

High immune response sires reduce disease incidence in North American large commercial dairy populations

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ABSTRACT

Genetic selection can play a key role in reducing disease incidence in cattle. Since 2013, semen from sires tested and identified to have superior immune response genetics has been available to commercial dairy producers. Health records collected in herd software from large commercial dairy farms in North America were interrogated to determine the impact of High Immune Response (HIR™) sires on disease incidence in commercial cow herds. Counts of disease incidences on 34 large herds (>500 cows) were analysed with a Poisson regression model. Diseases investigated included mastitis, metritis, lameness, mortality, heifer pneumonia, heifer diarrhoea and miscellaneous illnesses for up to 33,320 cows and 74,888 heifers (of which 2,397 cows and 10,625 heifers were sired by an Immunity+ sire). Significant reductions ($p < 0.05$) in the incidence of mastitis, lameness, heifer and cow mortality, and total disease incidence for cows was observed in progeny from sires classified as having a high EBV for overall adaptive immune response. It is noteworthy that all recorded diseases had reductions in frequency, both when considering the disease as count data and as a binary trait, however not all reductions were found to be significant. These results indicate that genetic selection for immune responsiveness through sire selection can significantly reduce disease incidence in commercial dairy cattle herds.

INTRODUCTION

The bovine adaptive immune system provides protection to a broad array of pathogens early in life (Aleri and others 2015), throughout the transition period (Spears and Weiss 2008) and throughout lactation (Ingvarsen and others 2003). Cattle with more robust immune systems have also been shown to be more reproductively fit likely due to lower incidences of uterine disease and infection (Sheldon and others 2009). Identifying animals with stronger immune responses can also help improve milk quality as measured by somatic cell count, and subsequently increase profitability for dairy producers. It has been shown that variation in immune responsiveness has a significant genetic component (Mallard and others 1998, Thompson-Crispi and others 2012), allowing dairy producers to breed cows that are more resistant to a diverse array of pathogens (Mallard and others 2015).

Researchers at the University of Guelph developed a patented technology to test the adaptive immune responsiveness of individual dairy animals. This High Immune Response (HIR™) technology assesses two types of adaptive immune responses, cell-mediated (CMIR) and antibody-mediated immune responses (AMIR) (Mallard and others 2011). Estimated Breeding Values (EBVs) are then calculated for each of these traits to classify an animal as a high (H), average (A) or low (L) responder

for AMIR and for CMIR. Animals that classify as high for both tests (HH) are then sub-classified as high overall immune responding animals. These are the animals that are expected to be resistant to a broad range of potential pathogens, both bacteriological and viral in nature (Emam and others 2014).

Disease incidence in high immune responders relative to their low and average immune responder counterparts has been tested in field trials. Thompson-Crispi and others (2012) found that high responders, defined as those with EBVs for AMIR and CMIR which are one standard deviation or greater than the population mean, had significantly lower incidence of three major diseases, mastitis, displaced abomasum and retained foetal membranes when compared to herd average. It was also found that high responders had empirically less metritis and ketosis than the herd average. HIR™ animals have also been shown to produce higher quality colostrum, including specific antibody, total IgG and β -Lactoglobulin (Wagter and others 2000, Fleming and others 2016), and respond better to commercial mastitis vaccines (Wagter and others 2000, Mallard 2014) without adverse effects on production traits (Wagter and others 2000, Stoop and others 2016).

The Semex Alliance (Guelph, Canada) purchased the exclusive rights to test sires for HIR, and now markets top ranking bulls as Immunity+. Immunity+

sires are those that tested as high responders for both AMIR and CMIR. Semex began marketing these sires internationally in 2013, and continues to do so today. The heritability of AMIR and CMIR ranges from 0.19 to 0.41 (Thompson-Crispi and others 2012). Therefore HIR sires are expected to pass these beneficial IR genes to their progeny producing offspring that are likely to have stronger immune responses. Commercial trials of HIR have shown reductions in disease frequency of between 17-32% when HIR animals are compared to herd average (Thompson-Crispi and others 2013, Mallard and Shannon 2015). Considering the heritability of immune responsiveness, it is expected that progeny of HIR™ bulls will be expected to have a relative decrease of 4-8% in disease incidence compared to herd-mates. Continuous use of Immunity+ bulls over several generations is expected to result in significant genetic improvement for disease resistance, in the same way that selection for other dairy traits with high to moderate heritability has achieved previously.

The objective of this study was to examine the impact of using Immunity+ sires on disease frequency in commercial populations. The incidence of disease in progeny of Immunity+ sires was compared to all other animals. Traits measured included mastitis, metritis and lameness, assuming overall lameness is an indicator of lameness caused by bacterial infection, especially digital dermatitis. Miscellaneous illnesses and incidence of mortality recorded on farm were also investigated. Heifer health data including pneumonia, diarrhoea and mortality were also examined.

MATERIALS AND METHODS

Health records

Cow and heifer disease data were obtained from on-farm software systems (DairyComp305 (Valley Agricultural Service, Tulare, USA), DHI-Plus (DHI Computing Services, Provo, USA) and PCDART (Northstar Cooperative, Lansing, USA)) from 47 herds across Canada (2 herds) and the United States (45 herds). Disease records related to the previous 2 years (2014-2016) and were recorded by herd managers and employees. Herd data was assessed for completeness and consistency of data recording for all relevant traits, and after quality control measures were applied, 34 herds were deemed to have health data of sufficient quality to be included in the analysis.

Quality control measures included having at least 1% incidence of a disease within the herd, and that the disease records for an animal were monitored for at least 180 days, as in Koeck and others (2012). Herds were removed from the analysis exclusively on the basis of data quality. Within each herd, health data was standardised for age of animal, to ensure that for each individual herd, average age of each group (Immunity+ and non-Immunity+) were the similar ensuring that average exposure to disease was consistent across groups. Following quality control measures records from a total of 33,320 cows and 74,888 heifers were available for analysis.

The number of animals included in the analysis for each trait is listed in Table 1. Not all herds recorded all disease traits. Data on each disease included animal, sire, disease event, and days in milk at time disease recorded. Multiple disease events for the same animal were only included if they occurred at least 10 days after a previous recording of the same disease to ensure it was a separate incidence and not a multiple recording of

Table 1. Number of herds, records and average disease incidences for major diseases from data (after quality control) taken from herd software of large dairies in Canada and the United States.

Trait	Number of Herds	Number of Animals (# Immunity+)	Average Frequency (Range)
Cows			
MASTITIS	23	30,576 (2,390)	0.309 (0.06-0.56)
PERSISTENT MASTITIS	23	30,576 (2,390)	0.048 (0.01-0.11)
METRITIS	17	19,363 (2,207)	0.057 (0.02-0.40)
LAMENESS	18	24,515 (1,950)	0.234 (0.03-1.30)
MISCELLANEOUS ILLNESS	11	18,699 (1,550)	0.058 (0.01-0.23)
MORTALITY	24	33,320 (2,544)	0.051 (0.03-0.14)
TOTAL DISEASE FREQUENCY	23	30,576 (2,397)	0.673 (0.21-2.01)
Heifers			
PNEUMONIA	18	31,590 (4,116)	0.098 (0.02-0.45)
DIARRHOEA	10	14,658 (2,086)	0.055 (0.01-0.34)
MORTALITY	34	74,888 (10,625)	0.081 (0.04-0.18)

the same event, as this would ensure any recording would include a new course of treatment. Unique disease incidences were then counted for each individual in each herd. The average incidence of each disease in the population of herds is reported in Table 1.

For cows, traits analysed included mastitis, metritis, lameness, miscellaneous illness, and mortality. Displaced Abomasum and Retained Foetal Membranes were not included due to a lack of herds with sufficient high quality data. The total number of disease events per animal were examined, as well as persistent mastitis. Persistent mastitis was defined as a binary trait, where any animal with at least 2 cases of mastitis was assigned a score of 1, and any animal with 1 or fewer mastitis cases was assigned 0. In the heifer data, pneumonia, diarrhoea and mortality traits were analysed.

Sires

All sires marketed by the Semex Alliance (Guelph, Canada) since 2013 have been tested for Immune Responsiveness. The immune response test measures both antibody and cell-mediated immune response, as described by Wagter and others (2000). Briefly, sires were immunised with known type 1 and 2 antigens (US Patent #7,258,858; Wagter and Mallard 2007) to stimulate the adaptive immune system. Blood samples were taken prior to and following immunisation to measure AMIR. Delayed-type hypersensitivity skin tests to the type 1 antigen were used to assess CMIR.

There were 108 and 3,248 Immunity+ and non-Immunity+ sires (including sires tested negative and un-tested sires) represented in the data set, respectively. Immunity+ sires were classified as such based on their Estimated Breeding Values (EBVs) for AMIR and CMIR. Pedigree records were available on 15,556 individuals, along with phenotypes for all tested sires (1,816) and for a population of tested cows from research and commercial trials (N=1,800). An animal model was used to estimate the breeding values for sires using AS-REML (Gilmour 1999). Genetic parameters estimated by Thompson-Crispi and others (2012) were used for AMIR and CMIR. EBVs for AMIR and CMIR were standardised, with a mean of 0 and a standard deviation of 1.

Overall immune response for each sire was calculated as the mean of standardised AMIR and CMIR EBVs. Sires with an overall immune response EBV greater than 1, and AMIR and CMIR EBVs greater than 0 were classified as high immune responding sires, and marketed by the Semex Alliance as Immunity+ sires. For this study, sires

were classified based on Immunity+ status, where Immunity+ sires were classified as “yes” and all other sires were classified as “no”.

Models

Analysis of disease incidence traits across groups (other than mortality) was carried out with a Poisson regression model using R statistical software (R Core Team 2014). A Poisson model was chosen as it is suitable for analysis of data that is heavily zero-inflated (Bae and others 2005). The model for disease events in cows was as follows:

$$Y_{ijkl} = \mu + P_i + H_j + IM_k + \beta_l A + e_{ijkl}$$

Where Y_{ijkl} is the count of disease incidences for a given individual over a given period of time for one of the disease traits, μ is the overall mean, P_i is the fixed effect of parity (1 to 4), H_j is the fixed effect of herd, IM_k is the fixed effect of sire Immunity status, β_l is a fixed regression on age(A), and e_{ijkl} is the random error term.

Mortality data was analysed using the same model terms, but using a binomial model with a logit link function. The logit link allows for prediction of an odds ratio. Coefficients obtained from logistic regression are in terms of the log odds, so e to the power of the log odds is equal to the relative odds ratio between an effect in the model and the term it is regressed upon. In this study, there were only 2 Immunity status categories for sires (Immunity+ versus non Immunity+), so the exponential of the effect estimate is equal to the odds ratio of disease occurrence for animals sired by an Immunity+ sire.

Marginal means and standard errors were predicted for each group using the predict function in R with average values for the other effects in the model.

Heifer data was analysed using the same model, but omitting the fixed effect for parity, as all heifers had equal (0) parity status. Marginal means were again estimated for each trait for heifers.

Odds ratios were estimated for each trait in the study using a binomial regression model. In this case animals were assigned 1 or 0, based upon whether they had ever been affected by a disease or not. Persistent mastitis was also analysed using a binomial regression, where animals with at least 2 lifetime cases of mastitis being assigned a 1 and all other individuals assigned 0.

RESULTS

Number of herds and records analysed for cows ranged from 11 and 18,699 (miscellaneous illness) to 24 and 33,320 (mortality), respectively (Table

1); 11 herds only had a sufficient number of Immunity+ daughters that were heifers, so they were excluded for cow analysis. Mastitis was the most frequently occurring disease in the study population, occurring at least once in 15.9% of animals in herds that routinely recorded its incidence. Lameness had the largest range of occurrence across herds, having between 3%-130% frequency in different herds, indicating a significant effect of environment as well as variable recording practices.

Immunity+ sired cows had significantly lower incidence of mastitis, lameness, and mortality (Table 2). Effect estimates from regression analysis, measuring the expected reduction in cases of a disease ranged from -0.003 (metritis) to -0.24 (mortality). Reductions in disease incidence were observed for Immunity+ sired animals for all diseases studied, however differences observed for metritis, persistent mastitis or miscellaneous illness were not significant in this data set. Table 2 also displays relative decreases in disease frequency in the population. Relative disease frequencies ranged between 0.35% and 20.58% and were generally greater than the 4-8% reduction that was expected based on sire selection intensity and heritability of AMIR and CMIR. The marginal means of each trait for the Immunity+ sired group compared to the rest of the population are shown in Figure 1. It was also found that cows from Immunity+ sires had a significant reduction in overall disease frequency, measured as the total number of all disease events.

Heifer disease incidence ranged from 5.5% (diarrhoea) to 9.8% (pneumonia) (Table 1). The number of herds and records, respectively, ranged from 10 and 14,658 (diarrhoea) to 34 and 74,888

Table 2. Effect estimates and significance values for Immunity+ sires versus non-Immunity+ sires for incidence of disease from data (after quality control) taken from herd software of large dairies in Canada and the United States.

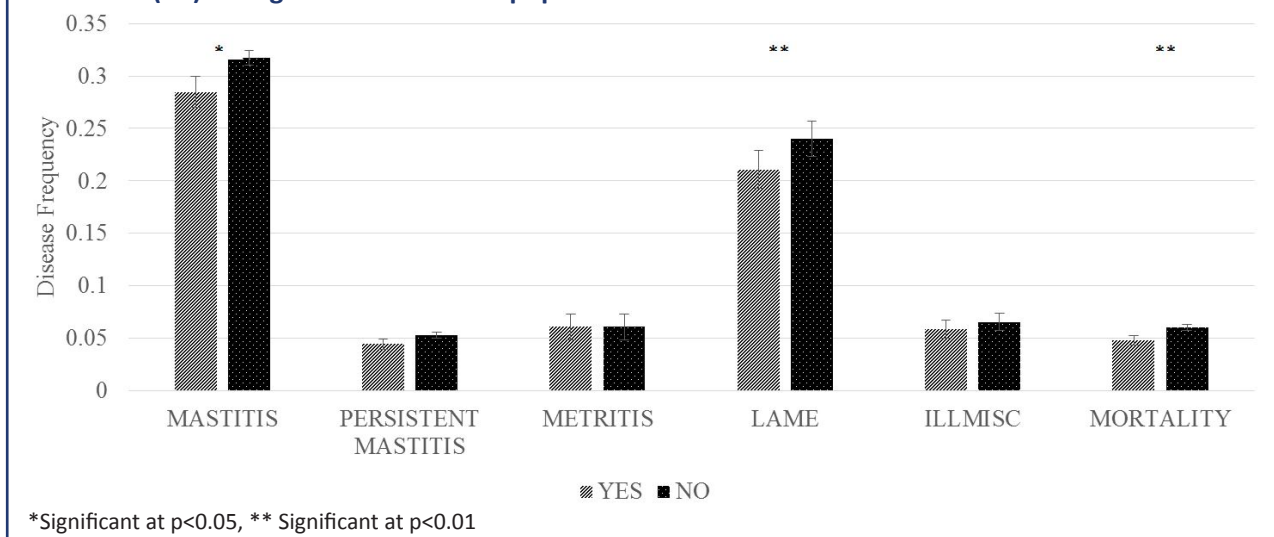
Trait	Effect Estimate ¹	p-value	Relative Decrease in Disease Incidence (%)
Cows			
MASTITIS	-0.108	0.035*	10.27
PERSISTENT MASTITIS	-0.191	0.121	16.64
METRITIS	-0.003	0.965	0.35
LAMENESS	-0.130	0.010*	12.20
MISCELLANEOUS ILLNESS	-0.110	0.144	10.43
MORTALITY	-0.244	0.007*	20.58
TOTAL DISEASE FREQUENCY	-.219	<0.001*	4.04
Heifers			
PNEUMONIA	-.019	0.617	1.93
DIARRHOEA	-.045	0.483	4.39
MORTALITY	-.194	<0.001*	16.28

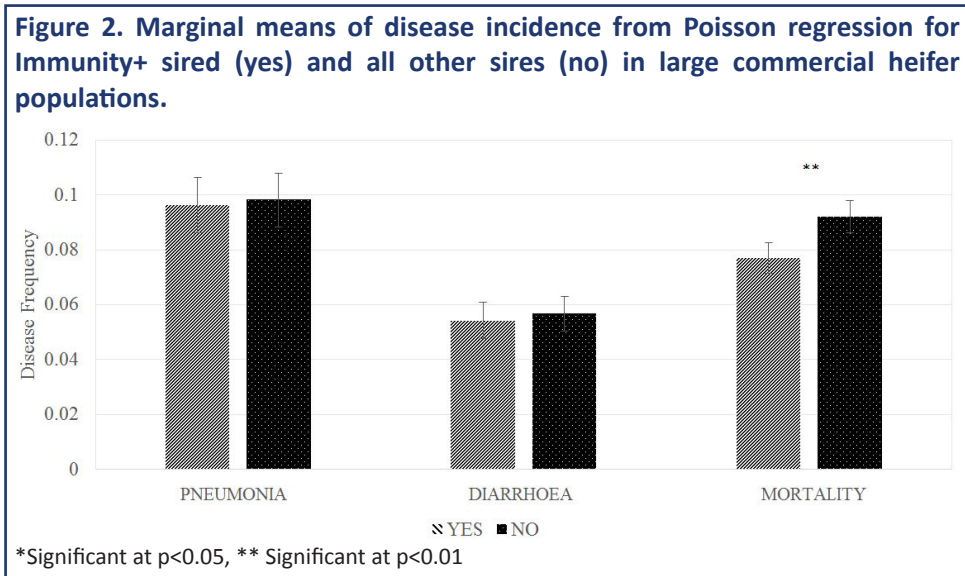
¹Estimated difference in disease incidence between an Immunity+ sired animal and an animal sired by any other sire given average environmental conditions.

*Indicates significance at p<0.05

(mortality). Heifer mortality was significantly lower in the Immunity+ sired group. Immunity+ sired heifers had less pneumonia and diarrhoea, however the effect was not statistically significant in this data set. The marginal means of each trait based on Immunity status groups are shown in

Figure 1. Marginal means of disease incidence from Poisson regression for Immunity+ sired (yes) and all other sires (no) in large commercial cow populations.





reduction from 1 in the odds ratio of daughters of Immunity+ sires for mortality, and a trend towards significance for diarrhoea.

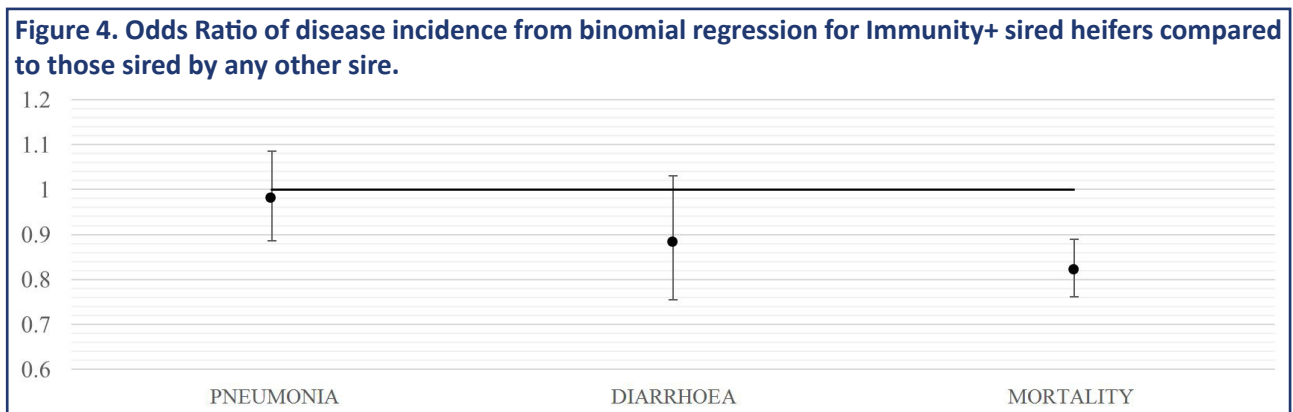
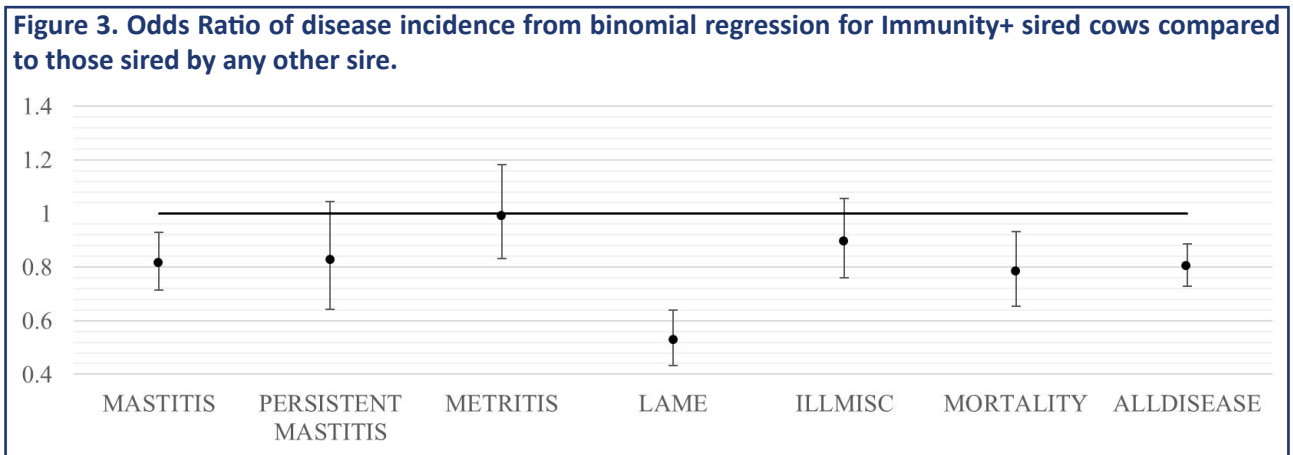
DISCUSSION

Incidence rates of major diseases recorded in this study are generally in line with those estimated in the literature (Riekerink and others 2008, Giuliodori and others 2013, Somers and others 2015), with

Figure 2.

The odds ratios of having at least 1 case of each disease for cows and heifers are shown in Figures 3 and 4, respectively. In the cow population, odds ratios ranged from 0.53 (lameness) to 0.99 (metritis). The odds ratio of a single disease incidence for daughters of Immunity+ bulls was significantly less than 1 for mastitis, lameness, mortality and the sum of all disease occurrences indicating a significant reduction in the chance of at least one case of each of these diseases in the Immunity+ population. In heifers there was a significant

some differences for specific traits. This is expected as incidence rates can vary greatly across herds depending on environmental factors and recording practices. The variation in incidence rates across herds, especially for lameness, may indicate that some herds only record severe clinical cases of disease events, whereas other herds record any signs of a disease or disorder, whether clinical or subclinical in nature, particularly as it relates to lameness. This issue is a common problem with the analysis of disease incidence field data. The statistical model used in this study is expected to



provide robust estimates provided the correlation between the incidences of severe and less severe cases of the same disease is sufficiently high (Cameron and Trivedi 2013).

A significant decrease in disease incidence was seen in the progeny of Immunity+ sires (Figure 1). This suggests that progeny from high immune response sires are recipients of immune genes that conferred a superior immunological response which better protected them from infectious diseases. This response is consistent with the findings of previous research where cows classified as having superior immune response (based on their own genetic merit) had a lower incidence of most major diseases (Wagter and others 2000, Pinedo and others 2009, Thompson-Crispi and others 2012, 2013, Cartwright and others 2015). In the current study, mastitis, lameness and mortality all had significantly lower incidence rates in the Immunity+ sired progeny. These traits have the highest incidence rates and the greatest economic impact in dairy cattle populations (Macrae and Esslemont 2015). A significant reduction in the incidence of such diseases can therefore be expected to have a large positive effect on the economics of a herd, as well as reduce the use of antibiotics.

A non-significant reduction in disease incidence was observed for persistent mastitis, metritis and miscellaneous illness. These diseases all have lower incidence rates, therefore it is more difficult to detect significant differences between populations. While a Poisson model was chosen to model the zero-inflated data, the ability to detect significance is still dependent on the frequency of non-zero events in the data (Channouf and others 2014). Nevertheless, point estimates indicate that a reduction in disease frequency was observed in the Immunity+ sired population for each of these diseases after accounting for herd and lactation effects. Relative decreases in disease frequency for these traits were all high enough to have a practical economic impact on a commercial dairy. The low average frequency of persistent mastitis explains why in Table 2 there is a significantly large point estimate for persistent mastitis, but no statistical significance was detected.

A binomial model was applied to the data, which were fit as binary traits (zero incidence vs. any number of incidences) to calculate the odds ratios for each disease between sire groups. Estimates for mastitis, lameness, mortality and all diseases significantly differed from 1, indicating that the odds of an animal being recorded for these diseases are significantly less if they were the progeny of

a high immune response sire. The odds ratio for lameness was 0.52, indicating that an animal that is the progeny of a high immune response sire is approximately half as likely to become lame at some point in their lifetime than an animal that is the progeny of a non-Immunity+ sire. The adaptive immune response system can play a crucial role in pathogen-induced lameness, and this response has been shown to have a significant genetic component (Banos and others 2013).

A significant reduction in heifer mortality was also observed for daughters of Immunity+ sires, suggesting a reduction in the incidence of severe diseases for these animals. In both cows and heifers, the cause of death was not identified, so that all mortality may not be related to disease, but it was assumed that the incidence of other causes of mortality were equal across groups. Adaptive immune response profiles can change significantly with age (Hine and others 2011) and a smaller reduction in disease frequencies in younger animals from high immune response sires might have been expected since adaptive immune response is dependent on previous exposure to a pathogen (Alberts and others 2002). However, a significant reduction in heifer mortality was observed in this study, possibly because individuals with a stronger adaptive immune response are also likely to have a stronger innate immune response.

Producer recorded disease events have been used recently to calculate genetic and genomic evaluations for health traits in many countries, including Canada (Jamrozik and others 2013) and the United States (Gaddis and others 2014). Such evaluations can potentially be used to help reduce the cost of disease on the farm. The effectiveness of genetic selection based on disease incidence records, however, is limited by the low heritability of these traits (Gernand and others 2012). Genomic selection, based on a cow reference population with genotypes and disease incidence phenotypes, or sires with progeny evaluations for the same traits, can be used to overcome the problem. However, the size of the reference population required to obtain sufficient prediction accuracy to achieve meaningful genetic progress for disease resistance is very large, given the low heritability of disease incidence traits. Studies carried out to date report a modest increase in selection accuracy when using genomic selection in this fashion (Gaddis and others 2014).

Selection for high immune response is a more direct route to reduce disease in commercial populations. Immune responsiveness is highly heritable (Thompson-Crispi and others 2012),

which is likely why it results in a significant decrease in disease frequency after even one generation of selection as has been demonstrated here. It is important to note, that selection for high immune response is selection for a more efficient immune system, which does not imply reducing the diversity of the repertoire of responses to antigens. On the contrary, it may lead to increased diversity in that repertoire as that diversity is associated with more effective resistance to disease. The positive effect of high immune response on growth rate and disease incidence has been reported previously in pigs selected for high and low immune responses but was not investigated here (Mallard and others 1992). The current study shows that, in a commercial setting, sires with a superior immune response can transmit their enhanced general disease resistance to their daughters, and thereby reduce the incidence of disease in their progeny compared to daughters of other sires. The genetic merit for other health and fitness traits were not studied here, but it has been found that Immune response has a low positive genetic correlation with most other health and fertility traits. It is assumed that the Immunity+ population is slightly superior in these other traits, however the genetic correlations are quite low, so differences in disease frequency should not be influenced heavily by this difference. Reductions in disease incidence were observed for all the diseases studied in both cows and heifers, although some were non-significant. Relative reduction in disease frequencies were even larger than projected in most cases. This may largely be due to those estimates being conservative in nature, however, for all diseases, the projected range was within the standard error meaning any variation from the predicted reductions in disease could be because of sampling, with one notable exception, death, which can be explained by high immune response animals being able to cope with pathogens of a severe nature more readily than herd-mates. The reductions were especially large for the incidence of mastitis, lameness and mortality, the most costly traits related to disease in dairy cattle today.

The impact of this study can have far-reaching effects on dairy producers as well as agricultural practices as a whole. Producers can expect to save money associated with expensive treatments of major diseases and losses. Another expected benefit of disease reduction is a decrease in the need for therapeutic antibiotic use on farm, which will only be increasingly important in the future.

This study emphasises the role genetic selection strategies can play in reducing the incidence of

disease and, as a consequence, reducing the costs associated with the treatment of disease on farms as part of a sustainable, long term solution to improving animal health and welfare.

CONFLICT OF INTEREST DECLARATION

One of the authors is employed by the Semex Alliance which markets High Immune Response genetics internationally.

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