SimHerd-Flex application for estimating the cost-benefit of Nedap CowControl system

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General description

Response Surface Model

A SimHerd-Flex application is a response surface model (RSM) of the full SimHerd model. An RSM describes the behavior of the full SimHerd model as good as possible, while easier and faster to use. In this documentation paper, the method and choices behind the RSM are presented. Figure 1 presents a simplified illustration of how an RSM is created.

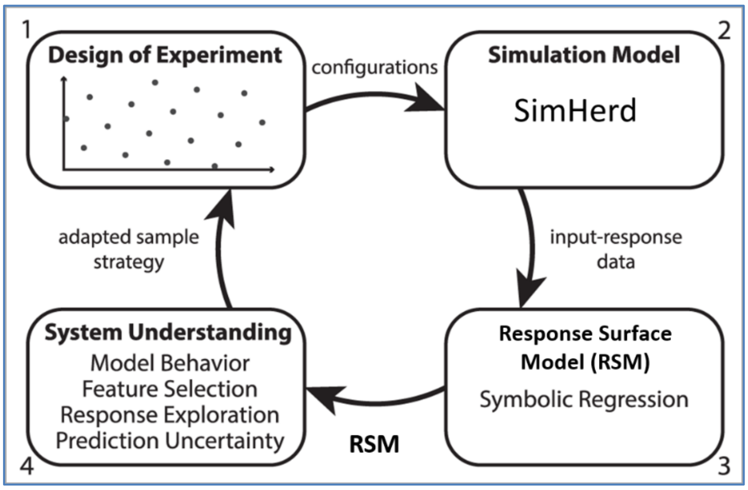

Figure 1: Making a Response Surface Model (RSM) modified after Willem en Stijven (2014)

Design of Experiment

Step 1 in the creation of an RSM (figure 1) is the Design of a simulation experiment to be executed with the full SimHerd model. The design of this study covered a total of 130 scenarios in which different levels of disease risk and severity, reproduction performance, culling rate, and milk yield. The economic results for these 130 different scenarios were then estimated using two different price levels and two different production systems. The 130 combinations of herd-specific settings can be interpreted as 130 different herds.

Simulation model with the full version of the SimHerd model

In step 2 (figure 1) each of the 130 scenarios were simulated by SimHerd over a period of 10 years. The simulated technical results (like milk yield per cow-year) and economic results (like Gross Margin (GM) per cow-year) of the last 5 simulation years were used in the next step.

RSM or symbolic regression

In step 3, a regression model was built to describe the simulated output parameters as a function of the model's input parameters. In other words, the regression model describes the simulated GM per cow-year (the dependent variable, y) as a function of the input parameters like the herd's disease risk and milk price (the independent variables, x's). This regression model is also referred to as the RSM. In step 4, it was evaluated to what extent the RSM was able to describe the 130 data points. Furthermore, the behavior of the RSM was studied when using input parameters (x's) beyond the range of original input parameters from the design of experiment (extrapolation). From these evaluations it was concluded that expanding the design of experiment and thereby re-running the RSM cycle (i.e. repeating steps 1 to 4 in Figure 1) was not necessary.

User-interface construction

The RSM is built into a spreadsheet in Microsoft Excel, where input parameters (the x's) are presented to the user as changeable parameters (blue + and – buttons in Figure 2). The output parameters (the y's) of the RSM represent the simulated change in for example milk yield and benefit. Accordingly, the profit per year is calculated as the benefit reduced by the yearly cost of the investment. The investment in this SimHerd-Flex application was the investment amount per cow of buying the Nedap CowControl system. The Excel spreadsheet was converted into html and be used on-line. The Nedap CowControl user-interface includes many functionalities and possibilities to show or hide different areas.

Figure 2: User-interface of the Nedap CowControl application of SimHerd-Flex

Simulating reduced disease severity in SimHerd

Before creating an RSM (Figure 1), the assumed effects of using the Nedap CowControl to early disease diagnosis on cow-level performance were defined.

Mastitis

The sensor finds the acute cases of mastitis earlier thereby reducing the severity. We assume that the overall occurrence of mastitis is unchanged, but the proportion of severe mastitis cases can be reduced. In SimHerd, two different mastitis types were defined: Mild mastitis (MM) and severe mastitis (SM). The two types of mastitis differed regarding their effect on cow level risk of dying or being culled, conception chance and milk yield. See details in Table 1. The parameterisation of the mastitis types was based on a literature review made for the project – see appendix 1.

Table 1: Parameterisation of new mastitis types in Nedap SimHerd Flex application, CM = Clinical Mastitis

Parameter	Param. expl.	Severe mastitis	Mild mastitis
Proportion of cases		15%	85%
Mortality	Risk of dying in week of CM	4%	1%
Culling	Risk of involuntary culling in week of CM	13,4%	1,3%
	Shortening of insemination period if CM (21 = one less cyklus before culling)	63	42
Reproduction	Effect of CM on chance of conception	0,4	0,7
	Duration of the effect of CM on conception chance	42	42
Milk yield	Effect of CM on milk yield – positive value = milk loss	0,425	0,075

Metabolic diseases and acute lameness

Beside mastitis, the Nedap CowControl system can also detect other diseases earlier and here a general assumption was made that installing the system would lead to milder clinical disease. The disease specific adjustments are shown in Table 2. Again, it was assumed that the Nedap CowControl system would not reduce disease prevalence but reduce the impact on milk production, mortatlity risk, culling risk and/or conception rate at cow level. The assumptions in table 2 are based on general information (literature and best-guesses) on the efficacy of sensors to detect diseases. In the References, a list of key-papers can be found.

Table 2: Parameterisation of milder cases of metabolic disease and acute lameness in SimHerd

Disease	Parameter	Without CowControl	With CowControl
Milk fever	Milk loss (maximal effect on daily milk yield)	0,09	0,041
	Mortality (risk of dying in week of disease)	0,13	0,022
Metritis	Milk loss (maximal effect on daily milk yield)	0,16	0,094
	Conception rate	0,74	0,87
Displaced abomasum	Milk loss (maximal effect on daily milk yield)	0,22	0,004
	Mortality (risk of dying in week of disease)	0,07	0,01
	Culling risk (risk of involuntary culling in week of disease)	0,13	0,02
Ketosis	Milk loss (maximal effect on daily milk yield)	0,161	0,051
	Conception rate	0,275	0,8
Acute lameness	Milk loss (maximal effect on daily milk yield)	0,055	0,041
	Mortality (risk of dying in week of disease)	0,042	0,021
	Culling risk (risk of involuntary culling in week of disease)	0,036	0,018
	Conception rate	0,43	0,72

Design of Experiment

A simulation experiment was designed with the purpose of covering the area of interest as well as possible. The aim was to estimate the economic value of early disease detection (= milder clinical disease) and improved heat detection and a higher conception rate while controlling for other parameters of herd management. Therefore, the area of interest in this project concerns the cow and heifer reproduction as well as the diseases for which Nedap CowControl has documented that the system can detect early disease signs.

Reproduction parameters

For cows, four levels of heat detection rate (HDR, range = 0.32-0.95) and conception rate (CR, range = 0.41-0.64) were defined. These ranges were selected to allow the estimation of a 20 percent point increase in both parameters when having Nedap CowControl installed.

For heifers, we needed to control for the proportion of heifers being slaughtered depending on the reproduction level. Therefore, nine levels of heifer reproduction were defined: Three levels of HDR (range = 0.25-0.85) * three levels of CR (range = 0.43-0.83), and a specific proportion of heifers being slaughtered for each of these combinations.

Disease parameters

The diseases that Nedap CowControl is able to detect are presented in Table 1. Further, we defined two types of mastitis – mild and severe – as earlier described. The assumption regarding the effects of earlier disease detection on the cow level performance have been described in previous sections.

In the study design, the three metabolic diseases were treated as one disease complex. Therefore, the user will not enter the incidence of each disease but instead a summation of cases of milk fever, ketosis, and displaced abomasum. Acute lameness was handled separately. In addition to the different severity levels of each disease (normal (without sensor) and mild (with sensor)), we also included two incidence levels for each disease/disease complex. The low incidence level was defined as the baseline risk of the given disease in an average herd and the high incidence level by doubling the low baseline risk. In scenarios not simulating a given disease's effects, the disease was included with original severity and a medium incidence level.

After parameterisation of the two new mastitis types (mild and severe), the occurrence of the two new types is simulated by defining different levels of the distribution between the two and let these distributions have effect at different levels of the baseline risk of mastitis. This gives us four levels of the new mastitis combining the baseline risk of mastitis in the herd and the proportion of these assumed to be severe:

- LFS = Low baseline risk (0.13) and few severe cases (0.05)
- LMS = Low baseline risk (0.13) and many severe cases (0.20)
- HFS = High baseline risk (0.40) and few severe cases (0.05)
- HMS = High baseline risk (0.40) and many severe cases (0.20)

Additionally, a medium level of mastitis was defined to be used in scenarios not simulating the effects of mastitis. For this, a medium baseline risk (0.25) and medium proportion of severe cases (0.11) were used.

Other KPI's

Other KPI's that are relevant when assessing the economic impact of a disease (by SimHerd) are the herd's milk yield level (two levels) and replacement rate (two levels). Based on experience with the SimHerd model, differences in these KPI's cause differences in the estimated economic value of a disease. In addition to the KPI's, two different levels of prices and costs were also created in the experiment.

Table 3: Combinations of disease and reproduction parameters with herd management parameters

Parameters	Levels	N combinations	Milk yield	Culling rate	N total
HDR, cows	4				
CR, cows	4	16	2	2	64
Metabolic disease, incidence	2				
Metabolic disease, severity	2	4	2	2	16
Mastitis, incidence	2				
Mastitis, severity	2	4	2	2	16
Acute lameness, incidence	2				
Acute lameness, severity	2	4	2	2	16
HDR, heifers	3				
CR, heifers	3	9		2	18
Total					**130**

In case of a full experimental design, exploring all possible combinations of all levels, the sum of combinations would have been 36.864. This would have resulted in a huge dataset of simulated results. Experience with the model tells us that not all combinations are relevant to study. Instead, the combinations shown in Table 3 were used. Reproduction parameters were not combined with different levels of disease risk. Instead, when simulating the different combinations of reproduction levels the risk of acute lameness and metabolic disease were held at the low level and mastitis risk were held at the medium level. And vice versa, when simulating at different disease risk the reproduction parameters were held at a medium level. In total, 130 unique scenarios were simulated.

In Table 4 the parameterization of eight of the 130 scenarios is presented as an example. These eight scenarios enable to estimate four economic values of the Nedap CowComfort systems at high levels of metabolic disease:

1) Value in a herd with high milk yield and low replacement rate (scenario 91 vs 95)
2) Value in a herd with high milk yield and high replacement rate (scenario 92 vs 96)
3) Value in a herd with low milk yield and low replacement rate (scenario 89 vs 93)
4) Value in a herd with low milk yield and high replacement rate (scenario 90 vs 94)

Table 4: Example of parameterization of 8 scenarios of the simulation experiment.

	Scenarios										
	91	**95**		**92**	**96**		**89**	**93**		**90**	**94**
MD - incidence	H	H		H	H		H	H		H	H
MD - severity	NS	WS		NS	WS		NS	WS		NS	WS
Milk yield level	H	H		H	H		L	L		L	L
Replacement rate	L	L		H	H		L	L		H	H
HDR - cows	M	M		M	M		M	M		M	M
CR - cows	M	M		M	M		M	M		M	M
HDR - heifers	M	M		M	M		M	M		M	M
CR - heifers	M	M		M	M		M	M		M	M
Mastitis	M	M		M	M		M	M		M	M
Lameness - incidence	L	L		L	L		L	L		L	L
Lameness - severity	NS	NS		NS	NS		NS	NS		NS	NS

MD = Metabolic disease, HDR = Heat detection rate, CR = Conception rate
H = High, M = Medium, L = Low.
NS = No sensor (original disease severity), WS = With sensor (mild disease severity)

Price effects

The 130 combinations were simulated given one standard set of prices (= low price in Table 4). Afterwards, the same 130 scenarios were combined with a price set where an extra, higher price level were defined for ten different price settings (= high price in Table 4). Now, the same 130 combinations were studied ten times. For each time, one of the ten price-levels was set at the high level, while keeping the other nine prices constant (at the low level). The 130 combinations were thereby simulated eleven times, resulting in a total of 1430 scenarios.

Table 5: The different levels of disease risks, other KPI's and prices and costs that were simulated in the simulation experiment behind the SimHerd-Flex application of the Nedap CowControl system.

	Level		
	Low	Med	High
Disease risk[1]			
Mastitis (sum of mild and severe)	19%	42%	75%
Metabolic diseases (MD) [2]	24%		44%
Acute lameness	4,5%		9,5%
Reproduction, cows			
Heat detection rate (HDR)	0,32	0,53/0,74	0,95
Conception rate (CR)	0,41	0,48/0,56	0,64
Reproduction, heifers			
Heat detection rate (HDR)	0,25	0,55	0,85
Conception rate (CR)	0,43	0,63	0,83
Other KPI's			
Milk yield potential, kg per 305 days	9500		12700
Culling risk	29%		38%
Prices and costs			
Milk price, kr. pr. kg ECM	2,6		3,6
Feed price, kr. pr. kg DM	1,45		2,175
Treatment costs, mild mastitis*	680		765
Treatment costs, severe mastitis*	680		1275
Treatment costs, MD* [1]	905		1358
Treatment costs, acute lameness*	308		462
Insemination costs, kr. pr. breeding	180		270
Sales price heifers, kr. pr. heifer	11000		16500
Slaughter price, kr. pr. cow	6500		9750
Other costs	300		1030

[1] Disease risk in cases per 100 cows

[2] Milk fever, ketosis, metritis and displaced abomasum

* kr. pr. case

Simulation modelling with SimHerd

SimHerd is a dynamic, stochastic, and mechanistic simulation model of dairy farm including youngstock (Østergaard et al. 2005). Each of the 130 scenarios were simulated by SimHerd over a period of 10 years. To avoid the influence of the initial herd, only the average results over the last 5 years were studied. The number of replicates used per simulation was 950. In Table 4 the simulated results of the six scenarios from Table 3 are presented.

Table 6: Simulated results from eight example scenarios earlier presented in Table 4

	Scenarios										
	91	95		92	96		89	93		90	94
MD - severity	NS	WS		NS	WS		NS	WS		NS	WS
MD cases per 100 cow year	25	41		31	34		36	41		31	34
Conception rate	0,34	0,35		0,35	0,35		0,34	0,35		0,35	0,35
Mortality, dead cows per 100 cow years	6,6	5,2		6,2	5,0		6,6	5,2		6,2	5,0
Kg milk per cow year	12677	12772		12607	12707		9459	9534		9433	9504
Replacement rate	0,32	0,30		0,42	0,41		0,32	0,30		0,42	0,41
Gross margin per cow year	17811	18045		17541	17763		11751	11943		11533	11717

Response surface model (RSM)

For all 1430 combinations of scenarios, prices and costs, the gross margin (GM) was simulated. The goal of making an RSM is to describe these simulated values for GM (the dependent variable, y) as a function of the input parameters (the independent variables, x's, as presented in Table 3).

Creating an RSM that describes GM is done in two steps.

Step 1: Describing the technical performance of the herd. Models are constructed using different technical performance parameters (such as milk per cow, surplus heifers sold, and percent milk delivered) as dependent variable (y) and include e.g. milk yield potential, reproduction performance, disease incidence, and culling rate as explanatory variables (x's).

One example is modelling the cow mortality (the dependent variable, y) without (*_NoSens*) or with sensor (*_WiSens*) installed as a function of the x's: milk yield potential of the cow (TopYield), the incidence of MD (*METAB_NoSens/_WiSens*), mastitis (*MILDMAS_BR, SEVEREMAS_BR*), and acute lameness (*KBB__NoSens/_WiSens*), the reproductive efficiency (*RE*_cows (calculated as a function of HDR and CR)) and the culling rate (*InvolCull*). The curve-linear model below contains main effects, as well as interaction terms between culling rate and disease incidence.

Table 7: Example of step 1 RSM model describing one aspect of the technical performance of the herd (cow mortality)

COW MORTALITY (dead cows per 100 cow years) given no sensor =			**COW MORTALITY (dead cows per 100 cow years) with sensor =**		
0,153879204	*	Intercept +	0,153879204	*	Intercept +
-0,000873583	*	TopYield +	-0,000873583	*	TopYield +
-46,39875301	*	InvolCull +	-46,39875301	*	InvolCull +
46,35090754	*	RE_cows +	46,35090754	*	RE_cows +
-150,5099151	*	I(RE_cows^2) +	-150,5099151	*	I(RE_cows^2) +
175,2033611	*	I(RE_cows^3) +	175,2033611	*	I(RE_cows^3) +
11,00403802	*	METAB_NoSens +	1,715319419	*	METAB_WiSens +
73,70935967	*	KBB_NoSens +	27,90184955	*	KBB_WiSens +
0,801036705	*	MILDMAS_BR +	0,801036705	*	MILDMAS_BR +
3,967936848	*	SEVMAS_BR +	3,967936848	*	SEVMAS_BR +
-149,9687689	*	InvolCull:METAB_NoSens +	114,5809606	*	InvolCull:METAB_WiSens +
3829,201753	*	InvolCull:KBB_NoSens +	5681,369633	*	InvolCull:KBB_WiSens +
-17,81113765	*	InvolCull:MILDMAS_BR +	-17,81113765	*	InvolCull:MILDMAS_BR +
-95,92388262	*	InvolCull:SEVMAS_BR	-95,92388262	*	InvolCull:SEVMAS_BR

Step 2: describing the economic performance of the herd (*DBprko1*=gross margin per cow-year, y's) as a function of the technical performance, like milk-yield per cow-year (*MlkPrKo*) but also prices and costs like milk-price (*KrPrEkm*) and feeding costs (*KrFeed*). In other words, the dependent variables from step 1 are used as independent variables in step 2.

Table 8: Step 2 RSM model estimating the gross margin per cow given input of estimations from step 1 RSM models

GROSS MARGIN per cow cow year =		
-155270,7251	*	(Intercept) +
-6,098982705	*	MlkPrKo.mean +
-130,7585475	*	DodkoPKo.mean +
-12,92986748	*	klvkviersolgt.mean +
-2,295468584	*	GnsAntKvier.mean +
-23,24897431	*	UdskPct.mean +
37,78647982	*	InsPrKo.mean +
25,68147244	*	InsPrKv.mean +
1554,467147	*	Leveringpct.mean +
28,50852981	*	METABprko.mean +
48,10619557	*	KBBprko.mean +
31,7069285	*	MILDMASprko.mean +
14,02228822	*	SEVEREMASprko.mean +
14,57502706	*	KrPrEkm +
-2302,046123	*	KrFeed +
-0,003027331	*	KrPrKlKv +
-31,69058494	*	KrPrKgKo +
0,13413656	*	KrNSBT +
-0,022213168	*	OevOmkKv +
-0,001718853	*	KrMetab +
-0,000725164	*	KrMas11 +
-0,007682716	*	KrMas4 +
-0,14589641	*	KrMas7 +
0,98106417	*	MlkPrKo.mean:KrPrEkm +
-0,450296881	*	MlkPrKo.mean:KrFeed +
0,062522192	*	MlkPrKo.mean:Leveringpct.mean +
0,005155318	*	klvkviersolgt.mean:KrPrKlKv +
6,219384062	*	UdskPct.mean:KrPrKgKo +
-0,007477205	*	METABprko.mean:KrMetab +
-0,009477758	*	KBBprko.mean:KrMas11 +
-0,006392759	*	MILDMASprko.mean:KrMas7 +
-0,017576959	*	SEVEREMASprko.mean:KrMas4 +
-1,054766457	*	InsPrKo.mean:KrNSBT +
-0,783173641	*	InsPrKv.mean:KrNSBT +
-0,004883333	*	GnsAntKvier.mean:OevOmkKv

User-interface construction

A spreadsheet was built in Excel in which all the above reported information was incorporated. The Excel sheet was accordingly converted into html, which is the application that the user works with.

In figure 4, the start screen of the user-interface is presented. A detailed tutorial of the user-interface is available on youtube. In this documentation, only a short description of the main elements is given. As described in the previous paragraph, in the first step of constructing an RSM, a first RSM model is created that describes the technical performance of the herd, like milk yield per cow-year. This RSM comes into play in the interface, as illustrated with 9 green arrows in figure 4.

1) Arrow 1 in figure shows that the RSM predicts an increase in milk yield of 133 kg, as a result of implementing CowControl.
2) The user can also specify that the level of milk yield is lower in *his* herd (arrow 2). By doing so, the expected milk yield (green 1) will also be lower.
3) It is the increase in yield, but also the reduction in replacement rate, that is responsible for the increase in Benefit / year (arrow 3), predicted by the RSM.
4) The user can specify the costs of the investment in CowControl (arrow 4).
5) These costs but also the productive life of the technology and the interest rate, determine the annual costs of the investment (arrow 5)
6) Based on the difference between the benefit and the costs, the profit as well as the payback period can be calculated (arrow 6)
7) The user can also show other technical results of the calculation (the amount of saved labor for example) by ticking boxes (box 7)
8) The user can show the assumptions that were used in the calculator; the assumptions behind improved reproduction or early diagnosis of health events, by ticking boxes (box 8).
9) Sheets in the top contain more information on specific calculations (arrow 9).

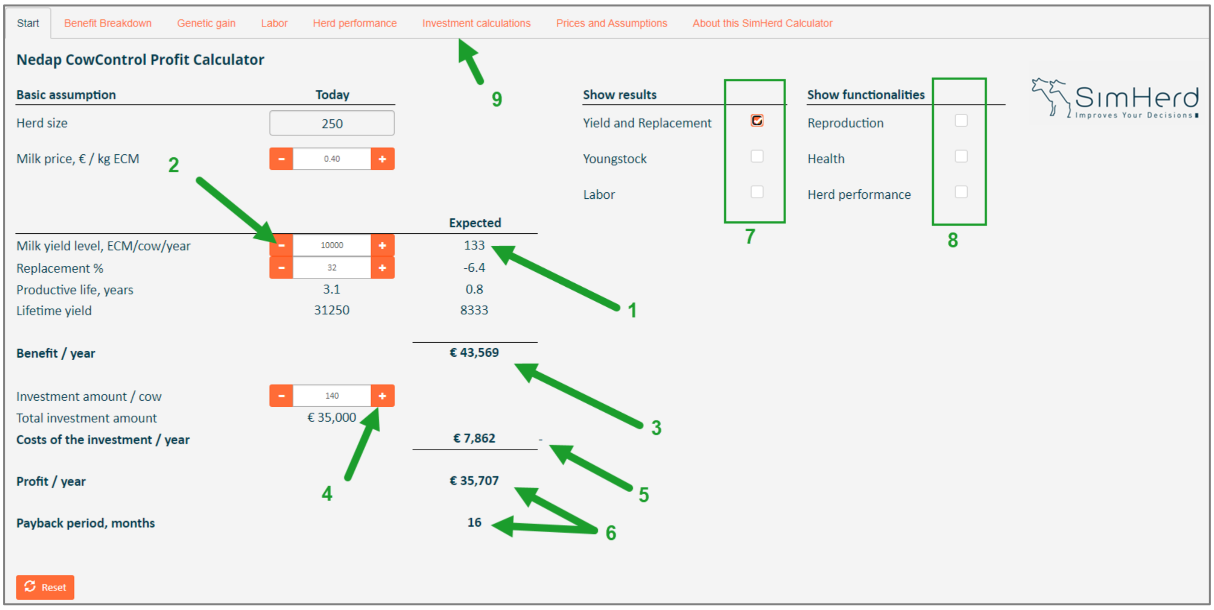

Figure 4: the start-screen of the user-interface of the Nedap CowControl Profit calculator

Appendix 1: literature study on mastitis incidence and severity

Review – Mastitis severity

General epidemiology

Considering different clinical mastitis (CM) severity – classification often used:

- Mild = Only changes in milk
- Moderate = Change of milk + local inflammation
- Severe = Systemic – fever, lack of appetite

Some studies consider pathogen type instead of clinical severity. Pathogens are typically separated into:

- Gram-positives (G+): *Streptococcus spp., Staphylococcus aureus, Staphylococcus spp.*
- Gram-negatives (G-): *Escherichia coli, Klebsiella, Citrobacter, Enterobacter, Pseudomonas*
- Other: *Arcanobacterium pyogenes, Mycoplasma, Corynebacterium bovis*, yeast, miscellaneous

Generally, the G- infections are associated with most severe clinical symptoms. Therefore, for this review, I have also included studies that does not specifically consider severity but alternatively have categorised the CM by pathogenic categories and thus consider G- CM as severe cases and G+/others as mild cases.

(Schmenger and Krömker, 2020) gives a general description of mastitis epidemiology on pathogen level (from herds in Northern Germany) – parity, lactation stage

- 9.1% of all clinical mastitis were severe cases, 35.7% moderate, 55.2% mild
- Not only coliforms involved in severe clinical mastitis – 26.5% of severe cases presented with S.Uberis

(Fuenzalida et al., 2015) found that 11.8% of clinical mastitis cases were severe mastitis, 26.9% moderate, 61.3% mild.

(Verbeke et al., 2014) found 63.1% of clinical cases mild, 29.9% moderate and 7% severe. However, in AMS herds, the distribution was 30.8, 39.2 and 40%, respectively!

In (Oliveira et al., 2013), the distribution of clinical mastitis cases with mild, moderate, and severe symptoms was 47.8, 36.9, and 15.3%, respectively.

(Vangroenweghe et al., 2020) concluded that first parity cows had a mild reaction to E.coli endotoxin IMM and therefore, they found no effect of E.coli vaccination on the severity of systemic clinical E.coli mastitis in first parity cows. (Bradley et al., 2015) demonstrated that the use of a polyvalent mastitis vaccine (StartVac, Hipra) reduced the severity of CM, the 305d culling rate (not mastitis specific cullings…) and an increased production of milk solids (12kg in the first 120 days). (Bradley et al., 2015) suggested that the vaccination reduced the butterfat:protein ratio thereby leading to general effects with cows being in a less severe negative energy balance.

Effects on milk production

In a review from 2003, (Seegers et al., 2003) summarised literature values for milk loss from CM to 375kg equal to 5% at lactation level for an 'average' CM occurring in the second month of lactation in a Holstein cow. In a very recent study of milk losses in relation to mastitis treatments in AMS herds, (Adriaens et al., 2021) found that at cow level across all parities and lactations stages the median relative milk loss during a period of -5 to 30 day around treatment was 17.2% equal to an absolute milk loss of 128 kg (see table below). In a 10.000 kg lactation this means that a single mastitis case has a relative impact of 1,28%. Also, from the table below it is clear that there is substantial variation in the estimates of the overall milk loss corresponding to a relative loss in a 10.000 kg lactation of 0,6% - 3,0%

Absolute and relative milk losses in perturbations at the cow level corresponding to cases of intramammary infections. The milk losses are expressed as the amount of milk lost, and thus in positive numbers.

	Absolute milk losses (kg) median, [Q25;Q75][3]	Relative losses (%) median, [Q25;Q75]
Overall	**128.0, [59.2;296.5]**	**17.2, [12.9;23.2]**
P1[1], LS1[2]	37.9, [26.2;69.6]	16.2, [12.6;22.5]
P1, LS2	110.9, [58.6;211.9]	15.4, [11.9;19.8]
P1, LS3	118.8, [59.5;237.0]	17.2, [13.0;23.5]
P2, LS1	59.3, [34.2;108.9]	16.0, [12.3;20.9]
P2, LS2	176.4, [83.9;386.6]	16.6, [12.3;22.1]
P2, LS3	128.3, [57.6;278.7]	18.7, [14.1;25.9]

[1] P: parity classes. P1 = first parity, P2 = 2nd parity and higher.
[2] LS: lactation stage classes: LS1 = days in milk (DIM) 0–20, LS2 = DIM 21–140, LS3 = DIM 141 to 305.
[3] Q: quartiles, Q25 = first quartile, Q75 = last quartile.

From Adriaens et al., 2021

There was substantial variation, and the distribution of the milk losses did not have a Gaussian shape; rather a heavy tail towards higher losses indication that many cases had a milk loss below the average whereas a few cases had very dramatic milk losses. The length of the milk yield perturbations varied with the lactation stage at the treatment day: 91, 52 and 60 % of the perturbation were shorter than 30 days for treatments performed in early (0-20 DIM), middle (21-120 DIM) and late lactation (121-305 DIM), respectively.

	Severity of clinical mastitis case												
	Mild (1)			Moderate (2)			Severe (3)			Overall			
Characteristic	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	P-value
SCC ($\log_{10}$) before enrollment[1]	164	5.3[a]	0.8	142	5.1[b]	0.8	47	4.9[b]	0.5	353	5.2	0.7	0.001
Milk production before enrollment[2]	167	44.6[a]	11.8	142	44.3[a]	10.9	47	48.8[b]	10.6	356	45.0	11.4	0.05
Postmilk after treatment[3]	174	41.4[a]	10.2	139	39.4[a]	11.3	41	38.2[a]	11.6	354	40.3	10.9	0.11
Milk deviation[4]	141	−3.7[a]	8.9	106	−5.1[a]	11.3	31	−11.2[b]	11.2	278	−5.1	10.3	0.001
DIM[5]	279	136.0[a]	—	215	136.0[a]	—	89	125.0[a]	—	583	133.0	—	0.82

[a,b]Means within a row with the same superscript are not significantly different ($P < 0.05$).
[1]Data were not available for all 583 cows.
[2]Production in kilograms per cow per day. Value from monthly DHI test 2 to 32 d previous to the enrolled case.
[3]Milk production (kg/cow per day) after enrollment at cow level was obtained at DHI monthly test occurring from 14 to 52 d after end of treatment.

1From Oliveira et al (2013)

(Oliveira et al., 2013) found that severe cases of CM were associated with a significantly larger negative deviation in kg milk when comparing the two closest test day milkings before and after the CM occurrence. Also, cows suffering from severe CM had a higher pre-MY and a lower pre-SCC than cows suffering from mild or moderate CM.

(Blum et al., 2014) characterised two types of inflammatory reactions to E.coli mastitis (graph a and b in figure) – **however few cows**! Short-term inflammation causing a <15% decrease in DMY and returning to normal within 30 days, and long-term inflammation causing >15% DMY decrease and a return to new, lower DMY in > 30 days. The estimated total loss of marketable milk in the study period was 200 L/cow with short inflammation and 1500 L/cow with long inflammation.

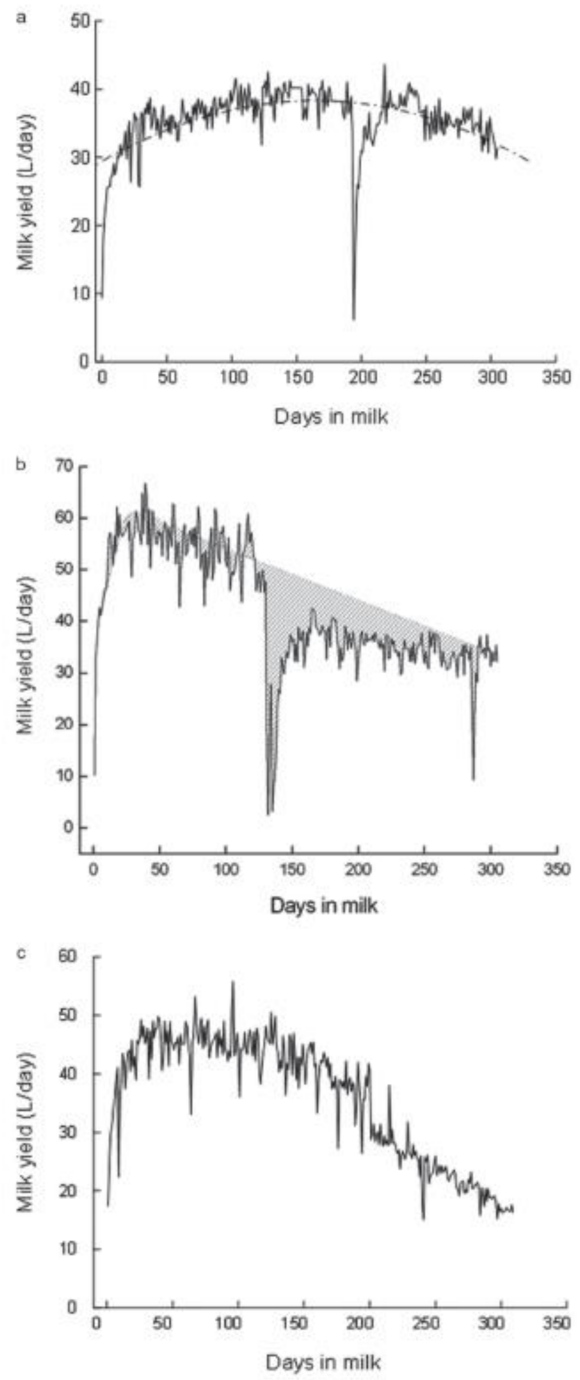

Fig. 1. (a) Lactation curve of cow 3013 representing a 'short inflammation' case. Actual milk yield (solid line), pred
was 10,900 L in 305 day la
'long inflammation' case wi
dicted milk yield (dashed line). The area between the two lines represents milk loss [predicted milk yield – actual milk yield; i.e., 14,524–12,814 = –1710 L milk]. (c) Lactation curve of cow 2732, representing a 'long inflammation' case with persistent intramammary infection. Total milk yield was 12,800 L.

From Blum *et al* (2014)

(Schukken et al., 2009) used data from 20.000+ lactations from 7 New York dairy herds to demonstrate the effect of repeated cases of CM on the milk yield. They found that the milk loss in cases with G- bacteria was 304 kg (228 kg) in multiparous (primiparous) cows in the 50 days following CM. G+ cases were associated with a milk loss of 128/133 kg for multiparous/primiparous cows. Lactation curves examples for different cases of repeated CM are shown in the figures below.

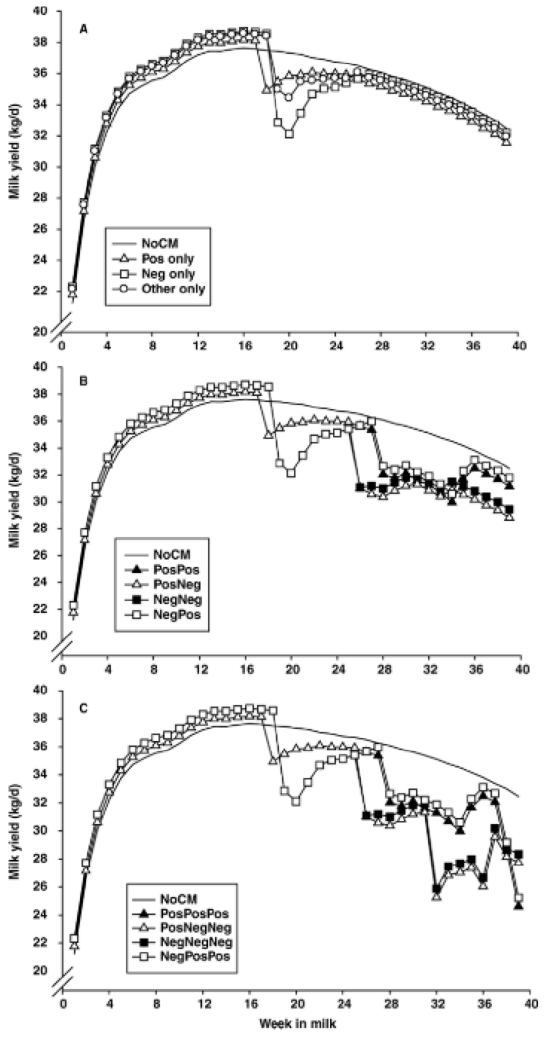

Figure 1. Lactation curves for A) primipara with no clinical mastitis (CM; ——), or only one case of 1 of 3 types of CM: gram-positive (Pos, Δ), gram-negative (Neg, □), or other (○); cases are assumed to occur during the median week of occurrence for each type; B) primipara with no CM (——), or selected combinations of 2 cases of CM sequentially: PosPos (▲), PosNeg (Δ), NegPos (□), or NegNeg (■); and C) primipara with no CM (——), or selected combinations of 3 cases of CM sequentially: NegPosPos (□), PosNegNeg (Δ), PosPosPos (▲), or NegNegNeg (■).

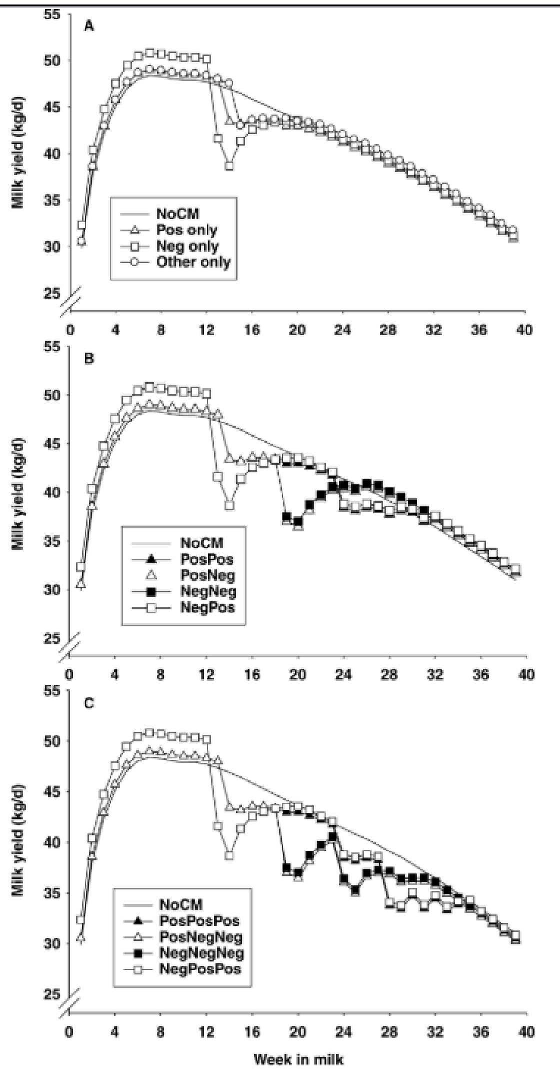

Figure 2. Lactation curves for A) multipara with no clinical mastitis (CM; ——), or one case of 1 of 3 types of CM: gram-positive (Pos, Δ), gram-negative (Neg, □), or other (○); cases are assumed to occur during the median week of occurrence for each type; B) multipara with no CM (——), or selected combinations of 2 cases of CM sequentially: PosPos (▲), PosNeg (Δ), NegPos (□), or NegNeg (■); and C) multipara with no CM (——), or selected combinations of 3 cases of CM sequentially: NegPosPos (□), PosNegNeg (Δ), PosPosPos (▲), or NegNegNeg (■).

From Schukken et al, 2009

(Gröhn et al., 2004) investigated the effect of pathogen-specific CM on the milk yield. The figure below illustrates the variation in daily milk yield in amplitude as well as duration between different pathogen-specific CM in parity 2+ cows.

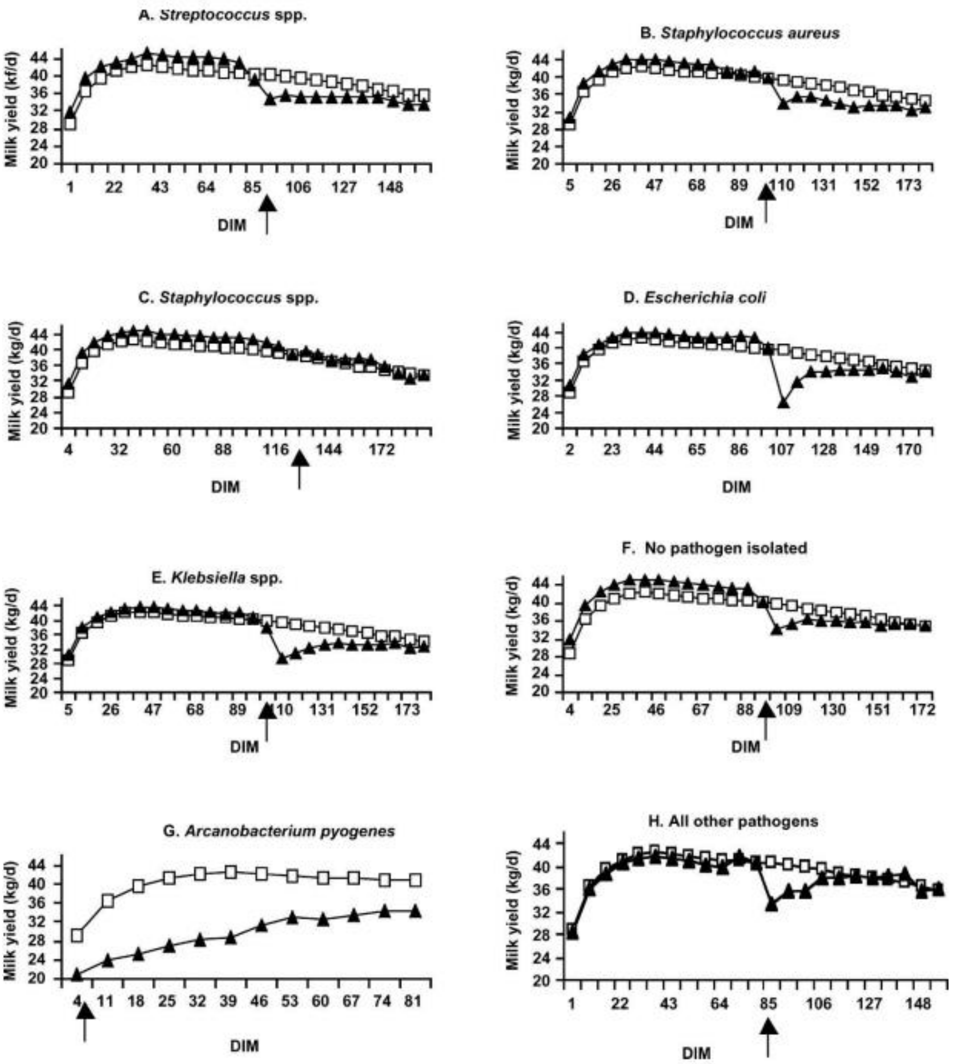

Figure 2. Lactation curves of 2 parity-2+ cows. One cow was infected with A) *Streptococcus* spp. B) *Staphylococcus aureus*, C) *Staphylococcus* spp., D) *Escherichia coli*, E) *Klebsiella* spp., F) no pathogen isolated, G) *Arcanobacterium pyogenes*, or H) all other pathogens (Panel H) (—▲—); the other cow was without the corresponding pathogen (—□—). The difference at each point of the lactation curves in each panel corresponds to the estimates in Table 5. The arrow indicates median DIM of diagnosis of the mastitic cow.

Effects on culling/mortality

(Oliveira et al., 2013) found that cows suffering from severe CM were 2.9 times more likely to be culled within 90 days of the CM occurrence. No obvious effect on culling with mild or moderate CM. The baseline risk of culling within 90 days of enrolment were 18.2% - for severe CM it was 30.9%. The baseline culling risk in the herds are not shown – only cows with CM were enrolled in the study.

			Severity of clinical mastitis case[1]							Severe compared with mild and moderate cases[2]	
	Overall		Mild (1)		Moderate (2)		Severe (3)				
Category	n	%	n	%	n	%	n	%	P-value	Odds ratio	CI
Removed [10]									0.04		
No	427	81.8	217	86.6	154	81.1	56	69.1			
Yes	95	18.2	34	13.5	36	18.9	25	30.9		2.9	1.4–3.8

From (Oliveira et al., 2013)

(Hertl et al., 2011) evaluated the effects of recurrent CM on mortality and culling. Here, they modelled the mortality over the first ten months of lactation and the effect of different types of mastitis and other explanatory factors. CM was primarily detected at milking by signs like warm, swollen udders or milk changes. However, also cases signaled by farm computer systems (increased conductivity + sudden milk drop) were included. Overall, the occurrence of a non-pathogen-specific CM in a given month was associated with an increased risk of dying – and recurrent cases within a month increased the risk greatly. Primiparous cows with first case were 3.9 times more likely to die than healthy cows, and with second or third case 8.2 or 17.1 times more likely, respectively. When separating into pathogen-specific cases (only older cows), only CM with gram-negative bacteria were associated with a significantly increased risk of dying.

A CM case had long term effect on the risk of culling: The culling risk was affected not only by CM in current month but also from CM occurring in previous month and earlier, and again; recurrent cases increased the risk of culling.

In the Excel file *'EffectsLitterature.xlsx'*, I have used the model estimates to create graphs illustrating the mortality and culling risk for the different pathogen specific CMs presented in the paper.

(Bar et al., 2008) presented a study of the effect of repeated episodes of CM on mortality and culling. As far as I can see, these data are the same as used in (Schukken et al., 2009) – analysed by repeated episode regardless of pathogen involved. Here, similar mortality and culling risks were showed.

Effects on reproduction

(Fuenzalida et al., 2015) evaluated the effect of occurrence and severity of subclinical or clinical mastitis events before or during the breeding risk period (-3 to +32 days around first AI, hormonal synchronization used) on the pregnancy rate of the first AI (= P/AI1). Mild as well as moderate-severe mastitis cases had a decreased chance of pregnancy at first AI (OR 0.71/0.54, p=0.004). Moderate/severe cases with either GN or GP bacteria were less likely to be pregnant than other cows including cows with moderate/severe mastitis but no bacterial growth (OR_{inf} = 0.41 vs $OR_{nogrowth}$ = 1.14, healthy = ref). Severity of case more important than etiology.

(Dalanezi et al., 2020) followed cows in five commercial herds. There was 273 control cows (no IMM infection), 191 with minor pathogens (CNS spp., corynebact) and 369 with major pathogens (Strept., E.coli, Kleibsiella, Staph. Aureus, Mycoplasma spp.). Analyses were also performed grouping cows by Gram bacteria class. Decreased chance of pregnancy at first AI were seen with any pathogen group compared to the control group. The risk of pregnancy loss was larger in the major pathogen group and the gram-negative group. Cows with IMM infection had more days open than control cows and the gram-negative group had more days open than the gram-positive group. See numbers in the table below.

Table 1. Effects of mastitis caused by different groups of pathogens (control, minor, or major) or by Gram class (positive or negative) on pregnancy per first AI, pregnancy loss, and days open in dairy cows[1]

Group[2]	Pregnancy/first AI, %	Pregnancy loss, %	Days open, d
Control	32.6 ± 0.02 (89/273)[a,A]	12.8 ± 0.02 (35/273)[a,A]	129.5 ± 1.9[a,A]
Minor	26.2 ± 0.03 (50/191)[ab]	16.7 ± 0.02 (32/191)[ab]	162.0 ± 4.1[b]
Major	20.1 ± 0.02 (74/369)[b]	22.2 ± 0.02 (82/369)[b]	175.1 ± 3.7[c]
Gram-positive	23.8 ± 0.02 (94/395)[AB]	17.2 ± 0.02 (68/395)[A]	172.7 ± 4.1[B]
Gram-negative	15.4 ± 0.03 (19/123)[B]	30.1 ± 0.03 (37/123)[B]	191.1 ± 7.45[C]

From (Dalanezi et al., 2020)

(Dalanezi et al., 2020) also performed a Cox proportional hazard regression on the days open in the different pathogen groups. The survival curves from these analyses are shown in the figures below. The hazard ratio of pregnancy was affected negatively in the major and the gram-negative groups.

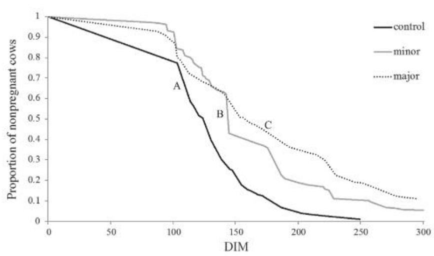

Figure 1. Survival curve of DIM to conception until 300 DIM for each group of cows. Control = cows with no mastitis events between calving and new pregnancy establishment. Minor = cows with mastitis caused by CNS or *Corynebacterium* spp. Major = cows with mastitis caused by *Staphylococcus aureus*, *Streptococcus agalactiae*, *Escherichia coli*, *Klebsiella* spp., *Mycoplasma* spp., *Streptococcus uberis*, or *Streptococcus dysgalactiae*. Letters (A–C) indicate that each individual survival curve was different ($P < 0.05$) from the other 2 survival curves.

Pathogen group

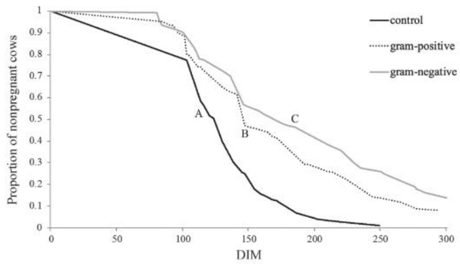

Figure 2. Survival curve of DIM to conception until 300 DIM for Gram bacteria class. Control = cows with no mastitis events between calving and new pregnancy establishment. Gram-positive = cows with mastitis caused by *Staphylococcus aureus*, CNS, *Streptococcus agalactiae*, *Streptococcus uberis*, or *Streptococcus dysgalactiae*. Gram-negative = cows with mastitis caused by *Escherichia coli* or *Klebsiella* spp. Letters (A–C) indicate that each individual survival curve was different ($P < 0.05$) from the other 2 survival curves.

Gram bacteria class

From (Dalanezi et al., 2020)

Similar results were found by (Lavon et al., 2019) in two epidemiological experiments evaluating the effects of pre-AI pathogen specific IMM infection and the pre-AI SCC levels on reproductive performance. Records of pre-AI IMM infections from 52.202 Holstein cows from 178 herds were used. The first experiment analysed the pathogen-specific effects plus the effects of SCC level. Results are shown in the table below. Furthermore, they performed refined analyses on the data from 6 farms. Here, they looked into the effects of IMM infection and SCC considering whether there was an IMM infection or raised SCC before or after return to cyclicity. Pre-AI IMI with *Streptococci* or *E.coli* lead to reduced Preg/1.AI: 42.3, 26.9, and 28.1% for control, *Streptococci* and *E.coli*, respectively.

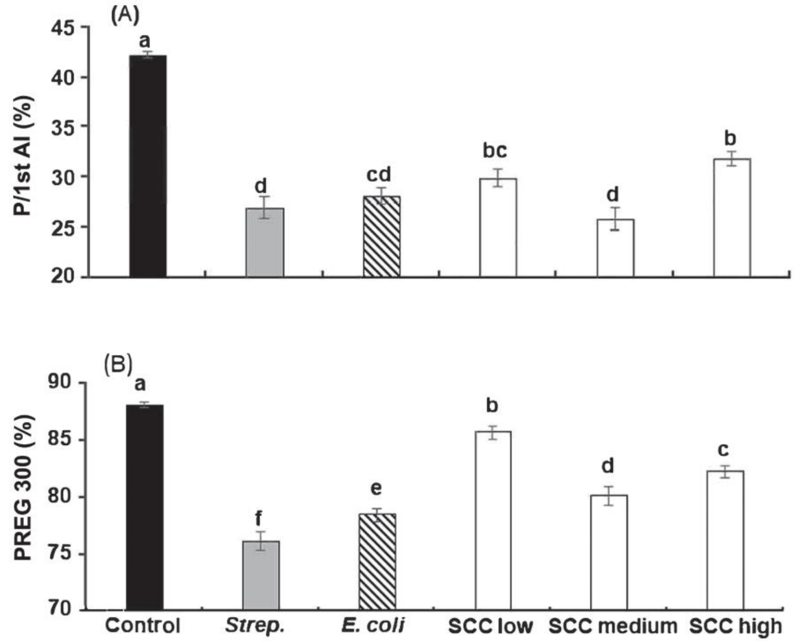

Figure 1. Effect of pathogen-specific mastitis due to *Streptococcus* (*Strep.*; n = 2,075) and *Escherichia coli* (n = 3,478) and effect of elevated SCC (3 groups: low, n = 3,509; medium, n = 1,961; high, n = 4,831) before first AI, versus uninfected controls (n = 36,348; with SCC levels <200,000), on (A) pregnancy per first AI (P/1stAI) and (B) pregnancy rate at 300 DIM (PREG 300) (Exp. 1). Data are presented as mean ± SEM. Different letters (a–f) denote significant differences at $P < 0.01$.

From (Lavon et al., 2019)

Summary

	Control	Mild	Moderate	Severe	Ref
Occurrence		48 - 63%	27 - 37%	7 - 15%	(Schmenger and Krömker, 2020) (Fuenzalida et al., 2015) (Verbeke et al., 2014) (Oliveira et al., 2013)
MY reduction/loss		Milk loss = 200 L/cow		1500 L/cow	(Blum et al., 2014)
		-3.7kg[a]	-5.1kg[a]	-11.2kg[a]	(Oliveira et al., 2013)
		-128 kg (59-297 kg P25/P75) with in 30 days around CM			(Adriaens et al., 2021)
Culling	-	13.5%	18.9%	30.9% OR = 2.9[b]	(Oliveira et al., 2013)
	Primiparous 0,69-1,98% Multiparous 4,04-5,84%	Primipara: Any CM -> OR = 6.6[c] Multipara: Gram+ CM -> OR = 1.7[c] Multipara: Gram- CM -> OR = 3.2[c] Primiparous, Any CM -> 4,7-13,1% Multiparous, G- CM -> 13,0-18,8% Multiparous, G+ CM -> 6,8-9,8% Multiparous, Other CM -> 7,6-11,0%			(Hertl et al., 2011) *CM in current month 10 m of lact*
Mortality	Primiparous 0,11-1,14% Multiparous 0,53-3,34%	Primipara: Any CM -> OR = 3.9[c] Multipara: 1. & 2. Gram- Case -> OR = 2.3-2.2[c] Primiparous, Any CM -> 0,43-4,50% Multiparous, G- CM -> 1,23-7,73% Multiparous, G+ CM -> 0,43-2,71% Multiparous, Other CM -> 0,72-4,50%			(Hertl et al., 2011) (se excel ark) *CM in current month 10 m of lact*
Preg 1.AI, %		Ctrl (non-IMI) = 32.6%	Min. patog. = 26.2% Gram+ = 23.8%	Maj. Patog = 20.8% Gram- = 15.4%	(Dalanezi et al., 2020)
		Ctrl (non-IMI) = 42.3%	*Streptococci* = 26.9% *E.coli* = 28.1%		(Lavon et al., 2019)
		OR = 0.71		OR = 0.54	(Fuenzalida et al., 2015)
Preg 300d		Ctrl, HR = 1.92	Min. patog., HR = 1.22 Gram+, HR = 1.36	Maj. Patog., HR = 0.81 Gram-, HR = 0.73	(Dalanezi et al., 2020)
		Ctrl = 83.3%	*Streptococci* = 76% *E.coli* = 76.3%		(Lavon et al., 2019)
	a = Difference in milk production (kg/cow per day) before (2-32 d) and after (14-52 d) enrolment case. Value from monthly DHI test. b = Compared to mild and moderate cases, odds of removal within 90 days c = Effect of CM in current month of lactation				

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