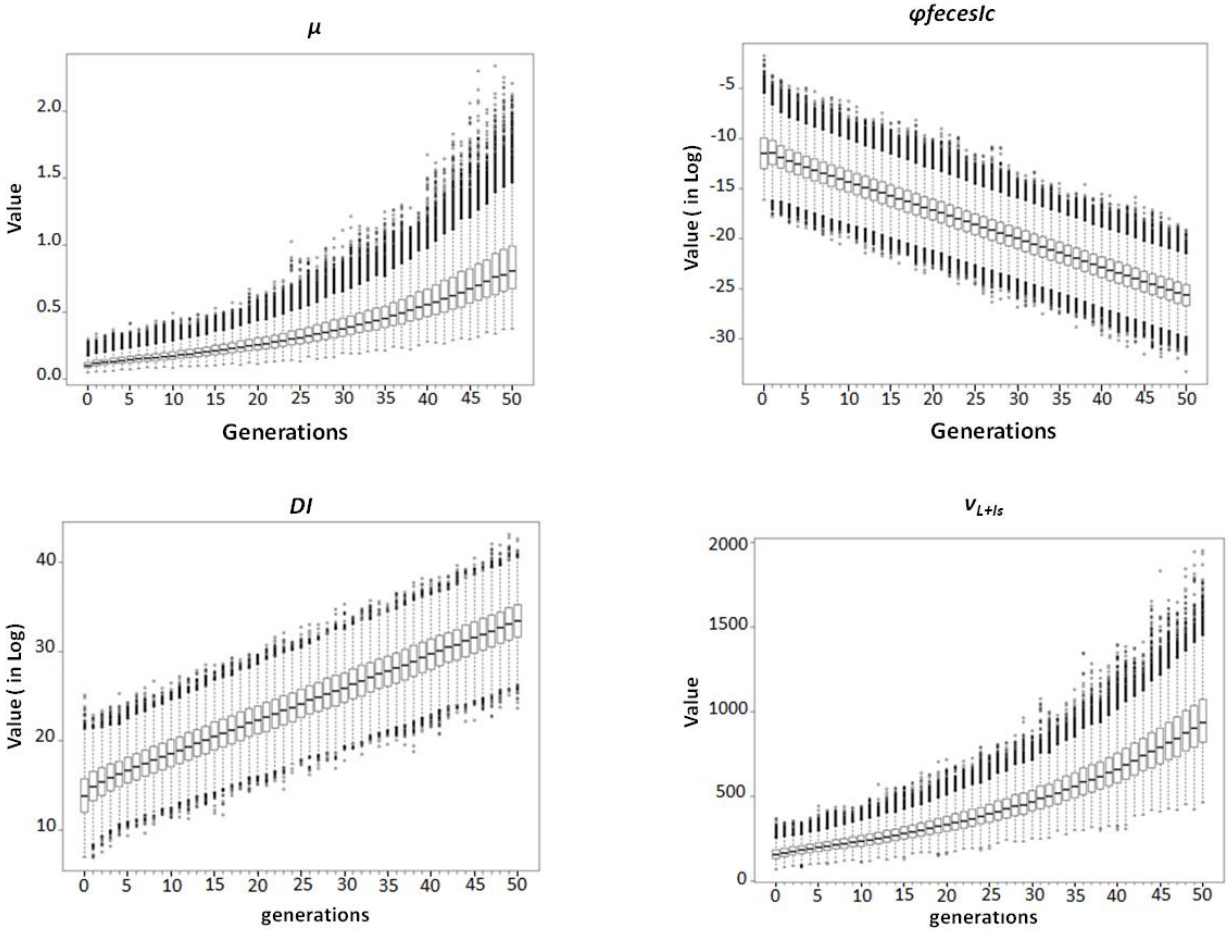

Figure 3: Evolution of the four selected phenotypic traits of resistance to paratuberculosis over 50 generations of selection: the most realistic scenario

A faster exponential evolution was observed in the most optimistic scenario (Figure4). The medians of the decay in susceptibility with age, the quantity of Map shed in faeces by high shedders and clinically affected animals, the duration of the incubation period, and the required infectious dose to be infected medians in the herd starting respectively from 0.1, 10^{-5}, 156, and 10^{6} in the initial population reached a higher value at the 50^{th} generation of selection(respectively 64.37, $6x10^{-26}$, 44697.35, and 10^{33}) than in the most realistic scenarios.

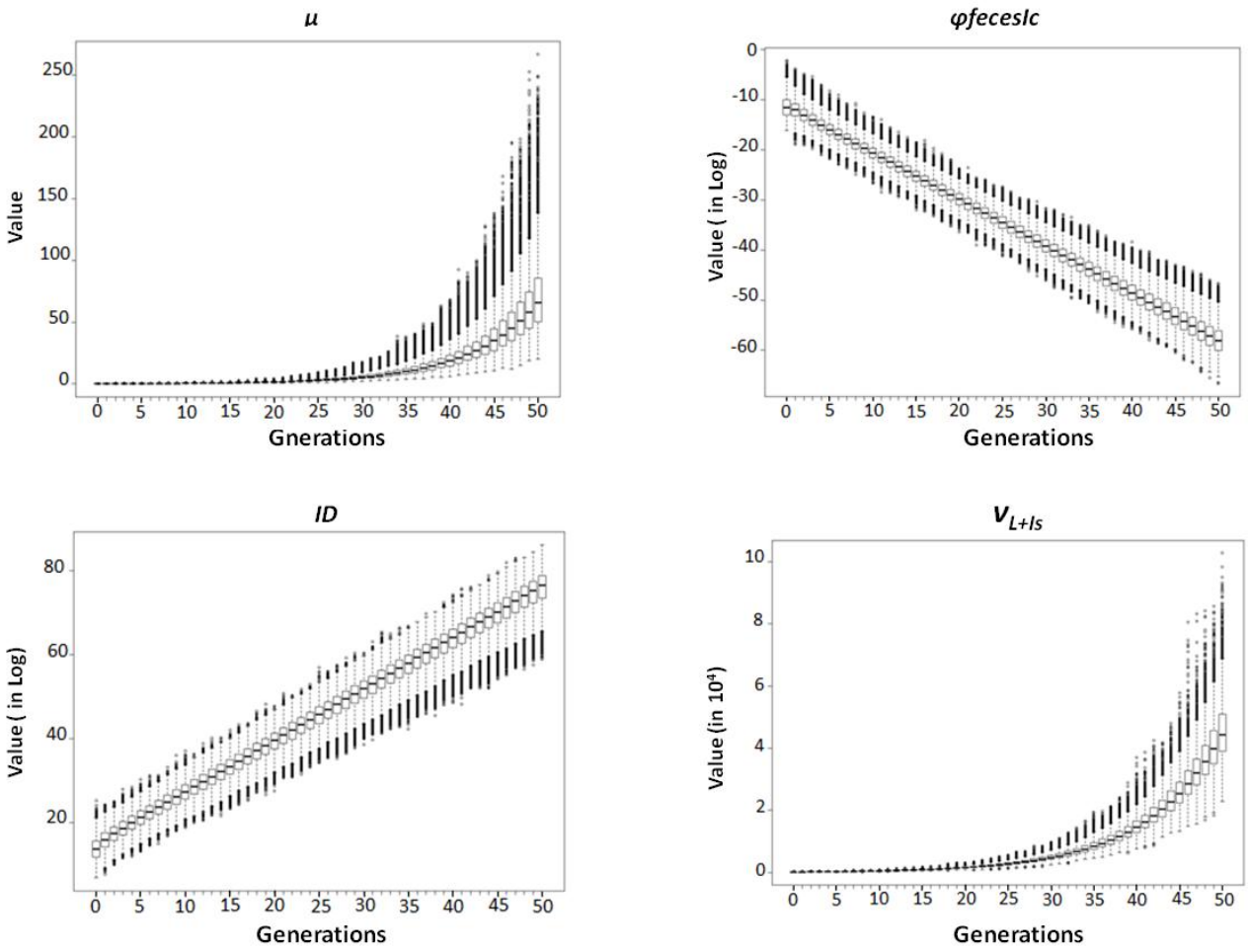

Figure 4: Evolution of the four selected phenotypic traits of resistance to paratuberculosis over 50 generations of selection: the most optimistic scenario

Only the most optimistic scenario allowed to reach one of the combination of selected traits values allowing a good control of paratuberculosis). The earliest combination of variation in the four selected traits that allow a good control of paratuberculosis at the herd scale was reached at the 8th generation of selection (24 years)when implementing the optimistic selection scenario (Table 3). Eighty combinations out of the 537 identified in section III as allowing a good control of paratuberculosis were reached at 8 generations of selection. The latest combinations were reached at 13generations of selection, respectively in the most optimistic and the most realistic.

Table 3: Earliest and latest generation time needed under selection to reach one of the combinations of phenotypic trait values that allow a good control of paratuberculosis at the herd scale.

	Time needed to reach the earliest combination	Time needed to reach the latest combination
worst scenario	>50	>50
realistic scenario	>50	>50
best scenario	8	13

Among the tested scenarios in the sensitivity analysis, we observed a variation in the medians of the decay in susceptibility with age, the quantity of Map shed in faeces by high shedders, and clinically affected animals, the duration of the incubation period, and the required infectious dose to be infected at the 50^{th} generation of selection respectively from 0.13, $6x10^{-26}$, 182.25, and $7x10^{6}$ to 64.37, $6.7x10^{-6}$, 44697.35, and 10^{33}. The global sensitivity analysis (Figure 5) showed that the variation in the median of each phenotypic trait at the 50^{th} generation was highly influenced by the sire index evolution factor (θ) that contributedto35% to up to 60% of the variance of trait medians. The factor of correlation between each phenotypic trait and composite genetic value ($\alpha_{trait\ i}$) was less influencing the medians of the corresponding traits than the sire evolution factor (θ)(up to 27 %). The influence of combination between the sire evolution factor (θ) and the factor of correlation between each phenotypic trait and composite genetic value ($\alpha_{trait\ i}$) on the variance of the median values of the decay in susceptibility with age, the quantity of Map shed in faeces by high shedders and clinically affected animals, the duration of the incubation period, and the required infectious dose to be infectedat 50 generations of selection were respectively up to 25%, 10%, 25%, and 30%.

The variance of the median value ofthe required infectious dose to be infected (*ID*)at 50 generations of selection was also influenced by the variance of the heritability (h^2) and the index precision (R^2). Interactions between the sire evolution factor (θ), the factor of correlation between each phenotypic trait and composite genetic value ($\alpha_{trait\ i}$), and the heritability (h^2) contributed to up to 5% of the variance of required infectious dose to be infectedat 50 generations of selection.

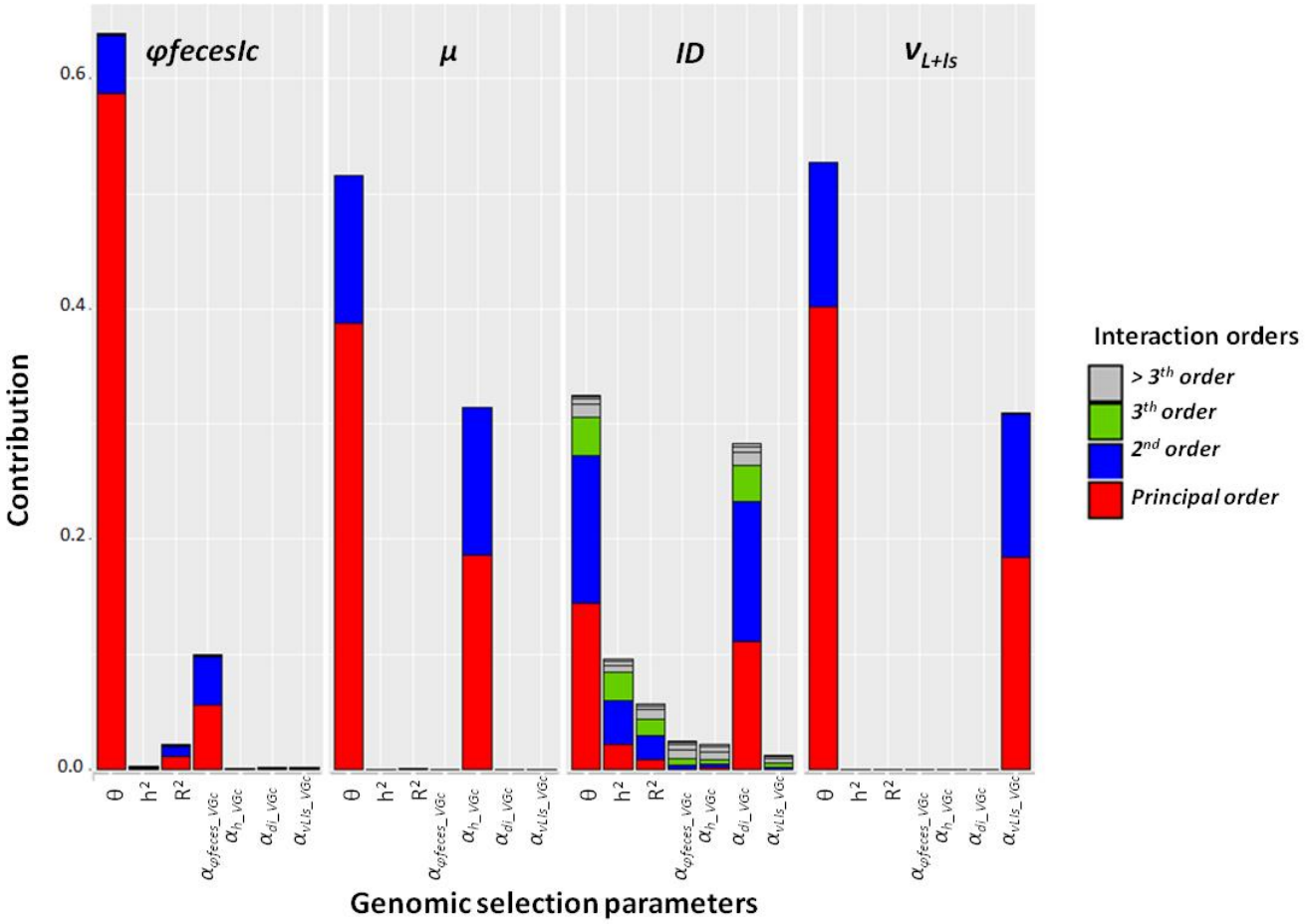

Figure 5: contribution of the genomic selection parameters to the variance of the median values of the four selected phenotypic traits at the 50th generation. See table 2 for genomic parameters definition and table 1 for phenotypic trait definition.

4. Discussion

This study highlighted that the selected phenotypic traits evolved exponentially in the realistic and the optimistic scenarios. In the worst selection scenario, there was no significant evolution of the traits under selection, despite a slight evolution of the selected traits was observed in the first four generations of selection. Regarding the high contribution of the sire index evolution factor to the variance of the trait medians at 50 generations of selection (from 35 to 60%), the absence of significant evolution of the traits in the worst scenario was caused by the non-evolution of the sire indexes during the selection time. At the first rounds of selection, the genetic gain induced by selection caused a slight evolution of the traits. The more we select for resistance with

the same sire, the lower the genetic gain will be. Therefore, we did not observe an evolution of the traits over the 50 generations of selection.

The simultaneous selection of the four phenotypic traits of resistance to paratuberculosis allowed to reach a combination of them that was assumed to represent a good control of the disease at the herd scale as earlier as8 generations of selection. Accounting for a replacement rate of about 33%, this combination could be reached at about 24 years after the starting of the genomic selection. This time to achieve a good control of paratuberculosis at the herd scale is considerably lower than Van Hulzen et al (2014) findings in which they concluded that at least 147 years of genetic selection based on sires are required to decrease susceptibility with age sufficiently to eradicate PTB. This difference in durations between the two studies could be explained by the higher genetic and phenotypic gains when using genomic selection approach instead of the genetic selection one (Boichard et al 2016), by the high contribution of the combined variations in the selected traits (Ben Romdhane et al 2017), and by the difference of targeted control (eradication vs. good control). The time needed to achieve a good control of paratuberculosis within a herd could be shortened even more by performing genomic selection both on sires and dams and by combining genomic selection with other control measures of the disease.

The implementation of the selection schemes tested in this study is still highly limited by the ability to identify genes coding for the selected phenotypic traits. We assumed in this work that genomic selection can be performed in each of the investigated traits independently. Current studies associated genomic parts to a phenotype of resistance to paratuberculosis (no detectable infection or no clinical signs in animals exposed to Map) without accounting for the phenotypic traits composing this resistance.

In this work, we assumed genomic selection model parameters largely inspired from existing selection of production traits. The value of these parameters in selection for resistance could be lower to in selection for production traits, which will slow the evolution of the selected traits. In addition, we assumed that genomic selection could be performed on the four traits simultaneously assuming a positive correlation between the traits. This assumption needs to be confirmed by genetic studies of the resistance to paratuberculosis. Negative correlations between the selected traits also could exist which could impair our predictions.

The sensitivity analysis showed that the phenotypic evolution of the four selected trait medians in the herd was mainly driven by the sire index evolution factor (θ) and The factor of correlation between each phenotypic trait and composite genetic value (α_{traiti}) respectively from the most to the least influential parameter of genomic selection. Therefore, genetic studies should aim to identify an accurate link between the selected traits and the composite genetic value. In the potential selection schemes of resistance to paratuberculosis based on sire selection we would have to select the most resistant sires in a given generation to use in artificial insemination programs (accounting the sire evolution over generations of selection). We assumed here that the sire index evolution factor (θ) was constant for more than 150 years of selection. The evolution of the index may slow over time which will decrease the gain from genetic selection over time.

The developed genomic selection model took in account simplified herd demography: dams are assumed to be fully replaced by more resistant animals every 3 years. A realistic demography is expected to make the evolution of the phenotypic traits lower that predicted in this study. The use of a model combining genomic selection, realistic demography and epidemiology of paratuberculosis will allow to estimate more accurately the time needed to reach a targeted prevalence of the disease within herd.

The heritability of resistance to paratuberculosis was estimated to range from 0.01 to 0.23(Behr and Collins 2010; Brian W. Kirkpatrick and Shook 2011; van Hulzen et al. 2011; Küpper et al. 2012; Zare et al. 2014). In order to estimate this heritability, the authors focused on the shedding of Map through different routes, response to diagnostic tests and the clinical state of animals assumed to be exposed to similar doses of bacteria. The resistance to paratuberculosis was there assumed to be a binary variable: resistant vs. non-resistant. As these studies accounted only for extreme phenotypes, the intermediate responses to Map exposure are underrepresented in the heritability estimation. Therefore, the real heritability of cattle resistance to paratuberculosis is expected to be higher than 0.23.

Chapter 6: General discussion:

The objective of this thesis was to assess the effectiveness of bovine paratuberculosis control strategies using genetic selection or decrease in calves exposure. In this purpose we adopted a modelling approach to test for the effects of implementing different control measures in a dairy herd. Four steps were necessary to reach the main goal of the thesis.

- Identification of potential genetically selectable phenotypic traits of bovine resistance to paratuberculosis and estimation of their variation in current animals.
- Identification of phenotypic traits of bovine resistance influencing the disease dynamics within a dairy herd
- Assessing the influence of the farming system specificities and herd prevalences on the effectiveness of conventional measures of paratuberculosis control
- Assessing of the effectiveness of genomic selection for paratuberculosis resistance to control the disease.

Reviewing published literature, we identified phenotypic traits of bovine resistance to paratuberculosis that vary among animals. We identified six phenotypic traits of resistance to paratuberculosis in bovine that were described in cattle population. We identified currently described ranges of variations in these traits of resistance to paratuberculosis in dairy cattle. These traits making cattle more resistant in response to Map exposure were assumed to be partly driven by a genetic component and could potentially be targeted by genetic selection for tuberculosis resistance.

We identified 14 phenotypic traits of potential cattle responses to Map exposure composing the resistance to paratuberculosis. These traits are involved in success of infection when exposed to Map, disease evolution in infected animals, shedding of Map through different routes, and the in utero transmission of infection to foetus. We highlighted that four of these phenotypic traits influenced Map spread within a closed dairy herd: (1) the decay in susceptibility with age, (2) the quantity of Map shed in

faeces by high shedders and clinically affected animals, (3) the duration of the incubation period, and (4) the required infectious dose to be infected. We noticed that interactions between these four influential phenotypic traits, in addition of their individual principal effects, contributed to up to 12% of variations in the monitored model outputs representing the disease dynamics within herd. Many combined variations in the four influential traits of resistance to paratuberculosis allowed achieving a good control of the disease in a dairy herd were identified.

We assessed the effectiveness of current paratuberculosis control measures and the disease dynamics I two different farming systems: western France and Ireland. These farming systems have different contact structures between animals, renewal rates, birth strategies and shedding of Map by infectious animals. as noticed by (C. Marcé et al., 2011), the disease dynamics was different between the two farming systems. Moreover, the effectiveness of conventional control strategies was different in the studies farming systems. We evidenced that these control strategies effectiveness is influenced by the farming system and the prevalence within the herd where they are implemented. We noticed that the most effective conventional control strategy as the same irrespective to the farming system or the within herd prevalence where it was implemented.

We assessed the potential of efficacy of genomic selection, based only on sire selection, to gain progress on the four previously identified phenotypic traits of resistance to paratuberculosis influencing Map spread within a dairy herd. Assuming a generation time step(whole population replacement by more resistant animals), we showed that values of the four selected traits allowing to achieve a good control of paratuberculosis could be reached within 8 to 13generation time steps

When simulating an optimistic set of values for the genomic selection model parameters. None of the variations in the four selected traits allowing a good control of the disease was reachable within less than 50 generations time steps when accounting even for realistic set of values for the genomic selection parameters.

1. Genetic selection for bovine resistance to paratuberculosis:

We identified all phenotypic traits of bovine resistance described in literature with a particular interest to their ranges of variations. These traits are difficult to observe in field study. Therefore most of the phenotypic traits variations are described in experimental infection works. We assumed that the variation of the traits of response to Map exposure is in part genetically driven and could potentially be selected. The identified traits of resistance to paratuberculosis were described in literature using the most observed average value of a trait (ei. incubation period, age when calves become no more susceptible to infection) and its extreme values (minimum infectious dose needed to be infected, minimum and maximum incubation period, possible infection of adult cows, …). The available observations were not sufficient to characterize the distribution among animals and to accurately estimate the variance of these phenotypic traits among animals. Therefore, observational data allowing a more complete description of variations in the phenotypic traits of resistance to paratuberculosis are needed.

We interested in 14 traits of bovine resistance to map exposure involved in the disease course, Map transmission, and shedding. We identified four phenotypic traits influencing Map spread dynamics within a Western European dairy herd. Regarding the high contribution of combined variations in these traits to Map spread within herd, it is more relevant to target simultaneously the four traits in future potential selection for paratuberculosis resistance.

The used model accounted for the most up to date knowledge about paratuberculosis infection course. We adopted a detailed definition of resistance to paratuberculosis. We accounted for several phenotypic traits that allow a separation between phenotypic traits, representing potentially not correlated mechanisms, of bovine resistance to paratuberculosis. We performed intensive simulations (up to 390 000 scenarios and 500 runs each) through a complete factorial design to assess the influence of variations in phenotypic traits of resistance to paratuberculosis on the disease dynamics. The complete factorial design using levels of variations in this study was easier to quantify the influence of each trait on the disease dynamics but required more simulated scenarios than a Latin hyper cube sampling approach.

Data about the variations of studied phenotypic traits is limited in literature. When information is available in literature, we assumed realistic ranges of variation in the studied traits. For traits not well described in literature, we assumed extreme ranges of variations. However, the four traits influencing the most Map spread the simulated variations were realistic and could potentially be reached using genetic selection. A higher variation than the simulated values of the phenotypic traits of resistance to paratuberculosis could allow identifying other traits influencing Map spread but these traits would be less influential that the four identified to highly influence Map spread.

The observation of phenotypic traits of resistance is difficult to observe in the field. Three of the phenotypic traits of resistance identified as influencing Map spread in a herds are difficult to measure using conventional diagnostic tests: the infectious dose required to be infected, the susceptibility decay with age and the duration of the incubation period. These traits are mainly measured in experimental infection. Regarding the large number of animal needed to identify genomic markers associated to paratuberculosis resistance, experimental infections to identify these genes would be very expansive and potentially impossible to perform. Therefore, indirect indicators based on conventional paratuberculosis surveillance tools and corresponding to the phenotypic traits influencing Map spread have to be defined. These indicators are expected to allow measuring and identifying animals with relevant phenotypic traits of resistance to paratuberculosis using observational field studies.

All the studied phenotypic traits were assumed to be genetically selectable. Further studies are needed to identify and quantify the link between genome parts and the traits of resistance to paratuberculosis. The existence of negative correlations between the selected phenotypic traits could highly limit the effectiveness of genomic selection to control paratuberculosis. The clear identification of the genetic components behind this resistance is necessary to know if the traits influencing Map spread could be selected simultaneously, independently from each other, and without negative correlations to traits of production in cattle.

We identified influential traits of resistance through simulation of Map spread after naïve close introduction in dairy herd. Accounting for an initial prevalence within simulated herd or possible introduction of the disease is more realistic and would increase the prevalence of infected and infectious animals, the persistence of the

disease and the cumulated incidence. Nevertheless, this don't change the traits previously identified as influencing the disease dynamics.

We developed a genomic selection model that explicitly represents the most recent knowledge on genetic resistance to paratuberculosis (relevant phenotypic traits to select and their variability in current animals) and mechanisms of phenotypic traits heritability. We assumed that phenotypic traits of bovine resistance influencing the disease dynamics in a herd (Ben Romdhane et al., 2017) could be selected by genomic selection approach. The model calibration with regards to the genomic selection model parameters was largely inspired from genomic selection of production traits in bovine. The genomic selection parameters could be different between resistance and production traits. Therefore, estimation of more accurate parameters of the genomic selection model has to focus in priority on those identified as influencing the effectiveness of selection.

We highlighted that a simultaneous sire based genomic selection of the four most influential traits of resistance to paratuberculosis allow to early (8 generation time steps in the model) achieve a good control of the disease assuming the an optimistic set of the genomic selection model parameters. We noticed that variations in the traits of resistance under selection were mainly influenced by the evolution of sire genetic value over time and the correlation between the genetic value and the selected traits. Therefore, more accurate estimation of these two parameters influencing the efficacy of genomic selection has to be produced. We assumed that the four phenotypic traits influencing Map spread within herd could be selected without accounting for the genetic component behind the traits or possible interaction between them and with other production traits. Future knowledge about genetic components related to the studied traits or correlations between them could easily be integrated to the model. Only one genetic marker associated to paratuberculosis resistance was positively correlate lactation persistence in cattle(Ruiz-Larrañaga et al., 2011; Sharma et al., 2006). The model could be extended to represent genomic selection of any phenotypic trait, including production traits and account for correlation between resistance to paratuberculosis and production performances.

The renewal in simulated herds was assumed to be only internal. This is mainly the case in western European dairy herds. Some animals could be introduced to increase

the herd sizes or to replace culled animals. Beaunée et al (2015) highlighted that buying at 3 animals per year produced a 50% probability of introducing Map in western French dairy herd. Representing the possible reintroduction of Map in our model would increase Map spread. However, this animal movement is not expected to change the influence of the studied phenotypic traits of resistance to paratuberculosis on the disease dynamics within herd.

2. Influence of the farming system on paratuberculosis control effectiveness

In this thesis we compared the paratuberculosis dynamics within a dairy herd in two geographically close but differently managed western European farming systems: western French and Irish dairy herds. These farming systems have different contact structure between animals, renewal rates, birth strategies and shedding of Map in infectious animals. The contact structure was previously identified by Marcé et al 2011 as influencing Map spread within herd. We evidenced that Map spread was slower in Irish dairy herds than in France. We highlighted that current control strategies of bovine paratuberculosis were more effective in Ireland that in western France herds. The effectiveness of bovine paratuberculosis control was also influenced by the within herd prevalence of the disease when implementing control measures. These findings suggested that expectation in term of ability to control paratuberculosis in dairy herds have to take into account the farming system specificities and the status of the herd regarding Map infection.

An existing individual based model of Map spread (Camanes et al in prep.) was extended to represent typical western French and Irish model. The models were calibrated based on real data from national cattle statistics and experts opinion. Even if the developed models were calibrated using real data, they need further validation by comparing their outputs to field data about paratuberculosis status in each farming systems.

We took into account real contact structure, culling rates, birth seasonality, grazing periods and Map shedding (with regards to the cattle breeds) in the two farming systems. The main advantage of the chosen approach was to show realistic differences in farming systems and their influence on paratuberculosis dynamics and

its control. Such approach, regarding the number of differences between the studied farming systems, didn't allow to investigate which farming practice influence the disease dynamics and the effectiveness of implemented control measures. A sensitivity analysis would allow to identify the farming system practices that influence the most Map spread and its control. Identifying these farming practices would help to expect paratuberculosis dynamics and the effectiveness of measures to control the disease in other not simulated farming systems.

We highlighted that the most and the less effective strategies to control paratuberculosis were the same in Irish and French dairy herds and in highly or moderately infected herds. This finding suggests that ranking of control strategies effectiveness is irrespective to the farming system or the within herd prevalence where the strategies are implemented.

The farming system specificities were here assumed to be constant over time. Farming practices in dairy farms changed during the last decades in developed countries to adapt their production to decision makers policies, consumer demands and evolution of technology (Barkema et al., 2015). These changes are expect to occur in future and would influence disease spread and the effectiveness of the current control strategies that will have to adapt to this evolutions.

3. Perspectives of future paratuberculosis control measures in dairy cattle

Current control strategies are not enough effective to control paratuberculosis. The effectiveness of these strategies is influenced by the farming practices. A decrease in calve exposure to Map present in the environment is difficult to implement inside the farm building and even more difficult when animals are outside during the grazing period. Implementing test and cull strategies, even if the diagnostic tests were able to detect all infected animals, doesn't offer a protection against the possible reintroduction of the disease. Therefore, genetic selection could enhance control paratuberculosis by limiting Map spread.

Genetic selection of resistant animals to paratuberculosis could be thought as a complementary control measure. Such potential selection was showed in this study to decrease Map spread and could then enhance control of paratuberculosis. Further genetic investigations are needed to identify genetic component to potentially

implement a genetic marker assisted selection of the relevant phenotypic traits of bovine resistance to paratuberculosis.

Modelling could be a relevant approach to study the effectiveness of paratuberculosis control strategies combining genetic selection and current control strategies. The developed individual based genomic selection model was designed to be easily integrated to the existing epidemiological model of Map spread. The resulting epidemio-genetic model could be a good tool to assess the effectiveness of strategies combining genomic selection and current control strategies. Such model has to take into account, the farming system specificities, the prevalence of paratuberculosis, and the potential reintroduction of infected animals in the simulated herds.

General conclusion

Accounting for all phenotypic traits that could be involved in paratuberculosis infection, transmission and shedding of Map, we identified 14 phenotypic traits representing different possible responses to Map exposure in cattle. These traits were assumed to be genetically driven and selectable. Out of these traits, four were identified to influence the paratuberculosis dynamics in a typical western European dairy herd: : (1) the decay in susceptibility with age, (2) the quantity of Map shed in faeces by high shedders and clinically affected animals, (3) the duration of the incubation period, and (4) the required infectious dose to be infected. Simultaneous variation in these influential traits contributed to up to 12% of the paratuberculosis dynamics in the herd. These results highlight the added value of performing genetic selection for paratuberculosis resistance simultaneously in these four phenotypic traits to control the disease.

Several combined levels of variation in the four influential traits on Map spread in the herd allowing to achieve a good control of paratuberculosis were identified. Using a genomic selection model for these traits based on sire selection, we noticed that combinations of variations in the selected traits allowing a good control of the disease could be achieved within 24 to 39 years of potential selection. These combined variation in the selected traits allowing a good control of the disease could only be achieved when assuming optimistic options in (1) the increase of sire genetic value over selection time, and (2) the correlation between the phenotypic traits and the genetic value (and index) of an animal.

The potential genomic selection of sire performed simultaneously on the four phenotypic traits of resistance to paratuberculosis influencing Map spread could enhance control paratuberculosis in dairy herds. The effectiveness of such selection could be highly limited by the ability to observe the target traits in the field and the potential existence of negative correlations between the selected traits.

The paratuberculosis dynamics was faster in the western French farming system than in the Irish one. These farming systems mainly differ by the contact structure between animals, the renewal of animas, the birth strategy and the shedding of Map by infectious animals. This finding suggests the existence of farming system practices that could enhance control the disease.

The effectiveness of conventional paratuberculosis control measures was different in both the studied farming systems. The effectiveness of these control measures was noticed to be influenced by the initial within herd prevalence of the disease. Therefore, expectations from current control measures of paratuberculosis have to take into account the farming system specificities and paratuberculosis prevalence in herds where control is implemented.

The most effective current control strategy of paratuberculosis had the highest effectiveness both in the Irish and western French farming system. This finding suggests that a unique most effective control strategy for paratuberculosis would have the best effectiveness in controlling the disease dynamics in western French and Irish dairy herds.

References

Al-Mamun, M.A., Smith, R.L., Schukken, Y.H., Gröhn, Y.T., 2016. Modeling of Mycobacterium avium subsp. paratuberculosis dynamics in a dairy herd: An individual based approach. J. Theor. Biol. 408, 105–117. doi:10.1016/j.jtbi.2016.08.014

Alfano, F., Peletto, S., Lucibelli, M.G., Borriello, G., Urciuolo, G., Maniaci, M.G., Desiato, R., Tarantino, M., Barone, A., Pasquali, P., Acutis, P.L., Galiero, G., 2014. Identification of single nucleotide polymorphisms in Toll-like receptor candidate genes associated with tuberculosis infection in water buffalo (Bubalus bubalis). BMC Genet. 15. doi:10.1186/s12863-014-0139-y

Allen, a R., Minozzi, G., Glass, E.J., Skuce, R. a, McDowell, S.W.J., Woolliams, J. a, Bishop, S.C., 2010. Bovine tuberculosis: the genetic basis of host susceptibility. Proc. Biol. Sci. 277, 2737–2745. doi:10.1098/rspb.2010.0830

Alpay, F., Zare, Y., Kamalludin, M.H., Huang, X., Shi, X., Shook, G.E., Collins, M.T., Kirkpatrick, B.W., 2014. Genome-Wide Association Study of Susceptibility to Infection by Mycobacterium avium Subspecies paratuberculosis in Holstein Cattle. PLoS One 9, e111704. doi:10.1371/journal.pone.0111704

Axford, R.F.E., Bishop, S.C., Nicholas, F.W., Owen, J.B., 2000. Breeding for Disease Resistance in Farm Animals, 2Nd edition. CABI publishing.

Barkema, H.W., von Keyserlingk, M.A.G., Kastelic, J.P., Lam, T.J.G.M., Luby, C., Roy, J.-P., LeBlanc, S.J., Keefe, G.P., Kelton, D.F., 2015. Invited review: Changes in the dairy industry affecting dairy cattle health and welfare. J. Dairy Sci. 98, 7426–7445. doi:10.3168/jds.2015-9377

Bastida, F., Juste, R.A., 2011. Paratuberculosis control: a review with a focus on vaccination. J. Immune Based Ther. Vaccines 9, 8. doi:10.1186/1476-8518-9-8

Beard, P.M., Stevenson, K., Pirie, a., Rudge, K., Buxton, D., Rhind, S.M., Sinclair, M.C., Wildblood, L. a., Jones, D.G., Sharp, J.M., 2001. Experimental paratuberculosis in calves following inoculation with a rabbit isolate of Mycobacterium avium subsp. paratuberculosis. J. Clin. Microbiol. 39, 3080–3084. doi:10.1128/JCM.39.9.3080-3084.2001

Beaudeau, F., Belliard, M., Joly, A., Seegers, H., 2007. Reduction in milk yield associated with Mycobacterium avium subspecies paratuberculosis (Map) infection in dairy cows. Vet. Res. 38, 625–634. doi:10.1051/vetres:2007021

Beaunée, G., Vergu, E., Ezanno, P., 2015. Modelling of paratuberculosis spread between dairy cattle farms at a regional scale. Vet. Res. 46, 111. doi:10.1186/s13567-015-0247-3

Beaunée, Vergu, Ezanno, 2015. Controlling the spread of Mycobacterium avium subsp. paratuberculosis at a regional scale based on internal biosecurity and animal movements, in: Proceeding of the Annual Meeting of SVEPM. Gent, belgium.

Begg, D.J., Whittington, R.J., 2008. Experimental animal infection models for Johne's disease, an infectious enteropathy caused by Mycobacterium avium subsp. paratuberculosis. Vet. J. 176, 129–145. doi:10.1016/j.tvjl.2007.02.022

Behr, M.A., Collins, D.M., 2010. Paratuberculosis: Organism, Disease, Control, Control. CABI, Wallingford, UK; Cambridge, USA.

Ben Romdhane, R., Beaunée, G., Camanes, G., Guatteo, R., Fourichon, C., Ezanno, P., 2017. Which phenotypic traits of resistance should be improved in cattle to control paratuberculosis dynamics in a dairy herd: a modelling approach. Vet. Res. 48, 62. doi:10.1186/s13567-017-0468-8

Benedictus, a., Mitchell, R.M., Linde-Widmann, M., Sweeney, R., Fyock, T., Schukken, Y.H., Whitlock, R.H., 2008. Transmission parameters of Mycobacterium avium subspecies paratuberculosis infections in a dairy herd going through a control program. Prev. Vet. Med. 83, 215–27. doi:10.1016/j.prevetmed.2007.07.008

Benedictus, G., Verhoeff, J., Schukken, Y.H., Hesselink, J.W., 2000. Dutch paratuberculosis programme history, principles and development. Vet. Microbiol. 77, 399–413. doi:10.1016/S0378-1135(00)00325-4

Bermingham, M.L., Brotherstone, S., Berry, D.P., More, S.J., Good, M., Cromie, A.R., White, I.M., Higgins, I.M., Coffey, M., Downs, S.H., Glass, E.J., Bishop, S.C., Mitchell, A.P., Clifton-Hadley, R.S., Woolliams, J. a, 2011. Evidence for genetic variance in resistance to tuberculosis in Great Britain and Irish Holstein-Friesian populations. BMC Proc. 5 Suppl 4, S15. doi:10.1186/1753-6561-5-S4-S15

Bermingham, M.L., More, S.J., Good, M., Cromie, a R., Higgins, I.M., Brotherstone, S., Berry, D.P., 2009. Genetics of tuberculosis in Irish Holstein-Friesian dairy herds. J. Dairy Sci. 92, 3447–3456. doi:10.3168/jds.2008-1848

Berry, D.P., Bermingham, M.L., Good, M., More, S.J., 2011. Genetics of animal health and disease in cattle. Ir. Vet. J. 64, 5. doi:10.1186/2046-0481-64-5

Berry, D.P., Good, M., Mullowney, P., Cromie, a. R., More, S.J., 2010. Genetic variation in serological response to Mycobacterium avium subspecies paratuberculosis and its association with performance in Irish Holstein-Friesian dairy cows. Livest. Sci. 131, 102–107. doi:10.1016/j.livsci.2010.03.007

Best, A., White, A., Boots, M., 2008. Maintenance of host variation in tolerance to pathogens and parasites. Proc. Natl. Acad. Sci. U. S. A. 105, 20786–91. doi:10.1073/pnas.0809558105

Bishop, S.., Stear, M.., 2003. Modeling of host genetics and resistance to infectious diseases: understanding and controlling nematode infections. Vet. Parasitol. 115, 147–166. doi:10.1016/S0304-4017(03)00204-8

Bishop, S.C., 2012. A consideration of resistance and tolerance for ruminant nematode infections. Front. Genet. 3, 168. doi:10.3389/fgene.2012.00168

Bishop, S.C., Morris, C.A.A., Bishop, S.C., Morris, C.A.A., 2007. Genetics of disease resistance in sheep and goats. Small Rumin. Res. 70, 48–59. doi:10.1016/j.smallrumres.2007.01.006

Bishop, S.C., Woolliams, J. a., 2014. Genomics and disease resistance studies in livestock. Livest. Sci., Genomics Applied to Livestock Production 166, 190–198. doi:10.1016/j.livsci.2014.04.034

Boichard, D., Ducrocq, V., Croiseau, P., Fritz, S., 2016. Genomic selection in domestic animals: Principles, applications and perspectives. C. R. Biol. 339, 274–277.

Carvajal, A.M., Huircan, P., Lepori, A., 2013. Single nucleotide polymorphisms in immunity-related genes and their association with mastitis in Chilean dairy cattle. Genet. Mol. Res. 12, 2702–2711. doi:10.4238/2013.July.30.8

Chiodini, R.J., Van Kruiningen, H.J., Merkal, R.S., 1984. Ruminant paratuberculosis (Johne's disease): the current status and future prospects. Cornell Vet. 74, 218–62.

Cho, J., Tauer, L.W., Schukken, Y.H., Smith, R.L., Lu, Z., Grohn, Y.T., 2011. Compartment Model for Controlling Infectious Livestock Disease: Cost-Effective Control Strategies for Johne's Disease In Dairy Herds.

Collins, M.T., Morgan, I.R., 1991. Epidemiological model of paratuberculosis in dairy cattle. Prev. Vet. Med. 11, 131–146. doi:10.1016/S0167-5877(05)80035-2

Collins, M.T., Wells, S.J., Petrini, K.R., Collins, J.E., Schultz, R.D., Whitlock, R.H., 2005. Evaluation of five antibody detection tests for diagnosis of bovine paratuberculosis. Clin. Diagn. Lab. Immunol. 12, 685–92. doi:10.1128/CDLI.12.6.685-692.2005

Crossley, B.M., Zagmutt-Vergara, F.J., Fyock, T.L., Whitlock, R.H., Gardner, I. a., 2005. Fecal shedding of Mycobacterium avium subsp. paratuberculosis by dairy cows. Vet. Microbiol. 107, 257–263. doi:10.1016/j.vetmic.2005.01.017

Daley, D.J., Gani, J., Gani, J.M., 2001. Epidemic Modelling: An Introduction. Cambridge University Press.

Davies, G., Genini 1b-, S., Bishop, S.C., Giuffra, E., 2009. An assessment of opportunities to dissect host genetic variation in resistance to infectious diseases in livestock. Anim. Anim. Consort. 3, 415–436. doi:10.1017/S1751731108003522

de Roode, J.C., Lefèvre, T., 2012. Behavioral Immunity in Insects. Insects 3, 789–820. doi:10.3390/insects3030789

Diekmann, Heesterbeek, J., 2000. Mathematical Epidemiology of Infectious Diseases: Model Building, Analysis and Interpretation - O. Diekmann, J. A. P. Heesterbeek, Wiley Series. John Wiley & Sons.

Domenech, J., Lubroth, J., Eddi, C., Martin, V., Roger, F., 2006. Regional and international approaches on prevention and control of animal transboundary and emerging diseases. Ann. N. Y. Acad. Sci. 1081, 90–107. doi:10.1196/annals.1373.010

Doré, E., Paré, J., Côté, G., Buczinski, S., Labrecque, O., Roy, J.P.P., Fecteau, G., 2012. Risk factors associated with transmission of Mycobacterium avium subsp. paratuberculosis to calves within dairy herd: A systematic review. J. Vet. Intern. Med. 26, 32–45. doi:10.1111/j.1939-1676.2011.00854.x

Doyle, T.M., 1958. Foetal infection in Johne's disease. Vet. Rec. 70, 215–218.

Eirin, M.E., Macias, A., Magnano, G., Morsella, C., Mendez, L., Blanco, F.C., Bianco, M. V., Severina, W., Alito, A., Pando, M. de los A., Singh, M., Spallek, R., Paolicchi, F.A., Bigi, F., Cataldi, A.A., 2015. Identification and evaluation of new Mycobacterium bovis antigens in the in vitro interferon gamma release assay for bovine tuberculosis diagnosis. Tuberculosis. doi:10.1016/j.tube.2015.07.009

Espejo, L.A., Godden, S., Hartmann, W.L., Wells, S.J., 2012. Reduction in incidence of Johne's disease associated with implementation of a disease control program in Minnesota demonstration herds. J. Dairy Sci. 95, 4141–4152. doi:10.3168/jds.2011-4550

Everitt, B.S., Hothorn, T., 2010. Cluster analysis: classifying Romano-British pottery and exoplanets, in: A Handbook of Statistical Analyses Using R. Taylor and Francis Group, pp. 315–348.

Ezanno, P., van Schaik, G., Weber, M.F., Heesterbeek, J.A.P., 2005. A modeling study on the sustainability of a certification-and-monitoring program for paratuberculosis in cattle. Vet. Res. 36, 811–826. doi:10.1051/vetres:2005032

FAO, 2017. FAOSTAT, 1993 to 2013.

Garcia, A.B., Shalloo, L., 2015. Invited review: The economic impact and control of paratuberculosis in cattle. J. Dairy Sci. 98, 5019–5039. doi:10.3168/jds.2014-9241

Giese, S., Ahrens, A., 2000. Detection of Mycobacterium avium subsp. paratuberculosis in milk from clinically affected cows by PCR and culture. Vet. Microbiol. 77, 291–297. doi:10.1016/S0378-1135(00)00314-X

Glass, E.J., 2004. Genetic variation and responses to vaccines. Anim. Health Res. Rev. 5, 197–208. doi:10.1079/AHR200469

Glass, E.J., Baxter, R., Leach, R.J., Jann, O.C., 2012. Genes controlling vaccine responses and disease resistance to respiratory viral pathogens in cattle. Vet. Immunol. Immunopathol. 148, 90–99. doi:10.1016/j.vetimm.2011.05.009

Good, M., Clegg, T., Sheridan, H., Yearsely, D., O'Brien, T., Egan, J., Mullowney, P., 2009. Prevalence and distribution of paratuberculosis (Johne's disease) in cattle herds in Ireland. Ir. Vet. J. 62, 597–606. doi:10.1186/2046-0481-62-9-597

Graham, A.L., Shuker, D.M., Pollitt, L.C., Auld, S.K.J.R., Wilson, A.J., Little, T.J., 2011. Fitness consequences of immune responses: Strengthening the empirical framework for ecoimmunology. Funct. Ecol. 25, 5–17. doi:10.1111/j.1365-2435.2010.01777.x

Grandjean, M., 2013. Etude longitudinale des profils d'excrétion de Mycobacterium avium subspecies Paratuberculosis existants chez des bovins en troupeaux laitiers infectés. Ecole Nationale Vétérinaire Agroalimentaire et de l'Alimentation Nantes Atlantique, Nantes, France.

Groenendaal, H., Zagmutt, F.J., Patton, E.A., Wells, S.J., 2015. Cost-benefit analysis of vaccination against Mycobacterium avium ssp. paratuberculosis in dairy cattle, given its cross-reactivity with tuberculosis tests. J. Dairy Sci. doi:10.3168/jds.2014-8914

HAGAN, W.A., 1938. Age as a Factor in Susceptibility to Johne's Disease. Cornell Vet. 28, 34–40.

Hickey, S., Morris, C., Dobbie, J., Lake, D., 2003. Heritability of Johne's disease and survival data from Romney and Merino sheep. Proc. New Zeal. Soc. Anim. Prod. 63, 179–182.

Hines, M.E., Stabel, J.R., Sweeney, R.W., Griffin, F., Talaat, A.M., Bakker, D., Benedictus, G., Davis, W.C., de Lisle, G.W., Gardner, I. a., Juste, R. a., Kapur, V., Koets, A., McNair, J., Pruitt, G., Whitlock, R.H., 2007. Experimental challenge models for Johne's disease: A review and proposed international guidelines. Vet. Microbiol. doi:10.1016/j.vetmic.2007.03.009

Huda, A., Jungersen, G., Lind, P., 2004. Longitudinal study of interferon-gamma, serum antibody and milk antibody responses in cattle infected with Mycobacterium avium subsp. paratuberculosis. Vet. Microbiol. 104, 43–53. doi:10.1016/j.vetmic.2004.08.011

Humphry, R.W., Stott, A.W., Adams, C., Gunn, G.J., 2006. A model of the relationship between the epidemiology of Johne's disease and the environment in suckler-beef herds. Vet. J. 172, 432–45. doi:10.1016/j.tvjl.2005.07.017

Husson, F., Josse, J., Le, S., Mazet, J., 2016. FactoMineR: Multivariate Exploratory Data Analysis and Data Mining.

Jørgensen, J.B., 1982. An improved medium for culture of Mycobacterium paratuberculosis from bovine faeces. Acta Vet. Scand. 23, 325–35.

Kadowaki, H., Suzuki, E., Kojima-Shibata, C., Suzuki, K., Okamura, T., Onodera, W., Shibata, T., Kano, H., 2012. Selection for resistance to swine mycoplasmal pneumonia over 5 generations in Landrace pigs. doi:10.1016/j.livsci.2012.03.014

Kalis, C.H.J., Collins, M.T., Barkema, H.W., Hesselink, J.W., 2004. Certification of herds as free of Mycobacterium paratuberculosis infection: actual pooled faecal results versus certification model predictions. Prev. Vet. Med. 65, 189–204. doi:10.1016/j.prevetmed.2004.07.005

Kalis, C.H.J., Hesselink, J.W., Barkema, H.W., Collins, M.T., 2001. Use of long-term vaccination with a killed vaccine to prevent fecal shedding of Mycobacterium avium subsp paratuberculosis in dairy herds. Am. J. Vet. Res. 62, 270–274. doi:10.2460/ajvr.2001.62.270

Keeling, M.J., Rohani, P., 2008. Modeling infectious diseases in humans and animals. Princeton University Press.

Kirkpatrick, B.W., Shi, X., Shook, G.E., Collins, M.T., 2011. Whole-Genome association analysis of susceptibility to paratuberculosis in Holstein cattle. Anim. Genet. 42, 149–160. doi:10.1111/j.1365-2052.2010.02097.x

Kirkpatrick, B.W., Shook, G.E., 2011. Genetic Susceptibility to Paratuberculosis. Vet. Clin. North Am. - Food Anim. Pract., Johne's Disease 27, 559–571. doi:10.1016/j.cvfa.2011.07.003

Klinkenberg, D., Koets, A., 2015. The long subclinical phase of Mycobacterium avium

ssp. paratuberculosis infections explained without adaptive immunity. Vet. Res. 46, 63. doi:10.1186/s13567-015-0202-3

Koets, A.P., Gröhn, Y.T., 2015. Within- and between-host mathematical modeling of Mycobacterium avium subspecies paratuberculosis (MAP) infections as a tool to study the dynamics of host-pathogen interactions in bovine paratuberculosis. Vet. Res. 46, 60. doi:10.1186/s13567-015-0205-0

Koets, a., Santema, W., Mertens, H., Oostenrijk, D., Keestra, M., Overdijk, M., Labouriau, R., Franken, P., Frijters, a., Nielen, M., Rutten, V., 2010. Susceptibility to paratuberculosis infection in cattle is associated with single nucleotide polymorphisms in Toll-like receptor 2 which modulate immune responses against Mycobacterium avium subspecies paratuberculosis. Prev. Vet. Med. 93, 305–315. doi:10.1016/j.prevetmed.2009.11.008

Kudahl, A.B., Østergaard, S., Sørensen, J.T., Nielsen, S.S., 2007. A stochastic model simulating paratuberculosis in a dairy herd. Prev. Vet. Med. 78, 97–117. doi:10.1016/j.prevetmed.2006.05.015

Kudahl, A.B.B., Nielsen, S.S.S., Østergaard, S., 2008. Economy, Efficacy, and Feasibility of a Risk-Based Control Program Against Paratuberculosis. J. Dairy Sci. 91, 4599–4609. doi:10.3168/jds.2008-1257

Küpper, J., Brandt, H., Donat, K., Erhardt, G., 2012. Heritability estimates for Mycobacterium avium subspecies paratuberculosis status of German Holstein cows tested by fecal culture. J. Dairy Sci. 95, 2734–9. doi:10.3168/jds.2011-4994

Kutzer, M.A.M., Armitage, S.A.O., 2016. Maximising fitness in the face of parasites: a review of host tolerance. Zoology 119, 281–289. doi:10.1016/j.zool.2016.05.011

Larsen, a. B., Merkal, R.S., Cutlip, R.C., 1975. Age of cattle as related to resistance to infection with Mycobacterium paratuberculosis. Am. J. Vet. Res. 36, 255–7.

Laurin, E.L., 2015. Study of shedding patterns of Mycobacterium avium subspecies paratuberculosis in feces, milk, and colostrum of dairy cows and the development of novel early detection methods for Johne's Disease. University of Prince Edward Island.

Lu, Z., Mitchell, R.M.M., Smith, R.L.L., Van Kessel, J.S.S., Chapagain, P.P.P., Schukken, Y.H.H., Grohn, Y.T.T., 2008. The importance of culling in Johne's disease control. J. Theor. Biol. 254, 135–146. doi:10.1016/j.jtbi.2008.05.008

Lu, Z., Schukken, Y.H., Smith, R.L., Grohn, Y.T., 2010. Stochastic simulations of a multi-group compartmental model for Johne's disease on US dairy herds with test-based culling intervention. J. Theor. Biol. 264, 1190–1201. doi:10.1016/j.jtbi.2010.03.034

MacQueen, J., 1967. Some methods for classification and analysis of multivariate observations.

Magnusson, M., Christiansson, A., Svensson, B., Kolstrup, C., 2006. Effect of different premilking manual teat-cleaning methods on bacterial spores in milk. J. Dairy Sci. 89, 3866–75. doi:10.3168/jds.S0022-0302(06)72429-8

Magombedze, G., Eda, S., Ganusov, V. V, 2014. Competition for antigen between Th1 and Th2 responses determines the timing of the immune response switch during Mycobaterium avium subspecies paratuberulosis infection in ruminants. PLoS Comput. Biol. 10, e1003414. doi:10.1371/journal.pcbi.1003414

Magombedze, G., Eda, S., Koets, A., Ganusov, V., Rohde, M., Griffiths, G., 2016. Can Immune Response Mechanisms Explain the Fecal Shedding Patterns of Cattle Infected with Mycobacterium avium Subspecies paratuberculosis? 11, e0146844. doi:10.1371/journal.pone.0146844

Marcé, C., Ezanno, P., Seegers, H., Pfeiffer, D.U., Fourichon, C., 2011. Predicting fadeout versus persistence of paratuberculosis in a dairy cattle herd for management and control purposes: a modelling study. Vet. Res. 42, 36. doi:10.1186/1297-9716-42-36

Marcé, C., Ezanno, P., Seegers, H., Pfeiffer, D.U.U., Fourichon, C., 2011. Within-herd contact structure and transmission of Mycobacterium avium subspecies paratuberculosis in a persistently infected dairy cattle herd. Prev. Vet. Med., Special Issue: SVEPM 2010 2010 Society of Veterinary Epidemiology and Preventive Medicine conference 100, 116–125. doi:10.1016/j.prevetmed.2011.02.004

Marcé, C., Ezanno, P., Weber, M.F., Seegers, H., Pfeiffer, D.U., Fourichon, C., 2010. Invited review: modeling within-herd transmission of Mycobacterium avium subspecies paratuberculosis in dairy cattle: a review. J. Dairy Sci. 93, 4455–70. doi:10.3168/jds.2010-3139

Martcheva, M., Lenhart, S., Eda, S., Klinkenberg, D., Momotani, E., Stabel, J., 2015. An immuno-epidemiological model for Johne's disease in cattle. Vet. Res. 46, 69. doi:10.1186/s13567-015-0190-3

MATTHEWS, H.T., 1947. On Johne's disease. Vet. Rec. 59, 397–401.

McAloon, C.G., Doherty, M.L., Whyte, P., More, S.J., McV Messam, L.L., Good, M., Mullowney, P., Strain, S., Green, M.J., 2016. Bayesian estimation of prevalence of paratuberculosis in dairy herds enrolled in a voluntary Johne's Disease Control Programme in Ireland. Prev. Vet. Med. 128, 95–100. doi:10.1016/j.prevetmed.2016.04.014

McAloon, C.G., Whyte, P., More, S.J., Green, M.J., O'Grady, L., Garcia, A., Doherty, M.L., 2016. The effect of paratuberculosis on milk yield—A systematic review and meta-analysis. J. Dairy Sci. 99, 1449–1460. doi:10.3168/jds.2015-10156

McDonald, W.L., Ridge, S.E., Hope, a F., Condron, R.J., 1999. Evaluation of diagnostic tests for Johne's disease in young cattle. Aust. Vet. J. 77, 113–119.

McSpadden, K., Caires, K., Zanella, R., 2013. The Effect of Mycobacterium avium subspecies paratuberculosis Exposure on Animal Health. Acta Sci. Vet. 41, 1095.

Mitchell, R.M., Medley, G., 2012. A meta-analysis of the effect of dose and age at exposure on shedding of Mycobacterium avium subspecies paratuberculosis (MAP) in experimentally infected calves and cows. Epidemiol. Infect. 140, 231–

246. doi:10.1017/S0950268811000689

Mitchell, R.M., Schukken, Y., Koets, A., Weber, M., Bakker, D., Stabel, J., Whitlock, R.H., Louzoun, Y., 2015. Differences in intermittent and continuous fecal shedding patterns between natural and experimental Mycobacterium avium subspecies paratuberculosis infections in cattle. Vet. Res. 46, 66. doi:10.1186/s13567-015-0188-x

Mitchell, R.M.M., Whitlock, R.H.H., Stehman, S.M.M., Benedictus, a., Chapagain, P.P.P., Grohn, Y.T.T., Schukken, Y.H.H., 2008. Simulation modeling to evaluate the persistence of Mycobacterium avium subsp. paratuberculosis (MAP) on commercial dairy farms in the United States. Prev. Vet. Med. 83, 360–380. doi:10.1016/j.prevetmed.2007.09.006

Morris, C.A.A., 2006. A review of genetic resistance to disease in Bos taurus cattle. Vet. J. 174, 481–491. doi:10.1016/j.tvjl.2006.09.006

Mortier, R.A.R., Barkema, H.W., Buck, J. De, De Buck, J., 2015. Susceptibility to and diagnosis of Mycobacterium avium subspecies paratuberculosis infection in dairy calves: a review. Prev. Vet. Med. 121, 189–198. doi:10.1016/j.prevetmed.2015.08.011

Mortier, R.A.R., Barkema, H.W., Bystrom, J.M., Illanes, O., Orsel, K., Wolf, R., Atkins, G., De Buck, J., 2013. Evaluation of age-dependent susceptibility in calves infected with two doses of Mycobacterium avium subspecies paratuberculosis using pathology and tissue culture. Vet. Res. 44, 94. doi:10.1186/1297-9716-44-94

Mortier, R.A.R., Barkema, H.W., Orsel, K., Wolf, R., De Buck, J., 2014. Shedding patterns of dairy calves experimentally infected with Mycobacterium avium subspecies paratuberculosis. Vet. Res. 45, 71. doi:10.1186/s13567-014-0071-1

Mortier, R.A.R., Barkema, H.W., Wilson, T.A., Sajobi, T.T., Wolf, R., De Buck, J., 2014. Dose-dependent interferon-gamma release in dairy calves experimentally infected with Mycobacterium avium subspecies paratuberculosis. Vet. Immunol. Immunopathol. 161, 205–10. doi:10.1016/j.vetimm.2014.08.007

Mortier, R. a R., Barkema, H.W., Negron, M.E., Orsel, K., Wolf, R., De Buck, J., 2014. Antibody response early after experimental infection with Mycobacterium avium subspecies paratuberculosis in dairy calves. J. Dairy Sci. 97, 5558–5565. doi:10.3168/jds.2014-8139

Mortier, R., Barkema, H.W., Orsel, K., Roy, G., Wolf, R., De Buck, J., 2013. Age and Dose Dependent Susceptibility to Mycobacterium avium subsp. paratuberculosis Infection in Dairy Cattle. WCDS Adv. Dairy Technol. 25.

Mortier, R., Orsel, K., Barkema, H.W., Atkins, G., Buck, J. De, 2011. Age and Dose Dependent Susceptibility to Mycobacterium Avium Subsp . Paratuberculosis in Dairy Cattle. WCDS Adv. Dairy Technol. University of Calgary.

Napolitano, G., Maximov, V., Holmes, J., Botts, F., Tinazay, T., 2013. TACKLING CLIMATE CHANGE THROUGH LIVESTOCK: A global assessment of emissions and mitigation opportunities.

Neibergs, H.L., Settles, M.L., Whitlock, R.H., Taylor, J.F., 2010. GSEA-SNP identifies genes associated with Johne's disease in cattle. Mamm. Genome 21, 419–425. doi:10.1007/s00335-010-9278-2

Nielsen, S.S., 2008. Transitions in diagnostic tests used for detection of Mycobacterium avium subsp. paratuberculosis infections in cattle. Vet. Microbiol. 132, 274–82. doi:10.1016/j.vetmic.2008.05.018

Nielsen, S.S., Toft, N., 2009. A review of prevalences of paratuberculosis in farmed animals in Europe. Prev. Vet. Med. 88, 1–14. doi:10.1016/j.prevetmed.2008.07.003

OIE-WAHIS, 2017. Système mondial d'information sanitaire- OIE (World Organisation for Animal Health) [WWW Document]. URL http://www.oie.int/fr/sante-animale-dans-le-monde/le-systeme-mondial-dinformation-sanitaire/systeme-mondial-dinformation-sanitaire/ (accessed 10.22.17).

Ott, S.L., Wells, S.J., Wagner, B.A., 1999. Herd-level economic losses associated with Johne's disease on US dairy operations. Prev. Vet. Med. 40, 179–192. doi:10.1016/S0167-5877(99)00037-9

Pauciullo, A., Küpper, J., Brandt, H., Donat, K., Iannuzzi, L., Erhardt, G., 2015. Wingless-type MMTV integration site family member 2 (WNT2) gene is associated with resistance to MAP in faecal culture and antibody response in Holstein cattle. Anim. Genet. 46, 122–132. doi:10.1111/age.12261

Pérez de Val, B., Nofrarías, M., López-Soria, S., Garrido, J.M., Vordermeier, H.M., Villarreal-Ramos, B., Martín, M., Puentes, E., Juste, R.A., Domingo, M., 2012. Effects of vaccination against paratuberculosis on tuberculosis in goats: diagnostic interferences and cross-protection. BMC Vet. Res. 8, 191. doi:10.1186/1746-6148-8-191

PHOCAS, F., BELLOC, C., BIDANEL, J., DELABY, L., DOURMAD, J.-Y., DUMONT, B., EZANNO, P., FORTUN-LAMOTHE, L., FOUCRAS, G., FRAPPAT, B., GONZALEZ-GARCIA, E., HAZARD, D., LARZUL, C., LUBAC, S., MIGNON-GRASTEAU, S., MORENO-ROMIEUX, C., TIXIER-BOICHARD, M., BROCHARD, M., 2017. Which animal breeding programs for agro-ecological livestock farming systems? INRA Prod Anim 30, 31–46.

Pinedo, P.J., Buergelt, C.D., Wu, R., Donovan, G.A., Williams, J.E., Rae, D.O., Smith, R.A., 2007. Genetic resistance to Johne's disease in four cattle breeds: a candidate gene case control study, preliminary results., in: Proceedings of the Fortieth Annual Conference American Association of Bovine Practitioners. American Association of Bovine Practitioners, p. 227–227\r312.

Pouillot, R.R., Dufour, B., Durand, B.B., 2004. A deterministic and stochastic simulation model for intra-herd paratuberculosis transmission. Vet. Res. 35, 53–68. doi:10.1051/vetres:2003046

Pradhan, A.K., Mitchell, R.M., Kramer, A.J., Zurakowski, M.J., Fyock, T.L., Whitlock, R.H., Smith, J.M., Hovingh, E., Van Kessel, J.A.S., Karns, J.S., Schukken, Y.H., 2011. Molecular epidemiology of Mycobacterium avium subsp. paratuberculosis

in a longitudinal study of three dairy herds. J. Clin. Microbiol. 49, 893–901. doi:10.1128/JCM.01107-10

Purdie, A.C., Plain, K.M., Begg, D.J., de Silva, K., Whittington, R.J., 2011. Candidate gene and genome-wide association studies of Mycobacterium avium subsp. paratuberculosis infection in cattle and sheep: A review. Comp. Immunol. Microbiol. Infect. Dis. 34, 197–208. doi:10.1016/j.cimid.2010.12.003

Råberg, L., Graham, A.L., Read, A.F., 2009. Decomposing health: tolerance and resistance to parasites in animals. Philos. Trans. R. Soc. Lond. B. Biol. Sci. 364, 37–49. doi:10.1098/rstb.2008.0184

Råberg, L., Sim, D., Read, A.F., 2007. Disentangling genetic variation for resistance and tolerance to infectious diseases in animals. Science 318, 812–4. doi:10.1126/science.1148526

R Core Team, 2016. R: A Language and Environment for Statistical Computing.

Raizman, E.A., Wells, S.J., Muñoz-Zanzi, C.A., Tavornpanich, S., 2011. Estimated within-herd prevalence (WHP) of Mycobacterium avium subsp. paratuberculosis in a sample of Minnesota dairy herds using bacterial culture of pooled fecal samples. Can. J. Vet. Res. 75, 112–6.

Rankin, J.D., 1962. The experimental infection of cattle with mycobacterium johnei. J. Comp. Pathol. Ther. 72, 113–117. doi:10.1016/S0368-1742(62)80013-7

Rankin, J.D., 1962. The experimental infection of cattle with Mycobacterium johnei. IV. Adult cattle maintained in an infectious environment. J. Comp. Pathol. 72, 113–117. doi:10.1016/S0368-1742(62)80013-7

Restif, O., Koella, J.C.C., 2004. Concurrent evolution of resistance and tolerance to pathogens 164. doi:10.1086/423713

Richardson, E., More, S., 2009. Direct and indirect effects of Johne's disease on farm and animal productivity in an Irish dairy herd. Ir. Vet. J. 62, 526–32. doi:10.1186/2046-0481-62-8-526

Riemann, H.P., Abbas, B., 1983. Diagnosis and control of bovine paratuberculosis (Johne's disease). Adv. Vet. Sci. Comp. Med. 27, 481–506.

Robins, J., Bogen, S., Francis, A., Westhoek, A., Kanarek, A., Lenhart, S., Eda, S., 2015a. Agent-based model for Johne's disease dynamics in a dairy herd. Vet. Res. 46, 68. doi:10.1186/s13567-015-0195-y

Robins, J., Bogen, S., Francis, A., Westhoek, A., Kanarek, A., Lenhart, S., Eda, S., 2015b. Agent-based model for Johne's disease dynamics in a dairy herd. Vet. Res. 46, 68. doi:10.1186/s13567-015-0195-y

Rodrick, J.C., 1996. Immunology: Resistance to Paratuberculosis. Vet. Clin. North Am. Food Anim. Pract. 12, 313–343. doi:10.1016/S0749-0720(15)30409-6

Rossiter, C.A., Burhans, W.S., 1996. Farm-specific approach to paratuberculosis (Johne's disease) control. Vet. Clin. North Am. Food Anim. Pract. 12, 383–415. doi:10.1016/S0749-0720(15)30413-8

Rossiter, C. a, Burhans, W.S., 1996. Farm-specific approach to paratuberculosis (Johne's disease) control. Vet. Clin. North Am. Food Anim. Pract. 12, 383–415.

Ruiz-Larrañaga, O., Manzano, C., Iriondo, M., Garrido, J., Juste, R.A., Estonba, A., 2007. Genetic association between bovine NRAMP1 and CARD15 genes and infection by Mycobacterium avium subsp . paratuberculosis, in: Nielsen, S.S. (Ed.), Proceedings of the 9th International Colloquium on Paratuberculosis, Tsukuba, Japan, 29 October - 2 November 2007. pp. 46–49.

Ruiz-Larrañaga, O., Manzano, C., Iriondo, M., Garrido, J.M., Molina, E., Vazquez, P., Juste, R.A., Estonba, A., 2011. Genetic variation of toll-like receptor genes and infection by Mycobacterium avium ssp. paratuberculosis in Holstein-Friesian cattle. J. Dairy Sci. 94, 3635–3641. doi:10.3168/jds.2010-3788

Rupp, R., Boichard, D., 2003. Genetics of resistance to mastitis in dairy cattle. Vet. Res. 34, 671–688. doi:10.1051/vetres:2003020

Sanchez, M.-P.M.P., Guatteo, R., Davergne, A., Grohs, C., Capitan, A., Blanquefort, P., Delafosse, A., Joly, A., Ngwa-Mbot, D., Biet, F., Fourichon, C., Boichard, D., 2016. Whole genome association analysis of resistance / susceptibility to paratuberculosis in French Holstein and Normande cattle. 13 Int. Colloq. Paratuberculosis 82.

Schmid-Hempel, P., 2011. Evolutionary parasitology : the integrated study of infections, immunology, ecology, and genetics. Oxford University Press.

Schneider, D.S., Ayres, J.S., 2008. Two ways to survive infection: what resistance and tolerance can teach us about treating infectious diseases. Nat. Rev. Immunol. 8, 889–95. doi:10.1038/nri2432

Scott, , Wells, J., C
K.R., Collins, J.E., Cernicchiaro, N., Whitlock, R.H., 2006. Evaluation of a Rapid Fecal PCR Test for Detection of Mycobacterium avium subsp. paratuberculosis in Dairy Cattle. Clin. VACCINE Immunol. 13, 1125–1130. doi:10.1128/CVI.00236-06

Seitz, S.E., Heider, L.E., Heuston, W.D., Bech-Nielsen, S., Rings, D.M., Spangler, L., 1989. Bovine fetal infection with Mycobacterium paratuberculosis. J. Am. Vet. Med. Assoc. 194, 1423–6.

Settles, M., Zanella, R., McKay, S.D., Schnabel, R.D., Taylor, J.F., Whitlock, R., Schukken, Y., Van Kessel, J.S., Smith, J.M., Neibergs, H., 2009. A whole genome association analysis identifies loci associated with Mycobacterium avium subsp. paratuberculosis infection status in US holstein cattle. Anim. Genet. 40, 655–662. doi:10.1111/j.1365-2052.2009.01896.x

Shalloo, L., Dillon, P., Rath, M., Wallace, M., 2004. Description and Validation of the Moorepark Dairy System Model. J. Dairy Sci. 87, 1945–1959. doi:10.3168/jds.S0022-0302(04)73353-6

Sharma, B.S., Leyva, I., Schenkel, F., Karrow, N.A., 2006. Association of Toll-Like Receptor 4 Polymorphisms with Somatic Cell Score and Lactation Persistency in Holstein Bulls. J. Dairy Sci. 89, 3626–3635. doi:10.3168/jds.S0022-

0302(06)72402-X

Singh, S.V., 2014. Recent Approaches in Diagnosis and Control of Mycobacterial Infections with Special Reference to Mycobacterium Avium Subspecies. Adv. Anim. Vet. Sci. 1–12. doi:10.14737/journal.aavs/2014/2.1s.1.12

Singh, S. V, Dhama, K., Chaubey, K.K., Kumar, N., Singh, P.K., Sohal, J.S., Gupta, S., Singh, A. V, Verma, A.K., Tiwari, R., Mahima, Chakraborty, S., Deb, R., 2013. Impact of host genetics on susceptibility and resistance to Mycobacterium avium subspecies Paratuberculosis infection in domestic ruminants. Pakistan J. Biol. Sci. 16, 251–266.

Smith, R.L., Schukken, Y.H., Gröhn, Y.T., 2015. A new compartmental model of Mycobacterium avium subsp. paratuberculosis infection dynamics in cattle. Prev. Vet. Med. 122, 298–305. doi:10.1016/j.prevetmed.2015.10.008

Snowder, G.D., Dale, L., Vleck, V., Cundiff, L. V, Bennett, G.L., Vleck, L.D. Van, 2006. Bovine respiratory disease in feedlot cattle: Environmental, genetic, and economic factors. J. Anim. Sci 84, 1999–2008. doi:10.2527/jas.2006-046

Snowder, G.D., Van Vleck, L.D., Cundiff, L. V, Bennett, G.L., 2005. Influence of breed, heterozygosity, and disease incidence on estimates of variance components of respiratory disease in preweaned beef calves. J. Anim. Sci. 83, 1247–61.

Sockett, D.C., Conrad, T.A., Thomas, C.B., Collins, M.T., 1992. Evaluation of four serological tests for bovine paratuberculosis. J. Clin. Microbiol. 30, 1134–9.

Stabel, J.R., Bradner, L., Robbe-Austerman, S., Beitz, D.C., 2014. Clinical disease and stage of lactation influence shedding of Mycobacterium avium subspecies paratuberculosis into milk and colostrum of naturally infected dairy cows. J. Dairy Sci. 97, 6296–6304. doi:10.3168/jds.2014-8204

Stabel, J.R.R., Palmer, M.V. V., Harris, B., Plattner, B., Hostetter, J., Robbe-Austerman, S., 2009. Pathogenesis of Mycobacterium avium subsp. paratuberculosis in neonatal calves after oral or intraperitoneal experimental infection. Vet. Microbiol. 136, 306–313. doi:10.1016/j.vetmic.2008.11.025

Stewart, D.J., Vaughan, J. a., Stiles, P.L., Noske, P.J., Tizard, M.L. V, Prowse, S.J., Michalski, W.P., Butler, K.L., Jones, S.L., 2007. A long-term bacteriological and immunological study in Holstein-Friesian cattle experimentally infected with Mycobacterium avium subsp. paratuberculosis and necropsy culture results for Holstein-Friesian cattle, Merino sheep and Angora goats. Vet. Microbiol. 122, 83–96. doi:10.1016/j.vetmic.2006.12.030

Subharat, S., Shu, D., Wedlock, D.N., Price-Carter, M., de Lisle, G.W., Luo, D., Collins, D.M., Buddle, B.M., 2012. Immune responses associated with progression and control of infection in calves experimentally challenged with Mycobacterium avium subsp. paratuberculosis. Vet. Immunol. Immunopathol. 149, 225–36. doi:10.1016/j.vetimm.2012.07.005

Sweeney, R.W., Whitlock, R.H., Rosenberger, A.E., 1992. Mycobacterium paratuberculosis isolated from fetuses of infected cows not manifesting signs of

the disease. Am. J. Vet. Res. 53, 477–480.

Thinsungnoen, T., Kaoungku, N., Durongdumronchai, P., Kerdprasop, K., Kerdprasop, N., 2015. The Clustering Validity with Silhouette and Sum of Squared Errors. doi:10.12792/iciae2015.012

Tixier-Boichard, M., Verrier, E., Rognon, X., Zerjal, T., 2015. Farm animal genetic and genomic resources from an agroecological perspective. Front. Genet. 6, 153. doi:10.3389/fgene.2015.00153

UN, 2017. World Population Prospects - Population Division - United Nations.

Vallee, H., Rinjard, P., 1926. Etudes sur l'entérite paratuberculeuse des bovides (note preliminaire). Rev. Générale Médécine Vétérinaire 35, 1–9.

van Hulzen, K.J.E., Koets, A.P., Nielen, M., Heuven, H.C.M., van Arendonk, J. a M., Klinkenberg, D., Rutten, V.P.M.G., Schukken, Y.H., 2014. The effect of genetic selection for Johne's disease resistance in dairy cattle: Results of a genetic-epidemiological model. J. Dairy Sci. 97, 1762–73. doi:10.3168/jds.2013-7032

van Hulzen, K.J.E.J.E., Koets, A.P.P., Nielen, M., Hoeboer, J., van Arendonk, J.A.M.A.M., Heuven, H.C.M.C.M., 2012. Genetic variation for infection status as determined by a specific antibody response against Mycobacterium avium subspecies paratuberculosis in milk of Dutch dairy goats. J. Dairy Sci. 95, 6145–6151. doi:10.3168/jds.2012-5616

van Hulzen, K.J.E.J.E., Nielen, M., Koets, A.P.P., de Jong, G., van Arendonk, J.A.M. a M., Heuven, H.C.M.C.M., 2011. Effect of herd prevalence on heritability estimates of antibody response to Mycobacterium avium subspecies paratuberculosis. J. Dairy Sci. 94, 992–997. doi:10.3168/jds.2010-3472

van Roermund, H.J.W., Weber, M.F., Graat, E.A.M., de Jong, M.C.M., 2002. Monitoring programmes for paratuberculosis-unsuspected cattle herds, based on quantification of between-herd transmission. 7th Int. Colloq. Paratuberculosis 371–375.

van Roermund, H.J.W.J.W., Bakker, D., Willemsen, P.T.J.T.J., de Jong, M.C.M.C.M., 2007. Horizontal transmission of Mycobacterium avium subsp. paratuberculosis in cattle in an experimental setting: calves can transmit the infection to other calves. Vet. Microbiol. 122, 270–279. doi:10.1016/j.vetmic.2007.01.016

Vázquez, P., Ruiz-Larrañaga, O., Garrido, J.M., Iriondo, M., Manzano, C., Agirre, M., Estonba, A., Juste, R. a., 2014. Genetic association analysis of paratuberculosis forms in Holstein-Friesian cattle. Vet. Med. Int. 2014, 1–8. doi:10.1155/2014/321327

Vissers, M.M.M., Driehuis, F., Te Giffel, M.C., De Jong, P., Lankveld, J.M.G., 2006. Improving farm management by modeling the contamination of farm tank milk with butyric acid bacteria. J. Dairy Sci. 89, 850–8. doi:10.3168/jds.S0022-0302(06)72148-8

Whitlock, R.., Wells, S.., Sweeney, R.., Van Tiem, J., 2000. ELISA and fecal culture for paratuberculosis (Johne's disease): sensitivity and specificity of each method. Vet. Microbiol. 77, 387–398. doi:10.1016/S0378-1135(00)00324-2

Whitlock, R.H., Buergelt, C., 1996. Preclinical and clinical manifestations of paratuberculosis (including pathology). Vet. Clin. North Am. Food Anim. Pract. 12, 345–356.

Whittington, R.J., Reddacliff, L.A., Marsh, I., McAllister, S., Saunders, V., 2000. Temporal patterns and quantification of excretion of Mycobacterium avium subsp paratuberculosis in sheep with Johne's disease. Aust. Vet. J. 78, 34–7.

WHITTINGTON, R.J., Sergeant, E.S., 2001. Progress towards understanding the spread, detection and control of Mycobacterium avium subsp paratuberculosis in animal populations. Aust. Vet. J. 79, 267–278. doi:10.1111/j.1751-0813.2001.tb11980.x

Whittington, R.J., Windsor, P.A., 2009. In utero infection of cattle with Mycobacterium avium subsp. paratuberculosis: a critical review and meta-analysis. Vet. J. 179, 60–9. doi:10.1016/j.tvjl.2007.08.023

Windsor, P.A., Whittington, R.J., 2010. Evidence for age susceptibility of cattle to Johne's disease. Vet. J. 184, 37–44. doi:10.1016/j.tvjl.2009.01.007

Yayo Ayele, W., Macháčková, M., Pavlík, I., 2001. The transmission and impact of paratuberculosis infection in domestic and wild ruminants. Vet. Med. (Praha).

Zanella, R., Settles, M.L., McKay, S.D., Schnabel, R., Taylor, J., Whitlock, R.H., Schukken, Y., Van Kessel, J.S., Smith, J.M., Neibergs, H.L., 2011. Identification of loci associated with tolerance to Johne's disease in Holstein cattle. Anim. Genet. 42, 28–38. doi:10.1111/j.1365-2052.2010.02076.x

Zare, Y., Shook, G.E., Collins, M.T., Kirkpatrick, B.W., 2014. Short communication: Heritability estimates for susceptibility to Mycobacterium avium subspecies paratuberculosis infection defined by ELISA and fecal culture test results in Jersey cattle. J. Dairy Sci. 97, 4562–4567. doi:10.3168/jds.2013-7426

Zare, Y., Shook, G.E., Collins, M.T., Kirkpatrick, B.W., 2014a. Genome-wide association analysis and genomic prediction of Mycobacterium avium subspecies paratuberculosis infection in US Jersey cattle. PLoS One 9. doi:10.1371/journal.pone.0088380

Zare, Y., Shook, G.E., Collins, M.T.M.M.T., Kirkpatrick, B.W.B.B.W., Nielsen, S., Bjerre, H., Toft, N., Chase, C., Hurley, D., Reber, A., Clarke, C., Lombard, J., Gardner, I., Jafarzadeh, S., Fossler, C., Harris, B., Ott, S., Wells, S., Wagner, B., Stabel, J., Shook, G.E., Chaffer, M., Wu, X., Ezra, E., Gonda, M., Chang, Y., Shook, G.E., Collins, M.T.M.M.T., Kirkpatrick, B.W.B.B.W., Hinger, M., Brandt, H., Erhardt, G., Berry, D., Good, M., Mullowney, P., Cromie, A., More, S., Attalla, S., Seykora, A., Cole, J., Heins, B., Mortensen, H., Nielsen, S., Berg, P., Hulzen, K. van, Nielen, M., Koets, A., Jong, G. de, Arendonk, J. van, Kupper, J., Brandt, H., Donat, K., Erhardt, G., Sechi, L., Scanu, A., Molicotti, P., Cannas, S., Mura, M., Jostins, L., Ripke, S., Weersma, R., Duerr, R., McGovern, D., Matukumalli, L., Lawley, C., Schnabel, R., Taylor, J., Allan, M., Settles, M., Zanella, R., McKay, S., Schnabel, R., Taylor, J., Kirkpatrick, B.W.B.B.W., Shi, X., Shook, G.E., Collins, M.T.M.M.T., Minozzi, G., Buggiotti, L., Stella, A., Strozzi, F., Luini, M., Pant, S., Schenkel, F., Verschoor, C., You, Q., Kelton, D., Zanella, R., Settles, M., McKay, S., Schnabel, R., Taylor, J., Hulzen, K. van, Schopen, G.,

Arendonk, J. van, Nielen, M., Koets, A., Shin, S., Cho, D., Collins, M.T.M.M.T., Collins, M.T.M.M.T., Gardner, I., Garry, F., Roussel, A., Wells, S., Collins, M.T.M.M.T., Collins, M.T.M.M.T., Kenefick, K., Sockett, D., Lambrecht, R., Mcdonald, J., Sockett, D., Carr, D., Collins, M.T.M.M.T., Cruickshank, J., Dentine, M., Berger, P., Kirkpatrick, B.W.B.B.W., Boichard, D., Chung, H., Dassonneville, R., David, X., Eggen, A., Aulchenko, Y., Ripke, S., Isaacs, A., Duijn, C. Van, Browning, S., Browning, B., Haldar, T., Ghosh, S., Aulchenko, Y., Koning, D. de, Haley, C., Amin, N., Duijn, C. Van, Aulchenko, Y., Uemoto, Y., Abe, T., Tameoka, N., Hasebe, H., Inoue, K., Minozzi, G., Williams, J., Stella, A., Strozzi, F., Luini, M., Bacanu, S., Devlin, B., Roeder, K., Thompson, E., Shaw, R., Burton, P., Clayton, D., Cardon, L., Craddock, N., Deloukas, P., Meuwissen, T., Hayes, B., Goddard, M., Schneider, J., Rempel, L., Snelling, W., Wiedmann, R., Nonneman, D., Peters, S., Kizilkaya, K., Garrick, D., Fernando, R., Reecy, J., Kizilkaya, K., Tait, R., Garrick, D., Fernando, R., Reecy, J., Fernando, R., Nettleton, D., Southey, B., Dekkers, J., Rothschild, M., Sing, T., Sander, O., Beerenwinkel, N., Lengauer, T., Wray, N., Yang, J., Goddard, M., Visscher, P., Sorge, U., Lissemore, K., Godkin, A., Hendrick, S., Wells, S., Jakobsen, M., Alban, L., Nielsen, S., Ruiz-Larranaga, O., Garrido, J., Manzano, C., Iriondo, M., Molina, E., Hollis-Moffatt, J., Phipps-Green, A., Chapman, B., Jones, G., Rij, A. van, Kotlowski, R., Bernstein, C., Silverberg, M., Krause, D., Lee, S., Werf, J. van der, Hayes, B., Goddard, M., Visscher, P., Kenny, E., Pe'er, I., Karban, A., Ozelius, L., Mitchell, A., Julia, A., Domenech, E., Ricart, E., Tortosa, R., Garcia-Sanchez, V., Yamazaki, K., Umeno, J., Takahashi, A., Hirano, A., Johnson, T., Cheung, Y., Watkinson, J., Anastassiou, D., Buchsbaum, S., Bercovich, B., Ziv, T., Ciechanover, A., Morange, P., Bezemer, I., Saut, N., Bare, L., Burgos, G., Fischer, A., Schmid, B., Ellinghaus, D., Nothnagel, M., Gaede, K., Haritunians, T., Jones, M., McGovern, D., Shih, D., Barrett, R., Fransen, K., Visschedijk, M., Sommeren, S. van, Fu, J., Franke, L., Chen, L., Su, L., Li, J., Zheng, Y., Yu, B., 2014b. Genome-wide association analysis and genomic prediction of Mycobacterium avium subspecies paratuberculosis infection in US Jersey cattle. PLoS One 9, e88380. doi:10.1371/journal.pone.0088380

Publications

RESEARCH PAPERS

R. Ben Romdhane, G. Beaunée, G. Camanes, R. Guatteo, C. Fourichon, P. Ezanno, 2017. Which phenotypic traits of resistance should be improved in cattle to control paratuberculosis dynamics in a dairy herd: a modelling approach. Vet. Res. 48, 62. doi:10.1186/s13567-017-0468-8

ORAL COMMUNICATION

R. BEN ROMDHANE, G. BEAUNEE, G. CAMANES, R. GUATTEO, C. FOURICHON, P. EZANNO, 2017; Identification of phenotypic traits of resistance to limit Map spread in a dairy cattle herd using a modelling approach. , Annual Meeting of the Society for Veterinary Epidemiology and Preventive Medicine, Inverness, Scotland, UK

G. CAMANES, A. JOLY, **R. BEN ROMDHANE,** P. EZANNO, 2016; How to avoid degradation of paratuberculosis prevalence in dairy cattle herd? An individual-based modelling approach. Modelling in Animal Health conference, Nantes, France

POSTERS

R. BEN ROMDHANE, G. BEAUNEE, G. CAMANES, R. GUATTEO, C. FOURICHON, P. EZANNO, 2016; «Which phenotypic traits of dairy cattle resistance to bovine paratuberculosis can enhance disease control at herd scale? ». 13th International Colloquium on Paratuberculosis, Nantes, France.

G. CAMANES, A. JOLY, **R. BEN ROMDHANE**, G. BEAUNNEE, P. EZANNO, 2016; « Accounting for individual characteristics in modelling the within-herd spread of bovine paratuberculosis». 13th International Colloquium on Paratuberculosis, Nantes, France.

R. BEN ROMDHANE, G. BEAUNEE, G. CAMANES, R. GUATTEO, C. FOURICHON, P. EZANNO, 2016; «Targeting phenotypic traits to improve resistance to paratuberculosis in dairy cattle: a modelling approach». Annual Meeting of the Society for Veterinary Epidemiology and Preventive Medicine, Elsinore, Denmark.

Additional file 1

Additional file 1: Description of the used within herd model of Map Spread

A Equations for the within-herd dynamic

The description of the model we used corresponds to the within-herd model described in [2] and based on [11]. The set of parameters used are described in tables 1, 2 and 3.

Notations

In the following equations, $X_{(t,a)}$ is the number of animals in health state X at time t and age a. Age is given in weeks until the entry in the adult stage (from 1 to cal, with intermediary stages w for weaning age, y for young heifers age, h for heifers age and u for maximal age in the susceptible compartments), then by age group (P_1 to P_{5+}). Some variables can have a prefix: "b" for births in health states X (bX), "N" for animals transiting between two health states (NX) and "s" for exits (mortality and culling) (sX). After entering the adult stage, flows corresponding to aging are noted using a superscript ng, whereas those remaining in the same age group are noted using a superscript sg. $N_{(t,a)}$ is the number of animals of age a at time t. Average duration in health states are noted by v_X. The remaining terms used are defined when introduced.

Equations for the updating of variables describing health states

In this section we introduce the equations for the updating of variables corresponding to the health states, for a given herd i.

Susceptible (S) and No more Susceptible (R)

$$S_{(t+1,a=1)} = bS_{(t)} - \text{N}T_{(t+1,a)}$$

$$S_{(t+1,a\in[2;52])} = \left[S_{(t,a-1)} - sS_{(t,a-1)}\right] - \text{N}T_{(t+1,a)}$$

$$R_{(t+1,53)} = S_{(t,52)} - sS_{(t,52)}$$

$$R_{(t+1,a\in[54;cal])} = R_{(t,a-1)} - sR_{(t,a-1)}$$

–

$$R_{(t+1,P_1)} = R^{sg}_{(t,P_1)} - sR^{sg}_{(t,P_1)} + R_{(t,cal)} - sR_{(t,cal)}$$

$$R_{(t+1,P_i\in[P_2;P_4])} = R^{sg}_{(t,P_i)} - sR^{sg}_{(t,P_i)} + R^{ng}_{(t,P_{i-1})} - sR^{ng}_{(t,P_{i-1})}$$

$$R_{(t+1,P_{5+})} = R_{(t,P_{5+})} - sR_{(t,P_{5+})} + R^{ng}_{(t,P_4)} - sR^{ng}_{(t,P_4)}$$

Transiently infected (T)

$$T_{(t+1,a=1)} = \; bT_{(t)} + \text{N}T_{(t+1,a)}$$

$$T_{(t+1,a\in[2;52])} = \left[T_{(t,a-1)} - sT_{(t,a-1)}\right] - \text{N}L_{(t+1,a)} + \text{N}T_{(t+1,a)}$$

$$T_{(t+1,a\in[53;cal])} = \left[T_{(t,a-1)} - sT_{(t,a-1)}\right] - \text{N}L_{(t+1,a)}$$

Latently infected (L)

$$L_{(t+1,a=2)} = \; \text{N}L_{(t+1,a)}$$

$$L_{(t+1,a\in[3;h])} = \; \left[L_{(t,a-1)} - sL_{(t,a-1)}\right] + \text{N}L_{(t+1,a)}$$

$$L_{(t+1,a\in[h+1;cal])} = \; \left[L_{(t,a-1)} - sL_{(t,a-1)}\right] - \text{N}Is_{(t+1,a)} + \text{N}L_{(t+1,a)}$$

$-$

$$L_{(t+1,P_1)} = \; \left[L^{sg}_{(t,P_1)} - sL^{sg}_{(t,P_1)} + L_{(t,cal)} - sL_{(t,cal)} + T_{(t,cal)} - sT_{(t,cal)}\right] - \text{N}Is_{(t+1,P_1)}$$

$$L_{(t+1,P_i\in[P_2;P_4])} = \left[L^{sg}_{(t,P_i)} - sL^{sg}_{(t,P_i)} + L^{ng}_{(t,P_{i-1})} - sL^{ng}_{(t,P_{i-1})}\right] - \text{N}Is_{(t+1,P_i)}$$

$$L_{(t+1,P_{5+})} = \left[L_{(t,P_{5+})} - sL_{(t,P_{5+})} + L^{ng}_{(t,P_4)} - sL^{ng}_{(t,P_4)}\right] - \text{N}Is_{(t+1,P_{5+})}$$

Moderate shedding (Is)

$$Is_{(t+1,a=h+1)} = \; \text{N}Is_{(t+1,a)}$$

$$Is_{(t+1,a\in[h+2;cal])} = \; \left[Is_{(t,a-1)} - sIs_{(t,a-1)}\right] - \text{N}Ic_{(t+1,a)} + \text{N}Is_{(t+1,a)}$$

$-$

$$Is_{(t+1,P_1)} = \; \left[Is^{sg}_{(t,P_1)} - sIs^{sg}_{(t,P_1)} + Is_{(t,cal)} - sIs_{(t,cal)}\right] - \text{N}Ic_{(t+1,P_1)} + \text{N}Is_{(t+1,P_1)}$$

$$Is_{(t+1,P_i\in[P_2;P_4])} = \left[Is^{sg}_{(t,P_i)} - sIs^{sg}_{(t,P_i)} + Is^{ng}_{(t,P_{i-1})} - sIs^{ng}_{(t,P_{i-1})}\right] - \text{N}Ic_{(t+1,P_i)} + \text{N}Is_{(t+1,P_i)}$$

$$Is_{(t+1,P_{5+})} = \left[Is_{(t,P_{5+})} - sIs_{(t,P_{5+})} + Is^{ng}_{(t,P_4)} - sIs^{ng}_{(t,P_4)}\right] - \text{N}Ic_{(t+1,P_{5+})} + \text{N}Is_{(t+1,P_{5+})}$$

High shedding and clinically affected (Ic)

$$Ic_{(t+1,a=h+2)} = \; \text{N}Ic_{(t+1,a)}$$

$$Ic_{(t+1,a\in[h+3;cal])} = \; \left[Ic_{(t,a-1)} - sIc_{(t,a-1)}\right] + \text{N}Ic_{(t+1,a)}$$

$-$

$$Ic_{(t+1,P_1)} = \; \left[Ic^{sg}_{(t,P_1)} - sIc^{sg}_{(t,P_1)} + Ic_{(t,cal)} - sIc_{(t,cal)}\right] + \text{N}Ic_{(t+1,P_1)}$$

$$Ic_{(t+1,P_i\in[P_2;P_4])} = \left[Ic^{sg}_{(t,P_i)} - sIc^{sg}_{(t,P_i)} + Ic^{ng}_{(t,P_{i-1})} - sIc^{ng}_{(t,P_{i-1})}\right] + \text{N}Ic_{(t+1,P_i)}$$

$$Ic_{(t+1,P_{5+})} = \left[Ic_{(t,P_{5+})} - sIc_{(t,P_{5+})} + Ic^{ng}_{(t,P_4)} - sIc^{ng}_{(t,P_4)}\right] + \text{N}Ic_{(t+1,P_{5+})}$$

Equations describing flows

New incoming (and outgoing) flows in each health states are mainly drawn using binomial laws.

Births (bX)

At each time step t, births are calculated with regards to the health state of the dam. These births are then distributed into S and T states

$$bS_{(t)} = \ bS^{R}_{(t)} + bS^{L}_{(t)} + bS^{Is}_{(t)} + bS^{Ic}_{(t)} \qquad \text{et} \qquad bT_{(t)} = \ bT^{L}_{(t)} + bT^{Is}_{(t)} + bT^{Ic}_{(t)},$$

where $bS^{X}_{(t)}$ et $bT^{X}_{(t)}$ $(X \in R, L, Is, Ic)$ represent the number of births at time t from cows in health state X:

$$\begin{aligned}
bS^{R}_{(t)} &\sim Bin\left(R_{(t,cal)} + \sum_{i=1}^{i=5}\left[R^{ng}_{(t,P_i)}\right]; 1-\sigma_B\right)\\
bS^{L}_{(t)} &= nbV^{L}_{(t)} - bT^{L}_{(t)}, \quad bT^{L}_{(t)} \sim Bin\left(nbV^{L}_{(t)}; p_L * \varphi_{p_{LIs}}\right)\\
bS^{Is}_{(t)} &= nbV^{Is}_{(t)} - bT^{Is}_{(t)}, \quad bT^{Is}_{(t)} \sim Bin\left(nbV^{Is}_{(t)}; p_{Is} * \varphi_{p_{LIs}}\right)\\
bS^{Ic}_{(t)} &= nbV^{Ic}_{(t)} - bT^{Ic}_{(t)}, \quad bT^{Ic}_{(t)} \sim Bin\left(nbV^{Ic}_{(t)}; p_{Ic} * \varphi_{p_{Ic}}\right)
\end{aligned}$$

In equations above, $nbC^{X}_{(t)}$ is the number of female calves alive born at time t. It is obtained from $nbV^{X}_{(t)}$, the number of female calves born at time t, from cows in the health state X:

$$\begin{aligned}
nbV^{L}_{(t)} &\sim Bin\left(L_{(t,cal)} + T_{(t,cal)} + \sum_{i=1}^{i=5}\left[L^{ng}_{(t,P_i)}\right]; 1-\sigma_B\right)\\
nbV^{Is}_{(t)} &\sim Bin\left(Is_{(t,cal)} + \sum_{i=1}^{i=5}\left[Is^{ng}_{(t,P_i)}\right]; 1-\sigma_B\right)\\
nbV^{Ic}_{(t)} &\sim Bin\left(Ic_{(t,cal)} + \sum_{i=1}^{i=5}\left[Ic^{ng}_{(t,P_i)}\right]; 1-\sigma_B\right)
\end{aligned}$$

We note that at the age of moving in the adult group (cal), all the animals in the health state T enter the health state L ($L_{(t,cal)} = L_{(t,cal)} + T_{(t,cal)}$). φ_{p_x} is a factor, varying from 100% to 0%, of decrease in probability of in utero transmission where x correspond to the dam giving birth in health states L and Is ($\varphi_{p_{LIs}}$) or Ic ($\varphi_{p_{Ic}}$).

Change in age group (X^x)

$$\begin{aligned}
X_{(t,P_i)} &= X^{sg}_{(t,P_i)} + X^{ng}_{(t,P_i)}\\
X^{ng}_{(t,P_i)} &\sim Bin\left(X_{(t,P_i)}; \frac{1}{\tau_{aa}}\right) \quad ; \quad \text{where } X = \{R, L, Is, Ic\},
\end{aligned}$$

and τ_{aa} is the average time spent in each of age group P_1 to P_4.

Exits (sX)

The mortality of calves during the first week of life is applied at birth and defined above in the section concerning births.
From age 1 to cal, mortality and culling rates σ_x are defined as:

- $a \in \{1;2\} \rightarrow \sigma_x = \sigma_{c1}$
- $a \in [3;w] \rightarrow \sigma_x = \sigma_{c2}$
- $a \in [w+1;cal] \rightarrow \sigma_x = \sigma_{c3}$

Then, exits following death and culling write as:
for $a = 1$:

$$sX_{(t,a)} \sim Bin\left(X_{(t,a)};\sigma_x\right), \quad \text{where } X = \{S,T\},$$

for $a \in [2;4]$:

$$sX_{(t,a)} = sale + death, \quad \text{where } X = \{S,T,L\}$$
$$sale \sim Bin\left(X_{(t,a)};\sigma_m\right)$$
$$death \sim Bin\left(X_{(t,a)} - sale;\sigma_x\right)$$

for $a \in [5;cal-11]$:

$$sX_{(t,a)} \sim Bin\left(X_{(t,a)};\sigma_x\right) \quad ; \quad X = \{S,R,T,L\}$$

for $a = cal - 10$, we consider management by heifers (safe management, keep all female calves):

$$Cows_{(t)} = \sum_{i=1}^{5} R_{(t,P_i)} + \sum_{i=1}^{5} L_{(t,P_i)} + \sum_{i=1}^{5} Is_{(t,P_i)} + \sum_{i=1}^{5} Ic_{(t,P_i)}$$
$$Heifers_{(t)} = \sum_{a=1}^{u} S_{(t,a)} + \sum_{a=u+1}^{cal} R_{(t,a)} + \sum_{a=1}^{cal} T_{(t,a)} + \sum_{a=1}^{cal} L_{(t,a)} + \sum_{a=1}^{cal} Is_{(t,a)} + \sum_{a=1}^{cal} Ic_{(t,a)}$$

If the number of heifers, $Heifers_{(t)}$, is greater than K_g or that the number of cows, $Cows_{(t)}$, is greater than K_v, we consider the sale of heifers:

$$sX_{(t,a)} = sale + death \quad ; \quad X = \{R,T,L,Is,Ic\}$$
$$sale \sim Bin\left(X_{(t,a)};\exp\left(-\sigma_h.(Cows_{(t)}/K_v)^6\right).((Heifers_{(t)}/K_g)^6)\right)$$
$$death \sim Bin\left(X_{(t,a)} - sale;\sigma_x\right)$$

where K_v is the capacity of the holding in number of cows (see Table 1) and $K_g = \sigma_P * K_v * (cal - h)$ is the capacity of the holding in number of heifers.

Otherwise, we do not consider the sale of heifers:

$$sX_{(t,a)} \sim Bin\left(X_{(t,a)};\sigma_x\right)$$

for $a \in [cal-9; cal]$:

$$sX_{(t,a)} = Bin\left(X_{(t,a)}; \sigma_x\right)$$

for $a \in [P_1; P_{5+}]$:

$$sX^x_{(t,P_i)} \sim Bin\left(X^x_{(t,P_i)}; \sigma_{Pi}\right), \quad \text{where } X = \{R, L, Is\},$$
$$sIc^x_{(t,P_i)} \sim Bin\left(Ic^x_{(t,P_i)}; \frac{1}{v_{Ic}}\right)$$

where v_{Ic} corresponds to the average time spent in the health state Ic.

New infections (S $\rightarrow$ T, except for *in-utero* transmission)

We have:

$$\text{N}T_{(t+1,a)} = inf^c_{(t+1,a)} + inf^m_{(t+1,a)} + inf^l_{(t+1,a)} + inf^g_{(t+1,a)}$$

Superscripts correspond to different possible routes of transmission, respectively colostrum (c), milk (m), local environment (l) and global environment (g). New infections by *in-utero* transmission are accounted for through births.

By age, the possible routes of infection are:

$$0 \underbrace{\longrightarrow}_{cmlg} 1 \underbrace{\rightarrow \cdots \rightarrow}_{mlg} \text{weaning} \underbrace{\rightarrow \cdots \rightarrow}_{lg} \text{grazing allowed} \underbrace{\rightarrow \cdots \rightarrow}_{\substack{\text{outdoor: } l \\ \text{indoor: } lg}} \text{limit of susceptibility}$$

Transmission through colostrum

It is consideblackcol that calves drink colostrum from their mothers during the first three days before drinking milk:

$$inf^c_{(t+1,a=1)} = \sum_1^{bS^{Is}_{(t)}} \left[Bern\left(1 - exp\left(-\frac{\beta_l \; q_c^{Is}}{\alpha}\right)\right)\right] + \sum_1^{bS^{Ic}_{(t)}} \left[Bern\left(1 - exp\left(-\frac{\beta_l \; q_c^{Ic}}{\alpha}\right)\right)\right],$$

with

$$q_c^{Is} \sim Bern(sh_{Is}) \times \left[3 \times b\left(10^5.Beta(8;8) + 1 + 10^3.Beta(1;25)\right)\right] * \varphi Milk_{Is},$$
$$q_c^{Ic} \sim Bern(sh_{Ic}) \times \left[3 \times b\left(10^5.Beta(8;8) + 10^{(3+10.Beta(50;200))}\right)\right] * \varphi Milk_{Ic}.$$

Where $\varphi Milk_x$ is a factor, varying from 100% to 0%, of decrease in quantity of bacteria shed in colostrum and milk by an animal in health state x (here x could be Is or Ic)

Transmission through milk

Regarding the age, we have:

$$a = 1: \quad inf^{m}_{(t+1,a)} \sim Bin\left(bS; 1 - exp\left(-\frac{\beta_l \; q_l \; \frac{4}{7}}{\alpha}\right)\right),$$

$$a \in \{2; w\}: \quad inf^{m}_{(t+1,a)} \sim Bin\left(\left[S_{(t,a-1)} - sS_{(t,a-1)}\right]; \left[1 - exp\left(-e^{(-\gamma(a-1))}.\frac{\beta_l \; q_l}{\alpha}\right)\right]\right),$$

with

$$q_l = \frac{7 \times d \times \left(Q^{milk}_{Is(t)} + Q^{milk}_{Ic(t)}\right)}{MilkTot_{(t)}},$$

where

$$Q^{milk}_{Is(t)} = \; 7 \times \varepsilon \times g_{Is} \times \left(\sum_{1}^{nbExcr^{Is}_{(t)}} (10^5.Beta(8;8)) + \sum_{1}^{nbLac^{Is}_{(t)}} (1 + 10^3.Beta(1;25))\right) * \varphi Milk_{Is},$$

$$Q^{milk}_{Ic(t)} = \; 7 \times \varepsilon \times g_{Ic} \times \left(\sum_{1}^{nbExcr^{Ic}_{(t)}} (10^5.Beta(8;8)) + \sum_{1}^{nbLac^{Ic}_{(t)}} 10^{(3+10.Beta(50;200))}\right) * \varphi Milk_{Ic},$$

$$MilkTot_{(t)} = \; 7 \times \varepsilon \times \left(nbLac^{R}_{(t)} + g_L.nbLac^{L}_{(t)} + g_{Is}.nbLac^{Is}_{(t)} + g_{Ic}.nbLac^{Ic}_{(t)}\right).$$

with

$$nbExcr^{Is}_{(t)} \sim Bin\left(nbLac^{Is}_{(t)}; sh_{Is}\right),$$

$$nbExcr^{Ic}_{(t)} \sim Bin\left(nbLac^{Ic}_{(t)}; sh_{Ic}\right),$$

$$nbLac^{R}_{(t)} \sim Bin\left(\sum_{i=1}^{i=5} R_{(t,P_i)}, prop\right),$$

$$nbLac^{L}_{(t)} \sim Bin\left(\sum_{i=1}^{i=5} L_{(t,P_i)}, prop\right),$$

$$nbLac^{Is}_{(t)} \sim Bin\left(\sum_{i=1}^{i=5} Is_{(t,P_i)}, prop\right),$$

$$nbLac^{Ic}_{(t)} \sim Bin\left(\sum_{i=1}^{i=5} Ic_{(t,P_i)}, prop\right).$$

Local transmission (in collective pens, $a \in [1; u]$)

$$inf^{l}_{(t+1,a)} \sim Bin\left(S_{(t,a-1)} - sS_{(t,a-1)}; p^{i}_{inf(t+1,a)}\right),$$

where

during housing period:

$$p^i_{inf(t+1,a)} = 1 - exp\left(-e^{(-\gamma(a-1))}.\frac{\beta_c E^i_{(t+1)}}{\alpha N^i_{(t+1)}}\right), \text{ and}$$

during grazing period, regarding the age,

$$a \in [1;26]: \quad p^i_{inf(t+1,a)} = 1 - exp\left(-e^{(-\gamma(a-1))}.\frac{\beta_c E^i_{(t+1)}}{\alpha N^i_{(t+1)}}\right),$$

$$a \in [27;u]: \quad p^i_{inf(t+1,a)} = 1 - exp\left(-e^{(-\gamma(a-1))}.\frac{\beta_o E^i_{(t+1)}}{\alpha N^i_{(t+1)}}\right).$$

$N^i_{(t+1)}$ is the total number of animals in environment i, across all health states, and E^i represents the quantity of bacteria in the environment, with i corresponding to the specific area.

Global transmission

This occurs up to the age allowing to go to the pasture (26 weeks - 6 months) during the grazing period, and up to the age limit for sensitivity (u) during the housing period:

$$inf^g_{(t+1,a)} \sim Bin\left(S_{(t,a)} - sS_{(t,a)}; p^g_{inf(t+1,a)}\right),$$

where

$$p^g_{inf(t+1,a)} = 1 - exp\left(-exp[-h(a-1)].\frac{\beta_g E^g_{(t+1)}}{\alpha N^g_{(t+1)}}\right), \quad \text{with} \quad E^g_{(t+1)} = \sum_{i=1}^{i=5} E^{\text{INT}i}_{(t+1)}$$

$E^{\text{INT}i}$ represents the quantity of bacteria in the environment where INTi corresponds to a specific area (see the section below about the dynamics of bacteria in the environments).

New latently infected ($\mathbf{T} \rightarrow \mathbf{L}$)

For $a < cal$:

$$\text{N}L_{(t+1,a\in[2;cal-1])} \sim Bin\left(T_{(t,a)} - sT_{(t,a)}; \frac{1}{v_T}\right).$$

After age cal, there are no more animals in T state:

$$\text{N}L_{(t+1,P_1)} = T_{(t,cal)} - sT_{(t,cal)}.$$

New subclinically infected (L → Is)

For heifers:

$$\text{N}Is_{(t+1,a\in[h+1;cal])} \sim Bin\left(L_{(t,a)} - sL_{(t,a)}; \frac{1}{v_L}\right).$$

For cows:

$$\text{N}Is_{(t+1,P_i)} \sim Bin\left(n; \frac{1}{v_L}\right),$$

with, regarding the age,

$$\begin{aligned}
P_1 \rightarrow n &= \left[L^{sg}_{(t,P_1)} - sL^{sg}_{(t,P_1)} + L_{(t,cal)} - sL_{(t,cal)} + T_{(t,cal)} - sT_{(t,cal)}\right], \\
\{P_2; P_4\} \rightarrow n &= \left[L^{sg}_{(t,P_i)} - sL^{sg}_{(t,P_i)} + L^{ng}_{(t,P_{i-1})} - sL^{ng}_{(t,P_{i-1})}\right], \\
P_{5+} \rightarrow n &= \left[L_{(t,P_{5+})} - sL_{(t,P_{5+})} + L^{ng}_{(t,P_4)} - sL^{ng}_{(t,P_4)}\right].
\end{aligned}$$

New clinically infected (Is → Ic)

For heifers:

$$\text{N}Ic_{(t+1,a\in[h+1;cal])} \sim Bin\left(Is_{(t,a)} - sIs_{(t,a)}; \frac{1}{v_{Is}}\right).$$

For cows:

$$\text{N}Ic_{(t+1,P_i)} \sim Bin\left(n; \frac{1}{v_{Is}}\right),$$

with

$$\begin{aligned}
P_1 \rightarrow n &= \left[Is^{sg}_{(t,P_1)} - sIs^{sg}_{(t,P_1)} + Is_{(t,cal)} - sIs_{(t,cal)}\right], \\
\{P_2; P_4\} \rightarrow n &= \left[Is^{sg}_{(t,P_i)} - sIs^{sg}_{(t,P_i)} + Is^{ng}_{(t,P_{i-1})} - sIs^{ng}_{(t,P_{i-1})}\right], \\
P_{5+} \rightarrow n &= \left[Is_{(t,P_{5+})} - sIs_{(t,P_{5+})} + Is^{ng}_{(t,P_4)} - sIs^{ng}_{(t,P_4)}\right].
\end{aligned}$$

New resistant (S → R)

At age u, the transition from compartment S to compartment R is done in a deterministic way.

Dynamics of bacteria in the environments (E)

The composition of the environments according to the season is the following:

$$\text{Grazing} : a = \overbrace{1 \cdots\cdots w}^{\text{INT1}} \overbrace{\cdots\cdots 26}^{\text{INT2}} \overbrace{\cdots\cdots\cdots\cdots\cdots\cdots h}^{\text{EXT1+EXT2}} \overbrace{\cdots\cdots\cdots cal}^{\text{EXT3}}$$

$$\text{Housing} : a = \overbrace{1 \cdots\cdots w}^{\text{INT1}} \overbrace{\cdots\cdots\cdots\cdots\cdots\cdots y}^{\text{INT2}} \overbrace{\cdots\cdots\cdots\cdots h}^{\text{INT3}} \overbrace{\cdots\cdots\cdots cal}^{\text{INT4}}$$

Dynamics of bacteria in the environments (E) are defined below:

$E^{\text{INT1}}_{(t+1)} = E^{\text{INT1}}_{(t)}.(1-\mu^{int}_g) + Q^{\text{TNS}}_{(t)}$. If pens are empty, it becomes $E^{\text{INT1}}_{(t+1)} = E^{\text{INT1}}_{(t+1)}.(1-\mu_{cp})$, where Q represents the quantity of bacteria shed.

During grazing period, we have:

$$\begin{aligned}
E^{\text{INT2}}_{(t+1)} &= E^{\text{INT2}}_{(t)}.(1-\mu^{int}_g) + Q^{\text{TS1}}_{(t)} \\
&\quad If \quad \sum_{a=w+1}^{a=26} SR_{t,a} + \sum_{a=w+1}^{a=26} T_{t,a} + \sum_{a=w+1}^{a=26} L_{t,a} == 0 \quad then \quad E^{\text{INT2}}_{(t+1)} = E^{\text{INT2}}_{(t+1)}.(1-\mu_{cp}) \\
E^{\text{INT3}}_{(t+1)} &= E^{\text{INT3}}_{(t)}.(1-\mu^{int}_g) \\
E^{\text{INT4}}_{(t+1)} &= E^{\text{INT4}}_{(t)}.(1-\mu^{int}_g) \\
E^{\text{INT5}}_{(t+1)} &= E^{\text{INT5}}_{(t)}.(1-\mu^{int}_g) \\
E^{\text{EXT1}}_{(t+1)} &= E^{\text{EXT1}}_{(t)}.(1-\mu^{ext}_g) + Q^{\text{TS2}}_{(t)} \\
E^{\text{EXT2}}_{(t+1)} &= E^{\text{EXT2}}_{(t)}.(1-\mu^{ext}_g) + Q^{\text{TY}}_{(t)} \\
E^{\text{EXT3}}_{(t+1)} &= E^{\text{EXT3}}_{(t)}.(1-\mu^{ext}_g) + Q^{\text{TH}}_{(t)} + Q^{\text{ISH}}_{(t)} + Q^{\text{ICH}}_{(t)}.
\end{aligned}$$

During housing period, we have:

$$\begin{aligned}
E^{\text{INT2}}_{(t+1)} &= E^{\text{INT2}}_{(t)}.(1-\mu^{int}_g) + Q^{\text{TS1}}_{(t)} + Q^{\text{TS2}}_{(t)} \\
&\quad If \quad \sum_{a=w+1}^{a=52} SR_{t,a} + \sum_{a=w+1}^{a=52} T_{t,a} + \sum_{a=w+1}^{a=52} L_{t,a} == 0 \quad then \quad E^{\text{INT2}}_{(t+1)} = E^{\text{INT2}}_{(t+1)}.(1-\mu_{cp}) \\
E^{\text{INT3}}_{(t+1)} &= E^{\text{INT3}}_{(t)}.(1-\mu^{int}_g) + Q^{\text{TY}}_{(t)} \\
E^{\text{INT4}}_{(t+1)} &= E^{\text{INT4}}_{(t)}.(1-\mu^{int}_g) + Q^{\text{TH}}_{(t)} + Q^{\text{ISH}}_{(t)} + Q^{\text{ICH}}_{(t)} \\
E^{\text{INT5}}_{(t+1)} &= E^{\text{INT5}}_{(t)}.(1-\mu^{int}_g) + Q^{\text{IS}}_{(t)} + Q^{\text{IC}}_{(t)} \\
E^{\text{EXT1}}_{(t+1)} &= 0, \quad E^{\text{EXT2}}_{(t+1)} = 0, \quad E^{\text{EXT3}}_{(t+1)} = 0.
\end{aligned}$$

Shed quantities of bacteria are defined, regarding the health states and the age, by:

unweaned calves T:

$$Q^{\text{TNS}}_{(t)} = \sum_{a=1}^{a=w} \left[7.f_1.10^6. \sum^{T_{(t,a)}} Beta(8.8;19) \right] * \varphi faeces_T,$$

weaned calves T, without access to grazing:

$$Q^{\text{TS1}}_{(t)} = \sum_{a=w+1}^{a=26} \left[7.f_2.10^6. \sum^{T_{(t,a)}} Beta(8.8;19) \right] * \varphi faeces_T,$$

weaned calves T, with access to grazing:

$$Q_{(t)}^{\mathrm{Ts2}} = \sum_{a=27}^{a=y} \left[7.f_2.10^6. \sum^{T_{(t,a)}} Beta(8.8;19) \right] * \varphi faeces_T,$$

young heifers T:

$$Q_{(t)}^{\mathrm{TY}} = \sum_{a=y+1}^{a=h} \left[7.f_Y.10^6. \sum^{T_{(t,a)}} Beta(8.8;19) \right] * \varphi faeces_T,$$

heifers T:

$$Q_{(t)}^{\mathrm{TH}} = \sum_{a=h+1}^{a=cal} \left[7.f_A.10^6. \sum^{T_{(t,a)}} Beta(8.8;19) \right] * \varphi faeces_T,$$

heifers Is:

$$\text{if } \sum_{a=h+1}^{a=cal} \left(Is_{(t,a)} \right) > 0 \ : \quad Q_{(t)}^{\mathrm{ISH}} = \sum_{a=h+1}^{a=cal} \left[7.f_A.10^{(4+10\times\sum^{Is_{(t,a)}} Beta(2.65;17))} \right] * \varphi faeces_{Is}$$

$$\text{else} \quad Q_{(t)}^{\mathrm{ISH}} = 0,$$

cows Is:

$$\text{if } \sum_{i=1}^{i=5} \left(Is_{(t,P_i)} \right) > 0 \ : \quad Q_{(t)}^{\mathrm{IS}} = \sum_{i=1}^{i=5} \left[7.f_A.10^{(4+10\times\sum^{Is_{(t,P_i)}} Beta(2.65;17))} \right] * \varphi faeces_{Is}$$

$$\text{else} \quad Q_{(t)}^{\mathrm{IS}} = 0,$$

heifers Ic:

$$\text{if } \sum_{a=h+1}^{a=cal} \left(Ic_{(t,a)} \right) > 0 \ : \quad Q_{(t)}^{\mathrm{ICH}} = \sum_{a=h+1}^{a=cal} \left[7.f_A.10^{(8+10\times\sum^{Ic_{(t,a)}} Beta(2;17))} \right] * \varphi faeces_{Ic}$$

$$\text{else} \quad Q_{(t)}^{\mathrm{ICH}} = 0,$$

cows Ic:

$$\text{if } \sum_{i=1}^{i=5} \left(Ic_{(t,P_i)} \right) > 0 \ : \quad Q_{(t)}^{\mathrm{IC}} = \sum_{i=1}^{i=5} \left[7.f_A.10^{(8+10\times\sum^{Ic_{(t,P_i)}} Beta(2;17))} \right] * \varphi faeces_{Ic}$$

$$\text{else} \quad Q_{(t)}^{\mathrm{IC}} = 0.$$

$\varphi faeces_x$, in the equation above is a factor of decrease in quantity of bacteria shed by an animal in health state x. x could be T, Is or Ic.

B Parameters ralated to population dynamics

Table 1: Parameters for management and population dynamics used in the *Mycobacterium avium subsp. paratuberculosis* (*Map*) infection dynamics model within a structublackcol dairy herd (reproduced from [2], Table 1).

Notation	Value	Definition	Source
σ_B	0.07	Mortality rate of calves at birth	$*$, [17]
σ_m	0.206	Exit rate of male calves, weeks 2 to 4 (per week)	
σ_{c1}	0.015	Death rate of female calves, weeks 1 and 2 (per week)	[17]
σ_{c2}	0.0035	Death rate of female calves, weeks 3 to weaning (per week)	[9]
σ_{c3}	0.00019	Death rate of heifers from weaning to entry in adult group (per week)	†
σ_h	0.011	Sale rate of bblackcol heifers 10 weeks before 1st calving	†
σ_{Ai}	0.27,0.25,0.31, 0.31,0.62	Yearly culling rate of cows in adult group i: 1, 2, 3, 4 and above 5 respectively (%)	$*$, [1]
w	10	Weaning age (weeks)	[12]
y	52	Age when entering the young heifer group (weeks)	
h	91	Age when entering the heifer group (weeks)	$*$
cal	130	Age when entering the adult group (weeks)	$*$, †
τ_{aa}	56.3	Mean time spent in adult age groups 1 to 4 (weeks)	$*$, †
b	5	Quantity of colostrum fed to calves (L/day for 3 days)	†
d	7	Quantity of milk fed to calves after 3 days (L/day/calf)	†
$prop$	0.85	Proportion of lactating cows	$*$
ε	25	Quantity of milk or colostrum produced (L/day/cow)	$*$
f_1	0.5	Quantity of feaces produced by a non-weaned calf (kg/day)	†
f_2	5.5	Quantity of feaces produced by a weaned calf (kg/day)	†
f_Y	10	Quantity of feaces produced by a heifer (kg/day)	†
f_A	30	Quantity of feaces produced by a cow (kg/day)	†
$Graz$	$[14-26]$	Grazing period (1 being the first week of the year)	†
K_c	110	Number of cows above which the heifer selling rate increases	

$*$ Agricultural statistics.

† Based on expert opinion.

C Parameters related to infection dynamics

Table 2: Parameters for infection and transmission used in the *Mycobacterium avium subsp. paratuberculosis* (*Map*) infection dynamics model within a structublackcol dairy herd (reproduced from [2] - Table 2).

Notation	Value	Definition	Source
p_X		Probability of *in utero* transmission for cow in health state X	[4, 26]
	$p_L = 0.149$	X = latently infected (L)	
	$p_{Is} = 0.149$	X = subclinically infected (Is)	
	$p_{Ic} = 0.65$	X = clinically affected (Ic)	
u	52	Maximal age in the susceptible compartment (weeks)	[6, 23]
γ	0.1	Susceptibility follows an exponential decrease : $exp(-\gamma(age-1))$	[27]
v_X		Mean time spent in health state X (weeks)	
	$v_T = 25$	X = transiently infectious (T)	[21]
	$v_L = 52$	X = latently infected (L)	[16, 14]
	$v_{Is} = 104$	X = subclinically infected (Is)	[13]
	$v_{Ic} = 26$	X = clinically affected (Ic)	†
sh_X		Probability of shedding in colostrum or milk for a cow in health state X	[20, 19]
	$sh_L = 0$	X = latently infected (L)	
	$sh_{Is} = 0.4$	X = subclinically infected (Is)	
	$sh_{Ic} = 0.9$	X = clinically affected (Ic)	
α	10^6	*Map* infectious dose	[3]
β_l	$5 \times 10^{-4} \times 7$	Transmission rate if ingestion of an infectious dose (per week)	‡
β_c	$5 \times 10^{-5} \times 7$	Transmission rate if one infectious dose is present in the local environment (per week)	[21]
β_g	$9.5 \times 10^{-7} \times 7$	Transmission rate if one infectious dose is present in the global environment (per week)	[21]
β_o	$5 \times 10^{-6} \times 7$	Transmission rate if one infectious dose is present in the pasture (per week)	‡
g_X		Decrease in milk production for cattle in health state X (per week)	[15]
	$g_{Is} = 1 - 0.11$	X = subclinically infected (Is)	
	$g_{Ic} = 1 - 0.25$	X = clinically affected (Ic)	
μ_k		Removal rate of Map from environment k	[7, 24]
	$\mu_g^{int} = 0.4$	all the environments (per week)	
	$\mu_g^{ext} = 1/14$	all the environments (per week)	
	$\mu_{cp} = 0.17$	collective pens (when empty)	

† Expert opinions.

‡ Parameters' values are assumed.

Table 3: Summary of published data and assumed distributions of the quantities of *Mycobacterium avium* subsp. *paratuberculosis* (*Map*) shed, depending on the health state (X) and the route of transmission (r) in the *Map* infection dynamics model within a structublackcol dairy herd (reproduced from [2] - Table 3).

Route of transmission (r)	**Health state (X)**	**Literature**				**Assumed distributions**
		Minimal value	**Maximal value**	**Mean value**	**Source**	
Map direct shedding in milk and colostrum (Map/L)	Subclinically infected	2.2×10^4	8.8×10^4	5×10^4	[20]	$10^5 \times Beta(8;8)$
	Clinically affected	-	-	5×10^4	[5]	$10^5 \times Beta(8;8)$
Map indirect shedding in milk and colostrum (faecal contamination) (Map/L)	Subclinically infected	0	2×10^{10}	40	[10, 22]	$1 + 10^3 \times Beta(1;25)$
	Clinically affected	700	2×10^{10}	14×10^4	[10, 22]	$10^{(3+10\times Beta(50;200))}$
Map shedding in faeces (Map/kg)	Transiently infectious	6×10^4	6.3×10^5	3×10^5	[21]	$10^6 \times Beta(8.8;19)$
	Subclinically infected	10^4	10^{15}	2.6×10^6	[18]	$10^{(4+10\times Beta(2.65;17))}$
	Clinically affected	10^8	10^{15}	10^{10}	[25, 8]	$10^{(8+10\times Beta(2;17))}$

Bibliography

[1] Beaudeau, F. (1999). *Review of culling and replacement practices in dairy cattle herds, Master Thesis. Institut Supérieur des Productions Animales.* PhD thesis, Rennes, France.

[2] Beaunée, G., Vergu, E., and Ezanno, P. (2015). Modelling of paratuberculosis spread between dairy cattle farms at a regional scale. *Veterinary Research*, 46:1–13.

[3] Begg, D. J. and Whittington, R. J. (2008). Experimental animal infection models for Johne's disease, an infectious enteropathy caused by Mycobacterium avium subsp. paratuberculosis. *The Veterinary Journal*, 176(2):129–145.

[4] Benedictus, A., Mitchell, R. M., Linde-Widmann, M., Sweeney, R., Fyock, T., Schukken, Y. H., and Whitlock, R. H. (2008). Transmission parameters of Mycobacterium avium subspecies paratuberculosis infections in a dairy herd going through a control program. *Preventive Veterinary Medicine*, 83(3-4):215–227.

[5] Giese, S. B. and Ahrens, P. (2000). Detection of Mycobacterium avium subsp paratuberculosis in milk from clinically affected cows by PCR and culture. *Veterinary Microbiology*, 77(3-4):291–297.

[6] Hagan, W. A. (1938). Age as a Factor in Susceptibility to Johne's Disease. *Cornell Veterinarian*, 28:34–40.

[7] Jørgensen, J. B. (1977). Survival of Mycobacterium paratuberculosis in slurry. *Nordisk Veterinaer Medicin*, 29(6):267–270.

[8] Jørgensen, J. B. (1982). An improved medium for culture of Mycobacterium paratuberculosis from bovine faeces. *Acta veterinaria Scandinavica*, 23(3):325–335.

[9] Jégou, V., Porhiel, J., and Brunschwig, P. (2006). Risk management factors affecting mortality among dairy calves herds in 80 herds in Brittany. In *Proc. Journées Bovines Nantaises*, Nantes.

[10] Magnusson, M., Christiansson, A., Svensson, B., and Kolstrup, C. (2006). Effect of Different Premilking Manual Teat-Cleaning Methods on Bacterial Spores in Milk. *Journal of Dairy Science*, 89(10):3866–3875.

[11] Marcé, C., Ezanno, P., Seegers, H., Pfeiffer, D. U., and Fourichon, C. (2011). Predicting fadeout versus persistence of paratuberculosis in a dairy cattle herd for management and control purposes: a modelling study. *Veterinary Research*, 42(36).

[12] Marcé, C., Guatteo, R., Bareille, N., and Fourichon, C. (2010). Dairy calf housing systems across Europe and risk for calf infectious diseases. *animal*, 4(09):1588–1596.

[13] Matthews, H. T. (1947). On Johne's disease. *The Veterinary Record*, 59(31):397–401.

[14] Nielsen, S. S. (2008). Transitions in diagnostic tests used for detection of Mycobacterium avium subsp. paratuberculosis infections in cattle. *Veterinary Microbiology*, 132(3-4):274–282.

[15] Nielsen, S. S., Enevoldsen, C., and Toft, N. (2006). Milk production losses associated with bovine paratuberculosis diagnosed from repeated testing. In *11th international Symposia of Veterinary Epidemiology and Economics*, Cairns.

[16] Nielsen, S. S. and Ersbøll, A. K. (2006). Age at Occurrence of Mycobacterium avium Subspecies paratuberculosis in Naturally Infected Dairy Cows. *Journal of Dairy Science*, 89(12):4557–4566.

[17] Rio, O. (1999). *Frequency and risks of mortality and health disorders of calves in dairy cattle herds* . PhD thesis, Nantes.

[18] Rossiter, C. A. and Burhans, W. S. (1996). Farm-specific approach to paratuberculosis (Johne's disease) control. *The Veterinary clinics of North America. Food animal practice*, 12(2):383–415.

[19] Streeter, R. N., Hoffsis, G. F., Bechnielsen, S., Shulaw, W. P., and Rings, M. (1995). Isolation of Mycobacterium-Paratuberculosis From Colostrum and Milk of Subclinically Infected Cows. *American Journal of Veterinary Research*, 56(10):1322–1324.

[20] Sweeney, R. W., Whitlock, R. H., and Rosenberger, A. E. (1992). Mycobacterium paratuberculosis isolated from fetuses of infected cows not manifesting signs of the disease. *American Journal of Veterinary Research*, 53(4):477–480.

[21] van Roermund, H. J. W., Bakker, D., Willemsen, P. T. J., and de Jong, M. C. M. (2007). Horizontal transmission of Mycobacterium avium subsp. paratuberculosis in cattle in an experimental setting: Calves can transmit the infection to other calves. *Veterinary Microbiology*, 122(3-4):270–279.

[22] Vissers, M. M. M., Driehuis, F., Te Giffel, M. C., De Jong, P., and Lankveld, J. M. G. (2006). Improving Farm Management by Modeling the Contamination of Farm Tank Milk with Butyric Acid Bacteria. *Journal of Dairy Science*, 89(3):850–858.

[23] Whitlock, R. H. and Buergelt, C. (1996). Preclinical and clinical manifestations of paratuberculosis (including pathology). *Veterinary Clinics of North America-Food Animal Practice*, 12(2):345–356.

[24] Whittington, R. J., Marshall, D. J., Nicholls, P. J., Marsh, I. B., and Reddacliff, L. A. (2004). Survival and dormancy of Mycobacterium avium subsp. paratuberculosis in the environment. *Applied and Environmental Microbiology*, 70(5):2989–3004.

[25] Whittington, R. J., Reddacliff, L. A., Marsh, I., McAllister, S., and Saunders, V. (2000). Temporal patterns and quantification of excretion of Mycobacterium avium subsp paratuberculosis in sheep with Johne's disease. *Australian Veterinary Journal*, 78(1):34–37.

[26] Whittington, R. J. and Windsor, P. A. (2009). In utero infection of cattle with Mycobacterium avium subsp. paratuberculosis: A critical review and meta-analysis. *The Veterinary Journal*, 179(1):60–69.

[27] Windsor, P. A. and Whittington, R. J. (2010). Evidence for age susceptibility of cattle to Johne's disease. *The Veterinary Journal*, 184(1):37–44.

UNIVERSITE BRETAGNE LOIRE

Oniris
ÉCOLE NATIONALE VÉTÉRINAIRE, AGROALIMENTAIRE ET DE L'ALIMENTATION
SANTÉ ET ALIMENTATION AU CŒUR DE LA VIE

Thèse de Doctorat

Racem BEN ROMDHANE

Titre de thèse : évaluation de l'efficacité de stratégies de maîtrise de la paratuberculose bovine: sélection génétique ou diminution de l'exposition dans les troupeaux

Title of thesis: Assessment of the effectiveness of bovine paratuberculosis control strategies: genetic selection or reduction of exposure in herds

Résumé

La paratuberculosis (PTB) est une maladie endémique des ruminants causée par *Mycobacterium avium* subsp. *paratuberculosis* (Map). Les stratégies de maîtrise actuelles ne sont pas suffisamment efficaces. La réponse à l'exposition à Map varie entre les animaux avec une part de déterminisme génétique. Des marqueurs génétiques pourraient permettre une sélection. L'objectif était d'évaluer par modélisation l'efficacité potentielle attendue de stratégies de maîtrise utilisant la sélection génétique ou la réduction de l'exposition en élevage.
Nous avons identifié quatre traits phénotypiques de résistance influençant principalement la propagation de Map à l'échelle du troupeau et montré la valeur ajoutée de leur amélioration simultanée. Nous avons évalué l'effet de l'environnement du troupeau et du système d'élevage sur la propagation et la maîtrise de Map. Nous avons montré une différence d'efficacité des stratégies de maîtrise les plus pertinentes entre deux systèmes d'élevage bovins laitiers contrastés d'Europe: l'ouest de la France et l'Irlande. Nous avons évalué l'efficacité que pourrait apporter la sélection génomique en évaluant le temps nécessaire pour atteindre des niveaux de variation des traits sélectionnés permettant un bon contrôle de l'infection sous l'hypothèse que des marqueurs de sélection soient disponibles. Nous avons identifié 2 paramètres du modèle de sélection génomique influents sur l'efficacité de la sélection. Notre modèle permet d'intégrer de nouvelles connaissances biologiques sur le déterminisme génétique de la résistance à Map pour évaluer des stratégies de maîtrise complexes comprenant une composante de sélection génomique.

Mots clés : modélisation épidémiologique, paratuberculose bovine, stratégies de maîtrise, sélection génomique, échelle du troupeau.

Abstract

Paratuberculosis (PTB) is an endemic disease of ruminants caused by *Mycobacterium avium* subsp. *paratuberculosis* (Map). Current control strategies are not effective enough. The response to Map exposure varies between animals with evidence of a partial genetic determinism. Genetic markers could allow selection. The objective was to assess the potential expected effectiveness of control strategies relying on genetic selection or reduction of exposure in herds, using a modelling approach.
We identified four phenotypic traits of resistance mainly influencing the spread of Map at the herd scale and showed the added value of their simultaneous improvement. We evaluated the effect of the herd environment and management on the spread and control of Map. We showed a difference in effectiveness of the most relevant control strategies between two contrasting dairy cattle systems in Europe: western France and Ireland. We evaluated the effectiveness of genomic selection by assessing the time required to reach levels of variation in the selected traits allowing to achieve a good control of infection, assuming that associated genomic markers could be available. Effectiveness of selection was mainly influenced by 2 of the parameters of the developed genomic selection model. Our model allows to account for future knowledge about the genetic determinism of cattle resistance to Map in order to assess the effectiveness of complex control strategies including a genomic selection component.

Key Words: epidemiological modelling, bovine paratuberculosis, control strategies, genomic selection, herd scale.

L'Université Bretagne Loire