One-year mortality and years of potential life lost following bloodstream infection among adults: A nation-wide population based study

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Summary

Background Limited data exist on long-term consequences of bloodstream infections (BSIs). We aimed to examine incidence, 1-year mortality, and years of potential life lost (YPLL) following BSI. We estimated the relative contribution of hospital-onset BSI (HO-BSI) and antibiotic-resistant BSI to incidence, mortality and YPLL.

Methods We used data from Israel's national BSI surveillance system (covering eight sentinel bacteria, comprising 70% of all BSIs) and the national death registry. Adults with BSI between January 2018 and December 2019 were included. The outcomes were all-cause 30-day and 1-year mortality, with no adjustment for co-morbidities. We calculated the age-standardized mortality rate and YPLL using the Global Burden of Disease reference population and life expectancy tables.

Findings In total, 25,376 BSIs occurred over 2 years (mean adult population: 6,068,580). The annual incidence was 209·1 BSIs (95% CI 206·5–211·7) per 100,000 population. The case fatality rate was 25·6% (95% CI 25·0-26·2) at 30 days and 46·4% (95% CI 45·5-47·2) at 1 year. The hazard of death increased by 30% for each decade of age (HR=1·3 [95% CI 1·2-1·3]). The annual age-standardized mortality rate and YPLL per 100,000 were 50·8 (95% CI 49·7-51·9) and 1,012·6 (95% CI 986·9-1,038·3), respectively. HO-BSI (6,962 events) represented 27·4% (95% CI 26·9-28·0) of BSIs, 33·9% (95% CI 32·6-35·0) of deaths and 39·9% (95% CI 39·5-40·2) of YPLL. HO-BSI by drug-resistant bacteria (3,072 events) represented 12·1% (95% CI 11·7-12·5) of BSIs, 15·6% (95% CI 14·7-16·5) of deaths, and 18·4% (95% CI 18·1-18·7) of YPLL.

Interpretation One-year mortality following BSI is high. The burden of BSI is similar to that of ischemic stroke. HO-BSI and drug-resistant BSI contribute disproportionately to BSI mortality and YPLL.

Funding None.

Keywords: Bacteremia; Bloodstream infection; Burden; Mortality; Population-based study

Introduction

Bloodstream infection (BSI) is one of the most serious acute infections. Relatively few population-based studies have examined the incidence of BSI. The estimated average annual incidence of BSI in multi-year population-based studies conducted in North America (USA and Canada) and Europe (Sweden, Norway, Denmark, England, Finland, Switzerland, and Spain) ranged between 91 and 220 per 100,000 population.[1,2] Higher incidence rates were reported in recent years from Switzerland and Finland, reaching 240 and 309 cases/100,000, respectively.[3,4] The case fatality rate (CFR) of BSI varied greatly by the affected population (i.e., patients' age, sex and comorbidities), the virulence of the pathogen and its resistance to antibiotics, the appropriateness and timeliness of antibiotic therapy, and whether the infection was community- or hospital-onset. A few population-based studies determined BSI-associated mortality; based on these studies, Goto and

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Research in context

Evidence before this study

We searched PubMed between January 1, 2000 and March 8, 2022 to identify population-based studies that estimated the burden of bacterial bloodstream infection (BSI) in adults. We used the terms ((population-based) AND (((burden) OR (incidence)) OR (mortality))) AND ((bloodstream infection) OR (bacteremia)) and limited the search to adult subjects (i.e. excluded articles on children only). The search yielded diverse studies that reported incidence and case fatality rate (CFR) of BSI in various geographic levels and various participants. We limited our focus to studies that included the entire population in a region or country, and both community- and hospital-onset bacterial BSI. The estimated average annual incidence of BSI in multi-year population-based studies conducted in North America (USA and Canada) and Europe (Sweden, Norway, Denmark, England, Finland, Switzerland, and Spain) ranged between 91 and 220 per 100,000 population. Higher incidence rates were reported in recent years from Switzerland and Finland, reaching 240 and 309 cases/100,000, respectively. Incidence increased by age, reaching 857 per 100,000 for the age group ≥75 years. The reported CFR of BSI reflected mainly short-term mortality (i.e., in-hospital or within 30 days) and ranged between 13-23%. Most studies focused on a single pathogen. We found only three studies that evaluated 1-year mortality following BSI caused by a broad range of pathogens. A study of BSI in Calgary Zone, Canada (patients ≥18 years of age) reported a 1-year all-cause CFR of 28·2%. A study of BSI in Funen County, Denmark (patients ≥15 years old) found a 1-year all-cause CFR of 41·4%. Another regional study in Denmark (all ages) found a 1-year all-cause CFR of 39·7%. We found no national population-based multi-pathogen studies evaluating 1-year mortality following BSI. We found no population-based studies that estimated years of potential life lost (YPLL) following BSI.

Added value of this study

We conducted a nation-wide population-based study of BSIs caused by eight sentinel bacteria (comprising 70% of all BSIs) in adults. We determined mortality up to 1 year following the BSI and calculated the age-standardized mortality rate and YPLL using the Global Burden of Disease (GBD) reference population and GBD life expectancy tables. We also estimated the relative contribution of hospital-onset BSI (HO-BSI) and of antibiotic-resistant BSI to the overall mortality and YPLL following BSI. To our knowledge, this is the first country-level study of the long-term mortality of BSI. Our calculation of the age-standardized BSI-associated mortality rate and YPLL rate enabled us to compare the burden of BSI to other causes of death presented in the GBD report.

Implications of all the available evidence

Adult patients with BSI have serious long-term consequences; nearly 50% die within 1 year. Mortality increased with age, but in all age groups, survival continued to decline for a year after the acute event. The burden of BSI was similar to that of ischemic stroke, with an estimated YPLL of 1,012·6 per 100,000 population. HO-BSI and drug-resistant BSI contribute disproportionately to YPLL. The estimates from this study should focus attention on the high burden of BSI and the need to improve preventive efforts.

Al-Hasan estimated the total number of BSIs and associated deaths and ranked BSI as one of the top seven causes of death in many high-income countries.[5]

Escherichia coli and *Staphylococcus aureus* are the predominant pathogens causing BSI, accounting for over 40% of BSIs.[6] In recent years, the proportion of BSI caused by Gram-negative bacteria (GNB), and particularly by antibiotic-resistant GNB, has increased.[6] Antibiotic resistance may affect both incidence and outcomes of BSI; observational data and a modelling study suggested that infections by resistant GNB occur in addition to, rather than replace, infections by susceptible bacteria, at least up to a certain point.[7,8] Pathogen distribution and outcome of BSI may vary by geographic region. For example, we found in Israel that the annual incidence and CFR of *E.coli* BSI are about twice as high as summarized in earlier reports from other high-income countries, mostly due to high resistance levels.[9]

Determining the burden of BSI is important for policymakers, who need to assign resources for different health conditions based on priority. However, accurate assessment of mortality following BSI is challenging for several reasons. First, focus on the underlying cause of death as written in the death certificate may hinder true assessment of BSI-associated mortality, as death is attributed to the underlying disease rather than to the BSI. Second, a focus on sepsis, an important clinical entity for which there are multiple etiologies, as the cause of death shifts the attention from BSI to one of its manifestations. Third, observational studies often examine mortality during the index hospitalization only or within 30 days, and duration of follow-up in clinical trials of antibiotic therapy for BSI last no more than 90 days.[10] However, long-term consequences of BSI may occur up to one year after the BSI event.[11] As a result, BSI-associated mortality may be underestimated and its importance underappreciated.

In Israel, the National Institute for Antibiotic Resistance and Infection Control (NIARIC) conducts continuous nationwide surveillance of BSIs caused by eight bacteria of public health importance. These sentinel bacteria cause 70% of all BSIs in Israel (unpublished data, NIARIC). In this population-based study, we aimed to describe the epidemiology and determine the burden of BSI caused by these sentinel bacteria in adults, specifically, mortality up to 1 year and years of

potential life lost (YPLL). We also aimed to estimate the relative contribution of hospital-onset BSI (HO-BSI) and of drug-resistant BSI to incidence, mortality and YPLL.

Methods

Study setting and participants

The study was based on surveillance data reported to the NIARIC by all 29 of Israel's acute care hospitals between January 2018 and December 2019. Patients younger than 18 years of age were excluded.

Data collection

In Israel, >99% of blood cultures positive for the study organisms are processed in hospital laboratories (unpublished data, NIARIC). These laboratories submit mandatory monthly reports on all blood cultures positive for the following eight sentinel bacteria: *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter baumannii, Streptococcus pneumoniae, Staphylococcus aureus, Enterococcus faecalis* and *Enterococcus faecium*. These reports included the following data: patients' unique identity number (UID), sex, date of birth, admission date, specimen collection date and time, ward where culture was taken, type of culture (aerobic, anaerobic, or pediatric), isolated organism, and results of antibiotic susceptibility testing (AST). We used UIDs to search for dates of death in the death registries of the Ministry of Health and the Ministry of the Interior. Death registry data were available until April 30, 2020. We used publicly available population data and all-cause mortality data by age and sex from the Central Bureau of Statistics (CBS). Life expectancy by age and sex was derived from the CBS's complete life tables for the years 2014–2018.

Blood culturing practices and laboratory processing

In Israel in 2019, among adults, the mean rate of blood cultures was 155·5 bottles per 1,000 patient-days. In most hospitals, the ratio of aerobic to anaerobic bottles was close to 1; therefore, the blood culturing rate was approximately 75 sets per 1,000 patient-days (unpublished data, NIARIC). By comparison, a median of 47·1 sets (interquartile range 27·0-105·6) per 1,000 patient-days was reported in the European Region in 2020.[12]

Blood cultures were processed at the participating hospital laboratories using automated systems, either BacT/ALERT® (bioMérieux SA, Marcy I'Etoile, France) or BACTEC™ (BD Biosciences, Sparks, USA). All laboratories performed bacterial identification using VITEK® MS or VITEK® 2 (bioMérieux SA) or MALDI-TOF (Bruker, Bremen, Germany). Susceptibility testing was performed in accordance with CLSI guidelines using VITEK® 2 (bioMérieux SA) or BD Phoenix™ (BD Biosciences) automated systems or by the disc diffusion method.

Definitions

We defined the date of the positive blood culture as the date that the blood was drawn. BSI onset was defined as the date of the first positive blood culture. Growth of the same organism within 14 days was considered the same BSI event and growth of the same organism after 14 days was considered a new event.[13] We defined a BSI as polymicrobial if an additional sentinel organism was isolated within 5 days of the first organism. Growth of a different organism after 5 days was considered a new event.[14] BSIs were classified as community-onset (CO) if the first positive blood culture was taken during the first 3 days of hospitalization, and HO if the first positive blood culture was taken on or after the fourth day, as per CDC guidance for HO LabID events.[13] The antibiotic resistance profile of each event was determined based on the antibiogram of the first culture. BSIs were defined as drug-resistant if at least one of the organisms fulfilled the following criteria: oxacillin or cefoxitin resistance for *S. aureus*, vancomycin or teicoplanin resistance for *E. faecalis* and *E. faecium*, extended-spectrum cephalosporin (3rd and 4th generation) resistance for *E. coli* and *K. pneumoniae*, and non-susceptibility to imipenem or meropenem for *E.coli, K. pneumoniae, A. baumannii* and *P. aeruginosa*. *E. coli and K. pneumoniae* were considered resistant to extended-spectrum cephalosporins if they were resistant to at least one drug in that class.

Mortality outcome

We examined all-cause mortality at 30 days and 1 year from BSI onset. For calculations of mortality, only the first event of BSI for each patient was included.

Statistical analysis

We summarized continuous variables by mean and standard deviation (SD), and categorical variables by proportion and 95% confidence interval (CI). Mortality rates were directly standardized to the Global Burden of Disease (GBD) reference population.[15] We calculated proportionate mortality as deaths following BSI divided by all deaths in Israel in 2018. For this calculation, only BSI events from 2018 were included.

We constructed Kaplan-Meier (KM) curves and used the log-rank test to compare survival between categories of age, sex, place of onset and drug resistance. We used Cox proportional hazards regression to compare the hazard of death between age groups in patients with BSI and the hazard of death following BSI between age groups in the total adult population. For the latter comparison, we simulated the Israeli population according to the age distribution in the years 2018–2019.

YPLL were calculated as the sum of years between age at death and expected age of death in Israel, by age and sex, taken from the CBS life tables. Age-standardized YPLL was calculated for 2018 only using the GBD reference population and GBD life expectancy tables.[15] We calculated the 95% CI for YPLL, by first deriving the 95% CI for the mean YPLL among patients who died and then multiplying its boundaries by the number of patients who died. The 95% CI for the standardized YPLL was calculated in the same manner, except that the standard deviation for the mean YPLL was calculated for grouped data, considering each age interval as a group and using the mean standardized YPLL for each group.

All mortality calculations omitted patients whose UID was missing or invalid, as they could not be matched to the death registry. Because we had mortality data only through April 2020, BSIs from May 2019 onward were not included in the calculations of 1-year CFR, mortality rate and YPLL.

Our analyses considered only the first BSI in calculating mortality, but death within 1 year could have been caused by a repeat BSI closer to the time of death. Therefore, we performed a sensitivity analysis, in which we calculated 1-year CFR only for patients without recurrent BSI within a year. The p-value for the sensitivity analysis was obtained by the chi square goodness of fit test.

All analyses were performed using SAS base version 9.4.

Ethics

This study was approved by the jurisdictional Institutional Review Board (IRB). The requirement for informed consent was waived for this analysis of national surveillance data.

Role of the funding source

No funding was received.

Results

Description of BSI events and incidence

A total of 25,376 BSIs by eight sentinel bacteria in 21,811 adults were reported in 2018-2019. (The mean adult population in those years was 6,068,580). Mean age was 71·2 (SD 16·6) years. For the 25,263 episodes for which the patient's sex was listed, 13,343 (52·8% [95% CI: 52·0-53·2]) were male. BSIs were CO in 17,290 (68·1% [67·6-68·7]) events and HO in 6,962 (27·4% [26·9-28·0]) events. The other 1,124 (4·4% [4·2-4·7]) events were unclassified (missing admission date).

The most common pathogen was *E. coli* (10,287 events, 40·5% [39·9-41·1]), followed by *S. aureus* (3,925, 15·5% [15·0-15·9]) and *K. pneumoniae* (3,760, 14·8% [14·4-15·3]); 1,663 events (6·6% [6·2-6·9]) were polymicrobial. The distribution of pathogens differed by sex and by place of onset (Figure 1 and Table S1). The onset of *E. coli* BSI was in the community in 8,444 events (48·8% [48·1-49·6] of all CO-BSIs) and in the hospital in 1,349 events (19·4% [18·4-20·3] of all HO-BSIs). *K. pneumoniae* was the predominant pathogen in HO-BSIs (1,361 events, 19·5% [18·6-20·5]). A total of 8,121 BSIs were classified as drug-resistant (32·0% [31·4-32·6] of all events). Drug-resistant BSI comprised 4,745/17,290

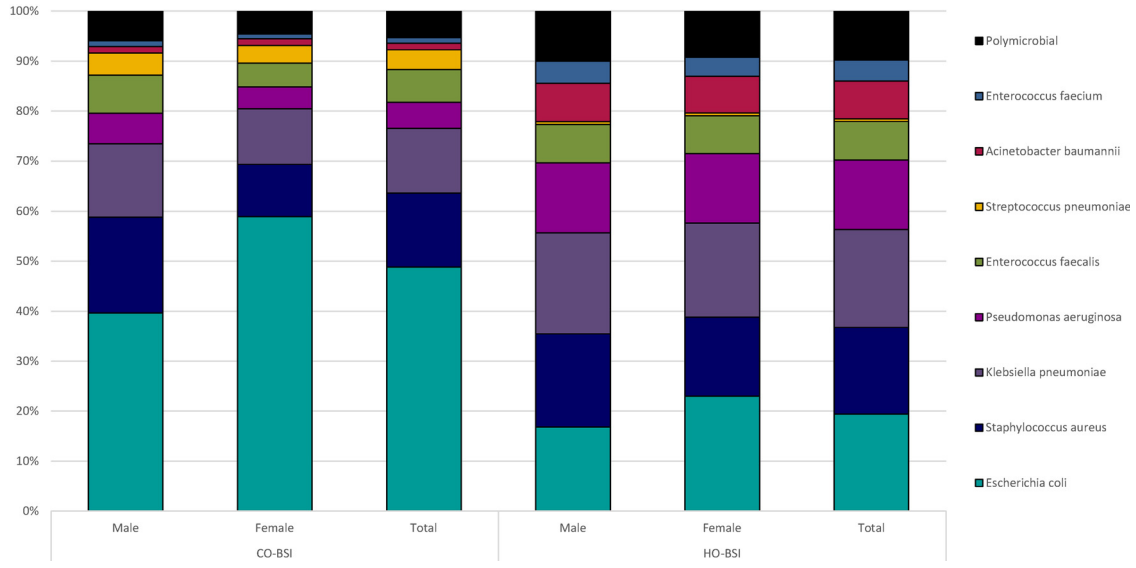


Figure 1. Pathogen distribution in bloodstream infections by eight sentinel bacteria, by sex and place of onset, Israel, 2018–2019. CO: community onset; HO: hospital onset.

Note: Polymicrobial refers to the presence of more than one of the eight sentinel bacteria.

(27·4% [26·8-28·1]) CO-BSIs and 3,072/6,962 (44·1% [43·0-45·3]) HO-BSIs.

The annual incidence of BSI was 209·1 BSIs (95% CI 206·5–211·7) per 100,000 adult population. Table S2 summarizes the pathogen-specific incidence of BSI by sex and place of onset. Incidence increased exponentially with age (Figure 2). The overall incidence was higher in males (225·2 BSIs [221·4-229·0] per 100,000), than in females (191·9 BSIs [188·5-194·4] per 100,000), with an IRR of 1·2 (1·1-1·2). However, the male to female ratio varied with age: in younger adults (18-39 years) the incidence was lower in males than in females (IRR 0·6 [0·5-0·6]), while males were at higher risk at ages ≥40 years (IRR 1·29,]1·26-1·33]) (Table S3).

CFR and mortality rate

Mortality data were available for 90% of patients (19,650/21,811 for 30-day mortality and 12,948/14,474 patients with 1 year of follow-up for 1-year mortality). The CFR was 25·6% (25·0-26·2) at 30 days and continued to rise up to 46·4% (45·5-47·2) at 1 year. The CFR was higher among males than females; at 30 days 27·4% (26·6-28·3) vs. 23·6% (22·7-24·4) and at 1 year 49·8% (48·6-51·0) vs. 42·6% (41·3-43·8) (RR=1·2 [1·1-1·2] for both 30-day and 1-year CFR). Pathogen-specific CFR, by sex and place of onset, is presented in Tables S4–S5. The CFR increased with age (Figure 3 and Tables S6-S7). The hazard of death increased by 30% for each additional decade of age (HR=1·30 [1·27-1·34]).

The annual mortality rate was 41·4 deaths (40·3-42·6) per 100,000 population for 30-day mortality and 74·6 deaths (72·7-76·4) per 100,000 for 1-year mortality. The mortality rate per 100,000 was 1·3-fold higher among males than females; 46·6 (44·8-48·3) vs. 36·0 (34·5-37·5) at 30 days and 84·0 (81·1-86·9) vs. 64·2 (61·8-66·7) at 1 year. The mortality rate per 100,000 population increased exponentially by age (HR=2·6 per decade [2·5-2·6]) (Figure 3 and Tables S6-S7). The annual age-standardized mortality rate (per 100,000) was 28·0 (27·2-28·8) for 30-day mortality and 50·8 (49·7-51·9) for 1-year mortality.

The 1-year survival curve of patients with BSI, stratified by age, is presented in Figure 4. In all age groups, survival continued to decline for a year after the acute event. The proportion of deaths occurring within 30 days vs. those occurring between 30 days and 1 year was similar across age groups, with the exception of patients ≥90 years, in which a higher proportion of deaths occurred within 30 days (62·7% [59·5-65·8] for patients ≥90 years vs 55·4% [54·0-56·7] for all other age groups combined) (Table S8).

Proportionate mortality

In 2018 there were 43,450 deaths among adults in Israel. For the 9,669 patients with BSI in 2018 for whom we had mortality data, 2,457 died within 30 days and 4,427 died within a year. Therefore, BSI proportionate mortality was 5·7% (5·4-5·9) for 30-day mortality and 10·2% (9·9-10·5) for 1-year mortality.

YPLL

Each patient with BSI who died lost on average 13·2 (SD 9·8) years of potential life. BSIs (regardless of outcome)

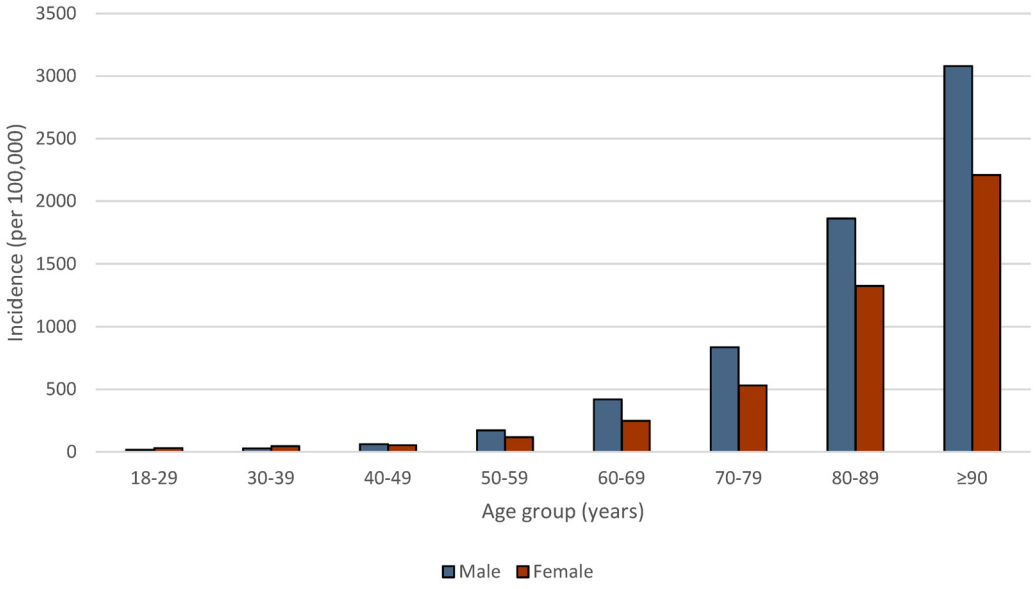


Figure 2. Annual incidence (cases/100,000 population) of bloodstream infections by eight sentinel bacteria in adults, by sex and age group, Israel, 2018-2019.

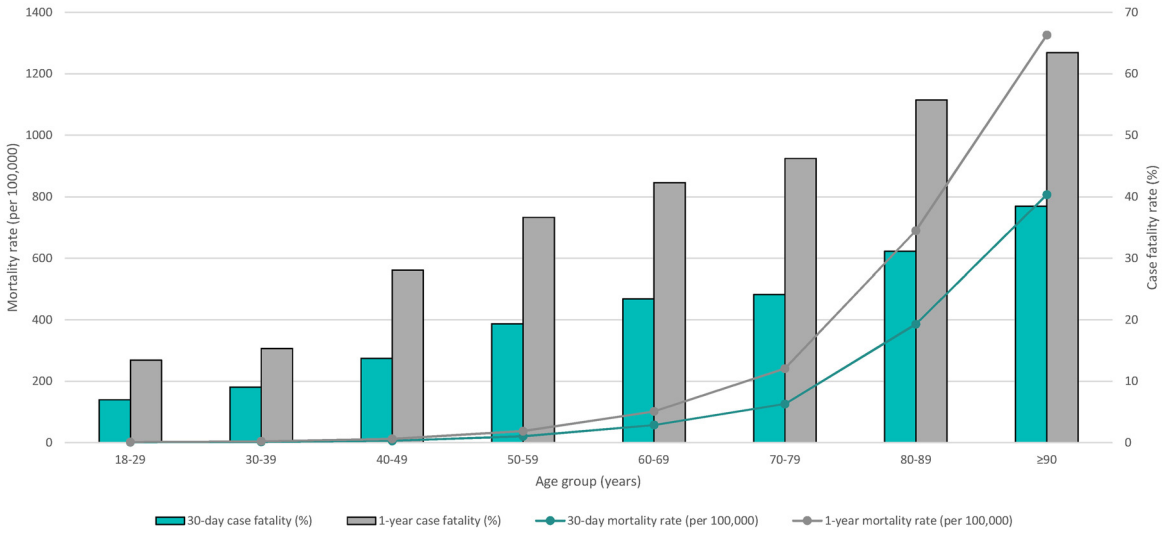
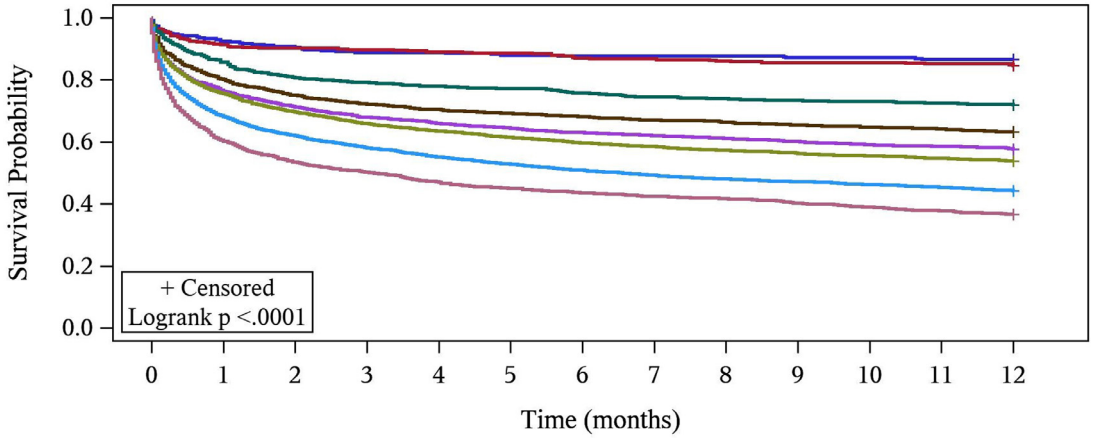


Figure 3. Thirty-day and 1—year case fatality rate and mortality rate (per 100,000) of bloodstream infections by eight sentinel bacteria, by age, Israel, 2018-2019.

led to an average YPLL of 6·2 (SD 9·4) years, i.e., preventing one case of BSI saves on average 6·2 potential life years. The annual age-standardized YPLL rate (per 100,000 population) was 548·7 (529·5-568·0) for 30-day mortality and 1,012·6 (986·9-1,038·3) for 1-year mortality.

Place of onset and drug resistance

Of all BSI-associated deaths within 1 year, 33·8% (32·6-35·1) occurred in HO-BSI (an average of 252 episodes [241-263] per 1,000,000 population per year), and 36·7% (35·5-38·0) occurred in drug-resistant BSI (an



18-29	357	324	317	313	313	311	309
30-39	437	394	389	380	376	374	371
40-49	616	498	480	467	455	450	444
50-59	1121	840	790	764	744	726	710
60-69	2330	1664	1536	1469	1425	1378	1349
70-79	3099	2164	1968	1850	1773	1721	1669
80-89	3599	2235	1983	1833	1729	1665	1596
90<=	1389	744	655	605	579	541	509

Figure 4. One-year survival of patients with bloodstream infections by eight sentinel bacteria, by age, Israel, 2018—2019.

average of 274 episodes [263-285] per 1,000,000 population per year). The latter translates into an age-standardized mortality rate of 19·0 (18·3-19·7) per 100,000. The distribution of BSIs, deaths within 1 year, and YPLL by place of onset and drug resistance is presented in Figure 5A. HO-BSI represented 27·4% (26·9-28·0) of BSI events, 33·9% (32·6-35·0) of deaths, and 39·9% (39·5-40·2) of YPLL. HO-BSI by drug-resistant bacteria represented 12·1% (11·7-12·5) of all BSIs, 15·6% (14·7-16·5) of deaths and 18·4% (18·1-18·7) of YPLL. The average (SD) YPLL for an adult with BSI (i.e., potential life years saved by preventing one case of BSI) was 4·6 (8·2) years if the BSI was CO and not drug resistant, 5·6 (8·0) years if CO and drug resistant, 9·2 (11·4) years if HO and not drug resistant, and 11·3 (11·9) years if HO and drug resistant. One-year survival was lower for patients with HO-BSI (36·1% [34·1-37·8]) compared to CO-BSI (59·6% [58·6-60·6[). One-year survival was lower for drug-resistant BSI vs. susceptible BSI, whether CO (48·8% [46·8-50·9] vs. 63·3% [62·1-64·4]) or HO (27·1% [24·7-29·5] vs. 42·3% [40·0-44·5]) (Figure 5B).

Sensitivity analysis

Sensitivity analysis excluding 3,228 patients with recurrent episodes of BSI within a year (22·3% of the total 14,474 patients with a 12 months follow-up) had a small effect on mortality: the 1-year CFR declined 1.5 percentage points, from 46·4% (45·5-47·2) to 44·9% (44·0-45·8) (p=0·003).

Discussion

We studied adult patients with BSI caused by eight sentinel bacteria, comprising approximately 70% of all BSIs. We found that nearly 50% of the affected patients died within 1 year. Death of an affected patient led to an average loss of 13·2 potential life years, and each event of BSI led to an average loss of 6·2 potential life years. The annual mortality rate was 74·6 per 100,000 population; these deaths accounted for approximately 10% of all deaths in Israel, and resulted in an estimated loss of 1,012·6 potential years of life per 100,000 population. The study results demonstrate that BSIs are among the most devastating acute conditions, with dramatic clinical, public health, and societal impacts. These impacts of BSI are not recognized by the public and by decision-makers, and may be underestimated by clinicians. This lack of awareness leads to lack of resources and efforts to prevent BSIs and their grave consequences.

Mortality statistics are often presented by ranking causes of death. Data are based on the underlying cause of death indicated on the death certificate, according to predefined rules. This process is prone to multiple biases.[16] One bias that leads to under-recognition of BSI as an important cause of death is that septicemia is often listed as the cause of death, deflecting attention from BSI itself to one of the clinical manifestations of severe infection.[17] Our study was based on a national surveillance database of BSIs cross-referenced with patients' death dates retrieved from the national death registry. This enabled us to overcome the limitations related to recording cause of death, and provided a more objective estimation of mortality following BSI. Our surveillance included only eight sentinel bacteria. These organisms rank among the top ten most common organisms isolated from blood cultures in the SENTRY surveillance program.[6] However they are responsible for approximately 70% of all BSIs in Israel. Thus, the data presented here underestimate the incidence and deaths from BSI. While the incidence of BSI by all pathogens can be extrapolated (i.e., by multiplying the observed number of BSIs by a factor of 1·4), the CFR varies by pathogen and therefore multiplication is too simplistic and may not yield an accurate estimate.

Population-based studies that are based on validated laboratory-based surveillance of BSI, preferably from the entire country, are the gold standard for estimating the incidence of BSI.[18] Previous articles from only two countries reported on the nationwide incidence of BSI. These reports were not restricted to specific pathogens or specific age groups. In England, Wilson et al. reported a rate of 189 BSIs per 100,000 in 2008.[19] In Finland, the incidence rose from 150 per 100,000 in 2004 to 309 per 100,000 in 2018.[4] In comparison, we found an incidence of 209 per 100,000 which included only eight pathogens and only adults, or approximately 300 per 100,000 adults if BSIs caused by all pathogens were captured. These results support the observation that BSI incidence is rising over time, driven, at least in part, by the rise in antibiotic resistance.[7] Differences in the definition of BSI episodes between studies, such as a 2-day window for polymicrobial BSI (vs. 5 days in our study) and a 30-day time window for a new event (vs. 14 days in our study), may also explain differences in the incidence reported by different studies.

The reported CFR of BSI in previous population-based studies considered mainly short-term mortality (i.e., in-hospital or within 30 days) and ranged between 13-23% (including both CO- and HO-BSI).[2,4,20–24] Long-term mortality following BSI has been reported only from Calgary, Canada and from Denmark. The study from Canada reported a 1-year CFR of 28% in adult patients with BSI.[25] Two regional studies in Denmark reported a 1-year CFR of 41·4% and 39·7%.[26,27] To our knowledge, our study is the first to look at 1-year mortality following BSI by key bacterial pathogens at the national level, and therefore provide a comprehensive assessment of the long-term survival following BSI. We showed that in all age groups, between 50 and 60% of the deaths occurred within 30 days, but survival continued to diminish until 1 year after the BSI event. Leibovici postulated that delayed mortality following bacteremia may be related to the direct consequences of

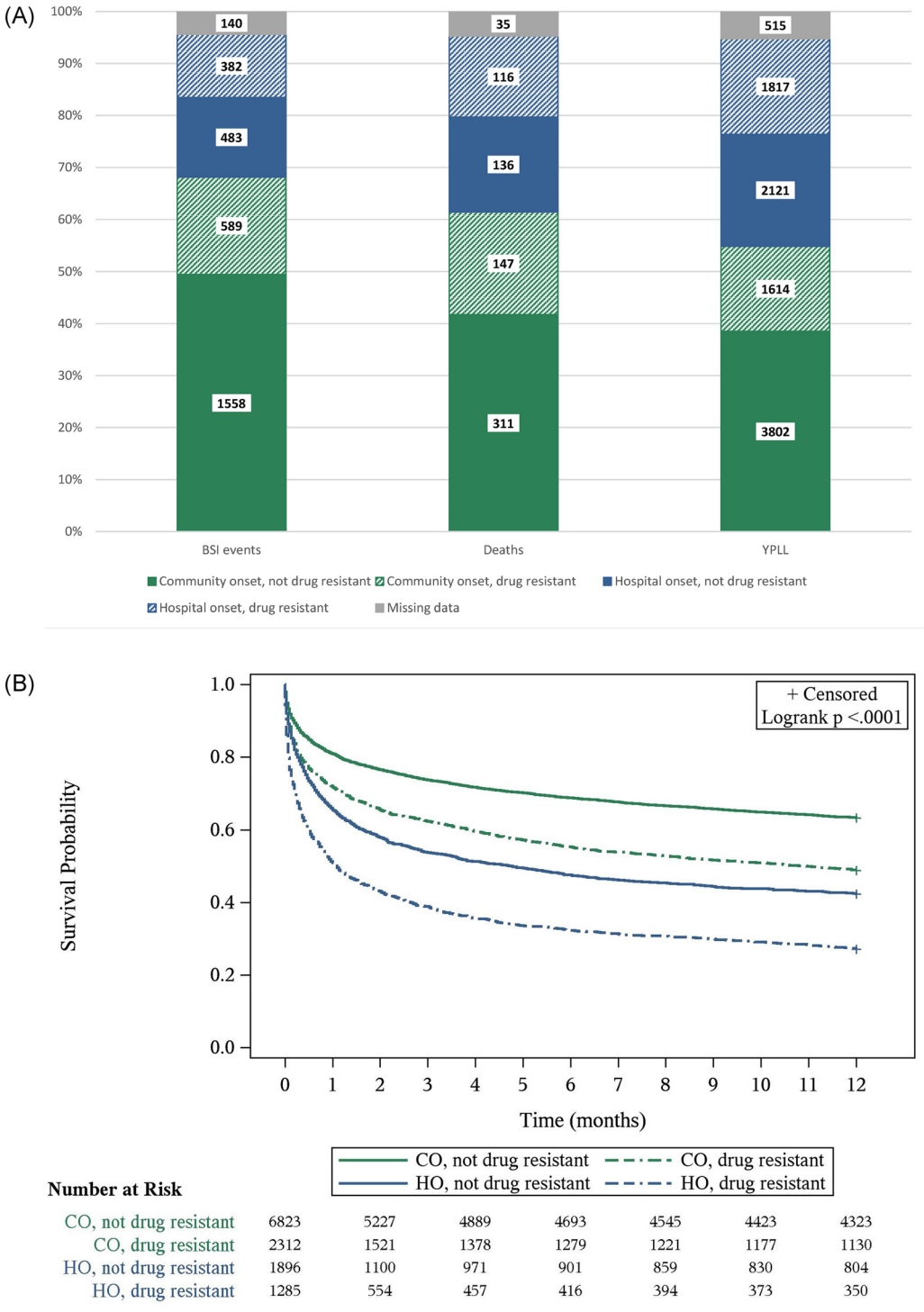


Figure 5. Bloodstream infection (BSI) events and outcomes by place of onset and drug resistance, Israel, 2018-2019. A) Distribution of BSI events, deaths within 1 year, and years of potential life lost (YPLL). (Numbers are per 1 million population) B) One-year survival. CO: community onset; HO: hospital onset.

infection (e.g., relapse or metastatic complication), an interaction with exacerbation of underlying disorders (e.g., cognitive and functional decline), or indirect consequences (as with other acute events).[28] More research is needed to assess the reasons for increased long-term mortality after bacteremia, and whether

reasons differ between age groups. This knowledge is necessary in order to formulate appropriate interventions to minimize these sequelae.

Our calculation of the age-standardized BSI-associated mortality rate and YPLL rate enabled us to compare the burden of BSI to other acute events as presented in the GBD report.[15] The age-standardized mortality rate following BSI in Israel (28·0 per 100,000 for 30-day mortality or 50·8 for 1-year mortality) is comparable to the global death rate from ischemic stroke (36·6 per 100,000), while the Israeli BSI YPLL rate (548·7 for 30-day mortality or 1,012·6 for 1-year mortality) is even higher than the global YPLL rate for ischemic stroke (521·8 per 100,000). This is worth noting because BSI has gained much less attention than ischemic stroke.[5] Attention motivates actions, and actions lead to results, as happened with stroke prevention and treatment: successful implementation of preventive strategies led to a dramatic reduction in stroke incidence in high-income countries.[29] For BSI, efforts have focused primarily on preventing intensive care unit (ICU)-acquired BSI, and particularly central line-associated BSI.[30] However, most BSIs begin outside the hospital (68% in our study) or in non-ICU wards.[31] Our findings should prompt decision-makers to direct attention and resources to BSI prevention. Similarly, advances in early diagnosis and better treatment may improve in-hospital CFR after BSI.

The proportion of drug resistance among BSI pathogens is increasing, both in community and in nosocomial events.[32] We found that HO-BSI, and particularly HO-BSI by drug-resistant bacteria, contributed 50% more to YPLL than to BSI incidence. Thus, interventions targeting these high-risk events are particularly warranted. We estimated the age-standardized mortality rate following drug-resistant BSI to be 19·0 per 100,000, concurring with the GBD's estimates of antimicrobial resistance.[33]

This study has several strengths. First, our database was based on a reliable nationwide surveillance system of positive blood cultures from all Israeli hospitals, including admission dates and AST. We used strict definitions of BSI, HO-BSI and drug-resistant BSI. Second, we were able to accurately track deaths after discharge, so that mortality could be assessed up to one year after BSI. Third, we calculated both mortality rate and YPLL rate, and were able to compare these estimates to the global burden of other diseases.

This study also has several limitations. We might have underestimated the true burden of BSI for the following reasons: 1) Surveillance covered eight sentinel bacteria, which represent 70% of all BSIs. 2) BSIs may have gone undetected if blood cultures were not taken or were taken after the start of antibiotic treatment. 3) Data on mortality were not available for all patients. On the other hand, we might have overestimated the burden of BSI for other reasons: 1) We analyzed crude mortality and could not establish if death was directly related to the infection or to the emergence or exacerbation of other conditions. 2) We did not have data on comorbidities, which may be more prevalent among patients with BSI. If these comorbidities are associated with shorter life expectancy, then we may have overestimated YPLL. Another limitation is that we could not distinguish between community-acquired BSI and healthcare-associated BSI (e.g., BSI acquired in a nursing home or outpatient dialysis center). This may have led to overestimation of the incidence, mortality and YPLL associated with CO-BSI.

In conclusion, BSI is associated with grave long-term consequences: nearly 50% of affected patients die within 1 year. The burden of BSI, which is similar to or even higher than ischemic stroke, justifies its inclusion as one of the most important causes of death. Attention and resources should be directed to prevention, as well as improved treatment of BSI and follow-up care.

Contributors

YC and VS designed the study. VS wrote the original draft of the manuscript. LW performed the statistical analysis. ET assisted in analyzing data and writing the manuscript. SFF, AN and PS assisted with data curation and methodology. MJS supervised the research. VS and LW directly accessed and verified the underlying data. All authors reviewed and approved the final manuscript.

Data sharing statement

The NIARIC's BSI database is a governmental database to which access is restricted by Israeli regulations.

Declaration of interests

Y.C. has received grants and personal fees from MSD, Pfizer, Roche, Qpex Pharmaceuticals, and Spero Therapeutics. All other authors report no potential conflicts of interest.

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Supplementary materials

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