BJA

British Journal of Anaesthesia, 119 (4): 626–36 (2017)

doi: 10.1093/bja/aex234
Advance Access Publication Date: 16 August 2017
Critical Care

Epidemiology of sepsis and septic shock in critical care units: comparison between sepsis-2 and sepsis-3 populations using a national critical care database

M. Shankar-Hari[1,2,3,*], D. A. Harrison[3], G. D. Rubenfeld[4] and K. Rowan[3]

[1]Guy's and St Thomas' NHS Foundation Trust, ICU Support Offices, 1st Floor, East Wing, St Thomas' Hospital, SE1 7EH, UK, [2]Division of Immunology, Infection and Inflammatory Diseases, Kings College London, SE1 9RT, UK, [3]Intensive Care National Audit & Research Centre, Napier House, 24 High Holborn, London WC1V 6AZ, UK and [4]Interdepartmental Division of Critical Care Medicine, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, D5 03, Toronto, Ontario M4N 3M5, Canada

*Corresponding author. E-mail: manu.shankar-hari@kcl.ac.uk

Abstract

Background: New sepsis and septic shock definitions could change the epidemiology of sepsis because of differences in criteria. We therefore compared the sepsis populations identified by the old and new definitions.
Methods: We used a high-quality, national, intensive care unit (ICU) database of 654 918 consecutive admissions to 189 adult ICUs in England, from January 2011 to December 2015. Primary outcome was acute hospital mortality. We compared old (Sepsis-2) and new (Sepsis-3) incidence, outcomes, trends in outcomes, and predictive validity of sepsis and septic shock populations.
Results: From among 197 724 Sepsis-2 severe sepsis and 197 142 Sepsis-3 sepsis cases, we identified 153 257 Sepsis-2 septic shock and 39 262 Sepsis-3 septic shock cases. The extrapolated population incidence of Sepsis-3 sepsis and Sepsis-3 septic shock was 101.8 and 19.3 per 100 000 person-years, respectively, in 2015. Sepsis-2 severe sepsis and Sepsis-3 sepsis had similar incidence, similar mortality and showed significant risk-adjusted improvements in mortality over time. Sepsis-3 septic shock had a much higher Acute Physiology And Chronic Health Evaluation II (APACHE II) score, greater mortality and no risk-adjusted trends in mortality improvement compared with Sepsis-2 septic shock. ICU admissions identified either as Sepsis-3 sepsis or septic shock and as Sepsis-2 severe sepsis or septic shock had significantly greater risk-adjusted odds of death compared with non-sepsis admissions ($P<0.001$). The predictive validity was greatest for Sepsis-3 septic shock.
Conclusions: In an ICU database, compared with Sepsis-2, Sepsis-3 identifies a similar sepsis population with 92% overlap and much smaller septic shock population with improved predictive validity.

Key words: sepsis; septic shock; intensive care; epidemiology; outcomes

In February 2016, a Task Force convened by the European Society of Intensive Care Medicine and the Society of Critical Care Medicine published new definitions for sepsis and septic shock (Sepsis-3).[1 2] Major differences between the new (Sepsis-3)[1 2] and old (Sepsis-2)[3] definitions will alter sepsis and septic shock epidemiology. The new sepsis definitions abandoned systemic inflammatory response syndrome (SIRS) criteria as the starting point for identifying sepsis, equated Sepsis-3 sepsis to Sepsis-2

Editorial decision: May 23, 2017; **Accepted:** June 21, 2017

Editor's key points

- Disease and syndrome definitions are somewhat arbitrary and differences in epidemiology can occur.
- The efficiency of medical research is enhanced when agreed disease and outcome criteria are used.
- Abandoning SIRS as the starting point for sepsis diagnosis does not alter the incidence as most patients with organ dysfunction also tend to have SIRS.
- Sepsis-3 septic shock is a high risk of death population.

severe sepsis[3] and, for the first time, provided specific criteria for operationalizing the definitions. Organ dysfunction was operationalized using the total Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score[1 4] and explicit criteria were proposed to define septic shock, harmonizing multiple criteria used in the literature.[2 5] Understanding the impact of changes in definitions on updated sepsis epidemiology is necessary to inform clinical care, future research and healthcare planning.

In this context, we tested the impact of the new sepsis definitions on epidemiology, by comparing Sepsis-2 severe sepsis/septic shock and Sepsis-3 sepsis/septic shock populations derived from the same high-quality national ICU database that covers 96% of the adult general ICUs and combined ICUs/high-dependency units in England. We compared the incidence, deaths, ICU and general population extrapolations, annual trends and predictive increment for acute hospital mortality of Sepsis-2 severe sepsis/septic shock and Sepsis-3 sepsis/septic shock over a 5 yr period between January 2011 and December 2015.

Methods

Data source

The Case Mix Programme is the national clinical audit for adult general ICUs in England. For consecutive admissions, trained data collectors collect sociodemographic, comorbidity and physiological data to precise rules and definitions, during the first 24 h following admission to ICU. Diagnostic data are determined clinically and coded using the hierarchical Intensive Care National Audit & Research Centre (ICNARC) Coding Method.[6] Collected data undergo extensive local and central validation prior to pooling into the Case Mix Programme Database (CMPD). Support for the collection and use of these data has been obtained under Section 251 of the National Health Service Act 2006 [approval number: PIAG 2–10(f)/2005].[7]

Case definitions

Our study evaluated sepsis and septic shock during the first 24 h following ICU admission. Sepsis-2 severe sepsis and septic shock have been operationalized in several different ways, whereas Sepsis-3 provided specific criteria, which we followed as closely as possible. We identified presence of infection from the reported primary (mandated) and secondary (optional) reasons for ICU admission, derived SIRS criteria and organ dysfunctions (based on SOFA score) using raw physiological and laboratory data from the first 24 h following ICU admission. For organs where the relevant physiology to define SOFA were not available, we derived organ dysfunction based on receipt of organ support, according to national Critical Care Minimum Dataset (CCMDS) definitions. As SOFA score categorizes organ function from 0 (normal) to 4 (most abnormal),[4] we used SOFA score $\geq$1 as organ dysfunction to define Sepsis-2 severe sepsis as proposed by Levy and colleagues[3] (page 1253). Our operationalizations of the Sepsis-2 and Sepsis-3 definitions are described in Table 1.

Analysis

After describing the Sepsis-2 and Sepsis-3 populations, we compared the trends in incidence, mortality and predictive validity of Sepsis-3 sepsis and septic shock. As unmeasured physiology was <5% in all sepsis case definitions data fields, we assumed unmeasured physiology to be normal. The primary outcome was all-cause acute hospital mortality. As missing data was <0.5% for the primary outcome, we performed complete case analyses in regression models, assuming missing data were missing at random, conditional on the model covariates.

Trends in incidence and extrapolations

We estimated the annual number of admissions to ICUs in England between January 2011 and December 2015 with sepsis and septic shock (by Sepsis-2 and Sepsis-3 definitions) by extrapolating the actual numbers for participating ICUs to the total number of ICUs in England for each year, as reported previously.[7] We converted these extrapolated numbers to population incidences (overall and by age categories and comorbidity status) using mid-year population estimates obtained from the Office for National Statistics.[8]

Trends in and risk factors for acute hospital mortality

We calculated unadjusted and adjusted trends in acute hospital mortality over the 5 yr study period for sepsis and septic shock (by Sepsis-2 and Sepsis-3 definitions) using logistic regression. Risk-adjusted trends were compared using four separate logistic regression models that adjusted for admission year, age, sex, ethnicity, severe co-morbidity [defined according to Acute Physiology And Chronic Health Evaluation (APACHE) II[9]] functional status, surgical status, illness severity (APACHE II acute physiology score[9]) and infection site.[7]

Assessment of predictive validity

We assessed the improvement in predictive validity both qualitatively, by comparing the difference in illness severity and mortality between the populations identified by Sepsis-2 and Sepsis-3, and quantitatively, using logistic regression models. For the logistic regression approach to be valid, the baseline model must use well-established risk predictors and outcomes as originally intended and the addition of the sepsis or septic shock category as a new predictor must improve model performance for the outcome predicted.[10] Thus, we derived a baseline model for acute hospital mortality, adjusted for admission year, age, sex, ethnicity, severe co-morbidity, functional status, surgical status and illness severity, using the overall population of all ICU admissions. Then, we compared the additional odds of dying from sepsis/septic shock compared with the non-sepsis population [adjusted odds ratios (OR)] and the increment in model fit using change in area under the curve (Δ-AUC), Bayesian Information Criterion (Δ-BIC) and Brier Scores when adding sepsis and septic shock (by Sepsis-2 and Sepsis-3 definitions) as new binary predictors within nested models.

Table 1 Operationalization of Sepsis-2 and Sepsis-3 definitions. *For defining Sepsis-2 septic shock, we operationalized the criteria used in the recent early, goal-directed therapy trials of hypotension or need for vasopressor therapy or serum lactate >4 mmol litre^{-1}.[32] †For defining Sepsis-2 and Sepsis-3 septic shock, we used highest blood lactate post-intensive care unit (ICU) admission and use of vasoactive drugs. The systemic inflammatory response syndrome (SIRS) criteria are detailed in the online supplement. For defining severe sepsis as per Sepsis-2 definitions, we followed the recommendations proposed by Levy and colleagues3 and we treated a Sequential Organ Failure Assessment (SOFA) score of 1 or more as organ dysfunction (page 1253 in Levy and colleagues).[3] As the baseline organ dysfunction is unknown in our study cohort, we assumed the baseline organ dysfunction was zero, as recommended in the Sepsis-3 consensus definitions (page 805 in Singer and colleagues)[1] and performed sensitivity analyses by excluding patients with a pre-existing comorbidity. We used a modified SOFA score to generate organ dysfunction. We derived respiratory, renal, cardiovascular, and haematological SOFA, as recommended by SOFA score categories, and recoded them as 0, 1 or ≥2 for each organ system. Neurological dysfunction was defined using Glasgow Coma Scale, with a score of 1 given for Glasgow Coma Score between 13 and 14 and a score ≥2 was for Glasgow Coma Score <13 and/or sedated/paralysed for the first 24 h. As we did not have bilirubin to define hepatic dysfunction, we used receipt of advanced liver support and coded that as hepatic SOFA score of ≥2. Advanced liver support is defined as acute on chronic hepatocellular failure requiring management of coagulopathy and/or portal hypertension (including liver purification and detoxification techniques). Cardiovascular dysfunction was derived as systolic blood pressure <90 mm Hg or mean arterial pressure <70 mm Hg or need for vasopressors to maintain blood pressure, identified by receipt of advanced cardiovascular support

Criteria	Sepsis-2	Sepsis-3
Infection	Reason for ICU admission	Reason for ICU admission
SIRS positive	Presence of two or more SIRS criteria	Not applicable
Organ dysfunction	SOFA score of 1 or more in any one organ system	SOFA score of 2 or more in any one organ system or SOFA score of 1 in two or more organ systems
(Severe) sepsis	Severe sepsis=infection AND SIRS positive AND ≥1 SOFA points	Sepsis=infection AND ≥2 SOFA points
Septic shock*†	Infection AND SIRS positive AND (cardiovascular SOFA ≥1 OR serum lactate concentration ≥4 mmol litre^{-1})	Infection AND cardiovascular SOFA ≥2 AND serum lactate concentration >2 mmol litre^{-1}

Sensitivity analysis

We performed two sensitivity analyses. First, we excluded patients with severe comorbidity, to account for the change in SOFA score of 2 required for operationalizing the Sepsis-3 criteria. The rationale for this analysis is that patients with comorbidity may have baseline organ dysfunction that could potentially contribute to SOFA score. Second, we reassessed all four regression models of predictive validity without including illness severity (APACHE II acute physiology score). The rationale for this analysis is that including illness severity in our original analyses may mask the incremental change in discrimination provided by the presence of organ dysfunction to diagnose sepsis.

All logistic regression models excluded readmissions of the same patient during the same hospital stay, used only admission day APACHE II acute physiology score for severity of illness adjustment (to avoid double weighting of organ dysfunction in models as the score includes respiratory, renal, hypotension and Glasgow coma score variables), were fitted with robust standard errors to account for clustering by ICU, and were reported as OR with 95% confidence intervals (CI). Reported P-values are two-sided and a P-value <0.05 was considered a statistically significant result. Continuous data were summarized as mean and standard deviation (SD), where normally distributed, and median and inter-quartile range, where not. Categorical data were presented as frequency and percentage. All analyses were performed using Stata/SE Version 14.2 (StataCorp LP, College Station, TX, USA).

Results

Descriptive comparison

Over the 5 yr study period, among 654 918 admissions to 189 adult general ICUs in England, there were 197 724 (30.2%) Sepsis-2 severe sepsis, 197 142 (30.1%) Sepsis-3 sepsis cases (Table 2) and 449 295 non-sepsis admissions (Supplementary Table S1). Among the sepsis cases, 189 243 met both definitions (92.0% of those meeting either definition) with 4.1% of Sepsis-2 severe sepsis cases not meeting stricter organ dysfunction criteria for Sepsis-3 and 4.0% of Sepsis-3 sepsis cases being SIRS negative. Among the sepsis admissions, there were 153 257 (77.5%) Sepsis-2 septic shock and 39 262 (19.9%) Sepsis-3 septic shock cases with 0.01% of Sepsis-3 septic shock cases being SIRS negative (Fig. 1). The distributions of age, sex, dependency status, ethnicity, presence of severe co-morbidity, surgical status and admission source were comparable between cohorts. Respiratory was the most common infection site and organ dysfunction in all cohorts with comparable distributions of other infection sites and organ dysfunctions. The acute illness severity, serum lactate concentrations and hospital mortality were higher in septic shock cohorts, with greatest severity in Sepsis-3 septic shock (Table 2; Fig. 2). Sepsis patients identified only by Sepsis-3 were older, with greater illness severity [APACHE II score mean (SD) 15.1 (7.2) *vs* 9.7 (3.9)] and higher mortality (22.3% *vs* 7.0%), when compared with those patients identified only by Sepsis-2 (Supplementary Table S2). The incidence of, and mortality from, Sepsis-2 severe sepsis, Sepsis-2 septic shock, Sepsis-3 sepsis and Sepsis-3 septic shock increased with age (Fig. 3).

Trends in incidence

The Sepsis-2 severe sepsis and Sepsis-3 sepsis accounted for a third of admissions to adult general ICUs in England over the 5 yr period. The extrapolated population incidence increased similarly for both from 88 to 102 per 100 000 person-years. The Sepsis-2 septic shock and Sepsis-3 septic shock accounted for 23.4% and 6.0%, respectively, of admissions to adult general

Table 2 Case mix characteristics for admissions to adult general intensive care units (ICU) in England with sepsis and septic shock (by Sepsis-2 and Sepsis-3 definitions). Adjusted OR (95% CI) refers to the additional risk of death because of sepsis or septic shock when compared with non-sepsis admissions using a fully adjusted logistic regression model. The regression models for Sepsis-3 sepsis and Sepsis-3 Septic shock are shown in Supplementary Tables S4 and S5. We used a modified Sequential Organ Failure Assessment (SOFA) score to generate organ dysfunction (see Table 1). †ΔAUC refers to the comparison of AUC between the two models with and without sepsis/septic shock category. ‡|ΔBIC| refers to the absolute difference in Bayesian Information Criterion between the two models: first without sepsis/septic shock category, and second with sepsis/septic shock category. A higher score points towards an improved regression model fit when adding the sepsis/septic shock variable. Any |ΔBIC| value >10 provides very strong support for the model when comparing model fits for the outcome. ¶Brier score is an aggregate measure of disagreement between the observed outcome and a model based prediction with a perfect prediction value of 0, a score of 0.25 for 50/50 prediction and a score of 0.2225 equates to $P=0.65$. SD, standard deviation; *n*, number; ED, Emergency department; APACHE II, Acute Physiology and Chronic Health Evaluation II; MDH, Musculoskeletal, Dermatological, Haematological; serum lactate, highest serum lactate concentrations measured in blood in the first 24 h of ICU admission; SIRS, systemic inflammatory response syndrome; IQR, inter-quartile range; LOS, length of stay; OR, odds ratio; 95% CI, 95% confidence intervals; AUC, area under the receiver operating characteristic curve

Parameter	Sepsis-2 severe sepsis *n*=197 724	Sepsis-3 sepsis *n*=197 142	Sepsis-2 septic shock *n*=153 257	Sepsis-3 septic shock *n*=39 262
Age in yr, mean (SD)	62.8 (17.2)	63.3 (16.9)	63.7 (16.9)	65.3 (15.0)
Sex female, *n* (%)	89 923 (45.5)	88 612 (45.0)	71 078 (46.4)	17 505 (44.6)
Ethnicity, *n* (%)				
White	178 249 (90.2)	177 829 (90.2)	138 557 (90.4)	35 033 (89.2)
Asian	7536 (3.8)	7465 (3.8)	5806 (3.8)	1671 (4.3)
Black	4459 (2.3)	4366 (2.2)	3159 (2.1)	885 (2.3)
Other	2288 (1.25)	2269 (1.2)	1754 (1.1)	541 (1.4)
Mixed	920 (0.5)	912 (0.5)	682 (0.5)	186 (0.5)
Not stated	4272 (2.2)	4301 (2.2)	3299 (2.2)	946 (2.4)
Dependency status, *n* (%)				
No dependency	137 113 (69.4)	135 771 (69.9)	105 266 (68.7)	29 098 (71.6)
Mild to moderate	57 081 (28.9)	57 770 (29.3)	45 182 (29.5)	10 748 (27.4)
Severe	3530 (1.8)	3601 (1.8)	2809 (1.8)	416 (1.1)
Past medical history, *n* (%)	39 477 (20.0)	39 917 (20.3)	31 086 (20.4)	8156 (20.9)
Severe comorbidity, *n* (%)				
Cardiovascular	2717 (1.8)	3380 (1.7)	2717 (1.8)	712 (1.8)
Respiratory	5855 (3.8)	8331 (4.2)	5855 (3.8)	1090 (2.8)
Liver	3866 (2.5)	4.690 (2.4)	3866 (2.5)	1291 (3.3)
Renal	3173 (2.1)	4282 (2.2)	3173 (2.1)	806 (2.1)
Metastatic disease	4104 (2.7)	4961 (2.5)	4104 (2.7)	1098 (2.8)
Haematological	5889 (3.8)	7236 (3.7)	5889 (3.8)	1664 (4.2)
Immunosuppressed	13 331 (8.7)	16 828 (8.5)	13 331 (8.7)	3551 (9.0)
Surgical status, *n* (%)				
Non-surgical	145 725 (75.2)	149 718 (76.0)	115 325 (75.3)	29 276 (75.4)
Elective surgical	8659 (4.4)	8219 (4.2)	6210 (4.1)	861 (2.2)
Emergency surgical	40 324 (20.4)	39 191 (19.9)	31 722 (20.7)	9135 (23.3)
Admission source, *n* (%)				
ED or not in hospital	45 451 (23.0)	45 633 (23.1)	37 244 (24.3)	10 887 (27.7)
Theatre	48 983 (24.8)	47 410 (24.1)	37 932 (24.8)	9996 (25.5)
Ward in hospital	88 393 (44.76)	88 968 (45.1)	67 310 (43.9)	15 926 (40.6)
Another ICU	13 299 (6.7)	14 529 (6.9)	9589 (6.3)	2181 (5.6)
Another hospital	1582 (0.8)	1588 (0.8)	1182 (0.8)	280 (0.7)
Illness severity scores, mean (SD)				
APACHE II physiology	13.5 (5.9)	13.7 (5.9)	14.4 (5.9)	17.0 (6.5)
APACHE II	18.2 (6.8)	18.5 (6.7)	19.2 (6.8)	22.0 (7.1)
Infection source, *n* (%)				
Respiratory	97 682 (49.4)	98 785 (50.1)	72 615 (47.4)	16 541 (42.1)
Gastrointestinal	52 022 (26.3)	50 799 (25.8)	40 977 (26.7)	12 310 (31.4)
Cardiovascular	4240 (2.1)	4264 (2.2)	3510 (2.3)	1121 (2.9)
Genitourinary	13 127 (6.6)	12 796 (6.5)	10 923 (7.1)	2388 (6.1)
MDH	10 710 (5.4)	10 499 (5.3)	8783 (5.7)	1968 (5.0)
Neurological	5817 (2.9)	5815 (3.0)	3933 (2.6)	605 (1.5)
Unknown	14 126 (7.1)	14 185 (7.2)	12 516 (8.2)	4329 (11.0)
SIRS status, *n* (%)				
0	0	894 (0.5)	0	33 (0.1)
1	0	7005 (3.6)	0	333 (0.9)
2	37 613 (19.0)	34 963 (17.7)	26 741 (17.5)	3875 (9.9)
3	84 759 (42.9)	80 987 (41.1)	64 649 (42.1)	14 905 (38.0)
4	75 352 (38.1)	73 293 (37.9)	61 867 (40.4)	20 116 (51.2)

Continued

Table 2 Continued

Parameter	Sepsis-2 severe sepsis n=197 724	Sepsis-3 sepsis n=197 142	Sepsis-2 septic shock n=153 257	Sepsis-3 septic shock n=39 262
Organ dysfunction, n (%)				
Cardiovascular SOFA				
0	48 175 (24.4)	45 951 (23.3)	3708 (2.4)	–
1	90 635 (45.8)	91 024 (46.2)	90 635 (59.1)	–
≥2	58 914 (29.8)	60 167 (30.5)	58 914 (38.4)	39 262 (100)
Respiratory SOFA				
0	18 602 (9.4)	14 665 (7.4)	13 793 (9.0)	1146 (2.9)
1	29 332 (14.8)	27 859 (14.1)	22 213 (14.5)	4143 (10.6)
≥2	149 770 (75.8)	154 618 (78.4)	117 251 (76.5)	33 973 (86.5)
Renal SOFA				
0	97 036 (49.1)	93 428 (47.4)	67 820 (44.3)	9075 (23.1)
1	33 926 (17.2)	34 656 (17.6)	27 370 (17.9)	6766 (17.2)
≥2	66 762 (33.8)	69 058 (35.0)	58 067 (37.9)	23.421 (59.7)
Haematological SOFA				
0	139 258 (70.4)	136 985 (69.5)	104 258 (68.0)	22 549 (57.4)
1	28 870 (14.6)	29 842 (15.1)	23 526 (15.4)	6861 (17.5)
≥2	29 596 (15.0)	30 315 (15.4)	25 473 (16.6)	9852 (25.1)
Neurological SOFA				
0	98 488 (49.8)	95 286 (48.3)	70 830 (46.2)	12 514 (31.9)
1	27 679 (14.0)	28 147 (14.3)	20 526 (13.4)	4292 (10.9)
≥2	71 557 (36.2)	73 709 (37.4)	61 901 (40.4)	22 456 (57.2)
Hepatic SOFA				
<2	195 573 (98.9)	194 946 (98.9)	151 308 (98.7)	38 283 (97.5)
≥2	2151 (1.1)	2196 (1.1)	1949 (1.3)	979 (2.5)
Serum lactate, mmol litre^{-1}				
Mean (SD)	3.0 (3.0)	3.0 (3.0)	3.4 (3.3)	5.9 (4.0)
Median (IQR)	2.0 (1.3–3.5)	2.0 (1.3–3.5)	2.3 (1.4–4.2)	4.5 (3.0–7.5)
>2 mmol litre^{-1}, n (%)	89 435 (48.1)	89 613 (47.9)	79 432 (54.7)	39 262 (100)
Outcomes				
ICU mortality, n (%)	43 183 (21.8)	44 130 (22.4)	39 294 (25.6)	18 338 (46.7)
ICU LOS (days), median (IQR)	3.8 (1.7–8.0)	3.8 (1.8–8.1)	4.0 (1.8–8.8)	5.2 (1.8–12.0)
Readmissions, n (%)	15 856 (8.0)	15 563 (7.9)	11 482 (7.5)	2243 (5.7)
Hospital mortality, n (%)	56 394 (31.1)	57 524 (31.8)	49 656 (35.1)	20 457 (55.5)
Risk-adjusted OR (95% CI)	1.16 (1.13–1.20)	1.16 (1.13–1.20)	1.30 (1.26–1.34)	2.44 (2.32–2.57)
P-value	P<0.001	P<0.001	P<0.001	P<0.001
ΔAUC[†]	0.83 vs 0.83	0.83 vs 0.83	0.83 vs 0.83	0.83 vs 0.83
|ΔBIC|[‡]	350.51	342.68	1067.56	5086.11
Brier score[¶]	0.120	0.120	0.120	0.119

ICUs in England over the 5 yr period. Sepsis-2 septic shock accounted for three-quarters of the severe sepsis population and the extrapolated population incidence increased from 69 to 79 per 100 000 person-years. In contrast, Sepsis-3 septic shock was only one-fifth of the sepsis population and with minimal change in the extrapolated population incidence over the 5 yr period (approximately 19 per 100 000 person-years) (Supplementary Table S3; Fig. 4).

Trends in, and risk factors for, acute hospital mortality

The acute hospital mortality for Sepsis-2 severe sepsis and Sepsis-3 sepsis were similar and decreased from 33% in 2011 to 30% in 2015. The acute hospital mortality for Sepsis-2 septic shock decreased from 37% in 2011 to 33% in 2015. In contrast, the acute hospital mortality for Sepsis-3 septic shock changed from 57% in 2011 to 56% in 2015. The extrapolated numbers of deaths are shown in Supplementary Fig. S1. The rate of improvement in unadjusted and risk-adjusted acute hospital mortality was significant for Sepsis-2 severe sepsis, Sepsis-3 sepsis and for Sepsis-2 septic shock. In contrast, no statistically significant trends in unadjusted or risk-adjusted acute hospital mortality were observed for patients meeting the Sepsis-3 septic shock case definition (Supplementary Table S4).

The independent risk factors for acute hospital mortality identified for Sepsis-3 sepsis and septic shock were increasing age, male, presence of severe comorbidity, increasing dependency and worsening APACHE II acute physiology score. Compared with the non-surgical group, surgical populations had lower risk of death. Compared with respiratory tract infections, gastrointestinal and genitourinary infections had lower risk of death (Supplementary Tables S5 and S6).

Assessment of predictive validity

As shown in Figure 2, Sepsis-2 severe sepsis and Sepsis-3 sepsis are similar cohorts, but Sepsis-3 septic shock was a more severe illness with a greater risk of death compared with Sepsis-2

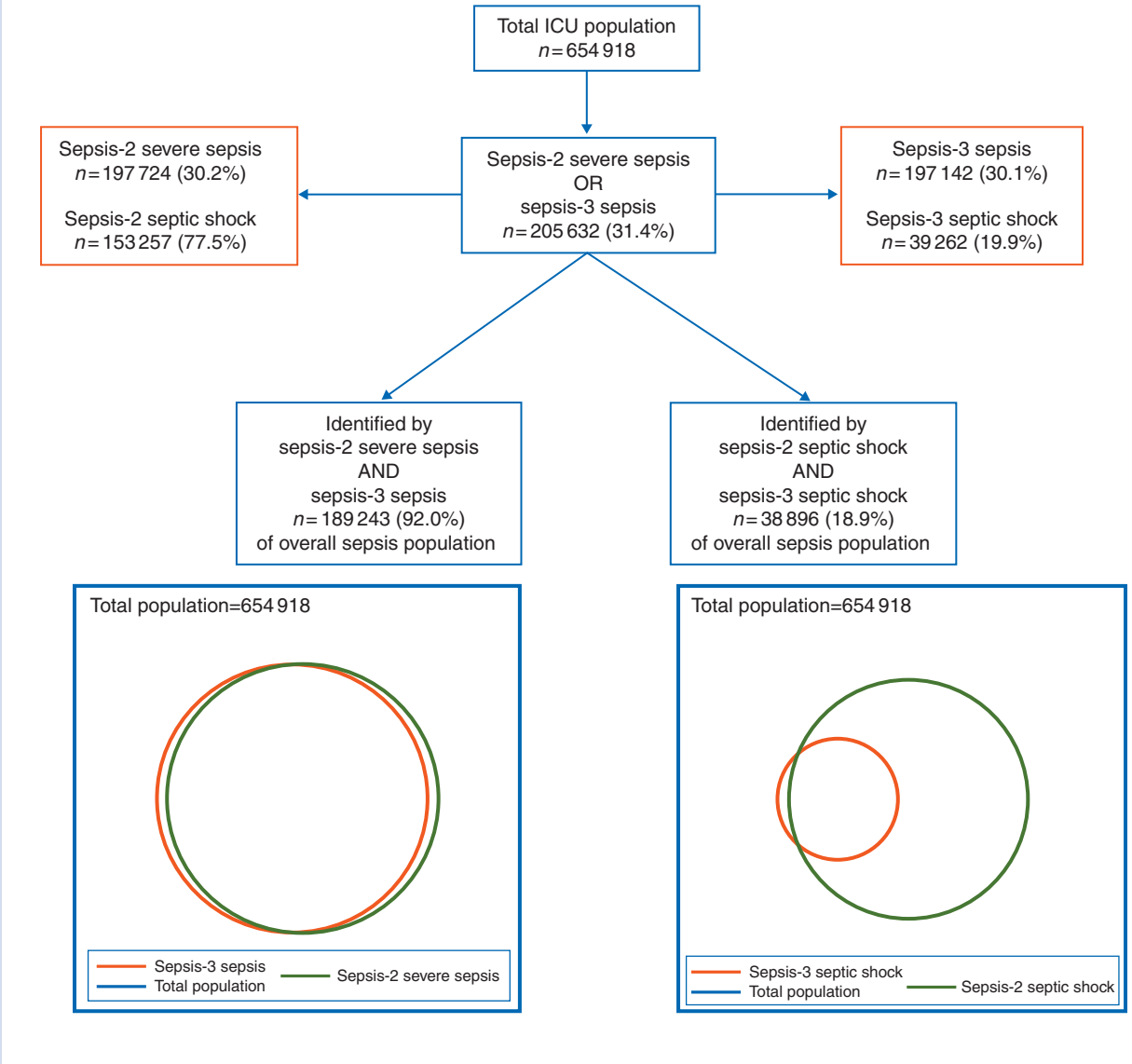

Fig 1 Flow diagram and Venn diagrams showing the relationship between Sepsis-3 and Sepsis-2 populations. Among the 205 632 sepsis patients, *n*=8481 (4.1%) were identified only by Sepsis-2 severe sepsis and *n*=7899 (3.8%) were identified only by Sepsis-3 sepsis operationalization. There were *n*=39 262 Sepsis-3 septic shock cases and *n*=153 257 Sepsis-2 septic shock cases. Among the 153 623 septic shock cases identified by either of the definitions, *n*=114 727 were identified only by Sepsis-2 septic shock and *n*=366 were identified by only by Sepsis-2 septic shock operationalization. Please note that Sepsis-2 septic shock and Sepsis-3 septic shock populations are included within the broader Sepsis-2 severe sepsis and Sepsis-3 sepsis categories, respectively.

septic shock. The population identified only by Sepsis-2 severe sepsis (SIRS positive with 1 point on SOFA) had lower mortality compared with that identified only by Sepsis-3 sepsis (SIRS negative with 2 or more points on SOFA; 7.0% *vs* 22.4%; Supplementary Table S2). The additional OR (95% CI) of dying from Sepsis-3 sepsis compared with ICU admissions without sepsis was 1.16 (1.13–1.20), which was similar to Sepsis-2 severe sepsis, implying similar predictive validity. The additional OR (95% CI) of dying from Sepsis-3 septic shock compared with ICU admissions without sepsis was 2.44 (2.32–2.57), which is much higher than Sepsis-2 septic shock and Sepsis-3 sepsis, implying a significantly better predictive increment with the Sepsis-3 septic shock diagnosis. The increment in AUC and BIC was greatest for Sepsis-3 septic shock, with a Brier score of 0.119 (Table 2).

Sensitivity analysis

The results of sensitivity analyses were consistent with the primary analyses. We observed improving trends risk-adjusted acute hospital mortality only in Sepsis-3 sepsis, OR per year 0.96 (0.94–0.97), $P<0.001$, and highest increment in predictive validity for Sepsis-3 septic shock, 2.28 (2.11–2.47), in patients without

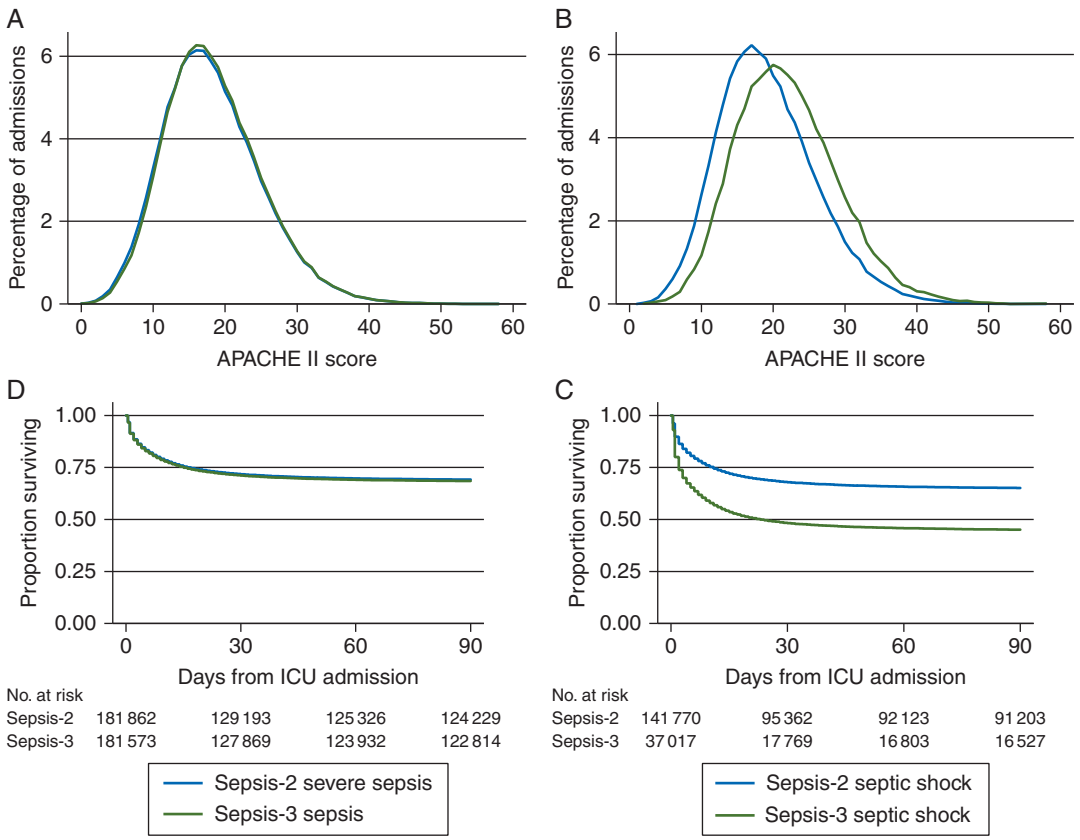

Fig 2 Comparison of the distribution of APACHE II scores and Kaplan–Meier survival curves between old and new sepsis populations. The APACHE II score distributions in Sepsis-2 severe sepsis and Sepsis-3 sepsis (A) and Sepsis-2 septic shock and Sepsis-3 septic shock (B), similar Kaplan–Meier survival curves for acute hospital mortality censored at 90 days for Sepsis-2 severe sepsis and Sepsis-3 sepsis (C) and significantly different Kaplan–Meier survival curves censored at 90 days for acute hospital mortality between Sepsis-2 septic shock and Sepsis-3 septic shock (D).

severe comorbidity. The highest increment in predictive validity was for Sepsis-3 septic shock in the regression models without illness severity (Supplementary Table S7).

Discussion

In ICUs in England, Sepsis-2 severe sepsis and Sepsis-3 sepsis definitions identify similar cohorts with 92% overlap. Between 2011 and 2015, incidence increased and risk-adjusted acute hospital mortality improved. Sepsis-3 septic shock criteria identify a much smaller population compared with Sepsis-2 septic shock, with very little increase in incidence between 2011 and 2015. When compared with non-sepsis admissions after risk adjustment, Sepsis-3 sepsis has 1.15 times, and Sepsis-3 septic shock 2.42 times, greater odds of death. The extrapolated population incidences of Sepsis-3 sepsis and septic shock in 2015 were 102 and 19 per 100 000 person-years, respectively. The corresponding annual adult ICU caseloads in England in 2015 were 45 200 and 8600 patients, respectively.

The descriptive epidemiology of Sepsis-3 sepsis in ICU setting is similar to that described previously for Sepsis-2 severe sepsis.[2 7] The incidence and mortality of Sepsis-3 sepsis and septic shock increase significantly with age and comorbidity.[11 12] The overall frequency of Sepsis-3 septic shock (six per 100 ICU admissions) was similar to previous reports in other ICU settings using the International Classification of Diseases codes for estimating septic shock incidence between 1993 and 2000.[2 13] The reduction in proportion of Sepsis-3 septic shock observed in our study is supported by the recently published secondary analysis of Vasopressin and Septic Shock Trial.[14] The increasing population incidence and decreasing trends in mortality of Sepsis-3 sepsis are consistent with what we would expect from our previous Sepsis-2 publications.[7 15] Sepsis-3 sepsis identifies SIRS-positive and SIRS-negative patients but with a greater degree of organ dysfunction. The higher mortality in the population identified only by Sepsis-3 (Supplementary Table S1) is secondary to greater severity of illness, which is an example of predictive validity intended by Sepsis-3 definitions.[1 16]

We present one of the first direct comparisons of old and new sepsis epidemiology, using a high-quality national ICU database with >90% potential ICU population coverage. We used primary or secondary reasons for admission to identify infection, to maximize sensitivity for identifying sepsis cases. We operationalized old and new definitions using raw physiology data and used consecutive admissions over a 5 yr period between 2011 and 2015, overcoming the challenges often

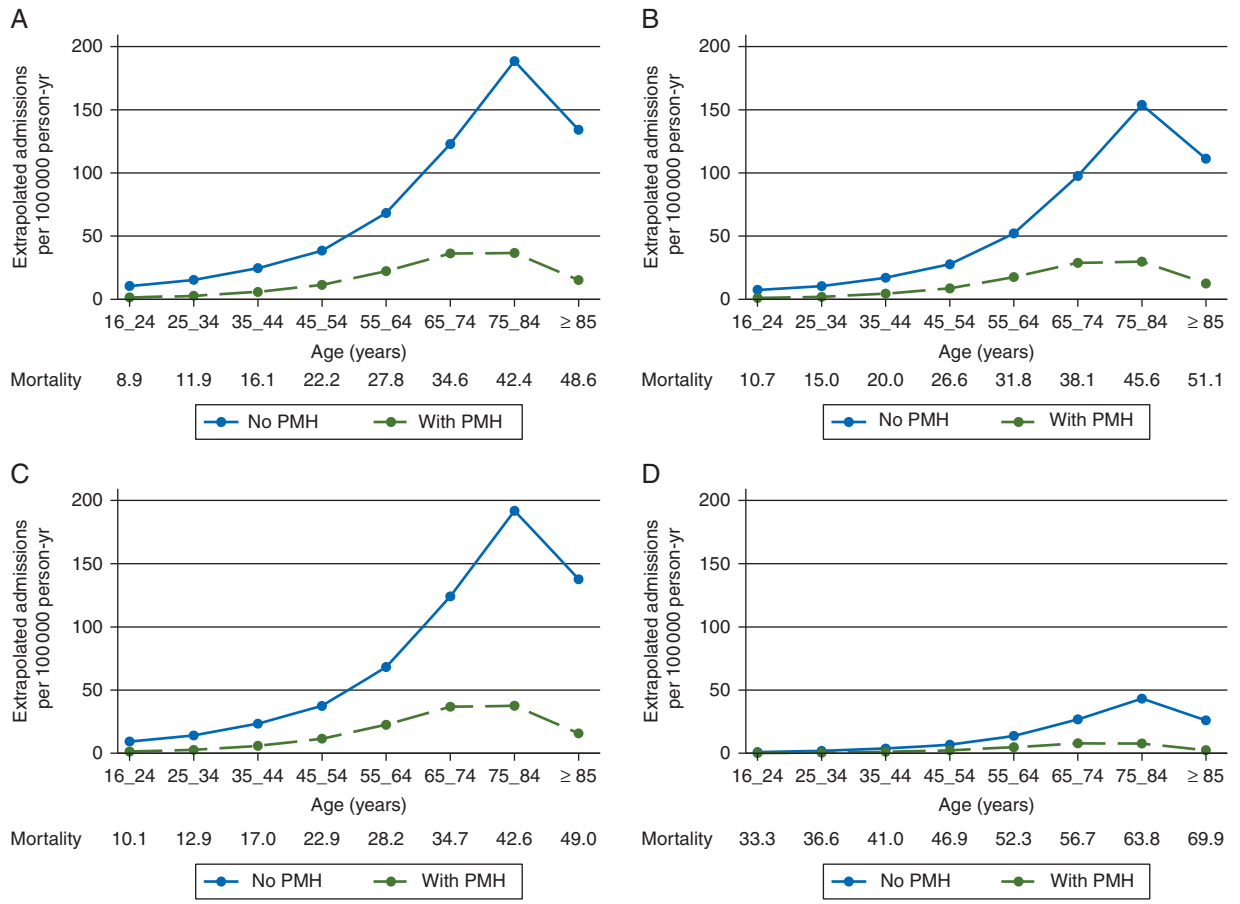

Fig 3 Age and severe comorbidity-specific extrapolated population incidence of, and age-category-specific crude acute hospital mortality from Sepsis-2 severe sepsis, Sepsis-2 septic shock, Sepsis-3 sepsis and Sepsis-3 septic shock. $P<0.001$ for trends in age-specific mortality rates for Sepsis-2 severe sepsis (A), Sepsis-2 septic shock (B), Sepsis-3 sepsis (C) and Sepsis-3 septic shock (D). Admissions without severe comorbidity were more common than admissions with severe comorbidities as defined using APACHE II definitions. PMH, past medical history of severe comorbidity.

highlighted with using insurance claims or reimbursement formulae for reporting sepsis epidemiology.[7 17–19] Editorials have argued that abandoning SIRS may result in delayed identification of high-risk sepsis population.[20–22] The rationale for abandoning SIRS criteria as the starting point of the nested sepsis illness model includes lack of discriminant validity,[1 16 23–25] occurrence of SIRS-negative sepsis in the ICU setting[7 26] and well-documented early immunosuppression in sepsis.[27] From our analysis, in the UK ICU setting, abandoning SIRS as the starting point for sepsis diagnosis does not alter the incidence as most patients with organ dysfunction also tend to have SIRS. The population identified by Sepsis-3 sepsis has a higher mortality, which is explained by greater burden of organ dysfunction when using SOFA ≥2 points as criteria. Admittedly, our results from ICU settings in England are not applicable to resource-limited settings,[2] sepsis in general wards[28] and in settings where there is established lactate screening as part of quality improvement initiatives.[29]

Our study has several limitations. Our study reports the epidemiology of adult ICU admissions with sepsis using data in the first 24 h of ICU admission, which potentially underestimates incidence. As England has among the lowest per capita ICU bed provision in Europe (3.5 to 7.4 per 100 000 population),[30 31] probability of underestimation is low as organ dysfunction will often be present on admission day. We derived our organ dysfunction using a modified SOFA score, as not all physiological parameters were present in the dataset. Although we did not use change in SOFA score as a result of lack of pre-admission organ dysfunction variables, we used the method recommended by the Sepsis-3 definitions paper for operationalizing SOFA where baseline organ dysfunction is not available and performed sensitivity analysis to support our inferences.[1] Although we used a sensitive definition for Sepsis-2 septic shock that potentially overestimates the Sepsis-2 septic shock incidence, our operationalization was used in three recent resuscitation trials[32] and was a common operationalization method in epidemiological studies of septic shock.[2] We do not have data on fluid resuscitation in all patients. However, in the recently completed UK-based, early, goal-directed therapy trial, 97% of patient received at least 2000 ml of fluid between hospitalization and prior to randomization,[33] implying that most patients in the study requiring inotropes would have received some form of resuscitation fluids. This assumption is also supported by the recent UK-wide National Confidential Enquiry Into Patient Outcome and Death report on

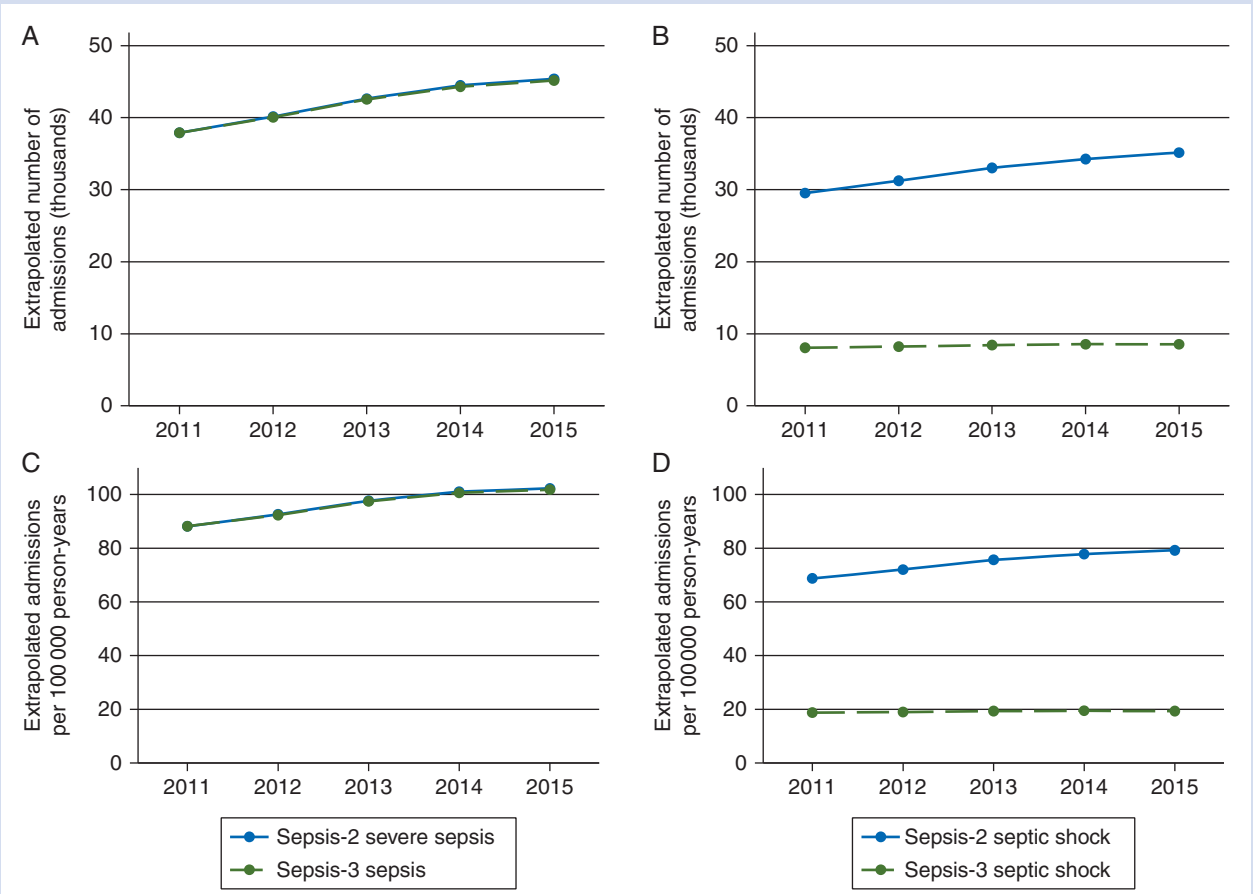

Fig 4 Comparison of the trends in extrapolated numbers of intensive care unit (ICU) admissions and numbers per 100 000 population between old and new sepsis populations. The extrapolated number of ICU admissions for Sepsis-2 severe sepsis and Sepsis-3 sepsis (A) and for Sepsis-2 septic shock and Sepsis-3 septic shock (B). The extrapolated numbers per 100 000 population person-years for Sepsis-2 severe sepsis and Sepsis-3 sepsis (C) and for Sepsis-2 septic shock and Sepsis-3 septic shock (D).

sepsis, which highlighted 82.5% of patients received resuscitation fluids prior to critical care admission.[34] To partially account for these issues, we used the admission day APACHE II acute physiology score that contains components of organ dysfunction weighted in the regression models presented and used acute hospital mortality as primary outcome, which is what APACHE II score is calibrated for. All our regression models had AUC >0.75 and Brier scores <0.2, implying good model fit and performance.[10] Although the clinical care, the decision to accept patient for ICU care and changes in process of care could influence incidence and outcomes over the study period, understanding the impact of these elements was not our study objective and must be considered for future research. Despite the limitations, our study provides a conceptual framework for future work in this area.

Our in-depth descriptive epidemiology of Sepsis-3 generates numerous fundamental analytical epidemiology questions. For example, Sepsis-3 sepsis focuses on organ dysfunction as a core illness characteristic, but interventional trials aimed at improving organ dysfunction have not consistently resulted in survival benefit.[35 36] We confirm that Sepsis-3 septic shock is a high risk of death population, which can be interpreted as better predictive validity and argued as prognostic enrichment resulting in potentially greater trial efficiency.[37] However, there is no proof that this cohort will necessarily have improved treatment response to trial interventions, which is predictive enrichment.[37 38] Thus, it is important to study the magnitude of risk reduction that is feasible in these populations, an essential component of future trial design. This updated epidemiology has implications for future trial design.

Conclusions

Our study shows that Sepsis-2 and Sepsis-3 definitions identified similar populations of sepsis cases with 92% overlap in ICU settings in England. Sepsis-3 also identifies a SIRS-negative population and a much smaller septic shock subpopulation with a greater risk of death, which highlight improved predictive validity of the Sepsis-3 definitions.

Authors' contributions

Conceived the study, contributed to the interpretation of data, critical revision of the manuscript and approved the final manuscript: M.S.-H., D.A.H., G.D.R. and K.R.

M.S.-H. and D.A.H. developed the statistical analysis plan and G.D.R. and K.R. provided critical revisions.
Performed the statistical analysis: M.S.-H. and D.A.H.
Wrote the first draft of the manuscript: M.S.-H.

All authors confirm to the accuracy or integrity of the work.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Acknowledgements

We thank both staff and patients in the ICUs participating in the Case Mix Programme. This independent research by M.S.-H. is supported by the National Institute for Health Research Clinician Scientist Award (NIHR-CS-2016-16-011). The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

Declaration of interest

The authors declare no conflict of interest directly applicable to this research.

References

1. Singer M, Deutschman CS, Seymour CW, *et al*. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA* 2016; **315**: 801–10
2. Shankar-Hari M, Phillips GS, Levy ML, *et al*. Developing a new definition and assessing new clinical criteria for septic shock: for the third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA* 2016; **315**: 775–87
3. Levy MM, Fink MP, Marshall JC, *et al*. 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. *Crit Care Med* 2003; **31**: 1250–6
4. Vincent JL, Moreno R, Takala J, *et al*. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996; **22**: 707–10
5. Shankar-Hari M, Bertolini G, Brunkhorst FM, *et al*. Judging quality of current septic shock definitions and criteria. *Crit Care* 2015; **19**: 445
6. Young JD, Goldfrad C, Rowan K. Development and testing of a hierarchical method to code the reason for admission to intensive care units: the ICNARC Coding Method. Intensive Care National Audit & Research Centre. *Br J Anaesth* 2001; **87**: 543–8
7. Shankar-Hari M, Harrison DA, Rowan KM. Differences in impact of definitional elements on mortality precludes international comparisons of sepsis epidemiology-a cohort study illustrating the need for standardized reporting. *Crit Care Med* 2016; **44**: 2223–30
8. National Staistics Online: Available from http://www.statistics.gov.uk/hub/population/population-change/population-estimates/index.html. (accessed 28 November 2016)
9. Quach S, Hennessy DA, Faris P, Fong A, Quan H, Doig CA. comparison between the APACHE II and Charlson Index Score for predicting hospital mortality in critically ill patients. *BMC Health Serv Res* 2009; **9**: 129
10. Steyerberg EW, Vickers AJ, Cook NR, *et al*. Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology* 2010; **21**: 128–38
11. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001; **29**: 1303–10
12. Mayr FB, Yende S, Angus DC. Epidemiology of severe sepsis. *Virulence* 2014; **5**: 4–11
13. Annane D, Aegerter P, Jars-Guincestre MC, Guidet B. Network CU-R. Current epidemiology of septic shock: the CUB-Rea Network. *Am J Respir Crit Care Med* 2003; **168**: 165–72
14. Russell JA, Lee T, Singer J, *et al*. The septic shock 3.0 definition and trials: a vasopressin and septic shock trial experience. *Crit Care Med* 2017; **45**: 940–8
15. Harrison DA, Welch CA, Eddleston JM. The epidemiology of severe sepsis in England, Wales and Northern Ireland, 1996 to 2004: secondary analysis of a high quality clinical database, the ICNARC Case Mix Programme Database. *Crit Care* 2006; **10**: R42
16. Seymour CW, Liu VX, Iwashyna TJ, *et al*. Assessment of clinical criteria for sepsis: for the third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA* 2016; **315**: 762–74
17. 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**: 1167–74
18. Whittaker SA, Mikkelsen ME, Gaieski DF, Koshy S, Kean C, Fuchs BD. Severe sepsis cohorts derived from claims-based strategies appear to be biased toward a more severely ill patient population. *Crit Care Med* 2013; **41**: 945–53
19. Rhee C, Gohil S, Klompas M. Regulatory mandates for sepsis care–reasons for caution. *N Engl J Med* 2014; **370**: 1673–6
20. Simpson SQ. New sepsis criteria: a change we should not make. *Chest* 2016; **149**: 1117–8
21. Sprung CL, Schein RM, Balk RA. The new sepsis consensus definitions: the good, the bad and the ugly. *Intensive Care Med* 2016; **42**: 2024–6
22. Williams JM, Greenslade JH, McKenzie JV, Chu K, Brown AF, Lipman J. Systemic inflammatory response syndrome, quick sequential organ function assessment, and organ dysfunction: insights from a prospective database of ED patients with infection. *Chest* 2017; **151**: 586–96
23. Churpek MM, Zadravecz FJ, Winslow C, Howell MD, Edelson DP. Incidence and prognostic value of the systemic inflammatory response syndrome and organ dysfunctions in ward patients. *Am J Respir Crit Care Med* 2015; **192**: 958–64
24. Shapiro N, Howell MD, Bates DW, Angus DC, Ngo L, Talmor D. The association of sepsis syndrome and organ dysfunction with mortality in emergency department patients with suspected infection. *Ann Emerg Med* 2006; **48**: 583–90, 590.e1
25. Jaimes F, Garces J, Cuervo J, *et al*. The systemic inflammatory response syndrome (SIRS) to identify infected patients in the emergency room. *Intensive Care Med* 2003; **29**: 1368–71
26. 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**: 1629–38
27. Hotchkiss RS, Monneret G, Payen D. Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy. *Nat Rev Immunol* 2013; **13**: 862–74

28. Churpek MM, Snyder A, Han X, *et al*. Quick sepsis-related organ failure assessment, systemic inflammatory response syndrome, and early warning scores for detecting clinical deterioration in infected patients outside the intensive care unit. *Am J Respir Crit Care Med* 2017; **195**: 906–11
29. Whippy A, Skeath M, Crawford B, *et al*. Kaiser Permanente's performance improvement system, part 3: multisite improvements in care for patients with sepsis. *Jt Comm J Qual Patient Saf* 2011; **37**: 483–93
30. Wunsch H, Angus DC, Harrison DA, *et al*. Variation in critical care services across North America and Western Europe. *Crit Care Med* 2008; **36**: 2787–93, e1–9
31. Rhodes A, Ferdinande P, Flaatten H, Guidet B, Metnitz PG, Moreno RP. The variability of critical care bed numbers in Europe. *Intensive Care Med* 2012; **38**: 1647–53
32. Prism Investigators, Rowan KM, Angus DC, *et al*. Early, Goal-Directed Therapy for Septic Shock - A Patient-Level Meta-Analysis. *N Engl J Med* 2017; **376**: 2223–34
33. Mouncey PR, Osborn TM, Power GS, *et al*. Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med* 2015; **372**: 1301–11
34. http://www.ncepod.org.uk/2015sepsis.html (Accessed 18 January 2017)
35. Gordon AC, Perkins GD, Singer M, *et al*. Levosimendan for the prevention of acute organ dysfunction in sepsis. *N Engl J Med* 2016; **375**: 1638–48
36. Gordon AC, Mason AJ, Thirunavukkarasu N, *et al*. Effect of early vasopressin vs norepinephrine on kidney failure in patients with septic shock: the VANISH randomized clinical trial. *JAMA* 2016; **316**: 509–18
37. Prescott HC, Calfee CS, Thompson BT, Angus DC, Liu VX. Toward smarter lumping and smarter splitting: rethinking strategies for sepsis and acute respiratory distress syndrome clinical trial design. *Am J Respir Crit Care Med* 2016; **194**: 147–55
38. Shankar-Hari M, Rubenfeld GD. The use of enrichment to reduce statistically indeterminate or negative trials in critical care. *Anaesthesia* 2017; **72**: 560–5

Handling editor: Paul Myles