

Supplementary file 3

Supplementary Table 5. *HRQoL in IMD survivors by instrument*

Author, y Country, SIGN	Design Population	N Follow-up (FU)	Outcome measure	IMD	HRQoL scores Control	p-value			
IT-QOL (0-3 years) - Infant and Toddler Quality of Life Questionnaire				Mean (range) [SE]					
Buysse 2008[24] NL 2+	FU of prospective cohort study of consecutive MSS PICU admissions (N=45) between 2001-2005 Control: Dutch population age-matched reference group Median age at infection: 3.7y Median age at FU: 4.8y OA: questionnaires filled out by parents	n=19 MSS aged 0-3y median 14 months after MSS in PICU	Physical abilities	[SE] 91 (10–100) [5.3]	[SE] 97 [0.5]	<0.05			
			General behaviour perceptions	67 (16–89) [3.9]	73 [0.7]	NS			
			General health perceptions	57 (20–83) [3.7]	79 [0.7]	<0.001			
			Parental impact: emotional	85 (32–100) [3.8]	92 [0.5]	<0.05			
			Parental impact: time	84 (24–100) [4.8]	93 [0.5]	NS			
			Family activity	75 (25–100) [5.7]	86 [0.7]	NS			
			Change in health	97 (50–100) [2.6]	56 [1.0]	<0.001			
			PedsQL – Paediatric Quality of Life Inventory				Mean [SD]		
			Sumpter 2011[40] UK 2+	Postal survey FU of parents of childhood meningitis survivors (34% with <i>N. meningitidis</i>) admitted from 1991-2007 (38% to PICU). N=100 parents median age at infection: 8m mean age at FU: 10y	n=97 parents (of IMD aged 5-16y) (n=64 uncompl, n=33 compl.) Control: UK normative data (core), US normative data (Fatigue)	Core PedsQL Total Score	76.60 (18.55)	84.6 (11.2)	<0.001
Physical Health Summary	82.62 (21.05)	89.1 (12.3)				0.004			
Psychosocial Health Summary	72.46 (20.15)	82.2 (12.7)				<0.001			
Emotional	66.15 (24.42)	78.3 (15.5)				<0.001			
Social	81.70 (22.60)	86.8 (15.4)				0.033			
School	69.52 (24.39)	81.5 (16.1)				<0.001			
Fatigue PedsQL Total Score	74.56 (22.72)	89.6 (11.4)				<0.001			
General	76.70 (24.14)	89.3 (13.3)				<0.001			
Sleep/rest	78.88 (21.50)	88.9 (14.7)				<0.001			
Cognitive fatigue	67.77 (29.94)	90.7 (15.2)				<0.001			

	OA: questionnaires filled out by parents	mean 8y after IMD				
			No difference between complicated and uncomplicated cases on total scores.			
TACQOL – “TNO-AZL Child Quality Of Life” (8-11 years)				Mean (range) [SE/SD]		
Grootenhu is 2007[52] NL 2+	Prospective study of HRQoL risk in children with different chronic conditions Control: n=913 Dutch population age-matched reference group Mean/median age at infection/FU: NA OA: questionnaire filled out by cases	n=38 survivors of severe IMD 1-7y after treatment	% of children at risk of HRQoL problems: Motor functioning Autonomy	45% 40%	NR NR	<0.001 <0.05
CHQ-PF50 (4-17 years) - Child Health Questionnaire - Parent form				Mean (range) [SE/SD]		
Buyse 2008[24] NL 2+	FU of a prospective cohort study of consecutive MSS PICU survivors (N=45) admitted between 2001-2005 Control: Dutch population age-matched reference group Median age at infection: 3.7y Median age at FU: 4.8y OA: questionnaires filled out by parents	n=26 MSS aged 1-17y median 14 months after MSS in PICU	Physical functioning Role functioning: Emotional/behaviour Self-esteem General health perceptions Physical total Psychosocial total	[SE] 98 (83–100) [0.9] 97 (33–100) [2.6] 80 (58–100) [2.3] 62 (9–100) [3.6] 52 (39–63) [1.2] 53 (21–65) [1.7]	[SE] 99 [0.2] 98 [0.4] 79 [0.6] 83 [0.7] 56 [0.3] 53 [0.3]	<0.05 NS NS <0.001 <0.001 NS
		n=21 with chronic complaints	Pain (n=10), behavioural/emotional problems (n=6), fatigue (n=2), motor skills problems (n=1), pes equinus (n=1), Raynaud phenomenon at amputated finger (n=1), sleep disturbances (n=1), and stuttering (n=1).			
Koomen 2005[39] NL	Nested case-control study of N=182 survivors of non-Hib bacterial meningitis (78% due to	n=182 meningitis aged 5-14y	Physical functioning Role functioning:	[SD] 97.9 [14.4]	[SD] 99.1 [4.3]	NS

2++	<i>N. meningitidis</i>) without severe sequelae Control: Dutch population 5-13y No information on PICU admission Mean age at infection: 2.4y Mean age at FU: 9.7y OA: Questionnaire for parents	n= 353 controls mean 7.4y after meningitis	Emotional/behaviour Self-esteem General health perceptions Physical total Psychosocial total	96.7 [18.5] 75.6 [22.1] 70.0 [29.8] 54.2 [13.6] 52.1 [12.5]	97.9 [7.2] 79.2 [11.0] 82.9 [13.4] 56.4 [5.7] 53.2 [6.4]	NS 0.001 <0.001 <0.001 0.05
		n=89 meningitis with problems n=93 meningitis without problems	Role functioning: Emotional/behaviour Bodily pain General behaviour Mental health Self esteem Parental impact: emotional Psychosocial total	[SD] 90.7 [18.3] 76.9 [24.1] 62.5 [19.0] 71.0 [15.6] 69.8 [12.7] 70.0 [21.0] 45.9 [8.6]	[SD] 96.7 [10.0] 85.0 [20.5] 77.3 [13.7] 80.4 [11.5] 75.6 [13.5] 84.4 [15.1] 52.6 [5.9]	0.004 0.02 <0.001 <0.001 0.001 <0.001 <0.001
Buyse 2007[51] NL 2+	FU of a retrospective cohort of consecutive MSS PICU survivors (N=145) admitted between 1988-2001 Control: Dutch population reference Median age at infection: 3.5y Median age at FU: 14.6y OA: questionnaire filled out by patients and parents	n=92 MSS aged 4-17y (parent-report) median 10y after MSS	Physical functioning Role functioning: Emotional/behaviour Self-esteem General behaviour General health perceptions Family activities Physical total Psychosocial total	92 (0–100) 92 (0-100) 76 (0-100) 78 (26-100) 64 (9-98) 89 (33-100) 51 (–5-62) 52 (19-65)	99 98 79 79 83 92 56 53	<0.001 <0.05 <0.05 NS <0.001 NS <0.001 NS
CHQ-CF87 (12-17 years) - Child Health Questionnaire - Child form				Mean (range) [SE/SD]		
Buyse 2007[51] NL 2+	FU of a retrospective cohort of consecutive MSS PICU survivors (N=145) admitted between 1988-2001. Control: Dutch population reference	n=38 MSS aged 12-17y (self-report) median 10y after MSS	Physical functioning Role functioning: Emotional Self-esteem General behaviour General health perceptions Family activities	95 (44–100) 93 (56–100) 77 (48–100) 87 (61–99) 66 (38–97) 88 (50–100)	96 89 75 81 74 80	NS NS NS <0.001 <0.01 <0.01

	Median age at infection: 3.5y Median age at FU: 14.6y OA: questionnaire filled out by patients and parents					
SF-36 / RAND-36 in adults (≥18y) – 36-Item Short Form Health Survey				Mean (range) [SD]		
Van de Beek 2002[47] NL 2++	FU of prospective observational cohort study from Dutch adults (16-65y) with bacterial meningitis discharged with good physical and mental recovery. n=25 <i>N. meningitidis</i> meningitis n= 25 age-matched controls Mean age at infection: NA Mean age at FU: 32.9y OA: interview of patients based on tests and questionnaires	n=25 meningitis aged 16-65y n=25 controls median 391d (14m) after meningitis	Physical functioning	83.6 [16.7]	81.9	NS
			Social functioning	83.9 [17.7]	86.9	NS
			Role limitation (physical)	61.9 [43.7]	79.4	NS
			Role limitation (emotional)	69.8 [42.0]	81.4	NS
			Mental health	73.7 [12.9]	76.8	NS
			Vitality	63.1 [15.7]	76.4	<0.001
			Pain	76.7 [20.3]	79.4	NS
			Experienced general health	68.3 [13.1]	72.7	NS
			p values versus Dutch reference data			
Borg 2009[37] UK 2+	FU of a prospective matched cohort study of adolescent IMD survivors (N=101 pairs, 40% meningitis plus septicaemia, 27% septicaemia, 54% ICU) Incident cases were collected through regional consultants in communicable disease control and clinicians Controls: matched controls of the same gender and the nearest date	n=101 matched adolescent pairs median 583d (21m) after IMD	Physical summary	48.4 [29.8]	51.8 [26.0]	0.4
			Mental summary	46.6 [30.2]	53.5 [23.9]	0.07

	of birth from the patient list of the case subject's general practitioner Age at infection: 15-19y Mean age at FU: 19.3y OA: interviews with patients based on questionnaires and neuropsychological tests					
Buyse 2007[51] NL 2+	FU of a retrospective cohort of consecutive MSS PICU survivors (N=145) admitted between 1988-2001. Control: Dutch population reference Median age at infection: 3.5y Median age at FU: 14.6y OA: questionnaire filled out by patients and parents	n= 48 MSS $\geq$18y (self-report) median 10y after MSS	Physical functioning Role limitation (physical) Social Functioning Bodily Pain General Mental Health Role limitation (emotional) Vitality General Health perceptions Physical Summary Psychosocial Summary	90 (20–100) 81 (0–100) 85 (25–100) 78 (10–100) 79 (48–100) 94 (33–100) 63 (30–90) 72 (35–100) 49 (9–61) 52 (36–61)	94 88 88 83 78 84 71 78 55 49	NS NS NS NS NS <0.01 <0.01 NS <0.001 <0.01
Schmand 2010[48] NL 2+ (9-year follow-up of van de Beek 2002[47])	FU of prospective observational cohort study from Dutch adults (16-65y) with bacterial meningitis discharged with good physical and mental recovery. No information on PICU admission n=11 <i>N. meningitidis</i> meningitis n= 12 age-matched controls	n=11 meningitis aged 16-65y n=12 control mean 9.3y after meningitis	Physical functioning Role limitation (physical) Role limitation (emotional) Vitality Mental health Social functioning Pain Experienced general health	89.5 [20.3] 90.9 [30.2] 84.8 [34.5] 68.2 [22.1] 74.5 [17.1] 87.5 [17.7] 87.0 [24.1] 77.3 [17.5]	85.8 [16.1] 85.4 [31.0] 94.4 [19.2] 66.3 [14.0] 79.3 [8.0] 85.4 [15.8] 76.7 [20.8] 74.2 [9.3]	NS NS NS NS NS NS NS

	Age at infection: 16-65y Mean age at FU: 41.6y OA: Interview of cases					
HUI-2 – Health Utilities Index 2				Single/multi-attribute utility scores		
Buysse 2008[53] NL 2+	FU of a retrospective cohort of consecutive MSS PICU survivors admitted between 1988-2001. (83% also had meningitis) (N=120/145 visited clinic for FU) Control: Dutch population aged 5-13y reference (n=1435) Median age at infection: 3.1y Median age at FU: 14.5y OA: medical interview of parents and patients based on questionnaires	n=120 MSS aged 4-31y n=1435 controls median 9.8y after IMD	Sensation	0.90 (0.18)	0.93 (0.12)	<0.01
			Mobility	0.97 (0.15)	1.00 (0.03)	<0.01
			Emotion	0.95 (0.10)	0.97 (0.08)	<0.05
			Cognitive	0.93 (0.16)	0.98 (0.06)	<0.01
			Self-care	0.97 (0.16)	0.99 (0.06)	NS
			Pain	0.96 (0.09)	0.99 (0.05)	<0.01
			Multi-attribute utility	0.88 (0.16)	0.94 (0.09)	<0.01
			VAS overall health	85.4 (15.3)	92.7 (9.2)	<0.01
Koomen 2005[39] NL 2++	Nested case-control study of N=182 survivors of non-Hib bacterial meningitis (78% due to <i>N. meningitidis</i>) without severe sequelae Control: Dutch population 5-13y No information on PICU admission	n=182 meningitis n= 353 controls mean 7.4y after meningitis	Sensation	0.92 (0.25)	0.96 (0.10)	0.001
			Mobility	1 (0.04)	1 (0.02)	NS
			Emotion	0.95 (0.20)	0.91 (0.11)	<0.001
			Cognitive	0.96 (0.13)	0.97 (0.06)	0.05
			Self-care	1 (0.04)	0.99 (0.11)	NS
			Pain	0.99 (0.04)	0.99 (0.03)	0.02
			Multi-attribute utility	0.93 (0.18)	0.92 (0.08)	NS
	Mean age at infection: 2.4y Mean age at FU: 9.7y OA: Questionnaire for parents	n=89 meningitis with problems n=93 meningitis without problems	Sensation	0.88 (0.16)	0.92 (0.14)	NS
			Mobility	0.99 (0.05)	1.00 (0)	NS
			Emotion	0.87 (0.16)	0.95 (0.10)	<0.001
			Cognitive	0.90 (0.10)	0.97 (0.06)	<0.001
			Self-care	0.99 (0.05)	1.00 (0.02)	NS
			Pain	0.98 (0.03)	0.99 (0.02)	0.01

			Multi-attribute utility	0.84 (0.14)	0.93 (0.09)	<0.001
HUI-3 – Health Utilities Index 3				Single/multi-attribute utility scores		
Buysse 2008[53] NL 2+	FU of a retrospective cohort of consecutive MSS PICU survivors admitted between 1988-2001. (83% also had meningitis) (N=120/145 visited clinic for FU) Control: Dutch population aged 5-13y reference (n=1435) Median age at infection: 3.1y Median age at FU: 14.5y OA: medical interview of parents and patients based on questionnaires	n=120 MSS aged 4-31y n=1435 controls median 9.8y after IMD	Vision	0.98 (0.10)	0.99 (0.04)	0.01
			Hearing	1.00 (0.0)	1.00 (0.04)	NS
			Speech	0.93 (0.16)	0.97 (0.08)	0.01
			Ambulation	0.97 (0.15)	0.99 (0.04)	<0.01
			Dexterity	0.98 (0.13)	1.00 (0.02)	<0.01
			Emotion	0.96 (0.07)	0.98 (0.07)	<0.01
			Cognition	0.90 (0.21)	0.97 (0.09)	<0.01
			Pain	0.94 (0.13)	0.98 (0.08)	<0.01
			Multi-attribute utility	0.82 (0.25)	0.93 (0.12)	<0.01
EQ-5D – EuroQOL				n/N (%)		
Al- Janabi 2015[54] UK 2++	Postal survey FU of family members (13y or older) of meningitis survivors (76% parents) No information on PICU admission provided n= 1053 family of survivors with long-term effects n= 517 family of survivors without long-term effects (controls) Mean age at infection: 11y Mean age at FU: 23y	n=1053 family of survivors with sequelae n=517 controls mean 12y after meningitis	Family-reported:	With sequelae	Without	
			Health status (utility value)	0.78	0.97	<0.001
			Mobility problems (%)	24%	1%	<0.001
			Self-care problems (%)	19%	1%	<0.001
			Usual activities problems (%)	37%	3%	<0.001
			Pain/discomfort problems (%)	38%	4%	<0.001
			Anxiety/depression (%)	46%	9%	<0.001
			The health status of survivors with meningitis sequelae was significantly worse than those without (mean difference 0.19 (95% CI: 0.17–0.22)). Most common sequelae were behavioural or emotional problems (28%), mild/moderate learning disabilities (16%), scarring or tissue damage (14%), balance problems (13%), and speech or language problems (11%).			

	OA: Questionnaire for parents/family members		
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CI: confidence interval; compl: complicated; d: day; FU: follow-up; Hib: *Haemophilus influenzae* type b; HRQoL: health-related quality of life; I/MD, invasive/ meningococcal disease; m: month; MSS: meningococcal septic shock; n: number in subcategory; N: total number; NR: not reported; NS: not significant; P/ICU: paediatric/ intensive care unit; SD: standard deviation; SE: standard error; SIGN: Scottish Intercollegiate Guidelines Network; VAS: visual analogue scale; uncompl: uncomplicated; y, year; NA: not available; OA: outcomes assessment;

Supplementary Table 6. HRQoL of caregivers by instrument

Author, Year SIGN	Design Population	N Follow-up	Outcome measure	HRQoL scores Comparator		p-value
GHQ-28/30 - General Health Questionnaire 28 or 30			n/N (%) or Mean [SD]			
Shears 2005[26] UK 2++	3-month FU of prospective cohort of consecutive 3-16y IMD survivors (N=78) (77% PICU, 42% meningitis plus septicaemia) Median age at infection: 6.8y Mean/median age at FU: NA At FU: N=60 children (46 PICU and 14 general admissions), N=68 mothers, N=53 fathers, N=57 teachers OA: interviews with parents and questionnaires filled out by parents and teachers	n=60 mothers, n=45 fathers (of MD with or without MSS survivors) mean 4.1m after IMD	Mental distress scores ≥5 for psychiatric disorder: Mothers Fathers	Admission 40/68 (59%) 22/53 (42%)	FU 26/60 (43%) 11/45 (24%)	
			No significant differences between PICU and general ward groups.			
Judge 2002[49] UK 2-	FU of 2-16y old IMD survivors admitted to a PICU (N=29) Mean age at infection: 5.7y Mean/median age at FU: NA OA: Interviews with cases and parents	n=27 mothers (of IMD survivors) mean 8.9m after IMD	High maternal psychiatric risk (scores≥4)	11/26 (42%)		
Ehrlich 2005[55] NL	Retrospective FU of parents of child survivors of severe MD treated in PICU (1993-2001).	n = 102 mothers and n=90 fathers (of IMD in PICU	GHQ-30 in parents At 3m At 6m	Mothers 8.71 [7.19] 10.71 [8.12]	Fathers 7.17 [8.33] 6.69 [4.82]	

2-	FU of 5 groups at 5 time points from 3 months to 7 years after IMD Controls: normative data for % over cut-off for psychological distress Age at infection: 1-18y Mean/median age at FU: NA OA: questionnaire filled out by parents	survivors) 3m to 7y after discharge from PICU	At 12m	6.96 [8.52]	5.90 [5.74]	
			At 24m	7.17 [8.91]	6.25 [6.36]	
			At 36 or more m	4.93 [6.39]	5.43 [7.90]	
Both mothers and fathers experience high mean levels of psychological distress after discharge (no significant differences in group means over time). High percentages of parents experience psychological distress after discharge compared with the normal population						
SF-36 - 36-Item Short Form Health Survey				Mean (range) [SE]		
Buyse 2008[24] NL 2+	FU of prospective cohort study of consecutive MSS PICU admissions (N=45) between 2001-5 Control: Dutch population age-matched reference group Median age at infection: 3.7y Median age at FU: 4.8y OA: questionnaires filled out by parents	n=45 parents median 14 months after MSS in PICU	SF-36 in parents:			
			Physical functioning	90 (45–100) [2.2]	92 [0.9]	NS
			Role limitation (physical)	87 (0–100) [4.3]	83 [2.5]	<0.05
			Social functioning	83 (13–100) [3.5]	86 [1.6]	NS
			Bodily pain	85 (22–100) [2.9]	79 [1.4]	<0.05
			General mental health	74 (8–100) [3.1]	76 [1.2]	NS
			Role limitation (emotional)	78 (0–100) [5.9]	81 [2.6]	NS
			Vitality	67 (20–100) [3.2]	67 [1.3]	NS
			General health perceptions	73 (10–100) [3.4]	78 [1.3]	NS
			Physical summary	54 (32–66) [1.1]	54 [0.5]	NS
			Psychosocial summary	49 (14–63) [1.9]	48 [0.8]	NS
		n=8 mothers	Reported anxiety or depression requiring professional help			
Buyse 2007[51] NL 2+	FU of a retrospective cohort of consecutive MSS PICU survivors (N=145) admitted between 1988-2001. Control: Dutch population reference	n=134 parents of MSS survivors	SF-36 in parents:			
			Physical functioning	87 (0–100)	89	<0.01
			Role limitation (physical)	83 (0–100)	82	<0.01
			Social functioning	89 (13–100)	84	<0.001
			Bodily pain	80 (0–100)	75	<0.001
			General mental health	79 (28–100)	76	<0.001

	Median age at infection: 3.5y Median age at FU: 14.6y OA: questionnaire filled out by patients and parents		Role limitation (emotional) Vitality General health perceptions Physical summary Psychosocial summary	87 (0–100) 68 (15–100) 75 (0–100) 50 (4–68) 53 (12–73)	86 68 74 52 49	<0.01 NS <0.05 NS <0.001
IES in parents - Impact of Event Scale				n/N (%)		
Shears 2005[26] UK 2++	3-month FU of prospective cohort of consecutive 3-16y IMD survivors (N=78) (77% PICU, 42% meningitis plus septicaemia) Median age at infection: 6.8y Mean/median age at FU: NA At FU: N=60 children (46 PICU and 14 general admissions), N=68 mothers, N=53 fathers, N=57 teachers OA: interviews with parents and questionnaires filled out by parents and teachers	n=58 mothers, n=43 fathers (of MD with/without MSS survivors) mean 4.1m after IMD	Risk for PTSD: Mothers Fathers	20/58 (38%) 8/43 (19%)		
			Mothers in PICU group had significantly higher total scores than those of ward-admitted children (median [quartiles] of 33 [22, 43] compared with 12.5 [8.5, 33]; p=0.009).			
Judge 2002[49] UK 2-	FU of 2-16y old IMD survivors admitted to a PICU (N=29) Mean age at infection: 5.7y Mean/median age at FU: NA OA: Interviews with cases and parents	n=27 mothers (of IMD survivors) mean 8.9m after IMD	High maternal psychiatric risk: Seeking help for above ()	13/27 (48%) 8/27 (29%)		
EQ-5D-5L in family members - EuroQOL5 Dimensions 5L				Utility scale 0-1		
Al-	Postal survey FU of family	n=1053 family of	Utility family members	0.87	0.91	<0.001

Janabi 2015[54] UK 2++	members (13y or older) of meningitis survivors (76% parents)	survivors with sequelae n=517 controls	Mobility problems	14%	13%	NS
	No information on PICU admission provided	mean 12y after meningitis	Self-care problems	3%	2%	NS
			Usual activities problems	14%	10%	<0.05
			Pain/discomfort problems	33%	27%	<0.05
			Anxiety/depression	40%	23%	<0.001
	n= 1053 family of survivors with long-term effects		Sequelae effect on utility:	Mean (95%CI)		
	n= 517 family of survivors without long-term effects (controls)	n = 184 closest and n = 178 second closest family members	closest family members	0.18 (0.1- 0.27)		<0.001
			2 nd closest family members	0.11 (0.04-0.18)		<0.01
			parents	0.14		<0.001
			siblings	0.36		<0.05
			partners	0.24		<0.001
			grand parents	0.14		NS
			children of survivors	-0.05		NS
	Mean age at infection: 11y Mmean age at FU: 23y					
	OA: Questionnaire for parents/family members		Sequelae in survivors was associated with lower health status for family members (mean difference 0.041 (95% CI: 0.024 to 0.058); can be interpreted as annual utility decrement. Exposed family members had 2.3 (95% CI: 1.8 to 2.9) times higher odds of reporting anxiety or depression, 1.4 (95% CI: 1.0 to 2.0) times higher odds of problems with usual activities, and 1.3 (95% CI: 1.0 to 1.6) times higher odds of pain or discomfort versus unexposed members.			

CI: confidence interval; FU: follow-up; HRQoL: health-related quality of life; I/MD: invasive/ meningococcal disease; m: month; MSS: meningococcal septic shock; N: total number; NS: not significant; PICU: paediatric intensive care unit; PTSD: post-traumatic stress disorder; SD: standard deviation; SE: standard error; SIGN: Scottish Intercollegiate Guidelines Network; y: year; NA: not available; OA: outcomes assessment;