

## Appendix

### Appendix 1. ICD-10-CM codes for serious infections.

Opportunistic infections (OI)	'B25.x', 'B02.xx', 'B37.xx', 'B58.xx', 'B59', 'B45.x', 'A32.xx', 'A43.x', 'B44.xx', 'B38.xx', 'B39.x', 'B40.xx', 'B27.1x', 'A15.7', 'A15.6', 'A15.0', 'A15.5', 'A15.6', 'A15.4', 'A15.8', 'A17.0', 'A17.1', 'A17.9', 'A18.4', 'A18.2', 'A18.6', 'A18.7', 'A19.2', 'A19.8', 'A19.9', 'B27.0x', 'A31.0', 'A31.1', 'A31.2', 'A31.8', 'A31.9', 'A17.81', 'A17.82', 'A17.89', 'A18.31', 'A18.32', 'A18.39', 'A18.01', 'A18.02', 'A18.03', 'A18.11', 'A18.12', 'A18.13', 'A18.15', 'A18.14', 'A18.17', 'A18.16', 'A18.18', 'A18.10', 'A18.50', 'A18.51', 'A18.52', 'A18.53', 'A18.54', 'A18.59', 'A18.81', 'A18.85', 'A18.89', 'A18.84'
Skin and soft tissue infections (SSTI)	'A46', 'B35.x', 'B36.x', 'L02', 'L03', 'B08.xxx', 'B09.xxx', 'A60.xx', 'L00', 'L01', 'L04', 'L05', 'L08', 'B00.1', 'B00.2', 'B00.7', 'B00.9', 'B01.8x', 'B01.9', 'B02.3x', 'B02.4', 'B02.5', 'B02.6', 'B02.7', 'B02.8', 'B02.9', 'B05.3', 'B05.4', 'B05.5', 'B05.6', 'B05.7', 'B05.8x', 'B05.9', 'B06.8x', 'B06.9', 'A36.3', 'K113', 'K114', 'K115', 'K116', 'K117', 'K118', 'K119', 'K120', 'K121', 'K122', 'L303', 'M726'
Urinary tract infection (UTI)	'N10', 'N72', 'A54.xx', 'A55', 'A56.xx', 'N45', 'N410', 'N412', 'N413', 'N300', 'N700', 'N710', 'N390', 'N733', 'N771'
Pneumonia	'J12', 'J13', 'J14', 'J15', 'J16', 'J17', 'J18', 'J10', 'J11', 'A48.1', 'B01.2', 'B05.2', 'B25.0'
Sepsis	'A40.x', 'A41.xx', 'A32.7', 'R572', 'R650', 'R651'

Appendix 2. Characteristics of patients with Sjögren's syndrome with a diagnosis of primary serious infections.

	OI (n=1,917)	SSTI (n=11,115)	UTI (n=3,704)	Pneumonia (n=29,276)	Sepsis (n=23,228)	Composite Infection (n=69,239)
<b>Age, mean (SE); Median</b>	62.4 (0.80); 64.3	62.4 (0.33); 61.8	61.8 (0.74); 62.9	67.4 (0.20); 68.5	66.4 (0.23); 67.2	65.8 (0.14); 66.8
<b>Age category</b>						
<50 years	371 (19.4%)	2,066 (18.6%)	1,034 (27.9%)	3,464 (11.9%)	2,984 (12.9%)	9,921 (14.4%)
50 - <65 years	571 (29.8%)	4,086 (36.8%)	875 (23.6%)	7,853 (27.0%)	6,590 (28.4%)	19,975 (28.9%)
65 - 79 years	782 (40.8%)	3,410 (30.7%)	1,092 (29.5%)	11,337 (38.9%)	8,813 (38.0%)	25,435 (36.8%)
≥80 years	191 (10.0%)	1,542 (13.9%)	702 (19.0%)	6,475 (22.2%)	4,819 (20.8%)	13,730 (19.9%)
<b>Sex</b>						
Male	198 (10.4%)	881 (7.9%)	113 (3.0%)	2,674 (9.2%)	2,238 (9.6%)	6,104 (8.8%)
Female	1,714 (89.6%)	10,218 (92.1%)	3,586 (97.0%)	26,458 (90.8%)	20,973 (90.4%)	62,950 (91.2%)
<b>Race</b>						
White	1,102 (57.5%)	8,102 (73.0%)	2,505 (67.6%)	20,230 (69.4%)	17,067 (73.5%)	49,006 (71.0%)
Black	162 (8.5%)	528 (4.8%)	156 (4.2%)	1,474 (5.1%)	1,508 (6.5%)	3,828 (5.5%)
Hispanic	182 (9.5%)	545 (4.9%)	374 (10.1%)	1,715 (5.9%)	1,543 (6.6%)	4,358 (6.3%)
Other/missing	471 (24.6%)	1,929 (17.4%)	669 (18.1%)	5,714 (19.6%)	3,093 (13.3%)	11,876 (17.2%)
<b>Deyo-Charlson score</b>						
0	382 (19.9%)	2,243 (20.2%)	714 (19.3%)	5,145 (17.7%)	3,131 (13.5%)	11,615 (16.8%)
1	603 (31.5%)	3,981 (35.9%)	1,154 (31.1%)	9,479 (32.5%)	6,211 (26.8%)	21,428 (31.0%)
≥2	932 (48.6%)	4,880 (43.9%)	1,837 (49.6%)	14,508 (49.8%)	13,869 (59.8%)	36,026 (52.2%)
<b>Income category</b>						
0-25 <sup>th</sup> percentile	350 (18.7%)	2,222 (20.4%)	677 (18.7%)	5,747 (20.1%)	4,770 (20.9%)	13,765 (20.3%)
25-50 <sup>th</sup> percentile	426 (22.7%)	2,551 (23.4%)	964 (26.7%)	6,953 (24.3%)	5,555 (24.4%)	16,450 (24.3%)
50-75 <sup>th</sup> percentile	464 (24.7%)	2,766 (25.4%)	972 (26.9%)	8,185 (28.6%)	6,201 (27.2%)	18,588 (27.4%)
75-100 <sup>th</sup> percentile	638 (34.0%)	3,341 (30.7%)	998 (27.6%)	7,713 (27.0%)	6,282 (27.5%)	18,972 (28.0%)
<b>Insurance</b>						
Private	580 (30.2%)	3,364 (30.3%)	1,150 (31.1%)	7,370 (25.3%)	5,363 (23.1%)	17,827 (25.8%)
Medicare	1,131 (59.0%)	6,583 (59.3%)	2,146 (57.9%)	19,430 (66.8%)	15,692 (67.6%)	44,981 (65.2%)
Medicaid	128 (6.7%)	726 (6.5%)	235 (6.3%)	1,431 (4.9%)	1,345 (5.8%)	3,864 (5.6%)
Other	44 (2.3%)	261 (2.4%)	61 (1.6%)	447 (1.5%)	486 (2.1%)	1,298 (1.9%)
Self	35 (1.8%)	165 (1.5%)	113 (3.0%)	396 (1.4%)	311 (1.3%)	1,020 (1.5%)
<b>Hospital region</b>						
Northeast	312 (16.3%)	2,054 (18.5%)	646 (17.4%)	5,000 (17.1%)	3,609 (15.5%)	11,622 (16.8%)
Midwest	584 (30.5%)	2,645 (23.8%)	759 (20.5%)	7,190 (24.6%)	5,115 (22.0%)	16,293 (23.5%)
South	596 (31.1%)	4,133 (37.2%)	1,410 (38.1%)	11,296 (38.6%)	8,135 (35.0%)	25,570 (36.9%)
West	425 (22.2%)	2,283 (20.5%)	888 (24.0%)	5,790 (19.8%)	6,368 (27.4%)	15,755 (22.8%)
<b>Hospital location/teaching</b>						
Rural	144 (7.7%)	972 (9.0%)	323 (8.9%)	3,792 (13.5%)	2,231 (9.7%)	7,463 (11.1%)
Urban non-teaching	540 (29.1%)	4,246 (39.2%)	1,528 (42.0%)	11,792 (41.9%)	8,439 (36.9%)	26,545 (39.4%)
Urban teaching	1,174 (63.2%)	5,604 (51.8%)	1,783 (49.1%)	12,573 (44.7%)	12,226 (53.4%)	33,359 (49.5%)
<b>Hospital bed size</b>						
Small	215 (11.3%)	1,696 (15.3%)	605 (16.3%)	4,647 (15.9%)	3,587 (15.5%)	10,749 (15.6%)
Medium	430 (22.5%)	2,910 (26.3%)	996 (26.9%)	8,241 (28.2%)	6,190 (26.8%)	18,767 (27.2%)
Large	1,263 (66.2%)	6,466 (58.4%)	2,103 (56.8%)	16,299 (55.8%)	13,340 (57.7%)	39,472 (57.2%)
<b>Discharge status</b>						
Rehabilitation or nursing facility	344 (19.0%)	1,650 (15.0%)	555 (15.1%)	5,052 (17.9%)	6,519 (31.0%)	14,121 (21.5%)
Home	1,465 (81.0%)	9,323 (85.0%)	3,115 (84.9%)	23,131 (82.1%)	14,503 (69.0%)	51,537 (78.5%)
<b>Length of stay in days</b>						
≤3	627 (32.7%)	4,881 (44.0%)	2,187 (59.0%)	11,121 (38.2%)	6,788 (29.2%)	25,603 (37.1%)
>3	1,290 (67.3%)	6,224 (56.0%)	1,517 (41.0%)	18,012 (61.8%)	16,423 (70.8%)	43,466 (62.9%)
<b>Died during hospitalisation</b>	97 (5.1%)	44 (0.4%)	9* (<1%)	826 (2.8%)	2,067 (8.9%)	3,043 (4.4%)
<b>Length of stay in days: mean (SE); median</b>	9.7 (0.88); 5.1	4.9 (0.09); 3.4	3.9 (0.11); 2.6	5.5 (0.06); 3.8	7.0 (0.11); 4.7	5.9 (0.05); 3.9
<b>Total hospital charges (US \$)</b>						
≤median	621 (32.4%)	5,821 (52.4%)	1,889 (51.0%)	12,018 (41.3%)	6,943 (29.9%)	27,293 (39.5%)
>median	1,296 (67.6%)	5,283 (47.6%)	1,815 (49.0%)	17,114 (58.7%)	16,268 (70.1%)	41,776 (60.5%)
<b>Total charge in US \$: mean (SE); median</b>	59,158 (6,847); 26,448	22,973 (611); 15,928	22,318 (735); 16,839	28,976 (562); 17,795	57,473 (1,221); 33,213	37,857 (553); 21,156

\*the count was between 1 and 10, and as per the NIS specifications, frequencies below 10 are not to be provided.

**Appendix 3.** Frequency of serious infections in Sjögren's syndrome patients over time.

	OI	SSTI	UTI	Pneumonia	Sepsis	Composite infection
1998-2000	161	572	263	2,881	658	4,536
2001-2002	175	618	154	2,126	482	3,555
2003-2004	106	732	238	2,419	575	4,069
2005-2006	169	983	248	2,917	770	5,086
2007-2008	233	1,103	224	3,167	1,237	5,964
2009-2010	170	1,526	312	3,681	2,593	8,281
2011-2012	349	1,796	480	4,225	3,803	10,654
2013-2014	225	1,710	385	3,980	5,455	11,755
2015-2016*	330	2,075	1,400	3,880	7,655	15,340

The ICD-9 codes used to define each infection category were as follows:

(1) opportunistic infections (OIs) that included tuberculosis (010–018), non-tuberculous mycobacteria (031), cytomegalovirus (078.5), Epstein-Barr virus (075), herpes zoster (053), candidiasis (112.4, 112.5, 112.81, 112.83), toxoplasmosis (130), pneumocystosis (136.3), cryptococcosis (117.5), listeriosis (027.0), nocardiosis (039), aspergillosis (117.3), coccidioidomycosis (114), histoplasmosis (115), and blastomycosis (116.0);

(2) skin and soft tissue infections (SSTIs; 040.0, 569.61, 681, 682, 785.4, 728.86, and 035);

(3) urinary tract infection (UTI; 590);

(4) pneumonia (003.22, 481.0, 513.0, 480, 482, 483, 485, and 486);

(5) sepsis/bacteremia (hereafter, sepsis; 038 and 790.7);

\*Estimates in this period reflect the only study period where ICD-codes transitioned from ICD-9-CM to ICD-10-CM, and therefore may be a little unstable.

**Appendix 4.** Serious infection rate in the general NIS cohort per 100,000 NIS population.

	OI	SSTI	UTI	Pneumonia	Sepsis	Composite infection	Total claims
1998-2000	159.53	974.93	313.48	3,398.42	989.47	5,835.83	103,665,051
2001-2002	139.43	1,097.63	335.19	3,303.16	919.34	5,794.75	72,617,381
2003-2004	138.89	1,269.23	352.31	3,260.20	1,088.62	6,109.25	74,571,583
2005-2006	143.86	1,490.70	350.89	3,235.99	1,451.26	6,672.71	75,919,595
2007-2008	138.64	1,531.68	336.98	2,891.86	1,834.90	6,734.07	76,366,797
2009-2010	138.62	1,627.18	350.97	2,849.14	2,223.62	7,189.53	75,086,597
2011-2012	130.48	1,688.87	343.20	2,791.79	2,948.98	7,903.32	73,447,261
2013-2014	121.39	1,665.59	324.30	2,578.24	3,939.63	8,629.14	70,956,610
2015-2016*	110.92	1,667.92	882.11	2,401.02	5,109.07	10,171.05	71,445,363

\*Estimates in this period reflect the only study period where ICD-codes transitioned from ICD-9-CM to ICD-10-CM, and therefore may be a little unstable.

**Appendix 5.** Rate of serious infections in Sjögren's syndrome patients over time using two different denominators.

	OI	SSTI	UTI	Pneumonia	Sepsis	Composite infection	Total NIS claims
<b>Rate per 100,000 NIS claims</b>							
1998-2000	0.16	0.55	0.25	2.78	0.63	4.38	103,665,051
2001-2002	0.24	0.85	0.21	2.93	0.66	4.90	72,617,381
2003-2004	0.14	0.98	0.32	3.24	0.77	5.46	74,571,583
2005-2006	0.22	1.29	0.33	3.84	1.01	6.70	75,919,595
2007-2008	0.31	1.44	0.29	4.15	1.62	7.81	76,366,797
2009-2010	0.23	2.03	0.42	4.90	3.45	11.03	75,086,597
2011-2012	0.48	2.45	0.65	5.75	5.18	14.51	73,447,261
2013-2014	0.32	2.41	0.54	5.61	7.69	16.57	70,956,610
2015-2016	0.46	2.90	1.96	5.43	10.71	21.47	71,445,363
P-value*	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	
<b>Rate per 100,000 Sjögren's syndrome claims</b>							
	OI	SSTI	UTI	Pneumonia	Sepsis	Composite infection	Sjögren's syndrome claims
1998-2000	395.67	1,405.75	646.35	7,080.36	1,617.10	11,147.70	40,690
2001-2002	526.19	1,858.20	463.05	6,392.45	1,449.28	10,689.16	33,258
2003-2004	272.23	1,879.91	611.23	6,212.44	1,476.71	10,449.95	38,938
2005-2006	374.56	2,178.63	549.65	6,464.98	1,706.56	11,272.16	45,120
2007-2008	421.16	1,993.75	404.89	5,724.56	2,235.96	10,780.33	55,323
2009-2010	236.52	2,123.07	434.07	5,121.25	3,607.55	11,521.07	71,877
2011-2012	409.28	2,106.20	562.90	4,954.73	4,459.85	12,494.14	85,272
2013-2014	254.42	1,933.62	435.35	4,500.48	6,168.37	13,292.25	88,435
2015-2016	339.59	2,135.32	1,440.70	3,992.80	7,877.54	15,785.95	97,175
P-value*	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	

\*P-value is from Cochran-Armitage two sided test for trend.

The first time-period is 3-year and the subsequent ones are 2-year duration.

Composite infection indicates any of the five infections as the primary diagnosis.

**Appendix 6.** Comparison of healthcare utilisation and mortality outcomes 1998-2000 (the first study period) versus 2015-2016 (the last study period) in Sjögren's syndrome patients with serious infections.

	OI	SSTI	UTI	Pneumonia	Sepsis	Composite Infection
<b>Length of stay in days &gt;3 days</b>						
1998-2000	116 (72.3%)	337 (58.8%)	118 (44.9%)	1,861 (64.6%)	473 (71.9%)	2,906 (64.1%)
2015-2016	195 (59.1%)	1,035 (49.9%)	540 (38.6%)	2,115 (54.5%)	5,250 (68.6%)	9,135 (59.6%)
<b>Died during hospitalisation</b>						
1998-2000	14 (8.7%)	<10* (<1%)	<10* (<1%)	135 (4.7%)	94 (14.3%)	248 (5.5%)
2015-2016	10 (3.0%)	15 (0.7%)	<10* (<1%)	85 (2.2%)	560 (7.3%)	670 (4.4%)
<b>Length of stay in days: mean (SE); median</b>						
1998-2000	10.3 (1.44); 7.5	5.3 (0.51); 3.4	4.0 (0.31); 2.8	6.3 (0.31); 4.2	6.9 (0.49); 4.9	6.3 (0.23); 4.1
2015-2016	10.7 (3.72); 4.0	4.4 (0.16); 3.0	3.6 (0.15); 2.6	5.1 (0.16); 3.3	6.7 (0.15); 4.5	5.8 (0.12); 3.7
<b>Total hospital charges (US \$) &gt;median</b>						
1998-2000	117 (72.9%)	327 (57.2%)	159 (60.3%)	1,800 (62.5%)	527 (80.1%)	2,931 (64.6%)
2015-2016	200 (60.6%)	820 (39.5%)	610 (43.6%)	2,085 (53.7%)	5,160 (67.4%)	8,875 (57.9%)
<b>Total charge in US \$: mean (SE); median</b>						
1998-2000	22,454 (3,359); 17,299	9,869 (1,044); 7,377	8,941 (1,014); 7,265	14,544 (1,113); 8,272	20,475 (2,692); 10,626	14,751 (877); 8,403
2015-2016	75,346 (13,613); 34,852	28,702 (1,511); 20,205	25,924 (1,102); 22,454	39,701 (1,755); 26,325	62,381 (2,027); 39,760	48,783 (1,220); 30,082

\* the count was <10, and as per the NIS specifications, frequencies below 10 are not to be shown.