# Serious infections in Sjögren's syndrome patients: a national U.S. study

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**Key words:** serious infections, Sjögren's syndrome, epidemiology, time-trends, incidence, mortality, healthcare utilisation

Availability of data and materials: these data are easily available from the Agency for Healthcare Research and Quality (AHRQ's) "Healthcare Cost and Utilization Project (HCUP)" and can be obtained after completing an on-line Data Use Agreement training session and signing a Data Use Agreement. The contact information for requesting the data is as follows: HCUP Central Distributor Phone: (866) 556-4287 (toll-free) Fax: (866) 792-5313 E-mail: HCUPDistributor@ahrq.gov

Competing interests and funding: page S52.

# ABSTRACT

**Objective.** To study the incidence, time-trends and outcomes of serious infections in Sjögren's syndrome (SS).

**Methods.** We examined the epidemiology, time-trends and outcomes of five serious infections (opportunistic infections (OI), skin and soft tissue infections (SSTI), urinary tract infection (UTI), pneumonia, and sepsis/bacteraemia) in hospitalised patients with SS, using the 1998-2016 U.S. National Inpatient Sample. Multivariable-adjusted logistic regression analyses analysed the association of patient, comorbidity and hospital characteristics with healthcare utilisation (hospital charges, length of hospital stay, discharge to non-home setting), and in-hospital mortality.

Results. We found 49,897,331 hospitalisations with serious infections in general population and 69,239 in patients with SS. Compared to serious infections hospitalisations in people without SS, SS patients were older, and more likely to be female, white or have Deyo-Charlson index score  $\geq 2$ . Serious infections during the study period 1998-2016 were: OI, 3%; SSTI, 19%; UTI, 6%; pneumonia, 37%; and sepsis, 34%. Serious infection rates/100,000 NIS hospitalisations increased from 1998-2000 to 2015-2016: OI, 0.16 to 0.46; SSTI, 0.55 to 2.90; UTI, 0.25 to 1.96; pneumonia, 2.78 to 5.43; sepsis, 0.63 to 10.71. In multivariableadjusted analyses, older age, Deyo-Charlson index score  $\geq 2$  and medium or large hospital bed size were associated with higher healthcare utilisation and in-hospital mortality. Medicare insurance, Northeast region, non-rural hospital were associated with higher healthcare utilisation outcomes only.

**Conclusion.** We quantified the increasing disease burden of serious infections in people with SS, and described its epidemiology. Association of factors with serious infection hospitalisation outcomes identifies potential targets for future interventions.

## Introduction

Sjögren's syndrome (SS) is a systemic autoimmune disease, characterised by dry eyes, dry mouth and systemic symptoms (1). The incidence and prevalence of SS in the general population increases with age and varies widely based on the definition and primary *vs*. secondary SS (2-4). The use of novel tools in disease phenotyping including neural networks is allowing a better understanding of disease subtypes and systemic manifestations (5, 6).

Hospitalisation in primary SS was higher than in population-matched controls, primarily related to endocrine/ metabolic and musculoskeletal disorders in a U.S. population-based study (7). The rates of hospitalisation, sick leave and early retirement decreased in a German cohort of patients with SS (8) and in a Swedish cohort of systemic connective tissue diseases from 1998 to 2016 (9). Whether hospitalisations related to serious infections in people with SS are following the same decline in incidence, in not known.

In a systematic review of infections in connective tissue diseases, most studies were limited to lupus or rheumatoid arthritis, and there were no studies that included patients with SS (10). SS is associated with lower risk of serious infections compared to lupus, 10% versus 17% (11); however, this rate seemed higher than in the general population. To our knowledge, none of the previously published studies of SS have systematically assessed incidence of serious infection hospitalisations in a national sample of patients with SS or associated healthcare utilisation or inpatient mortality, which was our study objective.

# Methods

We used the 1998–2016 U.S. Nationwide Inpatient Sample (NIS) to conduct this study. The NIS is a deidentified national all-payer inpatient

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healthcare database that represents a 20% stratified sample of all discharge records from all participating community hospitals from all participating states in the U.S. (12). NIS is a component of the healthcare cost and utilisation project (HCUP).

The University of Alabama at Birmingham's Institutional Review Board approved this study, and all investigations were conducted in conformity with the ethical principles of research (UAB X120207004). The IRB waived the need for an informed consent for this database study.

The study cohort included people admitted to the hospital with an international classification of diseases, ninth or tenth revision, clinical modification (ICD-9-CM or ICD-10-CM) code for serious infections in the primary diagnosis position, i.e., it was the principal diagnosis and the main reason for hospitalisation: (1) opportunistic infections (OI; 010.xx -018.xx, 031.xx, 078.5, 075.xx, 053.xx, 112.4, 112.5, 112.81, 112.83, 130.xx, 136.3, 117.5, 027.0, 039.xx, 117.3, 114.xx, 115.xx, 116.0); (2) skin and soft tissue infections (SSTI; 040.0, 569.61, 681.xx, 682.xx, 785.4, 728.86, and 035.xx); (3) urinary tract infection (UTI; 590. xx); (4) pneumonia (003.22, 481.0, 513.0, 480.xx, 482.xx, 483.xx, 485. xx, 486.xx); and (5) sepsis/bacteraemia (038.xx and 790.7), as previously reported (13, 14). These diagnostic codes have been shown to be valid in patients with rheumatoid arthritis with positive predictive values of 70% to 100% (15-17). We also used the ICD-10-CM codes for infections for the 2015-2016 data due to a coding system change to ICD-10-CM in 2015 in the U.S. (Appendix 1). We defined composite infection as hospitalisation with any of the five serious infections occurring as the primary diagnosis. SS was detected by the presence of ICD-9-CM or ICD-10-CM diagnostic codes (710.2 or M35.0) in non-primary position (any position after the primary DX1 position; i.e. secondary diagnoses for the hospitalisation) during the index hospitalisation (18), a valid approach with sensitivity of 95% and specificity of 96% (18).

We examined important covariates/ confounders, including age, sex, race, serious infection type [OI, SSTI, UTI, pneumonia, sepsis (13, 14)], median household income, insurance payer type, hospital characteristics (U.S. region, location/teaching status, bed size) and Devo-Charlson comorbidity index (19), a validated measure of medical comorbidity that includes 17 comorbidities with score ranging 0-25, higher score indicating more comorbidity load. Healthcare utilisation and in-hospital mortality were the outcomes of interest. For utilisation, we assessed total hospital charges above the median for each calendar year, the length of hospital stay above the median of 3 days, and discharge to non-home settings (rehabilitation or an inpatient facility).

# Statistical analyses

We followed the NIS survey analysis procedures that account for the weights, clusters and strata, including the modified weights with the change in sampling in 2012. We compared the summary statistics, including means and proportions. Considering the large sample size, we decided a priori to not perform tests of significance for unadjusted means or proportions between people with versus without SS and by the type of serious infection. Rates were calculated per 100,000 NIS claims. We analysed timetrends in rate of each serious infection using Cochran Armitage test. We performed multivariable-adjusted logistic regression analyses for each study outcome, adjusting for all covariates previously listed, based on their clinical importance. We decided a priori not to base models on statistical significance in unadjusted models, but rather to include all potentially important clinical and system-factor variables. We calculated odds ratios (OR) and 95% confidence intervals (CI). We used SAS 9.3 (Cary, N.C.) for all analyses.

# Results

There were 49,897,331 hospitalisations with serious infections in people without SS and 69,239 in those with SS. The average age of patients with SS with a primary diagnosis of one of the serious infections was 66 years, with a median of 67 years (Table I). Compared to patients admitted with serious infections without SS, people with SS admitted with a diagnosis of serious infection were older, and more likely to be female, white and have Deyo-Charlson index score  $\geq 2$  (Table I).

Of the serious infections, the most common during the study period 1998-2016 were pneumonia and sepsis: OI, 3%; SSTI, 19%; UTI, 6.4%; pneumonia, 37%; and sepsis, 34% (Appendix 2). People with pneumonia or sepsis were 5-7 years older than people with SSTI or UTI and 3-5 years older than those with OI (Appendix 2). Compared to other serious infections, sepsis was associated with higher proportion with discharge to non-home settings (15-19% vs. 31%), length of stay >3 days 41-67% vs. 71%), hospital charges above the median (48-68% vs. 70%), and in-hospital mortality (0.3-5% vs. 9%) (Appendix 2).

The frequency of serious infections increased in people with SS (Appendix 3). Rates of all serious infections increased in the general population, except for pneumonia and OI (Appendix 4). We noted that rates of each of the serious infections /100,000 NIS claims increased from 1998-2000 to 2015-2016: OI from 0.16 to 0.46; SSTI, 0.55 to 2.90; UTI, 0.25 to 1.96; pneumonia, 2.78 to 5.43; sepsis, 0.63 to 10.71; and composite infection, from 4.38 to 21.47 (Appendix 5; Fig. 1). Similar trends were seen when we used a different denomination of all SS claims, except that OI and pneumonia rates seemed to decline over time; composite infection serious infection rate increased from 11% in 1998-2000 to 16% in 2015-2016 of all SS hospitalisations (Appendix 5; Fig. 1). Unadjusted length of hospital stay and in-hospital mortality decreased, and total hospital charges increased for serious infections from 1998-2000 to 2015-2016 (Appendix 6). In multivariable-adjusted analyses, we found that older age, Deyo-Charlson index score  $\geq 2$ , sepsis and medium or large hospital bed size were each associated with higher healthcare utilisation outcomes and in-hospital mortality (Table II). Medicare insurance payer, Northeast region, urban teaching or nonteaching hospital were each associated

#### Table I. Demographic characteristics of infection hospitalisations in people with vs. without Sjögren's syndrome (SS).

1	SS dia	al claims with a non-primary SS diagnosis (n= 556,087)		No SS as secondary diagnosis + serious infection primary diagnosis* (n=49,897,331)		SS as secondary diagnosis + serious infection primary diagnosis* (n=69,239)	
Age, mean (SE); median	63.6	(0.07); 64.7	59.8	(0.08); 65.0	65.8	(0.14); 66.8	
Age category							
<50 years	98,126	(18.57%)	14,072,750	(28.42%)	9,921	(14.37%)	
50 - <65 years	157,820	(29.86%)	9,976,035	(20.14%)	19,975	(28.92%)	
65 - 79 years	185,560	(35.11%)	13,262,550	(26.78%)	25,435	(36.83%)	
≥80 years	86,950	(16.45%)	12,211,905	(24.66%)	13,730	(19.88%)	
Gender							
Male	41,604	(7.87%)	23,453,087	(47.38%)	6,104	(8.84%)	
Female	486,810	(92.13%)	26,043,737	(52.62%)	62,950	(91.16%)	
Race							
White	367,759	(69.59%)	29,709,865	(59.97%)	49,006	(70.95%)	
Black	35,228	(6.67%)	5,339,250	(10.78%)	3,828	(5.54%)	
Hispanic	28,269	(5.35%)	4,217,518	(8.51%)	4,358	(6.31%)	
Other/Missing	97,214	(18.40%)	10,274,318	(20.74%)		(17.19%)	
Deyo-Charlson score							
0	105,125	(19.89%)	15,672,213	(31.63%)	11,615	(16.82%)	
1	146,471	(27.72%)	12,915,947	(26.07%)	21,428	(31.02%)	
≥2	276,891	(52.39%)	20,957,575	(42.30%)	36,026	(52.16%)	
Income category							
0-25 <sup>th</sup> percentile	96,184	(18.54%)	12,965,912	(26.81%)	13,765	(20.31%)	
25-50 <sup>th</sup> percentile	122,809	(23.67%)	13,288,858	(27.47%)	16,450	(24.27%)	
50-75 <sup>th</sup> percentile	140,928	(27.17%)	11,598,980	(23.98%)	18,588	(27.43%)	
75-100 <sup>th</sup> percentile	158,861	(30.62%)	10,516,133	(21.74%)	18,972	(27.99%)	
Insurance							
Private	162,968	(30.88%)	10,939,064	(22.13%)	17,827	(25.84%)	
Medicare	317,498	(60.17%)	27,430,597	(55.48%)	44,981	(65.20%)	
Medicaid	28,838	(5.47%)	7,083,579	(14.33%)		(5.60%)	
Other	11,302	(2.14%)	1,501,213	(3.04%)	1,298	(1.88%)	
Self	7,058	(1.34%)	2,484,796	(5.03%)		(1.48%)	
Hospital location/teaching							
Rural	52,628	(9.99%)	7,025,233	(14.93%)	7,463	(11.08%)	
Urban non-teaching	198,459	(37.66%)	19,229,464	(40.88%)	26,545	(39.40%)	
Urban teaching	275,841	(52.35%)	20,788,447	(44.19%)	33,359	(49.52%)	
Discharge status							
Rehabilitation or skilled nursing facility (SNF)	104,585	(20.25%)	11,653,436	(25.42%)	14,121	(21.51%)	
Home	411,786	(79.75%)	34,193,380	(74.58%)	51,537	(78.49%)	
Length of stay in days							
≤3	257,685	(48.76%)	20,096,125	(40.56%)	25,603	(37.07%)	
>3	270,802	(51.24%)	29,449,610	(59.44%)	43,466	(62.93%)	
Died during hospitalisation							
Yes	9,428	(1.79%)	3,076,025	(6.21%)	3,043	(4.41%)	
No	518,675	(98.21%)	46,429,406	(93.79%)	65,997	(95.59%)	
Length of stay in days: mean (SE); median Total hospital charges (US \$)	5.1	(0.02); 3.1	6.0	(0.01); 3.7	5.9	(0.05); 3.9	
≤median	188,110	(35.59%)	21,128,028	(42.64%)	27,293	(39.52%)	
>median	340,377	(64.41%)	28,417,707	(57.36%)	41,776	(60.48%)	
Total hospital charges in US \$: mean (SE); media	n 36,699	(292); 21,562	34,623	(166); 16,831	37,857	(553); 21,156	
1998-2000	14,993	(361); 9,189	15,111	(911); 8,552	18,268	(340); 9,621	
2015-2016	53,227	(906); 33,652	53,575	(431); 28,776	48,783	(1,220); 30,08	
Hospital location/teaching							
Rural	52,628	(9.99%)	7,025,233	(14.93%)	7,463	(11.08%)	
Urban non-teaching	198,459	(37.66%)	19,229,464	(40.88%)	26,545	(39.40%)	
Urban teaching	275,841	(52.35%)	20,788,447	(44.19%)	33,359	(49.52%)	

\*The primary (or the principal) diagnosis indicated the first listed diagnosis defined as the condition to be chiefly responsible for the admission of the patient to the hospital for care. For this study of serious infection hospitalisations, we selected all hospitalisations with serious infection as the primary diagnosis.

with higher healthcare utilisation outcomes only (Table II).

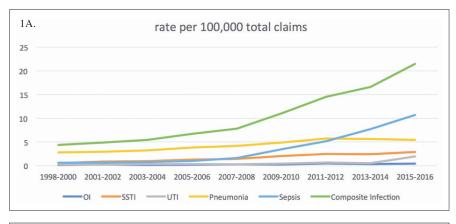
## Discussion

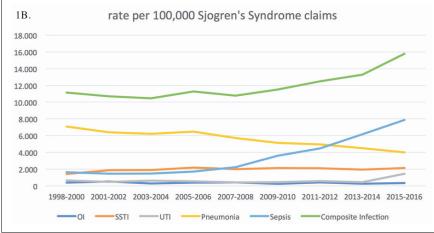
This national study of a large cohort of people with SS hospitalised with seri-

ous infections from 1998-2016 adds new knowledge. SS patients with serious infections were older, and more likely to be female, or have higher comorbidities. Our study found that pneumonia followed by sepsis accounted for more than 2/3rds of serious infections in people with SS. Unadjusted healthcare utilisation outcomes and in-hospital mortality were the highest for sepsis, followed by OI and pneumonia.

The increase in sepsis rates over the

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**Fig. 1.** Rate of serious infections in hospitalised people with Sjögren's syndrome per 100,000 total NIS claims (1A) and per 100,000 overall Sjögren's syndrome claims (1B). The y-axis shows rate per 100,000 hospitalisation claims.

study-period exceeded that of other serious infections. Sepsis rates in SS patients increased 17-fold from 0.63/100,000 claims in 1998-2000 to 10.7/100,000 in 2015-2016. Other serious infection rates increased by 1.9-7.8 fold. These increases in rates were more modest with the denominator of all SS hospitalisations at 4.9-fold for sepsis, and 0.6-2.2 fold for other serious infections. A greater increase in the rate of sepsis over time versus pneumonia and other serious infections may at least partially be due to upcoding pneumonia and other infections being coded as sepsis diagnosis in the more recent years (20-22). A general increase in serious infection hospitalisation over time may be due to SS populations getting older over time, increasing comorbidities, a lower threshold for hospitalisation and/ or general trends of increasing rates of serious infection hospitalisations in the U.S. (14, 23). A clinical implication of our finding is that early recognition of

infection, prompt treatment with antibiotic, antiviral, and/or antifungal drugs, and institution of programs to ensure optimal treatment adherence and follow-up of people with infections may help reduce the morbidity of serious infections in SS.

Despite the increase in the rates of serious infections over time, the crude mortality decreased over time (Appendix 6), which indicates an earlier recognition and treatment of serious infections, a lower threshold for hospitalisation, and/or better therapeutics in the more recent years. Our study highlights the differences in the rates of increase of hospitalisation with each serious infection in people with SS.

We found that older age, Deyo-Charlson index score  $\geq 2$  and medium or large hospital bed size were associated with higher healthcare utilisation and in-hospital mortality. Reasons for higher mortality in those admitted to hospitals with a larger bed is unclear. Importantly, income and race were not significantly associated with in-hospital mortality in this study of people with SS. Medicare insurance payer, Northeast region, non-rural hospital were each associated with higher odds of healthcare utilisation outcomes only, findings consistent with previous NIS studies in other conditions (24-26). Our study identifies modifiable and unmodifiable correlates of worse outcomes for serious infection hospitalisation in people with SS. Interventions targeting these modifiable factors can be developed and tested. These findings can also allow prognostication of outcome of these hospitalisations.

Study limitations must be considered while interpreting study findings. The NIS does not provide data on disease severity (systemic vs. glandular disease), organ manifestations of SS or the type of treatment (glucocorticoids vs. immunosuppressive drugs vs. others). We are unable to differentiate primary vs. secondary SS for serious infection hospitalisations. Therefore, we were unable to examine the effects of disease type, severity or treatment on the burden of serious infections and the associated outcomes, which needs to be examined in future studies. The use of ICD-9-CM codes may have led to misclassification bias despite the accuracy of codes for infection (13, 14) and SS (18), which likely biases the findings towards the null, making our estimates conservative. The unit of analysis in NIS is hospitalisations, not people. Findings may not generalisable to other country settings.

Our study strengths are the use of over almost 2 decades of U.S. national inpatient data, the inclusion of several potential confounders, including patient, comorbidity and system-level factors, the examination of time-trends, and a large sample size.

## Conclusion

Our study of the U.S. national sample found important epidemiologic trends for serious infection hospitalisations in SS. We noted increasing rates of each serious infection in people with SS. Crude mortality for hospitalised serious infection decreased over time in people with SS. We identified inde-

Table II. Multivariable-adjusted correlates of healthcare utilisation and in-hospital mortality in Sjögren's syndrome patients with serious	3
infections.	

	Hospital charges > median	Discharge to care facility	Length of hospital stay > median	In-hospital mortalit
	Adjusted odds ratio (95% CI)			
Age category				
<50 years	Ref	Ref	Ref	Ref
50 - <65 years	0.87 (0.77, 0.98)	1.79 (1.45, 2.21)	1.10 (0.97, 1.23)	1.48 (1.02, 2.14)
65 - 79 years	0.77 (0.67, 0.88)	3.03 (2.42, 3.79)	1.08 (0.94,1.23)	2.58 (1.74, 3.82)
≥80 years	0.71 (0.61, 0.82)	6.54 (5.18, 8.25)	1.19 (1.03, 1.38)	3.73 (2.49, 5.59)
Sex				
Male	Ref	Ref	Ref	Ref
Female	0.99 (0.87, 1.13)	1.12 (0.95, 1.33)	1.12 (0.99, 1.27)	0.68 (0.53, 0.88)
Race/ethnicity			()	
White	Ref	Ref	Ref	Ref
Black	1.03 (0.87, 1.22)	1.14 (0.92, 1.41)	0.97 (0.83, 1.15)	1.12 (0.76, 1.65)
Hispanic	1.04 (0.89, 1.22)	0.86 (0.69, 1.06)	1.07 (0.92, 1.25)	1.05 (0.74, 1.49)
Other/missing	1.00 (0.90, 1.10)	0.87 (0.76, 0.99)	1.08 (0.98, 1.20)	1.14 (0.89, 1.45)
Deyo-Charlson score	1.00 (0.90, 1.10)	0.87 (0.70, 0.99)	1.08 (0.98, 1.20)	1.14 (0.69, 1.45)
0	D . C	D_f	D-f	D.f
	<b>Ref</b>	<b>Ref</b>	<b>Ref</b>	<b>Ref</b> 1.12 (0.84, 1.51)
1	1.10 (0.99, 1.23)	1.18 (1.02, 1.37)	1.10 (0.99, 1.22)	
≥2	1.36 (1.23, 1.51)	1.52 (1.33, 1.74)	1.38 (1.25, 1.53)	1.42 (1.09, 1.85)
ncome category	104(002,110)			0.00 (0.70, 1.10)
0-25 <sup>th</sup> percentile	1.04 (0.93, 1.16)	1.26 (1.10, 1.45)	1.16 (1.04, 1.30)	0.90 (0.70, 1.18)
25-50 <sup>th</sup> percentile	0.91 (0.82, 1.00)	1.11 (0.98, 1.27)	1.06 (0.96, 1.18)	0.81 (0.63, 1.04)
50-75 <sup>th</sup> percentile	1.01 (0.92, 1.12)	1.13 (1.00, 1.28)	1.10 (1.00, 1.21)	1.02 (0.82, 1.27)
75-100 <sup>th</sup> percentile	Ref	Ref	Ref	Ref
Primary infection diagnosis				
Sepsis	Ref	Ref	Ref	Ref
OI	0.90 (0.71, 1.14)	0.66 (0.49, 0.88)	0.91 (0.72, 1.15)	0.57 (0.35, 0.94)
SSTI	0.38 (0.34, 0.43)	0.45 (0.39, 0.52)	0.54 (0.48, 0.60)	0.05 (0.03, 0.10)
UTI	0.40 (0.34, 0.47)	0.42 (0.34, 0.52)	0.29 (0.24, 0.34)	0.01 (0.00, 0.10)
Pneumonia	0.66 (0.61, 0.72)	0.45 (0.40, 0.50)	0.67 (0.62, 0.73)	0.31 (0.25, 0.37)
Insurance payer				
Medicare	1.12 (1.01, 1.25)	1.72 (1.48, 2.01)	1.20 (1.08, 1.33)	0.91 (0.69, 1.19)
Medicaid	1.03 (0.86, 1.23)	1.21 (0.92, 1.60)	1.00 (0.84, 1.18)	1.37 (0.87, 2.14)
Other	0.95 (0.71, 1.26)	1.33 (0.89, 1.98)	1.13 (0.86, 1.49)	1.18 (0.59, 2.33)
Private	Ref	Ref	Ref	Ref
Self	1.03 (0.76, 1.40)	1.02 (0.62, 1.67)	1.07 (0.79, 1.44)	0.81 (0.31, 2.12)
Hospital region		~ / /		、 ,,
Northeast	Ref	Ref	Ref	Ref
Midwest	0.75 (0.67, 0.84)	0.99 (0.86, 1.14)	0.76 (0.67, 0.85)	0.87 (0.64, 1.17)
South	0.91 (0.82, 1.01)	0.82 (0.71, 0.93)	0.86 (0.77, 0.96)	1.30 (1.00, 1.70)
West	0.95 (0.84, 1.07)	0.83 (0.71, 0.96)	0.59 (0.52, 0.66)	1.19 (0.91, 1.57)
Hospital location/teaching	0.55 (0.04, 1.07)	0.00 (0.11,000)	0.07 (0.02, 0.00)	1.17 (0.51, 1.57)
Rural	Ref	Ref	Ref	Ref
Urban non-teaching	2.62 (2.31, 2.98)	0.96 (0.82, 1.12)	1.30 (1.14, 1.48)	1.24 (0.90, 1.72)
Urban teaching	2.32 (2.05, 2.63)	0.90 (0.82, 1.12)	1.30 (1.14, 1.48) 1.22 (1.08, 1.39)	1.24 (0.90, 1.72)
e	2.02 (2.03, 2.03)	0.92 (0.79, 1.07)	1.44 (1.00, 1.37)	1.20 (0.93, 1.70)
Hospital bed size	Dof	Def	Dof	Dof
Small	Ref	<b>Ref</b>	Ref	Ref
Medium	1.27 (1.14, 1.43)	0.98 (0.85, 1.13)	1.15 (1.03, 1.29)	1.39 (1.03, 1.88)
Large	1.80 (1.62, 2.00)	1.03 (0.90, 1.17)	1.29 (1.16, 1.43)	1.57 (1.19, 2.07)

CI: confidence interval; Ref: reference category.

pendent correlates of healthcare utilisation and in-hospital mortality. Future studies can examine whether interventions, targeting systems of individuals can reduce mortality and improve utilisation outcomes in SS admitted with serious infections.

## Take home messages

1. Serious infection rates /100,000 NIS

hospitalisations in people with SS increased from 1998-2000 to 2015-2016 for OI, SSTI, UTI, pneumonia and sepsis, *i.e.* all five serious infections we studied.

- 2. The increase in sepsis rates over the study-period exceeded that of other serious infections in people with SS.
- 3. Unadjusted in-hospital mortality de-

creased over the study period from 1998 to 2016 for each serious infection in people with SS.

4. In multivariable-adjusted analyses, older age, Deyo-Charlson index score ≥2 and medium or large hospital bed size were associated with higher healthcare utilisation and inhospital mortality in people with SS with serious infections.

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#### **Competing interests**

There are no financial conflicts related directly to this study.

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