

Appendix for “The cost-effectiveness of an exclusive human milk diet for very low birth weight new-borns in Germany”

Part 1: Medical input parameters of the model.

Name	Mean	SD	Low	High	Probabilistic value	Source	Study period	Country	Comment
Cohort size	9519		8136	10903			2012-2016	GER	Weighted mean
<500gr	475		396	554		[1–5]	2012-2016	GER	yearly cases
500-749gr	1540		1227	1854		[1–5]	2012-2016	GER	yearly cases
750-999gr	2004		1741	2267		[1–5]	2012-2016	GER	yearly cases
1000-1249gr	2166		1868	2464		[1–5]	2012-2016	GER	yearly cases
1250-1499gr	3335		2905	3765		[1–5]	2012-2016	GER	yearly cases
- Probability NEC	5.70%	0.18%	4.94%	6.54%	Dirichlet(gamma(1;542.8))		1998-2001	USA	Weighted mean
<500gr	7.19%	0.47%	6.29%	8.18%	Dirichlet(gamma(1;34.15))	[6]	1998-2001	USA	adjusted by RR for P(NEC Sepsis)
500-749gr	8.67%	0.51%	7.69%	9.74%	Dirichlet(gamma(1;133.54))	[6]	1998-2001	USA	
750-999gr	6.86%	0.43%	6.03%	7.77%	Dirichlet(gamma(1;137.49))	[6]	1998-2001	USA	
1000-1249gr	5.48%	0.41%	4.71%	6.34%	Dirichlet(gamma(1;118.75))	[6]	1998-2001	USA	
1250-1499gr	3.56%	0.31%	2.98%	4.23%	Dirichlet(gamma(1;118.86))	[6]	1998-2001	USA	
-- Probability NEC surgical	29.03%	0.87%	21.81%	28.72%	beta(787.71;1925.29)		2012-2016	GER	Weighted mean
<500gr	52.71%	3.82%	44.93%	60.38%	beta(89.47;80.29)	[9]	2012-2016	GER	
500-749gr	43.79%	1.92%	39.98%	47.65%	beta(291.93;374.78)	[9]	2012-2016	GER	
750-999gr	30.35%	1.75%	26.93%	33.94%	beta(208.32;478.15)	[9]	2012-2016	GER	Redistributed across birth weights according to Jeschke 2016
1000-1249gr	21.01%	1.67%	17.80%	24.51%	beta(124.56;468.19)	[9]	2012-2016	GER	
1250-1499gr	12.15%	1.34%	9.64%	15.06%	beta(72.11;521.19)	[9]	2012-2016	GER	
--- Death background	Same as mortality of VLBW with No Complication								
--- Death due to NEC surgical	14.65%	1.07%	6.08%	15.68%	beta(159.85;931.15)		2000-2011	GER	Weighted mean
<500gr	19.53%	4.27%	6.71%	32.35%	beta(16.6;68.4)	[10]	2000-2011	GER	
500-749gr	18.39%	2.03%	13.01%	23.78%	beta(67.14;297.86)	[10]	2000-2011	GER	
750-999gr	14.94%	1.97%	10.78%	19.10%	beta(48.85;278.15)	[10]	2000-2011	GER	
1000-1249gr	7.34%	1.96%	3.50%	11.19%	beta(12.93;163.07)	[10]	2000-2011	GER	
1250-1499gr	6.03%	2.05%	1.64%	10.42%	beta(8.08;125.92)	[10]	2000-2011	GER	
---- Probability BPD NEC surgical	7.24%	0.27%	6.73%	7.78%	beta(689.33;8829.07)	[1–5]	2012-2016	GER	Average yearly cases between 2012 and 2016; Only cases with gestational age of >24 weeks
<500gr	52.08%	7.21%	37.19%	66.71%	beta(24.48;22.52)	[12]	2013-2014	KOR	Moderate and severe BPD

500-749gr	48.06%	2.84%	42.38%	53.78%	beta(148.52;160.48)	[12]	2013-2014	KOR	
750-999gr	40.84%	2.15%	36.60%	45.19%	beta(213.59;309.41)	[12]	2013-2014	KOR	
1000-1249gr	30.24%	1.96%	26.42%	34.27%	beta(165.7;382.3)	[12]	2013-2014	KOR	
1250-1499gr	18.25%	1.63%	15.13%	21.70%	beta(101.82;456.18)	[12]	2013-2014	KOR	
---- Probability SBS NEC surgical	19.39%	1.85%	15.87%	23.31%	beta(88.81;369.19)	[13]	2002-2005	USA	
<500gr	18.60%	2.15%	15.87%	23.31%	beta(60.81;266.19)	calc	2002-2005	USA	Cole 2008 found no significant difference in risk for SBS and birth weight when controlling for NEC.
500-749gr	18.60%	2.15%	15.87%	23.31%	beta(60.81;266.19)	calc	2002-2005	USA	
750-999gr	18.60%	2.15%	15.87%	23.31%	beta(60.81;266.19)	calc	2002-2005	USA	
1000-1249gr	21.37%	3.58%	15.87%	23.31%	beta(27.79;102.21)	calc	2002-2005	USA	
1250-1499gr	21.37%	3.58%	15.87%	23.31%	beta(27.79;102.21)	calc	2002-2005	USA	
---- Probability RoP NEC surgical	8.97%	0.25%	7.42%	10.83%	beta(1178.93;11967.07)		2008-2012	GER	Weighted mean
<500gr	26.74%	1.71%	20.61%	33.97%	beta(179.66;492.34)	[11]	2008-2012	GER	adjusted by RR for P(RoP NEC)
500-749gr	31.71%	1.00%	27.90%	35.84%	beta(680.42;1465.58)	[11]	2008-2012	GER	
750-999gr	9.55%	0.56%	7.68%	11.72%	beta(263.8;2499.2)	[11]	2008-2012	GER	
1000-1249gr	1.76%	0.24%	1.05%	2.78%	beta(53.96;3006.04)	[11]	2008-2012	GER	
1250-1499gr	0.27%	0.08%	0.07%	0.68%	beta(11.99;4489.01)	[11]	2008-2012	GER	
---- Probability CP NEC surgical	23.84%	3.25%	17.68%	30.92%	beta(40.76;130.24)	[7, 8]	>1974 & 2002-2004	USA	No weight stratification; Sonntag 2007 ignored due to low case numbers
---- Probability Neuro NEC surgical	0.39285714	0.09229619	0.21504283	0.59423179	beta(10.61;16.39)	[7]	2002-2004	USA	No weight stratification
---- Probability No complication NEC surgical	Complementary probability other complications/morbidities assuming independence, i.e. $1 - P(\text{BPD}) * P(\text{RoP}) * P(\text{SBS}) * P(\text{CP}) * P(\text{NI})$.								
-- Probability NEC medical	Complementary probability to the Probability of NEC surgical								
--- Death background	Same as mortality of VLBW with No Complication								
--- Death due to NEC medical	Same as mortality for NEC surgical								
---- Probability BPD NEC medical	Same as BPD probability for NEC surgical								
---- Probability RoP NEC medical	Same as ROP probability for NEC surgical								
---- Probability CP NEC medical	11.64%	2.33%	7.44%	17.09%	beta(21.88;166.12)	[7, 8]	>1974 & 2002-2004	USA	No weight stratification; Sonntag 2007 ignored due to low case numbers
---- Probability Neuro NEC medical	23.08%	6.75%	11.13%	39.33%	beta(8.77;29.23)	[7]	2002-2004	USA	No weight stratification
---- Probability No complication NEC medical	Complementary probability other complications/morbidities assuming independence, i.e. $1 - P(\text{BPD}) * P(\text{RoP}) * P(\text{CP}) * P(\text{NI})$.								

- Probability Sepsis	12.67%	0.12%	12.14%	13.21%	Dirichlet(gamma(1;1206.05))	calc	2012-2016	GER	Weighted mean
<i><500gr</i>	36.23%	1.18%	33.91%	38.59%	Dirichlet(gamma(1;172))	[9]	2012-2016	GER	adjusted by RR for P(NEC Sepsis)
<i>500-749gr</i>	19.74%	0.33%	19.11%	20.39%	Dirichlet(gamma(1;304.09))	[9]	2012-2016	GER	
<i>750-999gr</i>	20.06%	0.33%	19.42%	20.71%	Dirichlet(gamma(1;401.96))	[9]	2012-2016	GER	
<i>1000-1249gr</i>	5.91%	0.15%	5.61%	6.22%	Dirichlet(gamma(1;128.02))	[9]	2012-2016	GER	
<i>1250-1499gr</i>	6.00%	0.16%	5.70%	6.31%	Dirichlet(gamma(1;199.98))	[9]	2012-2016	GER	
Death background	General Mortality of VLBW without major morbidity								
Death Sepsis	17.46%	2.76%	12.33%	23.64%	beta(32.83;155.17)	[14]	2010	GER	
---- Probability BPD Sepsis	Same BPD probability as for NEC surgical								
---- Probability RoP Sepsis	2.80%	0.14%	2.32%	3.38%	beta(368.02;12777.98)		2008-2012	GER	Weighted mean
<i><500gr</i>	8.35%	1.07%	6.43%	10.60%	beta(56.09;615.91)	[11]	2008-2012	GER	adjusted by RR for P(RoP INEC)
<i>500-749gr</i>	9.90%	0.64%	8.71%	11.19%	beta(212.41;1933.59)	[11]	2008-2012	GER	
<i>750-999gr</i>	2.98%	0.32%	2.40%	3.66%	beta(82.35;2680.65)	[11]	2008-2012	GER	
<i>1000-1249gr</i>	0.55%	0.13%	0.33%	0.87%	beta(16.85;3043.15)	[11]	2008-2012	GER	
<i>1250-1499gr</i>	0.08%	0.04%	0.02%	0.21%	beta(3.74;4497.26)	[11]	2008-2012	GER	
---- Probability CP Sepsis	19.53%	2.44%	6.71%	32.35%	beta(51.56;212.44)	[7, 8]	>1974 & 2002-2004	USA	No weight stratification; Sonntag 2007 ignored due to low case numbers
---- Probability Neuro Sepsis	35.92%	3.07%	29.91%	42.27%	beta(87.64;156.36)	[7]	2002-2004	USA	No weight stratification
---- Probability No complication Sepsis	Complementary probability other complications/morbidities assuming independence, i.e. $1 - P(\text{BPD}) * P(\text{RoP}) * P(\text{CP}) * P(\text{NI})$.								
- Probabilitiy NEC + Sepsis	2.28%	0.12%	1.83%	2.82%	Dirichlet(gamma(1;217.16))				Weighted mean
<i><500gr</i>	7.12%	0.63%	5.93%	8.47%	Dirichlet(gamma(1;33.83))				adjusted by RR for P(NEC Sepsis)
<i>500-749gr</i>	4.68%	0.39%	3.95%	5.50%	Dirichlet(gamma(1;72.09))				
<i>750-999gr</i>	3.70%	0.32%	3.09%	4.40%	Dirichlet(gamma(1;74.22))				
<i>1000-1249gr</i>	0.85%	0.17%	0.56%	1.25%	Dirichlet(gamma(1;18.5))				
<i>1250-1499gr</i>	0.56%	0.13%	0.34%	0.86%	Dirichlet(gamma(1;18.52))				
NEC surgical + Sepsis	Same as proportion for NEC surgical without sepsis								
Death background	General Mortality of VLBW without major morbidity								
Death due to NEC	Mortality of NEC surgical combined with mortality of Sepsis								
BPD	Probability of BPD NEC combined with probability BPD Sepsis								
SBS	Same as probability for SBS for NEC without sepsis								
RoP	Probability of RoP NEC combined with probability RoP Sepsis								

CP	21.43%	10.97%	4.66%	50.80%	beta(2.79;10.21)	[7]	2002-2004	USA	
Neuro	50.00%	13.36%	23.04%	76.96%	beta(6.5;6.5)	[7]	2002-2004	USA	
No complication	Complementary probability other complications/morbidities assuming independence.								
NEC medical + Sepsis	Same as proportion for NEC medical without sepsis								
Death background	General Mortality of VLBW without major morbidity								
Death due to NEC	Mortality of NEC without NEC combined with mortality of Sepsis								
BPD	BPD of NEC combined with BPD of Sepsis								
RoP	RoP of NEC combined with RoP of Sepsis								
CP	20.00%	8.94%	5.73%	43.66%	beta(3.8;15.2)	[7]	2002-2004	USA	
Neuro	45.00%	11.12%	23.06%	68.47%	beta(8.55;10.45)	[7]	2002-2004	USA	
No complication	Complementary probability other complications/morbidities assuming independence, i.e. $1 - P(\text{BPD}) * P(\text{RoP}) * P(\text{CP}) * P(\text{NI})$.								
No NEC or sepsis	79.35%		81.08%	77.43%	Dirichlet(gamma(1;7553.39))				complementary probability other complications/morbidities; assuming independence
<i><500gr</i>	49.46%		53.86%	44.77%	Dirichlet(gamma(1;234.82))				
<i>500-749gr</i>	66.91%		69.25%	64.38%	Dirichlet(gamma(1;1030.48))				
<i>750-999gr</i>	69.38%		71.46%	67.13%	Dirichlet(gamma(1;1390.32))				
<i>1000-1249gr</i>	87.75%		89.12%	86.19%	Dirichlet(gamma(1;1900.33))				
<i>1250-1499gr</i>	89.88%		90.99%	88.60%	Dirichlet(gamma(1;2997.44))				
Death background	12.73%	0.41%	11.65%	13.91%	beta(838.92;5752.05)				
<i><500gr</i>	56.70%	4.91%	51.90%	61.60%	beta(57.08;43.59)	[11]	2008-2012	GER	180 day survival without major morbidity
<i>500-749gr</i>	37.80%	1.92%	35.70%	40.00%	beta(241.9;398.06)	[11]	2008-2012	GER	180 day survival without major morbidity
<i>750-999gr</i>	16.40%	1.09%	15.10%	17.90%	beta(190.45;970.86)	[11]	2008-2012	GER	180 day survival without major morbidity
<i>1000-1249gr</i>	6.20%	0.57%	5.40%	7.20%	beta(110.45;1671.05)	[11]	2008-2012	GER	180 day survival without major morbidity
<i>1250-1499gr</i>	3.10%	0.32%	2.60%	3.60%	beta(90.01;2813.51)	[11]	2008-2012	GER	180 day survival without major morbidity
BPD	Same BPD probability as for NEC surgical								
RoP	2.80%	0.14%	2.32%	3.38%	beta(368.02;12777.98)		2008-2012	GER	Weighted mean
<i><500gr</i>	8.35%	1.07%	6.43%	10.60%	beta(56.09;615.91)	[11]	2008-2012	GER	adjusted by RR for P(RoP INEC)
<i>500-749gr</i>	9.90%	0.64%	8.71%	11.19%	beta(212.41;1933.59)	[11]	2008-2012	GER	
<i>750-999gr</i>	2.98%	0.32%	2.40%	3.66%	beta(82.35;2680.65)	[11]	2008-2012	GER	
<i>1000-1249gr</i>	0.55%	0.13%	0.33%	0.87%	beta(16.85;3043.15)	[11]	2008-2012	GER	
<i>1250-1499gr</i>	0.08%	0.04%	0.02%	0.21%	beta(3.74;4497.26)	[11]	2008-2012	GER	
CP	14.96%	1.25%	12.57%	17.60%	beta(120.85;687.15)	[7]	2002-2004	USA	
Neuro	22.00%	1.46%	19.19%	25.02%	beta(177.78;630.22)	[7]	2002-2004	USA	

No complication	Complementary probability other complications/morbidities assuming independence, i.e. $1 - P(\text{BPD}) * P(\text{RoP}) * P(\text{CP}) * P(\text{NI})$.							
RR (NEC total)	0.400	0.141	0.528	0.357	lognormal(-0.992;0.14)	[15, 16]	2008/2010	USA
RR (NEC surgical)	0.452	0.468	1.131	0.152	lognormal(-0.79;0.47)	[15, 16]	2008/2010	USA
RR (Sepsis)	0.680	0.080	0.795	0.664	lognormal(-0.39;0.08)	[15, 16]	2008/2010	USA
RR (Sepsis + NEC)	0.272	0.011	0.420	0.274	lognormal(-1.30;0.01)			Combined
RR (mortality)	0.716	0.117	0.902	0.790	lognormal(-0.33;0.12)	[15, 16]	2008/2010	USA
RR (BPD)	0.849	0.048	0.933	0.846	lognormal(-0.16;0.05)	[16]		USA
RR (RoP)	0.551	0.184	0.789	0.515	lognormal(-0.60;0.18)	[16, 17]		USA
RR (CP)	0.90	-	1.00	1.00	1.00			
RR (Neurological)	0.90	-	1.00	1.00	1.00			I assumed in scenario analyses

Part 2a: Economic input parameter values.

Name	Mean	SD	Low	High	Probabilistic value	Source	Study period	Country	Comment
Costs EHDM	6,812 €		4,415 €	7,569 €	Not applicable				
<500gr	13,015 €		8,622 €	14,221 €	Not applicable				
500-749gr	11,895 €		7,863 €	13,221 €	Not applicable	Prolacta® Biosciences			
750-999gr	9,106 €		5,973 €	10,348 €	Not applicable				
1000-1249gr	5,208 €		3,359 €	5,760 €	Not applicable				
1250-1499gr	3,246 €		2,129 €	3,317 €	Not applicable				
Donor milk (litres)	3.71		2.93	3.28	Not applicable		[18]		
<500gr	7.08		5.67	7.18	Not applicable	[18]			
500-749gr	6.49		5.19	5.95	Not applicable	[18]			Only used in scenario analysis.
750-999gr	4.97		3.97	4.11	Not applicable	[18]			
1000-1249gr	2.81		2.25	1.65	Not applicable	[18]			
1250-1499gr	1.77		1.41	1.95	Not applicable	[18]			
Price donor milk (per litre)	65.00 €		60.00 €	90.00 €	Not applicable	Personal communication (Milk bank Leipzig)	2018	GER	
Costs BOV	223 €		223	223	Not applicable				
<500gr	612 €		612	612	Not applicable				
500-749gr	444 €		444	444	Not applicable				Only used in scenario analysis.
750-999gr	276 €		276	276	Not applicable				
1000-1249gr	108 €		108	108	Not applicable				
1250-1499gr	108 €		108	108	Not applicable				

LOS Factor

<500gr	1.49	0.04	1.43	1.58	gamma(1151;0.0013)	[9]	2002-2016	GER	
500-749gr	1.34	0.01	1.32	1.35	gamma(14960.29;0.0001)	[9]	2002-2016	GER	Available for categories <500gr, 500-999gr and 1000-1499gr
750-999gr									
1000-1249gr	0.75	0.01	0.74	0.77	gamma(7187.27;0.0001)	[9]	2002-2016	GER	
1250-1499gr									
LOS NEC	31.25	46.96	31.20	31.30	gamma(0.44;70.57)	[19]	2006-2016	GER	
LOS NEC mortality	20.81	47.00	20.22	21.40	gamma(0.2;106.18)	[19]	2006-2016	GER	
LOS Sepsis	8.39	6.89	8.38	8.39	gamma(1.48;5.66)	[19]	2006-2016	GER	
LOS Sepsis mortality	5.26	13.30	5.10	5.42	gamma(0.16;33.68)	[19]	2006-2016	GER	
LOS NEC + Sepsis	31.25	46.96	31.20	31.30	gamma(0.44;70.57)	[19]	2006-2016	GER	
LOS NEC + Sepsis mortality	13.03					[19]			Weighted average of NEC and sepsis.
LOS no complication									
<500gr									
500-749gr	74.15	61.29	74.15	74.15	gamma(1.46;50.67)	[19]	2006-2016	GER	
750-999gr									
1000-1249gr	20.49	21.56	20.49	20.49	gamma(0.90;22.68)	[19]	2006-2016	GER	
1250-1499gr									
LOS no complication mortality	11.67	32.48	11.66	11.68	gamma(0.13;90.37)		2006-2016	GER	
LOS RoP	12.64	24.01	12.61	12.67	gamma(0.28;45.60)	[19]	2006-2016	GER	
LOS SBS	29.13	34.84	29.00	29.26	gamma(0.70;41.67)	[19]	2006-2016	GER	
LOS BPD	25.57	34.19	25.53	25.60	gamma(0.56;45.73)	[19]	2006-2016	GER	
Basecase	3,376 €	18 €	3,342 €	3,461 €	gamma(36916.37;0.09)	[20]	2017	GER	
Direct Costs Cerebral Palsy	232,703 €	79,504 €	76,874 €	471,616 €	gamma(8.57;27163.25)	[21]	2017	GER	
Direct Costs Neurological	94,220 €	8,316 €	77,920 €	112,403 €	gamma(128.37;733.99)	[21]	2017	GER	
Life-time earnings	396,543 €	39,654 €	318,820.25 €	474,264.95 €	gamma(100;3965.43)	[22]	2017	GER	
Reduced productivity CP	48.1%		63.9%	42.6%	beta(12.98;13.48)	[23]	-	GER	
Reduced productivity Neurological	60.2%		77.8%	27.9%	beta(9.95;6.18)	[23]	-	GER	
Friction period	92	14.29	64	98	gamma(41.47;2.22)	[24]	2015	GER	

Part 2b: Diagnosis related groups (DRGs) used for cost calculations

Health state	Birth weight	DRG	Cost weight	Mean LOS	1 st day	1 st day	Deduction	Surcharge
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					deduction	surcharge		
No Complication	<500gr	P61B	36.02	104.40	34	122	1.02	0.34
	500-749gr	P61D	30.07	88.90	29	107	1.00	0.34
	750-999gr	P62B, P62C	23.28	71.42	22	89	0.97	0.32
	1000-1249gr	P63Z	9.30	42.00	13	60	0.66	0.21
	1250-1499gr	P64Z	6.91	32.70	10	51	0.62	0.21
NEC or Sepsis	<500gr	P61A	47.51	102.70	33	121	1.35	0.45
	500-749gr	P61C	46.40	114.50	37	132	1.18	0.43
	750-999gr	P62A	30.58	80.70	26	99	1.10	0.37
	1000-1249gr	P03C	12.03	47.40	15	65	0.00	0.00
	1250-1499gr	P03C	12.03	47.40	15	65	0.00	0.00
NEC + Sepsis	<500gr	P61A	47.51	102.70	33	121	1.35	0.45
	500-749gr	P61C	46.40	114.50	37	132	1.18	0.43
	750-999gr	P62A	30.58	80.70	26	99	1.10	0.37
	1000-1249gr	P03A, P03B	16.49	54.91	16	72	0.90	0.29
	1250-1499gr	P03A, P03B	16.49	54.91	16	72	0.90	0.29
Mortality	<500gr	P61E	6.19	11.50	0	24	0.00	0.53
	500-749gr	P61E	6.19	11.50	0	24	0.00	0.53
	750-999gr	P62D	9.72	17.00	5	1000	1.58	0.00
	1000-1249gr	P60A	0.72	1.40	0	1000	0.00	0.00
	1250-1499gr	P60A	0.72	1.40	0	1000	0.00	0.00
SBS	overall	G04Z, G50Z, G67A, G67B	0.89	5.84	1.45	12.21	0.33	0.08
RoP	overall	C63Z, C14Z	0.58	3.75	1	8.25	0.27	0.08
BPD	overall	E69D	0.48	3.00	1	6.00	0.24	0.11

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