Objectives: Sepsis generates signi cant global acute illness burden. The international variations in sepsis epidemiology (illness burden) have implications for region speci c health policy. We hypothesised that there have been changes over time in the sepsis de nitional elements (infection and organ dysfunction), and these may have impacted on hospital mortality.
Design: Cohort study.
Setting: We evaluated a high quality, nationally representative, clinical ICU database including data from 181 adult ICUs in England.
Patients: Nine hundred sixty-seven thousand ive hundred thirty-two consecutive adult ICU admissions from January 2000 to December 2012.
Interventions: None.
Measurements and Main Results: To address the proposed hypothesis, we evaluated a high quality, nationally representative, clinical, ICU database of 967,532 consecutive admissions to 181 adult ICUs in England, from January 2000 to December 2012, to identify sepsis cases in a robust and reproducible way. Multinomial logistic regression was used to report unadjusted trends in sep-

reported across ICU cohorts (3–6), with recent trended data indicating a decrease in mortality (7–9). However, interpretation of these data is challenging as it is likely that differences in the timing and trajectories of pre- and within hospital care, enhanced recognition (through campaigns such as the Surviving Sepsis Campaign (10) and the Sepsis Six in the United Kingdom [11]) and available ICU resources (the provision and use of ICU beds), will in uence the characteristics of the sepsis population admitted to ICU (3, 12–16). Currently, no international consensus exists for standardised reporting the

and percentage. Admissions with unmeasured physiology were assumed not to have met the sepsis case de nition. Data completeness exceeded 98% in all elds used for case selection, thus complete case analyses were used. All analyses were performed using Stata/SE Version 13.0 (StataCorp LP, College Station, TX).

RESULTS

Over the study period, 248,864 of the 967,532 admissions to adult general ICUs in England met the sepsis case de nition. The proportion and numbers of sepsis admissions increased from 23.5% in 2000 to 25.2% in 2012 (**Table 1**; **Fig. 1**, Supple-

57.7–58.4%) (**Fig2**, ***C*** and ***D***; S-Table-3, Supplemental Digital Content 1, http://links.lww.com/CCM/B941).

Adjusted Trends in Hospital Mortality by Infection and Organ Dysfunction

The adjusted trend for improvement in hospital mortality for sepsis admissions was signi cant (OR, 0.939; 95% CI, 0.934–0.945 per year; p < 0.001). Adjusted hospital mortality decreased signi cantly within each category of infection source and the rate of change over time varied signi cantly by infection source (respiratory, OR for risk category, 1, 0.947 [95% CI, 0.938–0.956] per year; cardiovascular, 0.937 [0.918–0.957] per year; gastrointestinal, 0.941 [0.933–0.950] per year; genitourinary, 0.938 [0.918–0.959] per year; musculoskeletal/dermatologic, 0.943 [0.925–0.962] per year; neurologic, 0.939 [0.919–0.960] per year; unknown, 0.919 [0.907–0.932]; all individual trends and test of homogeneity p < 0.001).

Adjusted hospital mortality also decreased signi cantly within each risk category but the rate of change was consistent across the risk categories (risk category 1, OR for respiratory source, 0.947 [95% CI, 0.938–0.956] per year; risk category 2, 0.947 [95% CI, 0.939–0.955] per year; risk category 3, 0.943 [95% CI, 0.935–0.950] per year; -5(e)3(r y)12(earTc 0 Tw 131K)-5(e)3(r]S0( )]TJ 0.118 Tw T* [(0.947 [95% CI,)30(o)15
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as 12.1% for risk category 1; 15.8% for risk category 4) and between infection sources (such as 13.2% for respiratory infection; 12.3% for urinary infections), despite differences in baseline mortality (year 2000) in these sepsis de nitional elements.

Relevance

Our study introduces the concept that differences in the contribution of each sepsis de nitional element such as source of infection and type and number of organ dysfunctions potentially contributes to the international variation observed across

highlighted in studies of sepsis epidemiology (7, 9, 25–30) namely, reliance on administrative/insurance claims data and use of either subjective sepsis codes (highly likely in uenced by awareness campaigns, in uential studies, and reimbursement formulae) or separate but asynchronous codes for infection and organ dysfunction, often coded at discharge.

Limitations

There are limitations to our study. First, our database was not primarily designed for ICU sepsis epidemiology, and therefore, the overall incidence of sepsis may be underestimated (i.e., some admissions may develop sepsis after the rst 24 hours in ICU). However, given the relatively low provision of ICU beds in England (higher threshold for admission) (23, 31) and with 80% of the study cohort having two or more organ dysfunctions in the rst 24 hours, the impact would likely be minimal. Second, the ICUs contributing to the dataset varied over time, which we addressed in our sensitivity analyses. Third, the organ dysfunction assessment was cross sectional. Fourth, the dataset contains planned and unplanned ICU admissions, where the physiology-modi- ed secondary to interventions such as uid management that would not be similarly captured by the organ dysfunction assessment (32) that is a common limitation of large database based epidemiology reports (33). Finally, changes to the health care system and increasing awareness of sepsis could have in uenced some of the observed improvements in outcome (34); however, assessment of effects of these changes was not the research question addressed by this study.

Future Research

De nitions are descriptions of illness and criteria provide the variables to identify a case (6). To-date, there are neither universally agreed standardized

CONCLUSIONS

The characteristics of our sepsis ICU population changed over time and so did the impact of de nitional elements on hospital mortality, which we propose preclude direct international comparisons of incidence and mortality. We illustrate a case for developing an international consensus on standardized reporting of sepsis epidemiology. This has important implications, both for health policy and benchmarking.

ACKNOWLEDGMENT

We thank both staff and patients in the ICUs participating in the Case Mix Programme. Dr. Shankar-Hari acknowledges the funding of NIHR Biomedical Research Centre at Kings Health Partners.

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