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SEPSIS IN THE ICU (J LIPMAN, SECTION EDITOR)

# Challenges to Reporting the Global Trends in the Epidemiology of ICU-Treated Sepsis and Septic Shock

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## Abstract

**Purpose of Review** It is widely believed that the epidemiology of sepsis and septic shock treated in the intensive care unit (ICU) is changing. However, quantifying changes in occurrence and outcomes of ICU-treated sepsis and septic shock are challenged by a number of factors related to study designs as well as varied local resource availability and practices. The authors conducted a structured literature review to examine contemporary studies reporting trends in the prevalence, incidence and case-fatality rates of ICU-treated sepsis and septic shock around the world and further attempted to extrapolate the recent epidemiological trends.

**Recent Findings** During 2015–2020, 13 observational studies with heterogenous methodologies were published from predominantly high-income countries that examined selected cohorts with ICU-treated sepsis, sepsis with end-organ failure (previously known as severe sepsis) and septic shock. The prevalence of sepsis and sepsis-related diagnoses ranged widely from 4.7–42.2% of ICU admissions. The population incidence varied widely between 88 and 370 cases per 100,000 for sepsis and 19 and 79 cases per 100,000 for septic shock. Mean case-fatality rates (deaths per number of cases, %) reported primarily as in-hospital deaths reduced from approximately 40–50% reported in previous years, to 30–40% in the past 5 years. There was a lack of recent studies specifically examining mortality at the population level.

**Summary** Contemporary studies have observed wide variation in prevalence and incidence of sepsis and septic shock along with reports of static or decreasing case-fatality rates, but we are not able to make generalised commentary on global trends from the results of existing studies. Further data from ICUs in low-income and middle-income countries is needed, and well-designed, consistent population-based studies are required in order to establish whether the burden of sepsis and septic shock is changing.

**Keywords** Sepsis · Septic shock · Severe infection · Intensive care unit · Epidemiology · Mortality

## Introduction

Understanding the burden of sepsis and septic shock in the intensive care unit (ICU) and monitoring for changing epidemiology is paramount for prioritising future resource and research allocations. On a global scale, sepsis resulting in shock and/or end-organ failure has been established as the commonest indication for admitting patients to ICU and the leading cause of ICU mortality [1, 2]. Several population studies have concluded that the incidence of hospital-treated sepsis has been steadily increasing over the past three decades, along with a downtrend in acute case-fatality rates [3–6]. Although similar trends have been suggested for ICU-treated sepsis and septic shock, confirmation with observational research has proven to be challenging, as it is an area of study prone to several biases.

Making global generalisations from regional ICU-treated sepsis literature is limited by disease and population heterogeneity, varied mortality reporting practice and non-standardised case definitions. A major change in sepsis literature in the last 5 years has been the shift in the definition of sepsis and septic shock from the SEPSIS-2 to SEPSIS-3 criteria [1]. Furthermore, 'severe sepsis', an entity that had been well-studied in the ICU setting until 2016, was removed and henceforth replaced with 'sepsis with end-organ failure' in contemporary definitions [1, 7, 8]. Another major issue is the

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differing regional practice paradigms, such as the varied thresholds for ICU admission between countries, which may be driven by differing ICU bed capacities and other resources around the world. Even within jurisdictions, management trends in other disease entities requiring ICU-level treatment may affect bed availability for patients with sepsis and in turn influence apparent rates of disease.

The goal of this report was twofold; firstly, it was to present a structured review of epidemiological studies focused on the prevalence, incidence and mortality outcomes of ICU-treated sepsis and septic shock in adults published in the last 5 years. Secondly, the authors aimed to use the existing literature to make generalised statements about the global trends for the aforementioned epidemiological determinants.

## Methods

PubMed® (2015–2020) was initially searched using the following Medical Subject Heading terms on 6 October 2020: 'sepsis' OR 'septic shock' OR 'severe sepsis' OR 'bloodstream infection' OR 'meningitis' OR 'pneumonia' OR 'urosepsis' OR 'abdominal infection' OR 'cellulitis' AND 'intensive care' OR 'ICU' AND 'epidemiology' OR 'mortality' OR 'death' AND 'trend'. Observational studies, clinical trials, clinical studies and case reports involving human patients aged ≥ 18 years were included. Studies that reported on mixed hospital and ICU cohorts were excluded.

Analysis was primarily descriptive and utilised a narrative format. Given the heterogeneity of the study designs and study populations, quantitative mathematical quantitative summary statistics were not calculated. Individual results were summarised where appropriate. Prevalence was defined as the number of cases out of all ICU admissions during the study period and reported as a percentage and incidence as the number of new cases amongst 100,000 population at risk over the study period. Case-fatality was defined as the percentage of deaths out of numbers of cases treated in the ICU and the incident mortality as deaths per 100,000 population at risk.

## Results

### Contemporary Studies (2015–2020)

We included 13 studies published between 2015 and 2020 (observation years 2003–2018) and these are summarised in Table 1. A further five studies were excluded as ICU-specific results were not available from reported mixed ICU and hospital cohorts [22–26]. Out of the 13 studies of interest, all but one was a prospective design [9•]. Only one study was from a single-centred cohort [12]. Most studies were from Europe [10, 11, 13, 14, 16, 17•, 20] or Asia [19, 21], with only one study each from Australia and New Zealand [9•], North America [12], South America [18] or Africa [15].

### Prevalence

Seven studies reported prevalence data for sepsis and septic shock at admission/during ICU stay [10–13, 18–20]. The study observation periods varied among a single-day [10, 18, 19], a month [13], 5 months [20], 7 years [11] and 8 years [12].

In the first of the three point-prevalence studies, the national daily prevalence of severe sepsis, as defined by the SEPSIS-2 criteria, treated in Polish ICUs was studied by Kubler et al. in two-single days in 2012 and 2013, respectively [10]. They observed a decrease by 4% of ICU beds [10]. This study was conducted as an online questionnaire to 320 accredited ICUs. However, responses were received from hospitals accounting for 50% of all Polish ICU beds in 2012 and only 30% in 2013 [10]. The intra-ICU difference in prevalence between the two study years was not reported to suggest how reduced participation may have impacted on the apparent reduced disease prevalence. In the second point-prevalence study, the SPREAD study was conducted in 317 ICUs in Brazil representing 12% of the total of that country [18]. Sepsis, as defined by SEPSIS-2, accounted for 30.2% of 2632 ICU admissions in a single day in 2014 [18]. In another similarly designed point-prevalence study involving 132 Turkish ICUs (10.4% of all Turkish ICU beds, over a single-day in 2016 found sepsis (based on SEPSIS-2 definition) accounted for 17.3% of 1499 ICU admissions and septic shock accounted for another 13.5% [19].

A month-long prevalence observation was reported in the German INSEP study, which found that sepsis with end-organ failure and septic shock accounted for 17.9% of 11,883 total ICU admissions combined between November and December 2013 [13]. The study divided the 133 ICUs involved into five strata categories based on overall hospital bed numbers and university affiliation. Pairwise testing found a 7.8% higher prevalence of sepsis with end-organ failure and septic shock in ICUs of non-university-affiliated hospitals compared to university-affiliated hospitals [13]. The authors concluded that this phenomenon was likely secondary to university hospitals having patients with sepsis treated in intermediate units not under the scope of their ICU-only observation [13]. However, they deemed it also plausible that university-affiliated hospitals are often tertiary trauma centres, where higher prevalence of trauma and neurological patients requiring ICU admission can offset the availability of beds for septic patients.

A 5-month-long observational cohort study out of 11 ICUs in Spain during 2011 was reported by Herran-Monge et al. [20]. A total of 262 cases of sepsis with end-organ failure and/or septic shock (both defined by the SEPSIS-2 criteria)

**Table 1** Epidemiological studies into ICU-treated sepsis, sepsis with end-organ failure and septic shock published between 2015 and 2020

| Reference | Publication year, country, design | Time frame | Sampling frame | No. of cases identified (% total ICU admissions if applicable) | % Hospital death |
|---|---|---|---|---|---|
| [9•] | 2015, Australia and New Zealand, retrospective | January 2000–December 2013 (14 years) | All cases in 172 ICUs | Sepsis - 109,663 (9.34%) | Sepsis - 36.1% (2000), 18.3% (2013) |
| [10] | 2015, Poland, prospective | 1 day in March 2012, 1 day in March 2013 | All cases in 320 ICUs | Sepsis - 1398 (50%) (2012), 860 (30%) (2013) | N/A |
| [11] | 2015, Poland, prospective | January 2003–December 2009 (7 years) | All cases of severe sepsis in 130 ICUs (2003–2007) and 40 ICUs (2008–2009) | Severe sepsis - 766 (2003), 337 (2009) | Severe sepsis -54% (2003), 46% (2009) |
| [12] | 2015, USA, prospective | January 2003–August 2011 (8 years, 7 months) | All cases in 1 ICU | 161 candidaemia sepsis and sepsis-related cases only; Sepsis - (27%), Severe sepsis - (31%) Septic shock - (40%) | Sepsis - 30% Severe sepsis - 44% Septic shock - 65% |
| [13] | 2016, Germany, prospective | November 2013–December 2013 (1 month) | All cases in 133 ICUs | Sepsis - 1503 (12.6%) | Sepsis - 40.4% |
| [14] | 2016, Czech Republic, prospective | January 2011–November 2013 (2 years and 10 months) | All cases of severe sepsis/septic shock in 17 ICUs | Sepsis/septic shock - 897 (4.7%) | Sepsis/septic shock - 40.7% |
| [15] | 2016, Rwanda, prospective | August 2013–October 2014 (14 months) | All cases in 2 ICUs | Sepsis- 176 (42.2%), Severe sepsis - 139 (33.3%) Septic shock - 81 (19.4%) | Sepsis - 64.8% Severe sepsis-71.2% Septic shock - 82.7% |
| [16] | 2017, Spain, prospective | January to December 2005 (12 months), January to December 2011 (12 months) | All cases of severe sepsis in 41 ICUs | Sepsis - 630 (2005), 718 (2011) | Sepsis - 44.0% (2005), 32.6% (2011) |
| [17•] | 2017, England, prospective | January 2011–December 2015 (5 years) | All cases in 189 ICUs | Severe sepsis - 189,243 (28.9%) Septic shock - 38,896 (5.9%) | Severe sepsis - 33% (2011), 30% (2015) Septic shock - 57% (2011), 56% (2015) |
| [18] | 2017, Brazil, prospective | 1 day in February 2014 | All cases in 317 ICUs | Sepsis - 794 (30.2%) | Sepsis - 55.7% |
| [19] | 2018, Turkey, prospective | 1 day in January 2016 | All cases in 132 ICUs | Sepsis - 163 (10.8%) Severe sepsis - 260 (17.3%) Septic shock - 203 (13.5%) | Sepsis - 31.2% Severe sepsis -55.7% Septic shock - 70.4 |
| [20] | 2019, Spain, prospective | February to June 2011 (5 months) | All cases of sepsis and/or septic shock | Severe sepsis and septic shock - 262 (14%) | Severe sepsis - 36.7% |
| [21] | 2020, Japan, prospective | December 2017–May 2018 (6 months) | All patients with suspected infection admitted to 22 ICUs | Sepsis - 530 (SEPSIS-2), 569 (SEPSIS-3), 501 (SEPSIS-2 or SEPSIS-3) | Sepsis - 21.7% (SEPSIS-2), 19.8% (SEPSIS-3) |

accounted for 14% of all ICU admissions, and this prevalence was not different to a cohort observation in 2002 [20].

Kubler et al. reported on a 7-year prevalence study from the Polish national severe sepsis registry using SEPSIS-1 definition from 2003 to 2009 [11]. Using an internet-based registry and online questionnaire, the author's encountered 4999 cases of sepsis with end-organ function from up to 130 ICUs at most participating in a given year. The registry only included patients with sepsis; thus, it did not report how prevalent sepsis was in the ICU as a percentage of all ICU admissions. Rather, the authors reported the prevalence of sepsis aetiology over the 7-year study period. Intra-abdominal infections accounted for 49% of cases, and surgical infections accounted for 56% of cases [11]. Gram-negative pathogens predominated in 58% of cases, gram-positive pathogens in 34% and fungi in 16% of cases [11].

An 8-year single-centre prevalence study of candidaemia sepsis was studied by Ng et al. in a USA-based ICU single-centre cohort study spanning 2003–2011 [12]. Over a study population of 16,074 ICU admissions, 161 candidaemia sepsis cases were identified of which 27% of these had sepsis and 40% septic shock [12].

## Incidence

Several studies have attempted to crudely estimate sepsis incidence rates through the use of prevalence data. In their previously mentioned study, Kubler et al. estimated incidence rates of 69 and 60 cases per 100,000 in Poland in 2012 and 2013, respectively [10, 11]. Similarly, the German INSEP study estimated combined sepsis with end-organ failure and septic shock accounting for 11.64 per 1000 ICU days or 51–95 per 100,000 person-years in 2013 [13]. The authors reported that this finding was comparable with a previous German cohort study conducted 10 years earlier where sepsis and septic shock accounted for 76 per 100,000 inhabitants [27]. The Brazilian SPREAD study calculated incidence from point-prevalence and length of stay, reporting that ICU sepsis incidence was 36.3 per 1000 patient-days [18]. This was then extrapolated to project a population incidence rate of 290 cases per 100,000. The authors reported that this projected population incidence rate was similar to meta-analysed hospital-based studies from high-income countries where the population incidence was 370 per 100,000 [28]. Herran-Monge et al. also estimated sepsis and/or septic shock incidence from prevalence data to account for 31 per 100,000 inhabitants in Spain/year [20].

Few contemporary studies have actually determined the incidence of sepsis and septic shock in populations, let alone reported how it has changed in recent years. Shankar-Hari et al. conducted a large-scale multicentre cohort observation to estimate the annual number of ICU admissions with sepsis and septic shock using both SEPSIS-2 and SEPSIS-3 definitions between 2011 and 2015 from 189 ICUs in England [17•]. The population at risk was determined through mid-year population estimates. Severe sepsis (SEPSIS-2) and sepsis (SEPSIS-3) accounted for a combined 33% of admissions to the 189 English ICUs over the 5-year study period population incidence increase for both from 88 to 102 cases per 100,000 person-years [17•]. In the case of septic shock, as per the SEPSIS-2 and SEPSIS-3 definitions, they accounted for 23.4% and 6% of admissions, respectively [17•]. SEPSIS-2 septic shock population incidence increased from 69 to 79 per 100,000 person-years. Contrastingly, a minimal increase in population incidence was reported with SEPSIS-3 septic shock—it accounted for only 19 per 100,000 person-years.

## Mortality Outcomes

Amongst the 13 studies included, all but one reported death outcomes [10]. Overall case-fatality rates for sepsis or septic shock were reported as 18.3 [9•]–82.7% [21]. Most of these studies were limited to assessment of in-hospital deaths only with data censored at discharge. These studies compared acute case-fatality rates between ICU patients with sepsis and ICU patients without sepsis [13], between sepsis and septic shock [12, 15, 17•, 19] and between sepsis definitions [9•, 13, 21]. Four studies reported temporal trends in case-fatality [9•, 11, 16, 17•].

Several studies compared the case-fatality rates between sepsis and septic shock cases with patients without these syndromes. The longitudinal German INSEP study reported that the ICU case-fatality rate of ICU-treated sepsis with end-organ failure or septic shock was 5.7 times greater than the ICU mortality rate amongst ICU-treated non-sepsis [13]. Similarly, the total hospital case-fatality rate in ICU-treated sepsis with end-organ failure or septic shock was 4.2 times greater than that in ICU-treated non-sepsis [13]. Defining septic shock by the SEPSIS-3 criteria led to a 6.6% higher ICU and hospital case-fatality than with the SEPSIS-2 definition [13].

Amongst the four studies that differentiated between sepsis and septic shock and reported outcomes separately, the latter was consistently associated with higher hospital case-fatality [12, 15, 17•, 19]. For instance, the study by Ng et al. from the USA found ICU-treated candidaemia sepsis resulted in 30% hospital case-fatality but septic shock resulted in 65% [12]. Similarly, a Rwandan study by Nzarora et al., involving 504 patients from the only two national ICUs between August 2013 and October 2014, found that sepsis and septic shock accounted for 64.8% and 82.7% hospital case-fatality, respectively [15]. The previously mentioned English study by Shankar-Hari et al. found that over 5 years, sepsis (SEPSIS-3) resulted in 31.8% hospital case-fatality and septic shock (SEPSIS-3) resulted in 55.5% case-fatality [17•]. The Turkish prevalence study by

Baykara et al. also showed that ICU-treated sepsis resulted in a 31.2% case-fatality but septic shock resulted in 70.4% case-fatality [19].

A Czech study by Uvizl et al. reported data on 1082 patients admitted to 17 ICUs over approximately 2 years with sepsis with end-organ failure or septic shock and found an average in-hospital mortality rate of 40.7% [14]. Patients transferred to the ICU from medical departments were associated with a 9.6% higher in-hospital mortality rate than those from surgical departments [14]. Receiving antibiotics within 1 h of arrival to the ICU was found to be associated with lower in-hospital mortality [14].

Abe et al. observed sepsis and septic shock across 22 ICUs in Japan, comparing outcome differences between patients diagnosed with sepsis defined by SEPSIS-2 and SEPSIS-3 [21]. A total of 618 patients with suspected infection were included, of whom 530 (85.8%) met the SEPSIS-2 definition and 569 (92.1%) met the SEPSIS-3 definition for sepsis. In-hospital case-fatality rates amongst patients with SEPSIS-2 and SEPSIS-3-defined sepsis were similar (21.7% and 19.8%, respectively). Patients exclusively identified with SEPSIS-2 or SEPSIS-3-defined sepsis had a 12.8% lower case-fatality. Patients who met SEPSIS-3 septic shock definition had 6.9% higher in-hospital case-fatality than those who met SEPSIS-2 septic shock definition.

Four of the included studies compared temporal trends in acute case-fatality rates, consistently reporting a reduction in hospital death rates with time [9•, 11, 16, 17•]. The Polish period prevalence study found sepsis with end-organ failure resulted in an 8% reduction in hospital case-fatality rates between 2003 and 2009 [11]. This trend was paralleled in a Spanish study by Sanchez et al. involving 41 Spanish ICUs, where sepsis with end-organ failure was associated with an 11.4% reduction in hospital case-fatality between 2005 and 2011 [16]. Similarly, the English study by Shankar-Hari et al. found that between 2011 and 2015, sepsis with end-organ failure was associated with a 3% reduction in hospital case-fatality, and septic shock was associated with a 1% reduction in hospital case-fatality [17•].

The only retrospective cohort study we included was by Kaukonen et al. and the authors reported the case-fatality outcomes for patients admitted with infection and end-organ failure to 172 mixed ICUs in Australia and New Zealand between 2000 and 2013 [9•]. Out of a total 109,663 ICU admissions with sepsis, 96,385 met the criteria of sepsis with systemic inflammatory response syndrome (SIRS) and 13,278 met the criteria of sepsis without SIRS [9•]. The rate of death in SIRS-positive sepsis patients significantly decreased by 17.8% between 2000 and 2013. Over that same period, in SIRS-negative patients, the rate of death decreased by 19.2%. These changes represented an annual rate of absolute decrease of 1.3% in each group, and a reduction in relative risk of 49.3% and 66.5%, respectively [9•].

Although most of the studies we identified reported case-fatality, none of the studies directly established the population mortality due to sepsis and septic shock. Kubler et al. crudely estimated a mortality rate of 65 per 100,000 in their prevalence study conducted in Poland [10, 29] and reported these in context with myocardial infarction and cancers of the lung, bronchi and trachea accounted at 49.4 and 58.6 deaths per 100,000, respectively [29].

## Discussion

The present report so far identifies and summarises the findings from recent observational studies from various regions and using varied methodologies to examine ICU-treated sepsis and septic shock. Based on the studies we recovered, sepsis and septic shock represent approximately one-quarter of ICU admissions and are associated with high hospital case-fatality rates. Although very limited, there is a suggestion that the occurrence and survival outcome of sepsis and septic shock may be simultaneously increasing in recent years. But the authors found that varied methodologies, resources and regional practices inevitably stifles our ability to make generalised statements about global epidemiological trends.

Quantifying the epidemiology of ICU-treated sepsis and monitoring changing trends is paramount to determining how we approach future clinical and research practices. On one hand, increasing sepsis incidence and/or mortality rates provides impetus for increased research funding, as well as optimisation of preventative and therapeutic interventions. On the other hand, decreasing incidence and/or mortality rates validate and promote further efforts at current initiatives such as the Surviving Sepsis Campaign [30] and may allow the reallocation of resources to other areas of potentially greater benefit. However, it must be emphasised that such use of data to guide decision-making is predicated on its validity.

It is widely believed that the incidence of sepsis and septic shock is increasing globally, and several factors have been deemed to contribute to this. The ageing of populations with increased rates of chronic co-morbidities predisposes a greater number of individuals for severe disease. Additionally, successes in ICU management of patients (i.e. severe trauma or post-cardiac arrest) may lead to a larger population of individuals at high risk for septic complications during convalescence [31]. Increasing rates of antimicrobial resistance may also be an important determinant [32].

The decreasing case-fatality rates observed in many studies may indicate improved ICU management and quality of care. But it may also be a result of a shifting population under study through the admission of larger numbers of less severely ill patients to ICUs who have an intrinsically better outcomes regardless of ICU-level interventions provided [14, 32].

**Table 2** Potential study design factors affecting the determination of occurrence and outcome of sepsis and septic shock

| Factor | Description | Potential effect |
|---|---|---|
| ICU bed availability | Variability in access to ICU beds may influence the threshold of admission decision to ICU. | Fewer beds mean only sicker patients admitted; therefore, incidence rates decrease and case-fatality rates increase. Bed availability is also affected by the occurrence of other disease entities requiring ICU admission. |
| ICU selection bias | Inclusion of selected ICUs in a study by means other than random selection | Tertiary academic ICUs may be more likely to participate and skew toward higher acuity and complexity of patients. Contrastingly, if a tertiary academic ICU provides trauma, burns and cardiothoracic services, there is potential to displace patients with sepsis to other non-tertiary ICUs excluded from studies. |
| Intermediate units | Some hospitals may have the capability to manage patients with ICU-worthy sepsis outside the ICU. | Limiting studies to ICU-treated sepsis fail to include occurrence and outcome data on patients who meet the criteria for ICU admission but are managed in intermediate units. |
| Case definitions | Differences in definitions such as SEPSIS2 versus SEPSIS 3 amongst studies | Use of new definitions will not be comparable to older studies. |
| Sampling bias | Need for biochemical information (lactate) in SEPSIS-3 definitions | Restricted access to lactate levels can lead to omission of potential sepsis cases. |
| Age factor | Population changes or differences with confounding variables such as age can impact occurrence data from a certain region | Lack of age adjustment can lead to studies showing higher incidence if older people who are increased risk live in an ICU catchment. |
| Database issues | Large, multicentre databases are at risk of having cases that are lost to follow-up, missing data or incorrect data entry | Data quality can be compromised—especially with some national studies that utilise online questionnaires to collect clinical information. Retrospective database audits also prone to missing data |
| Mortality outcome | Varied use of 30-day, ICU or in-hospital death between studies. | Potential underestimation of deaths by assessing death at shorter endpoints |
| Time-course variation | Patients are admitted to ICU at different points of their disease course. | Later admissions when patients are more unwell may potentially lead to reporting higher case-fatalities. Time-course variation also changes how disease duration is calculated. |
| Seasonal variation | Differences in caseloads, especially in point-prevalence studies at different times of the year | May have higher incidence of pneumonia in winter and diarrhoea in summer |

Study designs may influence the determination of sepsis and septic shock occurrence and outcome, and several considerations are summarised in Table 2. These may include the way cases are identified, how data are collected, how definitions are applied and how the results are expressed and reported [33]. The designs of studies included in this review varied considerably and included online questionnaires [10], national sepsis registries [11, 17•], hospital microbiology laboratory databases [12] and dedicated multicentre ICU sepsis patient databases [14–16, 18–21]. Time-course variability may play a major role in the determination of sepsis occurrence. Different patients meet the admission criteria for ICU at various points along the disease course that comprise the syndrome of sepsis. As such, cross-sectional studies of sepsis patients are less informative than studies that follow patients throughout their hospital and ICU admission course [8]. To some extent, even seasonal variability also has a role to limit our ability to extrapolate incidence from point-prevalence and aetiological origin—for instance, case-rates of pneumonia may increase in winter and diarrhoea in summer [8].

In an optimal study to define the occurrence and outcome of sepsis, all cases fulfilling an objective, pre-specified case definition would be prospectively identified amongst residents of a geographically defined population over a time period [34]. By including all cases, selection biases would be minimised [35, 36]. Furthermore, because the population at risk would be known (i.e. the census population of the area), incidence and mortality rates could be determined and standardised against a reference population for external generalisation [34]. This design standard, however, is often very difficult to achieve. Large national databases such as ANZICS APD and ICNARC, while limited by the routine variables collected, are able to approximate such designs and provide a standardised approach to case diagnosis [9•, 17•, 37•].

While the authors achieved their first objective to report the contemporary literature, we were unable to comment on general global epidemiological trends as there are several notable limitations in the existing literature that merit further discussion. The contemporary ICU-treated sepsis literature predominantly comes from high-income countries, which only represent a 13% minority of the world's population. Only a single study from a cohort in Rwanda, that housed two adult ICUs at the time of cohort observation in 2013, was representative of ICU practice in Africa [15]. To put this into perspective, the English study we reviewed, with only a national population five times the size of Rwanda, reported data from 189 ICUs [17•]. Thus, our understanding of sepsis and septic shock epidemiology is biased from a global perspective. Another consideration is that we focussed our review only on patients admitted to ICUs. Our intention in doing so was in part for practical reasons, the topic theme and our specialty interest. A substantial component of our review included prevalence or cross-sectional studies which are very limited designs [8]. Determination of crude incidence by using prevalence data as many papers in this review have done so is highly fraught with difficulty. It is also noteworthy that the studies we reviewed did not attempt to ascertain attributable mortality, and it must be recognised that while the acute cause of sepsis and septic shock is the 'precipitant,' many other factors including co-morbid illnesses play an important role in leading to a death outcome.

## Conclusion

In summary, there are many factors which may contribute to the changing prevalence, incidence and mortality outcomes associated with ICU-treated sepsis and septic shock. The authors are unable to make general statements about global trends with regard to these epidemiological determinants since the most recent literature includes heterogenous, yet problematic methodologies and are often reportings of region-specific findings. What would be useful are longitudinal population-based studies conducted in ICUs of high-income, medium-income and low-income countries across the globe in a standardised fashion in order to provide meaningful, high-quality epidemiological data to intensivists.

## Declarations

**Conflict of Interest** The authors declare no conflicts of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

## References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315(8):801–10.
2. Genga KR, Russell JA. Update of sepsis in the intensive care unit. J Innate Immun. 2017;9(5):441–55.
3. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med. 2003;348(16):1546–54.
4. Kumar G, Kumar N, Taneja A, Kaleekal T, Tarima S, McGinley E, et al. Nationwide trends of severe sepsis in the 21st century (2000-2007). Chest. 2011;140(5):1223–31.

5. Gaieski DF, Edwards JM, Kallan MJ, Carr BG. Benchmarking the incidence and mortality of severe sepsis in the United States. Crit Care Med. 2013;41(5):1167–74.
6. Bouza C, Lopez-Cuadrado T, Saz-Parkinson Z, Amate-Blanco JM. Epidemiology and recent trends of severe sepsis in Spain: a nationwide population-based analysis (2006-2011). BMC Infect Dis. 2014;14:3863.
7. Linde-Zwirble WT, Angus DC. Severe sepsis epidemiology: sampling, selection, and society. Crit Care. 2004;8(4):222–6.
8. Angus DC, Pereira CA, Silva E. Epidemiology of severe sepsis around the world. Endocr Metab Immune Disord Drug Targets. 2006;6(2):207–12.
9.• Kaukonen KM, Bailey M, Pilcher D, Cooper DJ, Bellomo R. Systemic inflammatory response syndrome criteria in defining severe sepsis. N Engl J Med. 2015;372(17):1629–38 **Large-scale international observational study conducted using data from the ANZICS APD**.
10. Kubler A, Adamik B, Ciszewicz-Adamiczka B, Ostrowska E. Severe sepsis in intensive care units in Poland–a point prevalence study in 2012 and 2013. Anaesthesiol Intensive Ther. 2015;47(4):315–9.
11. Kubler A, Adamik B, Durek G, Mayzner-Zawadzka E, Gaszynski W, Karpel E, et al. Results of the severe sepsis registry in intensive care units in Poland from 2003-2009. Anaesthesiol Intensive Ther. 2015;47(1):7–13.
12. Ng K, Schorr C, Reboli AC, Zanotti S, Tsigrelis C. Incidence and mortality of sepsis, severe sepsis, and septic shock in intensive care unit patients with candidemia. Infect Dis (Lond). 2015;47(8):584–7.
13. SepNet Critical Care Trials G. Incidence of severe sepsis and septic shock in German intensive care units: the prospective, multicentre INSEP study. Intensive Care Med. 2016;42(12):1980–9.
14. Uvizl R, Adamus M, Cerny V, Dusek L, Jarkovsky J, Sramek V, et al. Patient survival, predictive factors and disease course of severe sepsis in Czech intensive care units: a multicentre, retrospective, observational study. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2016;160(2):287–97.
15. Nzarora J BM, Riviello ED, Twagirumugabe T. Epidemiology and outcomes of sepsis in two intensive care units in Rwanda. American Journal of Respiratory and Critical Care Medicine. 2016;193(A3691).
16. Sanchez B, Ferrer R, Suarez D, Romay E, Piacentini E, Goma G, et al. Declining mortality due to severe sepsis and septic shock in Spanish intensive care units: A two-cohort study in 2005 and 2011. Med Int. 2017;41(1):28–37.
17.• Shankar-Hari M, Harrison DA, Rubenfeld GD, Rowan K. Epidemiology of sepsis and septic shock in critical care units: comparison between sepsis-2 and sepsis-3 populations using a national critical care database. Br J Anaesth. 2017;119(4):626–36 **Large-scale national observational study conducted using ICNARC standardised classification**.
18. Machado FR, Cavalcanti AB, Bozza FA, Ferreira EM, Angotti Carrara FS, Sousa JL, et al. The epidemiology of sepsis in Brazilian intensive care units (the Sepsis PREvalence Assessment Database, SPREAD): an observational study. Lancet Infect Dis. 2017;17(11):1180–9.
19. Baykara N, Akalin H, Arslantas MK, Hanci V, Caglayan C, Kahveci F, et al. Epidemiology of sepsis in intensive care units in Turkey: a multicenter, point-prevalence study. Crit Care. 2018;22(1):93.
20. Herran-Monge R, Muriel-Bombin A, Garcia-Garcia MM, Merino-Garcia PA, Martinez-Barrios M, Andaluz D, et al. Epidemiology and changes in mortality of sepsis after the implementation of surviving sepsis campaign guidelines. J Intensive Care Med. 2019;34(9):740–50.
21. Abe T, Yamakawa K, Ogura H, Kushimoto S, Saitoh D, Fujishima S, et al. Epidemiology of sepsis and septic shock in intensive care units between sepsis-2 and sepsis-3 populations: sepsis prognostication in intensive care unit and emergency room (SPICE-ICU). J Intensive Care. 2020;8:44.
22. Rhee C, Dantes R, Epstein L, Murphy DJ, Seymour CW, Iwashyna TJ, et al. Incidence and trends of sepsis in US hospitals using clinical vs claims data, 2009-2014. JAMA. 2017;318(13):1241–9.
23. Kim J, Kim K, Lee H, Ahn S. Epidemiology of sepsis in Korea: a population-based study of incidence, mortality, cost and risk factors for death in sepsis. Clin Exp Emerg Med. 2019;6(1):49–63.
24. Zhou J, Tian H, Du X, Xi X, An Y, Duan M, et al. Population-based epidemiology of sepsis in a subdistrict of Beijing. Crit Care Med. 2017;45(7):1168–76.
25. Huggan PJ, Bell A, Waetford J, Obertova Z, Lawrenson R. Evidence of high mortality and increasing burden of sepsis in a regional sample of the New Zealand population. Open Forum Infect Dis. 2017;4(3):ofx106.
26. Fleischmann-Struzek C, Mikolajetz A, Schwarzkopf D, Cohen J, Hartog CS, Pletz M, et al. Challenges in assessing the burden of sepsis and understanding the inequalities of sepsis outcomes between National Health Systems: secular trends in sepsis and infection incidence and mortality in Germany. Intensive Care Med. 2018;44(11):1826–35.
27. Engel C, Brunkhorst FM, Bone HG, Brunkhorst R, Gerlach H, Grond S, et al. Epidemiology of sepsis in Germany: results from a national prospective multicenter study. Intensive Care Med. 2007;33(4):606–18.
28. Fleischmann C, Scherag A, Adhikari NK, Hartog CS, Tsaganos T, Schlattmann P, et al. Assessment of global incidence and mortality of hospital-treated sepsis. Current Estimates and Limitations. Am J Respir Crit Care Med. 2016;193(3):259–72.
29. Wojtyniak B, Jankowski K, Zdrojewski T, Opolski G. Regional differences in determining cardiovascular diseases as the cause of death in Poland: time for change. Kardiol Pol. 2012;70(7):695–701.
30. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med. 2008;36(1):296–327.
31. Nasa P, Juneja D, Singh O, Dang R, Arora V. Severe sepsis and its impact on outcome in elderly and very elderly patients admitted in intensive care unit. J Intensive Care Med. 2012;27(3):179–83.
32. Thompson K, Venkatesh B, Finfer S. Sepsis and septic shock: current approaches to management. Intern Med J. 2019;49(2):160–70.
33. Cecconi M, Evans L, Levy M, Rhodes A. Sepsis and septic shock. Lancet. 2018;392(10141):75–87.
34. Laupland KB. Incidence of bloodstream infection: a review of population-based studies. Clin Microbiol Infect. 2013;19(6):492–500.
35. Laupland KB. Population-based epidemiology of intensive care: critical importance of ascertainment of residency status. Crit Care. 2004;8(6):R431–6.
36. Steckelberg JM, Melton LJ 3rd, Ilstrup DM, Rouse MS, Wilson WR. Influence of referral bias on the apparent clinical spectrum of infective endocarditis. Am J Med. 1990;88(6):582–8.
37.• Kaukonen KM, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. JAMA. 2014;311(13):1308–16 **Another large-scale international observational study of ICU-treated sepsis using data from the ANZICS APD**.