Genetic Basis and Risk Factors for Infectious and Noninfectious Diseases in US Holsteins. I. Estimation of Genetic Parameters for Single Diseases and General Health

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ABSTRACT

Health data collected from 1996 to 1999 from 177 herds in Minnesota and Wisconsin were analyzed to establish genetic basis for infectious and noninfectious diseases. Three types of health traits were targeted. First, available infectious conditions were used to identify animals that are superior in their general immunity (including innate immunity) for infectious diseases. Generalized immunity may be thought of as a combination of immune responses to a variety of immune system challenges. Second, single infectious and noninfectious diseases were analyzed separately. Third, infectious reproductive diseases as one category of related conditions, and cystic ovary disease as one category of 3 related noninfectious ovary disorders were studied.

Data were analyzed using a threshold model that included herd, calving year, season of calving, and parity as cross-classified fixed factors; and sire and cow within sires as random effects. Days at risk and days in milk at the beginning of a record were included by fitting the days as continuous covariates in the model. A heritability value of 0.202 ± 0.083 was estimated for generalized immunity. Heritability values of 0.141 and 0.161 were estimated for uterine infection and mastitis, respectively. Heritability of single noninfectious disorders ranged from 0.087 to 0.349. The amount of additive genetic variance recovered in the underlying scale of noninfectious disorders tended to zero when combining multiple conditions. The study supports combining infectious diseases into categories of interest but we do not recommend the same approach for noninfectious disorders.

(**Key words:** disease resistance, generalized immunity, genetic evaluation)

Abbreviation key: **BDIM** = days in milk at the beginning of a record, **CCL** = cystic corpora lutea, **COD** = cystic ovarian disease, **DAR** = days at risk, **GI** = generalized immunity, **ID** = infectious diseases, **IR** = infectious reproductive conditions, **MF** = milk fever, **TM** = threshold model, **UH** = udder health, **UI** = uterine infection.

INTRODUCTION

Over the past 4 decades, animal breeders have made tremendous improvement in production traits by selection. For controlling health-related traits, however, the animal production sector in the United States has mainly relied on medication, vaccination, and management techniques. The call for accompanying improvement of disease resistance in the high-producing dairy cow started more than 2 decades ago (e.g., Shanks et al., 1978; Hansen et al., 1979). The lack of a system to collect and use health information in the United States has been highlighted (Shook, 1989), and proposals for a national health evaluation system were initiated over a decade ago (Wiggans, 1994).

Numerous studies have investigated the genetic basis of disease resistance in US Holsteins, emphasizing the genetic potential of improving animal health (e.g., Lin et al., 1989; Lyons et al., 1991; Uribe et al., 1995). This potential has been demonstrated in Scandinavian breeds where breeders have selected for several health traits. Significant genetic change for clinical mastitis in Norwegian cattle has also been found (Heringstad et al., 2003).

In addition, advances on the biostatistical side introduced new techniques for the analysis of binary and ordered categorical traits into which many health measurements could be classified. Better genetic parameter estimation is expected when a threshold model (**TM**)

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Table 1. Number of herds and lactations, and the average number of lactations per herd for the years of the study. Number of lactations is calculated based on actual calvings per year.

Calving year ¹	Herds (no.)	Lactations (no.)	Lactations/ herd (no.)	Lactations/ herd (SD)
1996	133	3717	28	27
1997	157	7406	47	63
1998	139	8190	59	93
1999	120	5392	45	81
Total	177	24,705	140	228

¹Years 1996 and 1999 were incomplete.

that assumes an unobservable underlying and heritable scale is postulated (Gianola and Foulley, 1983; Harville and Mee, 1984). In particular, genetic variation estimated from a TM is usually higher than genetic variation estimated by fitting a linear model to the observed categories (Abdel-Azim and Berger, 1999; Hansen et al., 2002). Further, the TM allows estimating probabilities of observing individuals between any 2 boundary points, given certain model effects. This leads to estimating the probability of disease occurrence for daughters of sires included in the analysis. This facility, available in a TM analysis, allows for a ranking criterion of sires that is more interpretable than mixed model solutions.

Diseases can be classified into infectious and noninfectious. Infectious diseases are thought to be controlled immunologically, and the level of immunity varies across animals according to many factors, including genetics. In the current study, resistance specific to a single disease as well as generalized immunity for multiple related diseases are examined. Selected noninfectious disorders, those that are not caused by pathogens, are also studied. Risk factors for liability to studied diseases are identified and their magnitudes and directions are tested statistically. Emphasis is given to the genetic basis of a large category of infectious diseases.

MATERIALS AND METHODS

Data

Data were collected over 4 yr (1996 to 1999) from 177 herds in Minnesota and Wisconsin. Herd statistics per year are summarized in Table 1. Herds were required to be on DHIA and herdsmen agreed to perform complete health data recoding. Data recording was in 2 forms, electronically or by describing health conditions and treatments on forms provided to herdsmen. Data were collected periodically by personnel from Genex Cooperative Inc., and were entered into a database system at Iowa State University. A 3-digit numeric coding system

was used to define health conditions. Data included 24,705 lactations of 14,473 Holstein cows. Cows were sired by 1,303 US Holstein sires. Health information included diagnosis of condition, treatment cost and level of treatment, and sometimes severity of condition, such as in clinical mastitis.

Monitoring periods differed according to the enrollment dates of herds into the study. The monitoring period of a herd was taken as the period of time a herd spent on the study. Herds spent an average of 602 d on the study, with a range of 245 to 942 d for the first and the third quartiles, respectively. A herd monitoring period served as a factor in identifying records made by healthy cows, and in computing days at risk associated with lactation records of cows in the herd. The number of days data were collected on a cow in a given lactation was variable and was adjusted for in the analysis (Heringstad et al., 2001; de Haas et al., 2002). This was done by identifying start and end dates for lactation records. For a single lactation, start date was the later of calving date or herd start date. A lactation end date was the earliest of 450 d after herd start date; 1 d before next calving; selling, culling, or death of the cow; or herd end date. The difference in days between a lactation end and start dates was taken as days at risk (**DAR**), and no minimum was imposed on DAR. The average number of DAR for a given lactation over the 4-yr study was 281 d. This average was 270, 335, 332, and 135 d for calving years 1996 to 1999, respectively. Notice the shorter lactation averages of the first and last years of the study.

All cows in a herd were started at the same time. This introduced an additional source of variation because of the variable lactation stages of cows at their herd start date. The difference in days between a cow's starting date and its most recent calving date was taken as days in milk for a lactation at the start of the data collection period (**BDIM**), and was used in the model of analysis as a covariate (de Haas et al., 2002). If the preceding calving of a cow occurred more than 450 d before the herd start date or if calving occurred at or after the herd start date, BDIM was assigned a value of 0. Eighteen percent of lactations had started before their corresponding herd start dates and average BDIM in data was 31 d. The other 82% were for subsequent lactations of cows that existed at the herd start date or for cows that entered the herd (as replacements) later in the study.

A binary response variable was created for a disease or a group of diseases of interest. If a cow contracted the disease at least once over a lactation, a response of 1 was attributed to the record. For a cow that calved during the monitoring period of a herd and that was never recorded for the disease or group of diseases of

Table 2. Characteristics of data used in the genetic analysis of disease resistance.

Data set	Herds (no.)	Sires (no.)	Cows (no.)	Records (no.)
Infectious diseases	136	1267	12,701	22,177
Udder health	110	1218	10,864	19,152
Infectious reproductive	69	1184	8998	16,077
Uterine infection	41	1009	6094	10,874
Displaced abomasum	46	1039	6731	12,080
Cystic ovary	46	1011	5899	10,332
Cystic corpora lutea	29	899	4619	8489
Milk fever	22	847	4381	7883

interest, a healthy record with a response of 0 was created. Table 2 lists 8 conditions of interest along with characteristics of their corresponding data sets. Information about recurrence of a condition was part of the data. Recurrence was not considered within a lactation but was considered across lactations of a cow, i.e., a second record for the cow was created if it contracted the same disease at least once in a subsequent lactation.

Data sets in Table 2 differed in size because a minimum of 2 cases per herd was applied, i.e., to include a herd in the analysis, 2 disease cases must appear in the herd. Therefore, herds with no disease conditions were excluded from the analysis, which avoided the extreme category problem (Harville and Mee, 1984). No similar restrictions were imposed on sires.

Diseases of Interest

Infectious diseases. First, all available infectious conditions were used to identify animals that were superior in their generalized immunity (**GI**). Generalized immunity (including innate immunity) may be thought of as a combination of immune responses to a variety of immune system challenges to identify animals that are better able to respond to a variety of challenges. Selection for **GI** may genetically improve the overall health and performance of animals continuously exposed to unknown, new or old, infectious challenges. It may also be helpful in cases where selection for a single mode of resistance (i.e., single disease) adversely affects resistance to other diseases (Bishop, 2003).

At the immunological level, the distinction between selecting for resistance to a specific disease and generalized immunity may not be clear. For instance, allelic variants that positively affect immunity to many pathogens may be part of the innate immune system, hence their frequencies increase when selecting for a specific or generalized immunity. Mallard et al. (1998) (in pigs), and Pinard et al. (1992) and Sarker et al. (1999) (in chickens), demonstrated the feasibility of selecting for **GI** for several generations. In the current study, genetic

parameters for resistance to several diseases (immunologically controlled) are estimated for the purpose of genetic improvement of **GI**. This is achieved using data on diseases that are immunologically controlled. In addition to pigs and chicken, Kelm (1998) and Kelm et al. (2001) quantified general immune responsiveness of dairy sires. Up to 14 immune response traits were measured and genetic parameters of the traits were estimated.

Infectious conditions considered included mastitis and udder infections (3801 conditions); reproductive, respiratory, navel, and kidney infections (2139 conditions); and skin and foot infections (257 conditions). These conditions are caused by pathogens and, hence, resistance is thought to be immunologically controlled. Lactational incidents, not multiple disease conditions over a lactation, constituted the response variable used in the analysis.

Other infectious diseases. Liability to single infectious diseases was also studied. Mastitis [referred to as udder health (**UH**)] as a major infectious disease in the dairy cow was modeled. Mastitis conditions were reported according to infected quarters. In the current study, a cow that expressed symptoms of udder infection, regardless of the infected quarter, was assigned a response of 1.

In addition to mastitis, 3 reproductive infectious conditions were combined into one category and modeled as a single disease (**IR**). The category included uterine infection (661 conditions), retained placenta (322 conditions), and abortions caused by infection (325 conditions). Infection may not be the only cause of retained placenta but infection is a frequent consequence of retained placenta. The modeling of only uterine infection as a single reproductive condition was also studied and was compared with the **IR** category.

Noninfectious diseases. Noninfectious diseases are hard to aggregate and analyze together because of the different mechanisms controlling each disease. In the current study, displaced abomasum and milk fever were analyzed as major noninfectious conditions. In addition, a category of ovarian cysts was created by combining 3 major cystic disorders of the ovary: follicular cysts (296 conditions), luteinized follicular cysts (609 conditions), and cystic corpora lutea (**CCL**) (404 conditions). The category is usually referred to in the literature as cystic ovarian disease (**COD**) and is frequently thought of as one disease, clinically defined as the presence of an anovulatory follicle-like structure greater than 2.5 cm for 10 d or more in the absence of a corpus luteum (Morrow, 1980; Garverick, 1997). To compare genetic parameters estimated for the **COD** category, with its 3 types of cysts, to estimates obtained by ana-

lyzing a single type of cysts, CCL was analyzed separately.

Measures of Disease Frequencies

Two main epidemiological measures were used to determine the frequency of occurrence of each disease, prevalence and incidence rate. Prevalence was expressed as the number of existing cases of a disease divided by the population size. Only conditions recorded in 1998 were used to compute the 1-yr prevalence of each disease (Rothman and Greenland, 1998). The use of conditions of all 4 yr to evaluate 4-yr prevalence would have introduced inaccuracies because not all herds were being recorded over the longer period. For the infectious disease (ID) category, there were 1067 infected lactations and 7431 total lactation records available in 1998 to compute period prevalence.

A second measure for disease frequency that incorporates data over the whole trial period is incidence rate (Rothman and Greenland, 1998; de Haas et al., 2002). Incidence rate is expressed as the total number of affected lactations divided by the sum of the total number of days on trial for all cows, i.e., sum of DAR. For the analysis of ID, there were 6,425,136 DAR. Incidence rate, as an epidemiological measure, is very flexible in allowing study subjects to enter the study at different times and it makes handling of culls or deaths easy, for these simply contribute fewer days to the denominator (Bhopal, 2002). It must be realized, however, that incidence rate is a crude measure that assumes that the disease occurs evenly over time and across subjects.

Statistical Analysis

Models. Health data were analyzed with a threshold model (Harville and Mee, 1984). A linear mixed model was fit to an underlying continuous response variable that is both genetic and environmental in origin (Falconer, 1989). The model included herd, year of calving, season of calving, and parity as cross-classified fixed factors; and sire and cow within sire as nested random effects. Days at risk and BDIM were included by fitting the days as linear covariates in the model. Sire was treated as a random factor with a covariance structure proportional to the relationship matrix among sires. Relationships were traced through sires of sires and maternal grand sires of sires. Cow was also included as a random factor in the model to account for permanent cow effects. The linear model can then be expressed as

$$Y_i = \mu + \text{herd}_{a(i)} + \text{year}_{b(i)} + \text{season}_{c(i)} + \text{parity}_{d(i)} + \text{sire}_{f(i)} + \text{cow}_{g(i)} + \rho \text{DAR}_i + \delta \text{BDIM}_i + e_i$$

where a, b, c, d, f , and g are mapping functions (Harville and Mee, 1984) identifying the herd, year, season, parity, sire, and cow that correspond to the i th lactation in data ($i = 1$ to N and N is the total number of records in a data set of Table 2); ρ and δ are regression coefficients to be estimated; and DAR_i , BDIM_i , and e_i are days at risk, BDIM, and a residual component corresponding to the i th lactation, respectively. Six levels of season were considered that were functions of the month of calving so that $\text{season}_{c(i)}$ spans the 2 consecutive months, $2*c(i) - 1$ and $2*c(i)$, where $c(i) \in \{1, 6\}$. Five levels of parity were considered, where the fifth level is cows in their fifth and greater lactations. Year effect was composed of 4 levels, 1996 to 1999, and levels of herd, sire, and cow factors are listed in Table 2. Herd, year, and season were fit as separate factors as opposed to a herd-year-season factor to avoid the extreme-category problem resulting from very few records in a herd-year-season subclass.

Higher order polynomials for DAR and BDIM were tested along with other factors in the model. Model selection was performed in S-PLUS by fitting generalized linear fixed models of the binomial family (Venables and Ripley, 1998).

Let $\mathbf{y}$, $[Y_1, \dots, Y_N]'$, denote the underlying continuous response variable, $\mathbf{w}$, $[W_1, \dots, W_N]'$, denote the observable dichotomous response variable, then $\mathbf{y}$ could be expressed in matrix form as

$$\mathbf{y} = \mathbf{X}_1 \mathbf{b}_1 + \mathbf{X}_2 \begin{bmatrix} \rho \\ \delta \end{bmatrix} + \mathbf{Z}_1 \mathbf{u} + \mathbf{Z}_2 \mathbf{v} + \mathbf{e} \quad [1]$$

where $\mathbf{X}$, $[\mathbf{X}_1 \mathbf{X}_2]$, and $\mathbf{Z}$, $[\mathbf{Z}_1 \mathbf{Z}_2]$, are known matrices; $\mathbf{b}$, $[\mathbf{b}_1 \rho \delta]'$, is a vector of unknown fixed effects; $\mathbf{a}$, $[\mathbf{u} \mathbf{v}]'$, is a vector of unknown random effects of sires ($\mathbf{u}$) and cows ($\mathbf{v}$); and $\mathbf{e}$ is a vector of residuals. Further, $\mathbf{u} \sim \text{MVN}(\mathbf{0}, \sigma_u^2 \mathbf{D}_u)$, $\mathbf{v} \sim \text{MVN}(\mathbf{0}, \sigma_v^2 \mathbf{D}_v)$, and $\mathbf{e} \sim \text{MVN}(\mathbf{0}, \sigma_e^2 \mathbf{I})$, where $\mathbf{D}_u = \gamma \mathbf{A}$ and $\mathbf{D}_v = \lambda \mathbf{I}$, with $\mathbf{A}$ representing the relationship matrix among sires, $\gamma = \sigma_u^2 / \sigma_e^2$, and $\lambda = \sigma_v^2 / \sigma_e^2$. Finally, $\mathbf{y} \sim \text{MVN}(\mathbf{Xb}, \sigma_e^2 \mathbf{V})$ with $\mathbf{V} = \mathbf{I} + \mathbf{ZDZ}'$, where $\text{var}(\mathbf{a}) = \mathbf{D}$ which is a block diagonal matrix with two blocks, $\mathbf{D}_u$ and $\mathbf{D}_v$. The relationship between Y_i and W_i is taken to be

$$\begin{aligned} Y_i \leq 0 &\Leftrightarrow W_i = 0 \\ Y_i > 0 &\Leftrightarrow W_i = 1 \end{aligned} \quad [2]$$

In the analysis of our data, a standardized version of the TM equations was solved and estimates for fixed effects were obtained.

Sire solutions were obtained and represented sire transmitting abilities. Estimate of the parameters γ and λ were obtained and h^2 was estimated as $4\gamma/\sigma_p^2$,

Table 3. Epidemiological measures of disease frequency, additive genetic variances ($\hat{\gamma}$), and heritabilities for diseases.

Disease	Incidence rate	Prevalence ¹	Mean liability ²	($\hat{\gamma}$)	h^2 (SE)
Infectious diseases	0.00042038	0.1453	0.1218	0.059	0.202 (0.083)
Udder health	0.00030129	0.1038	0.0888	0.041	0.161 (0.0776)
Infectious reproductive	0.00017443	0.0618	0.0524	0.015	0.057 (0.0285)
Uterine infection	0.00013651	0.0506	0.0418	0.037	0.141 (0.0734)
Displaced abomasum	0.00009910	0.0331	0.0296	0.022	0.087 (0.041)
Cystic ovary	0.00015263	0.0453	0.0453	0.007	0.030 (0.047)
Cystic corpora lutea	0.00010406	0.0475	0.0320	0.028	0.110 (0.062)
Milk fever	0.00005335	0.0207	0.0162	0.095	0.349 (0.179)

¹One-year prevalence (1998).²Proportion of affected lactations.

and c^2 , proportion of the cow variance to the total variance, was estimated as λ/σ_p^2 , where $\sigma_p^2 = 1 + \gamma + \lambda$. Estimates of γ and λ along with their asymptotic variance covariance matrix were obtained by Matvec (Wang et al., 2003). Average information-REML, which is implemented in Matvec, with a probit link function was used in the analysis except for ID and UH where a Logit link function was used. With low incidence in data as encountered with single conditions, a probit link function was slower but more robust than a logit link function that did not always converge.

Standard errors of h^2 were estimated as $\sqrt{\text{Var}(h^2)}$, where $\text{Var}(h^2)$ was approximated by, $h^4\{\text{Var}(\gamma)/\gamma^2 + \text{Var}(\sigma_p^2)/\sigma_p^4 - 2[\text{Var}(\gamma) + \text{Cov}(\gamma, \lambda)]/(\gamma + \gamma^2 + \gamma\lambda)\}$. Similarly, the standard error of c^2 was approximated as the square root of $c^4\{\text{Var}(\lambda)/\lambda^2 + \text{Var}(\sigma_p^2)/\sigma_p^4 - 2[\text{Var}(\lambda) + \text{Cov}(\gamma, \lambda)]/(\lambda + \lambda^2 + \gamma\lambda)\}$. Variance of ratios can be found in Mood et al. (1974).

Hypothesis testing for important contrasts was performed on the underlying scale, model [1]. Seasonal and parity differences were tested for the health conditions studied to determine their magnitudes and directions as risk factors. Linear contrasts were tested in Matvec (Wang et al., 2003).

RESULTS AND DISCUSSION

Disease traits were coded as 1 when the disease occurred and 0 otherwise. As a result, greater values of solutions imply adverse association with disease occurrence and smaller values imply desirable association with disease resistance. Incidence rate, prevalence, mean liability, and heritability are listed for all diseases in Table 3.

Immunologically Controlled Disease Resistance

Infectious diseases. As listed in Table 3, the h^2 estimate of ID was 0.202 ± 0.083 . An estimate of the param-

eter c^2 was also obtained, 0.083 ± 0.0527 . The moderate heritability value for ID indicates the potential of selection to genetically improve generalized immunity. Compared with heritabilities of GI estimated from immune response traits, the current value is not as high. Pinard et al. (1992) obtained a heritability estimate of 0.31, and Sarker et al. (1999) obtained heritability estimates of 0.61 and 0.52 in selected lines for serum IgM and IgG levels, respectively.

Days at risk showed a positive relationship with occurrence of the diseases. Table 4 lists regression coefficients for both DAR and BDIM for all disease traits. An estimate of 0.0021 for ρ was found and was significantly different from 0 (0.0021 ± 0.0003 , $P < 0.01$). Figure 1A shows the effect of adjusting for DAR. Two fixed effect models with and without DAR were fit to the same data. When the DAR covariate was removed, disease occurrence was overestimated. Overestimation was more severe in lactations with fewer than 150 DAR. A slight underestimation was also noticed very late in lactation or with lactations that continued for over 350 d (Figure 1A).

Average number of DAR for lactations of the first and last years were less than those of the middle years. Therefore, accounting for year as a fixed factor in the model adjusted partly for the unequal number of DAR. This can be seen from Figure 1B, which shows that removing both year and DAR from the model further introduced more bias compared with Figure 1A, where year is included.

The regression coefficient of BDIM (δ) was also significantly different from 0 (-0.0055 ± 0.0007 , $P < 0.01$) but negative, which indicated more disease occurrences early in lactation, or equivalently reduced immunity with less BDIM.

Season solutions showed a positive difference (0.461 ± 0.082 , $P < 0.01$) between season 1 and season 4. Solution for season 1 was 0.31 and for season 4 was -0.15 . This difference indicates less disease occurrence or

Table 4. Regression coefficients for days at risk (DAR) and days in milk (BDIM) for disease traits.

Data set	DAR		BDIM	
	Coefficient	SE	Coefficient	SE
Infectious diseases	0.0021	0.00030	-0.0055	0.00070
Udder health	0.0053	0.00122	-0.0065	0.00089
Infectious reproductive	0.0012	0.00026	-0.0013	0.00060
Uterine infection	0.0011	0.00036	-0.0019	0.00104
Displaced abomasum	0.0007	0.00035	-0.0021	0.00090
Cystic ovary	0.0037	0.00038	-0.0019	0.00080
Cystic corpora lutea	0.0039	0.00052	0.0011	0.00098
Milk fever	0.0007	0.00061	-0.00032	0.00157

equivalently better GI for cows that calved in summer than in winter.

Disease occurrence across different parities did not seem to differ greatly. Lactation number was, however, a significant factor in the model and the solutions indicated that older cows (those in their fifth or greater lactation) had the poorest GI compared with cows in their first to fourth lactation. Average solution for lactations 1 to 4 was -0.028 vs. 0.12 as the solution for lactation 5. The null hypothesis $H_0: \text{parity}_{(5)} = \frac{1}{4} \sum_{i=1}^4 \text{parity}_{(i)}$

for the difference between $\text{parity}_{(5)}$ and the average of all other parities was rejected (-0.146 ± 0.058 , $P < 0.05$) confirming the reduced GI of older cows in data.

Udder Health. A moderate heritability value was estimated for mastitis, 0.161 ± 0.078 . The model did not include the cow factor because it hindered convergence. The model included an extra covariate for DAR^2 as the highest order significant polynomial for days at risk. Higher order polynomials for BDIM were not significant and were not included. The h^2 value estimated from data supports estimates reported in Uribe et al. (1995) and further assures the potential of genetic improvement of resistance to mastitis.

A positive regression coefficient, 0.0053 ± 0.00122 , was estimated for DAR and was significantly different from 0 ($P < 0.01$). The positive value indicates that disease frequency increases with DAR. A negative coefficient was estimated for BDIM (-0.0065 ± 0.00089). The value is larger in magnitude than the corresponding value estimated for ID indicating more importance to the stage of lactation when modeling udder health. The negative coefficient implies more mastitis in early lactation stages.

Season solutions showed increased udder health problems in winter than in summer, which is in agreement with other studies (e.g., Lescourret et al., 1995). Season 4 was the best and season 1 was the worst with a difference of 0.484 ± 0.099 ($P < 0.01$). Lactation solutions showed a trend toward more udder health problems with older cows but with no significant

difference between lactations 1 and 4. Solutions for lactations 1 to ≥ 5 were -0.24 , -0.13 , 0.0 , 0.03 , and 0.24 , respectively.

Infectious reproductive conditions. A heritability of 0.057 ± 0.0285 and c^2 of 0 were estimated for reproductive conditions immunologically controlled (infectious). This included uterine infection, abortion, and retained placenta. The analysis of only uterine infection (UI) as a single reproductive disorder resulted in h^2 estimate of 0.141 ± 0.0734 and c^2 estimate of 0. A positive regression coefficient on DAR was estimated for the UI data. The effect itself was important for modeling uterine infection ($\rho = 0.0011 \pm 0.00036$, $P < 0.01$). Season effect was also important for modeling UI with more disease in cows that calved in winter than in summer. A contrast of $\text{season}_{(4)} - \text{season}_{(1)}$ showed a significant difference ($P < 0.01$) of -0.382 ± 0.0846 . Levels of parity did not differ significantly from each other indicating similar risks for contracting the disease across cows in different parities.

Disease Resistance of Immunity-Unrelated Disorders

In the following, results of selected single diseases and a class of related ovary disorders are presented. Incidence rate and prevalence of immunity-unrelated disorders are generally less than infectious diseases whose resistance is immunologically controlled (Table 3). This resulted in smaller data sets and consequently larger standard errors of estimated genetic parameters.

Displaced abomasum. Cow variance converged to 0. Only 5 cows had the condition twice making repeatability difficult to estimate. The h^2 estimate, 0.087 ± 0.041 , was similar to that of Lyons et al. (1991). Regression coefficient on DAR, ρ , was positive but not significantly different from 0. Regression coefficient on BDIM, δ , on the other hand was significantly lower than 0 ($P < 0.05$) indicating more occurrences in the early stages of lactation.

Parity was an important risk factor for displaced abomasum; a positive association of parity with the occur-

Figure 1. A. Fitted values of a model without DAR (thick line) relative to fitted values of the complete model (thin line). B. Fitted values of a model without DAR and Year (thick line) relative to fitted values of the complete model (thin line). Vertical bars are unadjusted disease liability estimated from raw data.

rence of this disease was found, and solutions were 0.0, 0.10, 0.15, 0.28, and 0.23 for parities 1 to ≥ 5 . The difference, $parity_{(5)} - parity_{(1)}$, was significantly different from 0 (0.234 ± 0.073 , $P < 0.05$). Season solutions showed more occurrences of displaced abomasums in cows that calved in winter and spring than those calved in summer and fall.

Cystic ovarian disease. When the 3 major categories of ovarian cysts, cystic corpora lutea, follicular cysts, and luteinized follicular cysts were analyzed as cystic ovarian disease (COD), the heritability estimated was near 0 (0.030 ± 0.0470). A higher estimate was obtained when the single condition, CCL, was modeled alone, resulting in a heritability estimate of 0.110 ± 0.062 [note that the presence of CCL may not be considered a pathological condition if the CCL produce progesterone (Morrow, 1980)]. Results show that combining the 3 cystic disorders of the ovary, despite being closely related, resulted in almost no additive genetic variance ($\sigma_u^2 = 0.007$ for cystic ovarian disease vs. 0.028 for CCL, Table 3).

Days at risk had a positive, unfavorable, relationship with incidences of COD ($\rho = 0.0037 \pm 0.00038$, $P < 0.01$). Days in milk, on the other hand, had a negative relationship with incidences of COD ($\delta = -0.0019 \pm 0.0008$, $P < 0.05$) indicating more COD occurrences in early stages of lactation. Season of calving was identified as a significant risk factor. Cows that calved in winter were more likely to develop COD than those that calved

in summer and fall. The COD data showed a difference of -0.259 ± 0.0597 , ($P < 0.01$) for $(Season_3 + Season_4)/2 - (Season_1 + Season_6)/2$. However, there is no consensus in the literature about calving season as a risk factor for COD (Garverick, 1997). Finally, there was a positive, unfavorable association between high parity and the development of COD but there was no significant difference between the first 2 lactations and older lactations.

Milk fever. The heritability estimate of milk fever as a single metabolic disorder was 0.349 ± 0.179 . The value is much higher than the 0.09 estimated by Uribe et al. (1995) but smaller than the 0.40 estimated by Lyons et al. (1991) and similar to the 0.30 estimated by Lin et al. (1989). There was no evidence that season of calving was a significant risk factor but lactation number was a risk factor indicating higher incidences of milk fever in cows in their fourth or higher parities compared with cows in their earlier parities. The null hypothesis $H_0: \frac{1}{3} \sum_{i=1}^3 parity_{(i)} - (parity_{(4)} + parity_{(5)})/2 =$

0 was rejected (-0.871 ± 0.117 , $P < 0.01$). Parity is largely accepted in literature as a major risk factor for milk fever (e.g., Houe et al., 2001; Ostergaard et al., 2003) acting in the same direction as found in the current study.

Sufficiency of Health Data to Estimate Cow Variance

Cow was accounted for in the model of analysis, [1], as a random effect to adjust for permanent cow effects

Table 5. Frequency of cows with 1 affected lactation, with greater than 1 affected lactation, and with greater than 2 affected lactations. Estimates of the parameter λ and corresponding standard errors (SE) are shown.

Disease	Affected cows (no.)			$\hat{\lambda}$ (SE)
	1	>1	>2	
Infectious diseases	2108	287	19	0.0964 (0.0606)
Udder health	1333	180	8	NA ¹
Infectious reproductive	792	25	0	0 (0)
Uterine infection	434	10	0	0 (0)
Displaced abomasum	348	5	0	0 (0)
Cystic ovary	446	11	0	NA
Cystic corpora lutea	254	9	0	NA
Milk fever	122	3	0	NA

¹NA indicates that cow factor was not included in the model.

associated with repeated health records on the same cow. Cow factor included nonadditive genetic, three-quarters of the additive genetic, and other permanent nongenetic effects. Table 5 shows that health data did not always contain sufficient information to obtain reasonable estimates of cow variance. The parameter λ was either imprecisely estimated as for the ID category, or an estimate was not possible or converged to 0 in other cases. It can also be seen from Table 5 that recurrence of another affected lactation on the same cow was rare (columns ">1" and ">2"). Rarity of repeated affected lactations as a possible reason for 0 estimates of the parameter λ was verified by excluding extreme cows with multiple affected lactations and repeating the analysis for the ID category, i.e., after excluding records of 287 cows with 2 or more affected lactations (Table 5). The latter analysis resulted in a 0 estimate of λ . Further, repeating the analysis without cows with 3 or more affected lactations yielded a positive, but insignificant, estimate of λ , 0.0313 ± 0.1926 .

Rarity of repeated affected lactations is in many cases a characteristic of health data. It is reasonable to expect that cows that repeatedly get the same disease every lactation (e.g., UI) are not common. In other cases (e.g., mastitis), cows that repeatedly become infected are

likely to be culled. Finally, in our coding of health traits, multiple conditions over one lactation counted as one affected record. Fortunately, despite this characteristic of health data, there was no interest in estimating the parameter λ as opposed to the interest in γ that is entirely additive genetic.

Correlations Among Predicted Sire Transmitting Abilities for Disease Traits

Random sire effects of model [1] can be viewed as sire transmitting abilities. Correlation coefficients among predicted transmitting abilities of sires with 10 or more daughters for the 8 disease traits were calculated and the coefficients are listed in Table 6.

Correlations among predicted sire transmitting abilities for the 8 disease traits were positive and relatively stronger among infectious diseases than noninfectious diseases. Also, sire predicted transmitting abilities for the ID category were strongly correlated with transmitting abilities predicted for other infectious diseases, which indicates the desirable impact of selecting for generalized immunity on other infectious diseases. No practically useful correlation was found between the ID category and noninfectious diseases. Data overlap for some of the conditions listed in Table 6 contributed to the correlations.

CONCLUSIONS

The genetic basis of disease resistance has been established for both infectious and noninfectious diseases. Based on the moderate heritability estimated for a category of all infectious diseases, a substantial genetic component is thought to be associated with the immune system. This also implies that this category of infectious diseases may be used to select for individuals with improved generalized immunity. Predicted breeding values of sires for the category of infectious diseases were strongly correlated with breeding values predicted for single infectious diseases. This demonstrates further

Table 6. Correlations among sire estimated transmitting abilities using sires with 10 or more daughters for disease liability.¹

	ID	UH	IR	UI	DA	COD	CCL	MF
ID	1							
UH	0.789	1						
IR	0.724	0.386	1					
UI	0.535	0.262	0.714	1				
DA	0.202	0.281	0.132	-0.094	1			
COD	0.129	0.227	0.224	-0.030	-0.091	1		
CCL	0.125	0.137	0.151	-0.079	-0.004	0.655	1	
MF	0.006	-0.006	-0.008	-0.108	0.151	0.110	0.050	1

¹ID = Infectious diseases; UH = udder health; IR = infectious reproductive; UI = uterine infection; DA = displaced abomasum; COD = cystic ovarian disease; CCL = cystic corpora lutea; MF = milk fever.

the desirable impact of the category of infectious diseases as a selection tool. The study also found significant additive genetic components associated with resistance to specific infectious and noninfectious diseases.

The amount of additive genetic variance recovered in the underlying scale of noninfectious disorders tended to 0 when combining multiple conditions. Our study supports combining infectious diseases into categories of interest but does not support the same approach for noninfectious disorders.

Season of calving and parity are important environmental risk factors for disease liability. Statistical analyses showed that cold months increased the risk of contracting diseases and that resistance deteriorated in older cows. Our study also showed the importance of accounting for days at risk and days in milk at the beginning of a record when analyzing health records.

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REFERENCES

- Abdel-Azim, G., and P. J. Berger. 1999. Properties of threshold model predictions. *J. Anim. Sci.* 77:582–590.
- Bhopal, R. 2002. Concepts of epidemiology – An integrated introduction to the ideas, theories, principles and methods of epidemiology. Oxford University Press, Oxford, UK.
- Bishop, S. C. 2003. Breeding for disease resistance using genetics and epidemiology. Workshop at Iowa State University, Ames, IA.
- de Haas, Y., H. W. Barkema, and R. F. Veerkamp. 2002. Genetic parameters of pathogen-specific incidence of clinical mastitis in dairy cows. *Anim. Sci.* 74:233–242.
- Falconer, D. S. 1989. *Introduction to Quantitative Genetics*. 3rd ed. Longman, New York, NY.
- Garverick, H. A. 1997. Ovarian follicular cysts in dairy cows. *J. Dairy Sci.* 80:995–1004.
- Gianola, D., and J. L. Foulley. 1983. Sire evaluation for ordered categorical data with a threshold model. *Genet. Sel. Evol.* 15:201–224.
- Hansen, L. B., C. W. Young, K. P. Miller, and R. W. Touchberry. 1979. Health care requirements of dairy cattle. I. Response to milk yield selection. *J. Dairy Sci.* 62:1922–1931.
- Hansen, M., M. S. Lund, M. K. Sorensen, and L. G. Christensen. 2002. Genetic parameters of dairy characters, protein yield, clinical mastitis, and other diseases in the Danish Holstein cattle. *J. Dairy Sci.* 85:445–452.
- Harville, D. A., and R. W. Mee. 1984. A mixed-model procedure for analyzing ordered categorical data. *Biometrics* 40:393–408.
- Heringstad, B., R. Rekaya, D. Gianola, G. Klemetsdal, and K. A. Weigel. 2001. Bayesian analysis of liability of clinical mastitis in Norwegian cattle with a threshold model: Effects of data sampling method and model specification. *J. Dairy Sci.* 84:2337–2346.
- Heringstad, B., R. Rekaya, D. Gianola, G. Klemetsdal, and K. A. Weigel. 2003. Genetic change for clinical mastitis in Norwegian cattle: A threshold model analysis. *J. Dairy Sci.* 86:369–375.
- Houe, H., S. Ostergaard, T. Thilising-Hansen, R. J. Jorgensen, T. Larsen, J. T. Sorensen, J. F. Agger, and J. Y. Blom. 2001. Milk fever and subclinical hypocalcaemia. An evaluation of parameters on risk, diagnosis, risk factors, and biological effects as input for a decision support system for disease control. *Acta Vet. Scand.* 42:1–29.
- Kelm, C. S. 1998. Immunological parameters of Holstein bulls expressed within the context of a glucocorticoid-induced model of immunosuppression. Ph.D. Dissertation, Iowa State Univ., Ames, IA. University Microfilm No. AAC9911609.
- Kelm, S. C., A. E. Freeman, and M. E. Kehrli, Jr. 2001. Genetic control of disease resistance and immunoresponsiveness. *Vet. Clin. North Am. Food Anim. Pract.* 17:477–493.
- Lescouret, F., J. B. Coulon, and B. Faye. 1995. Predictive model of mastitis occurrence in the dairy cow. *J. Dairy Sci.* 78:2167–2177.
- Lin, H. K., P. A. Oltenacu, L. D. VanVleck, N. H. Erb, and R. D. Smith. 1989. Heritabilities of and genetic correlations among six health problems in Holstein cows. *J. Dairy Sci.* 72:180–186.
- Lyons, D. T., A. E. Freeman, and A. L. Kuck. 1991. Genetics of health traits in Holstein cattle. *J. Dairy Sci.* 74:1092–1100.
- Mallard, B. A., B. N. Wilkie, B. W. Kennedy, J. Gibson, and M. Quinton. 1998. Immune responsiveness in swine: Eight generations of selection for high and low immune response in Yorkshire pigs. *Proc. 6th World Congr. Genet. Appl. Livest. Prod., Armidale, Australia* 27:257–264.
- Mood, A. M., F. A. Graybill, and D. C. Boes. 1974. *Introduction to the Theory of Statistics*, 3rd ed. McGraw-Hill, New York, NY.
- Morrow, D. A. 1980. *Current Therapy in Theriogenology: Diagnosis, treatment and prevention of reproductive diseases in animals*. W. B. Saunders Company, Philadelphia, PA.
- Ostergaard, S., J. T. Sorensen, and H. Houe. 2003. A stochastic model simulating milk fever in a dairy herd. *Prev. Vet. Med.* 58:125–143.
- Pinard, M. H., J. A. M. Van Arendonk, M. G. B. Nieuwland, and A. J. Van der Zijpp. 1992. Divergent selection for immune responsiveness in chickens: Estimation of realized heritability with an animal model. *J. Anim. Sci.* 70:2986–2993.
- Rothman, K. J., and S. Greenland. 1998. *Modern Epidemiology*. 2nd ed. Lippincott-Raven, Philadelphia, PA.
- Sarker, N., M. Tsudzuki, M. Nishbori, and Y. Yamamoto. 1999. Direct and correlated response to divergent selection for serum immunoglobulin M and G levels in chickens. *Poult. Sci.* 78:1–7.
- Shanks, R. D., A. E. Freeman, P. J. Berger, and D. H. Kelly. 1978. Effect of selection for milk production on reproductive and general health of the dairy cow. *J. Dairy Sci.* 61:1765.
- Shook, G. E. 1989. Selection for disease resistance. *J. Dairy Sci.* 72:1349–1362.
- Uribe, H. A., B. W. Kennedy, S. W. Martin, and D. F. Kelton. 1995. Genetic parameters for common health disorders of Holstein cows. *J. Dairy Sci.* 78:421–430.
- Venables, W. N., and B. D. Ripley. 1998. *Modern and applied statistics with S-PLUS*. 2nd ed. Springer-Verlag New York, Inc., New York, NY.
- Wang, T., R. L. Fernando, and S. D. Kachman. 2003. *Matvec Users' Guide*, Version 1.03. Online. Available <http://statistics.unl.edu/faculty/steve/software/matvec/>. Accessed Apr. 15, 2004.
- Wiggans, G. R. 1994. Meeting the needs at the national level for genetic evaluation and health monitoring. *J. Dairy Sci.* 77:1976–1983.