Chapter 4

Diani lamb data

In this chapter we give a detailed description of the dataset that is used in this second part of the thesis. The dataset comes from an animal breeding program that was carried out by the International Livestock Research Institute (ILRI) from 1991 to 1996. The objective of the experiment was to study genetic resistance to naturally acquired gastro-intestinal nematodes in different breeds of sheep, namely the Red Maasai, Dorper and their crossbreeds. In Section 4.1 we highlight some of the factors that motivated the need for the breeding program. The experimental setup of the study is briefly outlined in Section 4.2 while we report the measurements that were collected in Section 4.3. In total there were 1785 lambs from this breeding experiment. Of these, 696(38%) lambs died while 94 (5%) were lost or stolen before they were one year old. The main causes of death experienced over the six years are reported in Section 4.4. Finally in Section 4.5 we give the motivation for the developments of the new techniques to analyse these data. These new methodologies are discussed in Chapters 5 and 6.

4.1 Background

In the tropics small ruminants (sheep and goats) are an important source of income for many smallholder farmers. They are primarily kept for meat production. However, the productivity of sheep in the tropics is often low compared with animals in temperate regions. An important factor contributing to this low productivity is high mortality rate;

in tropical environments between 20% and 50% of the lambs born can die before weaning (Gatenby, 1986, Mukasa-Mugerwe et al., 2000, Wilson et al., 1993). Sheep in these regions primarily graze natural pastures or utilise crop residues. It is then not surprising that infections with gastrointestinal (GI) nematode parasites (endoparasites) are commonly one of the major causes of mortality (Over et al., 1992).

Current control methods for GI nematode parasites focus on reducing contamination of pastures through anthelmintic treatment and/or controlled grazing (Barger, 1999). In Africa, the use of these control methods is limited by the high cost of anthelmintics, their uncertain availability and increasing frequency of drug resistance (Waller, 1997). There is also limited scope in many communal pastoral systems for controlled grazing. It appears unlikely that new broad-spectrum anthelmintics will be available in the near future because of the major costs associated with the development of new products. To date, no commercial vaccines are available to control GI nematode parasites (Smith, 1999). The characterization and utilization of host genetic variation for resistance to endoparasites is thus an alternative approach to control endoparasites.

Variation among sheep breeds in resistance to GI nematode parasites has been extensively studied over the past half century (Gray et al., 1995). The reported findings of the above mentioned experiment (Baker et al., 1999, 2003) now show strong evidence that the Red Maasai (R) are both more resistant and resilient to naturally acquired and artificial infections with GI nematode parasites than other breeds notably the Dorper (D). Resilience (or tolerance) is defined as the ability of the host to survive and be productive in the face of parasite challenge while resistance is defined as the initiation and maintenance of responses provoked in the host to suppress the establishment of parasites and/or eliminate parasite burdens (Baker et al, 2003).

The Red Maasai is an East African fat-tailed sheep breed, which is associated with the Maasai tribe found in northern Tanzania and south-central Kenya (Wilson, 1991). The Dorper breed was developed in South Africa in the 1940s by interbreeding the Dorset and the Blackhead Persian breeds (Milne, 2000). The Dorper has a reputation for being well adapted to harsh, arid conditions (Cloete et al., 2000) and was first imported into Kenya from South Africa in the 1960s. It is also a popular breed for meat production.

4.2 Experimental design

In the first year of the study (1991) Dorper and RxD ewes were mated to 12 Dorper and 12 Red Maasai rams in single sire mating groups of about 18 animals in a partial diallel design. In a diallel design purebred and half-crossbred dams are mated with purebred sires from each of the breeds. In the subsequent years all three ewe genotypes (Dorper, Red Maasai, RxD) were mated to 12 Dorper and 12 Red Maasai rams to generate six lamb breeds or crosses (Table 4.1). A total of 264 Dorper, 312 RxD and 138 Red Maasai ewes were used in the six years. About 7-8 new rams of each breed were used at each mating so that 35 different Red Maasai rams and 41 different Dorper rams were used over the entire study. All Dorper and Red Maasai rams purchased were as unrelated as possible to ensure a representative genetic sample.

Table 4.1: *Numbers of lambs born by year of birth and genotype (D=Dorper, R=Red Maasai), numbers treated for GI nematode parasites at one and two months of age prior to weaning, and numbers weaned at about three months of age and the deaths after weaning.*

Genotype	Year of Birth						
(Sire breed x Dam Breed)	1991	1992	1993	1994	1995	1996	Total
D x D	93	65	54	30	39	30	311
D x (R x D)	92	77	93	70	65	35	432
D x R	0	7	38	24	27	27	123
R x D	83	58	57	13	14	9	234
R x (R x D)	99	81	96	61	69	67	473
R x R	0	8	34	45	64	61	212
Total	367	296	372	243	278	229	1785
Number treated pre weaning	221	213	283	60	40	25	842
Number weaned	310	242	347	170	202	171	1442
Deaths or stolen							
Pre-weaning	58	54	25	73	75	58	343
Post-weaning	61	38	175	71	75	27	447

4.3 Data collected

Measurements of packed red cell volume (PCV), faecel egg count (FEC) and body weight (BWT) were taken from lambs up to about one year of age in batches of lambs born in each of the years 1991 to 1996. All lambs were weighed at birth and their BWT, PCV and FEC were subsequently recorded at one and two months of age. On either of these latter occasions, when individual lambs had a FEC greater than or equal to 2,000 eggs per gram (epg) and/or a PCV less than or equal to 20%, they were treated (drenched) with an anthelmintic drug. Packed cell volume and FEC were measured according to methods reported by Baker et al. (1999). PCV is the percentage of red blood cells to the total volume of a blood sample and in general gives a good indication of how anemic an animal is. Thus it is a good indicator of how well the animal is managing to cope with the pathogenic effects of the blood-sucking parasite *Haemonchus contortus*[1] which was the main parasite species that was found in this study. Faecel egg counts on the other hand are known to be highly correlated with worm counts (Woolaston and Baker, 1996). Packed cell volume is often used to measure resilience while FEC is used to measure resistance (Baker et al., 2003).

At about three months of age, the time of weaning, the lambs were again weighed, and blood and faecal samples collected for PCV and FEC, respectively. All lambs were then drenched. The lambs were then left to graze on pasture, separately from the ewes and rams. Every week a monitor group of about 50 lambs, made up of approximately equal numbers of lambs of each genotype and gender, was sampled and their mean FEC recorded. If the mean FEC was over 2,000 epg then, during two consecutive days, all lambs were weighed, faeces and blood samples taken for FEC and PCV respectively and the lambs were then drenched. This procedure was followed until the lambs reached on average one year of age resulting in five drenchings in each year except 1994 and 1996. In 1994 the lambs were drenched eight times post-weaning, while in 1996 six drenchings occurred. A sample of a few data lines is given in the appendix of this chapter while Figures 4.1 to

[1]Adult worms live in the stomach of ruminant animals, females depositing upto 10,000 eggs per day which pass out of the host in the faeces. After a day or two, first stage larvae (L1) hatch. The larvae feed on microorganisms in faeces and developing into the L2 larvae and then L3 larvae stages. L3 larvae are ingested with grass while grazing. Within the stomach the larvae molts two or three more times. In favorable conditions, adult worms develop and feed on the host's blood.

4.3 show scatter plots of the measurements recorded from weaning to 12 months for PCV and FEC and those from birth to 12 months for BWT, across the six years. In each plot individual profiles for a randomly selected sample of 15 lambs are highlighted. In these plots we see that although the lambs were all measured on the same day, the individual measurements are clustered around a particular age. This is due to the fact that in each year, lambs were born within a period ranging from 20-40 days. For example in Figure 4.1 the measurements are clustered around the age of 90 days in 1991 but around the age of 100 days in 1992.

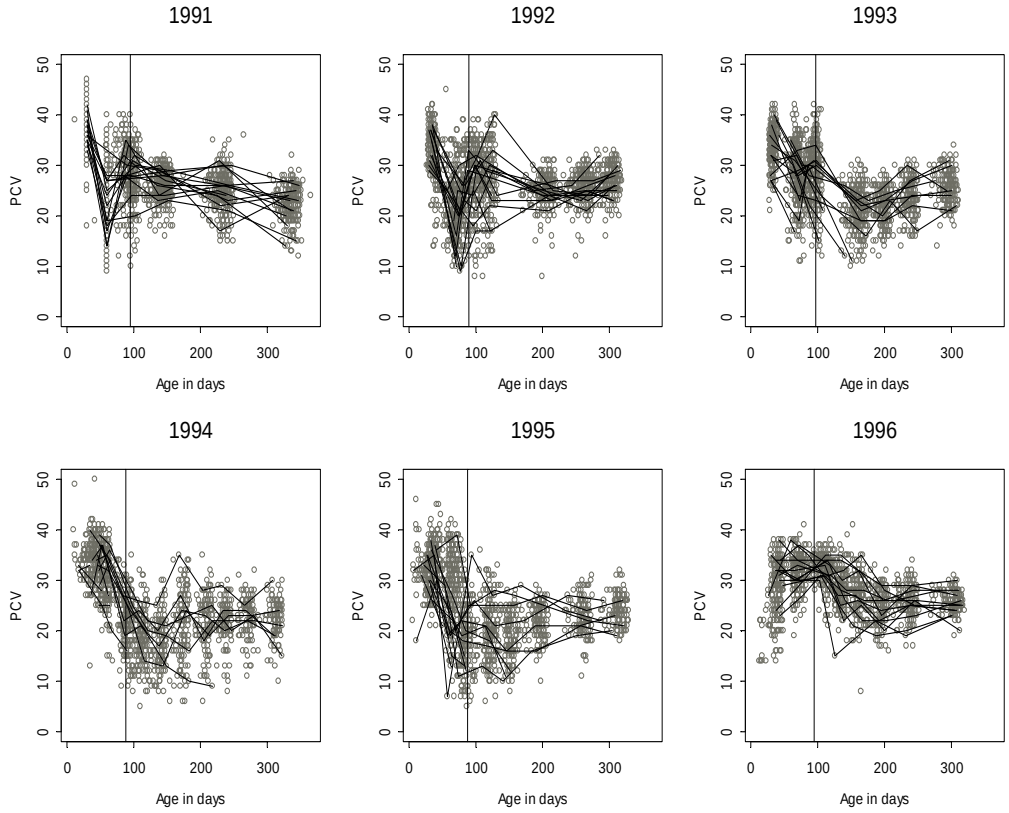


Figure 4.1: *PCV measurements for the years 1991 to 1996. Bold vertical line indicates when the lambs were weaned.*

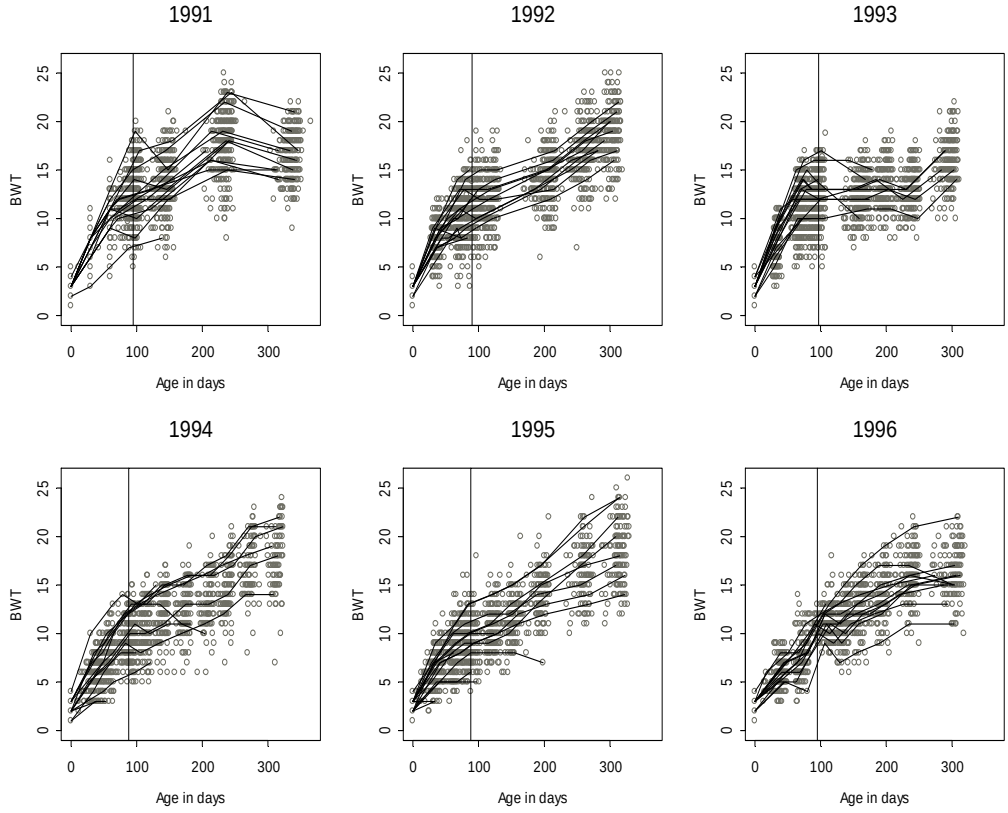


Figure 4.2: *Body weight measurements for the years 1991 to 1996. Bold vertical line indicates when the lambs were weaned.*

4.4 Causes of mortality

As noted in Section 4.1, mortality is the main contributing factor for low productivity of sheep in the tropics. Various causes of mortality were observed in the study. These were grouped into nine categories:

1) still births

2) mis-mothering, e.g. death from suffocation, starvation and weakness at birth

3) endoparasites

4) pneumonia

5) digestive disorders such as bloat and enteritis

6) accidents which included those killed by predators or from plant poisoning

7) lost or stolen

8) miscellaneous diseases such as coccidiosis, dystocia or foot rot

9) unknown causes.

Overall, the deaths resulting from accidents were included in the lost or stolen category since they were few, whilst deaths associated with digestive disorders were included in the miscellaneous category. Further, only two lambs in the pre-weaning period died from an unknown cause. These were also included in the miscellaneous category within this period. This resulted in six and five categories defining the cause of death in the pre-weaning and post-weaning periods, respectively. The break down of the these causes in the pre-weaning and post-weaning periods by genotype is given in Tables 4.2 and 4.3, respectively.

Overall, there were 1785 lamb from this experiment. Of these, 696 (39%) died while 94 (5%) were lost or stolen before they were one year old. Among the deaths, 343 (44%) occurred before weaning, of which about a third were associated with mis-mothering (Table 4.2). Pre-weaning endoparasite infections accounted for about a fifth of the deaths. The major cause of mortality in the post-weaning period was associated with endoparasite

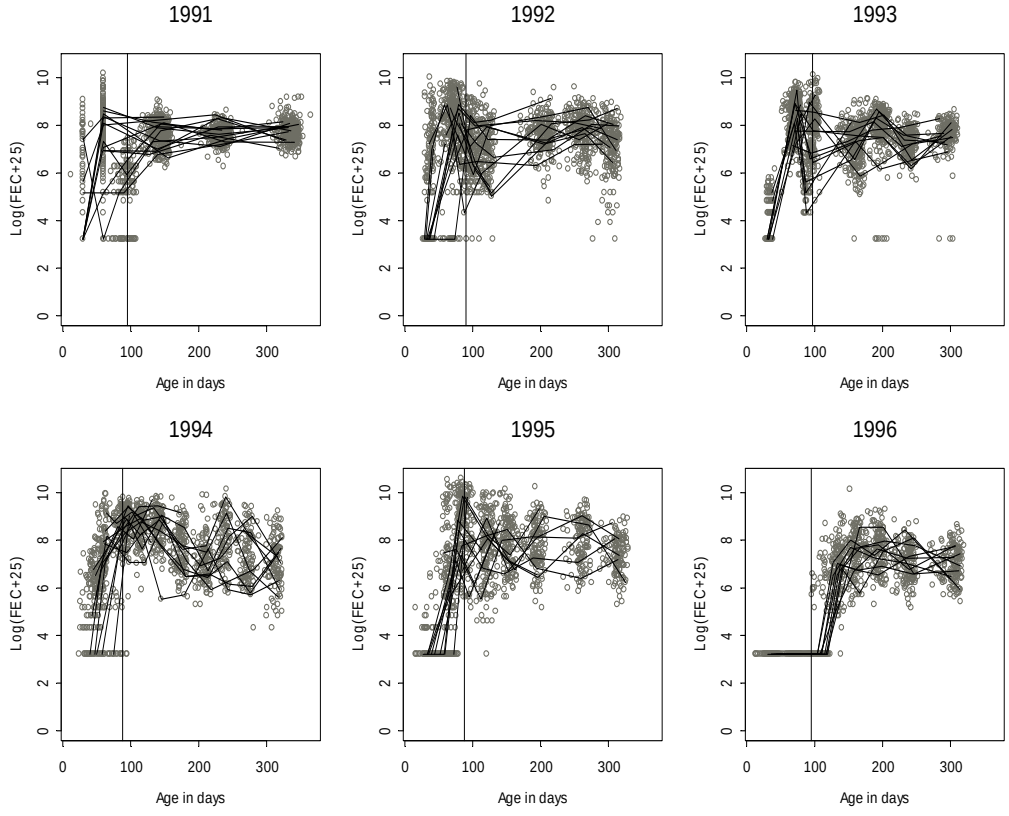


Figure 4.3: *Transformed* log*(FEC+25) measurements for the years 1991 to 1996. Bold vertical line indicates when the lambs were weaned.*

Table 4.2: *Numbers of deaths (proportions) in the pre-weaning (from birth to approximately 90 days) period by cause of death for lambs of different genotypes (D=Dorper, R=Red Maasai) and corresponding overall average mortality rates.*

	D x D	D x (R x D)	D x R	R x D	R x (R x D)	R x R	Total
Number born	311	432	123	234	473	212	1785
Cause of death							
Still births	7(0.08)	13(0.14)	2(0.09)	3(0.09)	7(0.09)	8(0.25)	40(0.12)
Mis-mothering	29(0.33)	29(0.31)	7(0.32)	10(0.29)	22(0.29)	10(0.31)	107(0.31)
Endoparasites	21(0.24)	22(0.24)	6(0.27)	7(0.21)	12(0.16)	3(0.09)	71(0.21)
Pneumonia	6(0.07)	10(0.11)	1(0.04)	5(0.15)	14(0.18)	1(0.03)	37(0.11)
Lost/Stolen	6(0.07)	10(0.11)	0(0.00)	6(0.18)	8(0.11)	2(0.06)	32(0.09)
Miscellaneous	19(0.22)	8(0.09)	6(0.26)	3(0.09)	12(0.16)	8(0.25)	56(0.16)
Total	88(0.28)	92(0.21)	22(0.18)	34(0.15)	75(0.16)	32(0.15)	343(0.19)

infections, accounting for 212 (47%) of the deaths (Table 4.3), while 62 (14%) were lost or stolen. Pre-weaning, average mortality was between 15 and 28% with the Dorper lambs having the highest mortality. The average mortality post weaning was between 17 and 47% which showed a decreasing trend with increasing proportion of Red Maasai in the genotype.

Table 4.3: *Numbers of deaths (proportions) post-weaning (from 90 to 365 days) period by cause of death for lambs of different genotypes (D=Dorper, R=Red Maasai) and corresponding overall average mortality rates.*

	D x D	D x (R x D)	D x R	R x D	R x (R x D)	R x R	Total
Number weaned	224	340	100	200	398	180	1442
Cause of death							
Endoparasites	49(0.46)	71(0.52)	21(0.48)	21(0.45)	28(0.42)	22(0.48)	212(0.47)
Pneumonia	16(0.15)	19(0.14)	4(0.09)	6(0.13)	13(0.20)	3(0.07)	61(0.14)
Lost/Stolen	14(0.13)	20(0.15)	2(0.05)	8(0.17)	13(0.20)	5(0.11)	62(0.14)
Miscellaneous	19(0.18)	23(0.17)	6(0.14)	8(0.17)	11(0.17)	9(0.20)	76(0.18)
Cause unknown	8(0.08)	5(0.04)	11(0.25)	4(0.08)	1(0.01)	7(0.15)	36(0.07)
Total	106(0.47)	138(0.41)	44(0.44)	47(0.24)	66(0.17)	46(0.26)	447(0.31)

4.5 Motivation

To assess the genetic resistance of the sheep, which was the objective of the experiment, BWT, PCV and FEC measurements collected at the individual time points (e.g. at weaning and 8 months) have been analysed using the classical linear mixed model (Baker et al., 1994, 1998, 2003, Baker, 1998). The estimated variance components from these analyses have been used to determine heritability estimates.

Heritability helps to explain the degree to which genes control expression of a trait such as BWT, PCV or FEC. In our case, it would be a measure of the degree (0 to 100%) to which the lambs resemble their father(or mother) for the specific trait of interest. For instance, let Y_{ij} denote the observed measurement of the trait of interest for the j^{th} lamb from the i^{th} sire, $i = 1, \ldots, G$ and $j = 1, \ldots, n_i$ at some time point (say 3 months). Then the simple linear mixed model used in this analysis is

$$Y_{ij} = \boldsymbol{x}_{ij}^T \boldsymbol{\beta} + s_i + \epsilon_{ij} \tag{4.1}$$

where $\boldsymbol{x}_{ij}$ is the incidence vector for the fixed effects, $\boldsymbol{\beta}$ is the vector of associated parameters, s_i is the random effect of the i^{th} sire and ϵ_{ij} is the random error term. The assumptions on the random terms are that the s_i are identically and independent distributed (i.i.d) $N(0, \sigma_s^2)$ terms and the ϵ_{ij}'s are i.i.d $N(0, \sigma_e^2)$. Further s_i and ϵ_{ij} are assumed to be independent. Model (4.2) is referred to as a sire model. The sire genetic contribution is then estimated using the heritability measure defined as

$$h_s^2 = \frac{4\sigma_s^2}{\sigma_s^2 + \sigma_e^2}. \tag{4.2}$$

where the numerator is an estimate of the genetic variance while the denominator estimates phenotypic variance. The phenotype of an animal corresponds to the observed measurements e.g., PCV, and is the combined effect of all genetic and environmental influences.

Baker et al. (2003) reports the heritability estimates for the traits BWT, PCV and log(FEC +25) (LFEC) at each measurement time (i.e., birth, 1 month, 2 months, weaning and all post-weaning time points). These analyses were carried out with the linear mixed model (4.2) using the restricted maximum likelihood (REML) estimation method. The ASREML programme of Gilmour et al. (1999) was used to estimate simultaneously both fixed effects and variance components. Their results show that the Red Massai have

higher resistance (lower FEC) and higher resilience (higher PCV) than Dorpers. Baker et al. (1994, 1998) report preliminary results of this study using similar methods of analysis as described above. The performance of the ewes that were dams of the lambs whose data are used in the current study was evaluated by Baker et al. (1999), also using linear mixed models. In that analysis, it was clearly shown that the Red Maasai ewes were more resistant and resilient to GI nematode parasites than the Dorper ewes in a sub-humid tropical environment.

In carrying out the linear mixed model analysis as that described above, only the animals that survived to the time points of interest were utilised. Methodologies such as survival analysis that use the information available for all animals up to the time they die or are lost to follow up can alternatively be used in this assessment. In Chapter 5, survival analysis using shared frailty models is used to assess variations in time to death of the genotypes. In this analysis BWT, PCV and LFEC are considered as time-varying covariates. Kalbfleisch and Prentice(1980) distinguish between two types of time-dependent covariates; *external* and *internal* covariates. External covariates are those whose values do not depend on the survival status of the individual, for example, the monthly rainfall amount. Internal covariates on the other hand are only measured as long as the individual is under observation, like BWT, PCV and FEC. Unlike the external covariates, the internal covariates carry information about the survival pattern of the individuals. For example, high PCV and low FEC values may be associated with higher chances of survival as these are indicators of the health status of the animal.

In the recent past, methodologies, which simultaneously use the information available in survival and such time-varying covariates, have been proposed in medical research. In Chapter 6 we describe and adapt this joint modelling methodology to the animal breeding data, where the time to death of the lamb is modelled jointly with either PCV, BWT or FEC.

VARIABLE	Description
NUMB	Animal number
DAM_ID	Dam identification number
DAM_BRD	Dam breed; 1-DxD, 2-RxD, 5-RxR
SIRE_ID	Sire identification number
SIRE_BRD	Sire breed
YEARB	Year of birth
BREED	Breed of lamb; 1-DxD, 2-RxD, 3-Dx(DxR), 4-Rx(RxD), 5-RxR, 6-DxR
SEX	Gender: 1:-Female, 2:-Male
BIRTHWT	Weight at birth
BIRTH_DT	Date of birth
DISP_DT	Date of death
DACTION	Action at disposal
DREASON	Death reason
DATE30	Date of one month
AGE30	Age at one month
WT30	Weight at one month
PCV30	PCV at one month
FEC30	FEC at one month :-99999 indicates that FEC was not recorded
DATE60	Date of two months
AGE60	Age at two months
WT60	Weight at two months
PCV60	PCV at two months
FEC60	FEC at two months
WEAN_DT	Date of weaning
AGEWEAN	Age at weaning
BIRTH_TY	Type of birth: 1:-single birth, 2:-twin
BIRTHDAY	Day of birthday in the calendar year from 1st January
DAMAGE	Age of the dam
WWT1	Day 1 BWT measurement at weaning
WWT2	Day 2 BWT measurement at weaning
WEANWT	Average of two weaning BWT measurements
WPCV1	Day 1 PCV measurement at weaning
WPCV2	Day 2 PCV measurement at weaning
WEANPCV	Average of two weaning PCV measurements
WFEC1	Day 1 FEC measurement at weaning
WFEC2	Day 2 FEC measurement at weaning
WEANFEC	Average of two weaning FEC measurements
DATE1	Date of 1st post-weaning measurements
AGE1	Age at the 1st post-weaning measurements
WT1A	Day 1 measurement of BWT at 1st post-weaning time point
WT1B	Day 2 measurement of BWT at 1st post-weaning time point
AVWT1	Average of the two BWT measurements at 1st post-weaning time-point
PCV1A	Day 1 measurement of PCV at 1st post-weaning time point
PCV1B	Day 2 measurement of PCV at 1st post-weaning time point
AVPCV1	Average of the two PCV measurements at 1st post-weaning time-point
FEC1A	Day 1 measurement of FEC at 1st post-weaning time point
FEC1B	Day 2 measurement of FEC at 1st post-weaning time point
AVFEC1	Average of the two FEC measurements at Day 1 post-weaning time-point
DATE2	Date of 2nd post-weaning measurements
AGE2	Age at the 2nd post-weaning measurements
WT2A	Day 1 measurement of BWT at 2nd post-weaning time point
WT2B	Day 2 measurement of BWT at 2nd post-weaning time point
AVWT2	Average of the two BWT measurements at 2nd post-weaning time-point
.	
.	

Obs	NUMB	DAM_ID	DAM_BRD	SIRE_ID	SIRE_BRD	YEARB	BREED	SEX
1	3225	5189	2	1974	1	91	3	1
2	3226	1682	1	1980	1	91	1	2
3	3227	5162	2	1972	1	91	3	2

Obs	BIRTHWT	BIRTH_DT	DISP_DT	DACTION	DREASON	DATE30	AGE30	WT30
1	2	06/13/91	11/05/92	5	12	07/13/91	30	6
2	3	05/28/91	10/26/92	2	25	06/27/91	30	8
3	.	05/31/91	05/31/91	6	31	.	.	.

Obs	PCV30	FEC30	DATE60	AGE60	WT60	PCV60	FEC60	WEAN_DT
1	39	0	08/12/91	60	8	14	7900	09/30/91
2	45	0	07/27/91	60	11	32	8150	09/30/91
3	.	99999		.	.	.	99999	.

Obs	AGEWEAN	BIRTH_TY	BIRTHDAY	DAMAGE	WWT1	WWT2	WEANWT	WPCV1
1	109	1	164	3	10	.	10	32
2	125	1	148	2	16	.	16	28
3	.	1	151	3	.	.	.	.

Obs	WPCV2	WEANPCV	WFEC1	WFEC2	WEANFEC	DATE1	AGE1	WT1A
1	.	32	350	99999	350	11/19/91	159	12
2	.	28	99999	99999	99999	11/19/91	175	19
3	.	.	99999	99999	99999			.

Obs	WT1B	AVWT1	PCV1A	PCV1B	AVPCV1	FEC1A	FEC1B	AVFEC1
1	12	12	26	27	27	2300	1500	1900
2	18	19	30	25	28	1800	700	1250
3	.	.	.	.	.	99999	99999	99999

Obs	DATE2	AGE2	WT2A	WT2B	AVWT2	PCV2A	PCV2B	AVPCV2
1	02/17/92	249	15	15	15	20	26	23
2	02/17/92	265	22	21	22	34	37	36
3	.	.	.	.	.	.	.	.

Obs	FEC2A	FEC2B	AVFEC2	DATE3	AGE3	WT3A	WT3B	AVWT3
1	2600	1700	2150	05/29/92	351	14	14	14
2	2950	1600	2275	05/29/92	367	20	20	20
3	99999	99999	99999	.	.	.	.	.

Obs	PCV3A	PCV3B	AVPCV3	FEC3A	FEC3B	AVFEC3	DATE4	AGE4
1	22	24	23	3000	3600	3300	07/21/92	404
2	19	29	24	4700	4300	4500	07/21/92	420
3	.	.	.	99999	99999	99999	.	.

Obs	WT4A	WT4B	AVWT4	PCV4A	PCV4B	AVPCV4	FEC4A	FEC4B
1	17	17	17	28	28	28	950	1600
2	23	22	22	31	29	30	750	1150
3	.	.	.	.	.	.	99999	99999

Obs	AVFEC4	DATE5	AGE5	WT5A	WT5B	AVWT5	PCV5A	PCV5B
1	1275	09/21/92	466	18	18	18	22	23
2	950	09/21/92	482	25	25	25	33	32
3	99999	.	.	.	.	.	.	.

Obs	AVPCV5	FEC5A	FEC5B	AVFEC5	DATE6	AGE6	WT6A	WT6B
1	22	99999	450	450		.	.	.
2	33	350	400	375		.	.	.
3	.	99999	99999	99999		.	.	.

Chapter 5

Application of shared frailty models

5.1 Introduction

In the previous chapter, we mentioned that alternative methods exist that can be used to model more adequately the information available for all animals up to the time they die or are lost to follow up. One such approach is using survival analysis. The main objectives under this approach are (1) to investigate the variation in lamb mortality among breeds and their crosses (genotypes); and (2) to investigate genetic variation for lamb mortality within genotypes.

Frailty models have been used for other species of livestock, for example in assessing the length of productive life in dairy cattle (Ducrocq et al., 1988), to assess viability of laying hens (Ducrocq, 2000), to obtain estimates of longevity of Swedish horses (Wallin et al., 2000) and sows (Yazdi et al., 2000) and to assessing genetic variation for disease resistance in growing pigs (Henryon et al., 2001). Both Cox and Weibull hazard models have been used in these studies although the parametric model has been used more extensively as it is less computer intensive than the Cox model.

Prior to carrying out any survival analysis using hazard models, we first investigated the shape of the hazard function. To this end non-parametric kernel density estimation methods were utilised. We used the estimator derived in Müller and Wang (1994) which

is described briefly in Section 5.2. From this assessment no parametric distribution was found to be appropriate for the hazard model and further analyses were carried out using the Cox PH and its extension, the shared frailty model. In Section 5.3 we discuss the analyses that we carried out and report the results in Section 5.4.
In most previous studies that use frailty models in animal research, heritability estimates for survival have been reported (Ducrocq et al., 1988, Ducrocq, 2000). In Section 5.5 we discuss briefly heritability estimation in survival analysis. The concluding remarks are given in Section 5.6.

5.2 Hazard function estimation

Consider the general hazard model of Section 2.1.3 given as

$$\lambda(t|\boldsymbol{x}_i) = \lambda_0(t)\phi(\boldsymbol{x}_i)$$

where the baseline hazard function $\lambda_0(t)$ may be left unspecified or it may be assumed to have some specific parametric form, thus determining the shape of the hazard function $\lambda(\cdot)$. We used non-parametric kernel based methods to determine this shape.
Non-parametric kernel estimation methods of the hazard function for right-censored data have received considerable attention in the statistical literature (Watson and Leadbetter, 1964, Ramlau-Hansen, 1983, Cheng, 1987, Müller and Wang, 1994). The main assumption made in these estimators about the unknown survival distributions is that the hazard functions vary smoothly over time.
In general a kernel estimator of a function f at a given point t is essentially a locally weighted average of the data from the interval $[t-b, t+b]$, where b is the bandwidth or window size. A critical factor in the performance of the kernel estimator is the choice of the bandwidth which determines the degree of smoothness. The larger the bandwidth, the greater the smoothness. More smoothness leads to lower variability but also generally leads to increased bias. Watson and Leadbetter (1964) introduced the kernel estimator for the hazard function for uncensored data and Ramlau-Hansen (1983) extended the kernel hazard function to right censored data. The most widely used estimator for the hazard function from right-censored data has been the fixed-bandwidth kernel-smoothed estimator.

Let T_i^o, $i = 1, \ldots, n$, be the observed time-to-event and let δ_i be the censoring indicator as defined in Section 2.1.2. Let $(T_{(i)}^o, \delta_{(i)})$ be the ordered observations where the ordering is according to T_i^o. The fixed bandwidth estimator is then defined as

$$\hat{\lambda}(t) = \frac{1}{b} \sum_{i=1}^{n} K\left(\frac{t - T_{(i)}^o}{b}\right) \frac{\delta_{(i)}}{n - i + 1} \tag{5.1}$$

where $K(\cdot)$ is a kernel function and b is the global bandwidth. Kernel functions are generally chosen to be symmetric probability density functions such as the normal density. The so-called Epanechnikov kernel $\left(K(x) = 0.75(1 - x^2) \text{for} -1 \leq x \leq 1\right)$ is a popular choice. The fixed-bandwidth kernel estimator however cannot adapt to unevenness in the distribution of the data. It tends to over-smooth in regions with many observations and under-smooth in regions with few observations. In the recent past, more flexible bandwidths such as the nearest neighbour (Tanner and Wong, 1984) and varying (local) bandwidths (Müller and Wang, 1990) have been suggested as alternatives to (5.1) in order to overcome this drawback associated with the fixed bandwidth. In addition bias problems have been found for fixed kernel estimators when estimating near the endpoints of the data. These problems arise when the support of the kernel exceeds the available data range. Owing to these boundary effects, varying kernel estimators that are more robust at the endpoints have been proposed (Hougaard et al., 1989, Müller and Wang, 1994). These type of kernels are often said to be boundary corrected or varying kernels.

We used the varying kernel and varying bandwidth estimator of Müller and Wang (1994) given as

$$\hat{\lambda}(t) = \frac{1}{b(t)} \sum_{i=1}^{n} K_t\left(\frac{t - T_{(i)}^o}{b(t)}\right) \frac{\delta_{(i)}}{n - i + 1}. \tag{5.2}$$

For this estimator both the bandwidth and the kernel function depend on the time point. Müller and Wang (1994) proposed the following polynomial boundary kernel that generalizes the Epanechnikov kernel

$$K_t(z) = \begin{cases} K_+(\frac{t}{b(t)}, z) & \text{if} \quad \{t : 0 \leq t < b(t)\} \\ \frac{3}{4}(1 - z^2) & \text{if} \quad \{t : b(t) \leq t \leq R - b(t)\} \\ K_-(\frac{R-t}{b(t)}, z) & \text{if} \quad \{t : R - b(t) \leq t \leq R\} \end{cases}$$

where R is the right endpoint of the data, $q = t/b(t)$ and on $[-1, q]$

$$K_+(q, z) = \frac{12(1 + z)}{(1 + q)^4} \left[(1 - 2q)z + \frac{(3q^2 - 2q + 1)}{2}\right],$$

while on $[-q, 1]$, $K_-(q, z) = K_+(q, -z)$. This correction allows the shape of the kernel to change on the boundary. This estimator has been implemented as an executable function in S-Plus (Mathsoft, 1999) and can be downloaded from http://www.stats.ox.ac.uk/pub/SWin/.

We estimated the hazard function separately for each of the six years (Figure 5.1). Within each year we also obtained the hazard function estimate for the Red Maasai and Dorper genotypes. As there were no Red Maasai lambs in 1991, the estimated hazard function for the Red Maasai was obtained only for the years 1992-1996.

This plot shows that the risk of mortality at any point in time is much lower for the Red Maasai than that of the Dorper. Although not shown, the risks of death for the other groups lay in between those for the pure breeds. The figure demonstrates the variable pattern in the hazard estimate across years with risk of mortality generally lower in 1991 and 1992 than in the other years. Due to this variability, further analysis was carried out using the Cox proportional hazards model where the baseline hazard is not restricted to be of a particular shape. In trying to understand the variable patterns of the estimated hazard function we also looked at the rainfall patterns across the six years (Figure 5.1). Peak rainfall was higher in 1993-1996 compared with 1991 and 1992. Except for 1996, when lambs were born earlier than in other years, peak rainfall patterns in the years appeared to be followed by a rise in risk of mortality as estimated by the hazard function. The month of birth of the lambs varied across the years as matings took place at intervals of 10 to 12 months. Further, 1994 had the highest average rainfall post-weaning. This could explain the higher number of post-weaning measurements collected in this year, as mentioned in Section 4.3.

5.3 Statistical analysis

Statistical analysis was done separately in the pre-weaning and post-weaning periods as the critical period for assessing genetic resistance to endoparasites in lambs is between weaning and 12 months of age, during which the immune system of the young animal is developing.

We saw in Section 4.4 that there were various causes of mortality. As an initial step, we investigated in both the pre-weaning and post-weaning periods whether the ranking of causes of death varied across breeds and also across the years. This assessment is

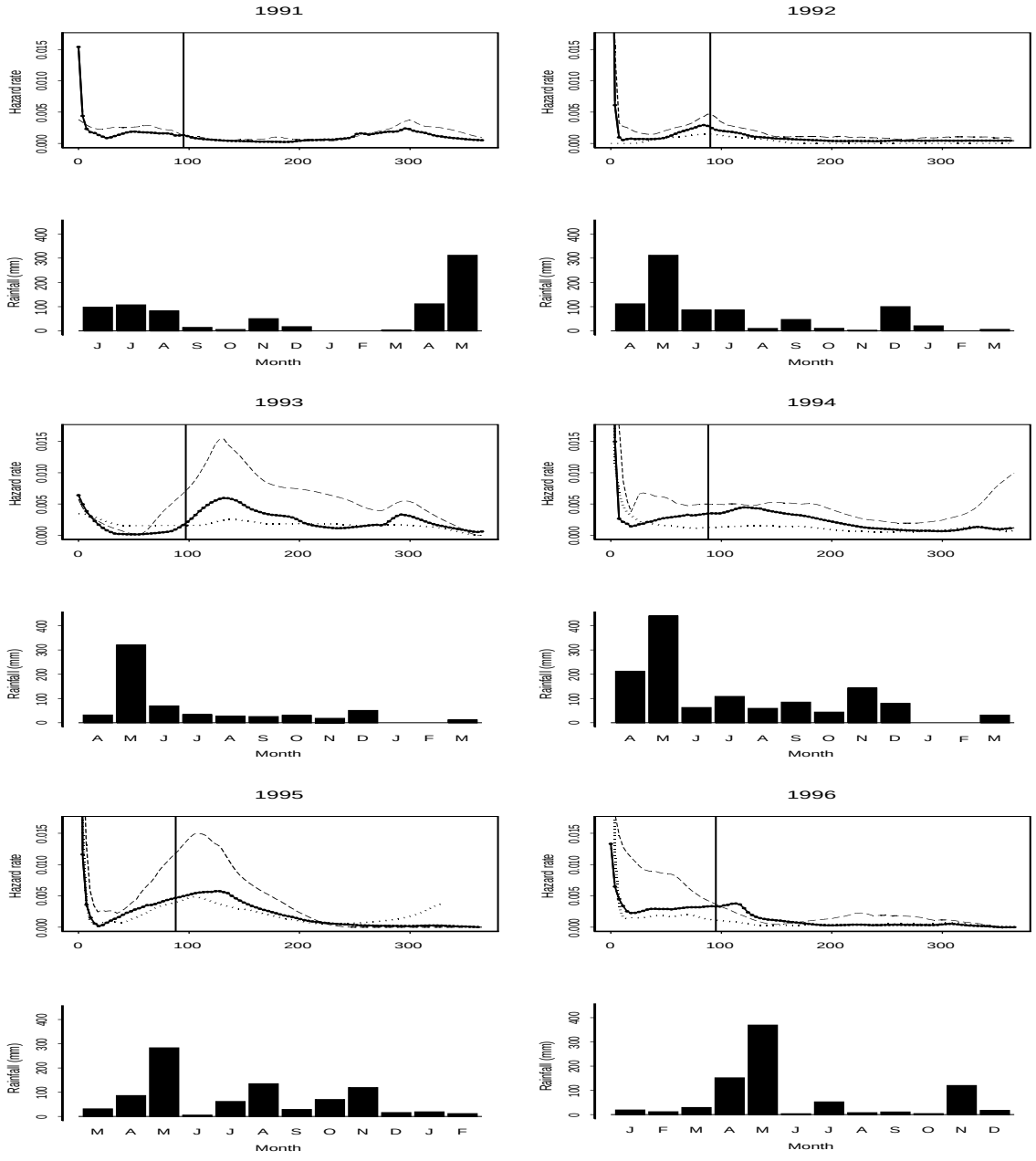


Figure 5.1: *Non-parametric estimate of the hazard function: dark line:-population average; dashed line:-Dorpers; dotted line:-Red Maasai and the associated rainfall patterns for a period of 12 months from the time of lambing. Bold vertical line indicates when the lambs were weaned.*

described in Section 5.3.1 while in Section 5.3.2 we give details of the survival analysis that was carried out.

5.3.1 Preliminary analysis

To assess whether the ranking of the various causes of mortality varied across genotype, a Poisson regression model (log-linear model, see Agresti, 1990) with genotype and cause of mortality as fixed effects was used. If Y_{ij} is the number of lambs experiencing the j^{th} cause of mortality from the i^{th} genotype, then Y_{ij} is a Poisson random variable with mean μ_{ij}. The observed values y_{ij} are the cell counts in Tables 4.2 and 4.3 for the pre- and post-weaning periods. The model used in this analysis is

$$\log(\mu_{ij}) = \mu + \vartheta_i^A + \vartheta_j^B \tag{5.3}$$

where

μ= the overall mean

ϑ_i^A=the breed main effects (6 levels)

ϑ_j^B=the cause of death main effects (6 levels pre-weaning and 5-levels post-weaning).

Model (5.3) is a log-linear model and its goodness of fit can be assessed using the deviance statistic

$$G^2 = 2\sum\sum y_{ij} \log\left(\frac{y_{ij}}{\hat{\mu}_{ij}}\right)$$

where $\hat{\mu}_{ij}$ are the estimated cell counts. The deviance statistic has an approximate chi-square distribution with $(i-1)(j-1)$ degree of freedom. If a breed by cause interaction term is included in (5.3) then the deviance is zero as the number of parameters to be estimated is equal to the number of cells in the table. The ratio of the estimated deviance for Model (5.3) to its degrees of freedom can also be used to check for overdispersion in the model. For a Poisson model as that postulated here the ratio should be close to unity. In this analysis the calculated deviance was 32.14 with 24 degrees of freedom (df) for the pre-weaning period, whilst that of the post-weaning period was 33.87 with 20 df. In both periods the ratio of the deviance to the degree of freedom was close to unity, indicating only a small over-dispersion. This implies that the interactions between genotype and cause of mortality in both periods were not significant (at 5%) when averaged over year. In total, the number of lambs that died or were lost in the six years were as follows (from Table 4.1): 118 (15%) in 1991, 92 (12%) in 1992, 200 (25%) in 1993, 144 (18%) in 1994, 151 (19%) in 1995 and 85 (11%) in 1996. Using a Poisson regression model (Model (5.3))

we also assessed the distribution of the various causes of these deaths across the years. The resulting deviances were 64.6 on 23 df and 137.1 on 19 df for the pre- and post-weaning periods respectively. This shows that the ranking of causes of mortality varied across years, particularly in the post-weaning period indicating a significant interaction between year and cause of mortality. For example, there was a large incidence of 'lost/stolen' lambs (22%) in 1993, and only one lamb in 1996 was diagnosed as dying due to endoparasites. The majority of deaths in this year had an unknown cause. Prior to weaning there was a higher proportion of deaths due to endoparasites in 1991 (43%) than the other years. There was a higher proportion of still births (26%) than average in 1995.

Based on these preliminary findings, further analysis was carried out with age of lamb at time of death (regardless of cause) as the response variable. The time of birth and time of weaning were taken as the time of origin in the pre-weaning and post-weaning periods respectively. Thus in the post-weaning period the time-to-event of the lamb was the residual life from weaning. The relevant event to the biologist was disposal of an animal, which included animals that either died or were stolen/lost. Thus all causes of mortality as described above were regarded as 'events'. For the pre-weaning period analysis, lambs that were weaned were censored, while those that were weaned and lived beyond 365 days (from birth) were censored in the post-weaning analysis. Still born lambs were however excluded. Analysis was carried out in S-Plus (Mathsoft, 1999) where the penalized likelihood approach (Section 2.4.4) is the implemented method of estimation for the Cox proportional hazards model.

5.3.2 Survival analysis

In all the analysis carried out terms for the fixed effects for genotype (6 levels), year of birth (6 levels), gender (2 levels) and age of the dam (5 levels) were always included. For ease of reference we will refer to these as the baseline covariates.

Subsequently the weight at birth was included as a curvilinear term (with linear and quadratic terms) in the pre-weaning period while the weight at weaning was included for the post-weaning period. The effect of time-varying body weight as an alternative to either birth weight or weaning weight was also assessed. PCV and FEC (post weaning) and anthelmintic treatment (pre weaning) were then additionally considered also as time-varying covariates. These analyses with time-varying BWT, PCV and FEC were carried

out in order to utilize more adequately all the measurements of these traits which were repeatedly recorded as described in Section 4.3. Packed cell volume and FEC could not be used for the pre-weaning analysis as they were not measured until one month of age. The effect of treatment in the pre-weaning period was assessed using a binary covariate whose values changed at the time of treatment. Thus the associated parameter estimate is the relative change in risk due to treatment. No first order interaction terms were found to be significant in the two periods and hence these were not considered further. The analysis carried out can be summarised as follows:

Baseline covariates

- Genotype
- Year of birth
- Gender
- Age of dam

Pre-weaning covariates

- Birth weight or time-varying body weight
- Treatment

Post-weaning covariates

- Weight at weaning or time-varying body weight
- Time dependent PCV
- Time dependent FEC

For each of the settings above two analyses were undertaken in each period. The first analysis used the Cox proportional hazards model

$$\lambda_i(t) = \lambda_0(t) \exp(\boldsymbol{x}_i^T(t)\boldsymbol{\beta}) \tag{5.4}$$

where $\lambda_i(t)$ is the hazard function for the i^{th} lamb, $i = 1, \ldots, n$, $\lambda_0(t)$ is the unspecified baseline hazard, $\boldsymbol{x}_i(t)$ is the incidence vector of the fixed effects for this lamb at time t and $\boldsymbol{\beta}$ the vector of associated parameters.

In the second analysis, a shared frailty model with sire included as the random effect term was used. Suppose that the i^{th} sire $i = 1, \ldots, G$ has n_i lambs then

$$\lambda_{ij}(t) = \lambda_0(t) \exp(\boldsymbol{x}_{ij}^T(t)\boldsymbol{\beta} + w_i) \tag{5.5}$$

where $\lambda_{ij}(t)$ is the hazard function for the j^{th} lamb, $j = 1, \ldots, n_i$ from the i^{th} sire, $\boldsymbol{x}_{ij}(t)$ is the incidence vector of the fixed effects at time t and $w_i, i = 1, \ldots, G$ is the

random sire effect. For models (5.4) and (5.5), the covariate vectors $\boldsymbol{x}_i(t)$ and $\boldsymbol{x}_{ij}(t)$ are only time-dependent if time-varying covariates such as FEC and PCV are considered. These time-varying covariates change values only at the measurement times as described in Section 4.3 and in between these time points the last observed value (LVCF) is used, resulting in a piecewise constant profile. In such cases the hazards are then proportional only between intervals in which the covariates remain constant (e.g. between 2 months and weaning). Thus the $\boldsymbol{\beta}$ parameter estimates associated with a factor variable for any model containing a time-varying covariate cannot be interpreted as overall relative risks across the pre- or post-weaning period. In such a model, these estimates can be thought as the relative risks only within intervals in which the covariate is constant (see Klein and Moeschberger, 1997, p. 275).

For the frailty term $u_i = \exp(w_i)$, we used both the log-normal and gamma frailty distributions given by (2.5) and (2.6) respectively.

5.4 Results

5.4.1 Effect of baseline covariates

The estimated survival curves for the different genotypes in the pre-weaning and post-weaning periods are shown in Figures 5.2 and 5.3 respectively. These curves are adjusted for the other factors (covariates), namely gender, age of dam and year of birth. To get these curves in each of the periods, a stratified Cox PH model (5.4) was first fitted to the data with breed as the stratification variable while the other baseline covariates were included in the model. Thus the hazard function for the j^{th} lamb from the k^{th} breed is

$$\lambda_{j(k)}(t) = \lambda_{0(k)}(t) \exp(\boldsymbol{x}_j^T \boldsymbol{\beta})$$

where $\lambda_{0(k)}$ is the common baseline hazard for the lambs from this breed and $\boldsymbol{\beta}$ is the vector of unknown parameters corresponding to year, gender and age of the dam effects. If we let $\hat{\boldsymbol{\beta}}$ be the vector of estimated parameters, then the estimated survival function at time t for lambs from the k^{th} breed is $\hat{S}_k(t) = \exp(-\hat{\Lambda}_0(t))$ where

$$\hat{\Lambda}_0(t) = \sum_{t_{(l)} \leq t} \frac{N_{(l)}}{\sum_{j \in R(t_{(l)})} \exp(\boldsymbol{x}_j^T \hat{\boldsymbol{\beta}})}$$

is the Breslow estimator of the cumulative baseline (see Section 2.4.2). This is evaluated with year of birth, age of dam and gender equal to the mean values for the data within each strata.

From Figure 5.2 it is observed that the Dorpers had the highest mortality at any point in

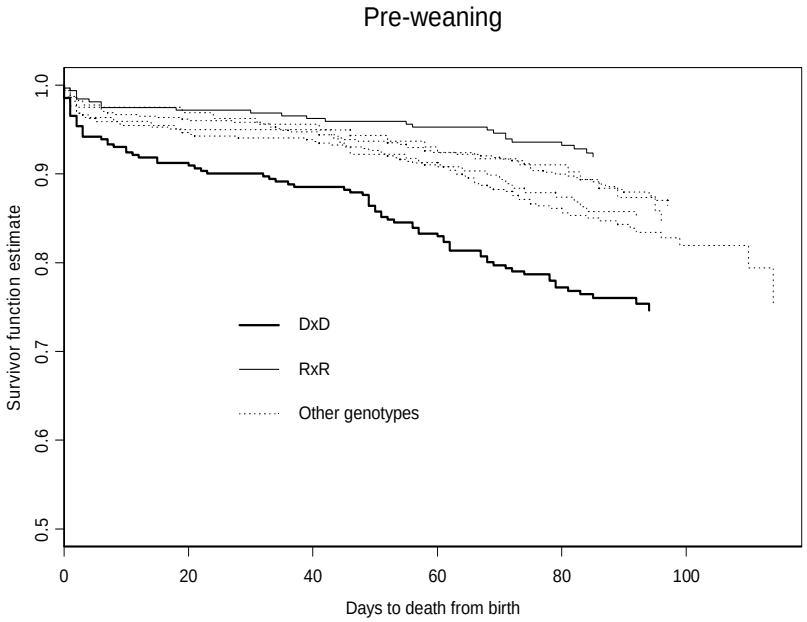


Figure 5.2: *Estimated survival curves for lambs of different genotypes in the pre-weaning period.*

time during the pre-weaning period, while Red Maasai had the lowest mortality. Throughout the post-weaning period (Figure 5.3) the Dorper had the highest average mortality while the R x (R x D) and the Red Maasai had the lowest mortality.

The $\log(-\log(\hat{S}_k(t))$ versus time plots for the different genotypes adjusted for the other factors show approximately parallel curves in the pre-weaning period (Figure 5.4). Some curves in the plots for the post-weaning period (Figure 5.5) show a tendency to cross between day 1 and day 40 after weaning, but are approximately parallel thereafter, thus the proportionality assumption holds during most of the study time.

The results of the fitted Cox PH and shared frailty hazard models are shown in Tables 5.1 and 5.2 for the pre-weaning and post-weaning periods, respectively. In both periods the shared frailty models gave parameter and standard error estimates for fixed effects which were essentially the same as those of the simpler Cox PH model. Further the parameter estimates from the gamma and log-normal frailty models were similar, with difference only

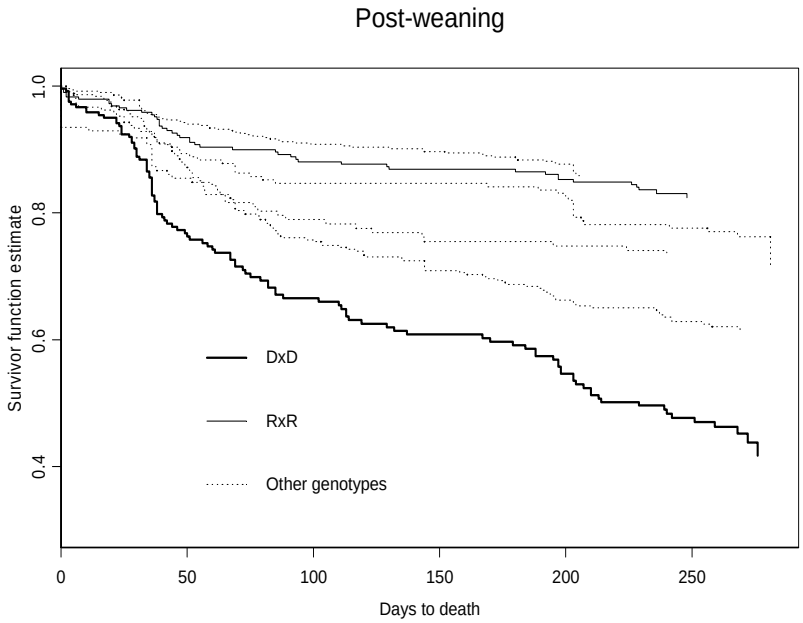


Figure 5.3: *Estimated survival curves for lambs of different genotypes in the post-weaning period.*

arising in the value of the estimated variance of the random term. Due to this and the fact that under the penalized partial likelihood approach there exists an explicit analytical formula for estimating the standard error of $\text{Var}(W) = \sigma^2$ for the log-normal distribution (Remark 6 in Section 2.4.4) only the results for this frailty distribution are tabulated.
A detailed interpretation of the parameter estimates for both periods from the shared frailty model are given below.

Genotype

The Dorper lambs were observed to have a higher relative risk of mortality than all the other genotypes. The relative risk of mortality for the D x (R x D) genotype relative to the Dorper lambs was 0.61 ($P< 0.01$) and this declined to 0.27 for the Red Maasai in the pre-weaning period ($P< 0.001$). A decreasing trend in the risk of mortality was observed with increasing proportion of Red Maasai in the genotype. In the post-weaning period the risk of mortality for the D x (R x D) genotype relative to the Dorper was 0.61 ($P<0.001$) and that for the Red Maasai 0.25 ($P<0.001$). The overall trends in the pre-weaning and the post-weaning periods were similar, with the exception that R x (R x D) lambs had the lowest risk of mortality post weaning. These trends are also observed in the estimated survival curves (Figs 5.2 and 5.3).

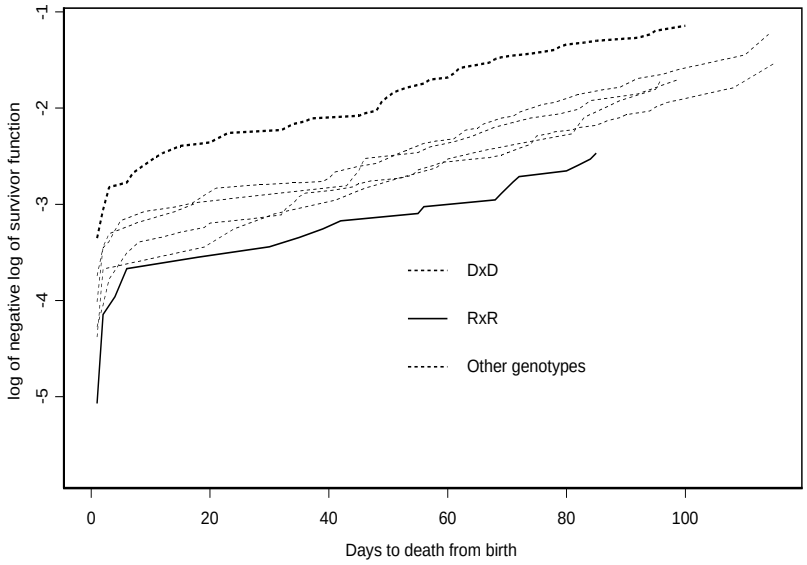


Figure 5.4: *Log of negative log of survival versus time in the pre-weaning period.*

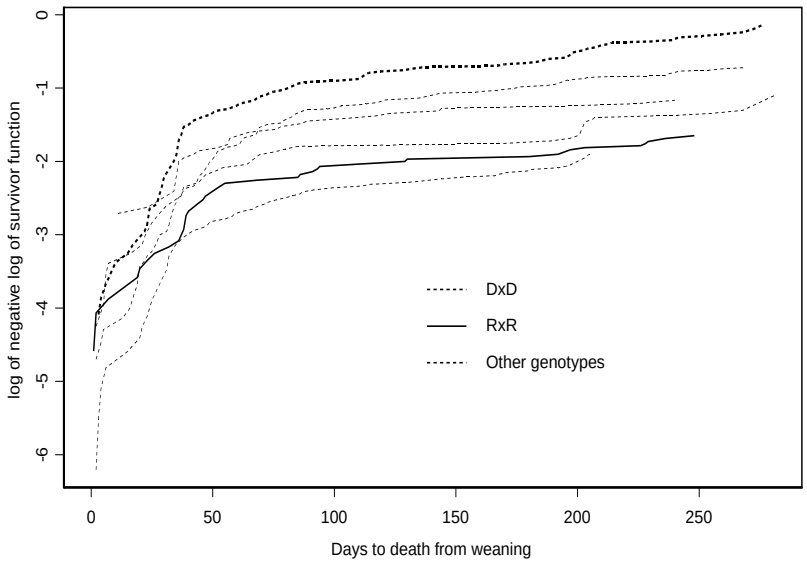


Figure 5.5: *Log of negative log of survival versus time in the post-weaning period.*

Year

Survival rates were different among years and appeared to be associated to some degree

Table 5.1: *Parameter estimates and hazard ratios (95% c.i.) from the Cox proportional hazards and the shared frailty models applied to survival time (regardless of cause) in the pre-weaning period.*

Effect	No. of lambs	Cox Proportional hazards model		Shared frailty hazards model	
	N	est±s.e.	HR(c.i.)	est± s.e.	HR(c.i.)
Genotype					
DxD	304	ref	1.00	ref	1.00
Dx(DxR)	419	-0.48±0.16	0.62(0.43,0.81)	-0.49±0.16	0.61(0.42,0.81)
DxR	121	-0.72±0.26	0.49(0.24,0.73)	-0.74±0.26	0.48(0.23,0.72)
RxD	231	-0.62±0.21	0.54(0.31,0.77)	-0.63±0.22	0.53(0.30,0.77)
Rx(RxD)	466	-0.83±0.17	0.44(0.29,0.58)	-0.85±0.18	0.43(0.2,0.58)
RxR	204	-1.29±0.25	0.28(0.14,0.41)	-1.32±0.26	0.27(0.13,0.40)
Year of birth					
1991	363	ref	1.00	ref	1.00
1992	293	0.26±0.20	1.29(0.78,1.81)	0.23±0.21	1.26(0.74,1.78)
1993	365	-1.05±0.28	0.35(0.16,0.54)	-1.07±0.29	0.34(0.15,0.53)
1994	236	0.99±0.20	2.70(1.62,3.78)	0.99±0.21	2.70(1.57,3.83)
1995	262	0.75±0.21	2.13(1.26,2.99)	0.74±0.22	2.10(1.19,3.01)
1996	226	0.64±0.22	1.90(1.07,2.73)	0.65±0.24	1.91(1.03,2.79)
Gender					
Females	837	ref	1.00	ref	1.00
Males	908	0.08±0.12	1.08(0.84,1.33)	0.07±0.12	1.07(0.83,1.32)
Age of dam					
<=2yrs	183	ref	1.00	ref	1.00
=3 yrs	403	0.08±0.24	1.09(0.58,1.60)	0.10±0.24	1.10(0.58,1.63)
=4 yrs	386	-0.08±0.25	0.92(0.47,1.37)	-0.07±0.25	0.93(0.48,1.39)
=5 yrs	383	0.09±0.24	1.09(0.58,1.61)	0.10±0.24	1.10(0.58,1.62)
>=6yrs	390	0.11±0.25	1.12(0.58,1.66)	0.11±0.25	1.12(0.58,1.66)
Sire					
variance (s.e.)		0.00		0.052(0.049)	

with variation in rainfall (Figure 5.1). In the pre-weaning period the risk of mortality was least in 1993, which was on average 34(%) that observed in 1991 (P<0.001) and highest in 1994, approaching three times that in 1991 (P<0.001). In the post-weaning period the risk of mortality was about 5 fold higher in 1993, 1994 and 1995 compared with 1991 and 1992. On the other hand the risk of mortality in 1996 was reduced by 8% (P<0.001) in the pre-weaning period when compared to 1991 but was similar in the post-weaning period. These findings concur with the hazard estimates shown in Figure 5.1 with 1993 having the lowest average risk in the pre-weaning period and the highest in the post-weaning period. Further the estimated hazard function was higher in the pre-weaning period in 1996 than

in 1991 but post weaning, the estimates are of the same magnitude.

Table 5.2: *Parameter estimates and hazard ratios (95% c.i.) from the Cox proportional hazards and the shared frailty models applied to survival time (regardless of cause) in the post-weaning period.*

Effect	No. of lambs	Cox Proportional hazards model		Shared frailty hazards model	
	N	est±s.e.	HR(c.i.)	est± s.e.	HR(c.i.)
Genotype					
DxD	223	ref	1.00	ref	1.00
Dx(DxR)	340	-0.48±0.13	0.62(0.46,0.78)	-0.51±0.13	0.60(0.44,0.76)
DxR	101	-0.78±0.19	0.46(0.28,0.63)	-0.79±0.19	0.45(0.28,0.62)
RxD	200	-1.00±0.18	0.37(0.24,0.50)	-1.02±0.19	0.36(0.23,0.49)
Rx(RxD)	398	-1.58±0.16	0.21(0.14,0.27)	-1.62±0.17	0.20(0.13,0.27)
RxR	180	-1.34±0.19	0.26(0.16,0.36)	-1.39±0.20	0.25(0.15,0.35)
Year of birth					
1991	309	ref	1.00	ref	1.00
1992	242	0.01±0.21	1.01(0.59,1.42)	-0.04±0.22	0.96(0.55,1.38)
1993	347	1.58±0.16	4.87(3.36,6.39)	1.60±0.17	4.95(3.29,6.60)
1994	170	1.45±0.19	4.27(2.66,5.87)	1.48±0.21	4.40(2.64,6.16)
1995	203	1.44±0.19	4.21(2.62,5.79)	1.45±0.21	4.25(2.52,5.98)
1996	171	0.50±0.25	1.64(0.84,2.45)	0.54±0.26	1.72(0.83,2.61)
Gender					
Females	695	ref	1.00	ref	1.00
Males	747	0.31±0.10	1.36(1.11,1.62)	0.32±0.10	1.38(1.12,1.65)
Age of dam					
<=2yrs	158	ref	1.00	ref	1.00
=3 yrs	340	-0.36±0.17	0.70(0.47,0.92)	-0.36±0.17	0.70(0.47,0.93)
=4 yrs	330	-0.63±0.17	0.53(0.35,0.71)	-0.64±0.18	0.53(0.35,0.71)
=5 yrs	314	-0.49±0.17	0.62(0.41,0.82)	-0.49±0.17	0.61(0.41,0.81)
>=6yrs	300	-0.79±0.18	0.46(0.29,0.62)	-0.79±0.19	0.46(0.29,0.62)
Sire					
variance (s.e.)		0.00		0.054(0.037)	

Gender

The risk of mortality for male lambs was about a third higher than that for female lambs during the post-weaning period ($P<0.01$), but there was no significant gender effect in the pre-weaning period.

Age of dam.

There was no significant effect of age of the dam on the risk of mortality in the pre-weaning period implying that mothering capability was independent of age. In the post-weaning period, however, the risk of mortality of lambs born to mothers that were two years of

age or younger was higher that of lambs born to older ewes. Compared with lambs born to 2-year old mothers the relative risk was 0.69 for lambs born to 3-year old mothers and 0.43 for lambs born to mothers aged six years or more (P<0.001).

Sire variance

The estimated sire frailty variance and its standard error under the log-normal frailty for the pre- and post-weaning periods are also shown in Tables 5.1 and 5.2. We also obtained the estimated frailties (u_i's) for the 76 sires for both the pre-weaning and post-weaning periods. To get a better visualisation of the frailty effect, we plotted the estimated survival

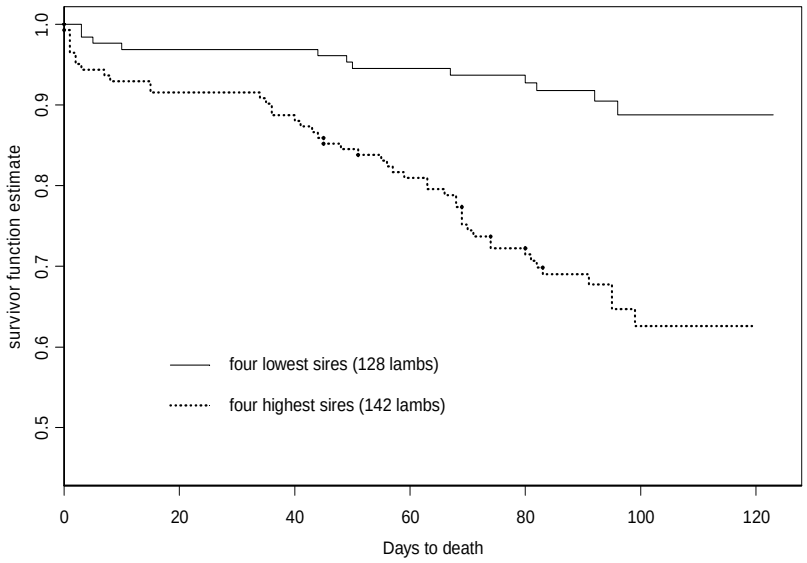


Figure 5.6: *Estimated survival curves for lambs from four sires with largest and four sires with lowest frailty estimates in the pre-weaning period.*

curves of lambs from the four sires with the highest and the four sires with the lowest frailty values (namely top and bottom 5% of the 76 sires). These curves are shown in Figs 5.6 and 5.7 for the two periods. In the pre-weaning period, of the four sires with the highest estimates of u_i, two were Dorpers and two were Red Maasai while those with the lowest estimates were all Dorpers. Post weaning, there were three Dorpers and one Red Maasai sire for both the high and the low estimates of the frailties (u_i's). None of these sires were the same in the two periods. It is observed in these plots that the lambs from the sires with high values experienced events earlier than the lambs from sires with

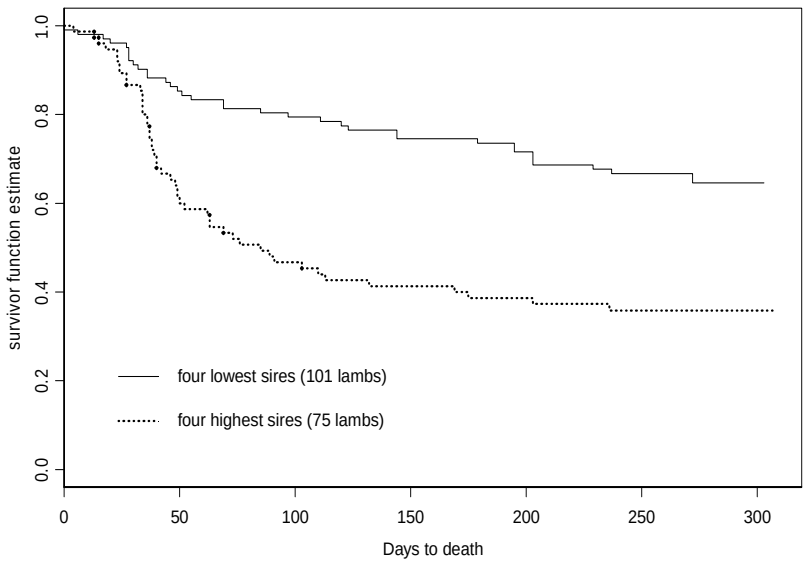
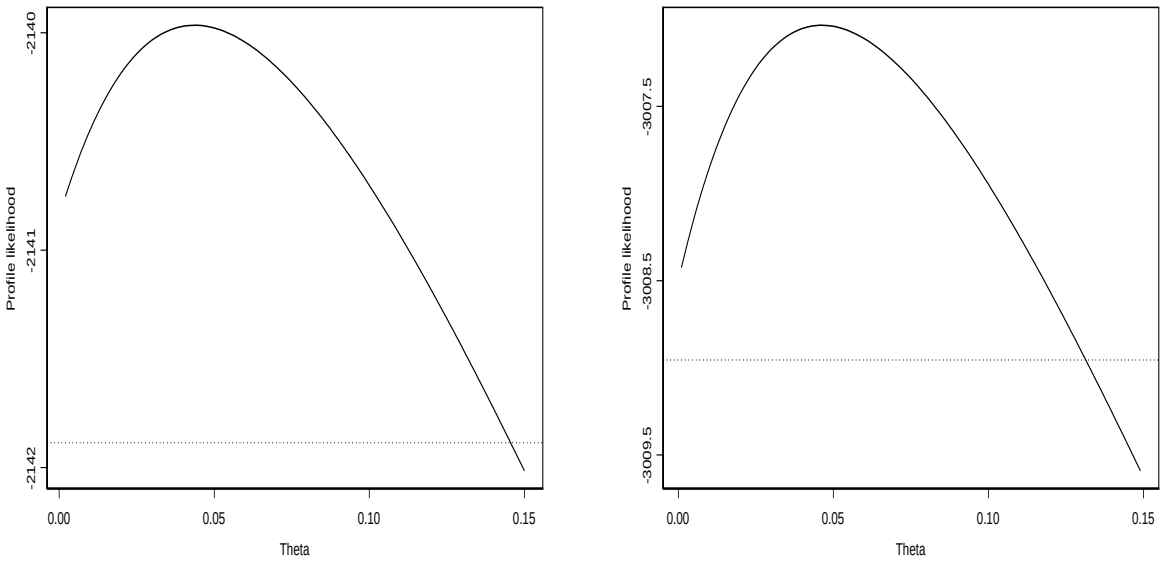


Figure 5.7: *Estimated survival curves for lambs from four sires with largest and four sires with lowest frailty estimates in the post-weaning period.*

low values. This not-withstanding, the estimated sire variance in the two periods was non-significant (at 5%). Figure 5.8 shows the profile log-likelihood for θ (sire variance) for the pre- and post-weaning periods. In each of this, the approximate 95% confidence interval (c.i.) for θ includes zero. This confidence interval is obtained by taking two values of θ for which the profile log-likelihood lies 1.92 units (dotted line in Figure 5.8) below the maximum profile log-likelihood value within each period. The respective log-likelihood values for the model with the baseline covariates with and without frailty were -2139.97 and -2140.34 for the pre-weaning period and -3007.35 and -3008.50 for the post-weaning period. If we conjecture that the theoretical results derived in Chapter 3 also hold for the current model (semi-parametric log-normal frailty model), then the likelihood ratio test statistics for the two periods are 0.74 and 2.3 with P-values 0.20 ($= Pr(\chi^2_1 > 0.74)/2$) and 0.07 ($= Pr(\chi^2_1 > 2.3)/2$) respectively. Thus, using either the approximate 95% c.i. or the likelihood ratio test, the null hypothesis ($H_0 : \theta = 0$) of no heterogeneity is not rejected in the two periods. This implies that the time-to-event of the lambs from the different sires are homogeneous.



(a) (b)

Figure 5.8: *Profile log-likelihood for θ (sire variance) for the (a) pre- weaning and (b) post-weaning periods.*

5.4.2 Effect of time-independent body weight

In this analysis the weight at birth or the weight at weaning was used additionally with the baseline covariates in the pre- and post-weaning periods respectively. In both periods there was a curvilinear relationship between body weight and risk of mortality. This relationship had significant linear and quadratic terms for birth weight in the pre-weaning period and weaning weight in the post-weaning period ($P<0.001$) (see first part of Tables 5.3 and 5.4). In the two periods the relative risk of mortality decreased quadratically with increased birth weight and weaning weight (Figure 5.9). This implies that lambs that were heavy in body weight at birth or weaning had lower risk of mortality when compared to lighter lambs. The detailed results for the baseline covariates are given in the first column of Tables 5.7 (pre weaning) and 5.8 (post weaning) at the end of this chapter.

Notably, in the pre-weaning period there was now no difference in the risk of mortality for lambs born in 1994 and 1995, when compared to those born in 1991. The higher risk observed earlier in the unadjusted model (Table 5.1) could be due to the fact that the

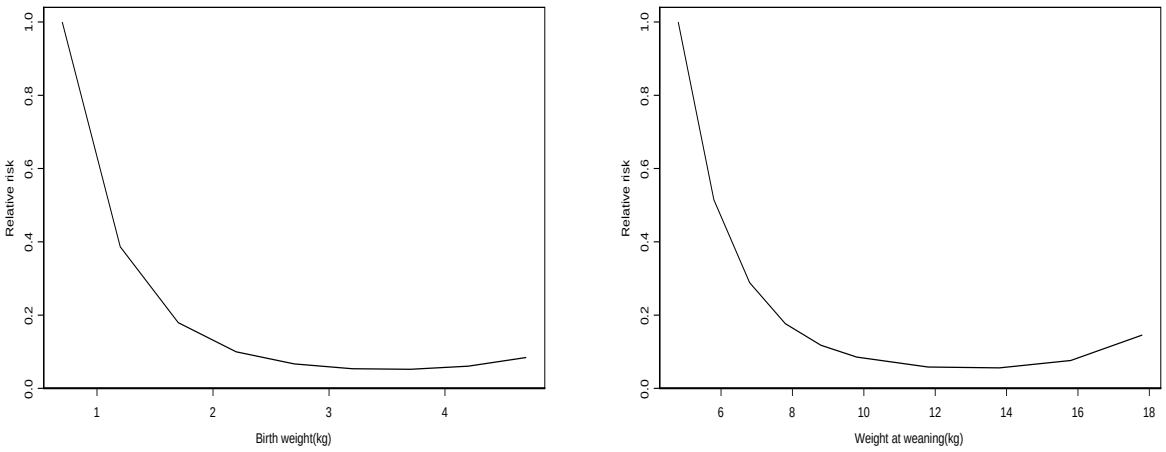
Table 5.3: *Parameter estimates from a shared frailty hazard model applied to survival time (regardless of cause), in the pre-weaning period for birth weight and time-varying body weight alternatively, and treatment, adjusted for baseline covariates.*

Covariate	Parameter estimate±s.e.	Covariate	Parameter estimate ±s.e
Birth weight (kg)		Time varying body weight (kg)	
- Linear	-2.38 ± 0.52	- Linear	-1.06 ± 0.11
- Square	0.323 ± 0.102	- Square	0.038 ± 0.008
Sire variance (s.e.)	0.066 (0.053)	Sire variance	0.067 (0.053)
Birth weight (kg)		Time varying body weight (kg)	
- Linear	-2.36 ± 0.52	- Linear	-1.04 ± 0.12
- Square	0.318 ± 0.102	- Square	0.035 ± 0.008
Treatment		Treatment	
- Not treated	reference	- Not treated	reference
- Treated	-0.51 ± 0.19	- Treated	-0.92 ± 0.20
Sire variance (s.e.)	0.067 (0.053)	Sire variance	0.063 (0.052)

lambs born in these two years were much lighter than those born in 1991 (see Figure 4.2). Further, when the weight at weaning was taken into account, the Rx(RxD) and RxR genotypes now had similar relative risk of mortality when compared to the Dorpers. In addition there was a non-significant effect of the age of dam after taking into account the weight of the lamb. This could be due to the biological fact that lambs born to young dams are lighter in body weight, possibly due to lower milk production of the dam in her first parity. This difference in body weight could have lead to the significant age of dam effect in the unadjusted model (Table 5.2).

5.4.3 Effect of time-dependent covariates

In Section 4.3, we reported that BWT, PCV and FEC were periodically recorded until the lambs were almost one year old. In this section we assess the effect of these traits on the risk of mortality as they evolve over time. The effect of anthelmintic treatment in the pre-weaning period was also assessed in the presence of both birth weight and time-varying body weight (Table 5.3). These time-varying covariates were additionally included in models with the baseline covariates. The detailed results for the baseline covariates for the pre- and post-weaning periods are given in Tables 5.7 and 5.9 in the appendix of this chapter.



(a) (b)

Figure 5.9: *The decrease in risk of mortality with increasing body weight at (a) birth in the pre-weaning period and (b) weaning in the post-weaning period, with other factors of genotype, gender, year and age of dam held constant in lambs raised.*

Body weight

In both the pre- and post-weaning periods, the risk of mortality associated with body weight decreased as lambs gained weight. Additionally, at each time point heavier lambs had a lower risk of mortality than lighter lambs (Figure 5.10). Pre weaning, the relative hazards of the other genotypes relative to Dorper were slightly decreased when adjusted for time-varying body weight and now ranged from 0.55 to 0.17 (Table 5.7).

In the post-weaning, the hazard ratios for other genotypes were also decreased after adjusting for body weight. As in the analysis with time-invariant body weight (Section 5.4.2), the Rx(RxD) and RxR genotype had the lowest but similar relative mortality when compared to the Dorper. There was also no difference in the risk of mortality for lambs born in 1994 and 1995 in both the pre- and post-weaning periods and the age of dam was not significant (Table 5.9).

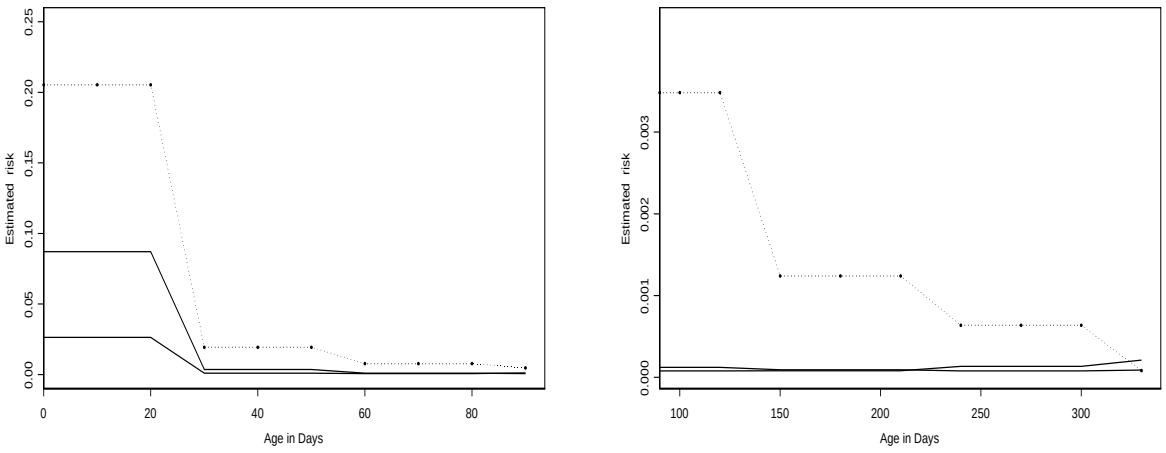
Treatment

The effect of treatment was only considered in the pre-weaning period since all lambs were treated together during the post-weaning period. The risk of mortality during the subsequent month for two lambs of the same weight was reduced by 0.40($P<0.001$) during

the next month when treated $(1 - \exp(-0.51))$ (Table 5.3).

Packed cell volume and faecal egg count

The means (standard deviations) of time-varying PCV and time-varying natural logarithm of FEC post-weaning were 25 (5.4) percent and 7.36 (1.27) log(epg+25), respectively. Both these time-dependent covariates had significant relationship with the risk of mortality when introduced in the model for the post-weaning period (Table 5.4). As noted in Section 5.3.2, these covariates are assumed to be piecewise constant. Between any two post-weaning sampling times for any two similar lambs from the same sire, and with PCV differing by one standard deviation, the risk of mortality of the lamb with the higher PCV relative to that of the lamb with the lower PCV ranged from 0.96 to 0.31 when the PCV ranged from 35 to 20 percent. On the other hand, if the natural logarithm of FEC for a lamb increased by one standard deviation, the relative risk of mortality of the lamb with the lower FEC relative to that of the lamb with the higher FEC ranged from 0.37 to 0.98 when the natural logarithm of FEC ranged from 10 (corresponding to 22,000 epg) to 7 (1,100 epg). When both variables were included simultaneously in the



(a) (b)

Figure 5.10: *Changes in risk of mortality with time-varying body weight in the (a) pre-weaning and (b) post-weaning periods for three lambs selected at random each month with body weights corresponding to the 2.5% (dashed line), 50% (thin line) and 97.5% (thick line) percentiles in the distribution of body weight. Ranges of body weight were: at birth (1.5 to 3.8 kg), 30 days (4.2 to 9.9 kg), 60 days (5.5 to 13.3 kg), weaning (6.3 to 16.7 kg), 150 days(7.5 to 17.8 kg), 240 days (9.1 to 21.3 kg) and 330 days (16.0 to 24.5 kg).*

Table 5.4: *Parameter estimates from a shared frailty hazard model applied to survival time (regardless of cause), in the post-weaning period for birth weight and time-varying body weight alternatively, and with time-varying PCV (%) and LFEC(*$\log e.p.g$*) adjusted for baseline covariates.*

Covariate	Parameter estimate±s.e.	Covariate	Parameter estimate ±s.e
Weaning weight		Time varying body weight	
- Linear	-1.36 ± 0.10	- Linear	-1.10 ± 0.07
- Square	0.050± 0.004	- Square	0.032 ± 0.003
Sire variance (s.e)	0.121 (0.051)	Sire variance (s.e.)	0.183 (0.064)
Weaning weight		Time varying body weight	
- Linear	-0.93 ± 0.11	- Linear	-0.79 ± 0.07
- Square	0.034± 0.005	- Square	0.024 ± 0.003
PCV		PCV	
- Linear	-0.45 ± 0.04	- Linear	-0.44 ±0.04
- Square	0.007 ± 0.001	- Square	0.007 ±0.001
Sire variance (s.e.)	0.102 (0.047)	Sire variance (s.e.)	0.108 (0.049)
Weaning weight		Time varying body weight	
- Linear	-1.27 ±0.11	- Linear	-1.04 ± 0.08
- Square	0.047± 0.005	- Square	0.030± 0.003
$\log(FEC+25)$		$\log(FEC+25)$	
- Linear	-0.07 ± 0.01	- Linear	-0.07 ± 0.01
- Square	0.001 ±0.0001	- Square	0.102 ± 0.050
Sire variance (s.e.)	0.093 (0.048)	Sire variance (s.e.)	0.105 (0.051)
Weaning weight		Time varying body weight	
- Linear	-0.90 ± 0.11	- Linear	-0.75 ± 0.08
- Square	0.033 ± 0.005	- Square	0.023 ± 0.003
PCV		PCV	
- Linear	-0.46 ± 0.04	- Linear	-0.45 ± 0.04
- Square	0.007 ± 0.001	- Square	0.007 ± 0.001
$\log(FEC+25)$		$\log(FEC+25)$	
- Linear	-0.07 ± 0.01	- Linear	-0.06 ± 0.01
- Square	0.001± 0.0001	- Square	0.001± 0.0001
Sire variance (s.e.)	0.077 (0.045)	Sire variance (s.e.)	0.087 (0.047)

model the significance of both effects was maintained, i.e., PCV and FEC tended to have additive effects on survival (Table 5.4).

The difference in the relative risk of mortality was slightly decreased for lambs with more than 50% Red Maasai in the genotype when adjusted for PCV. Including FEC had minimal effect.

Sire variance after adjusting for varying covariates.

Inclusion of body weight in the model, increased the value of the sire variance post weaning

Table 5.5: *Parameter estimates and hazard ratios (95% c.i.) for genotype from a shared frailty hazard model applied to survival time with cause of death only restricted to mis-mothering in the pre-weaning period and to endoparasite in the post-weaning period, adjusted for the baseline covariates.*

	Mis-mothering only			Endoparasites only		
Effect	No. of lambs	Parameter estimate±s.e.	Hazard ratio (c.i.)	No. of lambs	Parameter estimate±s.e.	Hazard ratio (c.i.)
Genotype						
DxD	304	ref	1.00	210	ref	1.00
Dx(DxR)	419	-0.50±0.27	0.61(0.29,0.92)	314	-0.38±0.19	0.68(0.43,0.94)
DxR	121	-0.82±0.44	0.44(0.06,0.82)	77	-0.78±0.28	0.46(0.21,0.71)
RxD	231	-0.57±0.38	0.57(0.14,0.99)	194	-1.01±0.28	0.36(0.17,0.56)
Rx(RxD)	466	-0.92±0.30	0.40(0.16,0.64)	346	-1.70±0.25	0.18(0.09,0.27)
RxR	204	-1.14±0.40	0.32(0.07,0.57)	130	-1.31±0.29	0.27(0.12,0.42)

Year 1996 is excluded from the analysis for endoparasites because there was only one case of death due to endoparasites in this year. For comparative purposes hazard ratios for all causes corresponding to those in Table 5.2 but excluding 1996 were 1.00, 0.59, 0.35, 0.32, 0.20 and 0.25, respectively.

(Table 5.4), but the variance decreased again when PCV and FEC were added. Alterations to the model pre weaning (Table 5.3), however, had no significant influence on the sire variance.

5.4.4 Effect of baseline covariates for mis-mothering and endoparasite deaths

Since 31% of the deaths pre weaning were due to mis-mothering and 47% were associated with endoparasites in the post-weaning period, analysis with the baseline covariates was repeated for these causes of death only within each of the respective periods. Lambs that died from other causes were censored. The endoparasite analysis excluded the year 1996 since only one death in this year was diagnosed post weaning as associated with endoparasites. The parameter estimates for genotypes in these model are given in Table 5.5. The relative hazard for the genotypes for mis-mothering deaths had same trend as that observed for all causes in the pre-weaning period (cf Table 5.1). Similar relative hazards for the genotypes were obtained for deaths due to endoparasites alone compared with deaths due to all causes (shared frailty column Table 5.2).

5.4.5 Effect of baseline covariates with lambs stolen/lost as censored records

In all the analyses that have been carried out above, the lambs that were stolen or lost were treated as events as mentioned in Section 5.3.1. The analysis with the baseline covariates for both pre and post weaning periods, was now repeated with records for lamb that were stolen/lost now censored. The results for genotype and year of birth estimates from the shared frailty model are given in Table 5.6. Similar relative hazard estimates were obtained for genotype in both the pre- and post-weaning periods (see shared frailty column Tables 5.1 and 5.2). The estimates for the years 1993-1996 were each slightly increased by about 38% in the pre-weaning period. Post weaning there was a slight decrease in the relative risk for 1993. A slight increase was observed for the years 1994-1996. This can be attributed to the fact that pre weaning, the years 1991-1992 accounted for 23(72%) of the lambs that were stolen/lost. In the post-weaning period lambs lost/stolen were: 9(15%) in 1991, 5(8%) in 1992, 39(63%) in 1993 and a total of 9(15%) for the years 1994-1996.

Table 5.6: *Parameter estimates and hazard ratios (95% c.i.) for genotype and year of birth adjusted for gender and age of dam from a shared frailty hazard model applied to survival time in the pre- and post-weaning periods, with stolen lambs censored.*

	Pre-weaning			Post-weaning		
Effect	No. of lambs	Parameter estimate±s.e.	Hazard ratio (c.i.)	No. of lambs	Parameter estimate±s.e.	Hazard ratio (c.i.)
Genotype						
DxD	304			223		
Dx(DxR)	419	-0.57±0.17	0.56(0.38,0.75)	340	-0.52±0.14	0.59(0.43,0.76)
DxR	121	-0.72±0.26	0.49(0.24,0.74)	101	-0.71±0.20	0.49(0.29,0.68)
RxD	231	-0.73±0.24	0.48(0.25,0.71)	200	-1.00±0.21	0.37(0.22,0.52)
Rx(RxD)	466	-0.90±0.19	0.41(0.25,0.56)	398	-1.68±0.19	0.19(0.12,0.25)
RxR	204	-1.40±0.27	0.25(0.12,0.38)	180	-1.38±0.22	0.25(0.15,0.36)
Year of birth						
1991	363			309		
1992	293	0.08±0.24	1.09(0.58,1.59)	242	-0.01±0.24	0.99(0.53,1.45)
1993	365	-0.90±0.29	0.41(0.17,0.64)	347	1.49±0.19	4.45(2.81,6.09)
1994	236	1.13±0.23	3.08(1.70,4.46)	170	1.60±0.22	4.97(2.86,7.08)
1995	262	0.91±0.24	2.48(1.34,3.62)	203	1.54±0.22	4.66(2.63,6.68)
1996	226	0.75±0.25	2.13(1.07,3.18)	171	0.60±0.28	1.82(0.81,2.82)

5.4.6 Heterosis

An additional analysis to assess for evidence of heterosis was also carried out in the pre- and post-weaning periods. This was achieved by substituting the genotype term in the model with baseline covariates with appropriate linear contrasts as given in Baker et al. (2003). In general heterosis is defined as the superior performance of crossbred animals relative to the average performance of the purebreds involved in the cross. This could be due to combining genes from different breeds thus concealing the effects of inferior genes. Two types of heterosis are the individual and maternal heterosis. Individual heterosis is the better performance of a crossbred animal over the average of the pure breeds. For example, a RxD lamb may perform better than the average of (DxD) and (RxR) lambs. Maternal heterosis is the better performance of a crossbred mother (such as increased litter size) relative to the average of the pure bred mothers.
In both periods there was no evidence of heterosis, either as a direct individual or maternal effect.

5.5 Heritability estimates

Often, when frailty proportional hazard models are fitted in animal studies, the frailty variance is utilised in the calculation of heritability estimates (Ducrocq et al., 1988, Ducrocq, 2000, Henryon et al., 2001, Southey et al., 2001, Yazdi et al., 2000). From the linear mixed models perspective in Chapter 4.5, we saw that the heritability estimate is the ratio of genetic variation to phenotypic variation given by (4.2). In the frailty model approach, Ducrocq and Casella (1996) derived the heritability estimate defined as

$$h_s^2 = \frac{4\sigma_s^2}{\sigma_s^2 + \frac{\pi^2}{6}} \tag{5.6}$$

where σ_s^2 is the estimated variance of the frailty term (sire variance in this case) and which provides an estimate of the genetic variation. The denominator as before is an estimate of the phenotypic variance, where $\frac{\pi^2}{6}$ is the variance of the standard extreme value distribution (Lawless, 1982). This latter variance comes from the relationship of the extreme value distribution with the Weibull distribution, when the response variable

(time-to-event) is transformed on to a log scale as shown below.
Consider the following frailty model

$$\lambda_{ij}(t) = \lambda_0(t)\exp(\boldsymbol{x}_{ij}^T\boldsymbol{\beta} + w_i) \tag{5.7}$$

where w_i is the random effect of the i^{th} sire and $\lambda_0(t)$ is assumed to follow a Weibull distribution. This implies that

$$\lambda_0(t) = \lambda\rho t^{\rho-1}$$

where λ and ρ are the scale and shape parameters, respectively. Thus the time-to-event has density

$$f_T(t) = \lambda\rho t^{\rho-1}\exp(\boldsymbol{x}_{ij}^T\boldsymbol{\beta} + w_i)\exp\left(-\lambda t^{\rho}\exp(\boldsymbol{x}_{ij}^T\boldsymbol{\beta} + w_i)\right).$$

Let Y be the log transformation of T (i.e., $Y = \log T$). Then the density of Y is

$$\begin{aligned} f_Y(y) &= \lambda\rho e^{y\rho}\exp(\boldsymbol{x}_{ij}^T\boldsymbol{\beta} + w_i)\exp\left(-\lambda e^{y\rho}\exp(\boldsymbol{x}_{ij}^T\boldsymbol{\beta} + w_i)\right) \\ &= \rho\exp\left[\left(\log\lambda + y\rho + \boldsymbol{x}_{ij}^T\boldsymbol{\beta} + w_i\right) - \exp\left(\log\lambda + y\rho + \boldsymbol{x}_{ij}^T\boldsymbol{\beta} + w_i\right)\right] \end{aligned}$$

If we let $\varepsilon = \log\lambda + Y\rho + \boldsymbol{x}_{ij}^T\boldsymbol{\beta} + w_i$ then ε has the density

$$f_\varepsilon(\varepsilon) = \exp(\varepsilon - \exp(\varepsilon))$$

which is the extreme value density, with variance as $\frac{\pi^2}{6}$ (Lawless, 1982). Hence Var(Y)=$\sigma_s^2 + \frac{\pi^2}{6}$ is taken as an estimate of the phenotypic variance. Thus heritabilility can be estimated as in (5.6). We note that this estimate is on a log-scale ($\log T$) and needs to be transformed back to the original scale. Using Taylor series expansion Ducrocq (1999a) derived the approximation

$$h_{sT}^2 = \left(\exp(\nu\rho)\right)^2\frac{4\sigma_s^2}{\sigma_s^2 + \frac{\pi^2}{6}} \tag{5.8}$$

for original time scale, where $\nu = E[\varepsilon]$.
Korsgaard et al. (1999) proposes a modified expression of the heritability estimate given as

$$h_s^2 = \frac{4\sigma_s^2}{\sigma_s^2 + \sigma_e^2 + \frac{\pi^2}{6}} \tag{5.9}$$

where σ_e^2 is the residual variability. For this model, the random effect term used in the frailty model is $w_{ij} = s_i + e_{ij}$ where s_i is the sire effect and e_{ij} is a residual effect of

the j^{th} animal from the i^{th} sire. We saw in Section 2.3 that conditional on the frailty, there is independence of the individuals in a cluster. Thus, the underlying assumption in Model (5.7) is that conditional on the sire effect, the lambs from the same sire are independent. This has the implication that either all the lambs from the same sire come from different mothers or that the maternal genetic effect is insignificant. In the random effect formulation proposed by Korsgaard et al. (1999), this independence assumption is relaxed. Nevertheless, this latter model is not within the class of shared frailty models as more than one random effect is used per cluster.

In a more recent paper Yazdi et al. (2002) use $\sigma_s^2 + 1$ as an estimate for the phenotypic variance, based on a model similar to (5.7) but without covariates (i.e., $\boldsymbol{x}_{ij} \equiv \mathbf{0}$). This is motivated by the fact that (5.8) had been observed to be sensitive to the choice of the Weibull shape parameter ρ.

All the above heritability estimate expressions have been derived from parametric frailty models with a Weibull baseline hazard. The use of $\frac{\pi^2}{6}$ or 1 in a Cox proportional hazards model is an open question under discussion. For this reason heritability estimates were not calculated in this study.

5.6 Discussion

Previous analyses of the lamb data used in this study has shown Red Maasai sheep to be more resistant and resilient to gastro-intestinal parasites and more productive than Dorper sheep (Baker, 1998, Baker et al., 1999, 2003). In the current analysis the overall lamb mortality averaged 19% in the pre-weaning period which is within the 12% to 50% range reported for lamb mortality for tropical sheep (Traore et al., 1985, Wilson et al., 1993). In the post-weaning period it was 31%. As in the previous analysis, the Red Maasai are shown to perform better than the Dorper in terms of survival. The Red Maasai had about a three quarter lower risk of mortality than the Dorper in both the pre- and post-weaning periods.

Although there were year-to-year variations in the proportions of deaths caused by endoparasites, the ranking of the frequency of this disease across genotypes was remarkably constant. Furthermore, when differences in survival post-weaning across breeds due to endoparasites were compared with corresponding differences for all causes of mortality,

similar results were obtained. This implies that the differences in survival manifested between Dorper and Red Maasai breeds were associated with a variety of causes of death, not only endoparasites. Indeed, prior to weaning endoparasites accounted for only one fifth of all deaths. This suggests that Red Maasai sheep are manifesting a degree of general adaptability to tropical conditions, which includes enhanced resistance to or torelance to specific diseases such as haemonchosis.

Survival of animals has often been analysed as binary traits (0/1 for alive or dead) at arbitrarily defined time points in the animal's life span. Only the overall mortality to specific time points is of interest in such an analysis. However, in survival analysis all the information available in the lifespan of an animal can be used efficiently, since censored observations and uncensored observations are combined in a single analysis. The loss in information when failure time is analyzed through a logistic rather than a survival analysis approach was assessed by Yazdi et al. (2002). One major advantage of this approach over that of logistic regression is the ability to incorporate covariates that vary with time such as treatment, body weight, PCV and FEC. Lambs with low PCV or high FEC on a given sampling occasion were more susceptible than others to high mortality during the next month, despite treatment. This association with mortality appears to be independent of body weight. This is an important result because it demonstrates that animals that have already been infected, resulting in a high FEC and low PCV, have a greater risk of mortality than those with more normal values. This is despite treatment that occurred on average every 5-6 weeks post-weaning. The risk of mortality was substantially lowered in the pre-weaning period by treatment, demonstrating the impact of treatment generally on mortality to weaning.

Time-varying body weight was also strongly associated with mortality. When introduced into the model post-weaning a large increase occurred in the value of the sire variance component. This implies that disease and body weight affected the chances of survival independently and that by adding body weight to the model the direct genetic influence of sire on survival associated with disease could be seen more clearly. By introducing PCV and FEC, variables associated with disease, into the model the sire variance was again reduced, confirming the indication of genetic differences in PCV and FEC among sires (Baker, 2003).

Frailty models have been used for other species of livestock, for example in assessing the length of productive life in dairy cattle (Ducrocq et al., 1988), to assess viability of lay-

ing hens (Ducrocq, 2000), in obtaining estimates of longevity of Swedish horses (Wallin et al., 2000) and sows (Yazdi et al., 2000) and for assessing genetic variation for disease resistance in growing pigs (Henryon et al., 2001). The frailty variance in this studies has been utilised in the calculation of heritability estimates (Ducrocq et al., 1988, Ducrocq (2000), Henryon et al., 2001, Southey et al., 2001, Yazdi et al., 2000). The definitions of heritability for survival proposed in the literature have been derived based on a parametric hazard model, with a Weibull baseline hazard. The use of these heritability definitions in a semi-parametric frailty model is an open question that has not been resolved. Due to this fact no heritability estimates were calculated in this study.

Finally, above we have only presented the results from the log-normal frailty model. As noted earlier, the results from the gamma frailty model were similar to those tabulated above. Corresponding to the shared frailty models fitted in Tables 5.1 and 5.2, the sire variance estimates from the gamma frailty model were 0.005 and 0.0326 respectively. These estimates translate to estimates for the parameter γ in the frailty model (2.6). Thus, the similarity of the results from this model to those from the log-normal frailty model may be due to the fact that the gamma tends to the log-normal when γ is small (see Section 2.3.2). No explicit expression exists for calculating standard errors for these variance estimates from the gamma model.

5.7 Appendix

Table 5.7: *Parameter estimates for baseline covariates in the pre-weaning period from a shared frailty hazard model with birth weight and time-varying body weight alternatively, and treatment.*

	Birth weight		Time-varying body weight	
	only	with Treatment	only	with Treatment
	est±s.e.	est±s.e.	est±s.e.	est±s.e.
Genotype				
DxD	ref	ref	ref	ref
Dx(DxR)	-0.55±0.16	-0.56±0.16	-0.59±0.16	-0.60±0.16
DxR	-0.78±0.27	-0.77±0.27	-0.83±0.26	-0.83±0.26
RxD	-0.71±0.23	-0.71±0.23	-0.75±0.23	-0.76±0.23
Rx(RxD)	-1.00±0.19	-0.99±0.19	-1.12±0.18	-1.11±0.18
RxR	-1.49±0.26	-1.49±0.26	-1.77±0.26	-1.76±0.26
Year of birth				
1991	ref	ref	ref	ref
1992	-0.02±0.22	-0.01±0.22	-0.26±0.22	-0.23±0.22
1993	-1.21±0.29	-1.19±0.29	-1.23±0.29	-1.18±0.29
1994	0.47±0.24	0.50±0.24	0.01±0.23	0.08±0.23
1995	0.34±0.24	0.39±0.24	0.06±0.23	0.13±0.23
1996	0.67±0.24	0.73±0.25	-0.04±0.24	0.07±0.25
Gender	ref	ref	ref	ref
Females				
Males	-0.17±0.12	-0.17±0.12	-0.26±0.12	-0.27±0.12
Age of dam				
<=2yrs	ref	ref	ref	ref
=3 yrs	0.19±0.24	0.20±0.24	0.36±0.24	0.39±0.24
=4 yrs	0.14±0.25	0.15±0.25	0.42±0.25	0.46±0.25
=5 yrs	0.33±0.25	0.34±0.25	0.55±0.24	0.59±0.25
>=6yrs	0.34±0.25	0.35±0.25	0.46±0.25	0.50±0.25

see Table 5.3

Table 5.8: *Parameter estimates for the baseline covariates in the post-weaning period from a shared frailty model with weight at weaning and also time-varying PCV and LFEC.*

	Weight at weaning			
	only	with PCV	with LFEC	with PCV & LFEC
	est±s.e.	est±s.e.	est±s.e.	est±s.e.
Genotype				
DxD	ref	ref	ref	ref
Dx(DxR)	-0.52±0.13	-0.52±0.14	-0.43±0.14	-0.47±0.15
DxR	-0.88±0.20	-0.82±0.20	-0.76±0.21	-0.75±0.21
RxD	-1.19±0.20	-0.99±0.20	-1.22±0.22	-1.06±0.22
Rx(RxD)	-1.69±0.19	-1.35±0.18	-1.58±0.19	-1.32±0.19
RxR	-1.68±0.22	-1.20±0.22	-1.44±0.22	-1.05±0.22
Year of birth				
1991	ref	ref	ref	ref
1992	-0.34±0.23	-0.59±0.24	-0.30±0.24	-0.46±0.25
1993	1.78±0.19	1.59±0.18	1.75±0.20	1.60±0.20
1994	0.95±0.23	-0.23±0.24	0.74±0.24	-0.17±0.26
1995	0.74±0.23	-0.46±0.25	0.34±0.26	-0.47±0.27
1996	0.75±0.28	0.61±0.28	0.63±0.29	0.55±0.29
Gender				
Females	ref	ref	ref	ref
Males	0.43±0.10	0.34±0.10	0.37±0.10	0.29±0.11
Age of dam				
<=2yrs	ref	ref	ref	ref
=3 yrs	-0.07±0.17	-0.20±0.17	-0.29±0.18	-0.35±0.19
=4 yrs	0.01±0.18	-0.18±0.19	-0.21±0.19	-0.26±0.20
=5 yrs	0.19±0.18	0.09±0.18	0.04±0.19	0.02±0.19
>=6yrs	-0.15±0.19	-0.27±0.20	-0.31±0.20	-0.33±0.21

see Table 5.4 first two columns

Table 5.9: *Parameter estimates for the baseline covariates in the post-weaning period from a shared frailty model with time-varying body weight, PCV and LFEC.*

	Time varying body weight			
	only	with PCV	with LFEC	with PCV & LFEC
	est±s.e.	est±s.e.	est±s.e.	est±s.e.
Genotype				
DxD	ref	ref	ref	Ref
Dx(DxR)	-0.54±0.14	-0.55±0.14	-0.45±0.14	-0.50±0.15
DxR	-0.91±0.19	-0.85±0.20	-0.78±0.21	-0.78±0.21
RxD	-1.22±0.21	-1.05±0.20	-1.22±0.22	-1.11±0.22
Rx(RxD)	-1.67±0.19	-1.39±0.18	-1.57±0.19	-1.37±0.19
RxR	-1.73±0.22	-1.29±0.22	-1.51±0.22	-1.16±0.22
Year of birth				
1991	ref	ref	ref	Ref
1992	-0.40±0.24	-0.60±0.24	-0.38±0.25	-0.51±0.25
1993	1.58±0.19	1.46±0.19	1.58±0.21	1.47±0.20
1994	0.89±0.23	-0.17±0.24	0.68±0.24	-0.16±0.26
1995	0.71±0.23	-0.40±0.25	0.30±0.26	-0.46±0.27
1996	0.42±0.28	0.40±0.28	0.37±0.29	0.34±0.29
Gender				
Females	ref	ref	ref	ref
Males	0.52±0.10	0.39±0.10	0.46±0.11	0.34±0.11
Age of dam				
<=2yrs	ref	ref	ref	ref
=3 yrs	-0.03±0.17	-0.20±0.17	-0.27±0.19	-0.35±0.19
=4 yrs	0.15±0.18	-0.13±0.19	-0.07±0.20	-0.21±0.20
=5 yrs	0.33±0.18	0.11±0.18	0.20±0.19	0.07±0.19
>=6yrs	0.00±0.19	-0.20±0.20	-0.14±0.20	-0.25±0.21

see Table 5.4 last two columns