Evidence based decisions to improve dairy herd fertility

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Abstract

Improvements to reproductive performance on dairy farms make an essential contribution to improvements in farm efficiency, which forms an important part of the economic and environmental sustainability of the industry. This project has extended investigations into improvements in reproductive performance by examining key contributing factors, such as health events, environmental conditions and management decisions made by farmers. This has been done by both analysing UK herd data using regression modelling and by developing and using a method for rapid evidence review. Evidence synthesis techniques were then used to combine multiple sources of information. Results from both of these techniques were then used within stochastic simulation models to evaluate the relative importance of the different factors.

Relationships between periparturient and early lactation health events and reproductive performance were explored using a rich agri-informatics dataset from 468 UK dairy herds. This updated existing literature on the relationships between commonly occurring health events and reproduction. This showed significant and negative associations between several important health events that generally occur in the crucial period between calving and the first weeks of lactation, and reproductive performance.

Current research knowledge in key areas of the field of dairy cow reproductive performance was identified. A systematic literature evaluation was carried out which included conversion of results into a mathematical format whereby they could be used further in the project as inputs for a decision model. Areas to be evaluated included heifer rearing, oestrus detection, genetics, endemic infectious disease, the dry period, energy balance and heat stress. These were then used as inputs to meta-analysis techniques to produce a pooled "result" summarising literature evidence in each of the areas.

The potential herd level impact of periparturient and early lactation events in comparison to background herd level factors was explored using simulation modelling. This allowed assessment of the association between the factors and herd level performance in contrast to their association at an individual cow level. This showed that although relevant to an individual lactation, the health events were less likely to have a substantial impact on reproductive performance at herd level.

Many of the most important factors influencing dairy cow reproductive performance identified by literature evaluation earlier in the project were contextualised using stochastic simulation modelling. Evidence from various sources were brought together and the impact of these factors was compared and quantified. This established that a number of these factors can have a considerable impact on performance and allowed these impacts to be quantified. The installation of automated activity monitors, the use of bulls with high fertility index scores and the reduction in the prevalence of subclinical ketosis appeared to have the greatest impact on reproductive performance.

This project has added to the scientific knowledge of dairy cow reproductive performance by exploring relationships between common factors and performance using established and more novel techniques and presenting results in simple and interpretable ways. Although substantial between herd variability remains unexplained by factors that were investigated, other substantial associations with reproductive performance have been explained, specified and quantified.

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1. Introduction

1.1 Current position of UK dairy industry and milk consumption

The number of dairy cows in the UK stood at 1.856 million in December 2020, a figure which is down 0.6% on the previous year and increases the rate of a recent downward trend, with milking cow numbers down 1.5% since 2014. Despite fewer cows, milk production per cow has increased, with overall national production experiencing a recent increase. Milk production in the UK declined steadily and consistently from just under 14 billion litres in 2000-01 to just under 13 billion litres in 2012-13 but has since reversed this trend to rise steadily and consistently to just under 15 billion litres produced in 2019-20. The most marked change in industry stratification however is in the number of dairy farms in the UK. This stood at 12,209 in 2019, down from 16,008 in 2009 and drastically reduced from 30,221 in 1999 (Shahbandeh 2021a, AHDB 2021a).

Trends in UK milk consumption are shown in Table 1.1 and indicate that although liquid milk usage has fallen in the last 20 years, the reduction has been offset by increases in milk products, especially cheese. Recent market analysis has shown that 80-95% of households had bought milk in the preceding 4 weeks, and the amount spent per household had increased slightly in recent years (though decreased slightly in real terms) with 167p per person per week spent in 2006 and 190p per person per week in 2019 (Shahbandeh 2021b, Uberoi 2021).

Agriculture accounted for more than 1.1% of UK Gross Domestic Product (GDP) in 1990 but this has more than halved in the last 30 years to 0.55% in 2020. Milk accounted for 16.4% of total agricultural output in the UK in 2020 and was worth £4.4bn in market prices. The UK agricultural industry provided approximately 60% of the food consumed in the UK in 2020 (Uberoi 2021, Anon 2021a). Although agriculture as a sector is reducing as a proportion of the UK economy, the sector remains essential to the population and milk production remains a key part of this. Despite falling cow numbers and a substantial decrease in the number of dairy farms, milk production and consumption continue to increase. Challenges remain for the UK's 12,000 dairy farmers to maintain output to meet demand.

Table 1.1 UK milk usage trends 2000-2020 (from Uberoi, 2021)

UK milk usage (million litres)	Year 2000	Year 2020	Percentage change between 2000 and 2020
Liquid consumption	6793	6254	-7.9%
Butter	270	398	+47.2%
Cheese	3037	4620	+52.1%
Cream	239	333	+39.4%
Yoghurt	Not recorded	531	Not recorded
Condensed milk	522	351	-32.8%
Milk powder	1821	888	-51.2%
Other manufacture	644	676	+4.9%

1.2 Threats to UK dairy industry

Consumption of alternatives to cow's milk is increasing rapidly in the UK, with younger age groups particularly purchasing plant-based alternatives, which are currently thought to be increasing in volume sold by over 5% per year. The total spent on plant-based milk alternatives reached £394 million in 2020, but this figure remains small in comparison to approximately £3 billion spent on liquid milk.

The plant-based milk alternative market is both increasing and changing rapidly. Almond milk was the most popular cow's milk alternative in 2020 (bought by 19% of consumers in a two-month period in 2020). This was followed by consumption of soya milk (16% of consumers), coconut milk (13%) and rice milk (6%). These figures were much higher amongst younger consumers, with 30% of the 35 to 44 age group purchasing almond milk in this two-month period, compared to 7% of over 55s. By 2021, a huge increase in year-on-year consumption of oat milk had made it the most popular plant-based milk alternative in the UK (Juliano 2018, Anon 2021b, McKevitt 2021).

Many of the reductions in the percentage of UK households purchasing liquid cow's milk and the accompanying increase in plant-based milk alternatives, especially in the purchasing patterns of younger people, are thought to be driven by concerns for the purchaser's own health. There is a perception that a vegan diet is likely to lead to reduced rates of cancer, high cholesterol, high blood pressure and certainly lactose intolerance than an omnivorous diet (Key 2014).

Other societal pressures to reduce milk consumption are based around concerns about the contribution of agriculture to carbon emissions. A direct contribution from agriculture, forestry and land use is thought to contribute more than 10% of total global greenhouse gas emissions. When other indirect food contributions are added (such as refrigeration, processing and packaging and transport) it is estimated that the production of our food is currently leading to over 25% of global emissions (Lynch 2021, Ritchie 2020, Anon 2021c). Livestock are likely to currently be contributing over 50% of these emissions from food production. This is made up of 31% directly from methane production through enteric fermentation in the guts of livestock, 16% from conversion of forests and grasslands to land for grazing, and 6% from crop production for animal feed (due to nitrous oxide and methane release from fertilisers and manure) (Poore 2018).

The dairy industry is thought to contribute more than 30% of the emissions coming directly from agriculture (de Vries 2019, Geber 2011, Opio 2013), amounting to as much as 2.1 gigatonnes of CO2 per year. Mitigation strategies for other sectors are much advanced compared to agriculture. Initial strategies for the dairy industry centre on increasing yield per cow, which although more intensive should decrease emissions per litre of milk produced despite emissions per cow increasing. This global crisis is often expressed on an international level but does seem to be starting to influence milk consumption in the UK, which forms an immediate threat to UK dairy farmers through a decreased market for their milk.

Other global issues also threaten individual UK dairy farmers. Non-UK nationals have provided reliable and skilled labour on UK dairy farms for many years. Recent increasing emphasis on reducing immigration numbers has impacted the number of workers available and many farmers are finding it difficult to recruit suitable staff. The dairy industry is starting to attempt to offset this by increasing the number of robotic milking machines installed but levels of staff remain difficult to manage and reinvestment in an alternative method of milking cows is not a viable option for many.

Since milk is a commodity, the price paid to farmers can fluctuate wildly in line with distant political and economic storms. Although not even an extreme example, the average UK price of 32.55 pence per litre in October 2021 was 8.5% above the same month in 2020, despite a very similar national volume of milk produced (UK Government 2021). As a result of the price fluctuations, often accompanied by large fluctuations in production costs such as fuel and concentrate feed, dairy farmers can find it difficult to plan and then to improve and to invest. These challenges drive the need for efficiency at a farm and industry level in order for the UK dairy industry to be sustainable in the future.

1.3 Reproduction in UK dairy herds

One of the most widely cited ways of improving efficiency is to maximise reproductive performance (Bello 2012). During the period 2000-2010 there was considerable emphasis on the decline of fertility in dairy cows, both in the UK and around the world (Bello 2012, Royal 2000, Lucy 2001). This trend was reported in the UK in a study of 214 UK herds from 2000 to 2007 with declines in reproductive performance from lactations starting from 2000 to 2005 followed by an uptick in reproductive performance from lactations starting from 2006 to 2007 (Hudson 2015).

More detailed review of elements of this process will be discussed in section 1.4. In short, this uptick in UK reproductive performance was reported to be principally as a result of improved submission rate (the rate at which cows are detected in oestrus and inseminated) rather than conception rate (the rate at which inseminated cows become pregnant) and theorised to be explained by increased use of oestrus detection aids, increased use of software to improve targeting of cows eligible for insemination and increased herd size resulting in an increase in the size of sexually active groups in oestrus (Hudson 2015).

The timing of this reversal may also be explained by incorporation of fertility indices into genetic bull selections (Wall 2002) and an increased focus on fertility performance which has permeated the industry, creating interest and a change in emphasis. Norman in 2009 in USA suggested a partial recovery in dairy fertility coinciding with the incorporation of daughter pregnancy rate into bull genetic evaluations in 2003, despite no apparent slowing down in the rate of increase of milk production per cow (Norman 2009).

Since 2010 UK trends have continued to improve. An annual report published on behalf of the commercial milk laboratory and data repository National Milk Records (NMR), and initially the University of Reading has highlighted the performance of a convenience sample of 500 herds. This represents 3-5% of UK herds over this period and usually allows consistency from one year to the next by using the same herds as in previous years with replacement herds added at random from the 5,000 total NMR herds. Table 1.2 has been brought together here from the 11 separate annual reports from 2010 to 2020 to show trends in key parameters.

Table 1.2 Trends in UK reproductive performance

- *from Hanks (2010-2020)*
- *Parameters defined in these reports as follows:*
- *Conception Rate/%= The number of conceptions as a percentage of the total number of services (services to cows culled are included) during the analysis period.*
- *Submission Rate/%= The percentage of cows that are eligible for service (42 days+ after calving and not barren or already pregnant) during the analysis period that are served per 21 day (oestrous cycle) period.*
- *Pregnancy Rate/%= The percentage of cows that are eligible for service (42 days+ after calving and not barren or already pregnant) during the analysis period that conceive per 21 day (oestrous cycle) period.*

Parameter/Year	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Conception Rate	32	31	31	32	33	32	34	34	35	35	35
Submission Rate	27	29	30	32	36	33	38	38	37	39	40
Pregnancy Rate	9	9	10	11	12	11	13	14	13	14	14

This shows a considerable improvement in this period, in both conception rate and submission rate, but with the overall pregnancy rate improvement fuelled mainly by improved submission rate.

1.4 Measurement of herd reproductive performance

It is important to be able to monitor reproductive performance on all dairy farms in order to assess current position, assess trends, compare against others and set targets. However, it is especially important to be able to determine whether improvements in herd reproductive performance would result in improvements in farm financial performance. Good fertility is inherently linked to income, principally through it's ability to deliver early lactation cows (with higher daily yields than late lactation cows), to deliver calves for sale or eventual herd improvement and to avoid culls with associated costs of replacement of the cull cow's place in the herd. The links between production and reproduction are discussed in more detail in section 1.7.

When measuring reproductive performance, it is important that parameters chosen are easy to use and comprehend by a wide ranging audience, that figures accurately represent true performance, are up to date and not historical, and allow detail to strip back the exact areas of poor performance in a multifactorial area.

1.4.1 Measuring reproductive performance using interval data

The time period between two calvings is one way of assessing reproductive performance. The calving interval parameter has been commonly used and can even be used from paper records to assess current and historic performance. It is usually used as an average (for example of cows calving in a calendar year) known as calving index. Although these measures often do not require software programmes to calculate and are easy to describe and understand, use of them can be accompanied by flaws.

The use of calving interval is generally retrospective since it requires the cow to calve a second time and therefore a cow conceiving today will not influence calving interval for another 281 days. In addition to this, there will often be a downward bias introduced since early calving cows (those with good reproductive performance) will calve first and alter the calving interval first and artificially enhance performance which will correct over time as later calving cows (with poorer reproductive performance) calve. Results are therefore firstly considerably historical, then inaccurate and very historical, then accurate but extremely historical.

Some cows (often those with poor reproductive performance) do not recalve and therefore do not contribute to the calving interval figure. Herds with high culling rates can therefore appear to have artificially good calving intervals. The distribution of the data when assessing the calving intervals from a group of cows is often right skewed (a heavy ‘tail’ of longer intervals). A measure of assessing spread from the central estimate should therefore be used, but this quickly removes both the requirement for easy calculation and straightforward explanation and comprehension by those discussing the results.

Other interval parameters representing smaller parts of the lactation can also be calculated, such as the average time from calving to conception and the average time from calving to first service. Calving to conception interval is less retrospective than calving interval as the end point of the interval is a successful insemination. Calving to first service interval provides information about a specific part of the reproductive process (submission in cows that are yet to receive an insemination).

1.4.2 Measuring reproductive performance using proportion or rate data

Calculation of rates show a proportion of cases in which a specified criterion is met (e.g. the proportion of cows receiving an insemination in a 21 day period, the proportion of inseminations leading to a pregnancy or the proportion of cows pregnant within 100 days of calving) in a given time period. Using rate data has the huge advantage of being less retrospective than using interval data.

Success of service has been measured using a rate, with the proportion of inseminations being successful being known in the UK as “conception rate”. The term “pregnancy rate” would perhaps be more appropriate since this is in reality an assessment of the proportion of cows that are diagnosed as pregnant at pregnancy diagnosis (the number that conceived and subsequently lost the pregnancy, often around 16 days post insemination would likely have made the "conception rate" far higher than the "pregnancy rate").

1.4.3 The components of reproductive performance and 21 day pregnancy rate

When assessing reproductive performance, it is often useful to start by evaluating the components of successful reproductive management. Broadly speaking, this comes down to inseminating a large proportion of the cows that are eligible and having a high proportion of those inseminated becoming pregnant. The management decisions and health events that farmers must tackle are simply involved with maximising these two areas.

1.4.3.1 Submission for insemination

Oestrus detection is a complex and very important area and will often be a main determinant of overall fertility performance in a herd (Tenhagen 2004). When evaluating performance it is important to consider the accuracy of oestrus detection (the proportion of inseminated cows that were in oestrus) and the sensitivity of oestrus detection (the proportion of cows in oestrus that were inseminated).

The period of the lactation immediately after the voluntary waiting period (VWP, the time between calving and when a cow is determined eligible for insemination on that farm) is crucial to herd reproductive performance. The 24 day first service submission rate (the proportion of cows inseminated in the 24 days after their VWP ends) effectively reflects the proportion of cows receiving a first insemination at the first opportunity. It is important to remember that first service submission rates can also be affected by periparturient or early lactation disease (cows affected by uterine or ovarian disease may have reduced rates).

1.4.3.2 Conception or pregnancy

It is also essential to ensure that as many inseminations as possible lead to a pregnancy. As discussed above this is straightforward to measure, using the proportion of inseminations that lead to a pregnancy. This will be described as conception rate from this point, to allow the ability to distinguish from the more encompassing term “21 day pregnancy rate” discussed below.

Regular and early pregnancy diagnosis means that the conception rate can usually be assessed accurately with only a 1 to 2 month delay from when the inseminations occurred. Not all herds use pregnancy diagnoses either by examination of the uterus per rectum or by in line milk sampling. In these herds, conception rates are assessed using non-return to service after a specified period of time or a subsequent calving. The former is clearly heavily affected by return to service submission rate (as herds where ability to detect returns to service is poor will have a higher non-return rate), while the latter makes analysis retrospective.

1.4.3.3 Monitoring reproductive performance using three-week time periods

One of the most useful and least retrospective methods of monitoring reproductive performance is to measure the proportion of eligible cows that become pregnant every 21 days (de Vries 2005). This can be referred to as “fertility efficiency” but is most commonly known as “21 day pregnancy rate” and will be referred to as such for the remainder of this project.

Increasingly this is being used in conjunction with the proportion of eligible cows that are served in the three-week period (submission rate) and the proportion of cows served that become pregnant. In this way, the key elements of reproductive performance are monitored over time with a minimum delay. The eligible population (determined separately for each 21-day block) is defined as cows intended for breeding that have passed through the VWP and that are not yet pregnant. This three-weekly summary provides an early indication of whether submission or conception is currently the main limiting factor.

It is essential to be able to pinpoint what area is most contributing to overall poor reproductive performance. This may lead to the need to go back to a series of parameters, including interval parameters, to aid the building of a full picture. Regular reviews of reproductive performance are increasingly used by farmers and their veterinary surgeons and advisers to determine trends and assess areas where change is required.

1.5 Role of the veterinary surgeon in improving reproductive performance

Routine fertility visits (often known as routines or RFVs) have been a bedrock of cattle practice in the UK for several decades. They provide a regular point of contact with a farmer, often not needing diary reminders and taking place on a very regular basis, usually either weekly, fortnightly or four-weekly on the same day of the week. They serve as an opportunity to discuss any issue about the relationship between the practice and the farm, a regular income source for the practice, a social event, a chance to examine any sick animals, a chance to inspect groups of animals and their environments and certainly an opportunity to examine and advise on the fertility status of individual cows and of herd reproductive performance.

It becomes the responsibility of the veterinary surgeon assigned to the farm to manage the relationship. As a minimum it is expected that the individual cows presented will be examined with proficiency and that attempts at treatment to reduce the calving interval of individual cows are logical, understandable and cost effective. Work at this level usually involves examining individual cows for pregnancy diagnosis, for non-detection of oestrus and for checks for ovarian and uterine disease after calving.

Many farms expect veterinary surgeons to be comfortable monitoring herd reproductive performance on the farm, information which usually originates either from direct downloads of information from the farm's software or from information collected and stored by a third party (especially milk recording companies). Although there are commonly used farm adviser programmes that generate parameters to allow analysis, as well as graphics and reports, it is increasingly useful to be able to adapt data in a variety of formats in order to quickly assess a farm's current position.

Use of this information at routine fertility visits (either through giving advice on information presented by the farmer from their own software or by bringing reports prepared in advance for discussion) is expected in work at this level. This might include monitoring of the 21 day pregnancy rate over time for the individual farm, comparing it to other farms and breaking down any trends identified, into for example showing that conception rate has reduced over a hot spell of weather in summer or since the introduction of a policy of fixed time AI for cows not served by 70 days in milk. Further skills required for veterinary surgeons attempting to work in this area include the ability to assimilate information and identify small numbers of key points and provide very brief and succinct summaries that are likely to result in the farmer understanding the problem and the advice required to improve the situation.

It is often appropriate to conduct regular fertility reviews at intervals such as every 3,6 or 12 months depending on the size of the herd. This is often done by the veterinary surgeon that normally performs the herd's routine fertility visit but extra information or opinion can be useful if this is performed by another veterinary surgeon in the practice or from an external organisation. This would normally also incorporate other herd health areas and may be an excellent opportunity to discuss how, for example, culls for fertility fit into the herd's overall culling policy. Or it may be an opportunity to discuss methods to improve overall submission rate such as the introduction of activity meters and likely financial returns on this investment. It is usually of benefit to include all farm staff and family members involved in the farm business in this discussion to improve motivation and make sure any plans, especially those involving investment, can realistically be achieved.

Veterinary surgeons in UK cattle practice are used to evolving their skills and service offerings to their clients. Since routine fertility visits are such a staple part of the relationship between farm and practice, and since reproductive performance is such an important area to the farm financially and usually has considerable scope for improvement, they may be the most obvious starting point for the development of skills that are currently less commonly used. Probabilistic techniques such as the use of stochastic simulation modelling are not commonly used currently to aid decision making by farmers. Examples of this would for example be to use simulation to assess the associations between a herd policy of a dry period length of 35, 42, 49 or 56 days and production, reproduction, mastitis and lameness. Such an approach could aid farmers to make better decisions with probabilities attached to outcomes and a likelihood of offering advice that could greatly enhance herd performance and profitability.

1.6 Use of data in assessment of herd reproductive performance

1.6.1 Traditional methods of collection of reproductive performance data

There is naturally a huge range across the 12,000 UK dairy farmers in levels of interest and ability with technology. There are many herds who rely principally on paper records such as a daily dairy diary and do not milk record every month. These farms may rely on their individual veterinary surgeon or adviser performing a bespoke bureau service or rely on their own data skills or judgement to analyse reproductive performance.

Seasonal calving herds can often present a related but different challenge for bringing reliable data into analysis programmes. Seasonal calving herds will often for example milk record every other month, or twice after calving and twice before dry off only, or quarterly to coincide with Johne's disease milk serology testing. As a result, the quality of data is often not as high as otherwise comparable all year round calving herds. In addition, seasonal calving herds are also often more comfortable using different parameters to all year round calving herds. It can therefore often require data to be sought from different sources and using different terminology.

Reproductive performance data can also be recorded by a milk recording technician, which can result in a reasonable amount of information being stored and available on farm office and parlour software. There is a good uptake of this service, with NMR (one of the milk recording organisations) recording more than 40% of the UK dairy herds (Hanks 2010-20). This system can garner a lot of information, often with little input directly from the farmer, but the data can lack detailed events and its existence does not necessarily equate to a farmer understanding and wanting to use it.

1.6.2 On farm software

Software systems either as standalone systems or supplied as part of the technology associated with the milking parlour or robots are being used increasingly for day to day management. These allow farmers to record individual cow data which can be integrated with other information (often from the milking machine and on cow sensors) to allow sophisticated analysis of reproductive performance. The data recorded in this way are increasingly recorded at the side of the cow (or via transcription on to the farm office computer) in real time and vary considerably in the level of detail that is recorded. A reasonable degree of technological ability is required but as herd sizes have increased, the popularity of computer recording systems have also increased, and in many herds the cows can now be identified and information about their clinical history and performance described only by reference to software records.

The original purpose of herd software systems, to allow easier and more efficient day to day management of the herd, has been supplemented by the ability to also use them to readily monitor performance across the herd, and to identify potential areas for improvement. Farmers can see the benefits to their businesses of routine performance monitoring and management through their own data and often their own recording of it.

Biosensors are increasingly used both in day to day individual cow management and more in depth herd level analysis (Hudson 2018). On animal sensors measuring activity and using it to predict oestrus are the most high profile example, but both on animal and in line sensors are used in further areas. These include rumination, milk flow, concentrate feed intake, electrical conductivity of milk, body temperature and force plates. These have many uses, including identifying mastitis, lameness, individual sick cows and predictions of timings for insemination. In many cases, many sources of data are brought together and algorithms applied to detect any abnormalities from the normal. This will often present the farmer with action lists (such as cows to be examined for sickness) and graphs showing trends over time which aid decision making for treatments.

1.6.3 Big data

Big data has been discussed as a concept for more than 25 years and is a well known phrase to many in society, permeating medicine, industry, financial services, marketing, retail and business. It has been defined in many ways since the first 4 ‘Vs’ (volume, velocity, variety and veracity) were described in 2001 with attempts to add more ‘Vs’ and even ‘Ps’ (Kitchin 2013, Kitchin 2016, Diebold 2012, Lupton 2015) to aid definition. The original term is intended to describe a large dataset and a range of techniques of manipulating and analysing it to draw conclusions.

The definition of what constitutes large volume can vary according to the user of the data but as computational power increases, the ability to store and manipulate the data (and thus use it more effectively) continues to increase. It can be difficult to bring together data sources (variety) as a result of trying to integrate different software programmes. Computational power will also limit velocity (the speed with which data can be brought together, collected and later analysed). Data quality (veracity) becomes a key limiting factor, with the phrase ‘garbage in, garbage out’ a warning to assess sources, apply techniques to identify missing data and be prepared to remove data found to not meet standards of accuracy.

Big data is used throughout society, with common examples being:

- the use of previous history and algorithms to generate marketing and advertising by social media companies,
- the use of tracking to aid logistics by delivery firms and firms relying on supply chains
- the matching of product supply and demand by supermarkets and other retailers

- the use of clinical data to predict risk of future diseases by government health services

Big data concepts will be used in this project in various aspects of the definition; considering the use of big data in the dairy industry to allow more robust analysis of reproductive performance, using large datasets to assess associations between periparturient health events and reproductive performance and bringing together sources to allow construction of stochastic simulation models.

1.6.4 Use of data in large scale benchmarking and in research

The quality and size of datasets filled with dairy farm events in the UK remain variable, but data is increasingly recorded, and further discussion may be required (particularly around data protection and privacy) to make anonymised versions more readily available to interested parties. As such it would be desirable to have a resource available for researchers to utilise and possibly other farmers to use for comparison of performance. These datasets should be able to allow huge retrospective studies covering reproduction, production, health events and management decisions. Extraction of the data as a result of it being held in a variety of formats may be a challenge and it may require collaboration between industry stakeholders to bring information together.

Milk recording companies typically hold most of the data that has been brought together above the level of the individual farm. Annual reports based on data which is owned and stored centrally by NMR (Hanks 2010-20) provide an up to date screenshot of 500 herds and act as a reference point for current performance in a number of areas.

The majority of herds included in large milk recorded databases in the UK record little health event information, with the recording of periparturient events being particularly variable. As such, one of the first tasks for a researcher is often to assess herd data recording quality and therefore assess which herds have robust data that can be used for further analysis.

Datasets from on-farm computer recording systems tend to be much more detailed and quality of record keeping is often better, but such data tends to be harder to access, since it often needs to be retrieved from farms on an individual basis. Several steps therefore need to be employed by the researcher in order to get a final spreadsheet to work with. Not only would the researcher need to collect data, but also to manipulate and "clean" it, in order to get it into a format that can allow comparison between large numbers of herds. More work is required to make sure that any data held is at least available as published case reports and allows farmers to make a comparison with median figures of parameters (from large numbers of herds) against their own animals.

1.6.5 The use of evidence from multiple sources

Bringing together information from various sources occurs at various stages within the industry. Farmers and external companies who work with them use it at an individual herd level to assess herd performance and aid management. Researchers bring performance data from several herds together to examine the information to consider associations between factors and performance. It can be a technological challenge to bring together data from various farm sources to allow assessment of reproductive performance. When attempting to bring research information together it is of vital importance to use robust data when appropriate and to synthesise quantitative data from other published sources in a systematic way.

Scientific research and evidence to support associations between diseases and across populations are being increasingly used at a larger scale than an individual research study. Methods of synthesising evidence from existing literature are discussed in more detail in chapter 3. Briefly these encompass review articles which summarise information from a series of similar publications. These are based around scrutiny of the quality of the research study designs and methods and thorough searching for publications using consistent search terms. Reviews of different thoroughness and speed can be conducted, with the most scientifically robust being the systematic review which is being used increasingly in dairy cow research to comprehensively answer clinical questions (Oehm 2019, Beaver 2019, Francoz 2017). This review technique will often involve quantitative analysis of the findings of other studies, with meta-analysis commonly being used to create a pooled summary effect of the association investigated by all of the similar papers.

When attempting to design tools for further use it is essential to have evaluated the evidence thoroughly to allow solid construction of models and an expectation that conclusions drawn can be based on the most robust information available.

1.6.6 The use of stochastic simulation

Once big data has been assimilated and cleaned it is available for further analysis. It is common to attempt to make associations between aspects of the data, which often culminates in the creation of logistic regression models with output such as odds ratios describing relationships. These are ways of associating input parameters with an outcome or outcomes and show change in the odds of the outcome as a result of the occurrence of the input. Whilst this is often statistically robust, it does not always allow reasonable exploration of the association between the various inputs to the model and can be difficult and confusing for the reader of the research to interpret. A number of techniques can be used to analyse large retrospective datasets, one of which is stochastic modelling, which attempts to overcome the issue of counterintuitive presentation of results and a lack of emphasis on the association between inputs and outputs given the complex associations with other inputs to the model.

Reproduction in cattle is an example to illustrate this issue; large datasets can exist but can be difficult to analyse and allow relationships to be explored as a result of a large number of conflicting health events and management techniques that can influence it. When using traditional statistical techniques it can be difficult, for example, to elucidate the association between the probability of pregnancy and changing oestrus detection methods given that a variety of other oestrus detection methods, levels of periparturient disease, endemic infectious disease and environmental conditions may also be changing.

Following the construction of a stochastic model, simulation is used to create a large number of iterations of the conversion of an input drawn randomly from a predetermined distribution and converted into an output value using the workings of the model (the algorithm or calculation). The large number of iterations of this process allows for consideration of uncertainty in the relationship between the inputs and outputs. The outputs and the corresponding inputs that helped to generate them are then stored and allow further exploration of the relationship between inputs and outputs, often by logistic regression models exploring data from a larger distribution and other techniques such as correlation and partition of variance. This stochastic approach may offer not only the deterministic scenario analysis created by an algorithm generating outputs from one set of likely inputs, but also allow expression of uncertainty.

Stochastic modelling is a flexible technique that is increasingly used in research. Researchers are often able to initially explore associations between inputs and outputs of traditional models using their own research data and then use simulation to explore the relationships in more detail, often using the relationships from the initial models as building blocks. It has been employed in medicine and public health for some years and is increasingly being used to aid the analysis of agricultural data.

Dairy farms with on farm software and particularly biosensors and the data generated by milking machines appear to be ideal candidates for its use. As computational power has increased and the ability of researchers to create and utilise mathematical code has become more widespread, so some of the initial blocks to this technique have been removed. As a result, it is likely that the techniques will increasingly move through scientific research to be of more direct use by farmers through answering specific questions and creating decision support tools. Therefore, it will be possible to use deterministic algorithms linking inputs and outputs to evaluate the impact of uncertainty on decisions through stochastic modelling.

Farmers with large herds will often request assistance or pose questions of their advisers concerning herd level management decisions or investment choices. Traditionally these have been answered using experience of the problem reinforced by evidence sources and existing data from the farm on current performance. The use of stochastic simulation modelling should aid the adviser by allowing a large range of possible inputs to be explored and probabilities of certain outputs being determined. Examples of questions farmers may pose include:

- Should I buy biosensors to help me detect oestrus and if so, how many more pregnancies would I expect to get?
- Should I install fans to help reduce the reduction in conception rate I get most summers?
- Should I start to use bulls of higher fertility index than I currently use in order to get heifer replacements with better reproductive performance?

This use of stochastic simulation to answer individual farm questions, or the design of a decision support tool based around synthesis of evidence from multiple sources and simulation would represent a way in which science can instigate changes in agriculture and in the farm sector of the veterinary profession.

1.7 Economics of production, reproduction and culling

1.7.1 Link between production and reproduction

Production and reproduction are intimately linked on dairy farms. There is a strong negative correlation between yield and fertility. Better reproduction usually leads to better production (Bello 2012). It is always essential to remember that the farmer's principle objective is usually trying to maximise milk sold. While there are other sources of income available from the herd, mainly through the sale of animals (culls of milking cows or sale of beef or breeding animals for other herds, some of which will also be increased by improving reproductive performance), the vast majority of income is derived from milk sales. Therefore, it is essential to principally consider reproductive performance in terms of how it affects milk sold.

1.7.2 The lactation curve and the calving cycle

When assessing these two intimately related and conflicting drivers of farm income, consideration must be given to the features of a typical graph of a lactation curve, with a steady incline to peak at about 60 days and then a much shallower tail off to dry off. Shapes of lactation curves have been given a lot of emphasis (such as by the use of the MilkBot equation, Ehrlich 2011) and many farmers consider the profiles of the lactation curve of individual cows in terms of the size of the peak and the rate of decay towards the tail at dry off in some detail.

In simple terms it is desirable to have a high peak and a slow decline. Cows in late lactation give less milk per day, have a lower margin over purchased feed and have a worse feed conversion efficiency than a cow in early lactation (Britt 2003). Effectively cows in late lactation are less profitable and therefore in the vast majority of cases it is highly desirable for cows to spend as little time as possible in late lactation and to get back to their next peak milk yield as quickly as possible. It is generally accepted that extending the calving interval above a certain level will result in a decrease in profitability (Gonzalez-Recio 2004, Evans 2006a, LeBlanc 2007).

It is therefore important for profitability, for cows to spend as long as possible in early lactation as a proportion of lifetime from first calving and an appropriate but not extended period dry. Very short or absent dry periods are associated with large reductions in milk yield in the next lactation (Steeneveld 2013). Therefore, to guard against this, very short calving intervals could result in an increase in the proportion of the cow's productive life spent dry. This could create the concern that this would exceed the increase in productivity due to increased time spent in early lactation, leading to a decrease in average lifetime daily production.

The point (value of calving interval) at which these effects are in balance is highly controversial, but it is widely accepted that a very small proportion of the UK national herd calve at intervals which are too short and that there is substantial scope to improve profitability through better reproduction. The length of calving interval at which a further reduction does not improve profitability has historically been considered to be 365 days (Esslemont 2003). In most herds there is plenty of scope for improvement in reproductive performance before this debate becomes relevant and required.

1.7.3 Cost of better reproductive performance

There are certainly conflicting opinions to the theory that virtually all herds would make more money if they could improve the herd reproductive performance. Extended lactations of up to 18 months as a standard (often with 3 times a day milking also as a standard) are frequently discussed (Sehested 2019, Sorensen 2008, Stefanon 2002). Cows with high peaks and long and high persistence of milk yield are often displayed as examples of how this system should work and discussion had of the reduced proportion of lifetime spent dry and the reduced costs associated with a reduced number of calvings affected by periparturient and early lactation diseases.

Few would argue that there are substantial costs associated with inseminations, with veterinary interventions around insemination and calving, and with calving associated diseases. Furthermore, many argue that there is a reduction in yield as a result of pregnancy in early lactation cows (Ragsdale 1924, Olori 1997).

1.7.4 Benefit of better reproductive performance

Reproductive performance has an influence on the profitability of dairy herds through three main routes:

- affecting the number of days between successive calvings
- affecting the proportion of the herd culled annually because of failure to conceive
- generating calf sales

By reducing the calving interval, the next lactation starts sooner, and each early lactation day replaces a day at the end of the previous lactation. Increased milk production can therefore be seen as the predicted mean daily yield for the new lactation minus the mean daily yield for the end of the previous lactation. An increase in milk production will result in an increase in feed requirement to support the higher yield. It is therefore not the absolute value of milk sales gained that is important, but the margin associated with that gain.

In simplest terms, the cost of culling a cow can be estimated by the cost of purchasing (or not being able to sell) a similar replacement (often heifer) animal at the point of calving, minus the sale value of the culled cow. Where homebred replacements are used each cow culled requires a homebred replacement which could otherwise be sold.

Improved herd reproductive performance leads to less failure to conceive culls which either allows a reduced replacement rate of the herd (and thus less heifers need to be retained) or allows more voluntary culling (for example for low production animals). Both of these situations may lead to an increase in farm income.

A cow calving more frequently will produce more calves during her lifetime. Calf value can be extremely important, to the minority of farms that sell potential breeding replacements to other herds, but particularly to the majority that sell beef calves. The majority of farmers also want to have as many heifers available as possible to allow more options for culling the less productive cows in the herd.

1.7.5 Economic cost of poor reproductive performance

Attempting to put a price on the economic impact of poor reproductive performance is challenging because the units of culling for fertility and extended calving intervals can vary substantially between farms, and it is difficult to calculate standard figures that will be applicable across a range of circumstances. Attempts have been made to bring together the costs, with a recognized method being the FERTEX score (Esslemont 2002). This provides an estimate of the total lost profit per year due to suboptimal reproductive performance by adding together losses from calving interval, culling and service costs.

More recently attempts have been made to consider a large range of inputs which can be adjusted for an individual farm (such as lactation curves, body weights, risk of culling, labour costs, feed intakes and insemination costs) and simulate economic returns when a range of inputs are changed by the user (De Vries 2019). The Florida Dairy Computer Programme then returns outputs for net return per cow per year for a range of 21 day pregnancy rates from 9% to 42% and in varying situations, such as a reduced milk price or specific herd profiles such as cows with low persistence or early culling for failure to conceive. As a result, the user of the programme can assess predicted economic returns for improvements in herd 21 day pregnancy rate for their own herd.

1.8 Set and established farm policies that can influence reproductive performance

Across the 12,000 dairy herds in the UK there are a large range of management practices, and of course a large range of objectives for the individual businesses and indeed personalities and styles of running a small enterprise. Some of these differences are individual preferences by the owners in how to run their businesses and their lives. Other differences are interpretations of efficiencies and methods the owners believe will make them more successful.

Many farmers utilise advisers to aid them in their decision making. Many of these interactions can be of benefit to the individual choices that the farmer makes. Some of the choices discussed in section 1.8 are decisions a farmer has made in order to run a more successful business and therefore are policy decisions that can be discussed with advisers, rationalised economically and considered for change or investment. However, a number are set policies that are ingrained in the way the farm is run that are perceived to be very unlikely to be changed. It therefore becomes a challenge to a motivated adviser to try to help alter such a fundamental farm policy in order to make the farm business run more efficiently. Increasingly since these policy decisions are often so personal to the farm, the use of decision support tools and the increasing use of data to support economic arguments can become more useful. This can allow the farmer to explore many situations using their own farm data, often in their own time. Some of these set farm policies, that are often difficult to change, are thought to have a substantial impact on reproductive performance and are discussed below.

One of the most fundamental choices concerns breed of cow and genetic differences within breed, which allow the farmer to set a rough target for both yield and emphasis on hereditary levels of fertility. The majority of the control a farmer has in this area is through choice of bull and the emphasis they place on factors such as longevity, yield and fertility itself through financial and fertility indices can be a large part of what can be controlled by the farmer. For example, primary selection for production over decades has led to cows with poorer reproductive performance (Weigel 2017, de Vries 2005).

They can also impact fertility performance through decisions they make on their cows and heifers through which animals they choose to breed to a dairy and which a beef bull and therefore which dams will contribute replacements to the herd. They can for example choose cows with high yield and no regard to their fertility to breed replacements from, which may result in a decline in herd reproductive performance in the future. Both the hereditary aspects of yield and the hereditary aspect of fertility are likely to have a substantial impact on reproductive performance as an individual criterion and to an extent are largely within the farmer's choice and control. The use of genomic testing is increasing and is likely to allow the farmer better control of reproductive performance (and many other traits) through more accurate ranking of heifer crops on a series of inherited traits (Cole 2018, Lucy 2019).

In a similar way as the farmer controlling the type and number of animals entering the herd, they also have the ability to control which animals leave the herd and when. Which animals are 'on the cull list' will influence the direction of various traits in the herd and is entirely within the choice of the farmer. A farmer that always culls more heavily for poor fertility than for persistent mastitis or temperament will likely improve their herd reproductive performance more quickly than another farmer who takes the opposite position.

Calving the herd all year round, or whether they will calve in a season or block is a further decision which is also relatively fixed. This is often in either spring or autumn, or occasionally both spring and autumn within the same herd, or across several herds under the same ownership.

Seasonal calving has increased in recent years, mostly due to the adoption of extensive, low-input systems such as those often found in Ireland and New Zealand. When following this method closely, a large proportion of the herd calve within a short period of time in early spring. Most of the herd are therefore at peak lactation (and the breeding season) to coincide with that of maximal grass quality and growth rate. Autumn calving herds will often follow similar methods with an emphasis on high submission rates, paddock grazing and effective utilisation of grazing but are often slightly higher yielding yet also attempting to utilise cheap spring grass effectively, for them as a convenient food while cows are in the second half of pregnancy.

Seasonal calving herds in the UK typically breed for a period of 12-18 weeks, and cows not conceiving within this time period are either culled or retained for re-breeding a year later in single block herds and six months later in dual block herds. Cows that slip blocks usually have severely reduced profitability. There is a huge emphasis on reproductive efficiency in seasonally calving herds (Morton 2010, Ribeiro 2013), which often focuses on high submission rates, calving replacement heifers at 21 to 24 months of age early in the block and strong consideration of the use of bulls that score highly on fertility indices, often at the expense of other traits such as frame and yield.

In year-round calving herds, there is less pressure on generating pregnancies within a specified period of time. In the few comparisons between large numbers of herds using either all year round or seasonal calving, reproductive performance is often higher for seasonal calving herds (Morton 2010). Differences in management of the system has even led to a divergence in reproductive parameter recording, with seasonally calving herds often referring to 3 week cycles from the beginning of the mating period (such as 6 week in calf rate) and ultimately a single figure for ‘empty rate’ (the percentage of cows eligible for service on the planned start of mating that ended up not pregnant within the block).

Another key decision in a herd’s breeding policy is the length of the voluntary waiting period (VWP). This is defined as the period after calving when a cow is electively not served even if seen in oestrus and is normally set as a herd policy under the farmer’s control. It is often set at 42, 50 of even 60 days. It is often used due to the perception that conception rate will be reduced as a result of ovarian or uterine disease or negative energy balance. Since increasing the VWP will decrease the herd’s submission rate it is important to balance the relative importance of the conception risk and submission rate in order to maximise overall reproductive performance. Recent work by Fodor (2018) found that the odds of pregnancy by 200 days in milk was higher in herds without a VWP or with a VWP less than 50 days, compared to herds with a VWP greater than 50 days (OR 1.45; 95% confidence intervals 1.12-1.88). Herds with extended VWPs are becoming less common.

In comparison to VWP (when they decide to start breeding), farmers also have to decide when to stop breeding in some instances. Some farmers will run a very strict days in milk or number of services criteria for when to stop serving a cow. Policies such as this often lead to improved reproductive performance in terms of 21 day pregnancy rate, but at the expense of an increase in costs through increased failure to conceive culling.

1.9 Impact of health events, management decisions and the cow's environment on reproductive performance

Many health events, management decisions and factors affecting the cow's immediate environment are associated with reproductive performance. Some of these relationships are quantified in chapters 2 and 3 and they are briefly introduced in section 1.9.

1.9.1 Periparturient and early lactation events

Periparturient and early lactation events are typically diseases of the reproductive tract (such as endometritis and cystic ovarian disease) but also encompass any interruption to the normal calving process and involution of the reproductive tract in the first 42 days of the lactation. This can therefore include disorders such as retained foetal membranes, assisted calving, metritis and occurrence of multiple births. Lactational incidence rates are reported to be between 2 and 10% for the periparturient events around calving (Hayes 2012) and up to 25% for the early lactation disease endometritis (Leblanc 2002).

Associations between these events (which are heavily associated with each other) and reproductive performance are discussed in more detail in chapter 2. In brief terms, any events that are considered to impair the normal events of calving, uterine involution and resumption of ovarian cyclicity may lead to impaired herd reproductive performance. This may be as a result of increased bacterial contamination of the uterus after calving, increased influence of inflammatory mediators on developing follicles or reduced feed intakes and consequent negative energy balance as a result of systemic disease (Potter 2010, Williams 2007, Dervishi 2016).

1.9.2 Endemic infectious disease

Various widespread endemic infectious diseases of cattle in the UK are often seen as present or absent by farmers and despite the possibility of the use of vaccines in the case of some diseases, can remain uncontrolled and can lead to substantial losses. Among the causes of loss are decreased milk production, reduced calf growth rates, increased culling and mortality. Reduced reproductive performance is also possible.

Leptospirosis and Infectious Bovine Rhinotracheitis (IBR) are commonly discussed as having an impact on fertility, but evidence supporting associations between infection with these diseases and reduced reproductive performance is not comprehensive at a herd level. Reduced conception rates (Dhaliwahl 1996) and increased calving to conception intervals (Guitian 1999) were found in cows seropositive to Leptospirosis compared to seronegative cows in relatively small studies at an individual cow level. More recent evidence and review of associations between IBR and reproduction have taken place (Sayers 2017, Wathes 2020). The level of any associations remain unclear and mechanisms for pathology of the reproductive tract caused by IBR virus have yet to be fully ascertained (Wathes 2020).

It is possible clinically to find examples of suspected introduction of persistently infected (PI) animals to Bovine Viral Diarrhoea Virus (BVD), seroconversion of naïve animals to the virus, a reduction in fertility parameters and subsequent birth of further BVD PI animals. BVD virus is known to cause early embryonic death and this often manifests itself in reduced conception rates and extended intervals between inseminations (McGowan 1993). However associating BVD and reduced reproductive performance on an individual farm is often very difficult since disease transmission between animals is difficult to assess and the clinical effects of infection of the virus can often only be seen months or years later. Equally a vaccination policy introduced as a result of identifying antibody or antigen positive animals does not always lead to demonstrative increases in reproductive performance. Evidence of the benefits of control of BVD at a herd level on reproductive performance are required.

Johnes's disease is typically associated with milk production loss and especially increased culling. The association between infection with Johne's disease and reproduction is uncertain, with some studies associating the disease with improved performance (Raizman 2007, Lombard 2005) and some with decreased performance (Smith 2010, Johnson-Ifearulundu 2000). Studies often conflict on diagnostic method, with some using blood or milk ELISA and some faecal culture, and some both. As a result, associations can be hard to determine when attempting to bring evidence together. The mechanism of association is also unclear. It is hypothesised that improved reproduction is caused by increased early culling of Johne's positive cows or by reduced milk yield and that decreased reproduction is caused by negative energy balance and loss of body condition as a result of chronic scour.

1.9.3 Oestrus detection

A large majority of UK dairy farms use artificial insemination rather than natural service for the majority of inseminations. Some farmers do choose to use natural service exclusively which will alter their fertility management and can alter their performance drastically. Focus tends to be around ensuring the bull is of high fertility, remains free from lameness and that any deficiency in either area is detected and corrected rapidly. When managing cows focus is usually on ensuring they are able to conceive as early as possible after calving through minimising the effect of uterine and ovarian diseases.

In a herd where artificial insemination (AI) is used there is an additional requirement for oestrus detection, so that cows may be inseminated at a time that maximises the likelihood of conception. In addition to the choice of whether to artificially inseminate at all (which is likely to reduce submission rate substantially compared to herds using natural service), farmers have choices over oestrus detection methods. These are discussed in detail throughout the project. Investment in this area has become common in UK dairy farms.

A sample of 832 dairy herds in Canada that returned questionnaires (from 9,000 herds that were sampled) were investigated for a number of factors relating to oestrus detection and their performance analysed (Denis-Robichaud 2016). Average 21 day submission rate for these herds was 44.1% indicating that more than half of eligible cows were not inseminated in a 21 day period. Performance from UK herds currently appears to be similar (40% from the NMR 500 herd report in 2020, Hanks 2010-20) and therefore many UK dairy farmers consider varying ways to improve these results.

Although other factors are expected to be associated with duration and intensity of oestrus behaviour and are discussed where appropriate elsewhere in section 1.9, improving the methods used to detect cows in oestrus are a priority for many farmers. Traditional methods have included observing for visible behavioural signs, oestrus rub devices or paint applied to the tail head to show cows that have been standing to be mounted and attempting to increase the size of groups of cows in oestrus through prostaglandin injections so that oestrus behaviour is more obvious.

Hormonal intervention programmes continue to become more sophisticated and the majority of programmes now used prioritise the ability to inseminate at a fixed time (fixed time AI or synchronisation of oestrus) to avoid the need for observation of visible signs of oestrus behaviour. More than 20% of Canadian herds may use fixed time AI as their principal method of oestrus detection (Denis-Robichaud 2016). These programmes are believed to increase 21 day pregnancy rate through vastly improved 21 day submission rates as a result of timed insemination without the need to assess the stage of a cow’s oestrous cycle (Santos 2017).

As biosensors dramatically increase in use, more herds use activity monitoring as a means of detecting whether a cow is showing behavioural signs of oestrus. Cows walk longer distances when in oestrus (Lopez-Gatius 2005). This was used as the principal method of oestrus detection by 10% of herds in 2016 (Denis-Robichaud 2016). The use of activity monitoring to aid oestrus detection is also believed to drive improved reproductive performance through improved 21 day submission rate, with LeRoy 2018 determining a 21 day submission rate of 80%.

1.9.4 Negative energy balance

High yielding dairy cows have a large energy demand from production of milk and are often unable to meet this demand from their dietary ration. Fat mobilisation occurs in these circumstances to produce energy. There will always be a balance of energy partitioning between the current calf (milk production) and the future calf (reproduction) (Friggens 2010). Therefore, levels of milk production will impact on energy balance which will impact on reproductive performance. Negative energy balance (NEB) during early lactation can reduce fertility by several mechanisms.

This is firstly through a long-lasting effect of NEB on developing follicles. Energy deficiency impairs responsiveness of the hypothalamus to oestradiol, which leads to reduced GnRH pulse frequency and then LH pulse frequency, which reduces ovulation of the dominant follicle (Walsh 2007).

Secondly cows with high milk yields and subsequently a frequent occurrence of NEB will often have reduced submission rates as a result of reduced duration of oestrus and intensity of oestrus behaviour (Lopez 2004). High milk yields are supported by high dry matter intake and high blood flow through the liver and increased catabolism of oestradiol can result (Wiltbank 2006). Reduced oestradiol will lead to reduced oestrus behaviour since this hormone is responsible for this behaviour.

Negative energy balance can also be associated with reduced reproductive performance through reduced progesterone levels. As with oestradiol, this may result from increased dry matter intake, increased liver blood flow, and increased progesterone catabolism.

Plasma progesterone concentration in the days immediately following conception can have a substantial influence on conception rates (Han 2006). NEB can delay the first ovulation after calving (Garnsworthy 2008), resulting in a delay in a commencement of luteal activity (CLA). Corpora lutea from early oestrous cycles after calving produce lower plasma progesterone concentrations (Villa-Godoy 1988) and therefore cows that have delayed CLA are more likely to be inseminated in early cycles and therefore have lower plasma progesterone concentrations.

In conditions of NEB, levels of insulin like growth factor (IGF-1) can be reduced. This can change the internal environment of the oviduct and uterus, effectively reducing normal post calving repair of the endometrium. This can be detrimental to the survival of a developing embryo (Wathes 2007, Fenwick 2008) and result in reduced conception rate.

There is an association between NEB and several periparturient production diseases in dairy cattle (such as metritis and displaced abomasum). Since these diseases are also associated with reduced reproductive performance, an increase in NEB will have an indirect detrimental effect on reproduction through an increased incidence of production diseases.

1.9.5 Heat stress

High temperatures have been associated with reduced reproductive performance and are implicated in reduced conception rates in summer compared to winter in all year round calving, housed herds. Whilst the impact of very hot weather can be quickly apparent with immediate effects, longer term physiological effects also appear to be an issue and can show as reduced performance for some weeks after weather has cooled (Wolfenson 2000).

Measurement of air conditions in the immediate environment of housed dairy cows is being done increasingly and is usually assessed using the temperature-humidity index

(THI). Several studies have investigated the relationship between THI and reproductive performance (Hagiya 2017, Schuller 2014). Ravagnolo (2002) determined that the relationship between THI and non return rate at 45 days (NRR45) was linear between THI of 50 and 68 before the NRR45 reduces between THI values of 68 and 84.

Heat stress is particularly associated with reduced fertility in dairy cattle through an impact on conception rates (Garcia-Ispierto 2007), thought to be as a result of an impact on oocyte maturation and early embryo development. There may also be an impact on submission rates through a negative effect on the incidence, intensity and duration of standing oestrus (Jordan 2003). Conception rates are thought to be affected by at least 3 different mechanisms.

Firstly there appears to be a substantial impact on selection and dominance of the follicle and prevention of the growth of oocytes. There is a reduction in the steroidogenic capacity of the theca and granulosa cells of the selected follicle, so reducing LH and oestradiol. Hence, there is poor follicle maturation, delayed follicle selection and a reduction in the degree of dominance of the dominant follicle (Dash 2016).

Heat stress also leads to reduced blood progesterone concentration. Reduced appetite and dry matter intake result in reduced secretion of progesterone by theca cells which results in lowered plasma progesterone levels (De Rensis 2003). This can lead to abnormal oocyte maturation, implantation failure and early embryonic death.

Finally, the intrauterine environment of the cow can be compromised. High temperatures can compromise endometrial function and alter its secretory activity, which may lead to termination of the pregnancy through reduced likelihood of embryo implantation. This results from a decrease in blood flow to the uterus and increased intrauterine temperature. In addition to very early embryonic loss, these changes increase the chances of suppressed embryonic development and loss after the maternal recognition of pregnancy at 16 days gestation (Hansen 2007).

1.9.6 Age at first caving

Many farmers are conscious of the cost of heifer rearing, which is amplified by the increasing number of heifers reared away from the main farm as a result of increasing herd sizes. Discussion is therefore frequent on the benefit of reducing mean age at first calving to 23-25 months as advised by Cooke (2013) and Wathes (2014). Although heifer growth rates will have slowed substantially prior to first calving, growth trajectories suggest that most cows will grow into their third lactations (Cooke 2013). It is likely that this growth will require dietary energy, and energy will be partitioned into growth and production over reproduction (Berry 2009). Therefore, since younger heifers will need to grow more, any decrease of age at first calving below 23 months is likely to lead to reduced fertility (Evans 2006).

There are more heifers calving above the target age than below it and this is also likely to impair subsequent reproductive performance (Ettema 2004). This is thought to be due to these heifers having a higher average body condition score and mobilising increased body fat leading to increased metabolic, production or periparturient diseases.

1.9.7 Length of dry period

Dry period length has typically been 56-60 days which has traditionally been thought to be a compromise time period to allow development of mammary tissue for milk production, to allow longer dry cow antibiotics to be used to improve cure rates of intramammary infections, whilst at the same time not allowing reduced lifetime milk yield as a result of long periods of time not producing milk.

Most farmers will have a target length of dry period which they use for the majority of cows in the herd. This remains typically 56-60 days but is shortened in some herds to 42 days and has been investigated to be shorter than this in a number of studies (Gumen 2005, Watters 2009, Chen 2015). There are also a number of cows in herds that deviate from the length of dry period set out in herd policies as a result of individual management or health factors such as low milk yield, low or high body condition score or attempts to cure persistent mastitis.

The association between length of dry period and reproduction is thought to principally be due to milk yield and negative energy balance. Reducing dry period length leads to reduced yields and therefore less negative energy balance and therefore improved reproductive performance (Chen 2017, Kuhn 2006). Since increasing dry period length is less likely to be a herd policy (more often it will occur in individual cows), the mechanism for the likely reduced fertility in the subsequent lactation has not been elucidated. In a similar way to shortening lengths, it may be as result of increased milk yield or perhaps due to an increase in periparturient disease as a result of an increased likelihood of cows with a high body condition score.

1.9.8 Genetics

There is a strong correlation between high milk yield and decreased reproductive performance, which may be as high as 0.40 (Fu 2017). Selection for milk production from 1975 onwards (Rauw 1998) has been implicated in inadvertently breeding less fertile cows (Royal 2000, Lucy 2001, Rauw 1998, Pryce 2002). Since heritability of milk yield is relatively high, often over 0.30 (Schneider 1986), it has proved relatively straightforward to increase herd yields through genetic selection.

The relatively low heritability of many fertility parameters, with most being less than 0.05 has made any attempts at progress to even reverse declining fertility challenging

(Royal 2000). As a result, genetic selection for improvement in fertility has proved difficult. Identification of the timing of commencement of luteal activity with a heritability of between 0.16 and 0.27 (and it's correlation with other reproductive parameters) has helped to begin improvements in the last 15 years since Wall (2002) described the use of a fertility index to reverse fertility decline in the UK.

The UK fertility index was first introduced in May 2005 to allow attempts to improve reproductive performance through genetic selection. The index which is based around financial returns of the choices made identifies bulls as being in a range of -15 to +15. A bull with an above average (positive) value will sire daughters with improved reproductive parameters including calving interval. AHDB quote that every point increase in Fertility Index, (say from -3 to –2), will be transmitted as a decrease in calving interval by half a day and improve non return rates by 0.5% (AHDB 2020). The six heritable traits that contribute to the index, which are either direct measures of fertility (1,2,5,6) or have strong correlations with fertility (3,4), are collected on a bull's daughters across the UK dairy herd are shown in Figure 1.1.

1. Calving Interval
2. Non return rate
3. Body condition score
4. Measure of milk yield around insemination
5. Days from calving to first insemination
6. Number of inseminations needed to get a cow in calf

Figure 1.1 Heritable traits contributing to UK fertility Index, from AHDB Fertility Index Factsheet, 2020.

1.10 Summary, aims and objectives

1.10.1 Significance of this work

Reproduction remains essential to the operation and profitability of UK dairy herds. It also represents an area where there is a scope for improvement, which would be likely to have immediate effects on calf sales, milk sold and longevity within the dairy herd.

Many farmers are hugely aware of this and are constantly looking for ways to improve and assessing which one of many steps to take or investments to make. Big data is being used increasingly to help make better decisions. This project attempts to combine these two fields to help UK dairy farmers improve herd fertility.

The multifactorial nature of reproduction may represent a barrier to improvement, and it appears to be difficult to prioritise which improvement to make in one of the many areas of a given herd's current position. Therefore, the ultimate aim of this project is to show how existing evidence fits together to create the opportunity for farmers and their advisers to make sound investment and management decisions that will improve the fertility of their herds. It is hoped that this project will be of help principally to UK dairy farmers, but also to their advisers and the dairy industry and its consumers.
Although national fertility performance appears to be improving from a trough in about 2008, the improvements have taken place variably and there are a large number of farms where substantial improvements could be made.

It is hoped that this work will be perceived as true "close-to-farm" research: the aim is to enhance understanding of how the large body of existing knowledge fits together and improve decision making around which interventions are most likely to be beneficial in specific situations. Maximising the value derived from existing knowledge to enhance performance on UK dairy farms is the key objective. It is hoped that the better understanding of associations between potential investment decisions and reproductive performance established here will facilitate this.

1.10.2 Aims and Objectives

The aim of this project is to combine new and current quantitative data on factors affecting dairy cow fertility to develop a stochastic simulation model for use in furthering understanding of associations between management decisions or health events and the probability of pregnancy at a herd level on hundreds of thousands of herds.

To achieve this, the project has four objectives.

Objective 1:

To explore relationships between periparturient and early lactation health events and reproductive performance using a rich agri-informatics dataset from 468 UK dairy herds. This will update existing literature on the relationships between commonly occurring health events and reproduction.

Objective 2:

To identify current research knowledge in the field of dairy cow reproductive performance. A systematic literature evaluation is carried out which will include conversion of results into a mathematical format whereby they can be used further in the project as inputs for a decision model. Areas to be evaluated will include heifer rearing, oestrus detection, genetics, endemic infectious disease, the dry period, energy balance and heat stress.

Objective 3:

To explore the context of the periparturient and early lactation events in comparison to background herd level factors using simulation modelling. This will allow assessment of the association between the factors and herd level performance in contrast to their association at an individual cow level.

Objective 4:

To contextualise many of the most important factors influencing dairy cow reproductive performance using stochastic simulation modelling. Evidence from earlier chapters will be brought together and the impact of these factors will be compared and quantified.

Chapter 2 Assessment of the association between periparturient and early lactation disease and reproductive performance in UK dairy herds

2.1 Introduction

Periparturient and early lactation events include a range of conditions with multifactorial causes. They include infectious diseases of the reproductive tract (metritis and endometritis), endocrine related disorders of the ovary (cystic ovarian disease and other ovarian abnormalities), metabolic disease of the cow (milk fever) and events related to obstetrics (dead calves, twin births, assisted calving and retained foetal membranes). This wide range of initial causes share in common that they can lead to an interruption to the normal calving process and involution of the reproductive tract in the first 42 days of the lactation.

Periparturient and early lactation events happen to dairy cows in the UK with typical lactational incidence rates ranging between 3.6% of lactations affected by retained foetal membranes to 14.9% affected by vulval discharge in 40 herds over a 10 year period (Esslemont 2002). This contrasts with mastitis and lameness which were presented as occurring with an incidence rate of between 22% and 29% (lameness) and 34% and 51% (mastitis) in the same herds over the same time period (Esslemont 2002). Although limited to a single occurrence in each lactation, the health events that occur at calving or early in the lactation can have significant impacts on the production, reproduction and in some cases culling that can follow. This can result in 305 day milk yields being reduced by 259kg as a result of metritis and by 753kg as a result of retained foetal membranes (Dubuc 2011).

Events that are considered to impair the normal events of calving, uterine involution and resumption of ovarian cyclicity may lead to impaired reproductive performance. Reduced feed intakes and consequent negative energy balance as a result of a protracted or difficult calving, systemic disease or demands of twin or large calves can all interrupt this normal process. This can also be interrupted by contamination of the uterine lumen with bacteria, leading to infection of the uterus and increased exposure of the follicle within the ovary (Leblanc 2002, Potter 2010, Williams 2007, Dervishi 2016). Multifactorial causes lead to the occurrence of periparturient and early lactation health events and the subsequent impact of each is thought to be wide ranging, leading to both other health events, and reduced fertility.

Animals calving twins are thought to be more likely to have retained foetal membranes (Nir Markusfeld 2003), more likely to suffer from dystocia (Bell 2007) and more likely to have reduced feed intakes and to lose body condition, both of which may predispose to negative energy balance and this cause may be as a result of reduced gestation length and therefore less time on a pre-calving diet (Bell 2007). Twin pregnancies are also associated with interrupted uterine involution which is thought to be important in ensuring reproductive efficiency. This is as a result of the larger uterus associated with twin pregnancies compared to single pregnancies (Mellado 1994, Sheldon 2008). There is thought to be a complex interaction between twins and several of the other periparturient events (Nir Markusfeld 2003). Twin births have been found to have a range of incidences of 2.8% to 4.2% by three studies (Peeler 1994, Domecq 1997, Bell 2007) and to be associated with increased calving to conception intervals of between 9 and 22 days by three studies (Mellado 1994, Esslemont 2002, Bell 2007).

The birth of a dead calf is often the result of a disturbed calving (Potter 2010). Possible causes of death include a delay to parturition due to malpositioning or foetal oversize. Any correction or intervention may have an impact on normal uterine involution and elimination of uterine bacterial contamination. Stillbirth and dystocia, and stillbirth and retained foetal membranes are strongly correlated (Nir Markusfeld 2003) and it is difficult to separate the effects of each disease. It may therefore be that dystocia and RFM are having the largest effect on fertility performance. Potter (2010) concluded that traumatic disturbances to the reproductive tract such as these had the biggest association with endometritis, and this therefore may be the cause of the impaired reproductive performance. Dead calves have been found to have a range of incidences of 6.6% to 9.4% by three studies (Markusfeld 1997, McDougall 2001, Bicalho 2007) and to be associated with increased calving to conception intervals of between 17 and 88 days by three studies (Mangurkar 1984, Esslemont 2002, Bicalho 2007).

Assisted calving has a complex interaction to make both stillbirth and retained foetal membranes more likely (Nir Murkusfeld 2003). As a factor itself it may cause impaired fertility through the increased likelihood of trauma to the reproductive tract, meaning that elimination of bacteria from the uterus will take longer (Potter 2010). This is an essential part of a return to pregnancy (Sheldon 2008). Assisted calvings have been found to have a range of incidences of 5.9% to 13.6% by three studies (Whittaker 2004, Hayes 2012, Piccardi 2016) and to be associated with increased calving to conception intervals of between 16 and 49 days by three studies (Coleman 1985, Djemali 1987, Simerl 1992).

Hypocalcaemia (also known as milk fever) can have marked clinical effects, most dramatically resulting in paresis and recumbency. An individual recumbent cow has a large likelihood of early, involuntary culling and a reduced milk yield in the subsequent lactation (Esslemont 2002). Milk fever is also likely to be associated with other events, such as assisted calving, dead calf and foetal membranes and is likely to result in delayed removal of post calving bacterial contamination, leading to metritis and endometritis. Milk fever is also associated with cows with increased parity and increased milk yield. Direct associations with impaired reproductive performance are less often discussed. Milk fever has been found to have a range of incidences of 5.0% to 8.0% by three studies (Rajala 1998, Whittaker 2004, Chiwome 2017) and to be associated with increased calving to conception intervals of between 0 and 13 days by three studies (Borsberry 1989, Harman 1996, Hayes 2012).

Retained foetal membranes are also an indication of impairment to a normal calving and retention is thought to lead to trauma to the endometrium and an increased likelihood of bacterial contamination of the uterus leading to endometritis. There appear to be further complex interactions between retained membranes and other health events (Nir Markusfeld 2003) with an interaction with metritis also thought to occur (Mellado 1994). Retained foetal membranes has been found to have a range of incidences of 4.1% to 6.6% by three studies (Emmanuelson 1998, Joosten 1998, Hayes 2012) and to be associated with increased calving to conception intervals of between 5 and 22 days by three studies (Emmanuelson 1998, Esslemont 2002, Hayes 2012).

Metritis is diagnosed in the first 21 days after calving either by clinical signs of pyrexia, an abnormal bloody or mucopurulent discharge on examination or by a systemically ill cow. It is also detected by the characteristics of smell and colour from the discharge itself in an otherwise healthy cow that had not been detected as abnormal. Metritis and endometritis are often associated in the same cow, and both can have substantial effects on future reproductive health by causing inflammation of the uterus, impaired ovarian function (Sheldon 2008) and ultimately a suboptimal environment for the development of a conceptus. Metritis has been found to have a range of incidences of 12.1% to 17.0% by three studies (Leblanc 2002, Barrett 2009, Piccardi 2016) and to be associated with increased calving to conception intervals of between 22 and 36 days by three studies (Benzaquen 2007, Giuliodori 2013, Piccardi 2016).

Endometritis is the inflammation of the endometrium after 21 days post-calving and is a common sequalae to retained foetal membranes and metritis (Sheldon 2008). The abnormal purulent vulval discharge that characterises this condition is indicative of continuing bacterial contamination of the uterine lumen which reduces the likelihood of successful implantation of the conceptus (Leblanc 2002). Endometritis has been found to have a range of incidences of 16.9% to 28.4% by three studies (Leblanc 2002, Benzaquen 2007, Piccardi 2016) and to be associated with increased calving to conception intervals of between 28 and 70 days by three studies (Leblanc 2002, Barrett 2009, Giuliodori 2013).

Uterine disease can lead to ovarian disease in the same parity through the local effects of the *Escherichia coli* endotoxin LPS and the host inflammatory mediator TNFalpha on the ovary (Williams 2007, Sheldon 2008). However, cystic ovarian disease (and other ovarian abnormalities) can also begin as a result of the failure of ovulation due to stress-induced interference with luteinising hormone (LH) pulses and surges (Dobson 2000). The stress-induced interference can continue after the resolution of the original cystic ovarian structure. Since LH pulses can continue to be affected, cows can continue to not show oestrus behaviour, not ovulate, and produce follicles of low quality for a prolonged period after calving. This can all result in impaired fertility, more obviously at the time the cyst is present, but also for some time after it has either ovulated or become atretic. Cystic ovarian disease has been found to have a range of incidences of 2.7% to 15.9% by three studies (Rajala 1998, McDougall 2001, Cattaneo 2015) and to be associated with increased calving to conception intervals of between 64 and 77 days by three studies (Borsberry 1989, Kim 2005, Cattaneo 2015).

One of the significant drawbacks of a comparison of the reproductive performance of populations of cows that were affected by a health event and those that were not is that in many cases there is an interaction between the health events (for example the occurrence of twins is likely to make the occurrence of retained foetal membranes more likely, Bell 2007) and between other factors such as milk yield and parity and the health events. For example, increased milk yield is likely to be associated with impaired reproductive performance (Bello 2012) and therefore without accounting for yield it is difficult to assess whether retained foetal membranes were more likely to impair reproductive performance alone, or because they were made more likely by increased yield. Without accounting for other potential explanatory variables, it is difficult to determine the true association between an individual health event (such as milk fever) and reproductive performance.

Studies have been performed making associations between various periparturient diseases (Nir Markusfeld 2003) and between various diseases and reproductive performance (Ribeiro 2013, Loeffler 1999) using multivariable models. A large number and range of studies show the incidence of a large number of health events at calving and in early lactation and their impacts on subsequent reproduction. However, the use of multivariable logistic regression models to account for confounding, and the use of random effects to improve correction for unmeasured factors is rare in this area. The aim of this chapter is to include a large range of health events and other herd level factors as explanatory variables in a multivariable logistic regression model. This model will then be used to explore relationships between clinical disease events that are commonly occurring and are focussed on the periparturient and early lactation period, and reproductive performance.

2.2 Materials and Methods

2.2.1 Data collection and processing

Data used in this study comes from a dataset collected from the farm clients of 20 veterinary surgeons throughout England and Wales, as described by Hudson (2012). The data came from a variety of herd management software programmes and from bureau services provided by veterinary practices or milk recording organisations. Data had previously been anonymised, extracted from software into Microsoft Access and data outside of the years 2000-2009 removed. The data were restructured so that each line represented a parity and contained basic details about that parity such as animal ID and calving date.

Records were searched in order to assign relevant individual cow events that had been recorded by the farm to match to the basic parity details. As most management software allows the user to configure events freely, a variety of search terms were used in order to capture events recorded under different names. The search terms were based on a complete list of every event name recorded in the database, and the author's experience of the default setups of the more common recording software systems. Examples of the search terms used to search the database for health event characteristics can be found in Table 2.1. The original dataset consisted of 646,000 parities from 468 herds.

Table 2.1 Event characteristic search terms for data extraction

Health event characteristic	Search Term(s)
Milk fever (MF)	Event "milk fever", "milkfever", "hypoc*"
Retained foetal membrane (RFM)	Event "retained*", "RFM", "RP", "cleansing", "held cl*"
Twins	Derived from OffSprLive and OffSprDead
Dead calf	Derived from OffSprLive and OffSprDead
Assisted calving	Comment/result/category of calving event - "*help*", "*aid*", "*hard*", "*assist*", "dyst*" or "malp*" or "*oversize*"
VLD (vulval discharge)	Event "VLD", "endo*", "dirty", "washout", "vulval discharge", "whites", "metritis", "metricure", "metrijet" OR comment/result/category of PNC/ONO/*FERT*
Cyst	Event "cyst", "cystic", "COD"
OOA (other ovarian abnormality)	Event "no structures", NS", "ONO"
Service/ insemination	Event - "SERVED" or relevant software event type

2.2.2 Data quality screening and processing

The data were restructured so that each parity could be identified by the cow ID, the year and the herd, background events such as insemination dates, calving dates and 305 day yield amalgamated, and a series of periparturient and early lactation health events recorded next to each parity as binary events with a code of either 1 (event occurred) or 0 (event did not occur). As recording of event and other data were variable between herds and over time, data quality screening was carried out in order to produce a robust dataset for analysis. This took three stages- the recoding of individual events deemed to be unrepresentative, the exclusion of individual parities and the exclusion of herd years.

The 305 day milk yield for cows that exited the herd prior to 305 days was converted from the existing cumulative figure to a 305 day equivalent figure based on current milk produced using a mean lactation curve (for primiparous or multiparous cows) to avoid using an unrepresentatively low figure. Health events that appeared to have been entered with unexpected dates relative to calving dates (such as a retained foetal membrane case 35 days after calving) were recoded as having not occurred and the parity retained. Dates of final insemination and subsequent calving were checked against the software-calculated conception date, and where this revealed a discrepancy a date 281 days before the subsequent calving entered, following accepted standard gestation lengths (McGuirk 1998, McGuirk 1999).

Individual parities were in some cases determined to be inaccurately recorded or unrepresentative outliers and were therefore excluded. Exclusion criteria included calving to conception intervals of less than 20 or more than 420 days, two conception dates recorded by two different recording methods being more than 14 days apart, a cow with a 305 day yield of less than 3000 or more than 18000 litres, or the cow exiting the herd less than 7 days after calving.

In order to estimate the frequency of event recording, data were restructured into herd-years (data summarised for each herd in each calendar year) such as herd01_year2008, in order to facilitate assessment of which herd-years were likely to contain the required data. Each herd year was then analysed further in order to ascertain the quality of the data from that herd year. A large number of herds under recorded periparturient and early lactation events, either by only recording them sporadically and potentially inaccurately or by not recording them at all.

2.2.3 Dataset restructuring for model building

Table 2.2 describes three datasets that were developed following removal of parities that did not meet the initial required criteria. Dataset B was produced by sorting the herd years within Dataset A by event incidence and all of the herd years that did not record any of the seven principle health events (twins, dead calf, assisted calving, milk fever, retained foetal membranes, vulval discharge and cyst) were discarded. Dataset C was produced by sorting the herd years within Dataset B by event incidence and the herd years in the lowest 25% by event incidence of each of the seven principle health events (twins, dead calf, assisted calving, milk fever, retained foetal membranes, vulval discharge and cyst) were discarded.

Table 2.2 Description of Datasets A, B and C

Dataset	Origin	Number of herd years represented	Number of parities included
A	All parities from 468 herds, with the majority of these covering 10 years	4564	603121
B	Parities from herd years where at least one event was recorded at least once	1872	321027

C	Parities from herd years where all events were recorded at least once, and the herd years with the lowest 25% of incidence of disease were then excluded	25	6262

Datasets B and C had any herd years containing less than 50 parities removed. Uterine events were recoded according to event occurrence before and after 21 days and ovarian events were recoded according to disease occurrence before and after 42 days. Figure 2.1 shows an example for one health event of the low level of recording of periparturient and early lactation events in the majority of herd years. The 25 herd years in Dataset C represented 14 different herds and from cows calving in 7 of the 10 years of the original dataset.

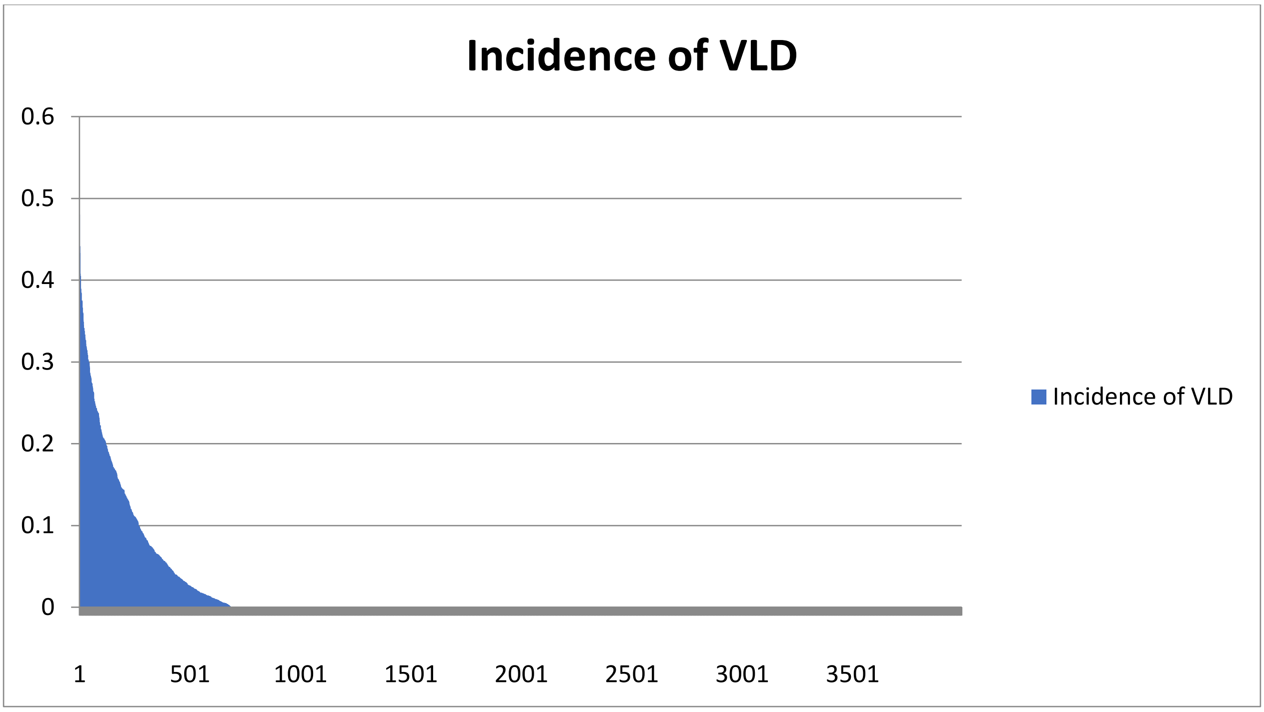

Figure 2.1 Herd years (x axis) ordered by lactational incidence of vulval discharge (y axis) for Dataset A of 603,121 parities from 4564 herd years

Datasets B and C were then restructured into a format where each line represented a 7 day risk period in every lactation between 28 and 300 days in milk (therefore up to 40 risk periods per parity). Cows were censored if they were culled, died or became pregnant. Occurrence of pregnancy was recorded as a binary event for each risk period.

2.2.4 Model building

Discrete time survival analysis was used within a logistic multivariable regression model to explore the associations between the outcome variable, the probability of a cow becoming pregnant in a given 7 day risk period, conditional on her not already having become pregnant, and 17 potential explanatory variables. These variables included 11 periparturient and early lactation health events. All variables are listed in Table 2.3.

Table 2.3 Potential explanatory and outcome variables for each 7 day risk period

Basic Variable	**Variable type**
	Outcome
Becomes pregnant	Binary
	Explanatory- risk period level
Days in milk at start of risk period	Continuous
Month of risk period	Categorical
	Explanatory- parity level
Parity	Categorical
Month of calving	Categorical
Year of calving	Categorical
305 day milk yield	Continuous
Twins	Binary
Dead Calf	Binary
Assisted calving	Binary
Milk Fever	Binary
Retained Foetal Membranes	Binary

Vulval discharge first diagnosed less than 21 days	Binary
Vulval discharge first diagnosed more than 21 days	Binary
Cyst first diagnosed less than 42 days	Binary
Cyst first diagnosed more than 42 days	Binary
Other ovarian abnormality first diagnosed less than 42 days	Binary
Other ovarian abnormality first diagnosed more than 42 days	Binary

A 4 level hierarchical random effects structure (risk period within parity within cow within herd) was rejected because a high proportion of cows were only contributing one parity, so there was little variation between parities within. A 3 level hierarchical model (risk period within cow within herd) was initially constructed, with risk periods nested within cows, nested within herds. The model took a conventional form (Yang 2003):

$\text{Pregnant}_{ijt} \sim$ Bernoulli probability (mean = Π_{ijt})

$\text{Logit}(\Pi_{ijk}) = \alpha + \boldsymbol{\beta}_1\mathbf{X}_{ijk} + \boldsymbol{\beta}_2\mathbf{X}_{jk} + \boldsymbol{\beta}_3\mathbf{X}_k + u_{jk} + v_k$

where i, j and k denote the i^{th} timepoint for the j^{th} cow in the k^{th} herd, Π_{ijk} the fitted probability of Pregnant_{ijk} (the outcome of whether the j^{th} cow from the k^{th} herd became pregnant at the i^{th} timepoint), α the regression intercept, $\mathbf{X}_{ijk}$ the vector of timepoint level covariates, $\boldsymbol{\beta}_1$ the coefficients for covariates $\mathbf{X}_{ijk}$, $\mathbf{X}_{jk}$ the vector of cow level covariates, $\boldsymbol{\beta}_2$ the coefficients for covariates $\mathbf{X}_{jk}$, $\mathbf{X}_k$ the vector of herd level covariates, $\boldsymbol{\beta}_3$ the coefficients for covariates $\mathbf{X}_k$, u_{jk} the random effect to reflect residual variation between cows and v_k the random effect reflecting residual variation between herds. During model building it became apparent that model fit was unacceptable with this random effects structure. Removal of the cow level random effect resulted in satisfactory fit so a two level model was adopted.

Model building was carried out in MLwiN version 2.20 (Rasbash 2010). Initial model building was carried out using iterative gerneralised least squares estimation (IGLS) for initial parameter estimation. Final parameter estimation was carried out using Markov chain Monte Carlo (MCMC) in R (R 2017) using a burn in chain length of 5000 and monitoring chain lengths of at least 20000 iterations. Estimate traces were visually assessed for satisfactory convergence.

Models were built using forward selection, with explanatory variables retained in the model if the magnitude of the central coefficient estimate was more than twice the standard error (equivalent to $p<0.05$). Discarded variables were individually reintroduced and retained if they satisfied the above criteria. First-order interactions between health event explanatory variables were tested, as were interactions between days in milk and health event variables. Not all potential explanatory variable interaction terms were tested as the association with health events across the lactation were the main clinical focus of the modelling. Interaction terms between health events were tested to account for the possibility that the association between health events and the probability of pregnancy changed in a non-linear fashion as the lactation progressed. Polynomial terms were explored for days in milk and milk yield and were applied if they fitted the data more closely than the original variable.

Two models were constructed using Dataset B (1872 herd years) and Dataset C (25 herd years). A sensitivity analysis was performed to assess for the introduction of sampling bias. Odds ratios were created for both models and compared. The direction of the effects was generally similar between the two models, but coefficient sizes were smaller with Dataset B (as would be expected in the presence of substantial missing event data) and Dataset B was therefore discarded. Dataset C containing 96008 blocks from 6262 parities from 4679 cows from 25 herd years from 14 herds was used for final parameter estimation. Odds ratios for explanatory variables found to be associated with the probability of pregnancy per unit time were created by exponentiation of the central estimate and 95% highest posterior densities (HPDs) created by exponentiation of the 95% coverage interval of the MCMC chains.

2.2.5 Model checking and model fit

Regression validations are commonly used as a step to assess model fit (Green 2009). In order to do this, the data was subset 16 times according to various different characteristics of the explanatory variables (this included several of the health event variables as well as some randomly determined explanatory variable categories, for example parity 4 and the calving month of June). In addition, the data was sorted according to the probability of pregnancy into deciles. For each form of subset full MCMC chains were used to generate predictions for that subset and observed proportion of pregnancy for each subset compared to the prediction. Fit was considered acceptable.

2.2.6 Model predictions

In order to produce more intuitive graphical representation of the association between health events and the probability of pregnancy, the model was used to predict the probability of pregnancy for each 7 day risk period from day 28 to day 150 of the lactation for pairs of hypothetical cows. All other variables were kept at mean values, with the only difference being the occurrence or absence of specific health events found to be associated with pregnancy. These were presented as comparative individual event line charts. In addition, a summary bar chart of the 100 day in calf rate for lactations affected and unaffected by the events was created. The individual bars were calculated by multiplying the probabilities that the cow does not become pregnant from each risk period up to 100 days in milk together and subtracting this figure from one.

Population Attributable Fractions (PAFs) were determined for the 6 periparturient and early lactation events remaining in the model by generating predictions for an alternative version of the data where each event in turn was set to zero for every risk period. So, for example, for the retained foetal membrane PAF an overall predicted probability of pregnancy was calculated from the original dataset and compared to a prediction for probability of pregnancy for a version of the dataset where retained foetal membranes was set to zero for every risk period. By creating a ratio of the two figures we create a PAF for the occurrence of retained foetal membranes. This was repeated for each iteration of the MCMC chains, calculating PAF for each iteration of the chain allowing the creation of a central estimate and confidence intervals for the set of PAFs.

2.3 Results

2.3.1 Descriptive statistics

Summary statistics are shown in Table 2.4 describing herd production and reproduction performance based on mean and distribution figures for the 14 herds. Mean lactational incidence figures for the 25 herd years from these 14 herds are shown in Table 2.5. These figures include the five periparturient and six early lactation health events which were initially used in model building. Five of these events (twins, dead calf, milk fever, and both cysts and other ovarian abnormalities diagnosed before 42 days in milk) were not retained in the final model construction. Lactational incidence was considered to be within typical incidence recorded in the literature (Borsberry 1989, Fourichon 2001, Leblanc 2002, Hayes 2012, Piccardia 2016).

Table 2.4 Summary descriptive statistics about the 14 dairy herds

	100 day in calf rate (%)	200 day in calf rate (%)	305 day milk yield (kg)	Calving index (days)	Culling rate (% of calvings)	Herd size
Min	26.9	56.4	7295	384	11.2	80
25%	30.9	62.1	8147	399	19.1	114
50%	35.9	68.3	9118	407	21.4	179
75%	40.8	70.1	9789	414	25.3	321
Max	48.7	80.2	10544	424	30.2	642

Table 2.5 Mean lactational incidence of 11 periparturient and early lactation health events

Event	**Mean Lactational incidence**
Twins	3.4
Dead calf	5.5
Assisted calving	11.5
Milk Fever	5.3
Retained Foetal Membranes	6.3
Vulval Discharge Diagnosed 21 Days or Less Post Calving	9.0
Vulval Discharge Diagnosed More Than 21 Days Post Calving	8.2
Cyst Diagnosed 42 Days or Less Post Calving	1.2
Cyst Diagnosed More Than 42 Days Post Calving	10.0
Other Ovarian Abnormality (OOA) Diagnosed 42 Days or Less Post Calving	0.0

Other Ovarian Abnormality Diagnosed More Than 42 Days Post Calving	0.9

2.3.2 Output from multilevel discrete time survival model

The logistic regression model output is recorded in table 2.6. Odds ratios (ORs) can be interpreted as the odds of a pregnancy as a result of the explanatory variable in ratio to the odds of pregnancy for a reference category. A number of the explanatory variables not related to health events in the period around and after calving were associated with the odds of pregnancy during a given 7 day risk period. For example, the odds of pregnancy reduced with increasing parity in reference to a parity 1 animal, with a parity 5 or greater animal having an OR (and 95% HPD) of 0.674 (0.613-0.736). The odds of pregnancy was also reduced by increasing yield and days in milk. There were also associations between a calving month of February and March and the odds of pregnancy decreasing and a risk period month of November and December and the odds of pregnancy increasing.

Six of the explanatory variable health events were associated with the outcome variable. Odds ratios for two periparturient events (assisted calving and retained foetal membranes) and for four early lactation events (vulval discharge diagnosed before and after 21 days and the disorders of the ovary caused by cysts or other causes diagnosed after 42 days) can be seen in Table 2.6.

Interaction terms between the health events and the natural logarithm of days in milk were inserted into the model to improve model fit since the health events were considered likely to have a decreasing association with the probability of pregnancy per unit time as days in milk increases. The OR greater than one for these interaction terms indicate that for each of the six events the association with pregnancy reduces as the lactation proceeds.

Table 2.6 Parameter estimates for discrete time survival model with pregnancy during a 7 day risk period as the outcome variable

				95% HPD	Interval
Model term	***n***	**Coefficient**	**Odds Ratio**	**Lower**	**Upper**
Intercept	96008	-5.41		-5.60	-5.18
Parity 1	23055		Reference		
Parity 2	24288		0.929	0.850	1.00
Parity 3	16649		0.899	0.821	0.988
Parity 4	11777		0.844	0.756	0.941
Parity 5 or Greater	20239		0.674	0.613	0.736
Days In Milk ^1	96008	6.47×10^{-2}		6.10×10^{-2}	6.80×10^{-2}
Days In Milk ^2	96008	-4.10×10^{-4}		-4.35×10^{-4}	-3.87×10^{-4}
Days In Milk ^3	96008	7.50×10^{-7}		6.96×10^{-7}	8.06×10^{-7}
Centred 305 Day Milk Yield ('000kg) ^1	96008		0.956	0.940	0.971
Centred 305 Day Milk Yield ('000kg) ^2	96008		0.994	0.989	1.00
Risk Period Month Other	77910		Reference		
Risk Period Month November or December	18098		1.13	1.05	1.22
Calving Month Other	82001		Reference		
Calving Month February or March	14007		0.845	0.772	0.919
No Assisted Calving	84967		Reference		
Assisted Calving	11041		0.343	0.154	0.773
No Retained Foetal Membranes	89969		Reference		
Retained Foetal Membranes	6039		7.24×10^{-2}	2.25×10^{-2}	0.318
No Vulval Discharge Diagnosed 21 Days or Less Post Calving	87375		Reference		
Vulval Discharge Diagnosed 21 Days or Less Post Calving	8633		0.233	8.43×10^{-2}	0.571
No Vulval Discharge Diagnosed More Than 21 Days Post Calving	88089		Reference		
Vulval Discharge Diagnosed More Than 21 Days Post Calving	7919		5.87×10^{-3}	1.36×10^{-3}	2.53×10^{-2}
No Cyst Diagnosed More Than 42 Days Post Calving	86450		Reference		
Cyst Diagnosed More Than 42 Days Post Calving	9558		1.38×10^{-3}	4.45×10^{-4}	5.00×10^{-3}

No Other Ovarian Abnormality Diagnosed More Than 42 Days Post Calving	95108		Reference		
Other Ovarian Abnormality Diagnosed More Than 42 Days Post Calving	900		3.60×10^{-6}	1.08×10^{-8}	6.52×10^{-4}
Assisted Calving * Natural Logarithm of Days In Milk	11041		1.22	1.03	1.45
Retained Foetal Membranes * Natural Logarithm of Days In Milk	6039		1.66	1.25	2.16
Vulval Discharge Diagnosed 21 Days or Less Post Calving * Natural Logarithm of Days In Milk	8633		1.28	1.06	1.58
Vulval Discharge Diagnosed More Than 21 Days Post Calving * Natural Logarithm of Days In Milk	7919		2.65	1.95	3.53
Cyst Diagnosed More Than 42 Days Post Calving * Natural Logarithm of Days In Milk	9558		3.59	2.75	4.46
Other Ovarian Abnormality Diagnosed More Than 42 Days Post Calving * Natural Logarithm of Days In Milk	900		10.9	3.93	33.3
Dead Calf * Other Ovarian Abnormality Diagnosed More Than 42 Days Post Calving	56		12.7	2.03	68.6
Vulval Discharge Diagnosed More Than 21 Days Post Calving * Other Ovarian Abnormality Diagnosed More Than 42 Days Post Calving	181		5.00×10^{-2}	5.23×10^{-3}	0.375

2.3.3 Predictions of model fit

Posterior predictions were then assessed for various different subsets of the data and found to fit it well. Figure 2.2 shows various categorical subsets of explanatory variables with the observed probabilities of pregnancy all within the 95% coverage intervals of the predicted probabilities. Similarly Figure 2.3 shows observed probabilities of pregnancy within the 95% coverage intervals for the predictions for subsets of risk deciles.

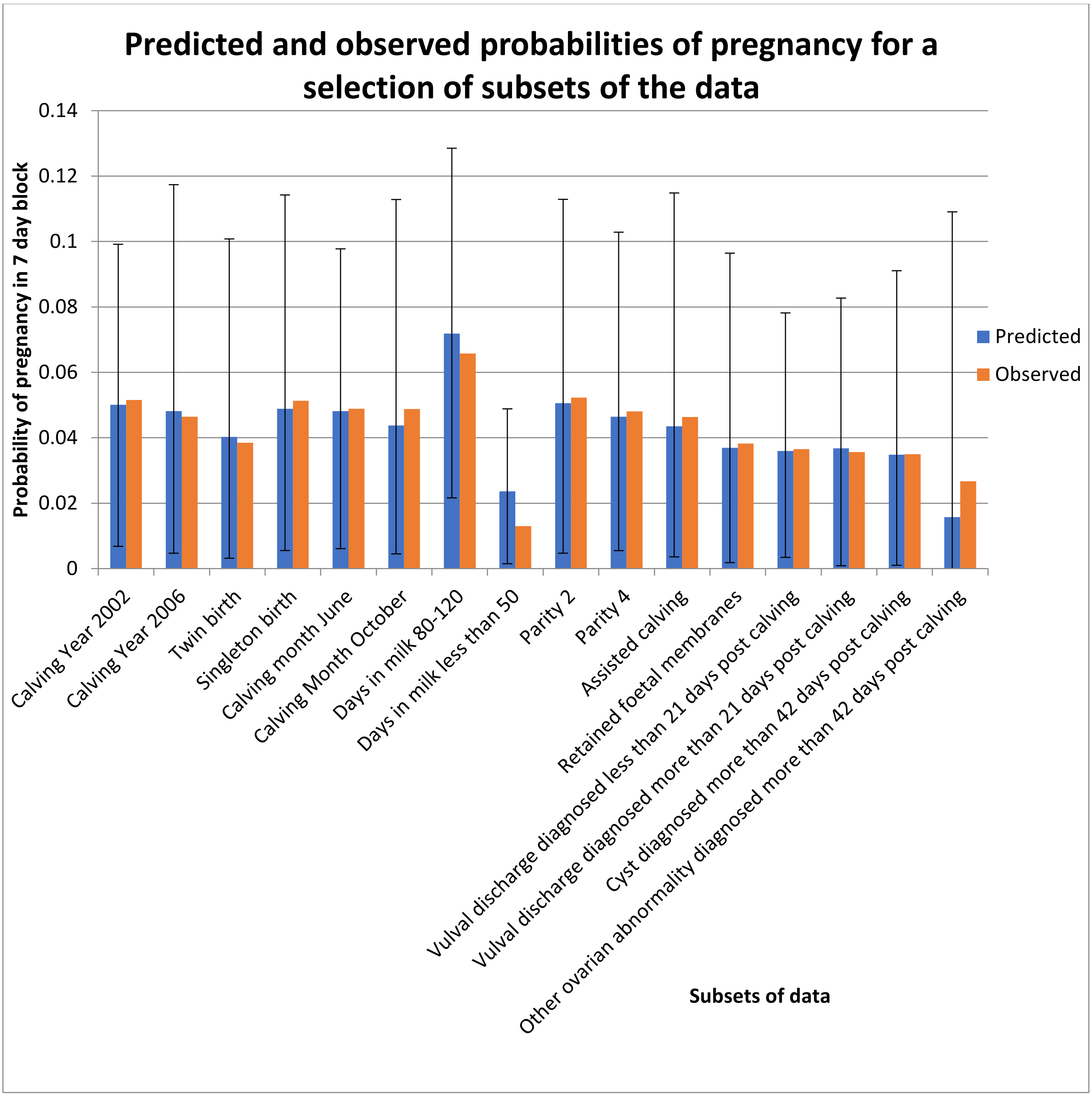

Figure 2.2 Comparison between Predicted and observed probabilities of pregnancy for a selection of subsets of the data. Full Markov Chain Monte Carlo chains were used to generate predictions for each subset and observed proportion of pregnancy for each subset was compared to the predictions. Error bars indicate 95% coverage interval.

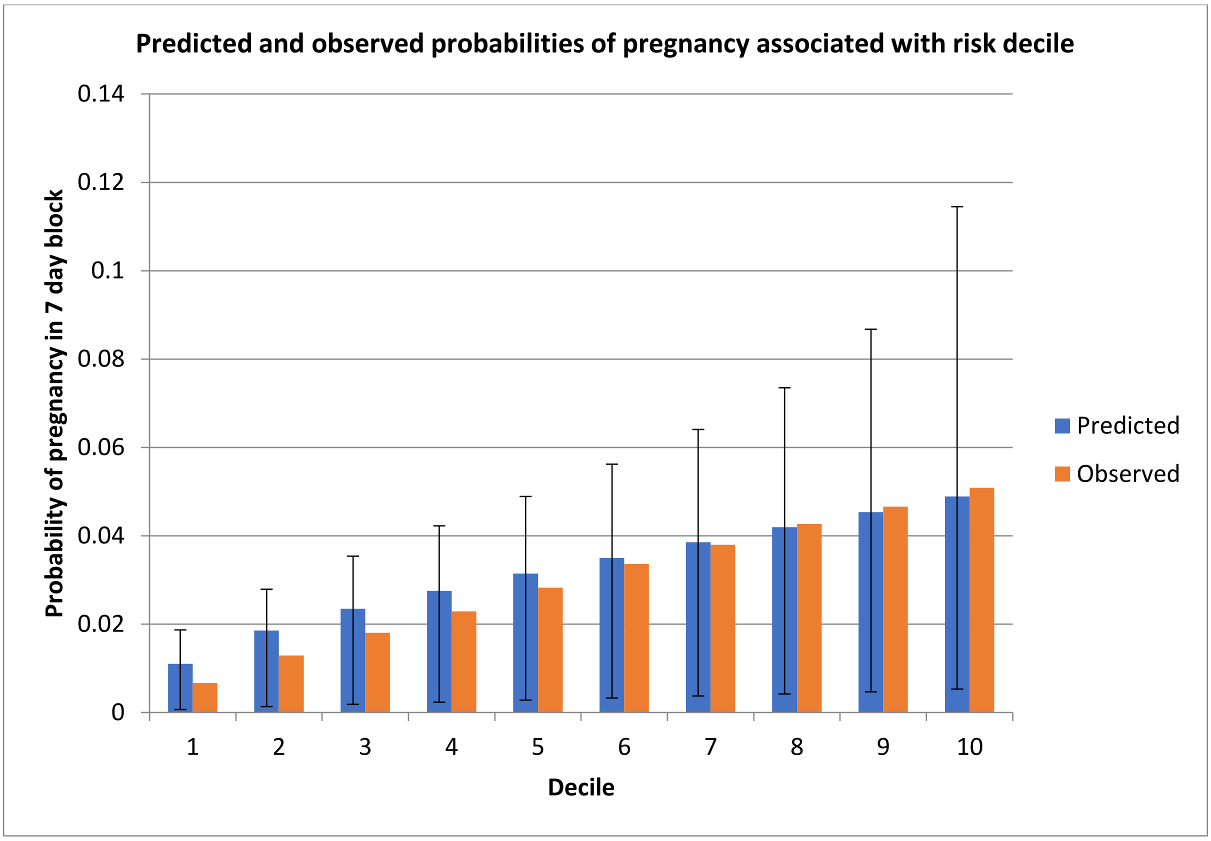

Figure 2.3 Comparison between Predicted and observed probabilities of pregnancy for risk deciles within the data. Full Markov Chain Monte Carlo chains were used to generate predictions for each subset and observed proportion of pregnancy for each subset was compared to the predictions. Error bars indicate 95% coverage interval.

2.3.4 Model predictions of the probability of pregnancy

Figures 2.4 to 2.9 each represent model predictions for six health events. They demonstrate the probability of pregnancy in each 7 day risk period between 28 and 150 days in milk for pairs of hypothetical cows which both followed the population means for all other explanatory variables. They were only differentiated by the presence or absence of each of the health events that were significantly associated with the probability of pregnancy per unit time in the logistic regression model. These are presented as line charts with solid blue lines representing unaffected lactations and dashed lines representing 95% coverage intervals around these predictions. Solid red lines (with dotted lines for 95% coverage intervals) represent predicted probability of pregnancy for increasing days in milk for cows affected by one of the health events, which differ in each plot.

Although of different shapes, the six paired curves follow a similar form, with a small difference between affected and unaffected at 28 days in milk (but with narrow confidence intervals that do not overlap). This difference between the paired curves increases until approximately 100 days in milk when the paired lines begin to converge. In the majority of predictions there remains a difference between the paired lines at 150 days in milk but often with overlapping confidence intervals. The probability of pregnancy per unit time has not begun to decrease by 150 days in milk for the affected cows for the majority of the plots (represented by the six red lines).

Of the six events, there is the largest difference between the paired affected and unaffected cows for predicted probability of pregnancy for the event other ovarian abnormality diagnosed at greater than 42 days in milk. The events cystic ovarian disease diagnosed after 42 days after calving and vulval discharge diagnosed after 21 days after calving (usually termed endometritis) also show a marked difference between the paired cows, which is particularly stark between 60 and 120 days in milk.

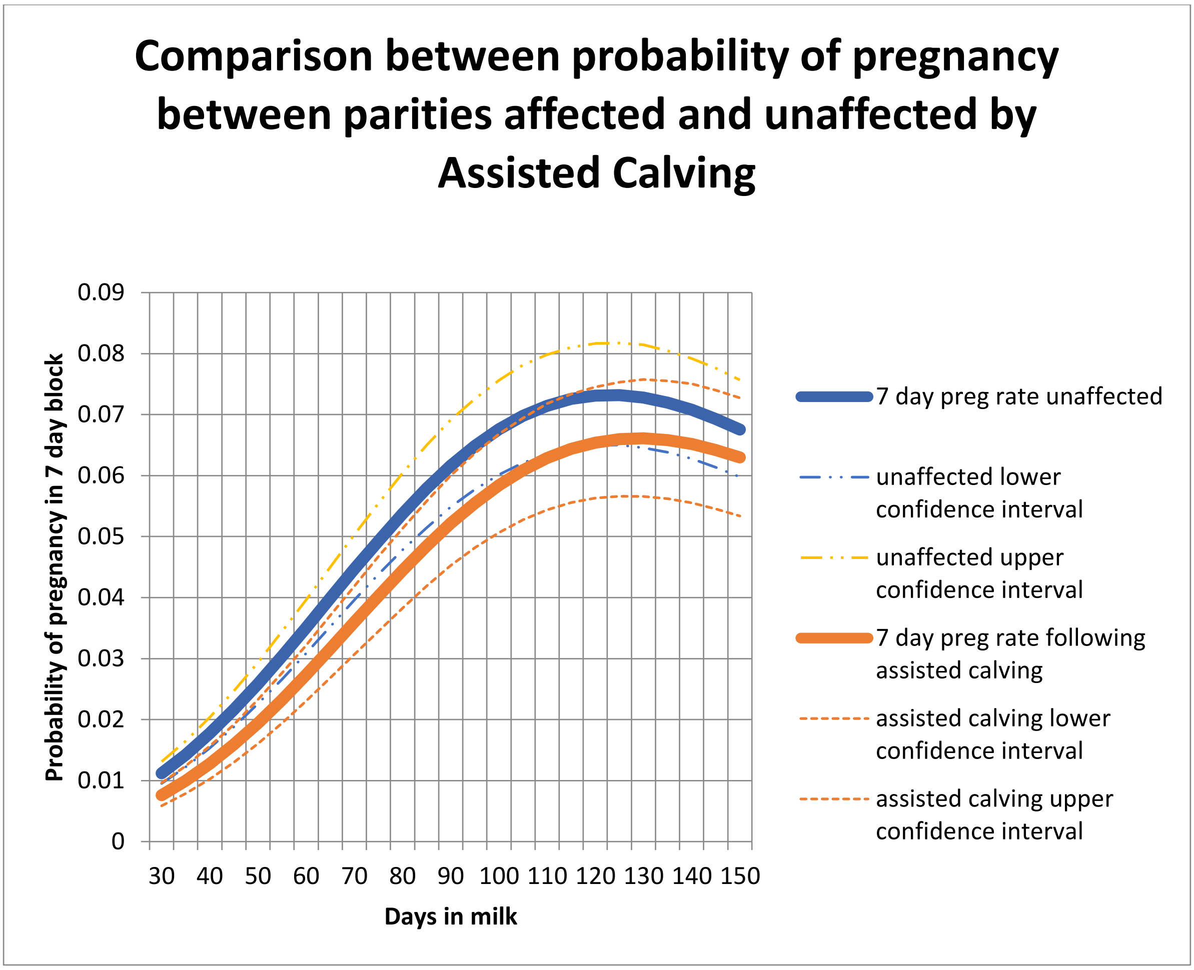

Figure 2.4 Model predictions of the probability of pregnancy between 28 and 150 days in milk for lactations affected and unaffected by assisted calving

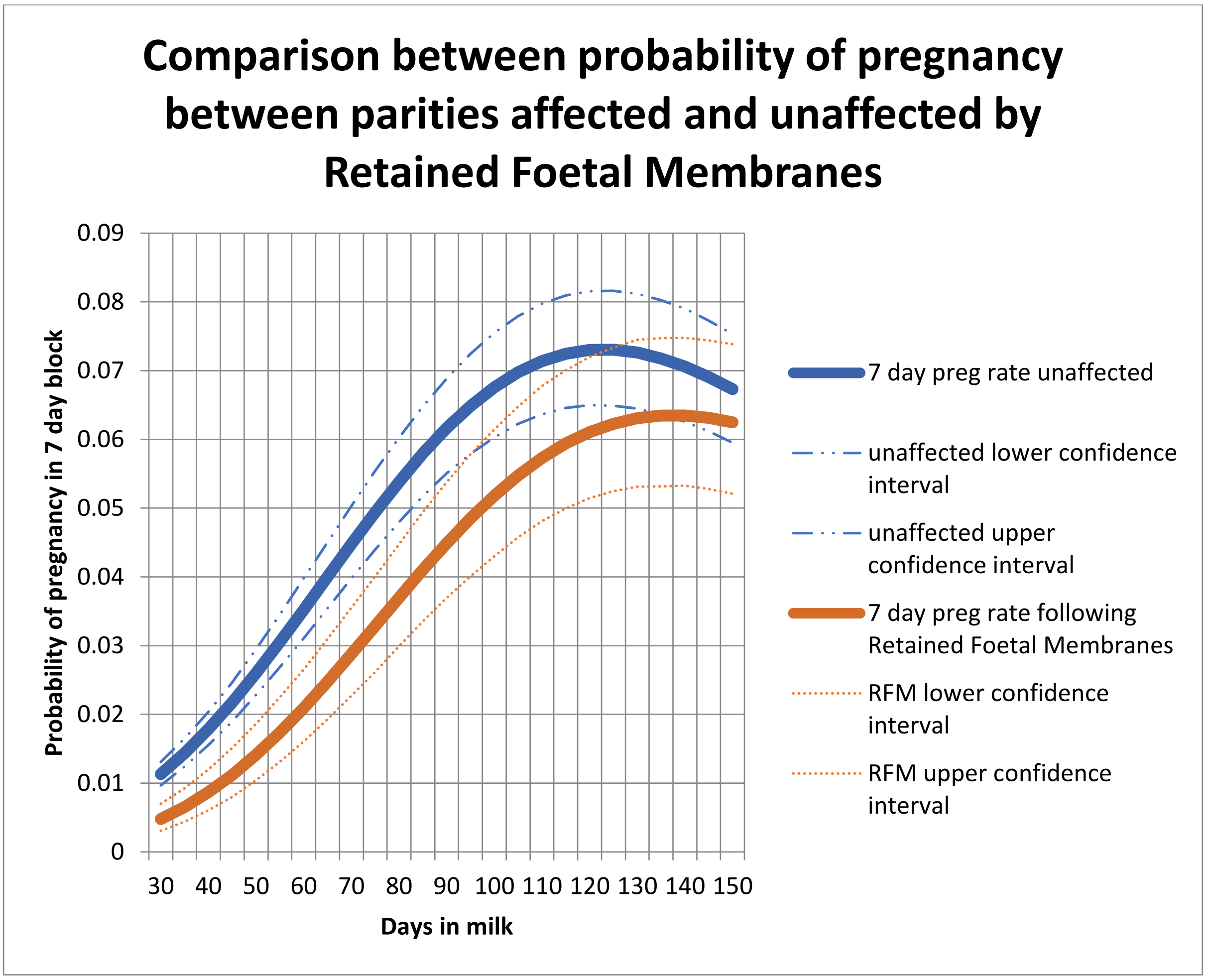

Figure 2.5 Model predictions of the probability of pregnancy between 28 and 150 days in milk for lactations affected and unaffected by retained foetal membranes

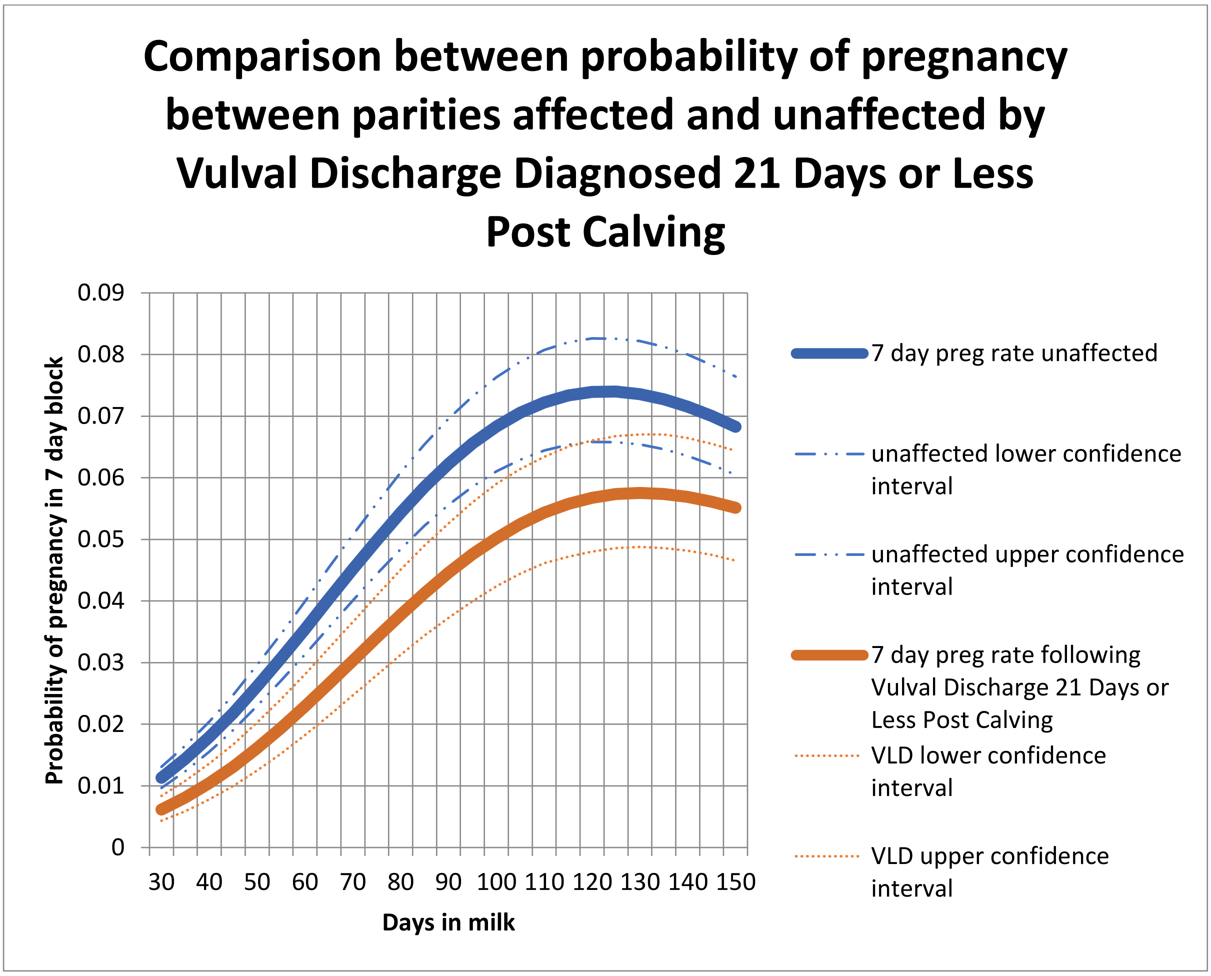

Figure 2.6 Model predictions of the probability of pregnancy between 28 and 150 days in milk for lactations affected and unaffected by vulval discharge diagnosed less than 21 days post calving

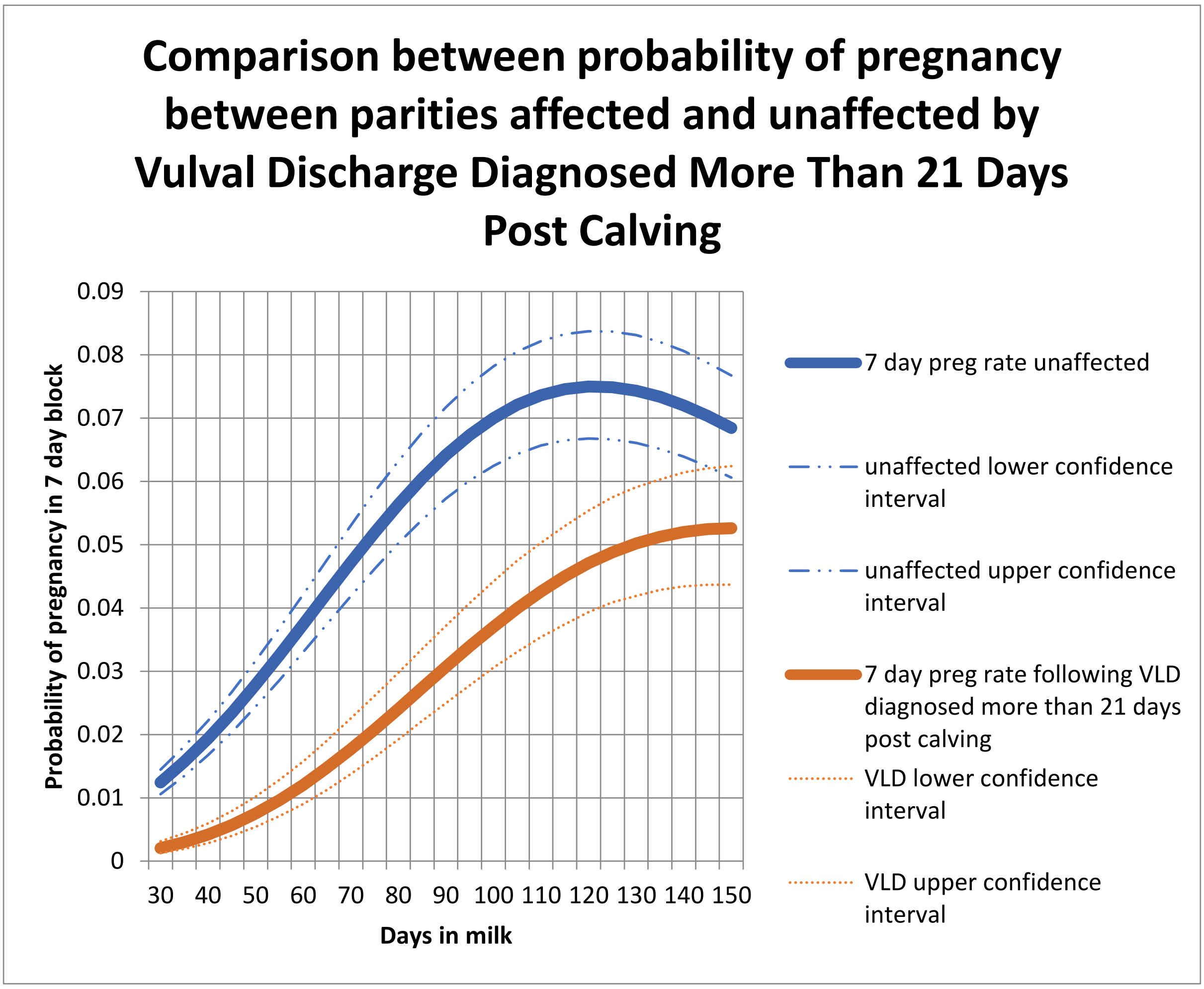

Figure 2.7 Model predictions of the probability of pregnancy between 28 and 150 days in milk for lactations affected and unaffected by vulval discharge diagnosed more than 21 days post calving

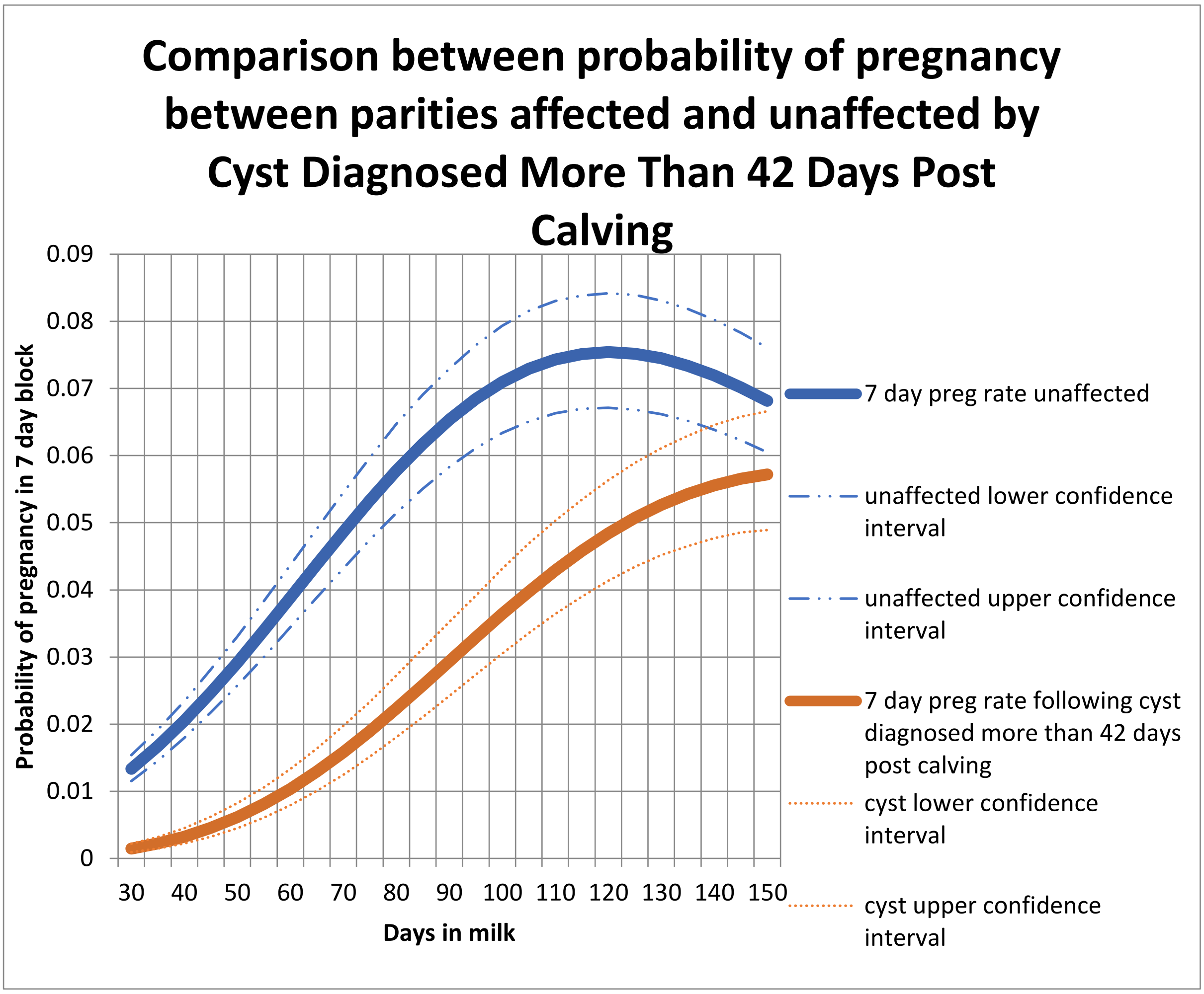

Figure 2.8 Model predictions of the probability of pregnancy between 28 and 150 days in milk for lactations affected and unaffected by cyst diagnosed more than 42 days post calving

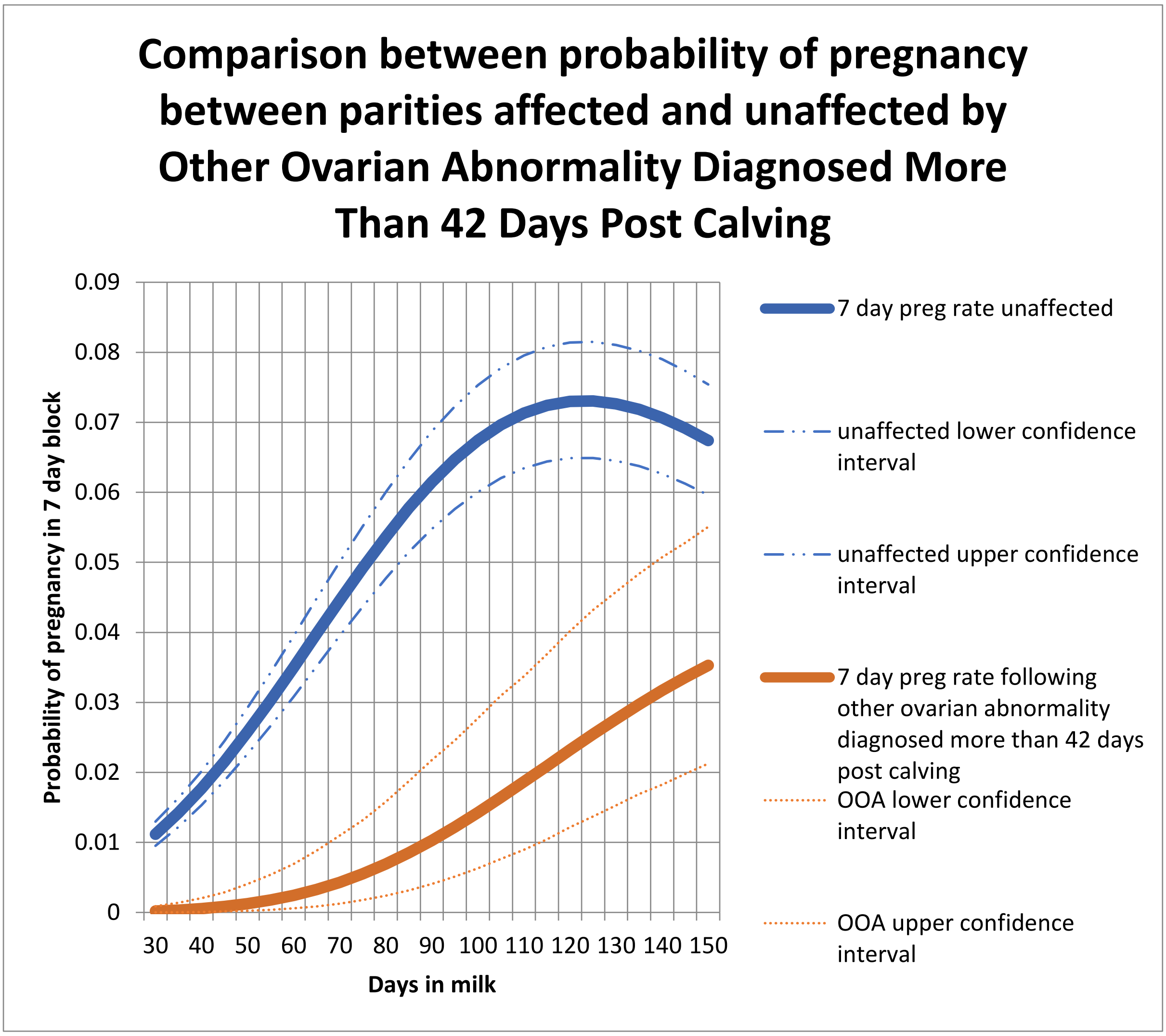

Figure 2.9 Model predictions of the probability of pregnancy between 28 and 150 days in milk for lactations affected and unaffected by cyst diagnosed more than 42 days post calving

Figure 2.10 represents a summary of the model predictions for the probability of pregnancy per unit time, by showing the 100 day in calf rate for lactations affected by the six health events, again with all other variables unchanged between the predicted lactations between the two groups. This has been calculated from the probabilities of pregnancy for each of the 7 day risk periods prior to 100 days in milk. This shows a reduction in the probability of pregnancy for all six of these explanatory variables and is particularly marked for the events diagnosed more than 21 days into the lactation. Although the probability of pregnancy prior to 100 days in milk following diagnosis of an

OOA is only 0.02, this may have less of an impact on a population of cows as a result of the considerably lower lactational incidence of this event. The use of PAFs allows this to be considered as they take into account both effect size and lactational incidence.

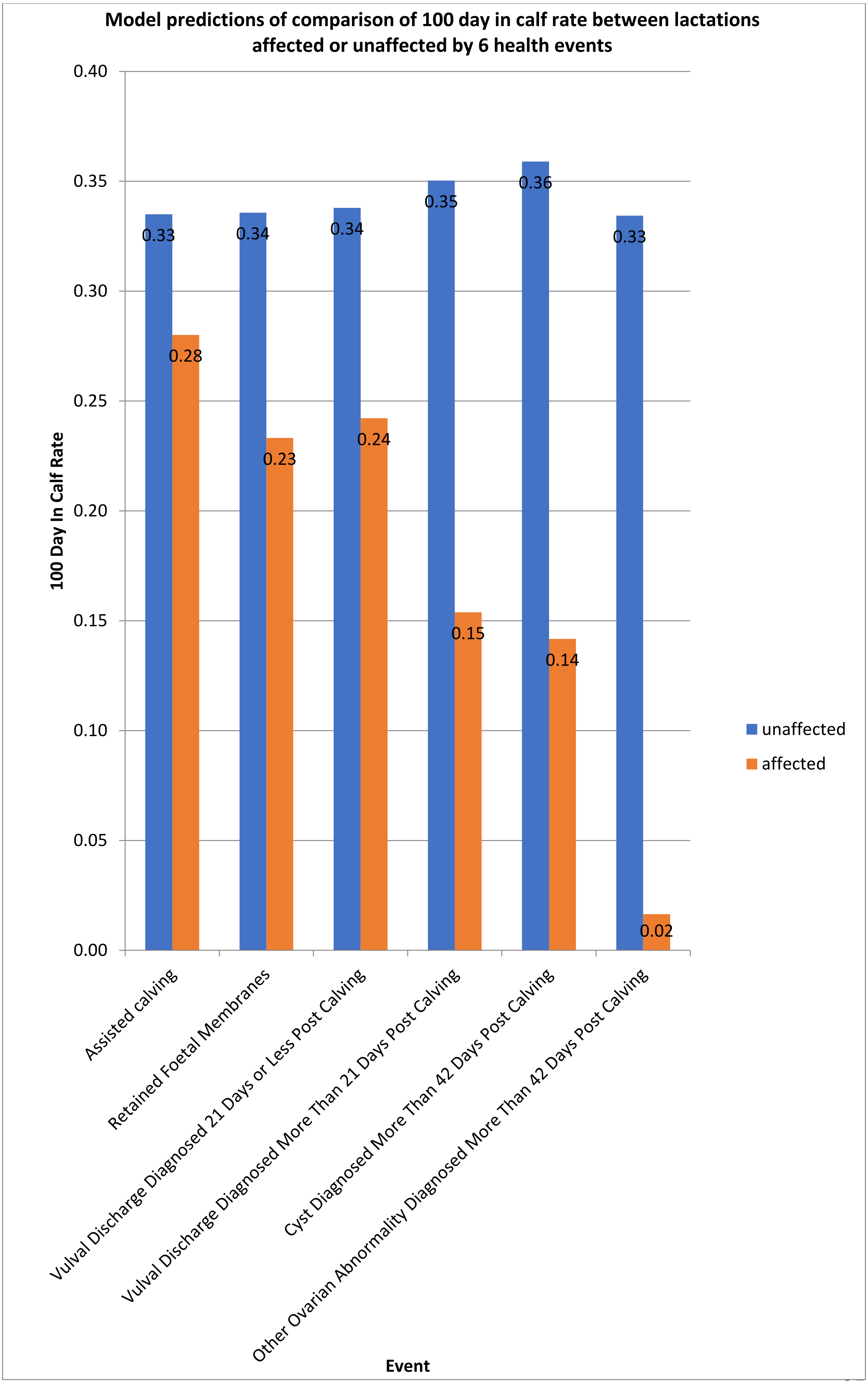
Model predictions of comparison of 100 day in calf rate between lactations affected or unaffected by 6 health events
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
100 Day In Calf Rate
0.33
0.28
0.34
0.23
0.34
0.24
0.35
0.15
0.36
0.14
0.33
0.02
Assisted calving
Retained Foetal Membranes
Vulval Discharge Diagnosed 21 Days or Less Post Calving
Vulval Discharge Diagnosed More Than 21 Days Post Calving
Cyst Diagnosed More Than 42 Days Post Calving
Other Ovarian Abnormality Diagnosed More Than 42 Days Post Calving
Event
unaffected
affected

Figure 2.10 Comparison between model predictions of 100 day in calf rate for lactations affected or unaffected by six periparturient or early lactation events.

2.3.5 Population Attributable Fractions

Table 2.7 shows population attributable fractions (PAF) for the six events identified as having an association with the probability of pregnancy per unit time. PAF is a method of further explaining the association between the explanatory and outcome variables from the logistic regression model and is a recognised method of determining the impact on the health of a population as the result of the exposure of the population to that event (Mansournia 2018, Brady 1998). PAF is defined by Mansournia (2018) as follows: 'the fraction of all cases of a particular disease or other adverse condition in a population that is attributable to a specific exposure; PAF equals (O − E)/O, where O and E refer to the observed number of cases and the expected number of cases under no exposure, respectively.

In the case of the health event explanatory variables from the logistic regression model, the percentage of PAF for each event in Table 2.7 indicates the reduction in the percentage of pregnancies per unit time that has occurred as a result of the health event. Despite a much reduced odds of pregnancy as a result of OOA occurring compared to other health events at the level of the individual risk period, the PAF for OOA is much lower for this event as a result of the event since PAF is assessed at the level of the population, and the lactational incidence of OOA is much lower.

The sum of the PAFs for the 6 events of nearly 11% indicates that a substantial reduction in the probability of pregnancy per unit time is expected as a result of the additive effect of their occurrence. However, an 11% increase in the probability of pregnancy would only be expected to occur in the hypothetical situation of the lactational incidence of all six events becoming zero, which would be difficult to achieve clinically.

Table 2.7 Population attributable fractions for six periparturient and early lactation health events associated with the probability of pregnancy per unit time

Event	**PAF %**	**Lower Confidence Interval**	**Upper Confidence Interval**
Assisted Calving	**1.48**	0.40	2.53
Retained Foetal Membranes	**1.04**	0.37	1.67
Vulval Discharge Diagnosed 21 Days or Less Post Calving	**2.01**	1.18	2.80
Vulval Discharge Diagnosed More Than 21 Days Post Calving	**2.94**	2.19	3.66
Cyst Diagnosed More Than 42 Days Post Calving	**2.96**	2.16	3.73
Other Ovarian Abnormality Diagnosed More Than 42 Days Post Calving	**0.50**	0.26	0.71

3.4 Discussion

The work in this chapter has established that there are significant associations between a number of periparturient and early lactation health events and the subsequent reproduction of dairy cows. The periparturient events assisted calving and retained foetal membranes and the early lactation events vulval discharge before 21 days, vulval discharge after 21 days, cystic ovarian disease after 42 days and other ovarian abnormalities after 42 days were all associated with impaired fertility. This reduced the predicted probability of pregnancy before 100 days of lactation by between 5% and 31% in affected cows compared to otherwise equivalent unaffected cows.

There is considerable evidence from the literature on the associations between a number of periparturient and early lactation health events (that often have a lactational incidence of between 5 and 20%) and reproduction at the level of the individual lactation or insemination (Djemali 1987, Simerl 1992, Esslemont 2002, Hayes 2012, Giuliodori 2013, Piccardi 2016, Leblanc 2002, Barrett 2009, Kim 2005, Cattaneo 2015). These have established, often using univariate analysis techniques, that individual health events reduce the probability of pregnancy at an individual lactation level.

The use of random effects discrete time survival regression analysis in this chapter has a number of advantages compared to many studies in this area, principally in that it allows other explanatory variables to be accounted for and therefore allows the separation of the impacts of different health events in the same model. Without the use of multivariable modelling it becomes difficult to know which of many interacting health events (such as twins and retained foetal membranes), which often occur in sequence in the lactation, was responsible for the subsequent poor reproductive performance. Milk fever, twins and dead calf were not found to be associated with reproductive performance once their associations with other interlinked diseases were separated by the model. In this study the only significant impacts of these on reproduction appeared to be via making other events (such as retained foetal membranes or assisted calving) more likely.

Other studies that have used multivariable modelling to allow the other variables to be accounted for have drawn similar conclusions (Loeffler 1999, Ribeiro 2013). This work aimed to investigate the calving and early lactation periods and therefore included only events that occur at this time. Direct comparison with other published work is therefore challenging as a result of different explanatory variables not being included.

However, Loeffler (1999) used some of the same health events as inputs to a logistic regression model as were used in this work and also established an association between cystic ovarian disease and reproductive performance. However, despite also establishing an association between metritis and reproduction, quantitative comparisons between results are not possible due to, among other reasons, contrasting disease definitions (Loeffler defining metritis as an infection of the uterus throughout the lactation, rather than being limited to the first 21 days, as was classified in the work in this project).

Ribeiro (2013) also used a variety of diseases that occur throughout the lactation as explanatory variables to multivariable models. Although these variables differ from the work in this chapter, some comparisons can be made. Using similar disease definitions their work showed a reduction in the odds of pregnancy per AI of 36% for endometritis, 62% for metritis and 48% for assisted calving for cows affected by these conditions compared to unaffected cows. Different methodology and inclusions to the models make exact comparisons with the work in this project impossible.

This model structure (discrete time survival analysis) has also allowed analysis and presentation of how the relationship between reproduction and disease changes through lactation through the use of predictions. Line charts such as these show not just that a periparturient event does reduce fertility, but by how much and crucially at which stages of the lactation this is most pronounced. The use of predictions of probability of pregnancy allow an immediate visual comparison between affected and unaffected cows.

A large number of studies have reported lactational incidence of health events. The diseases, and other disturbances to a normal calving and post partum return to cyclicity are events that are reported to occur in between 2% and 30% of lactations. This figure is some way below the incidence rates of mastitis and lameness, but these events are frequent and can have substantial impacts on production and culling in addition to associations with reproduction. Incidence rates from this work appear to be comparable to other studies (Esslemont 2002, Whitaker 2004), with periparturient events ranging from 3.4% for twins to 11.2% for assisted calving and early lactation events ranging from 0.9% for other ovarian abnormalities to 10.0% for cystic ovarian disease.

PAFs were determined for the 6 periparturient and early lactation events that remained in the model by generating predictions for an alternative version of the data where each event in turn was set to zero for every risk period and compared to observed probability of pregnancy from the model. This determined that between vulval discharges diagnosed before and after 21 days, uterine disease was reducing the probability of pregnancy per unit time by nearly 5%. PAFs suggest that of the six events identified as being associated with reproductive performance, early lactation events made the largest reductions in the probability of pregnancy per unit time. Interventions in this area, for example by diagnosing and treating cases of uterine and ovarian disease earlier in the lactation may result in improved herd reproductive performance in herds with high incidences of these diseases.

The results from the model in this chapter have only been used for inferences on the data that supplied the model and have not been used to make predictions on comparable data from other herds and therefore the concern about overfitting has not been investigated. Should the model be used for this purpose it would be logical to attempt to detect whether the model represents patterns that are specific to the data using cross validation techniques. Should this be found to be the case, a new model construction would be required.

The dairy industry and national herd reproductive performance have changed in the years since this data from 2000 to 2009 was collected but it would seem unlikely that the changes in this time (for example an improvement in national herd submission rate, Hanks 2010-2020) will have included a change in the relationships between health events and reproduction. Similarly, despite the 'big data' that was initially reworked, the model was built using data from approximately 1% of the original parities collected. Although this is a substantial reduction, it is important to consider that model checking ensured that the model fitted the data used well.

However, it is also important to consider whether selection bias has occurred and whether any changes would not represent a typical UK herd should these results be utilised by the industry (for example to consider alterations to herd management policies). Basic descriptive statistics presented in Table 2.4 suggest that the 14 herds used in this model were of similar size to the average for UK dairy herds but had a lower culling rate and a higher milk yield. By definition of their inclusion in this study, they keep records well. These factors may suggest that results from these herds may not be completely replicated should a more random sample of 14 herds be collected in the future.

The work in this chapter adds to discrete time survival models investigating the associations between mastitis and lameness, and reproduction (Hudson 2012, Hudson 2014). Areas of further extension for future models and datasets may include the addition of further clinical conditions such as displaced abomasa, or subclinical ketosis diagnosed at routine monitoring, or the building of more sophisticated models incorporating a series of any health events recorded on dairy farms. In the years since the dataset on which this chapter was based was collected, software programmes and farmer interest in herd performance data have increased. Repeating the study on more herds using current data would allow comparisons to be drawn and assessment on whether the associations established in this work between health events and reproduction have altered.

Chapter 3 Systematic evidence review of factors associated with reproductive performance

3.1 Introduction

3.1.1 Chapter Objectives

This chapter describes a systematic literature evaluation, exploring associations between health events, farm management decisions and environmental conditions, and dairy cow reproductive performance. The first chapter objective is to summarise existing evidence across key areas in a format which can be used within a simulation framework to evaluate which factors are most important in which situations.

Further output is through the exploration of the relationship between commonly (and often historically) used interval fertility data and more intuitive (and often more recent) means of expressing reproductive performance such as 21 day pregnancy rate. Techniques of literature searching, assimilation and the methods of summarising a broad ranging topic are also discussed.

For each factor a systematic literature evaluation has been performed, using standard techniques, in order to identify published studies (meeting quality criteria for study design and statistical robustness) which provide quantitative evidence on the impact of the factor on reproductive performance. Relative risks of pregnancy per unit time as a means of expressing the difference in likelihood of pregnancy between an affected and an unaffected comparison population are established.

3.1.2 Critical appraisal of studies

There is a consistent agreement that studies of different designs provide different weights of evidence to support a scientific argument, the so called 'hierarchy of evidence' (Murad 2016, Burns 2011). As a result of this, in order to construct a robust review of literature or identification of papers upon which to build an argument, it is logical to consider different study designs or publications reviewing literature in a particular field. For example, a systematic review will generally carry more weight than a randomised controlled trial, which itself will carry more weight than a cohort study and in turn a case report (Guyatt 2008). As a result of this it is important in the context of this chapter to consider the type of study as well as other assessments of the quality of the paper when considering whether it can be included.

When determining the quality of research, assessment of the standard of reporting of the methods and results, the study design and how logically the study has been placed within the broader literature is critical. Study types high in the 'hierarchy of evidence' and studies using high quality reporting, design and execution allow the reader to trust the findings and add weight to any scientific argument put forward when using the study as a reference for future work. For example, randomised control trials are often seen as high quality evidence, but poor design and implementation can make them unreliable (Barton 2000). High quality observational studies may provide stronger evidence than poor quality randomised control trials, which have a high risk of bias, raising questions about the validity of the findings.

Critical appraisal of studies is therefore important to assess the risk of bias and the reliability of the results. Critical appraisal tools are useful when reading scientific studies, to help to determine whether the research is of good quality, and to enable comparison between different studies (Ma 2020). Numerous tools for assessing study quality exist, including the checklists from Critical Appraisals Skills Programme (CASP) and the Centre for Evidence-based Veterinary Medicine (CEVM) at the University of Nottingham.

3.1.3 Evidence review techniques

Standard techniques to review published literature are increasingly being used to assimilate information from published work to make sure that data retrieved, and conclusions drawn can be considered consistent, logical and robust and to attempt to ensure no areas are missed. This becomes important to ensure a literature review is conducted thoroughly (so allowing a researcher's work to be placed in an appropriate context). It also becomes essential when using techniques to draw out knowledge and data from other sources.

Methods of how to conduct different types of review, such as a systematic review and a rapid review have been described (Grant 2009, Young 2014). A systematic review, often using meta-analysis techniques within the review framework is the gold standard but can be very slow and labour intensive (Miwa 2014). A rapid review is much quicker and designed to answer a specific clinical question, often with a less structured way of conducting the review. However, it can omit relevant studies, which can alter significance or associations when using meta-analyses (Marshall 2019).

Grindlay (2012) reviewed the coverage of veterinary journals by nine bibliographic databases and concluded that when attempting to find papers from a wide range of journals, the use of CAB Abstracts (CABI publisher) allowed a much greater coverage than any other database and therefore advised it's use in the first instance. Combination with a second database increased coverage further, and the same review concludes that Medline (US National Library of Medicine publisher) may be best placed since it has a focus on biomedical topics.

Once the most appropriate databases are selected, it is next important to use the correct search terms, in order to identify as many possible papers that meet the relevant criteria. To aid the development of search terms, questions can be asked which can define a problem and aid the gathering of evidence in an attempt to answer them (Richardson 1995). The paradigm of evidence-based medicine (EBM) recommends the formulation of clinical questions in terms of the problem/population, intervention, comparison, and outcome (Huang 2006, Sayers 2008). Together, these elements comprise a PICO framework. Although this was developed to facilitate the formulation of clinical queries, it has been extended to aid the finding of high-quality evidence.

3.1.4 Combining results from multiple sources of evidence

Since reproductive performance in dairy cattle is a broad area with many contributing factors, which are often hard to measure and hard to contextualise between each other, it can be challenging to know which steps to take to make improvements. As such, despite it being a well researched area, it is one in which attempts to bring together evidence from different sources can also be challenging.

The use of systematic reviews is a recognised technique to bring together sources of evidence and much greater weight can be brought to conclusions than for individual studies, through the use of meta-analysis techniques to synthesise the findings of several studies. Meta-analysis as part of review articles has been conducted in dairy reproduction (Rabiee 2005, Fourichon 2000, Lean 2009) to look at individual topics such as the use of fixed time artificial insemination (AI) programmes.

Bringing together a large number of factors in this area has only been done through review articles (Crowe 2018). While review articles can be a useful way of introducing genuine research and advancing knowledge if carefully structured (Snyder 2019), they are often not quantitative and therefore can be subjective. By methodically performing a series of reviews and using meta-analysis techniques to pool results across studies, the work in this chapter has identified key studies in each area, converted output from each into a standard unit and combined these to give a pooled effect for each area. This allows the opportunity to develop the results further to explore their relative associations with reproductive performance.

3.2 Materials and Methods

3.2.1 Factors influencing reproductive performance

Factors thought to be associated with reproductive performance were identified through discussion with the project team and collaborators and unstructured literature searching. The longlist of areas was very consistent across the project team and collaborators and very aligned with areas covered in key textbook chapters in the area of dairy cow reproduction and therefore was considered appropriate. Factors were initially grouped according to categories of management, disease, environment and genetics. From an initial longlist, a shortlist of 11 factors were selected which were subjectively felt to have a substantial impact on dairy cow reproduction and considered to be important to UK dairy farmers.

Consideration was given to the boundaries of the project such that it was essential to cover a range of topics to allow assessment of the relative importance of factors to reproductive performance later in the project. At the same time, it was considered that if the initial longlist had been used that a review of evidence could not be conducted in sufficient depth and a number of important evidence sources may have been missed. The factors to be investigated were in some cases subdivided into several categories and were as follows:

- Subclinical ketosis

- Oestrus detection
    - Use of fixed time AI/ synchronisation
    - Use of automated activity meters
- Endemic infectious disease
    - BVD
    - Johne's Disease
    - Leptospirosis
    - IBR
- Length of dry period
- Genetics
- Heat stress
- Age at First Calving.

3.2.2 Search terms

Clinical questions were constructed in a PICO framework (in terms of the population, intervention, comparison, and outcome) in order to particularly define the factor that was to be investigated and the change in that factor that may lead to impaired reproductive performance. An example of this (using BVD virus) would be as follows:

"In <dairy herds (P)> what effect would <uncontrolled high levels of BVD virus (I)> have compared to <naïve or steady low levels of BVD virus (C)> on <reproductive performance (O)>?"

The outcome (O) terms (<reproductive performance>) remained constant throughout. The population (P), intervention (I) and comparison (C) terms for the factors can be seen in Table 3.1.

Table 3.1 PICO terms for factors investigated for their impact on reproductive performance

Factor	Population	Intervention	Comparison
Subclinical ketosis	<dairy cows>	<ketosis as measured by blood biochemistry in the first 2 weeks of lactation>	<no ketosis>
Age at first calving	<first lactation heifers>	<an extended rearing period>	<a standard rearing period>
Length of dry period	<second lactation or greater dairy cows>	<having a lactation following an extended dry period length>	< having a lactation following a standard dry period length>
Genetics	<dairy herds>	<use of high fertility index bull>	<use of an average fertility index bull>
Heat Stress	<dairy cows>	<high temperature and humidity>	<normal temperature and humidity>
BVD virus	<dairy herds>	<uncontrolled high levels of BVD virus>	<naïve or steady low levels of BVD virus>
Johne’s Disease	<dairy cows>	<being positive to Johne’s disease>	< being negative to Johne’s disease>
Leptospirosis	<dairy herds>	<uncontrolled high levels of Leptospirosis>	<naïve or steady low levels of Leptospirosis>
IBR	<dairy herds>	<uncontrolled high levels of IBR virus>	<naïve or steady low levels of IBR virus>
Fixed time AI	<dairy herds>	<using fixed time AI following ovsynch>	<traditional oestrus detection methods>

Automated activity monitors	<dairy herds>	<using automated activity monitors>	<traditional oestrus detection methods>

Searching for literature was done using a searching framework that was as repeatable and consistent as possible between factors, while recognising that there were inevitably differences in the volume, quality and detail of studies in each area. The use of PICO based questions aided the design of the search terms that were to be employed during these literature searches and helped to frame the populations of cows or herds that were to be compared. An example of this method is shown in Figure 3.1 using BVD virus as an example.

Database Used
Database: CAB Abstracts <1910 to 2016 Week 46>
Search Strategy:

Level One

1 cow.mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes] (85399)
2 cows.mp. (293714)
3 cattle.mp. (647659)
4 bovine.mp. (147878)
5 bovines.mp. (5072)
6 bos.mp. (596109)
7 1 or 2 or 3 or 4 or 5 or 6 (713642)

Level Two
8 bovine viral diarrhoea.mp. (2428)
9 bovine viral diarrhea.mp. (2719)
10 bovine pestivirus.mp. (91)
11 bovine viral diarrhoea virus.mp. (1717)
12 pestivirus.mp. (14005)
13 bovine viral diarrhea virus.mp. (2441)
14 bovine viral diarrhoea virus 1.mp. (169)
15 bovine viral diarrhea virus 1.mp. (1043)
16 Bovine viral diarrhea virus 1.od. (1031)
17 bovine viral diarrhoea virus 2.mp. (18)
18 bovine viral diarrhea virus 2.mp. (505)
19 BVDV.mp. (2680)
20 BVD.mp. (5221)
21 mucosal disease.mp. (5192)
22 bovine mucosal disease.mp. (45)
23 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 (14879)
24 7 and 23 (8371)

Level Three
25 pregnant.mp. (64695)
26 pregnancy.mp. (120243)
27 pregnancy rate.mp. (7814)
28 pregnancy outcome.mp. (1274)
29 reproduction.mp. (101930)
30 preg rate.mp. (4243)
31 pregnancy risk.mp. (3587)
32 21 day pregnancy rate.mp. (103387)
33 conception rate.mp. (10077)
34 conception risk.mp. (5270)
35 fertility.mp. (167609)
36 reproductive performance.mp. (26462)
37 submission rate.mp. (6586)
38 submission risk.mp. (2854)
39 serve rate.mp. (1948)
40 oestrus detection rate.mp. (3105)
41 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 (404480)
42 24 and 41 (991)

Figure 3.1 Use of levels to ensure thorough search terms are entered into bibliographic databases, to ensure a high percentage of relevant papers are detected; in this example search terms used to identify papers associating BVD and reproduction in cattle

Further detail on the searching methods employed utilising these search terms in given in section 3.2.4. The levels shown identify the population (level 1 brought in populations of cattle) and the outcome (level 3 brought in reproductive parameters) and the intervention and comparison (level 2 brought in the factor involved- typically a management decision or health event, in this example bovine viral diarrhoea virus (BVD)). Search terms varied across the 11 factors investigated, with levels 1 and 3 remaining similar between factors and level 2 being changed with each factor.

3.2.3 Inclusion criteria for studies

As part of the literature searching process, assessments of the studies were conducted. Consideration was given to appropriate study design, sample size, understandable and comprehensive analytical methods, completeness of description of methods, consistent and understandable presentation of results, and context placement in introduction and discussion sections. Consistency of search methods, assessment of study quality and inclusion criteria were considered important, but some flexibility included to allow relevant studies to be obtained across a range of factors. Inclusion and exclusion criteria for selected studies are listed in Table 3.2.

Table 3.2 Inclusion and exclusion criteria for studies

Criteria	Inclusion	Exclusion
Population of interest	Bovine Dairy cattle	Any other species Beef cattle
Publication type	Randomised Controlled Trials Controlled trials without randomisation Cohort studies Case-control studies Case series Case study Cross sectional studies	Narrative reviews Conference proceedings
Subject	Make reference to reproductive performance and dairy cattle and factor involved within the title or abstract of the paper.	No reference to reproductive performance and dairy cattle and factor involved within title and abstract
Measurement	Presence of a control/comparison group Quantitative presentation of results	Absence of a control/comparison group No quantitative presentation of results

	Measure of uncertainty (standard error, confidence intervals)	No measure of uncertainty (standard error, confidence intervals)
Language	English	Any language other than English
Publication type	Full study reported Published literature Abstracts (full methods and results available)	Non-peer reviewed Grey literature Abstracts (methods and results not available) Book/ book section/generic
Availability	Able to obtain through University of Nottingham library or inter-library loan or by request	Cannot obtain whole manuscript

3.2.4 Search methods

It has been deemed essential when conducting literature reviews and searches for evidence to maintain a consistent, repeatable and justifiable approach (Xiao 2017, Munn 2018). Since the aim of this project is to bring together a large scope of research covering the broad topic of dairy cow reproduction, it can be considered that a series of reviews needed to be conducted. Since bringing together a series of reviews to evaluate the interaction between them has not commonly been undertaken in veterinary research, it was deemed appropriate to conduct 11 separate appropriate reviews for the 11 factors investigated, which while not completely identical, could be explained using a consistent methodology.

Since the 11 areas of interest listed above had a wide range of levels of published data, different approaches were used to identify papers containing suitable data associating each factor and reproductive performance in dairy cows, whilst ensuring a consistent and efficient search process. Searches were initially conducted using 3 level search terms using Medline and CAB Abstracts databases (as described by Grindley 2012). A search of CAB Abstracts (1910-2017) and Medline (1948-2017) using the OVID interface was performed. The abstract, title, original title, broad terms and heading words were searched using search terms as described in 3.2.2. Each search was linked with the

Boolean terms AND or OR. An illustrative example of this is as follows: [cow] OR [bovine] AND [BVD] OR [pestivirus] AND [pregnancy rate] OR [submission rate]. A more comprehensive illustration is seen in Figure 3.1.

Many of the factors investigated are areas of considerable research interest and therefore returned large numbers of papers despite the use of rigorous and detailed search terms. When initial searches using CAB and Medline databases returned more than 1000 papers, it was deemed necessary to reduce the number of papers returned by conducting a search through the database Web of Science with reduced search terms (this might include the search terms [cattle], [reproduction] and [BVD] for example). Although this method may reduce the number of papers returned and therefore introduce the possibility of high quality papers being missed, it did allow searching of specific journals deemed likely to contain the most relevant papers to the topic.

When the approach above using Web of Science returned more than 500 papers, it was deemed appropriate to reduce the search terms further. In this circumstance, review articles were identified using search terms in Web of Science and reference and citation lists checked to identify relevant papers that met the inclusion criteria, contained relevant evidence and met quality of publication criteria.

Each title was reviewed and then the abstract retrieved of any paper deemed to have a relevant title. Abstracts were reviewed, and where the abstract suggested the study was relevant to the area under consideration the full paper was reviewed, and results collated if they met the criteria.

3.2.5 Final search strategy for each factor

Since there was a large range of papers found (in terms of numbers and suitability) when exploring associations between management decisions or health events and reproductive performance, it was decided to conduct an evidence review using different methods for each factor. Consistency between methods was considered desirable but absolute consistency not achievable within the project boundaries and therefore different numbers of level 2 search terms were used in initial database searching, and in some cases searches using different methods employed (as described in section 3.3.4) in order to efficiently identify the most relevant studies for each factor. Table 3.3 shows two typical and contrasting search strategies.

Table 3.3 Illustration of methods used when searching for papers containing data associating management decision or health event and reproductive performance in dairy cattle using Leptospirosis and subclinical ketosis as examples

Search method and result of search	**Endemic infectious disease-Leptospirosis**	**Subclinical ketosis**
CAB Abstracts/Medline Advanced Search	Identified over 900 papers, once exclusion criteria applied 13 papers identified for further assessment	Identified over 1000 papers, Web of Science basic search conducted
Web of science basic search	Not required	Identified over 1000 papers, Web of Science review article search conducted
Web of science review article search	Not required	3 recent review articles identified from high impact factor journals Each referenced papers thought to be relevant from their titles and the majority were referenced by all 3 review papers. 18 papers identified for further assessment
Final method employed	CAB Abstracts/Medline Advanced Search	Web of science review article search

Papers identified	13 papers identified through assessment of titles but on reading abstracts or full publications, 0 met inclusion criteria (for example studies in beef cattle, or not published in peer reviewed publications, or inadequate methodology)	18 papers identified through references of review articles. 13 met inclusion criteria having reviewed abstracts 6 met inclusion criteria having reviewed full publications
Number of papers to be used	0	6
Result of literature search	Since no papers were identified, unable to further explore association between Leptospirosis and reproductive performance	6 papers with quantitative evidence to be utilised, allowing exploration of association between subclinical ketosis and reproductive performance

Following the individual evidence reviews, varying numbers of papers were identified for each factor (Table 3.4). For 7 of the 11 factors, between 4 and 6 suitable papers were identified. For 2 factors (Leptospirosis and IBR) no studies were deemed to meet the inclusion criteria and as a result these factors were not investigated further. Alternative approaches were taken for genetics and heat stress (described in section 3.4).

Table 3.4 Number of papers identified following evidence reviews for each factor investigated

Factor	Papers Identified
Subclinical Ketosis	6
Age at First Calving	5
Length of Dry Period	5
Genetics	Index
Heat Stress	1
Endemic Infectious Disease- BVD	4

Endemic Infectious Disease- Leptospirosis	0
Endemic Infectious Disease- Infectious Bovine Rhinotracheitis	0
Endemic Infectious Disease- Johne's Disease	4
Oestrus Detection- Fixed Time AI	6
Oestrus Detection- Automated Activity Monitors	5

3.2.6 Converting results to a consistent outcome measure

In broad terms the outcome measures contained within papers identified as suitable were reported as relative risks or odds ratios from regression models of binary outcomes (such as conception outcomes) or as pregnancies per unit time or as intervals from a calving. They had results (with measures of uncertainty) for both control and intervention groups and were either interval measures or proportions for binary outcomes.

In order to combine results from multiple papers to produce a single estimate for each factor, a method was required to convert results from each study into a consistent outcome measure. Relative risk of pregnancy per unit time was chosen as this represented overall reproductive performance, is widely accepted as being the most appropriate measure of overall reproductive performance (Denis-Robichaud 2016) and was the format required for the simulation model later in the project. Odds ratios were converted to relative risks using standard methods (Zhang 1998).

Generally, studies illustrating results using intervals reported calving interval as the outcome; where other intervals were reported these were converted to a calving interval equivalent (for example by adding a gestation period length to a calving to conception interval figure). Outputs from studies using interval outcome measures were converted to relative risk of pregnancy per unit time using the following methodology.

A simple deterministic model was built in Microsoft Excel (Microsoft Corporation 2018) to explore the proportion of cows in a herd conceiving in each 21 day block of a lactation under different 21 day pregnancy rates. This was used to calculate calving interval for various values of 21 day pregnancy rate. This produced the relationship shown in fig 3.3, to which a quadratic regression line was fitted, enabling conversion of a given calving interval to an equivalent 21 day pregnancy rate. As values of voluntary waiting period or decision point of the lactation for culling were unknown for most studies, a range of values for these were explored, producing a family of curves similar to the curve shown in fig 3.2. Although the different curves gave different "point" values for 21 day pregnancy rate corresponding to a given calving interval, there appeared to be little difference in the ratios between the two calving interval values established when assessing the intervention and comparison, so the curve in Figure 3.2 was used across all studies.

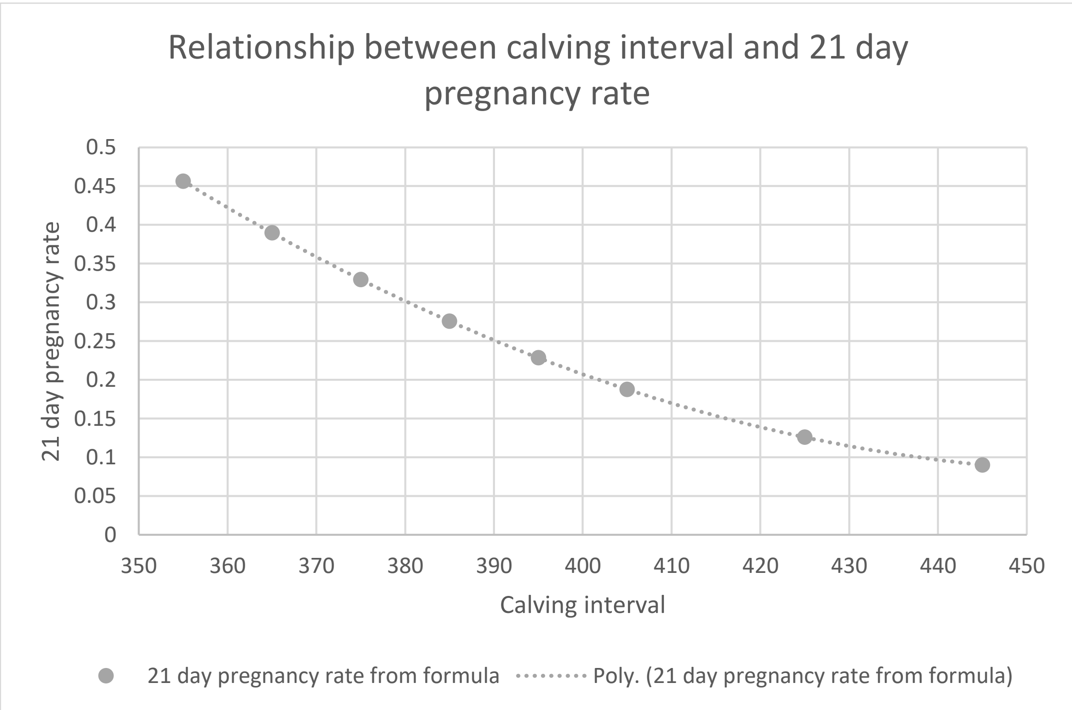

Figure 3.2 Relationship between calving interval and 21 day pregnancy rate. .The points and line show a fitted line for a function of the form y=ax^2 + bx + c where y= 21 day pregnancy rate and x = calving interval

Studies reporting results using interval measures generally used a confidence interval or standard error to illustrate uncertainty in results. Where this was the case, 1000 draws of calving interval were taken from a normal distribution produced from the mean and standard deviation based on the published result. Each of the 1000 resulting calving intervals was converted to a 21 day pregnancy rate using the quadratic regression line described above. This was done for both intervention and comparison groups, and the ratio between the two 21 day pregnancy rates calculated at each iteration. The mean and 95% confidence interval for this set of 1000 ratios were used to represent central estimates and confidence intervals for relative risk for this paper.

3.2.7 Pooling of multiple relative risks to create a summary relative risk using meta-analysis techniques

A summary table for each factor was then produced illustrating the relative risks for each area of interest for each paper. Once finalised, the relative risk results from each paper were then combined to allow a final association between each area (such as subclinical ketosis) and reproductive performance. The Metafor package (Viechtbauer 2010) in R was used to combine the results by random effects meta-regression (Berkey 1995) on log-relative risks (as they are designed to cope with error symmetrical around a central estimate). These were then converted back to relative risks to create a final combined pooled estimate and 95% confidence interval for relative risk in each area of interest. Data were presented in Forest Plots for each factor.

3.3 Results

Of the 11 factors originally searched for evidence, 9 have results describing the association between the factor and reproductive performance listed below. As described in section 3.2, searches for literature for Leptospirosis and IBR did not yield suitable studies. The approach and results associating both heat stress (in section 3.3.4) and genetics (in section 3.3.5), and reproduction are described below.

Results are presented from the other 7 of the 11 investigated factors as summary tables displaying the papers identified, their outcomes, and brief summaries of the study population and comparisons made between the intervention and comparison groups. For these factors, forest plots are presented using meta-analysis to show a pooled summary estimate of the association between the factor and reproductive performance. Two diamonds at the bottom of the plots illustrate this estimate with the range of spread of the diamond showing the precision of confidence of the estimate. Within the plot, the relative weight that each study provides is represented by the size of the square on the line associated with that study. This weighting of each is also described as a percentage contribution to the model.

Heterogeneity between studies has been assessed as part of this technique (as shown by I^2 percentage at the bottom left of the plot). In brief terms, a value above 50% represents large heterogeneity and above 25% modest heterogeneity (Ioannidis 2008). This can be seen for example for the forest plot for Johne’s disease studies (in section 3.3.7). Values such as this suggest that the observed effect of Johne’s disease between studies differ more from each other than would be expected from within study variation alone (Guddat 2012). In this circumstance the random effects model would be more appropriate to be used to summarise the pooled estimate of the effect of Johne’s disease on reproduction. It can be seen that there is a wider range of confidence in the summary estimate for this model than for the common effects model. This suggests a low level of confidence in the association between Johne’s and reproduction. This is also suggested by the large diamond for the random effects estimate, the fact that the diamond crosses the vertical line indicating a lack of difference between the intervention and comparator groups and the fact that the confidence intervals for this model are either side of the figure zero.

In contrast, the forest plot for subclinical ketosis (in section 3.3.1), which also has an I^2 value above 50% indicating that the random effects model is likely to be more appropriate, has a diamond with a small range of confidence intervals which do not cross zero, suggesting that there is a greater likelihood that there is an association between subclinical ketosis and reproduction from the pooled estimate of the results from the selected papers.

The forest plots for age at first calving and length of dry period (in sections 3.3.2 and 3.3.3) have I^2 values of 0%, representing homogeneity between studies within the meta-analysis. This indicates that the same effect from the factors is likely to be provided in all studies. In these factors, the common effects model would be most appropriate to be used to summarise the pooled estimate of the effect of the factors on reproductive performance. For both of these models, small diamonds which do not cross zero indicate a difference between the intervention and comparison groups and therefore an association between both length of dry period and age at first calving, and reproductive performance.

3.3.1 Subclinical ketosis

The results of searches for studies presenting associations between subclinical ketosis and reproductive performance are shown below (Table 3.5 and Figure 3.3). Six studies were identified with all showing similar relative risks and confidence intervals suggesting a decreased likelihood of pregnancy of a range of 13% and 61% as a result of subclinical ketosis. This resulted in a pooled estimate with narrow confidence intervals that do not cross zero.

Table 3.5 Relative risk of pregnancy for cows with subclinical ketosis compared to cows without subclinical ketosis (indicating the decrease in likelihood of pregnancy as a result of subclinical ketosis)

Paper	Country	Sample Size	Groups	Outcomes	**RR**	Lower Confidence Interval	Upper Confidence Interval
Walsh 07	Canada	796 cows in 25 herds	Either BHB >1000 week 1 post partum or >1400 week 2 post partum v BHB not elevated in either week	Calving to conception interval 124 v 108	**0.734**	0.601	0.884
Ospina 10	USA	2259 cows in 91 herds	BHB >1000 3-14d post partum v not elevated	HR 0.87	**0.870**	0.712	1.062
McArt 12	USA	1717 cows in 4 herds	BHB >1200 at any of 6 tests 3-16d post partum v not elevated	Calving to conception interval 104 v 96	**0.870**	0.717	1.035
Ribeiro 13	USA	957 cows in 2 herds	NEFA >700 at 7 or 14d post partum v not elevated	OR 0.52	**0.575**	0.402	0.798
Cook 01	UK	410 cows in 3 herds	Milk acetone >0.4 12-60d post partum v paired cow <0.3	Calving to conception interval 138.7 v 84.7	**0.399**	0.208	0.718
Rutherford 16	UK	203 cows in 3 herds	BHB >1200 7-21d post partum v not elevated	Adjusted services per conception 2.8 v 2.0	**0.720**	0.573	0.902

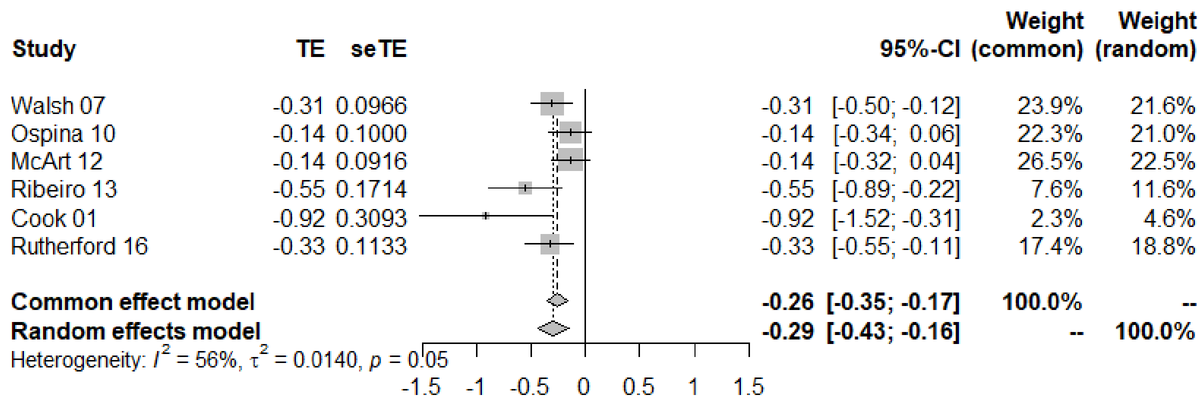

Figure 3.3 Forest Plot showing pooled estimate of association between subclinical ketosis and reproductive performance from 6 studies

3.3.2 Age at first calving

The results of searches for studies presenting associations between age at first calving and reproductive performance are shown below (Table 3.6 and Figure 3.4). Five studies were identified with all showing similar relative risks and confidence intervals suggesting a decreased likelihood of pregnancy of a range of 8% and 32% in the first lactation as a result of calving following an extended rearing period. This resulted in a pooled estimate with narrow confidence intervals that do not cross zero.

Table 3.6 Relative risk of pregnancy for heifers calving after extended rearing period compared to heifers calving after normal rearing period

Paper	Country	Sample Size	Groups	Outcomes	**RR**	Lower Confidence Interval	Upper Confidence Interval
Cooke 13	UK	445 heifers in 17 herds	26-30m v 23-25m	Calving to conception interval 137 v 117	**0.683**	0.452	1.021
Ettema 04	USA	1905 heifers in 3 herds	>750d v 700-750d	Calving to conception interval 154.5 v 148.6	**0.900**	0.752	1.069
Eastham 12	UK	396,534 heifers	26m v 24m	Calving interval 428 v 423.6	**0.918**	0.883	0.954

Krpalkova 14a	Czech Republic	780 heifers in 2 herds	>750d v 700-750d	Calving interval 418.8 v 408.5	**0.819**	0.552	1.181
Krpalkova 14b	Czech Republic	18139 heifers in 33 herds	>800d v 750-799d	Calving interval 401.2 v 396.4	**0.916**	0.668	1.204

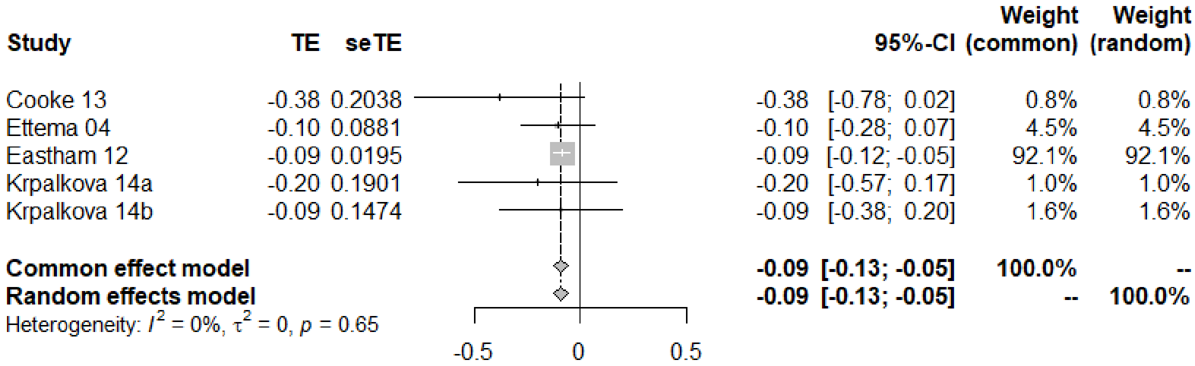

Figure 3.4 Forest Plot showing pooled estimate of association between age at first calving and reproductive performance from 5 studies

3.3.3 Length of Dry Period

The results of searches for studies presenting associations between length of dry period and reproductive performance are shown below (Table 3.7 and Figure 3.5). Five studies were identified with all showing similar relative risks and confidence intervals suggesting a decreased likelihood of pregnancy of a range of 1% and 28% in the subsequent lactation as a result of calving following an extended dry period. This resulted in a pooled estimate with narrow confidence intervals that do not cross zero.

Table 3.7 Relative risk of pregnancy for cows calving after extended dry period compared to cows calving after standard dry period

Paper	Country	Sample Size	Groups	Outcomes	**RR**	Lower Confidence Interval	Upper Confidence Interval
Pinedo 11	Chile	145984 cows	77-142d v 53-76d	Calving to conception interval 131.9 v 128.9	**0.950**	0.931	0.976

Kuhn 07	USA	118736 cows	71-80d v 56-60d	Days open 132 v 129	**0.970**	0.939	1.000
Hossein-Zadeh 13	Iran	384717 cows	71-80d v 51-60d	Calving interval 413.9 v 411.6	**0.987**	0.966	1.008
Kuhn 06	USA	318276 cows	71-80d v 56-60d	Days open 151 v 148	**0.952**	0.932	0.973
El-Tarabany 15	Egypt	1000 cows in 1 herd	<75d v 60-75d	Days open 182 v 140	**0.716**	0.533	0.935

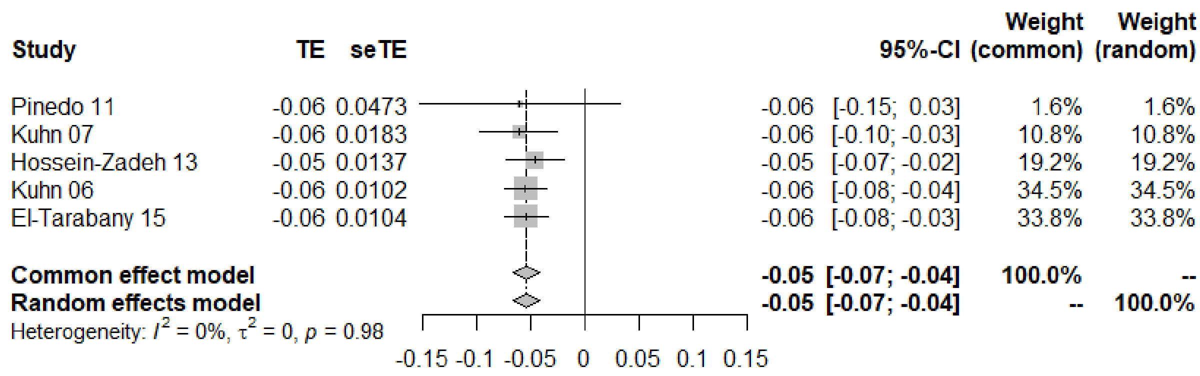

Figure 3.5 Forest Plot showing pooled estimate of association between length of dry period and reproductive performance from 5 studies

3.3.4 Genetics

A comparison of two bull choices is shown in Table 3.8. This is based on figures determined by the AHDB fertility index (AHDB 2020). The relative risk presented represents the increased likelihood of pregnancy as a result of using the mean figure for the top 50 Holstein bulls ranked on Fertility Index from the AHDB bull report publication (AHDB 2021b), in comparison to an ‘average bull’ as determined by AHDB. The UK fertility index has been used since 2005 following initial methodology determined by Wall 2002 with proofs republished twice per year.

Each increase of a point in Fertility Index represents a prediction of a 0.5 day decrease transmitted to the calving interval for the daughter of the bull. Since the mean of the top 50 bulls on Fertility Index is 16.8, this equates to a calving interval decrease of 4.2 days for the daughter (since the sire contributes half the genetic potential for fertility to the daughter). The intervention and comparator calving intervals of the daughters from a top 50 bull and an average bull were converted to 21 day pregnancy rates using the quadratic fitted line described in section 3.3.6 and a ratio of these 2 rates created to represent a relative risk of pregnancy as a result of using a high fertility index bull. This has been determined to be representative of the choice a farmer may make when advised to select bulls for improved reproductive performance, where they had not previously considered this.

Table 3.8 Relative risk of pregnancy for daughters from top 50 fertility index bulls compared to daughters from 'average' bulls

Fertility Index top 50 bull	
Relative risk	1.085
Lower confidence interval	1.072
Upper confidence interval	1.117
Calving interval of daughter of 'average' bull	400.0
Calving interval of daughter of top 50 bull	395.8
21 day pregnancy rate of daughter of 'average' bull	0.207
21 day pregnancy rate of daughter of top 50 bull	0.225

3.3.5 Heat Stress

A comparison of the likelihood of pregnancy at different Temperature Humidity Index (THI) values is shown in Table 3.9. These results have been transformed from results presented in a large scale study of more than 150,000 inseminations from 550 herds in southern USA (Ravagnolo 2002). Although a number of papers were identified following initial evidence searches, this paper was the only one to meet inclusion criteria. Since the paper met inclusion criteria and was referenced as a high quality paper in review articles about heat stress, results from the paper were used to create a relative risk of pregnancy following heat stress.

The authors of the paper presented 45 day non-return rates at THI values from 50 to 82 as a measure of reproductive performance. These values were converted to odds ratios through the use of a logistic regression model and transformed to relative risks using standard methods. Since reproductive performance was only reduced at THI values above 62, the pooled values of inseminations below 64 have been used as comparators and the risk of pregnancy at each value from 64 to 82 considered as intervention values against this reference in Table 3.9.

Table 3.9 Relative risk of pregnancy at higher values of THI compared to values of 62 and below

THI	Relative Risk	Lower Confidence Interval	Upper Confidence Interval
64	0.976	0.959	0.992
66	0.955	0.939	0.972
68	0.946	0.930	0.962
70	0.920	0.903	0.936
72	0.898	0.882	0.914
74	0.848	0.832	0.864
76	0.827	0.809	0.844
78	0.800	0.783	0.817
80	0.753	0.735	0.772
82	0.685	0.666	0.704

3.3.6 BVD

The results of searches for studies presenting associations between BVD and reproductive performance are shown below (Table 3.10 and Figure 3.6). Four studies were identified with all showing similar relative risks and confidence intervals suggesting a decreased likelihood of pregnancy of a range of 0% and 15% in cows from herds with high levels of BVD virus seropositivity, compared to cows from herds with low levels of seropositivity. This resulted in a pooled estimate with narrow confidence intervals, and a negative central estimate, but with confidence intervals either side of zero, suggesting a lack of difference between the association with reproductive performance between the intervention and comparison groups.

Table 3.10 Relative risk of pregnancy for BVD high positive herds compared to BVD negative herds

Paper	Country	Sample Size	Groups	Outcomes	**RR**	Lower Confidence Interval	Upper Confidence Interval
Niskanen 95	Sweden	213 herds	High v low	Calving interval 394 v 385	**0.845**	0.750	0.941
Robert 04	France	6149 herds	High v low	RR 1.00	**1.000**	0.980	1.020
Heuer 07	New Zealand	590 herds	High v low	Calving to conception interval 89.9 v 87.5	**0.960**	0.924	0.996
Valle 01	Norway	1620 herds	After and before seroconv	Calving interval 394.4 v 393.7	**0.991**	0.819	1.172

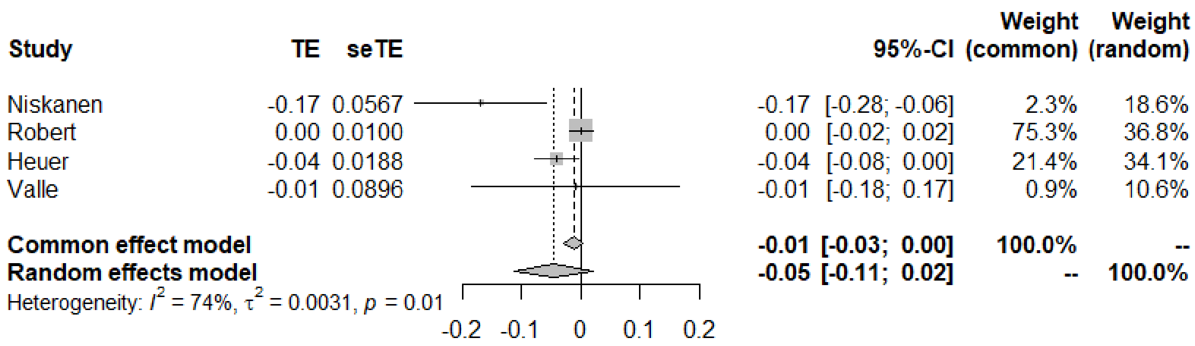

Figure 3.6 Forest Plot showing pooled estimate of association between BVD and reproductive performance from 4 studies

3.3.7 Johne's Disease

The results of searches for studies presenting associations between Johne's Disease and reproductive performance are shown below (Table 3.11 and Figure 3.7). Four studies were identified showing quite different relative risks to each other and wide confidence intervals suggesting a range in likelihood of pregnancy from a decrease of 62% to an increase of 10%, in cows seropositive or faecal culture positive, compared to negative cows, reflecting a lack of certainty in any associations between the disease and reproductive performance. This was reflected in a pooled estimate with wide confidence intervals, and a negative central estimate, but with confidence intervals a large distance from zero, suggesting a lack of difference between the association with reproductive performance between the intervention and comparison groups.

The heterogeneity between studies suggests a large disagreement in study findings. This is most apparent in a large study showing increased likelihood of pregnancy (with narrow confidence intervals) in cows with Johne's disease (Marce 2009), which disagrees with the findings of two other studies (Raizman 2007, Johnson- Ifearulundu 2000), which show a decreased likelihood of pregnancy.

Table 3.11 Relative risk of pregnancy for Johne's Disease positive animals compared to Johne's Disease negative animals

Paper	Country	Sample Size	Groups	Outcomes	**RR**	Lower Confidence Interval	Upper Confidence Interval
Van Leeuwen 10	Canada	2876 cows from 151 herds	Seropos v seroneg from random sample	OR 1.05	**1.049**	0.575	1.514
Marce 09	France	48,914 cows from 1069 herds	Seropos v seroneg from neg herds	RR 1.10	**1.100**	1.050	1.150
Raizman 07	USA	1052 cows from 2 herds	Faecal pos v faecal neg	OR 0.36	**0.377**	0.188	0.731
Johnson-Ifearulundu 00	USA	533 cows from 5 herds	Faecal pos or seropos v Faecal neg or seroneg	Days open 146.9 v 119	**0.609**	0.329	1.075

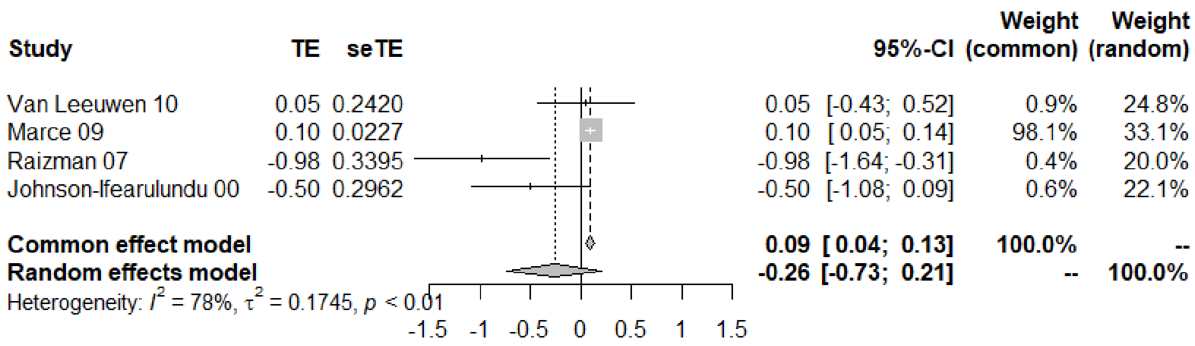

Figure 3.7 Forest Plot showing pooled estimate of association between Johne's Disease and reproductive performance from 4 studies

3.3.8 Fixed Time AI

The results of searches for studies presenting associations between the use of fixed time AI and reproductive performance are shown below (Table 3.12 and Figure 3.8). Six studies were identified. Four of these studies showed relatively similar relative risks and confidence intervals suggesting an increased likelihood of pregnancy of a range of 6%

and 28% in cows from herds with using fixed time AI, compared to cows from herds using visual oestrus detection.

A fifth study (Tenhagen 2004) showed a large relative risk of 2.003 but with very large confidence intervals suggesting large uncertainty in the results, which is reflected in the low weighting of this study to the meta-analysis model pooled effect. The sixth study (Jemmeson 2000) showed the opposite association- in this study the use of fixed time AI was associated with a reduced likelihood of pregnancy with narrow confidence intervals. These six studies resulted in an unclear association between fixed time AI and reproduction from the pooled estimate, with narrow confidence intervals, and a positive central estimate, but with confidence intervals either side of zero. This suggests a lack of difference between the association with reproductive performance between the intervention and comparison groups.

Table 3.12 Relative risk of pregnancy with use of Fixed Time AI compared to other oestrus detection methods

Paper	Country	Sample Size	Groups	Outcomes	**RR**	Lower Confidence Interval	Upper Confidence Interval
Denis-Robichaud 16	Canada	832 herds	Visual v FTAI v AAM	21dPR 16.8 v 17.9 v 16.8	**1.066**	0.975	1.167
de la Sota 98	USA	304 cows in 1 herd	Visual v FTAI	Days open 90.0 v 77.6	**1.229**	1.038	1.466
Fodor 18	Hungary	23784 cows in 34 herds	Visual v FTAI	Calving to conception interval 143 v 132	**1.278**	0.541	2.232
Jemmeson 00	Australia	620 cows in 8 herds	Visual v FTAI	OR 0.69	**0.881**	0.755	0.994
Stevenson 99	USA	308 cows in 1 herd	Visual v FTAI	Calving to conception interval 112 v 110	**1.058**	0.776	1.378
Tenhagen 04	Germany	650 cows in 1 herd	Visual v FTAI	Days open 117.0 v 94.4	**2.003**	0.230	7.529

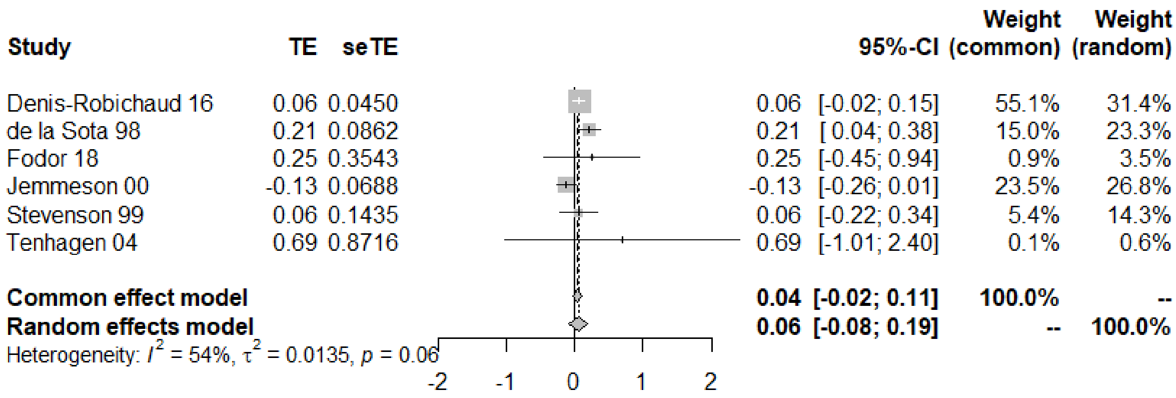

Figure 3.8 Forest Plot showing pooled estimate of association between Fixed Time AI and reproductive performance from 6 studies

3.3.9 Automated Activity Monitors

The results of searches for studies presenting associations between automated activity monitors and reproductive performance are shown below (Table 3.13 and Figure 3.9). Five studies were identified with all showing similar relative risks and confidence intervals suggesting an increased likelihood of pregnancy of a range of 3% and 41% as a result of the use of automated activity monitors. Although three of the studies individually had confidence intervals that crossed zero, the pooled estimate of all 5 studies did not, with relatively narrow confidence intervals.

Table 3.13 Relative risk of pregnancy with use of Automated Activity Monitors compared to other oestrus detection methods

Paper	Country	Sample Size	Groups	Outcomes	**Relative Risk**	Lower Confidence Interval	Upper Confidence Interval
Denis-Robichaud 16	Canada	832 herds	Visual v FTAI v AAM	21dPR 16.8 v 17.9 v 16.8	**1.003**	0.887	1.123
Marques 20	USA	4200 cows from 1 herd	Existing methods v AAM	95d post AI 31.1 v 36.3	**1.180**	0.955	1.454
Neves 15	Canada	223 herds	Before and after AAM introduction	21d PR 14.9 v 17.0	**1.143**	1.020	1.269

Michaelis 14	Germany	676 cows from 1 herd	Visual v AAM	200d HR of pregnancy 1.41	**1.410**	1.110	1.790
Veronese 19	USA	4200 heifers from 1 herd	Mounting devices v AAM	73d post AI 34.3 v 27.5	**1.268**	0.812	1.857

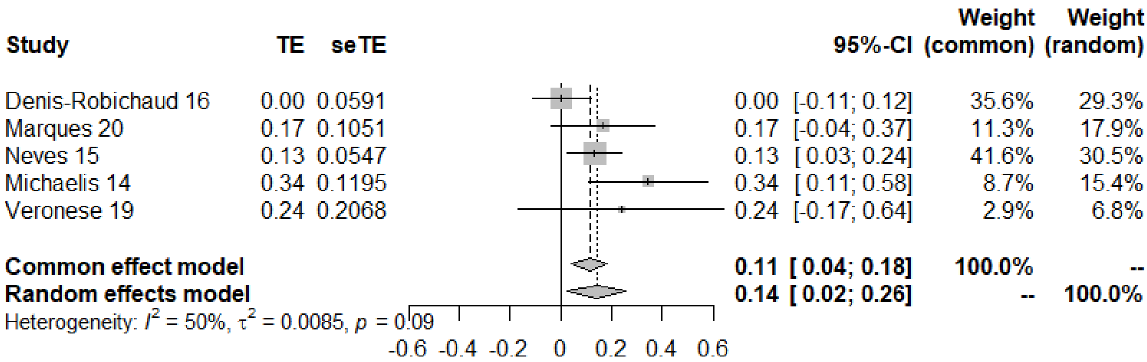

Figure 3.9 Forest Plot showing pooled estimate of association between Automated Activity Monitors and reproductive performance from 5 studies

3.3.10 Summary of Results

Table 3.14 summarises the results for this chapter. The relative risk of pregnancy per unit time for the intervention cow or herd in comparison to the risk of pregnancy for the comparison cow or herd is shown for each factor, with each population group described and confidence intervals around this pooled estimate. The relative risk figures have been derived from the exponentiation of the pooled estimates derived by meta-analysis and displayed in the Forest plots in earlier sections. The genetics and heat stress relative risk figures have been described above.

Table 3.14 Summary of evidence associating factors with reproductive performance. Each section has an accompanying explanation of being affected and unaffected by the factor. A relative risk of pregnancy when affected by the factor compared to being unaffected, and confidence intervals are displayed

Parameter	Intervention population	Comparison population	Relative Risk	Lower confidence interval	Upper confidence interval
Subclinical Ketosis	Cows with ketosis measured by biochemistry, generally BHB in first 2 weeks post calving	Cows with normal ketone parameters on blood biochemistry	**0.745**	0.648	0.856
Age at First Calving	First lactation heifers following an extended heifer rearing period, generally greater than 26 months	First lactation heifers following a standard heifer rearing period, generally 24 months	**0.914**	0.881	0.948
Length of Dry Period	Lactation following extended dry period, generally 71-80 days	Lactation following standard dry period length, generally 56-60 days	**0.947**	0.936	0.958
Genetics and bull choice	Use of top 50 fertility index bull (mean 16.8 FI from Aug 2020 AHDB evaluation)	Use of bull determined 'average for population of bulls' under AHDB criteria	**1.085**	1.072	1.117

Heat stress	Temperature humidity index of 76 (for example 25 degrees C at 80% humidity)	Temperature humidity index of 62 or less (for example 17 degrees C at 70% humidity)	**0.827**	0.809	0.844
BVD	Herds with uncontrolled BVD infection, generally high seropositivity without vaccination	Herds naïve or stable low prevalence of seropositivity to BVD	**0.955**	0.893	1.021
Johne's Disease	Cows seropositive or faecal culture positive to Johne's disease	Cows seronegative or faecal culture negative to Johne's disease	**0.770**	0.481	1.235
Fixed time AI	Herd policy use of fixed time AI following Ovsynch protocol	Herd policy of AI on observed oestrus	**1.057**	0.922	1.212
Automated Activity Monitors	Herd use of activity monitors to aid oestrus detection	No activity monitors	**1.151**	1.025	1.293

3.4 Discussion

A large review of the literature exploring associations between both management techniques and health events and reproductive performance has been conducted. Although this has not been constructed as a narrative review summarising key papers and discussing current and future challenges to attempts to improve reproductive performance, it has allowed a summary through a consistent format and importantly through quantitative assessment. Key papers have been found, assessed for quality and the results assimilated and summarised into relative risks of pregnancy between two populations of animals across each technique or event.

The use of systematic reviews following recognised methodology is thought to be the gold standard way of assessing literature in a specific field and the use of any other methods risk missing key papers and altering any conclusions that are drawn (Marshall 2019). Although full systematic reviews have not been conducted in this chapter, evidence has been synthesised through a consistent and thorough method to allow the use of meta-analysis to obtain a pooled estimate of association with reproduction in a number of key areas.

As a general principle, each meta-analysis in the published literature has been constructed to answer a specific scientific question posed by the author at that point in time. Any future meta-analysis on that broad topic within a review will inevitably ask a different question and have different and more up to date studies available to bring together to help answer that question.

In a number of areas of this chapter, a meta-analysis has been conducted to reliably answer the question of what level of association there is between an event or management technique and reproduction. Therefore, a number of meta-analyses are now available to help answer research questions and aid decision making by farmers and their advisers.

There are however a number of areas in which this method has not allowed complete conclusions to be drawn. Despite following recommended search methods, insufficient papers were found to quantitatively assess the relationship between Leptospirosis and IBR, and reproductive performance. A more thorough systematic review in this area, perhaps encompassing all endemic infectious diseases may have found more suitable studies and extending inclusion criteria (perhaps for example to translate articles from other languages into English) may also have brought more articles into the evidence gathering process.

Despite a robust search method which found several articles on each topic, there was some contradiction between study findings which made it difficult to assess the association between Johne's disease and reproductive performance. More intricately designed questions and search terms may have separated the subclinical stages of Johne's disease (where the disease may be associated with improved reproductive performance) and the clinical stages of Johne's disease (where the disease may be associated with decreased reproductive performance). Better use of search terms may for example have brought more studies that could have allowed one or both disease stages to be investigated, with more reliable associations elucidated.

In a similar way, the association between the use of fixed time AI and reproduction may have been distorted by attempts to maintain a consistent methodology between factors. A paper using fixed time AI in seasonally calving herds was included (Jemmeson 2000) which found a reduced likelihood of pregnancy as a result of the use of fixed time AI. Excluding this paper may have resulted in a significant association since the remainder of the papers found an increased likelihood of pregnancy. An evidence review of only this factor may have allowed the exclusion of papers around seasonally calving herds (they were not excluded to maintain consistency of methodology since these papers may have been useful in other areas).

Despite attempts to maintain consistency, the methods of searching and reviewing have not been constant between factors. This has meant that for some factors it has been very difficult to find papers and in others difficult to know which ones of a huge number to exclude. The lack of consistency may result in missed papers, which may result in less ability to compare the associations with reproductive performance between factors. This can only be remedied by conducting full systematic reviews of each factor.

The genetics and bull choice relative risk of pregnancy per unit time summary result was determined using a different method. The direct use of the UK fertility index methodology may have introduced errors, despite the index being based on previously published work (Wall 2002, Wall 2003) and updated regularly according to results from the national herd. Integration with methods used to calculate the index, rather than the summary of the index itself may be a useful future development of this project.

The findings recorded in this chapter can be utilised to crudely compare different management techniques or reductions in health events and the relative risks of pregnancy may in simple terms allow discussion between farmers and their advisers about what steps may be of benefit to a herd's reproductive performance. Although crude, the work in this chapter does allow much easier comparison between the relative effects in each area of reproductive performance. For example, in some areas, study quality can be variable and with many different outcome measures (for example the use of a large number of different interval parameters).

For areas in which an investment in an area in an attempt to improve reproductive performance is a simple binary choice (for example when considering better control of BVD virus or the use of activity monitors or a herd policy of fixed time AI), a direct comparison between the likely outcome of each of the three interventions is possible just from these results. But for factors like changes to the incidence of subclinical ketosis or endometritis the interventions apply to some but not all cows and therefore a direct comparison with each other or with the binary choices such as the use of activity monitors is more challenging. However, one of the key aims of this chapter is to establish inputs in these areas to a simulation model built to assess the association between a range of these inputs and 21 day pregnancy rate.

It is expected that the findings from this chapter will be developed further. The framework used remains flexible and can be extended and updated by performing full systematic reviews in each area, which are more likely to have a more repeatable literature searching method and thus ensure the meta-analyses conducted are more detailed and accurate. As described in section 3.2.1, there were several areas subjectively thought to be important that were excluded as a result of limitations of the project boundaries. These included male factors (such as the use of multiple bulls within a straw or the use of sexed semen or using inseminators from external companies) and many other factors influencing a cow’s immediate environment (such as cubicle comfort and feed space). These could be returned to and their inclusion may add further to the contextualisation of the varying effects of factors on reproductive performance.

Chapter 4 The use of simulation to investigate the association between periparturient and early lactation health events and reproduction

4.1 Introduction

Reproduction is considered an essential contributor to efficiency and has a role to play in ensuring the dairy industry is financially and environmentally sustainable at all levels, from individual units to globally. The field is very well studied compared to many other areas of veterinary epidemiology. However, the multifactorial nature of fertility makes it difficult to evaluate the potential value of alternative strategies to improve performance.

Chapter 2 adds to many studies quantifying the association between periparturient and early lactation health and fertility (Esslemont 2002, Bell 2007, Bicalho 2007, Dubuc 2011, Hayes 2012, Giuliodori 2013, Cattaneo 2015, Piccardi 2016), and further supports the detrimental impact of increasing incidence of these health events on the probability of a successful insemination for an individual cow. However, it does not allow assessment of the value a reduction in the incidence of these events would have on improving herd level reproductive performance. As such it remains unclear what impact investment in steps to improve for example uterine and ovarian health may have on herd fertility.

The motivation of dairy farmers will inevitably differ between units and many would consider that even if improving periparturient and early lactation health were not to lead to an improvement in overall herd reproductive performance, doing so would still be of considerable benefit to their herd. Alternative motivations may include improved animal welfare, reduced labour costs, reduced culling or even improved individual cow fertility leading to continuing a particular family line within a herd.

Probabilistic sensitivity analysis is a technique widely used in health economics to evaluate cost-effectiveness of interventions. It is used where a model has multiple inputs which have the potential to influence the model outcomes. Each input is assigned a distribution, and a value for each input is drawn from that input's distribution at each iteration of the simulation. By running the model over a large number of iterations, the joint probability space of the various inputs is covered, and relationships between inputs and outcomes evaluated, often through the use of regression modelling of the simulation output.

Probabilistic sensitivity analysis (PSA) draws values for inputs from probability distributions and uses simulation to explore the interrelationship between sets of inputs and outputs around a complex system (Adalsteinsson 2013). PSA is increasingly used in veterinary population studies where increasing amounts of data are available. Since reproduction at a herd level has complex inputs, PSA can be used to rationalise their importance and provide information for farmers attempting to rank various options for herd improvement and investment.

Dairy cow reproduction is a highly suitable subject for the use of PSA through simulation modelling, since it consists of sequential, defined steps leading to a cow becoming pregnant. Many simulation models of varying complexity are reported in the literature (Archer 2015, Bekara 2019, Liang 2017). The work reported in this chapter adds to the investigation of the association between the endemic diseases mastitis and lameness and reproduction (Hudson 2012, Hudson 2014, Hudson 2015). These studies identified that many such associations were strongly statistically significant and had relatively large effect sizes (as measured, for example, by odds ratios through the use of inferential statistical modelling). However, altering the incidence or prevalence of mastitis or lameness in a herd would be unlikely to influence the herd's overall reproductive performance by a meaningful amount in most situations when further assessed using stochastic simulation modelling.

In this chapter PSA is used to assess model inputs with uniform distributions, such that all values within a plausible range are equally likely to be drawn with each iteration of the simulation. The aim of this work is to evaluate the change in herd reproductive performance resulting from changes in the incidence of periparturient and early lactation health events relative to other background herd level inputs.

4.2 Materials and Methods

4.2.1 Use of the output from a discrete time survival model

The random effects discrete time survival regression model described in chapter two determined explanatory variables that were significantly associated with reproductive performance, specifically the probability of pregnancy in 7-day risk periods. These explanatory variables were used as input parameters for the stochastic simulation model described in this chapter (Table 4.1). The model terms from the preceding logistic regression model were used to determine how the probability of pregnancy was associated with each input variable for each simulated lactation.

4.2.2 Description of distributions of input variables

The types of variable and distributions from which values were drawn are shown in Table 4.1. Input values were drawn from uniform distributions considered plausible and thought to be encompassing a typical range of values for the majority of UK herds. The distributions were not expected to represent the real life population, but to allow a full range of plausible scenarios so that the relationship between periparturient and early lactation health events, and reproductive performance could be fully explored. Both herd level inputs and risk period within each lactation level inputs were drawn from distributions based on the herd level parameters.

Table 4.1 Input parameters used at each level of simulation and distributions from which inputs were drawn.

Input variable	Type	Input distribution
Herd level		
Submission rate (proportion of eligible cows inseminated every 21 days)	Continuous	Uniform (0.1, 0.7)
Conception risk (proportion of inseminations leading to a pregnancy)	Continuous	Uniform (0.1, 0.5)
Herd average 305 day milk yield (kg)	Continuous	Uniform (6000, 12000)
Proportion of herd which are first lactation	Continuous	Uniform (0.2, 0.3)
Proportion of calvings affected by Assisted Calving	Continuous	Uniform (0., 0.1)
Proportion of calvings affected by Retained Foetal Membranes	Continuous	Uniform (0., 0.1)
Proportion of calvings affected by Vulval Discharge at less than 21 days in milk	Continuous	Uniform (0., 0.1)
Proportion of calvings affected by Vulval Discharge at more than 21 days in milk	Continuous	Uniform (0, 0.25)
Proportion of calvings affected by Cystic Ovarian Disease at more than 42 days in milk	Continuous	Uniform (0, 0.05)
Proportion of calvings affected by Other Ovarian Abnormality at more than 42 days in milk	Continuous	Uniform (0, 0.025)
Lactation level		
Lactation number	Categorical (1, 2, 3, 4, >4)	Multinomial, based on proportion of herd in lactation 1 from herd inputs and remainder of herd split across lactations in same proportions as observed data
305 day milk yield (kg)	Continuous	Betapert, centred on herd average, draws in range +/- 3000kg
Occurrence of Assisted Calving	Binary	Binomial, with probability based on background herd proportion
Occurrence of Dead Calf	Binary	Binomial, with probability based on background herd proportion
Occurrence of Retained Foetal Membranes	Binary	Binomial, with probability based on background herd proportion
Occurrence of Vulval Discharge at less than 21 days in milk	Binary	Binomial, with probability based on background herd proportion
Occurrence of Vulval Discharge at more than 21 days in milk	Binary	Binomial, with probability based on background herd proportion

Occurrence of Cystic Ovarian Disease at more than 42 days in milk	Binary	Binomial, with probability based on background herd proportion
Occurrence of Other Ovarian Abnormality at more than 42 days in milk	Binary	Binomial, with probability based on background herd proportion

4.2.3 Simulation model construction

A stochastic simulation model was constructed in a step wise manner, as described in Figure 4.1. The simulation was constructed using R.4.1.2 (R core Development Team). A total of 500,000 herds were simulated with each herd consisting of 500 lactations. This process was started by drawing both herd level and lactational level values from within their determined distributions. This included not only health events from the previous chapter, but also age structure of the herd and input of the herd's background submission rate and conception rates.

Age structure was included by firstly determining the herd percentage of heifers from a uniform distribution. The proportion of ages of the remainder of the herd was then determined by considering the percentage of heifers and then using the age structure from the original data from chapter 3 to decide the structure of the remainder of the herd from the proportion of cows that were in each lactation for this simulated herd (categorised into lactations 2, 3, 4 and 5 or greater).

The six periparturient and early lactation health events considered to be associated with reproductive performance in the previous logistic regression model (assisted calving, retained foetal membranes, vulval discharge at less than 21 days in milk, vulval discharge at greater than 21 days in milk, cystic ovarian disease at greater than 42 days in milk and other ovarian abnormalities at greater than 42 days in milk) were included as herd level input parameters and draws taken from a uniform distribution of a plausible range.

Herd yield and herd reproductive performance (background herd submission and conception rates that differ between herds and would not otherwise be explained by explanatory variables to the model) were also drawn from uniform distributions across a plausible range.

Once overall herd values were determined, draws for the first lactation for that herd were taken. These were based on binomial distributions (so for example each animal could be affected or unaffected by assisted calving) with the probability of being affected determined by the proportion affected in the background herd level. Individual animal lactation number and milk yield were also drawn from distributions based on background herd level proportions and values respectively. Individual cow yield for that lactation was based around a betapert distribution from the herd’s yield with a range of 3000 litres either side of the herd yield.

The estimates of the association between health event and the probability of pregnancy from chapter two were used to calculate the probability of pregnancy in each 7-day risk period. The lactation proceeded from a voluntary waiting period of 42 days through as many as 37 risk periods, each of 7 days. The lactation was thus simulated to one of two end points- either pregnancy or 300 days in milk. Cows that reached 300 days in milk were therefore determined to be empty and considered equivalent to a cow culled for failure to conceive.

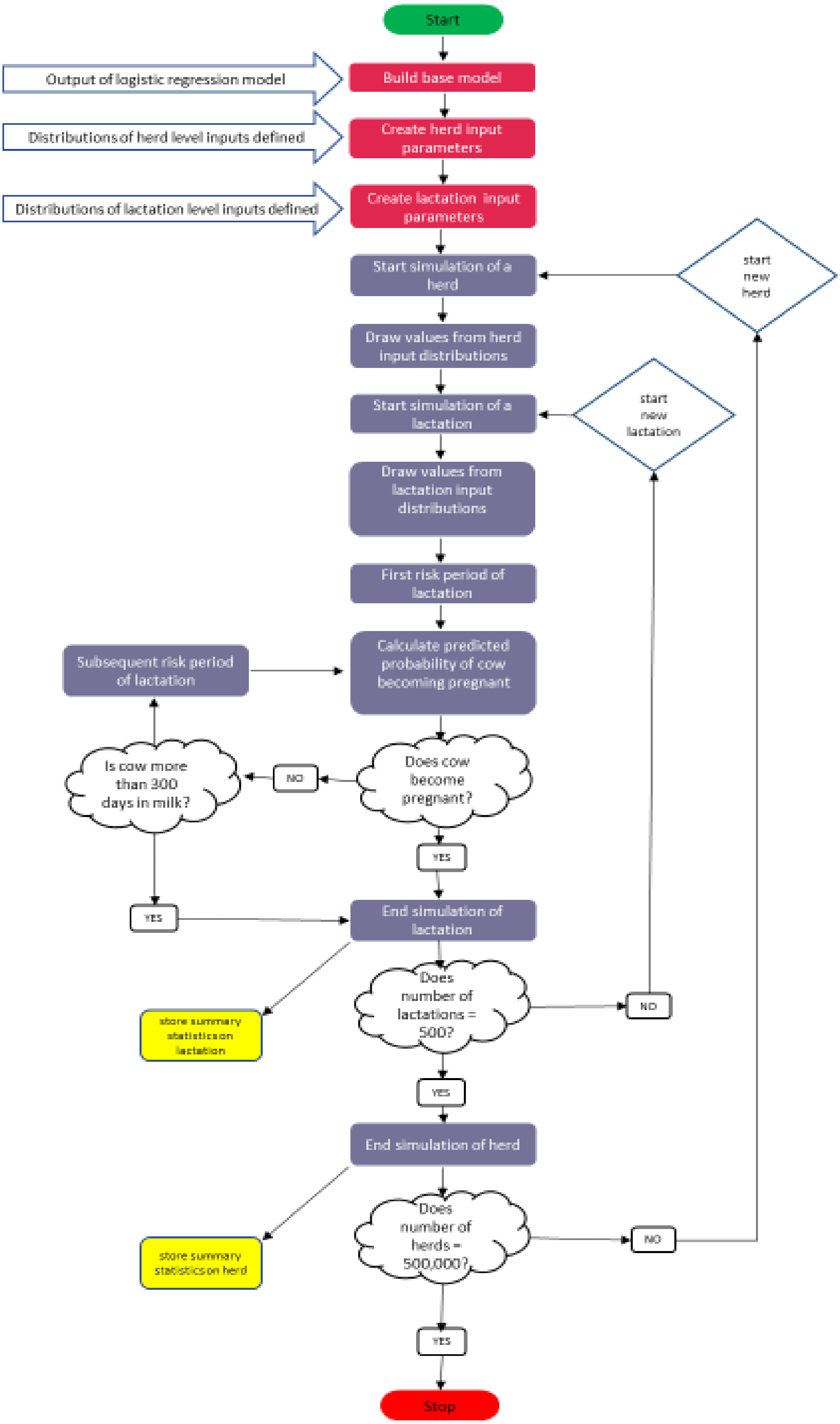

Figure 4.1 Overview of simulation model process.

4.2.4 Recording of outcomes

A summary of each lactation was collected with reproductive performance outcomes- a binary outcome of pregnancy, a binary outcome of failure to conceive, the calving interval for that cow (calculated as days to conception +281) and the number of eligible 7 day blocks for each cow, as well as lactation inputs. After 500 lactations were simulated, the herd data were stored with a summary of inputs and outcomes as an average from the 500 lactations.

On completion of each herd, and after summary statistics were recorded, a further herd was simulated. Simulations proceeded until summary data were recorded for each of 500,000 herds. For each herd 21 day pregnancy rate was calculated from the number of pregnancies and the number of eligible 7 day blocks. In order to determine whether the number of simulated herds was adequate, subsets of the full simulation model output were taken and the estimates and errors from the regression models of a series of subsets and the full model output were compared. Since results with 250,000 herds were very similar to those from the full dataset, it was concluded that increasing the number of simulated herds to more than 500,000 was unlikely to increase the validity and robustness of the results.

4.2.5 Analysis of results

Information about the association between model inputs and outcome were initially illustrated using high density scatterplots which were presented in a group to contrast the varying associations between inputs on outcomes. Spearman rank correlation coefficients further illustrated the non-parametric correlations between the variables. A multiple regression model was constructed from the summary output from the stochastic model. This was used to partition variance in 21-day pregnancy rate between herd input parameters and to predict the effect of changes in the input variables. A tornado plot illustrated the predicted change in 21-day pregnancy rate when changing each input from median to upper quartile of its distribution, while keeping the other input variables at their median values. These changes again allowed a visual contrast between varying associations between inputs on reproductive performance.

4.3 Results

4.3.1 Distribution of inputs and outcomes

The simulation was run for 500 lactations for 500,000 herds and input distributions were designed to explore very thoroughly a large range of plausible input values. This can be seen in Figure 4.2, which demonstrates the values of herd inputs that were recorded alongside summary reproductive performance for each herd. The input values demonstrated in these histograms are from uniform distributions. The individual points that were included are a mean value from each of the 500 lactations that make up each of the simulated herds.

Despite being from uniform distributions, the histogram bins are not of even height throughout. This is as a result of a relatively small herd size of 500 cows, resulting in a limited number of values the input can take. For example, 1 case from the 500 cows would equate to 0.002, 2 cases would equate to 0.004, 3 cases would equate to 0.006. This explains the blocky nature of some of the histograms, which is a circumstance of where the breaks between histogram bins fall- for example some bins would contain both 0.02 and 0.04, whilst the next bin would only have 0.06, and therefore the second histogram bin would appear lower than the first, despite the uniform distribution.

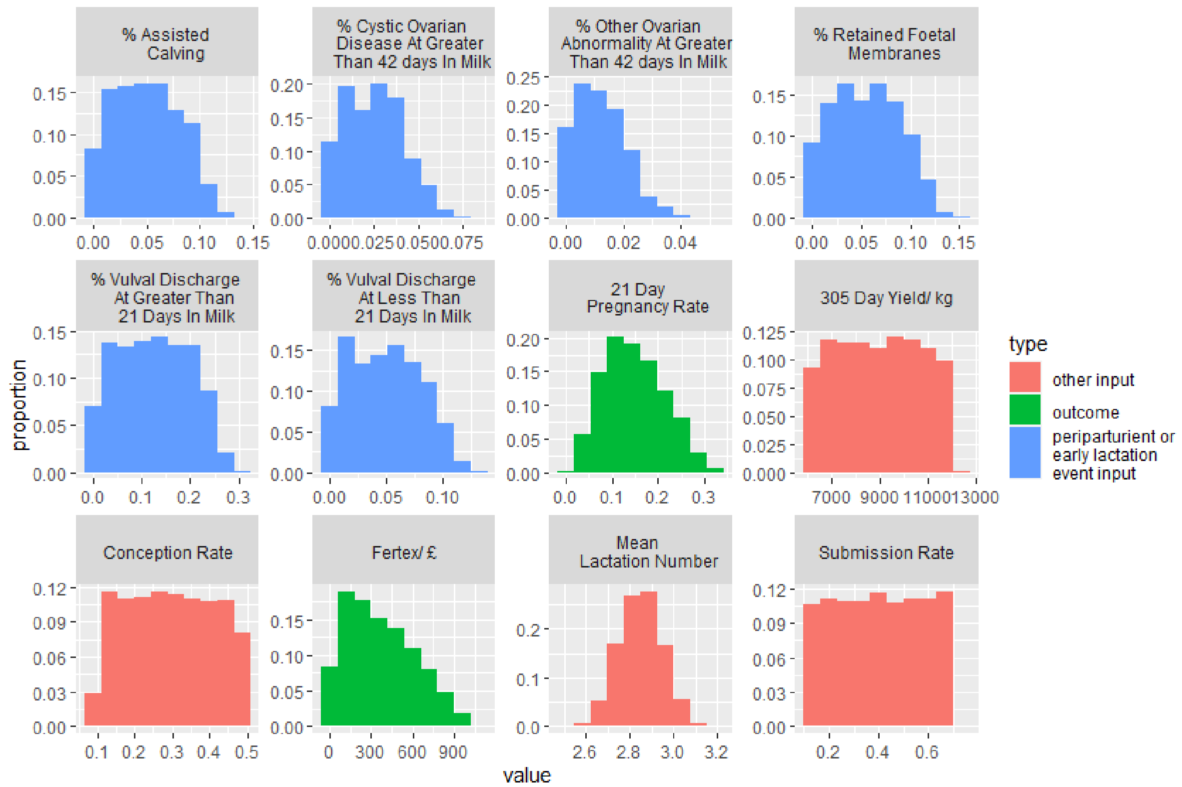

Figure 4.2 Histograms showing proportion of herds with mean value of input parameters across the range of distribution of inputs and illustration of the distribution of 21 day pregnancy rates as outcomes across 500,000 simulated herds

4.3.2 Association between variables and outcomes

High density scatterplots and corresponding Spearman rank correlation coefficients (rs) demonstrating the relationship between herd level input parameters and herd 21 day pregnancy rate are shown in Figure. 4.3. These show a very weak negative correlation between the 6 periparturient and early lactation health parameters and the outcome variable. This can be seen by a square appearance to the point densities with no distinct concentration of dark colours. Of the 6 events, vulval discharge diagnosed at greater than 21 days in milk showed the strongest negative correlation with the outcome, but there was very little appearance of concentration of points to the bottom right of the scatter plot. Milk yield showed a similar concentration of dark coloured density with a very slight pattern of an increased concentration of results in the bottom right corner and a weak negative Spearman rank correlation of -0.105, representing a very small decrease in reproductive performance with increasing yield.

In contrast, both submission rate and conception rate showed a strong positive correlation with 21 day pregnancy rate, as shown by Spearman rank correlation coefficients of 0.627 (conception rate) and 0.726 (submission rate). Although the high density scatterplots reflect this, with herds with low submission and conception rates having low 21 day pregnancy rates and herds with high submission and conception rates having high 21 day pregnancy rates, there is a pronounced difference with herds with low input variables and a low outcome being more concentrated than those with high input variables. In addition, this concentrated effect is more pronounced for submission than conception, suggesting a closer association between low submission and low performance than between low conception and low performance.

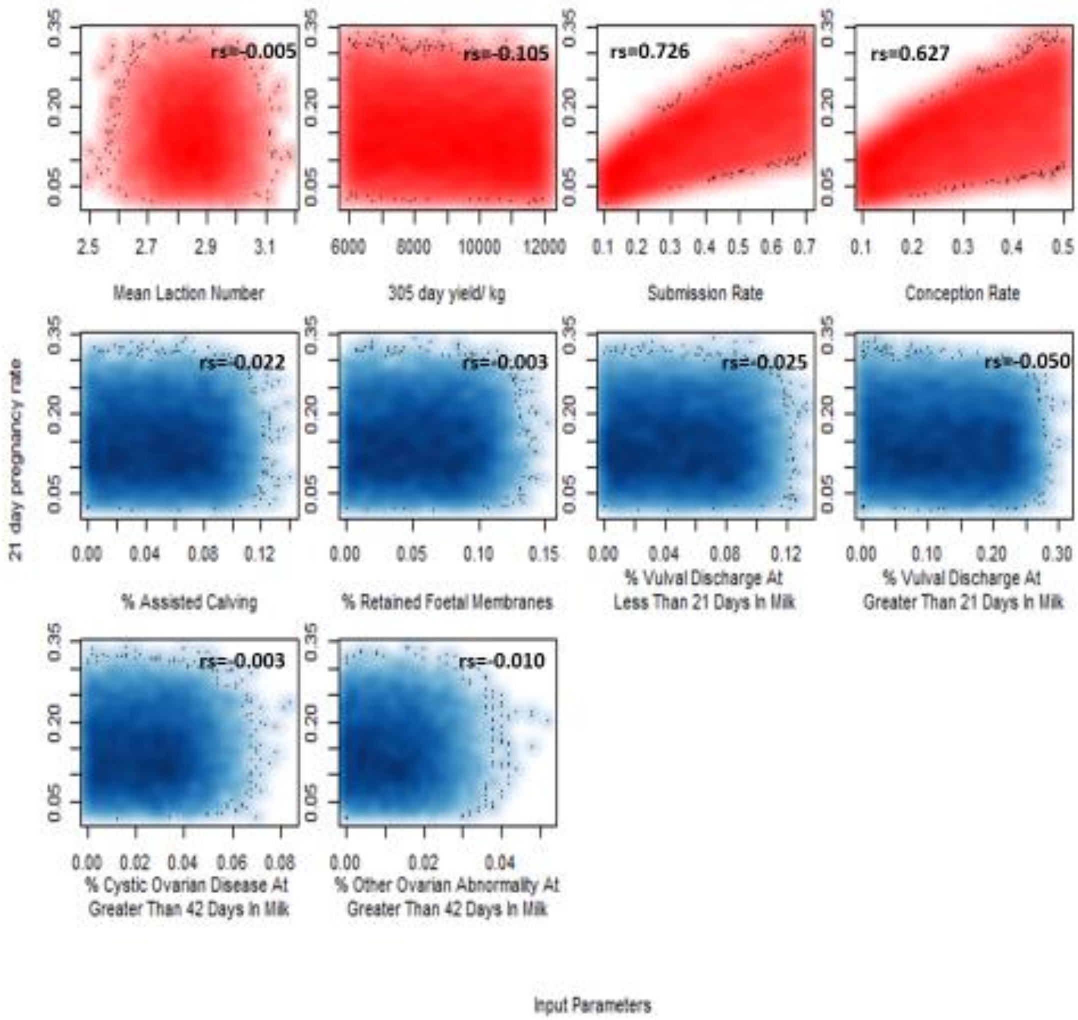

Figure 4.3 High density scatterplots showing associations between herd-level input variables and herd 21 day pregnancy rate from 500,000 simulated herds.
Darker colours equate to higher concentration of data points. rs= Spearman rank correlation coefficient

4.3.3 Multiple regression analysis

The results of partition of variance using regression analysis are shown in Table 4.2. Each individual line of the table reflects the proportion of variance in 21 day pregnancy rate that is explained by each individual input, when also considering the variation explained by the other inputs. It can be seen that a huge proportion (over 93%) of variance was explained by a combination of submission and conception rates and a tiny proportion (just over 0.5%) by periparturient and early lactation events. Of these health events, variance partitioned by vulval discharge diagnosed at greater than 21 days explained the highest figure at 0.424%.

Table 4.2 Output of regression model and partition of variance in 21 day pregnancy rate between input parameters

Input parameter	**Regression coefficient**	**Standard Error**	**% Variance Explained**
Mean Lactation Number	-0.010	0.001	0.023%
% Assisted Calving	-0.015	0.005	0.005%
% Retained Foetal Membranes	-0.032	0.004	0.027%
% Vulval Discharge at Less than 21 Days In Milk	-0.024	0.005	0.013%
% Vulval Discharge at Greater than 21 Days In Milk	-0.057	0.002	0.424%
% Cystic Ovarian Disease At Greater Than 42 Days In Milk	-0.062	0.009	0.023%
% Other Ovarian Abnormality At Greater Than 42 Days In Milk	-0.097	0.016	0.018%
305 Day Yield/ kg	0.000	0.000	1.226%
Submission Rate	0.269	0.001	52.992%
Conception Rate	0.356	0.001	40.910%
TOTAL			**95.662%**

The predicted effects of changing input variables on 21 day pregnancy rate are illustrated in the tornado plot in fig 4.4. Changing to upper quartile submission and conception rates had a much larger impact on herd 21-day pregnancy rate than changes to periparturient event distributions. Of these, uterine disease had the largest impact (a predicted increase of 0.293% in the outcome), with nearly equivalent predicted effects from vulval discharge diagnosed before 21 days in milk and after 21 days in milk. This demonstrates that a combined increase in early uterine disease from 5% to 7.5% of lactations, and of later uterine disease from 12.5% to 18.75% of lactations would be expected to reduce 21 day pregnancy rate by a relatively small amount. In contrast, an increase in 21 day submission rate from 40% to 55% would be expected to increase 21 day pregnancy rate by more than 4%. The results of this modelling clearly demonstrate that health events around calving and early lactation have a small effect on herd reproductive performance compared to background submission rate and background conception rate.

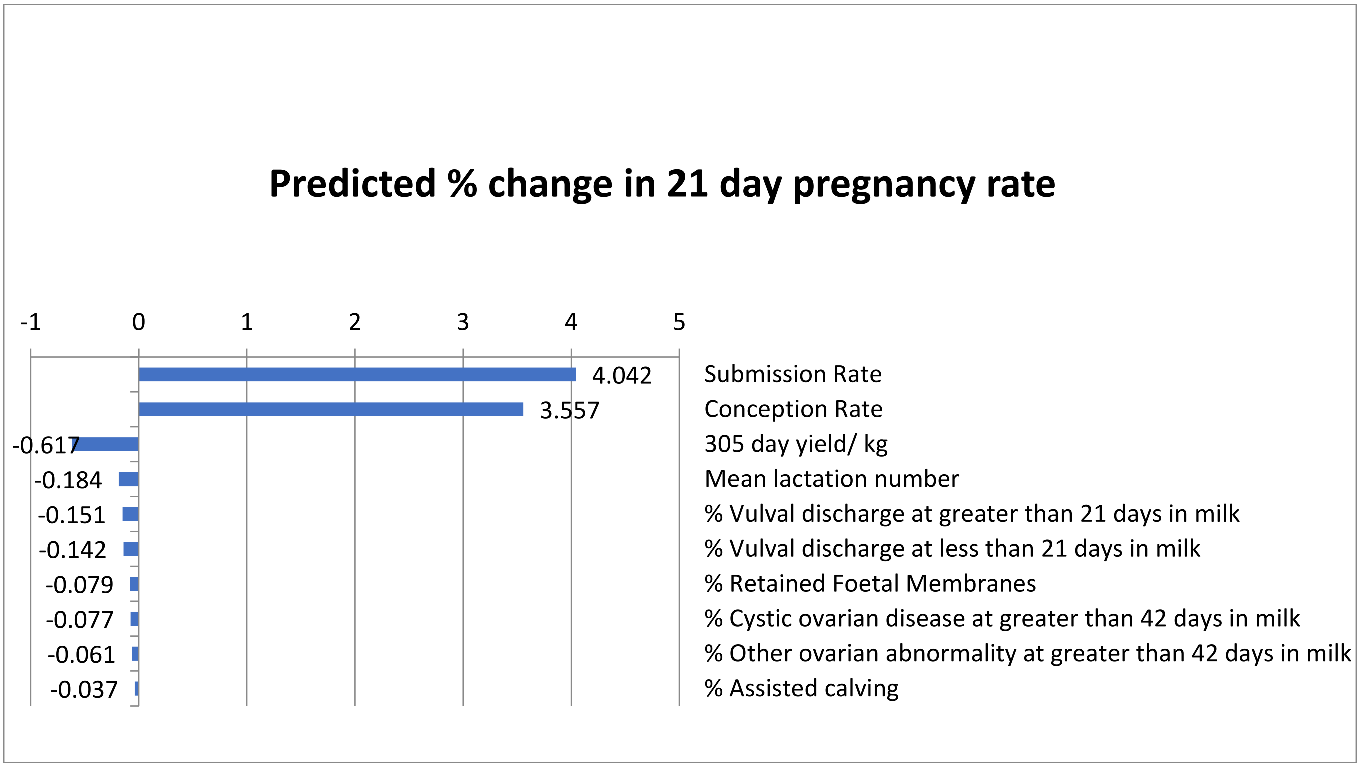

Figure 4.4 Tornado plot showing predicted percentage change in 21 day pregnancy rate with 25% increase in value of input parameter from the median value to the upper quartile (UQ) of its input distribution while other input parameters remain unchanged at the median values of their input distributions.
The input parameters are listed at the right of the plot and the change in the distributions from median to UQ are listed below. For example, the predicted effect of moving from a proportion of lactations affected by vulval discharge at greater than 21 days in milk of 12.5% (the median of the input distribution) to 18.75% (the UQ of the input distribution) would be a decrease in herd 21 day pregnancy rate of 0.151%.

Submission Rate (median 40% to UQ 55%)

Conception Rate (30% to 40%)

Mean lactation number (2.825 to 3.0125)

% Vulval discharge at greater than 21 days in milk (12.5% to 18.75%)

% Vulval discharge at less than 21 days in milk (5% to 7.5%)

% Retained Foetal Membranes (5% to 7.5%)

% Cystic ovarian disease at greater than 42 days in milk (2.5% to 3.75%)

% Other ovarian abnormality at greater than 42 days in milk (1.25% to 1.875%)

% Assisted calving (5% to 7.5%)

305 day yield/ kg (9,000 to 10,500)

4.3.4 Investigation of extreme input values

The kernel density plots shown in Figure 4.5 further demonstrate the weak association between periparturient and early lactation health events and reproductive performance. Similarly they also show the strong association between submission and conception rates and 21 day pregnancy rate. The red and blue lines in these plots represent extreme ends of a range of clinically plausible values. Where the 2 lines follow a very similar shape, there is an indication that values from different ends of the input distribution result in little difference in reproductive performance.

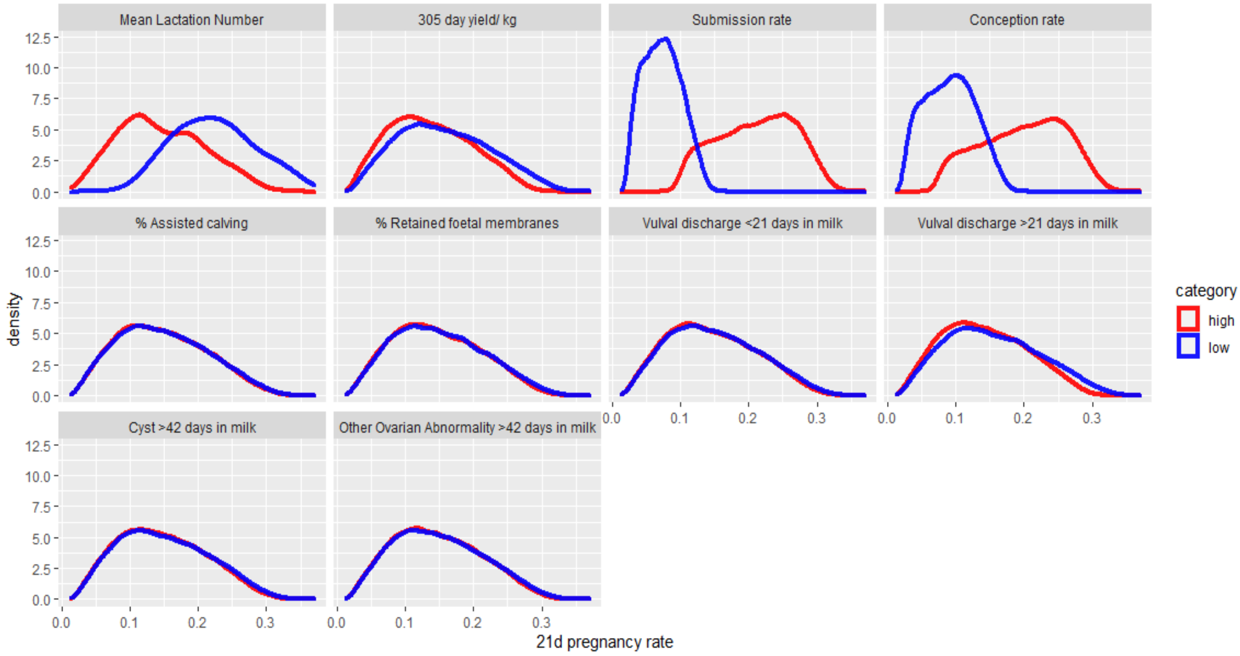

Figure 4.5 Kernel density plots showing density of herd 21 day pregnancy rates associated with extreme high or low input parameter values
The red and blue lines indicate high and low input values respectively. The input parameters with high and low input values are listed below:

Mean lactation number (low less than 2.5 and high more than 3.1)
305 day yield/ kg (less than 7,000 and more than 11,000)
Submission Rate (less than 20% and more than 60%)
Conception Rate (less than 20% and more than 40%)
% Assisted calving (less than 1% and more than 9%)
% Retained Foetal Membranes (less than 1% and more than 9%)
% Vulval discharge at less than 21 days in milk (less than 1% and more than 9%)
% Vulval discharge at greater than 21 days in milk (less than 2% and more than 20%)
% Cystic ovarian disease at greater than 42 days in milk (less than 0.5% and more than 4%)
% Other ovarian abnormality at greater than 42 days in milk (less than 0.25% and more than 2%)

Very little difference can be seen between high and low levels in the middle and bottom rows for the health events. As previously described, vulval discharge diagnosed greater than 21 days in milk showed the biggest association with a difference in 21 day pregnancy rate detectable for herds with an incidence of less than 2% compared to greater than 20%. In contrast herds with very low submission and conception rates have a very clearly lower 21 day pregnancy rates than herds with very high rates, and these herds also have a much tighter distribution of 21 day pregnancy rates (as indicated by higher peaks in density of the blue lines in these plots).

4.4 Discussion

Periparturient and early lactation events have been associated with impaired reproductive performance at an individual cow level, with literature supporting large effects of cases of uterine diseases, ovarian diseases and retained foetal membranes on the subsequent fertility of affected cows. For example, endometritis was found to increase calving to conception interval by between 28 and 70 days by three studies (Leblanc 2002, Barrett 2009, Giuliodori 2013). Cystic ovarian disease was found to increase calving to conception interval by between 64 and 77 days by three studies (Borsberry 1989, Kim 2005, Cattaneo 2015). Retained foetal membranes were found to increase calving to conception interval by between 5 and 22 days by three studies (Emanuelson 1998, Esslemont 2002, Hayes 2012). These effects were confirmed in chapter 2 with reduced model predictions of probabilities of pregnancy by 100 days of lactation for endometritis, cystic ovarian disease and retained foetal membranes of 20%, 22% and 11%.

Use of this simulation model demonstrated that these events are unlikely to have a substantial impact on herd level reproduction under most typical farm scenarios. The association between herd periparturient and early lactation events and herd reproductive performance is strong but of a small effect size despite strong associations and effects between the events and reproduction at a lactation level. A huge proportion (over 93%) of variance from the regression model was explained by a combination of submission and conception rates and a tiny proportion (just over 0.5%) by periparturient and early lactation events. Farmers assessing their own herd reproductive performance may consider that improvements to other factors that improve submission rate and conception rate would be of greater benefit to overall performance than reductions in the incidence of periparturient and early lactation health events.

Of these health events, variance partitioned by vulval discharge diagnosed at greater than 21 days explained the highest figure at 0.424%, which was more than 80% of the variance partitioned by all of the events. This finding is in contrast to individual cow level associations between fertility and periparturient and early lactation disease, where, as discussed above, cystic ovarian disease is often found to have a comparable effect on an individual affected cow.

A common criticism of stochastic simulation modelling is that unjustified assumptions are often made about parameter input distributions. The use of clinical judgement to determine input variable ranges is used commonly. The inputs for both the herds and lactations used in this simulation model were drawn from a distribution of values decided upon by the author. The use of clinical judgement to determine input ranges is also a common criticism of the technique of stochastic simulation (Corlu 2020). It is possible that the selected ranges of distributions were not representative and that this could influence the outcome of the work.

There was no requirement in this instance for the overall distribution of the output value of the simulation model to be representative of a real situation- for example a realistic estimate of the total lost reproductive performance in a particular herd or to replicate the 21 day pregnancy rate of all 12,000 UK dairy herds. If that were required it may be important to ensure that the input distributions were representative. But in order to thoroughly explore the relationships between inputs and outcome, some of the more extreme ends of the input distribution also need exploring thoroughly. It was considered more important to explore all possible combinations of inputs to particularly develop a knowledge of rarer combinations of events (such as herds with very high or low rates for any inputs).

The model simulated 500,000 herds and sensitivity analysis was performed to assess whether increasing this number would change the output. It was found that there was no difference between the results of regression models created from this dataset and from randomly selected smaller subsets of it. However, further sensitivity analysis may have included further assessments of distributions, such as comparing the output when normal rather than uniform distributions were used, or by narrowing or widening the range of input distributions.

High levels of reproductive performance are vital when attempting to maximise efficiency on dairy farms but assessing which areas around this topic to alter in order to improve this performance can be difficult, due to the multifactorial nature of the process. This chapter has highlighted that it is essential to consider all potential explanatory variables to avoid exaggerated inference of an association.

Detailed knowledge exists in many corners of the literature surrounding dairy cow fertility but bringing together these areas to achieve clarity on the most important factors influencing levels of reproductive performance can be challenging. This simulation model could be supplemented and further developed to assess the association between further herd level inputs and reproduction. This will require inputs from further studies investigating different factors and may ultimately allow farmers to rank alternative investments that could improve their herds.

Chapter 5 Evidence synthesis in dairy cow reproduction and contextualisation using stochastic modelling

5.1 Introduction

This chapter brings together data synthesised in chapters 2 and 3 and utilises similar methods to those used in chapter 4; using stochastic simulation modelling to create a large dataset for further analysis. Data from this simulation were then used to create a regression model to explore associations between a large range of factors thought to impact reproductive performance and 21 day pregnancy rate. Chapter 5 expands the previous chapters and brings conclusions, by adding results from existing literature to allow more potential interventions or factors to be considered, with the objective of putting the factors into an appropriate context.

Reproduction in dairy cattle remains a complex area with many possible variables influencing potential improvements in performance. It encompasses a large scope of biological and agricultural systems and influences on it can include complex technology, detailed management and large background information on genetics. Attempts to determine the extent of individual influences on performance at cow and herd level are common in the literature of this area, but decisive attempts to assess the magnitude of associations in relation to each other are much rarer.

Attempts to discuss the complex nature of the interaction between potential variables can also be found in the literature. It is recognised that this is an area in which contextualisation has proved difficult (Hudson 2011), with Mee (2012) suggesting it to be a 'wicked problem'. 'Wicked problems' (in contrast to 'tame problems') were first discussed in 1973 when discussing difficulties over transport policy. They are thought to be issues characterised by a lack of consensus over the solution, hampered by a lack of scientific progress to allow resolution, a lack of a set goal and set rules of how to achieve the goal, they persist as problems and are constantly redefined by parties attempting to solve them from different directions (Mee 2012, Coyne 2005, Rittel 1973).

There are a number of studies that have attempted to rank explanatory variables on their association with reproductive performance (Loefler 1999, Schefers 2010, Caraviello 2006, Fodor 2018). These have used a variety of statistical methods including logistic regression models, machine learning algorithms and survey questionnaires.

Bringing together evidence sources and the construction of models using these sources has been proposed when looking to improve dairy cow reproductive performance (Crowe 2018) and attempts made to implement these techniques (McNamara 2013). Simulation has been utilised to explore relationships in reproduction in dairy cows, with the aim of presenting a range of outcomes with probabilities of occurrence attached as a result of herd management techniques as explanatory variables (Archer 2015). The cost of reproductive losses as a result of various scenarios has been simulated (Meadows 2005, Bekara 2019).

The use of a large range of evidence sources of various types (including expert opinion and quantitative data) to provide inputs for complex stochastic models using Bayesian methods has been discussed with regard to infectious diseases in humans for some decades. This has particularly involved planning for epidemics and mapping their progression, with reference to HIV and influenza widespread in the literature (Birrell 2018, De Angelis 2014, Ratmann 2012). This has extended to cattle infectious disease outbreaks and mapping of epidemics. This has particularly encompassed Foot and Mouth Disease outbreaks in the UK (Pomeroy 2017).

This chapter describes the use of PSA to weave together these techniques and attempt to rank a series of inputs on their level of association with reproductive performance. In doing so, it attempts to draw meaningful conclusions from information presented in earlier chapters and put context to a complex issue which has considerable economic importance to the UK dairy industry.

5.2 Materials and Methods

5.2.1 Sources of inputs into stochastic model

Various sources of data were used to supply inputs to the simulation model used in this chapter. The explanatory variables that were significantly associated with reproductive performance from the random effects discrete time survival regression model described in chapter 2 were used to investigate periparturient and early lactation disease. A regression model created using a large dataset of 312 herds described in Hudson (2018) was used to give the probability of pregnancy at different days in milk, parity and yield. Further explanatory variables were provided from summary relative risks and confidence intervals from chapter three. These explanatory variables were used as input parameters for the stochastic simulation model described in this chapter (Table 5.1).

5.2.2 Description of distributions of input variables

The types of variable and distributions from which values were drawn are shown in Table 5.1. Input values were drawn from uniform distributions considered plausible and thought to be encompassing a typical range of values for the majority of UK herds. The ranges were not expected to represent true herd distributions, but to allow a full range of plausible scenarios so that the relationship between health events and management decisions, and reproductive performance could be fully explored. Both herd level inputs and risk period within each lactation level inputs were drawn from distributions based on the herd level parameters.

Table 5.1 Input parameters used at each level of simulation and distributions from which inputs were drawn.

Input variable	Type	Input distribution
Herd level		
Submission rate (proportion of eligible cows inseminated every 21 days)	Continuous	Uniform (0.4, 0.65)
Conception rate (proportion of inseminations leading to a pregnancy)	Continuous	Uniform (0.35, 0.45)
Herd average 305 day milk yield (kg)	Continuous	Uniform (6000, 12000)
Proportion of herd which are first lactation	Continuous	Uniform (0.2, 0.3)
Proportion of lactations affected by Johne's Disease	Continuous	Uniform (0., 0.2)
Proportion of 7 day risk periods affected by High THI	Continuous	Uniform (0, 0.2)
Proportion of lactations affected by Retained Foetal Membranes	Continuous	Uniform (0., 0.1)
Proportion of lactations affected by Vulval Discharge at less than 21 days in milk	Continuous	Uniform (0., 0.1)
Proportion of lactations affected by Vulval Discharge at more than 21 days in milk	Continuous	Uniform (0, 0.3)
Proportion of lactations affected by Cystic Ovarian Disease at more than 42 days in milk	Continuous	Uniform (0, 0.1)
Proportion of lactations affected by subclinical ketosis	Continuous	Uniform (0.02, 0.5)
Proportion of lactations following a long dry period	Continuous	Uniform (0, 0.2)
Proportion of lactations following a high age at first calving	Continuous	Uniform (0, 1)
Use of fixed time AI	Binary	Binomial (0, 1)
Use of activity monitors	Binary	Binomial (0, 1)
Use of fertility index	Binary	Binomial (0, 1)
Herd with high level of uncontrolled BVD virus	Binary	Binomial (0, 1)
Lactation level		
Lactation number	Categorical (1, 2, 3, 4, $>$ 4)	Multinomial, based on proportion of herd in lactation 1 from herd inputs and remainder of herd split across lactations in same proportions as observed data

305 day milk yield (kg)	Continuous	Betapert, centred on herd average, draws in range +/- 3000kg
Occurrence of Subclinical Ketosis	Binary	Binomial, with probability based on background herd proportion
Occurrence of Long Dry Period	Binary	Binomial, with probability based on background herd proportion
Occurrence of High Age at First Calving	Binary	Binomial, with probability based on background herd proportion
Occurrence of Retained Foetal Membranes	Binary	Binomial, with probability based on background herd proportion
Occurrence of Vulval Discharge at less than 21 days in milk	Binary	Binomial, with probability based on background herd proportion
Occurrence of Vulval Discharge at more than 21 days in milk	Binary	Binomial, with probability based on background herd proportion
Occurrence of Cystic Ovarian Disease at more than 42 days in milk	Binary	Binomial, with probability based on background herd proportion
Occurrence of Johne's Disease	Binary	Binomial, with probability based on background herd proportion
Risk period level		
Occurrence of High THI day	Binary	Binomial, with probability based on background herd proportion

5.2.3 Simulation model construction

A stochastic simulation model was constructed in a step wise manner (this followed a similar process to Figure 4.1 in chapter four, with a large number of herds of 500 cows simulated following draws from pre-defined herd and lactation inputs). The simulation was constructed using R.4.1.2 (R core Development Team). A total of 640,000 herds were simulated with each herd consisting of 500 lactations. This process was started by drawing both herd level and lactational level values from within their determined distributions. This included health events from chapter two, age structure of the herd, input of the herd's background submission rate and conception rates and herd management and health events from which data was synthesised in chapter three.

Age structure was included by firstly determining the herd percentage of heifers from a uniform distribution. The proportion of ages of the remainder of the herd was then determined by considering the percentage of heifers and then using the age structure from the original data from chapter two to decide the structure of the remainder of the herd from the proportion of cows that were in each lactation for this simulated herd (categorised into lactations 2, 3, 4 and 5 or greater).

The four periparturient and early lactation health events with the largest associations with reproductive performance that were elucidated in Chapter four (retained foetal membranes, endometritis, metritis and cystic ovarian disease) were included as herd level input parameters and draws taken from a uniform distribution of a clinically plausible range. Herd yield and herd reproductive performance (submission rate and conception rate) were also drawn from uniform distributions across a clinically plausible range. Five continuous variables from Chapter 3 (prevalences of Johne's disease, heifers calving old, long dry periods, subclinical ketosis and proportion of high THI days) were included as explanatory variables and draws taken from uniform distributions of plausible ranges. Four binary variables from Chapter 3 (herd BVD status, use of fixed time AI, use of activity monitors and use of a genetic fertility index for bull selection) were included and draws taken from a binomial distribution.

Once overall herd values were determined, draws for the first lactation for that herd were taken. These were based on binomial distributions (so for example each animal could be affected or unaffected by retained foetal membranes) with the probability of being affected determined by the proportion affected in the background herd level. Individual animal lactation number and milk yield were also drawn from distributions based on background herd level proportions and values respectively. Individual cow yield for that lactation was based around a betapert distribution from the herd's yield with a range of 3000 litres either side of the herd yield.

The estimates of the association between explanatory variables and the probability of pregnancy from chapters 2 and 3 were used to calculate the probability of pregnancy in each 7-day risk period. The lactation proceeded from a voluntary waiting period of 42 days through as many as 37 risk periods, each of 7 days. The lactation was thus simulated to one of two end points- either pregnancy or 300 days in milk. Cows that reached 300 days in milk were therefore determined to be empty and considered equivalent to a cow culled for failure to conceive.

5.2.4 Recording of outcomes

A summary of each lactation was collected with reproductive performance outcomes- a binary outcome of pregnancy, a binary outcome of failure to conceive, the calving interval for that cow (calculated as days to conception +281), the number of eligible 7 day blocks for each cow and the number of inseminations, as well as lactation inputs. After 500 lactations were simulated, the herd data was stored with a summary of inputs and outcomes as an average from the 500 lactations. On completion of each herd, and after summary statistics were recorded, a further herd was simulated. Simulations proceeded until summary data was recorded for each of 640,000 herds. Summaries of this data are presented in Table 5.2, illustrating summary statistics and confirming the explanatory variables and reproductive outcomes involved with the initial stochastic model for this chapter. For each herd, 21 day pregnancy rate was calculated from the number of pregnancies and the number of eligible 7 day blocks.

Table 5.2 Summary of herd input explanatory variables and stochastic model outcomes

Variable	Number of herds	Mean	Standard Deviation	Median	Minimum	Lower Quartile	Upper Quartile	Maximum
Herd Input Explanatory Variables								
Proportion of Heifers	640000	0.250	0.029	0.250	0.200	0.225	0.275	0.300
305 day yield/ ‘000 kg	640000	9.003	1.731	9.003	6.000	7.505	10.500	12.000
Submission Rate	640000	0.525	0.072	0.525	0.400	0.462	0.588	0.650
Conception Rate	640000	0.400	0.029	0.400	0.350	0.375	0.425	0.450
Prevalence of Subclinical Ketosis	640000	0.260	0.138	0.260	0.020	0.140	0.380	0.500
Prevalence of High Age at First Calving	640000	0.500	0.288	0.500	0.000	0.250	0.749	1.000
Prevalence of Long Dry Periods	640000	0.100	0.058	0.100	0.000	0.050	0.150	0.200
Use of Fertility Index	640000	0.500	0.500	0.000	0.000	0.000	1.000	1.000
Herd BVD status	640000	0.501	0.500	1.000	0.000	0.000	1.000	1.000

Prevalence of Johne's Disease	640000	0.100	0.058	0.100	0.000	0.050	0.150	0.200
Proportion of High THI days	640000	0.100	0.058	0.100	0.000	0.050	0.150	0.200
Prevalence of Retained Foetal Membranes	640000	0.050	0.029	0.050	0.000	0.025	0.075	0.100
Prevalence of Endometritis	640000	0.150	0.087	0.150	0.000	0.075	0.225	0.300
Prevalence of Metritis	640000	0.050	0.029	0.050	0.000	0.025	0.075	0.100
Prevalence of Cysts	640000	0.050	0.029	0.050	0.000	0.025	0.075	0.100
Use of Fixed Timed AI	640000	0.499	0.500	0.000	0.000	0.000	1.000	1.000
Use of Activity Monitors	640000	0.499	0.500	0.000	0.000	0.000	1.000	1.000
Reproductive Performance Outcomes								
Number of Inseminations	640000	1417.182	173.300	1403.000	893.000	1290.000	1531.000	2285.000
Calving Interval	640000	405.866	9.449	406.063	368.825	399.300	412.600	440.710
Number of Failures to Conceive	640000	45.617	23.979	42.000	0.000	27.000	60.000	180.000
Number of eligible 7 day blocks	640000	7473.629	1171.792	7423.000	3763.000	6621.000	8275.000	12414.000

Number of pregnancies	640000	454.383	23.979	458.000	320.000	440.000	473.000	500.000
21 day pregnancy rate	640000	0.188	0.039	0.185	0.078	0.160	0.214	0.397

5.2.5 Analysis of results

Information about the association between model inputs and outcome were initially illustrated using high density scatterplots for continuous input variables and box and whisker plots for binary input variables which were presented in a group to contrast the varying associations between inputs on outcomes. Spearman rank correlation coefficients further illustrated the non-parametric correlations between the variables.

A multiple regression model was constructed from the summary output from the stochastic model. This was used to partition variance in 21-day pregnancy rate between herd input parameters and to predict the effect of changes in the input variables. Qualitative sensitivity analysis was performed to assess the relative influence of each input (as described by Pianosi 2016). A tornado plot illustrated the predicted change in 21-day pregnancy rate when changing each input by an amount deemed to be reasonably comparable, while keeping the other input variables at their median values. These changes allowed a visual contrast between varying associations between inputs on reproductive performance.

In order to determine whether a sufficient number of iterations of the simulation had been performed, subsets of the full simulation model output were taken and the estimates and errors from the regression models of a series of subsets were compared. Since results with 320,000 herds were very similar to those from the full dataset, it was considered unlikely that including a larger number of iterations would materially change the results.

5.3 Results

5.3.1 Association between input variables and outcomes

High density scatterplots demonstrating the relationship between continuous herd level input parameters and herd 21 day pregnancy rate and box and whisker plots demonstrating the relationship between binary herd level input parameters and herd 21 day pregnancy rate are shown in Figure 5.1. Spearman rank correlation coefficients are shown within Table 5.3.

Submission rate and conception rate show a strong positive correlation with 21 day pregnancy rate, with highest point density on the bottom left of the scatterplots (indicating the highest correlation between herds with low submission rates and low 21 day pregnancy rates). There is a very clear pattern of changing colours on the plots as rates increase with increasing 21 day pregnancy rate, with this increase being more marked for submission than conception. This is also reflected in the respective Spearman rank correlations (with high values for both but considerably more marked for submission (0.623) than conception (0.313)). This suggests a closer association between lower submission and lower 21 day pregnancy rate than between lower conception and lower 21 day pregnancy rate.

Milk yield had a strong negative correlation with reproductive performance, with the red and orange colours on the scatterplot (reflecting density of herds) being concentrated to the bottom right of the plot. This intensity of herds showed an even more marked (yet inverse) pattern to submission rate, with a high density of herds over 10,000 litres with lower than average 21 day pregnancy rates.

The remaining 9 scatterplots all show that the input variables have a much lower correlation with reproductive performance than the 3 inputs described above. The point density appears constant as the prevalence on the x axis increases. The most obvious asymmetry to the plots are for subclinical ketosis and to a lesser extent for endometritis where increasing prevalence shows a decrease in 21 day pregnancy rate. This is also reflected in Spearman coefficients of -0.181 and -0.094 respectively.

All four of the dual box and whisker plots show a difference between the two values of the input variables. This is most marked for the use of activity monitors, where there is a clear increase in 21 day pregnancy rate in herds where activity monitors were used. Smaller but still visually apparent differences between the two plots for the use of a fertility index and for the use of fixed time AI can be seen, with use of these management techniques in herds being associated with increased 21 day pregnancy rates. There is also a difference between the 2 plots for BVD, with the herds with lower 21 day pregnancy rates being those with uncontrolled BVD virus in the herd (coded 1) compared to herds naïve to BVD (coded 0).

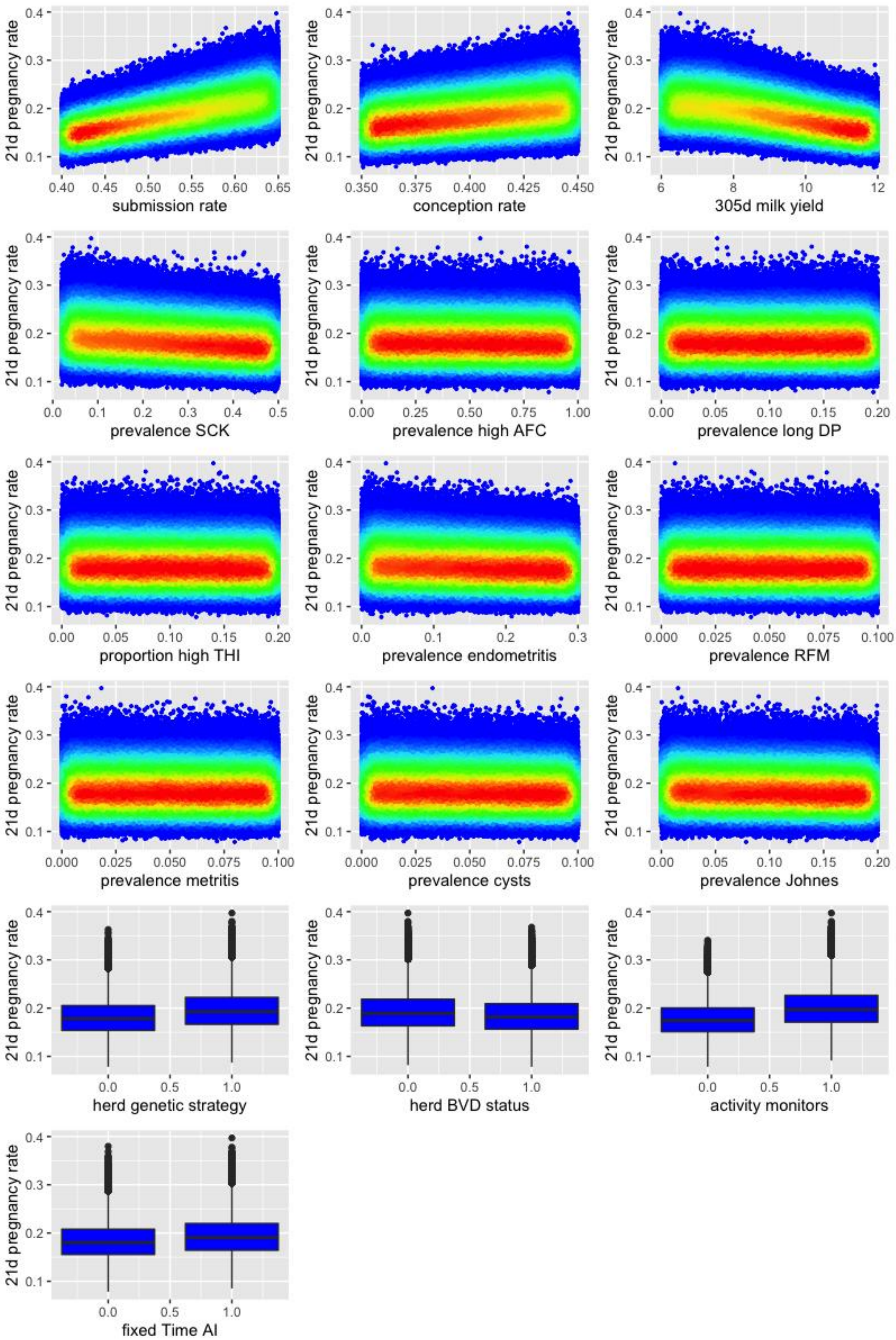

Figure 5.1 High density scatterplots and box and whisker plots showing associations between herd-level input variables and herd 21 day pregnancy rate from 640,000 simulated herds.

In the case of the high density scatterplots warmer colours represent highest point density (with a reducing scale from red to yellow to green to blue)

5.3.2 Multiple regression analysis

The results of partition of variance using regression analysis are shown in Table 5.3. Each individual line of the table reflects the proportion of variance in 21 day pregnancy rate that is explained by each individual input, when also considering the variation explained by the other inputs. A large proportion (73.3%) of variance was explained by a combination of submission and conception rates and milk yield. A much smaller combined percentage (20.3%) of variance was explained by the other 13 explanatory variables. Of these, the biggest variance in the model is explained by the use of activity monitors (8.6%), the use of a genetic fertility index (3.6%) and the prevalence of subclinical ketosis (3.5%).

Table 5.3 Spearman rank correlation coefficients and output of regression model and partition of variance in 21 day pregnancy rate between input parameters

Input parameter	Spearman Rank Correlation Coefficient	Regression coefficient	Standard Error	% Variance Explained
Submission Rate	0.623	0.337	0.000172	38.181
Conception Rate	0.313	0.441	0.000430	10.438
305 day yield/ kg	-0.497	-0.011	0.000007	24.690
Prevalence of Subclinical Ketosis	-0.181	-0.054	0.000090	3.546
Prevalence of High Age at First Calving	-0.026	-0.004	0.000043	0.086
Prevalence of Long Dry Periods	-0.011	-0.007	0.000215	0.012
Proportion of High THI days	-0.022	-0.018	0.000215	0.068
Use of Activity Monitors	0.284	0.023	0.000025	8.648
Use of Fixed Timed AI	0.127	0.010	0.000025	1.728
Prevalence of Endometritis	-0.094	-0.046	0.000143	1.024
Prevalence of Retained Foetal Membranes	-0.012	-0.019	0.000430	0.020
Prevalence of Metritis	-0.013	-0.018	0.000430	0.018
Prevalence of Cysts	-0.033	-0.049	0.000429	0.132
Herd BVD status	-0.099	-0.008	0.000025	1.040
Prevalence of Johne's Disease	-0.058	-0.041	0.000215	0.360

Use of Fertility Index	0.182	0.015	0.000025	3.598
TOTAL				93.590

The predicted effects of changing input variables on 21 day pregnancy rate are illustrated in the tornado plot in Figure 5.2. Changing to upper quartile background submission and conception rates (the herd level variation in submission and conception rates unexplained by all the other model inputs) and lower quartile herd milk yield had a much larger impact on herd 21-day pregnancy rate than changes to a number of the inputs that represented variables the farmer may consider investigating, such as the majority of the periparturient events and lactations following long dry periods or prolonged heifer rearing periods.

However, there were a number of the input variables represented by health or management factors that could be changed by a farmer that did compare with the impact of the causes of unspecified contributors to submission and conception rates on 21 day pregnancy rate. These included the use of activity monitors, the use of fixed time AI, the use of the fertility index to select bulls and the control of BVD virus. All of these inputs are predicted to increase 21 day pregnancy rate by between 0.75% and 2.5%.

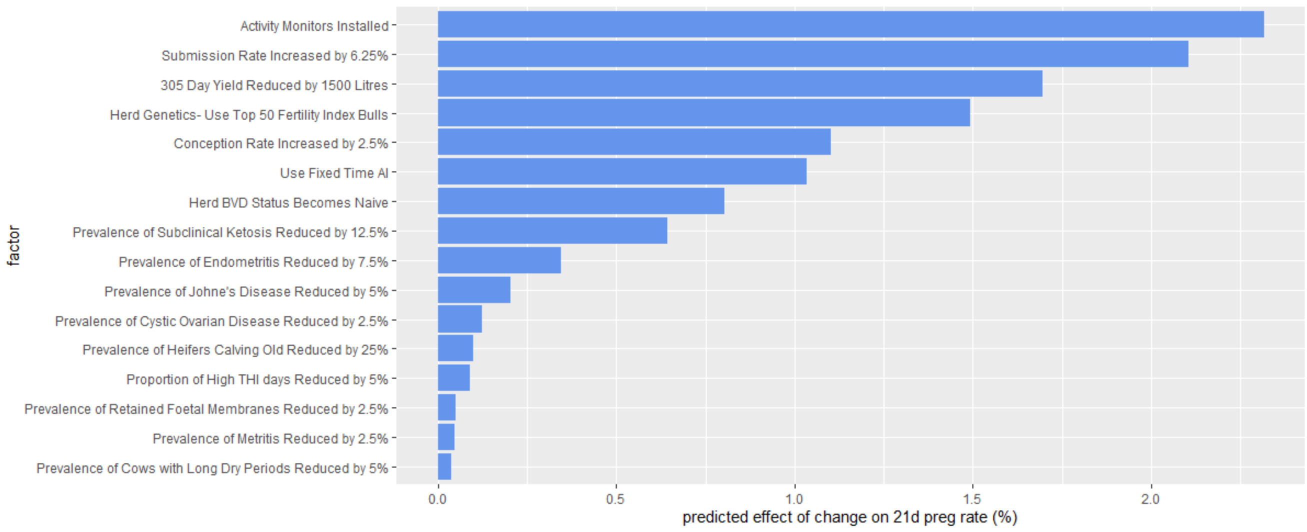

Figure 5.2 Tornado plot showing predicted percentage change in 21 day pregnancy rate with 25% change in value of continuous input parameter from the median value of its input distribution or with change from false to true in binary variables, while other input parameters remain unchanged at the median values of their input distributions.

The change in the input parameters are listed at the left of the plot and the values that the inputs were changed from and changed to are listed below.

For example, the predicted effect of changing from a herd 305 day yield of 9000 litres (the median of the input distribution) to 7500 litres (the lower quartile of the input distribution) would be an increase in herd 21 day pregnancy rate of approximately 1.7%.

Use of Activity Monitors (0 to 1)
Submission Rate (52.5% to 58.75%)
305 day yield/ kg (9,000 to 7,500)
Use of Fertility Index (0 to 1)
Conception Rate (40% to 42.5%)
Use of Fixed Timed AI (0 to 1)
Herd BVD status (1 to 0)
Prevalence of Subclinical Ketosis (26% to 14%)
Prevalence of Endometritis (15% to 7.5%)
Prevalence of Johne's Disease (10% to 5%)
Prevalence of Cystic Ovarian Disease (5% to 2.5%)
Prevalence of High Age at First Calving (50% to 25%)
Proportion of High THI days (10% to 5%)
Prevalence of Retained Foetal Membranes (5% to 7.5%)
Prevalence of Metritis (5% to 7.5%)
Prevalence of Long Dry Periods (10% to 5%)

5.4 Discussion

Various techniques have been used to measure associations between a large number of factors and reproductive performance in dairy cows. Many of these studies have been able to determine associations between factors such as endometritis and infection with Johne's disease, and fertility at an individual cow level. The use of meta-analysis (often within a broader systematic review) has been able to bring together several studies asking similar research questions to ascertain a summary estimate, often presented as a single relative risk with 95% confidence intervals (Lean 2009).

Other literature has examined association between factors such as infection with BVD virus (Robert 2004) and the use of activity monitors (Neves 2015) and reproduction at a herd level. There have also been attempts to use meta-analysis to bring together several studies to examine association between a factor such as the use of fixed time AI and reproduction at a herd level (Rabiee 2005). However, studies encompassing the whole scope of dairy cow reproduction at a herd level have generally been left to review articles (Cardoso Consentini 2021) which often summarise the factors involved but are unable to quantify their described associations with reproductive performance. In contrast, the findings of this chapter have allowed associations between explanatory variables and reproduction to be quantified and simultaneously put into context against other factors.

Stochastic simulation modelling in Chapter 4 allowed the conclusion that although endemic periparturient diseases had important associations with reproduction at the individual cow level, they had limited associations at the herd level, in contrast to background herd submission and conception rates. Output from the regression model in this chapter allowed a similar conclusion- that a majority of the variance in the model output data could be accounted for by background herd submission and conception rates; that is factors that influence these two determinants of 21 day pregnancy rate that could not be more closely specified.

A more sophisticated stochastic model was used in this chapter, with considerably more input variables. These variables included factors that are likely to influence background submission rates (such as use of automated activity monitors) and background conception rates (such as control of BVD virus) and some that are likely to influence both (such as use of the use of a fertility index for bull selection or prevalence of subclinical ketosis). Partly as a result of this inclusion, the output of partition of variance tables and the shape of the tornado plots in this chapter appear different to those in chapter 4. Variance partitioned by this model into background herd rates has been reduced in proportion and replaced by that partitioned into specified explanatory variables, which may have been part of the unspecified background rates in the previous chapter.

However, there were further differences between the construction of the two models that may help to explain the difference in the partition of variance results. As was discussed in section 4.4, clinical judgements made concerning the range of the chosen distribution may materially alter the output of the simulation model. Since it was determined that a much larger model had been built in this chapter, with a much larger number of explanatory variables, it was considered important (for a given number of iterations of the simulation) to explore the parameter spaces for the other input variables more thoroughly. Therefore, it was decided that it was less important to simulate as full a realistic range of background submission and conception rate values. Since the background submission and conception rate inputs vary so much less than in chapter four, they will inevitably appear to be less important compared to the other inputs to the simulation model.

The model used in this chapter simulated 640,000 herds and sensitivity analysis was performed to assess whether increasing this number would change the output. It was found that there was no difference between the results of regression models created from this dataset and from randomly selected smaller subsets of it. As a further development to this project, and prior to development of a proposed decision support tool, further sensitivity analysis will be performed to further assess different distributions of background submission and conception rates and the distributions of the other explanatory variables. For example, this will allow comparison of the output and partition of variance from regression models using the output, when normal rather than uniform distributions are used, or when the range of input distributions is widened or narrowed.

By partitioning variance in specific areas that farmers and their advisers can readily appreciate and understand, this work has identified, quantified and illustrated factors that are commonly associated with reproductive performance. This allows farmers and their advisers to consider investment decisions with a weight of evidence behind them and some quantifiable expectation of how much this may benefit their unit.

The ultimate aim of the stochastic simulation was to allow contextualisation and quantification of the impact of the many different factors that influence reproductive performance and attempt to show how they fit together. Part of this is to show the amount of impact of each in a way that can be quickly appreciated and the use of a tornado plot to show this can be readily understood. Binary changes at a herd level (such as control of BVD virus and starting to use fixed time AI) can be easily compared in this way and a comparison of two different improvements in 21 day pregnancy rate appreciated quickly.

Unfortunately any changes that affect only a proportion of cows in the herd (such as the incidence of endometritis or subclinical ketosis) cannot be as easily compared using the current graphics as the change of incidence of disease entered on the plot are choices that may ultimately not be universally accepted. To improve this, a tool that allows the user to change various inputs to suit their farm and see the impact will be of much more use.

The work in this chapter has been based around a technique known as probabilistic sensitivity analysis which allows research results to be accounted for, explained and put into the context of other results. This approach also allows answers to be produced based on probabilities, which are intuitive and realistic. It is expected that one of the most practical uses of this research for the agricultural sector will be in the development of decision support tools, an area of increasing interest (Ferchiou 2021).

For example, at any point in time a farmer may be considering their herd's current position on control of BVD virus, the performance of current oestrus detection methods and the effect of heat stress during the summer months, and their combined impact on herd reproductive performance. Results from this chapter could be used within a decision support tool to predict the impact of any management change on 21 day pregnancy rate and thus allow them to make a transparent comparison between any suggested investments or management changes.

The amount of variance from the regression model that was explained by a combination of background unspecified submission and conception rates (48.5%) is much larger than the amount explained by a combination of all of the specified explanatory variables (20.3%). However, this magnitude of difference is very different to the unspecified compared to specified difference in the previous chapter (93% compared to 0.5%).

Of the specified explanatory variables, variance in the model explained by automated activity monitors is 8.6%, genetics and bull choice 3.6% and subclinical ketosis 3.5%. These three factors are all perceived to be areas of interest in the industry. Nutritional management (such as feed presentation and ration content), transition cow management, and the immediate environment of the cow are all likely to influence the incidence of subclinical ketosis and are very regular discussion points and areas where farmers are constantly striving to change and improve. Both the use of bull choices to improve herd fertility and automated activity monitors to improve oestrus detection are developments of the past 10-15 years that are perceived to have contributed to the improvements in the reproductive performance of the national herd in the same time period. These are areas that are considered regularly when farmers are considering what to alter and where to look for improvements. Findings from this chapter suggest that these three areas are important areas for agricultural scientists to continue to investigate- how to further improve cow feeding and comfort, biosensors and software programmes and the reliability of bull genetic profiles.

Ultimately it is hoped that the research findings will make existing knowledge around dairy cow reproduction more accessible to end users and help to improve UK dairy cow reproductive performance as a result.

Chapter 6 Discussion

6.1 Key findings

This project has furthered investigations into the associations between common health events and management decisions made by farmers, and the reproductive performance of their herds. This has been done by both analysing UK herd data using regression modelling and by developing and using a method for rapid evidence review. Evidence synthesis techniques were then used to combine multiple sources of information. Results from both of these techniques were then used within a stochastic simulation model to evaluate the relative importance of the different factors.

Chapter 2 showed significant associations between several important health events that generally occur in the crucial period between calving and the first weeks of lactation, and reproductive performance.

Chapter 3 developed both methods of reviewing evidence and methods to convert between different reproductive parameters. These were then used as inputs to meta-analysis techniques to produce a pooled "result" summarising literature evidence in a number of areas.

Chapter 4 furthered the findings from the logistic regression model in Chapter 2 and explored the context of the periparturient and early lactation events in comparison to herd submission and conception rates, using stochastic simulation. This showed that although relevant to an individual lactation, the health events were less likely to have a substantial impact on reproductive performance at herd level.

Chapter 5 used stochastic simulation to bring together key data from Chapters 2 and 3 to contextualise and assess the impact of a number of events and decisions on reproduction on dairy farms. This established that a number of these factors can have a considerable impact on performance and allowed these impacts to be quantified.

6.2 General discussion of overall project themes

Reproduction sits alongside milk production, calf sales and strategic culling as a key facet of the workings and income generation of a dairy herd. Reproductive parameters can be hard to use and interpret and factors that influence performance can be hard to contextualise and rank. This work has attempted to aid this process in a way that can be visualised and interpreted by farmers and their advisers and establish associations with reproduction that can aid farmers in their decision making and investment choices.

Advisers to farmers are often keen to establish a framework of factors that happen commonly and have a large impact. This research has investigated a proportion of the factors thought to influence reproductive performance, some of which affect as many as 20% of cow lactations (in terms of health events) or are considered daily for cows eligible for insemination (such as oestrus detection).

Reproduction remains a frustration for farmers with attempts to improve performance often perceived to be slow and costly. There does seem to be widespread acceptance that there is room for improvement with very few herds entering performance levels where discussion is required about whether further improvement would be profitable. However, a small improvement has been seen in the performance of the national herd in the past decade and this has motivated farmers that changes can bring benefits and that investment can be cost effective and improve income. It is therefore essential to be able to determine which of many factors are most likely to improve performance, and to estimate by how much. This work aids this by bringing together evidence from many reviewed sources to establish what improvements to 21 day pregnancy rate would be expected across typical herds.

There is considerable evidence from the literature on the associations between a number of periparturient and early lactation health events (that often have a lactational incidence of between 5 and 20%) and reproduction at the level of the individual lactation or insemination (Borsberry 1989, Leblanc 2002, Esslemont 2002). This has established that the health events reduce the probability of pregnancy at an individual lactation level. The use of random effects discrete time survival regression analysis in this project has a number of advantages, not least that many potential confounding variables can be accounted for appropriately and that it allows analysis and presentation of how the relationship between reproduction and disease changes through lactation. This project has supported existing literature using a recent sample of UK herds, establishing lactational incidence figures and the association with pregnancy at points in time for an individual lactation. These results have been illustrated in ways to confirm the impact of the events at various stages of the lactation.

However, when the output of the regression model was used to explore these associations using stochastic simulation modelling of 500,000 herds, it was established that the health events were unlikely to markedly influence reproductive performance at herd level and that other factors were much more substantial influences on herd level reproduction. These were principally herd level factors such as the yield and especially background submission and conception rates.

Farmers are often determined to reduce incidence of retained foetal membranes and uterine and ovarian disease. Population attributable fraction calculations suggest that in rare cases, for example if a herd has very high lactational incidence rates of several of these health events concurrently, that a large reduction in incidences may be accompanied by significant improvement in reproductive performance. In this case a substantial return on financial investment in changes around periparturient and early lactation health may be achieved. However it is likely that any reduction in incidence of these events will perhaps improve the performance of a minority of individual cows but will not improve herd performance markedly and they should look elsewhere when considering where to attempt to improve, and to invest, should improvements in overall herd reproductive performance be their main motivation.

Evidence synthesis has been used extensively to put various studies in context and to attempt to answer complex clinical questions by reviewing and bringing together data from a variety of sources, using study designs such as systematic reviews and techniques such as meta-analysis. This has been done in the field of dairy cow reproduction to aid others contextualise information and answer questions (for example de Boer 2014 performed a systematic review of diagnostic tests for reproductive tract infection and inflammation).

A variety of data from a variety of sources illustrating factors known to be associated with reproductive performance have been brought together in Table 3.14 in Chapter 3. This has allowed summary estimates of the effect of different illustrative scenarios in each of the key areas to be produced, importantly also with a representation of the degree of uncertainty in the research evidence in the summary figures. These intuitive and straightforward numbers can be easily interpreted and allow dairy farmers to determine an estimate of what impact a change to herd management may make on a typical farm, according to evidence from a number of sources in the scientific literature.

Drawing conclusions on overall performance on this information alone still remains challenging since it would remain difficult to compare the impact of changes to factors that influence every risk period in the herd (such as changes to policies on the control of

BVD virus and activity monitors) with changes that apply only to certain cows in the herd (such as changes to the incidence of subclinical ketosis or endometritis). Putting these factors into context, by the use of stochastic modelling allows more understanding of how best to fit potential improvements together.

Using probabilistic techniques and stochastic modelling to illustrate results remains rare in veterinary literature, with studies only becoming more frequent in the last few years (Archer 2015, Bekara 2019, Liang 2017). The use of this technique in this project is thought to aid establishing context between factors that a farmer can influence and invest in. It will avoid over interpretation of research findings from individual studies and therefore avoid the over emphasis on certain health events and management techniques. Complex management decisions can be aided by establishing and illustrating how existing evidence fits together and therefore the likely impact of each factor in context of other factors in reproductive performance in dairy cattle, which remains a complex multifactorial area.

Assimilation of data from literature and attempts to bring it together to provide summaries are commonly done by review articles, often by invitation in order to fill gaps in research knowledge and to help readers to put existing literature into context and help answer clinical questions. These review articles have the advantage of being wide ranging and can allow the author to summarise a large scope, for example an area as large as the factors that influence reproductive performance in dairy cattle (Crowe 2018, Consentini 2021, Walsh 2011, Sheldon 2003, Berry 2016). They have the disadvantage of not quantitatively assessing the data between studies and any assessment of study quality and design remain subjective.

Meta-analysis is a technique that brings together data from several studies and quantitatively summarises it. Meta-analysis is used in review articles as a way of answering a particular scientific question by assessing and weighting the evidence behind it and coming to a single quantitative conclusion that is usually easy for the reader to understand and robust in terms of study design. This technique has been used thoroughly in reproduction in dairy cattle (Rabiee 2005, Abdelli 2017, Fourichon 2000). In terms of widescale evidence gathering, meta-analysis remains an excellent way of answering a specific question. However, since the aim of this project was to effectively bring together a series of questions, it was not possible to find examples of meta-analyses in the veterinary literature that fully answered the question of what steps needed to be taken to improve reproduction in dairy cows. Therefore, a series of different meta-analyses were performed, and further techniques used to integrate their summary estimates.

The use of a combination of evidence gathering and assimilating techniques, inferential statistical modelling and stochastic simulation modelling has allowed this project to contextualise many of the most important factors influencing dairy cow reproductive performance in a way that has not yet been done. It is hoped that these findings will aid farmers and their advisers with information that has not been presented in this way before.

The use of models to support decision making in agriculture is increasing, and with increasing computational power, models are becoming increasingly sophisticated (Ferchiou 2021, Kebreab 2019, Alawneh 2018). As this field continues to develop, it is expected that data from many sources will be integrated to improve descriptive analyses and degree of representation of distributions that act as model inputs. This project has in contrast introduced evidence from literature in lots of related areas of reproduction into the model and allowed the propagation of uncertainty into the model outputs.

Gathering and assessing evidence has been used extensively in human medicine, with systematic reviews including meta-analysis forming an essential part of the evidence required to justify interventions and diagnostic tests on a single topic for the National

Health Service (such as Ilic 2018, Jones 2019). Bringing together evidence sources across a range of topics and then attempting to integrate them would appear to provide powerful weight to support decision making. For example, Yuan 2020, brought together a range of evidence around risk factors for type 2 diabetes and used Multivariable Mendelian randomisation (MR) to assess the importance of one of these risk factors. The use of simulation modelling following meta-analysis techniques is not well represented in the literature with most of the studies in this area in the fields of epidemics in humans such as those caused by influenza and HIV (Birrell 2018, De Angelis 2014) and animals such as caused by Foot and Mouth Disease (Pomeroy 2017). The current project uses a combination of these methods to further research in dairy cow reproduction.

6.3 Limitations of the project

The UK dairy herd is thought to be made up of up to 20% seasonally calving herds and 80% all year round calving herds (Gooderham 2021, Tasker 2017). There are differences in management requirements across the different systems and one of the most discussed differences and motivations for seasonal calving concerns the perception of focussing on one aspect of the calving cycle at a time across the herd, which has substantial implications for reproductive performance. The general perception that overall performance is better in seasonal than all year round herds is supported by few articles (Morton 2010 being one of the few articles to compare the reproductive performance between the two systems directly).

This project has been based around all year round calving systems since they constitute the majority of UK herds. The dairy industry has begun to look at a series of ways of satisfying the different requirements of seasonal herds (for example AHDB now suggest the use of a different fertility index for bull selections) and any future work involving decision support tools may need to consider the different priorities and management of the two systems. This may require the development of a different dataset from a simulation model, or work in parallel with simulation models already created in the area of seasonal calving reproductive performance modelling (Fenlon 2017).

One of the reasons systematic reviews and work involving meta-analyses are considered to rank highly on a scale of hierarchy of evidence of scientific publications is due to the large number of publications involved. This does mitigate the concern about an over reliance on the data and scientific scrupulousness of other individual unknown researchers. The studies contributing to the evidence synthesis chapter 3 were all critiqued for study design and data quality, but this does not allow assessment of publication bias. This 'file drawer' problem (Scargle 2000) occurs when researchers do not publish non-significant findings or those thought to not reinforce a desired argument, preferring only to publish work with large associations or significance. This therefore can lead to the possibility of falsely large effects of interventions and unreliability of results. There are methods to attempt to identify and correct publications bias, including the use of funnel plots to assess where studies may be positioned in terms of their findings (odds ratio) and distribution from central estimate (standard error). However, these plots can also be misinterpreted and analysis of them can be difficult (Sterne 2011).

Extensive attempts were made to ensure only high quality data was used. This included data cleaning of a dataset from 468 UK herds and inclusion criteria for studies that resulted in removal of studies thought to be designed poorly or not including robust results. In some areas, despite often starting investigations with a large dataset, smaller datasets were used in the interests of high quality. This included the use of 25 herd years from 14 herds which were determined to have well recorded periparturient and early lactation health events, despite initially exploring data from 468 herds. A reduction in dataset size can introduce sampling bias, and a concern that the remaining herds are not representative of the original dataset, or of all UK herds, resulting in a different relationship between the events and reproductive performance being established, compared to a typical UK dairy herd.

Assessment of study quality and of robustness of data presentation resulted in the exclusion of large numbers of studies. In some instances, it was no longer possible to explore a topic due to a lack of any suitable studies (for example there were not herd level studies associating Leptospirosis and reproductive performance). In other areas few studies remained within the inclusion criteria and further transformation of published data was required to allow the topic to remain within the study. For example, when assessing the association between THI and reproduction, one large scale study remained suitable and expansion of the published data was required by simulation of the study results.

The inputs for both the herds and lactations to the simulation models were drawn from a distribution of values created by the clinical experience of the author and colleagues. It is possible that the selected ranges of distributions are not representative and that this could influence the outcome of the work. Although the use of clinical judgement to determine input variable ranges is a common method, it is also a common criticism of the technique of stochastic simulation (Corlu 2020).

The majority of the input draws were taken from uniform distributions and therefore no shape was put on the range of values from which values could be drawn and no attempt made to replicate a 'real life' set of values (for example from data from existing herds). This was done intentionally to allow the exploration of all possible combinations of inputs to particularly develop knowledge of rarer combinations of events (such as herds with very high or low rates for any inputs). There was therefore no attempt made to simulate a range of herds with similar 21 day pregnancy rates to the 12,000 UK dairy herds (which would have allowed the opportunity to check our model outputs against sample real life UK herds).

6.4 Extensions of the project

The creation of tools to help answer clinical questions is a natural extension of stochastic simulation and is becoming used more extensively (Rose 2016, Cabrera 2018) to aid farmers in making better evidence based decisions. The use of decision support tools in other health and production areas (Green 2007, Hyde 2017, Hyde 2021) has already proven popular and useful. This approach can be extended into decision making around reproductive performance using the results of this project.

This will allow producers and their advisers to explore the likely impact of a wide range of given interventions (such as BVD vaccination, investment in oestrus detection technology or investment in fans and misting systems) on the reproductive performance of the herd, given the information the farmer already knows (such as current 21 day pregnancy rate, proportion of heifers calving old and incidence of endometritis). The foundations for this method have been laid in earlier published work (Green 2010) but the approach will be extended in this project.

The use of such a decision support tool (Figure 6.1) would allow a farmer to explore a scenario (for example changing the prevalence of subclinical ketosis from 30% to 20%) and be presented with outputs in a simple, intuitive and probabilistic way. Outputs could include a new median predicted herd 21 day pregnancy rate, a likelihood of improvement in fertility performance shown as a percentage and a graph showing the predicted range of outcomes. It would be important to present the likely impact of a given intervention not only as a central (or “most likely”) estimate (as with simpler deterministic decision support tools), but also with a probability of achieving specific levels of 21 day pregnancy rate. It is hoped that this approach will provide a quantitative estimate of the likely change in performance which would result from a given intervention, as well as the degree of certainty associated with this change.

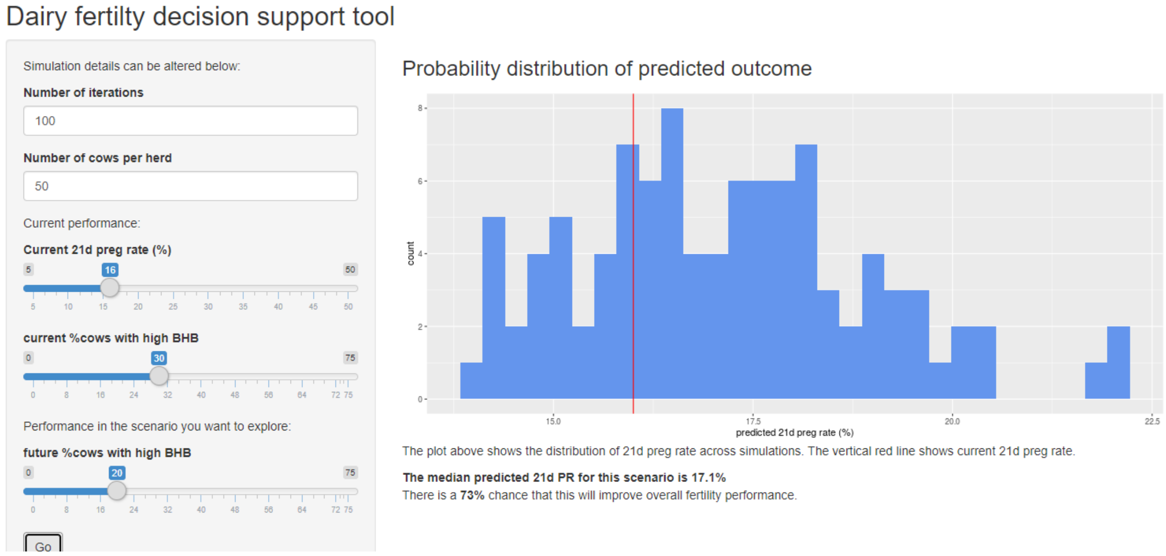

Figure 6.1 Example of dairy fertility decision support tool

As has been discussed in earlier chapters, farm income is often determined by reproductive performance but also importantly by milk production and culling and replacement policies. This work using simulation and support tools may be extended further to investigate associations and investment decisions between the health and management factors already presented, and these vitally important indicators of income. 21 day pregnancy rate has been used as an outcome throughout the project and this is a figure that farmers are increasingly using to summarise their herd's fertility. Extending this interchangeably with outcomes in pounds sterling may also be a useful explanation to aid impact and context.

The events and decisions determined to be most important and those for which evidence was available to allow associations to be explored were included in the results of chapters 3 and 5. Extensions of these areas would be possible and could be considered for further simulation modelling and any further extensions such as support tools. Areas may include the cow's immediate environment (such as feed space and ration presentation, cubicle surface and dimensions), farm environment (such as rainfall or price of concentrate feed) and male factors (such as sperm numbers per straw and use of external company inseminators).

6.5 Conclusions

Reproductive performance is an essential part of the day to day management of UK dairy herds. This project has added to the scientific knowledge of this area, exploring relationships between common factors and performance using established and more novel techniques, and presenting results in simple and interpretable ways. Although substantial between herd variability remains unexplained by factors that were investigated, other substantial associations with reproductive performance have been explained, specified and quantified.

The UK dairy industry continues to face substantial challenges to allowing the individual dairy farmer to sustain an income and way of life. Continuing the improvements in reproductive performance of the national herd made in the last decade are an essential part of confronting these challenges. Scope for improvement remains considerable and it is to be hoped that techniques employed, and results presented here will help to sustain interest and aid decision making.

References

Abdelli, A., Raboisson, D., Kaidi, R., Ibrahim, B., Kalem, A., Iguer-Ouada, M., 2017. Elevated non-esterified fatty acid and β-hydroxybutyrate in transition dairy cows and their association with reproductive performance and disorders: A meta-analysis. Theriogenology 93, 99-104.

Adalsteinsson E., Toumi, M., 2013. Benefits of probabilistic sensitivity analysis - a review of NICE decisions. J Mark Access Health Policy. 6, 1.

AHDB, 2020. Fertility Index Factsheet. [www document]. URL https://media.ahdb.org.uk/media/Default/Imported%20Publication%20Docs/Dairy%20fertility%20genetic%20index%20factsheet.pdf (Accessed 30.12.21).

AHDB, 2021a. UK and EU cow numbers. [www document]. URL https://ahdb.org.uk/dairy/uk-and-eu-cow-numbers AHDB 2021 (Accessed 30.12.21).

AHDB, 2021b. AHDB Available Holstein Bulls. [www document] URL https://breedingdairy.ahdbdigital.org.uk/tables.asp?preview=1&t=SAC_Bull_report_pli_Int_semen_available_HOL&i=1&b=HOL#.Yc5qbWh_rIX (Accessed 30/12/21).

Alawneh, J.I., Henning, J., Olchowy, T.W.J., 2018. Functionality and Interfaces of a Herd Health Decision Support System for Practising Dairy Cattle Veterinarians in New Zealand. Front Vet Sci. 23, 5:21.

Anon, 2021a. The cream of the vegan milk crop- sales of oat milk overtake almond in the UK. Mintel Press Team. [www document]. URL https://www.mintel.com/press-centre/food-and-drink/the-cream-of-the-vegan-milk-crop-sales-of-oat-milk-overtake-almond-in-the-uk (Accessed 30.12.21).

Anon, 2021b. United Kingdom: GDP share of agriculture. [www document]. URL https://www.theglobaleconomy.com/United-Kingdom/share_of_agriculture/ (Accessed 30.12.21).

Anon, 2021c. Historical GHG Emissions. Online climate data platform. [www document]. URL https://www.climatewatchdata.org/ghg-emissions?end_year=2018&source=PIK&start_year=1850. (Accessed 30.12.21).

Archer, S.C., Hudson, C.D., Green, M.J., 2015. Use of Stochastic Simulation to Evaluate the Reduction in Methane Emissions and Improvement in Reproductive Efficiency from Routine Hormonal Interventions in Dairy Herds. PLoS ONE 10(6), e0127846.

Barton, S., 2000. Which clinical studies provide the best evidence? The best RCT still trumps the best observational study. BMJ (Clinical research ed.) 321 (7256), 255–256.

Barrett, A.J., Murray, R.D., Christley, R.M., Dobson, H. Smith, R.F., 2009. Effects of the administration of oxytocin or carbetocin to dairy cows at parturition on their subsequent fertility. Veterinary Record 165, 623-626.

Beaver, A., Meagher, R.K., von Keyserlingk, M.A.G., Weary, D.M., 2019. Invited review: A systematic review of the effects of early separation on dairy cow and calf health. J Dairy Sci. 102 (7), 5784-5810.

Bekara, M.E.A., Bareille, N., 2019. Quantification by simulation of the effect of herd management practices and cow fertility on the reproductive and economic performance of Holstein dairy herds. J Dairy Sci. 102(10), 9435-9457.

Benzaquen, M.E., Risco, C.A., Archbald, L.F., Melendez, P., Thatcher, M.J., Thatcher, W.W., 2007. Rectal Temperature, Calving-Related Factors, and the Incidence of Puerperal Metritis in Postpartum Dairy Cows. J. Dairy Sci. 90, 2804–2814.

Bell, M.J., Roberts, D.J., 2007. Effect of twinning on the feed intake, performance and health of dairy cows. Livestock Science 107, 274–281.

Bello, N.M., Stevenson, J.S., Tempelman, R.J., 2012. Invited review: Milk production and reproductive performance: Modern interdisciplinary insights into an enduring axiom. Journal of Dairy Science 95 (10), 5461-5475.

Berkey, C.S., Hoaglin, D.C., Mosteller, F., Colditz, G.A., 1995. A random-effects regression model for meta-analysis. Stat Med. 14 (4), 395-411.

Berry, D.P., Cromie, A.R., 2009. Associations between age at first calving and subsequent performance in Irish spring calving Holstein–Friesian dairy cows. Livestock Science 123 (1), 44-54.

Berry, D.P., Friggens, N.C., Lucy, M., Roche, J.R., 2016. Milk Production and Fertility in Cattle. Annual Review of Animal Biosciences 4 (1), 269-290

Bicalho, R.C., Galva˜o, K.N., Cheong, S.H., Gilbert, R.O., Warnick, L.D., Guard, C.L., 2007. Effect of Stillbirths on Dam Survival and Reproduction Performance in Holstein Dairy Cows. J Dairy Sci 90, 2797-2803.

Birrell, P.J., De Angelis, D., Presanis, A.M., 2018. Evidence Synthesis for Stochastic Epidemic Models. Statistical science: a review journal of the Institute of Mathematical Statistics 33 (1), 34–43.

Borsberry, S., Dobson, H., 1989. Periparturient diseases and their effect on reproductive performance in five dairy herds. Vet Rec 124, 217-219

Brady, A., 1998. Adjusted population attributable fractions from logistic regression. Stata Tech Bull 42, 8-12.

Britt, J.S., Thomas, R.C., Speer, N.C., Hall, M.B., 2003. Efficiency of converting nutrient dry matter to milk in Holstein herds. Journal of Dairy Science 86, 3796–3801.

Burns, P.B., Rohrich, R.J., Chung, K.C., 2011. The levels of evidence and their role in evidence-based medicine. Plast Reconstr Surg. 128(1), 305-310.

Cabrera, V., 2018. Invited review: Helping dairy farmers to improve economic performance utilizing data-driving decision support tools. Animal 12 (1), 134-144.

Cardoso Consentini, C.E., Wiltbank, M.C., Sartori, R., 2021. Factors That Optimize Reproductive Efficiency in Dairy Herds with an Emphasis on Timed Artificial Insemination Programs. Animals (Basel). 11(2):301.

Caraviello, D.Z., Weigel, K.A., Fricke, P.M., Wiltbank, M.C., Florent, M.J., Cook, N.B., Nordlund, K.V., Zwald, N.R., Rawson, C.L., 2006. Survey of management practices on reproductive performance of dairy cattle on large US commercial farms. J Dairy Sci. 89 (12), 4723-35.

Cattaneo, L., Signorini, M.L., Bertoli, J., Bartolome, J.A., Gareis, N.C., Dıaz, P.U., Bo, G.A., Ortega, H.H. 2014. Epidemiological Description of Cystic Ovarian Disease in Argentine Dairy Herds: Risk Factors and Effects on the Reproductive Performance of Lactating Cows. Reprod Dom Anim 49, 1028–1033.

Chen, J., Gross, J.J., van Dorland, H.A., Remmelink, G.J., Bruckmaier, R.M., Kemp, B., van Knegsel, A.T.M., 2015. Effects of dry period length and dietary energy source on metabolic status and hepatic gene expression of dairy cows in early lactation. Journal of Dairy Science 98, 1033–1045.

Chen, J., Soede, N.M., Remmelink, G.J., Bruckmaier, R.M., Kemp, B., van Knegsel, A.T.M., 2017. Relationships between uterine health and metabolism in dairy cows with different dry period lengths. Theriogenology 101, 8-14.

Chiwome, B., Kandiwa, E., Mushonga, B., Sajeni, S., Habarugira, G., 2017. A study of the incidence of milk fever in Jersey and Holstein cows at a dairy farm in Beatrice, Zimbabwe. Journal of the South African Veterinary Association 88 (0), e1–e6.

Cole, J., VanRaden, P., 2018. Symposium review: Possibilities in an age of genomics: The future of selection indices. J. Dairy Sci. 101, 3686–3701.

Coleman, D.A, Thayne, W.V., Dailey, R.A., 1985. Factors affecting reproductive performance of dairy cows. J Dairy Sci 68, 1793-1803.

Cook, N.B., Ward, W.R., Dobson, H., 2001. Concentrations of ketones in milk in early lactation, and reproductive performance of dairy cows. Vet Rec. 148 (25), 769-72.

Cooke, J., Cheng, Z., Bourne, N., Wathes, D., 2013. Association between growth rates, age at first calving and subsequent fertility, milk production and survival in Holstein-Friesian heifers. Open Journal of Animal Sciences 3, 1-12.

Corlu, C.G., Akcay, A., Xie, W., 2020. Stochastic simulation under input uncertainty: A Review. Operations Research Perspectives 7, 100162

Coyne, R. 2005. Wicked Problems Revisited. Design Studies 26, 5-17.

Crowe, M.A., Hostens, M., Opsomer, G., 2018. Reproductive management in dairy cows - the future. Ir Vet J 71, 1-13.

Dash, S., Chakravarty, A.K., Singh, A., Upadhyay, A., Singh, M., Yousuf, S., 2016. Effect of heat stress on reproductive performances of dairy cattle and buffaloes: A review. Veterinary World 9 (3), 235-244.

De Angelis, D., Presanis, A.M., Conti, S., Ades, A.E., 2014. Estimation of HIV burden through Bayesian evidence synthesis. Statist Sci. 29, 9–17.

de Boer, M.W., LeBlanc, S.J., Dubuc, J., Meier, S., Heuwieser, W,, Arlt, S., Gilbert, R.O., McDougall, S., 2014. Invited review: Systematic review of diagnostic tests for reproductive-tract infection and inflammation in dairy cows. J Dairy Sci. 97 (7), 3983-99.

de la Sota, R.L., Burke, J.M., Risco, C.A., Moreira, F., DeLorenzo, M.A., Thatcher, W.W., 1998. Evaluation of timed insemination during summer heat stress in lactating dairy cattle. Theriogenology 49 (4), 761-70.

Denis-Robichaud, J., Cerri, R.L.A., Jones-Bitton, A., LeBlanc, S.J., 2016. Survey of reproduction management on Canadian dairy farms. J Dairy Sci. 99 (11), 9339-9351.

De Rensis, F., Scaramuzzi, R.J., 2003. Heat stress and seasonal effects on reproduction in the dairy cow: A review. Theriogenology 60, 1139-1151.

Dervishi, E., Zhang, G., Hailemariam, D., Dunn, S.M., Ametaj, B.N., 2016. Occurrence of retained placenta is preceded by an inflammatory state and alterations of energy metabolism in transition dairy cows. J Anim Sci Biotechnol. 26, 7, 26.

de Vries, A., Risco, C.A., 2005. Trends and seasonality of reproductive performance in Florida and Georgia dairy herds from 1976 to 2002. J Dairy Sci. 88(9), 3155-65.

de Vries, M., Zahra, W. A., Wouters, A. P., van Middelaar, C. E., Oosting, S. J., Tiesnamurti, B., Vellinga, T. V., 2019. Entry Points for Reduction of Greenhouse Gas Emissions in Small-Scale Dairy Farms: Looking Beyond Milk Yield Increase. Frontiers in Sustainable Food Systems, 3 [49].

De Vries, A., van Leeuwen, J., Thatcher, W.W., 2019. Economics of Improved Reproductive Performance in Dairy Cattle AN156/AN156, 8/2005, EDIS 2005 (9).

Dhaliwal, G.S., Murray, R.D., Dobson, H., Montgomery, J., Ellis, W.A., 1996. Reduced conception rates in dairy cattle associated with serological evidence of Leptospira interrogans serovar hardjo infection. Vet Rec. 139 (5), 110-114.

Diebold, F.X., 2012. A Personal Perspective on the Origin(s) and Development of 'Big Data': The Phenomenon, the Term, and the Discipline. PIER Working Paper 13-003.

Djemali, M., Freeman, A.E., Berger, P.J., 1987. Reporting of dystocia scores and effects of dystocia on production, days open, and days dry from dairy herd improvement data. J Dairy Sci 70, 2127-2131.

Dobson, H., Smith, R.F., 2000. What is stress, and how does it affect reproduction? Animal Reproduction Science 60–61, 743–752.

Domecq, J.J., Skidmore, A.L., Lloyd, J.W., Kaneene, J.B., 1997. Relationship between body condition scores and conception at first artificial insemination in a large dairy herd of high yielding Holstein cows. J Dairy Sci 80, 113-120.

Dubuc, J., Duffield, T.F., Leslie, K.E., Walton, J.S., LeBlanc, S.J., 2011a. Randomized clinical trial of antibiotic and prostaglandin treatments for uterine health and reproductive performance in dairy cows. J. Dairy Sci. 94, 1325–1338.

Dubuc, J., Duffield, T.F., Leslie, K.E., Walton, J.S., Leblanc, S.J., 2011b. Effects of postpartum uterine diseases on milk production and culling in dairy cows. J Dairy Sci. 94 (3), 1339-46.

Eastham, N.T., Coates, A., Cripps, P., Richardson, H., Smith, R., Oikonomou, G., 2018. Associations between age at first calving and subsequent lactation performance in UK Holstein and Holstein-Friesian dairy cows. PLoS ONE 13 (6), e0197764.

Ehrlich, J.L., 2011. Quantifying shape of lactation curves, and benchmark curves for common dairy breeds and parities. Bovine practitioner 45 (1), 88-95.

El-Tarabany, M.S., 2015. Effects of non-lactating period length on the subsequent calving ease and reproductive performance of Holstein, Brown Swiss and the crosses. Anim Reprod Sci. 158, 60-67.

Emanuelson, U., Oltenacu, P.A., 1998. Incidences and effects of diseases on the performance of Swedish dairy herds stratified by production. J Dairy Sci 81, 2376-2382.

Esslemont, R.J., Kossaibati, M., 2002. DAISY Research Report No. 5: The costs of poor fertility and disease in UK dairy herds - Trends in DAISY herds over 10 seasons. University of Reading, UK.

Esslemont, R.J., 2003. The costs of poor fertility and what to do about reducing them. Cattle Practice 11, 237–250.

Ettema, J.F., Santos, J.E., 2004. Impact of age at calving on lactation, reproduction, health, and income in first-parity Holsteins on commercial farms. J Dairy Sci. 87 (8), 2730-42.

Evans, R.D., Wallace, M., Shalloo, L., Garrick, D.J., Dillon, P., 2006a, Financial implications of recent declines in reproduction and survival of Holstein-Friesian cows in spring-calving Irish dairy herds. Agricultural Systems 89 (1), 165-183.

Evans, R.D., Wallace, M., Garrick, D.J., Dillon, P., Berry, D.P., Olori, V., 2006b. Effects of calving age, breed fraction and month of calving on calving interval and survival across parities in Irish spring-calving dairy cows. Livestock Science 100 (2–3), 216-230.

Fenlon, C., O'Grady, L., Doherty, M.L., Dunnion, J., Shalloo, L., Butler, S.T., 2017. The creation and evaluation of a model predicting the probability of conception in seasonal-calving, pasture-based dairy cows. J Dairy Sci. 100 (7), 5550-5563.

Fenwick, M.A., Fitzpatrick, R., Kenny, D.A., Diskin, M.G., Patton, J., Murphy, J.J. and Wathes, D.C., 2008. Interrelationships between negative energy balance (NEB) and IGF regulation in liver of lactating dairy cows. Domestic Animal Endocrinology 34, 31–44.

Ferchiou, A., Lhermie, G., Raboisson, D., 2021. New standards in stochastic simulations of dairy cow disease modelling: Bio-economic dynamic optimization for rational health management decision-making. Agricultural Systems, 194, 103249.

Fodor, I., Abonyi-Tóth, Z., Ózsvári, L., 2018. Management practices associated with reproductive performance in Holstein cows on large commercial dairy farms. Animal 12(11), 2401-2406.

Fourichon, C., Seegers, H., Malher, X., 2000. Effect of disease on reproduction in the dairy cow: a meta-analysis. Theriogenology 53 (9), 1729-1759.

Fourichon, C., Beaudeau, F., Bareille, N., Seegers, H., 2001. Incidence of health disorders in dairy farming systems in western France. Livestock Production Science 68, 157–170.

Francoz, D., Wellemans, V., Dupré, J.P., Roy, J.P., Labelle, F., Lacasse, P., Dufour, S., 2017. Invited review: A systematic review and qualitative analysis of treatments other than conventional antimicrobials for clinical mastitis in dairy cows. J Dairy Sci. 100 (10), 7751-7770.

Friggens, N.C., Disenhaus, C., Petit, H.V., 2010. Nutritional sub-fertility in the dairy cow: towards improved reproductive management through a better biological understanding. Animal 4 (7),1197-1213.

Fu, X., Lu, L., Huang, X., Wang, Y., Tian, K., Xu, X., Fang, J., Cheng, L., Guo, Z., Tian, Y., 2017. Estimation of Genetic Parameters for 305 Days Milk Yields and Calving Interval in Xinjiang Brown Cattle. Agricultural Sciences, 8, 46-55.

Garcia-Ispierto, I., Lopez-Gatius, F., Bech-Sabat, G., Santolaria, P., Yaniz, J.L., Nogareda, C., De Rensis, F., Lopez-Bejar, M., 2007. Climate factors affecting conception rate of high producing dairy cows in northeastern Spain. Theriogenology 67, 1379-1385.

Garnsworthy, P.C., Sinclair, K.D., Webb, R., 2008. Integration of physiological mechanisms that influence fertility in dairy cows. Animal 2, 1144–1152.

Gerber, P., Vellinga, T. V., Opio, C., Steinfeld, H., 2011. Productivity gains and greenhouse gas emissions intensity in dairy systems*.* Livestock Science*,* 139(1-2), 100-108.

Giuliodori, M.J., Magnasco, R.P., Becu-Villalobos, D., Lacau-Mengido, I.M., Risco, C.A., de la Sota, R.L., 2013. Metritis in dairy cows: risk factors and reproductive performance. J Dairy Sci. 96 (6), 3621-31.

González-Recio, O., Pérez-Cabal, M.A., Alenda, R., 2004. Economic value of female fertility and its relationship with profit in Spanish dairy cattle. J Dairy Sci. 87 (9), 3053-61.

Gooderham, C., 2021. How many block calving herds are there in the country? [www document]. URL https://ahdb.org.uk/news/how-many-block-calving-herds-are-there-in-the-country (accessed 31.12.21).

Grant, M.J., Booth, A., 2009. A typology of reviews: an analysis of 14 review types and associated methodologies. Health Info Libr J. 26 (2), 91-108.

Green, M.J., Leach, K.A., Breen, J.E., Green, L.E., Bradley, A.J., 2007. National intervention study of mastitis control in dairy herds in England and Wales. Veterinary Record 160, 287-293.

Green, M.J., Medley, G.F., Browne, W.J., 2009. Use of posterior predictive assessments to evaluate model fit in multilevel logistic regression. Vet Res. 40 (4), 30.

Green, M.J., Medley, G.F., Bradley, A.J., Browne, W.J., 2010. Management interventions in dairy herds: exploring within herd uncertainty using an integrated Bayesian model. Vet Res. 41 (2), 22.

Guddat, C., Grouven, U., Bender, R., Skipka, G., 2012. A note on the graphical presentation of prediction intervals in random-effects meta-analyses. Syst Rev. 28, 1, 34.

Guitian, J., Thurmond, M.C., Hietala, S.K., 1999. Infertility and abortion among first-lactation dairy cows seropositive or seronegative for Leptospira interrogans serovar hardjo. J Am Vet Med Assoc. 215 (4), 515-8.

Gümen, A., Rastani, R.R., Grummer, R.R., Wiltbank, M.C., 2005. Reduced dry periods and varying prepartum diets alter postpartum ovulation and reproductive measures. Journal of Dairy Science 88, 2401–2411.

Guyatt, G.H., Oxman, A.D., Kunz, R., Vist, G.E., Falck-Ytter, Y., Schünemann, H.J., GRADE Working Group, 2008. What is "quality of evidence" and why is it important to clinicians?.BMJ (Clinical research ed.) 336 (7651), 995–998.

Hagiya, K., Hayasaka, K., Yamazaki, T., Shirai, T., Osawa, T., Terawaki, Y., Nagamine, Y., Masuda, Y., Suzuki, M., 2017. Effects of heat stress on production, somatic cell score and conception rate in Holsteins. Anim Sci J. 88 (1), 3-10.

Han, H., Austin, K. J., Rempel, L. A., Hansen, T. R., 2006. Low blood ISG15 mRNA and progesterone levels are predictive of non-pregnant dairy cows. Journal of Endocrinology 191 (2), 505-512.

Hanks, J., Kossaibati, M., 2010-2020. Key Performance Indicator (KPI) studies of UK dairy herds. [www document] URL https://www.interherdplus.com/annual-kpi-studies/ (accessed 30.12.21)

Hansen, P.J., 2007. Exploitation of genetic and physiological determinants of embryonic resistance to elevated temperature to improve embryonic survival in dairy cattle during heat stress. Theriogenology 68 (1), S242-S249.

Harman, J.L., Griihn, Y.T., Erb, H., Casella, G., 1996. Event-time analysis of the effect of season of parturition, parity, and concurrent disease on parturition-to-conception interval in dairy cows. Am J Vet Res 57, 640-645.

Hayes, E.P.B., Christley, R.M., Dobson, H., 2012. Effects of periparturient events on subsequent culling and fertility in eight UK dairy herds. Vet Rec., 170 (21), 540.

Heuer, C., Healy, A., Zerbini, C., 2007. Economic Effects of Exposure to Bovine Viral Diarrhea Virus on Dairy Herds in New Zealand. Journal of Dairy Science, 90 (12), 5428-5438.

Hossein-Zadeh, G.N., Mohit, A., 2013. Effect of dry period length on the subsequent production and reproduction in Holstein cows. Spanish Journal of Agricultural Research 11 (1), 100-108.

Huang, X., Lin, J., Demner-Fushman, D., 2006. Evaluation of PICO as a knowledge representation for clinical questions. AMIA Annu Symp Proc 2006, 359-63.

Hudson, C., 2011. Understanding the factors affecting dairy cow fertility. Vet Rec. 168 (11), 299-300.

Hudson, C.D., Bradley, A.J., Breen, J.E., Green, M.J., 2012. Associations between udder health and reproductive performance in United Kingdom dairy cows. J Dairy Sci. 95 (7), 3683-97.

Hudson, C.D., Huxley, J.N., Green, M.J., 2014. Using Simulation to Interpret a Discrete Time Survival Model in a Complex Biological System: Fertility and Lameness in Dairy Cows. PLoS ONE 9 (8), e103426.

Hudson, C.D., Bradley, A.J., Breen, J.E., Green, M.J., 2015a. Dairy herd mastitis and reproduction: using simulation to aid interpretation of results from discrete time survival analysis. Vet J. 204 (1), 47-53.

Hudson, C.D., 2015b. Big data and the dairy cow: factors affecting fertility in UK herds. PhD thesis, University of Nottingham. document_url: http://eprints.nottingham.ac.uk/28896/1/Hudson%20PhD%202015.pdf

Hudson, C.D., M.J. Green, M.J., 2018a. Associations between routinely collected Dairy Herd Improvement data and insemination outcome in UK dairy herds. Journal of Dairy Science 101 (12), 11262-11274.

Hudson, C., Kaler, J., & Down, P., 2018b. Using big data in cattle practice. In Practice 40 (9), 396-410.

Hyde, R.M., Remnant, J.G., Bradley, A.J., Breen, J.E., Hudson, C.D., Davies, P.L., Clarke, T., Critchell, Y., Hylands, M., Linton, E., Wood, E., Green, M.J., 2017. Quantitative analysis of antimicrobial use on British dairy farms. Veterinary Record 181, 683-683.

Hyde, R.M., Green, M.J., Hudson, C.D., Down, P.M., 2022. Improving growth rates in preweaning calves on dairy farms: A randomized controlled trial. Journal of Dairy Science 105 (1), 782-792.

Ilic, D., Djulbegovic, M., Jung, J.H., Hwang, E.C., Zhou, Q., Cleves, A., Agoritsas, T., Dahm, P., 2018. Prostate cancer screening with prostate-specific antigen (PSA) test: a systematic review and meta-analysis BMJ 362, k3519.

Ioannidis, J.P.A. 2008. Interpretation of tests of heterogeneity and bias in meta-analysis. Journal of Evaluation in Clinical Practice 14, 951-957.

Jemmeson, A., 2000. Synchronising ovulation in dairy cows with either two treatments of gonadotropin-releasing hormone and one of prostaglandin, or two treatments of prostaglandin. Aust Vet J. 78 (2), 108-11.

Johnson-Ifearulundu, Y.J., Kaneene, J.B., Sprecher, D.J., Gardiner, J.C., Lloyd, J.W., 2000. The effect of subclinical Mycobacterium paratuberculosis infection on days open in Michigan, USA, dairy cows. Prev Vet Med. 46 (3), 171-81.

Jones, N.R., Roalfe, A.K., Adoki, I., Hobbs, F.D.R., Taylor, C.J., 2019. Survival of patients with chronic heart failure in the community: a systematic review and meta-analysis. Eur J Heart Fail. 21 (11), 1306-1325.

Jordan, E.R., 2003. Effects of Heat Stress on Reproduction. Journal of Dairy Science 86, E104 – E114.

Juliano, L., 2018. The Grocer: Synthetic Milk. [www document]. URL https://harris-interactive.co.uk/wp-content/uploads/sites/7/2018/10/Synthetic-Milk-Grocer-Report-FINAL.pdf (Accessed 30.12.21).

Kebreab, E., Reed, K.F., Cabrera, V.E., Vadas, P.A., Thoma, G., Tricarico, J.M., 2019. A new modeling environment for integrated dairy system management. Anim Front. 9 (2), 25-32.

Key, T.J., Appleby, P.N., Crowe, F.L., Bradbury, K.E., Schmidt, J.A., Travis, R.C., 2014. Cancer in British vegetarians: updated analyses of 4998 incident cancers in a cohort of 32,491 meat eaters, 8612 fish eaters, 18,298 vegetarians, and 2246 vegans. The American Journal of Clinical Nutrition 100 (S1), 378S–385S.

Kim, K.D., Ki, K.S., Kang, H.G., Kim, I.H., 2005. Risk factors and the economic impact of ovarian cysts on reproductive performance of dairy cows in Korea. Journal of Reproduction and Development 51 (4), 491-498.

Kitchin, R., 2013. Big data and human geography: Opportunities, challenges and risks. Dialogues in Human Geography 3 (3), 262–267.

Kitchin R,. McArdle, G., 2016. What makes Big Data, Big Data? Exploring the ontological characteristics of 26 datasets. Big Data & Society 3 (1).

Krpálková, L., Cabrera, V.E., Vacek, M., Stípková, M., Stádník, L., Crump, P., 2014a. Effect of prepubertal and postpubertal growth and age at first calving on production and reproduction traits during the first 3 lactations in Holstein dairy cattle. J Dairy Sci. 97 (5), 3017-27.

Krpálková, L., Cabrera, V.E., Kvapilík, J., Burdych, J., Crump, P., 2014b. Associations between age at first calving, rearing average daily weight gain, herd milk yield and dairy herd production, reproduction, and profitability, Journal of Dairy Science 97 (10), 6573-6582.

Kuhn, M.T., Hutchison, J.L., Norman, H.D., 2006. Effects of length of dry period on yields of milk fat and protein, fertility and milk somatic cell score in the subsequent lactation of dairy cows. J Dairy Res. 73 (2), 154-62.

Kuhn, M.T., Hutchison, J.L., Norman, H.D., 2007. Dry period length in US Jerseys: characterization and effects on performance. J Dairy Sci. 90 (4), 2069-81.

Lean, I.J., Rabiee, A.R., Duffield, T.F., Dohoo, I.R., 2009. Invited review: Use of meta-analysis in animal health and reproduction: methods and applications. J Dairy Sci. 92 (8), 3545-65.

LeBlanc, S.J., Duffield, T.F., Leslie, K.E., Bateman, K.G., Keefe, G.P., Walton, J.S., Johnson, W.H., 2002. Defining and diagnosing postpartum clinical endometritis and its impact on reproductive performance in dairy cows. J Dairy Sci. 85 (9), 2223-36.

LeBlanc, S., 2007. Economics of improving reproductive performance in dairy herds. Adv. Dairy Technol. Vol 19, Advances in Dairy Technology 19, 201–214.

LeRoy, C.N.S., Walton, J.S., LeBlanc, S.J., 2018. Estrous detection intensity and accuracy and optimal timing of insemination with automated activity monitors for dairy cows. J Dairy Sci. 101 (2), 1638-1647.

Liang, D., Arnold, L.M., Stowe, C.J., Harmon, R.J., Bewley, J.M., 2017. Estimating US dairy clinical disease costs with a stochastic simulation model. J Dairy Sci., 100(2), 1472-1486.

Loeffler, S.H., de Vries, M.J., Schukken, Y.H., 1999. The effects of time of disease occurrence, milk yield, and body condition on fertility of dairy cows. J Dairy Sci. 82 (12), 2589-2604.

Lombard, J.E., Garry, F.B., McCluskey, B.J., Wagner, B.A., 2005. Risk of removal and effects on milk production associated with paratuberculosis status in dairy cows. J Am Vet Med Assoc. 227 (12), 1975-81.

Lopez, H., Satter, L.D., Wiltbank, M.C., 2004. Relationship between level of milk production and estrous behavior of lactating dairy cows. Anim. Reprod. Sci. 81, 209–223.

López-Gatius, F., Santolaria, P., Mundet, I., Yániz, J.L., 2005. Walking activity at estrus and subsequent fertility in dairy cows. Theriogenology 63 (5), 1419-29.

Lucy, M.C., 2001. Reproductive loss in high-producing dairy cattle: Where will it end? J. Dairy Sci. 84, 1277-1293.

Lucy, M.C., 2019. Symposium review: Selection for fertility in the modern dairy cow—Current status and future direction for genetic selection. J. Dairy Sci. 102, 3706–3721.

Lupton, D., 2015. The thirteen Ps of big data. The Sociological Life. [www document]. URL https://simplysociology.wordpress.com/2015/05/11/the-thirteen-ps-of-big-data/ (Accessed 30.12.21).

Lynch, J., Cain, M., Frame, D., Pierrehumbert, R., 2021. Agriculture's Contribution to Climate Change and Role in Mitigation Is Distinct From Predominantly Fossil CO_2-Emitting Sectors. Front Sustain Food Syst. 3, 4:518039.

Ma, L.L., Wang, Y.Y., Yang, Z.H., Huang, D., Weng, H., Zeng, X.T., 2020. Methodological quality (risk of bias) assessment tools for primary and secondary medical studies: what are they and which is better? Mil Med Res. 7 (1), 7.

Mangurkar, B.R., Hayes, J.F., Moxley, J.E., 1984. Effects of calving ease-calf survival on production and reproduction in Holsteins. J Dairy Sci 67, 1496-1509.

Mansournia, M.A., Altman, D.G., 2018. Population attributable fraction. BMJ 360, k757.

Marcé, C., Beaudeau, F., Bareille, N., Seegers, H., Fourichon, C., 2009. Higher non-return rate associated with Mycobacterium avium subspecies paratuberculosis infection at early stage in Holstein dairy cows. Theriogenology, 71 (5), 807-816.

Markusfeld, 0., Galon, N., Ezra, E., 1997. Body condition score, health, yield and fertility in dairy cows. Vet Rec 141, 67-72.

Marshall, I.J., Marshall, R., Wallace, B.C., Brassey, J., Thomas, J., 2019. Rapid reviews may produce different results to systematic reviews: a meta-epidemiological study. J Clin Epidemiol. 109, 30-41.

Marques, O., Veronese, A., Merenda, V.R., Bisinotto, R.S., Chebel, R.C., 2020. Effect of estrous detection strategy on pregnancy outcomes of lactating Holstein cows receiving artificial insemination and embryo transfer. J Dairy Sci. 103 (7), 6635-6646.

McArt, J.A., Nydam, D.V., Oetzel, G.R., Overton, T.R., Ospina, P.A., 2013. Elevated non-esterified fatty acids and β-hydroxybutyrate and their association with transition dairy cow performance. Vet J. 198(3), 560-70.

McDougall, S. 2001. Effects of periparturient diseases and conditions on the reproductive performance of New Zealand dairy cows. New Zealand Veterinary Journal 2001 49 (2), 60-67.

McGowan M.R., Kirkland P.D., Richards S.G., Littlejohns, I.R., 1993. Increased reproductive losses in cattle infected with bovine pestivirus around the time of insemination. Vet Rec. 133 (2), 39-43.

McGuirk, B., Going, I., Gilmour, A., 1998. The genetic evaluation of beef sires used for crossing with dairy cows in the UK 1. Sire breed and non-genetic effects on calving survey traits. Animal Science 66 (1), 35-45.

McGuirk, B., Going, I., Gilmour, A., 1999. The genetic evaluation of UK Holstein Friesian sires for calving ease and related traits. Animal Science 68 (3), 413-422.

McKevitt, F., 2021. Britain's most chosen dairy brands. [www document]. URL https://www.kantar.com/uki/inspiration/fmcg/britains-most-chosen-dairy-brands (Accessed 30.12.21)

McNamara, J.P., Shields, S.L., 2013. Reproduction during lactation of dairy cattle: Integrating nutritional aspects of reproductive control in a systems research approach, Animal Frontiers 3 (4), 76–83.

Meadows, C., Rajala-Schultz, P.J., Frazer, G.S., 2005. A spreadsheet-based model demonstrating the nonuniform economic effects of varying reproductive performance in Ohio dairy herds. J Dairy Sci. 88 (3), 1244-54.

Mee, J.F. 2012. Reproductive issues arising from different management systems in the dairy industry. Reprod Domest Anim. 47 (S5), 42-50.

Mellado, M., Reyes, C., 1994. Associations between periparturient disorders and reproductive efficiency in Holstein cows in northern Mexico. Prev Vet Med 19, 203-212.

Michaelis, I., Burfeind, O., Heuwieser, W., 2014. Evaluation of oestrous detection in dairy cattle comparing an automated activity monitoring system to visual observation. Reprod Domest Anim. 49 (4), 621-628.

Microsoft Corporation, 2018. Microsoft Excel. URL https://office.microsoft.com/excel.

Miwa, M., Thomas, J., O'Mara-Eves, A., Ananiadou, S., 2014. Reducing systematic review workload through certainty-based screening. J Biomed Inform. 51, 242-53.

Morton J.M., 2010. Interrelationships between herd-level reproductive performance measures based on intervals from initiation of the breeding program in year-round and seasonal calving dairy herds. J. Dairy Sci. 93, 901-910

Munn, Z., Peters, M.D.J., Stern, C., Tufanaru, C., McArthur, A., Aromataris, E., 2018. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. BMC Med Res Methodol. 18 (1), 143.

Murad, M.H., Asi, N., Alsawas, M., Alahdab, F., 2016. New evidence pyramid. BMJ Evidence-Based Medicine 21, 125-127.

Neves, R.C., LeBlanc, S.J., 2015. Reproductive management practices and performance of Canadian dairy herds using automated activity-monitoring systems. J. Dairy Sci. 98, 2801–2811.

Nir Markusfeld, O., 2003. What are production diseases, and how do we manage them? Acta Vet Scand Suppl. 98, 21-32.

Niskanen, R., Emanuelson, U., Sundberg, J., Larsson, B., Alenius, S., 1995. Effects of infection with bovine virus diarrhoea virus on health and reproductive performance in 213 dairy herds in one county in Sweden. Prev. Vet. Med. 23, 229–237.

Norman, H.D., Wright, J.R., Hubbard, S.M., Miller, R.H., Hutchison, J.L., 2009. Reproductive status of Holstein and Jersey cows in the United States. J. Dairy Sci. 92, 3517-3528.

Oehm, A.W., Knubben-Schweizer, G., Rieger, A., Stoll, A., Hartnack, S., 2019. A systematic review and meta-analyses of risk factors associated with lameness in dairy cows. BMC Vet Res 15, 346.

O'Hagan, A., 2004. Bayesian statistics: Principles and benefits in van Boekel, A.J.S., Stein, A., van Bruggen, A.H.C., (Eds.), Bayesian Statistics and Quality Modelling in the Agro-Food Production Chain. Chapter 3, Wageningen University and Research Center, Wageningen, the Netherlands 31-45.

Olori, V.E., Brotherstone, S., Hill, W.G., McGuirk, B.J., 1997. Effect of gestation stage on milk yield and composition in Holstein Friesian dairy cattle. Livestock Production Science 52 (2), 167-176.

Opio, C., Gerber, P., Mottet, A., Falcucci, A., Tempio, G., MacLeod, M., Vellinga, T., Henderson, B., Steinfeld, H., 2013. Greenhouse gas emissions from ruminant supply chains – a global life cycle assessment. Food and Agriculture Organization of the United Nations.

Ospina, P.A., Nydam, D.V., Stokol, T., Overton, T.R., (2010). Associations of elevated nonesterified fatty acids and beta-hydroxybutyrate concentrations with early lactation reproductive performance and milk production in transition dairy cattle in the northeastern United States. J Dairy Sci. 93 (4), 1596-1603.

Peeler, E.J., Otte, M.J., Esslemont, R.J., 1994. Inter-relationships of periparturient diseases in dairy cows. Veterinary Record 134 (6), 129-132.

Pianosi, F., Beven, K., Freer, J., Hall, J.W., Rougier, J., Stephenson, D.B., Wagener, T., 2016. Sensitivity analysis of environmental models: A systematic review with practical workflow. Environmental Modelling & Software 79, 214-232.

Piccardi, M., Romero, G., Veneranda, G., Castello, E., Romero, D., Balzarini, M., Bó, G.A., 2016. Effect of puerperal metritis on reproductive and productive performance in dairy cows in Argentina. Theriogenology 85, 887–893.

Pinedo, P., Risco, C., Melendez, P., 2011. A retrospective study on the association between different lengths of the dry period and subclinical mastitis, milk yield, reproductive performance, and culling in Chilean dairy cows. J Dairy Sci. 94 (1), 106-15.

Pomeroy, L.W., Bansal, S., Tildesley, M., Moreno-Torres, K.I., Moritz, M., Xiao, N., Carpenter, T.E., Garabed, R.B., 2017. Data-Driven Models of Foot-and-Mouth Disease Dynamics A Review. Transboundary and emerging diseases, 64 (3), 716–728.

Poore, J., Nemecek, T., 2018. Reducing food’s environmental impacts through producers and consumers. Science, 360(6392), 987-992.

Potter, T.J., Guitian, J., Fishwick, J., Gordon, P.J., Sheldon, I.M., 2010. Risk factors for clinical endometritis in postpartum dairy cattle. Theriogenology 74 (1), 127-34.

Pryce, J., Veerkamp, R., 2001. The incorporation of fertility indices in genetic improvement programmes. BSAP Occasional Publication 26 (1), 237-249.

Pryce, J.E., Coffey, M.P., Brotherstone, S.H., Woolliams, J.A., 2002. Genetic Relationships Between Calving Interval and Body Condition Score Conditional on Milk Yield. J. Dairy Sci. 85, 1590–1595.

R Core Team, 2017. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.

Rasbash, J., Charlton, C., Browne, W.J., Healy, M., Cameron, B., 2010. MLwiN Version 2.2, Centre for Multilevel Modelling, University of Bristol

Rabiee, A.R., Lean, I.J., Stevenson, M.A., 2005. Efficacy of Ovsynch program on reproductive performance in dairy cattle: a meta-analysis. J Dairy Sci. 88 (8), 2754-70.

Raboisson D., Mounié M., Maigné E., 2014. Diseases, reproductive performance, and changes in milk production associated with subclinical ketosis in dairy cows: a meta-analysis and review. J Dairy Sci. 97(12), 7547-63.

Ragsdale, A.C., Turner, C.W., Brody, S., 1924. The effect of gestation upon lactation in the dairy cow. J. Dairy Sci. 7, 24-30

Raizman, E.A., Fetrow, J., Wells, S.J., Godden, S.M., Oakes, M.J., Vazquez, G., 2007. The association between Mycobacterium avium subsp. paratuberculosis fecal shedding or clinical Johne's disease and lactation performance on two Minnesota, USA dairy farms. Prev Vet Med. 78 (3-4), 179-95.

Rajala, P.J., Gro¨hn, Y.T., 1998. Disease occurrence and risk factor analysis in Finnish Ayrshire cows. Acta Vet. Scand. 39, 1–13.

Ratmann, O., Donker, G., Meijer, A., Fraser, C., Koelle, K., 2012. Phylodynamic inference and model assessment with approximate Bayesian computation: Influenza as a case study. *PLoS Comput Biol. 8* Article ID e1002835+

Rauw, W.M., Kanis, E., Noordhuizen-Stassen, E.N., Grommers, F.J., 1998. Undesirable side effects of selection for high production efficiency in farm animals: a review. Livestock Production Science 56 (1), 15-33.

Ravagnolo, O., Misztal, I., 2002. Effect of heat stress on non return rate in Holsteins: Fixed-model analyses. J. Dairy Sci. 85, 3101-3106.

Ribeiro, E.S., Lima, F.S., Greco, L.F., Bisinotto, R.S., Monteiro, A.P.A., Favoreto, M., Ayres, H., Marsola, R.S., Martinez, N., Thatcher, W.W., Santos, J.E.P., 2013. Prevalence of periparturient diseases and effects on fertility of seasonally calving grazing dairy cows supplemented with concentrates. Journal of Dairy Science 96 (9), 5682-5697.

Richardson, W.S., Wilson, M.C., Nishikawa, J., Hayward, R.S., 1995. The well-built clinical question: a key to evidence-based decisions. ACP J Club. 123 (3), A12-3.

Ritchie, H., Roser, M., 2020. CO_2 and Greenhouse Gas Emissions. Published online at OurWorldInData.org. [www document]. URL https://ourworldindata.org/ghg-emissions-by-sector (Accessed 30.12.21).

Rittel, H.W.J., Webber, M.M., 1973. Dilemmas in a General Theory of Planning. Policy Sciences, 4 (2), 155

Robert, A., Beaudeau, F., Seegers, H., Joly, A., Philipot, J.M., 2004. Large scale assessment of the effect associated with bovine viral diarrhoea virus infection on fertility of dairy cows in 6149 dairy herds in Brittany (Western France). Theriogenology, 61 (1), 117-27.

Rose, D.C., Sutherland, W.J., Parker, C., Lobley, M., Winter, M., Morris, C., Twining, S., Ffoulkes, C., Amano, T., Dicks, L.V., 2016. Decision support tools for agriculture: Towards effective design and delivery. Agricultural Systems 149, 165-174.

Royal, M.D., Darwash, A.O., Flint, A.P.E., Webb, R., Woolliams, J.A., Lamming, G.E., 2000. Declining fertility in dairy cattle: Changes in traditional and endocrine parameters of fertility. Anim.Sci. 70, 487-501.

Rutherford, A.J., Oikonomou, G., Smith, R.F., 2016. The effect of subclinical ketosis on activity at estrus and reproductive performance in dairy cattle. J Dairy Sci. 99 (6), 4808-4815.

Santos, V.G., Carvalho, P.D., Maia, C., Carneiro, B., Valenza, A., Fricke, P.M., 2017. Fertility of lactating Holstein cows submitted to a Double-Ovsynch protocol and timed artificial insemination versus artificial insemination after synchronization of estrus at a similar day in milk range. J Dairy Sci. 100 (10), 8507-8517.

Sayers, A., 2008. Tips and tricks in performing a systematic review. Br J Gen Pract. 58 (547), 136.

Sayers, R.G., 2017. Associations between exposure to bovine herpesvirus 1 (BoHV-1) and milk production, reproductive performance, and mortality in Irish dairy herds. J Dairy Sci. 100 (2), 1340-1352.

Scargle, J.D., 2000. Publication Bias: The "File-Drawer" Problem in Scientific Inference. Journal of Scientific Exploration 14 (1), 91–106.

Schefers, J.M., Weigel, K.A., Rawson, C.L., Zwald, N.R., Cook, N.B., 2010. Management practices associated with conception rate and service rate of lactating Holstein cows in large, commercial dairy herds. J Dairy Sci. 93 (4), 1459-67.

Schneider, J.C., Van Vleck, L.D., 1986. Heritability Estimates for First Lactation Milk Yield of Registered and Nonregistered Holstein Cows. Journal of Dairy Science 69 (6), 1652-1655.

Schüller, L.K., Burfeind, O., Heuwieser, W., 2014. Impact of heat stress on conception rate of dairy cows in the moderate climate considering different temperature-humidity index thresholds, periods relative to breeding, and heat load indices. Theriogenology 81 (8), 1050-7.

Sehested, J., Gaillard, C., Lehmann, J., Maciel, G., Vestergaard, M., Weisbjerg, M., Kristensen, T., 2019. Review: Extended lactation in dairy cattle. Animal 13 (S1), S65-S74.

Shahbandeh, M., 2021a. Total milk production in the United Kingdom (UK) from milk year 2001/02 to 2020/21 [www document]. URL https://www.statista.com/statistics/298770/milk-production-in-the-united-kingdom-uk/ (accessed 30.12.21).

Shahbandeh, M., 2021b. Average expenditure per person per week on milk and milk products (excluding cheese) in the United Kingdom (UK) from 2006 to 2018/19 (in pence) [www document]. URL https://www.statista.com/statistics/284198/milk-and-milk-products-weekly-household-expenditure-in-the-united-kingdom-uk/ (accessed 30.12.21).

Sheldon, I.M., Dobson, H., 2003. Reproductive challenges facing the cattle industry at the beginning of the 21st century. Reprod Suppl. 61, 1-13.

Sheldon, I.M., Williams, E.J., Miller, A.N.A., Nash, D.M., Herath, S., 2008. Uterine diseases in cattle after parturition. The Veterinary Journal 176, 115-121.

Simerl, N.A., Wilcox, C.J., Thatcher, W.W., 1992. Postpartum performance of dairy heifers freshening at young ages. J Dairy Sci 75, 590-595.

Smith, R.L., Strawderman, R.L., Schukken, Y.H., Wells, S.J., Pradhan, A.K., Espejo, L.A., Whitlock, R.H., Van Kessel, J.S., Smith, J.M., Wolfgang, D.R., Gröhn, Y.T., 2010. Effect of Johne's disease status on reproduction and culling in dairy cattle. Journal of Dairy Science 93 (8), 3513-3524.

Snyder, H, 2019. Literature review as a research methodology: An overview and guidelines. Journal of Business Research 104, 333-339.

Sorensen, A., Muir, D.D., Knight, C.H., 2008. Extended lactation in dairy cows: effects of milking frequency, calving season and nutrition on lactation persistency and milk quality. Journal of Dairy Research 75, 90–97.

Steeneveld, W., Schukken, Y.H., van Knegsel, A.T.M., Hogeveen, H., 2013. Effect of different dry period lengths on milk production and somatic cell count in subsequent lactations in commercial Dutch dairy herds. J. Dairy Sci. 96, 2988–3001.

Stefanon, B., Colitti, M., Gabai, G., Knight, C.H., Wilde, C.J., 2002. Mammary apoptosis and lactation persistency in dairy animals. J Dairy Res. 69 (1), 37-52.

Sterne, J.A.C., Sutton, A.J., Ioannidis, J.P.A., Terrin, N., Jones, D.R., Lau, J., Carpenter J., Rücker, G., Harbord, R.M., Schmid, C.H., Tetzlaff, J., Deeks, J.J., Peters, J., Macaskill, P., Schwarzer, G., Duval, S., Altman, D.G., Moher, D., Higgins, J.P., 2011. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 343, d4002

Stevenson, J.S., Kobayashi, Y., Thompson, K.E., 1999. Reproductive performance of dairy cows in various programmed breeding systems including OvSynch and combinations of gonadotropin-releasing hormone and prostaglandin F2 alpha. J Dairy Sci. 82 (3), 506-15.

Tasker, J., (2017). Block v year-round calving: Which is best for you? [www document]. URL https://www.fwi.co.uk/livestock/dairy/block-v-year-round-calving-which-is-best-for-you (accessed 30.12.21).

Tenhagen, B.A., Drillich, M., Surholt, R., Heuwieser, W., 2004. Comparison of timed AI after synchronized ovulation to AI at estrus: reproductive and economic considerations. J Dairy Sci. 87 (1), 85-94.

Uberoi, E., 2021. UK Dairy Industry Statistics. House of Commons Library [www document]. URL https://researchbriefings.files.parliament.uk/documents/SN02721/SN02721.pdf (accessed 30.12.21).

UK Government, 2021. National statistics: United Kingdom milk prices and composition of milk: October 2021. [www document]. URL https://www.gov.uk/government/statistics/uk-milk-prices-and-composition-of-milk/united-kingdom-milk-prices-and-composition-of-milk-statistics-notice-data-for-june-2019 (accessed 30.12.21).

Valle, P.S., Martin, S.W., Skjerve, E., 2001. Time to first calving and calving interval in bovine virus diarrhoea virus (BVDV) sero-converted dairy herds in Norway. Prev Vet Med. 51 (1-2), 17-36.

Vanleeuwen, J.A., Haddad, J.P., Dohoo, I.R., Keefe, G.P., Tiwari, A., Tremblay, R., 2010. Associations between reproductive performance and seropositivity for bovine leukemia virus, bovine viral-diarrhea virus, Mycobacterium avium subspecies paratuberculosis, and Neospora caninum in Canadian dairy cows. Prev Vet Med. 1; 94 (1-2), 54-64.

Veronese, A., Marques, O., Moreira, R., Belli, A.L., Bilby, T.R., Chebel, R.C., 2019. Estrous characteristics and reproductive outcomes of Holstein heifers treated with 2 prostaglandin formulations and detected in estrus by an automated estrous detection or mounting device. J Dairy Sci. 102 (7), 6649-6659.

Viechtbauer, W., 2010. Conducting Meta-Analyses in R with the metafor Package. Journal of Statistical Software 36 (3), 1–48.

Villa-Godoy, A., Hughes, T.L., Emery, R.S., Chapin, L.T., Fogwell, R.L., 1988. Association between energy balance and luteal function in lactating dairy cows. J Dairy Sci. 71 (4), 1063-72.

Wall, E., Coffey, M., Simm, G., Brotherstone, S., Stott, A.W., Santarossa, J., Flint, A.P.F., Royal, M.D., Woolliams, J.A., 2002. Introducing a UK fertility index. Cattle Practice 10, 373- 378.

Wall, E., Brotherstone, S., Woolliams, J.A., Banos, G., Coffey, M.P., 2003. Genetic Evaluation of Fertility Using Direct and Correlated Traits. J. Dairy Sci. 86, 4093–4102.

Walsh, R.B., Walton, J.S., Kelton, D.F., LeBlanc, S.J., Leslie, K.E., Duffield, T.F., 2007. The effect of subclinical ketosis in early lactation on reproductive performance of postpartum dairy cows. Journal of Dairy Science 90, 2788–2796.

Walsh, S.W., Williams, E.J., Evans, A.C., 2011. A review of the causes of poor fertility in high milk producing dairy cows. Anim Reprod Sci. 123 (3-4), 127-138.

Wathes, D.C., Fenwick, M., Cheng, Z., Bourne, N., Llewellyn, S., Morris, D.G., Kenny, D., Murphy, J., Fitzpatrick, R., 2007. Influence of negative energy balance on cyclicity and fertility in the high producing dairy cow. Theriogenology 68, S232–S241.

Wathes, D.C., Pollott, G.E., Johnson, K.F., Richardson, H., Cooke, J.S., 2014. Heifer fertility and carry over consequences for life time production in dairy and beef cattle. Animal 8 (S1), 91-104.

Wathes, D.C., Oguejiofor, C.F., Thomas, C., Cheng, Z., 2020. Importance of Viral Disease in Dairy Cow Fertility. Engineering (Beijing) 6 (1), 26-33.

Watters, R.D., Wiltbank, M.C., Guenther, J.N., Brickner, A.E., Rastani, R.R., Fricke, P.M., Grummer, R.R., 2009. Effect of dry period length on reproduction during the subsequent lactation. Journal of Dairy Science 92, 3081–3090.

Weigel, K.A., VanRaden, P., Norman, H., Grosu, H., 2017. A 100-Year Review: Methods and impact of genetic selection in dairy cattle—From daughter–dam comparisons to deep learning algorithms. J. Dairy Sci. 100, 10234–10250.

Whitaker, D.A., Macrae, A.I., Burrough, E., 2004. Disposal and disease rates in British dairy herds between April 1998 and March 2002. Veterinary Record 155, 43-47.

Williams, E.J., Fischer, D.P., Noakes, D.E., England, G.C., Rycroft, A., Dobson, H., Sheldon, I.M., 2007. The relationship between uterine pathogen growth density and ovarian function in the postpartum dairy cow. Theriogenology 68 (4), 549-59.

Wiltbank, M.C., Lopez, H., Sartori, R., Sangsritavong, S., Gumen, A., 2006. Changes in reproductive physiology of lactating dairy cows due to elevated steroid metabolism. Theriogenology 65, 17–29.

Wolfenson, D., Roth, Z., Meidan, R., 2000. Impaired reproduction in heat-stressed cattle: Basic and applied aspects. Anim. Reprod. Sci. 60-61, 535-547.

Xiao, Y., Watson, M., 2019. Guidance on Conducting a Systematic Literature Review. Journal of Planning Education and Research 39 (1), 93-112.

Yang, M., Goldstein, H., 2003. Modelling survival data in MLwiN 1.20, Centre for Multilevel Modelling, University of Bristol

Young, I., Waddell, L., Sanchez, J., Wilhelm, B., McEwen, S.A., Rajić, A., (2014). The application of knowledge synthesis methods in agri-food public health: recent advancements, challenges and opportunities. Prev Vet Med. 113 (4), 339-55.

Yuan, S., Larsson, S.C. 2020. An atlas on risk factors for type 2 diabetes: a wide-angled Mendelian randomisation study. Diabetologia 63, 2359–2371.

Zhang, J., Yu, K.F., 1998. What's the Relative Risk? A Method of Correcting the Odds Ratio in Cohort Studies of Common Outcomes. JAMA. 280 (19), 1690–1691.