Benchmarking the Incidence and Mortality of Severe Sepsis in the United States*

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Background: In 1992, the first consensus definition of severe sepsis was published. Subsequent epidemiologic estimates were collected using administrative data, but ongoing discrepancies in the definition of severe sepsis produced large differences in estimates.

Objectives: We seek to describe the variations in incidence and mortality of severe sepsis in the United States using four methods of database abstraction. We hypothesized that different methodologies of capturing cases of severe sepsis would result in disparate estimates of incidence and mortality.

Design, Setting, Participants: Using a nationally representative sample, four previously published methods (Angus et al, Martin et al, Dombrovskiy et al, and Wang et al) were used to gather cases of severe sepsis over a 6-year period (2004–2009). In addition, the use of new *International Statistical Classification of Diseases*, 9th Edition (ICD-9), sepsis codes was compared with previous methods.

Measurements: Annual national incidence and in-hospital mortality of severe sepsis.

Results: The average annual incidence varied by as much as 3.5-fold depending on method used and ranged from 894,013 (300/100,000 population) to 3,110,630 (1,031/100,000) using the methods of Dombrovskiy et al and Wang et al, respectively. Average annual increase in the incidence of severe sepsis was similar (13.0% to 13.3%) across all methods. In-hospital mortality ranged from 14.7% to 29.9% using abstraction methods of Wang et al and Dombrovskiy et al. Using all methods, there was a decrease in in-hospital mortality across the 6-year period (35.2% to 25.6% [Dombrovskiy et al] and 17.8% to 12.1% [Wang et al]). Use of ICD-9 sepsis codes more than doubled over the 6-year period (158,722 – 489,632 [995.92 severe sepsis], 131,719 – 303,615 [785.52 septic shock]).

Conclusion: There is substantial variability in incidence and mortality of severe sepsis depending on the method of database abstraction used. A uniform, consistent method is needed for use in national registries to facilitate accurate assessment of clinical interventions and outcome comparisons between hospitals and regions. (*Crit Care Med* 2013; 41:1167–1174)

Key Words: case fatality; epidemiology; mortality; outcomes; sepsis; trends analysis

The term *sepsis* has been in use for over two millennia (1), but it was not until two decades ago that a consensus definition of the clinical syndrome was reached (2, 3). Prior to 1992, heterogeneous groups of patients were enrolled in sepsis trials, leading to variability in estimates of incidence and mortality (2). In response, the American College of Chest Physicians and Society for Critical Care Medicine defined sepsis, severe sepsis, and septic shock as a spectrum of disease resulting from a host response to systemic infection (3–5). This standardization facilitated the recognition of sepsis as a substantial burden to the U.S. healthcare system. The Centers for Disease Control and Prevention listed "septicemia" as the 11th leading cause of death nationwide in 2009 (6). Severe sepsis, defined as sepsis associated with new organ dysfunction, hypoperfusion, or hypotension has a high ICU admission rate and

*See also p. 1361.

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was recently estimated to cost the U.S. healthcare system $24.3 billion in 2007 (7).

To determine national trends in the epidemiology of severe sepsis, researchers have used *International Statistical Classification of Diseases*, 9th Edition (ICD-9), codes linking infection to new organ dysfunction (8–18). However, substantial differences in methodology have led to disparate estimates. Angus et al (8) estimated an annual incidence of severe sepsis of 750,000 cases (300/100,000 population) and an in-hospital mortality rate of 28.6% in 1995. Martin et al (14) estimated a incidence of severe sepsis of 256,000 cases in 2000 (81/100,000). Dombrovskiy et al (13) reported a incidence of 391,000 cases (134/100,000) of severe sepsis with an in-hospital mortality rate of 37.7% in 2003. Finally, Wang et al (12) found 571,000 annual emergency department (ED) cases nationally between 2001 and 2003. Debate continues concerning the true incidence of severe sepsis in the United States and around the world (19, 20). The relation between these competing abstraction methods remains unknown. A population-based analysis in Sweden recently reported that the incidence and mortality of severe sepsis varied threefold depending on method used (21). Additionally, in 2002 and 2003, specific ICD-9 codes for sepsis, severe sepsis, and septic shock (995.91, 995.92, and 785.52, respectively) were introduced, but their suitability for epidemiologic analysis remains unknown.

As therapies for severe sepsis evolve, the derivation of accurate and consistent estimates of the national incidence and mortality is critical for proper distribution of limited health care resources. Beyond this, the focus on publicly reported outcomes between regions and hospital systems requires a means by which to ensure uniform reporting. As prospective collection of such data appears elusive, consistent use of administrative data remains essential. In this study, we use four previously published (8, 12–14) methods for identification of sepsis, as well as the new sepsis codes to benchmark national variability in incidence and mortality over a 6-year period (2004–2009). We hypothesized that different methodologies of capturing cases of severe sepsis would result in disparate estimates of incidence and mortality.

METHODS

Data

We performed a nationally representative retrospective cohort study using the Nationwide Inpatient Sample (NIS) from 2004 to 2009. The NIS is the largest all-payer, publicly available inpatient database in the United States, developed as part of the Healthcare Cost and Utilization Project sponsored under the Agency for Healthcare Research and Quality. The database contains approximately 8 million hospital stays each year from 1,050 hospitals in 44 states (in 2009), representing a 20% sample of U.S. acute care hospitals. The Nationwide Inpatient Sample stratified sampling methodology allows for generation of nationally representative estimates of incidence and mortality. Over 100 clinical and nonclinical elements are available from each hospital stay, including primary and secondary diagnoses, procedures, discharge status, patient demographics, and hospital length of stay. Hospital-level characteristics including geographic region, urban vs. rural location, ownership, teaching status, and bed size are used to provide a weight for individual hospitals and ensure nationally representative data. Since 2003, the 20% sample closely approximates 1/5 of the national incidence with individual hospital weights tending to be close to 5. Further details are available at http://www.hcup-us.ahrq.gov/nisoverview.jsp. Given the de-identified nature of the administrative data, this study was declared to be exempt by the Institutional Review Board at the University of Pennsylvania.

Patients

Severe sepsis was defined as documented infection, including the ICD-9 code for sepsis (995.91) and the presence of new organ dysfunction or the ICD-9 code for severe sepsis (995.92) or septic shock (785.52). To compare the incidence of severe sepsis by year, four previously published methods were used (**Fig. 1**) (8, 12–14). These methods used ICD-9 codes for infection listed as a primary or secondary diagnosis paired with at least one diagnosis of new organ dysfunction, including dysfunction of the respiratory, cardiovascular, renal, hepatic, coagulation, and central nervous systems (**Online Appendix**, Supplemental Digital Content 1, http://links.lww.com/CCM/A616). Among these four methods, there is considerably more variation in ICD-9 capture technique for infection than for organ dysfunction. Specifically, Angus et al (8) used 1,286 codes for infection and 13 codes for acute organ dysfunction. Martin et al (14) defined severe sepsis using six codes for infection including

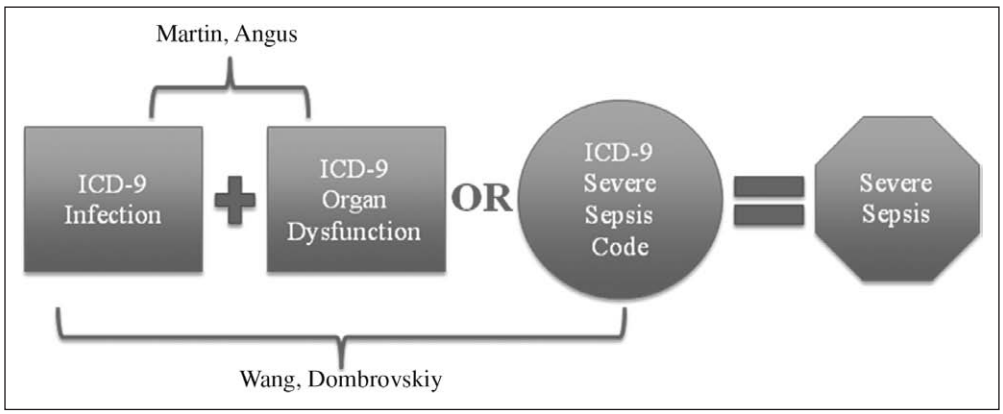

Figure 1. Previous use of *International Statistical Classification of Diseases*, 9th Edition (ICD-9), codes to determine National Epidemiologic Estimates. National estimates of the incidence and mortality of severe sepsis were generated using ICD-9 codes to pair infection to organ dysfunction or an ICD-9 severe sepsis code (995.92), introduced in 2002. Both Angus et al (8) and Martin et al (14) utilized data collected prior to 2002 and thus did not include 995.92. Dombrovskiy et al (13) and Wang et al (12) used separate databases that included 995.92.

bacteremia, septicemia, and fungemia. Dombrovskiy et al (13) used 18 ICD-9 codes for infection, including the new sepsis specific codes. Finally, Wang et al (12) combined a similar set of codes for infection and acute organ dysfunction as Angus et al (8) with ED temperature and hypotension.

Primary and secondary diagnoses, procedures, admission source, hospital disposition, demographic variables including age, sex, and total length of stay were obtained from the NIS. Annual incidence (per 100,000 population) was calculated using annual estimates of the 2004–2009 U.S. adult population, accessed at the U.S. Census Bureau's website (http://www.census.gov/popest/national/asrh/NC-EST2009-sa.html). In-hospital mortality was calculated as the ratio of in-hospital deaths to total cases of severe sepsis by year and compared by each of the four methods. Number and type of organ dysfunctions by year were compared by each method. In theory, the new ICD-9 sepsis codes introduced in 2002 and 2003 could be used to generate national estimates without including codes for infection and organ dysfunction. Therefore, ICD-9 codes for severe sepsis (995.92) and septic shock (785.52) were used to independently compare incidence over the 6-year period. Patients less than or equal to 18 years old were excluded.

Statistical Analysis

Descriptive analyses were performed using SAS software (SAS Institute, Cary, NC, Version 9.2), as well as SAS-callable SUDAAN, Version 10.0.1 (Software for the Statistical Analysis of Correlated Data, Version 10.0.1), to account for weighted frequencies and provide national estimates. Average annual change in incidence was calculated by comparing the most recent year of data with the earliest year of data (2009 vs. 2004) and assuming constant proportional (i.e., exponential) annual change.

RESULTS

Patient Characteristics and Organ Dysfunction

Distribution of patients in different age ranges was similar across the four methods; methods by Angus et al (8) and Wang et al (12) included a higher percentage of females than the methods by Martin et al (14) and Dombrovskiy et al (13) (**Table 1**). The number and type of organ dysfunctions varied by abstraction method. Overall, the cohorts of Dombrovskiy et al (13) and Martin et al (14) had a higher mean number of organ dysfunctions and longer length of stay.

Incidence

A total of 39,893,459 hospitalizations were found from 2004 to 2009, representing a weighted total of 196,096,962 admissions to all U.S. acute care hospitals across the 6-year period. The four separate methods yielded the following incidences of severe sepsis per 100,000 population across the 6-year period:

TABLE 1. Patient Characteristics and Organ Dysfunction

	Angus et al (8)	Wang et al (12)	Dombrovskiy et al (13)	Martin et al (14)
Total patients, 2003–2009 (unweighted *n*)	12,267,065 (2,489,751)	13,980,089 (2,837,265)	4,067,836 (827,014)	5,001,750 (1,017,198)
Female (%)	52.3	53.0	49.7	49.4
Age (%)				
18–54	20.2	19.2	20.7	22.2
55–64	16.0	16.1	16.9	17.3
65–74	20.7	21.5	21.1	21.1
75–84	26.3	26.6	25.5	24.6
85 and above	16.8	16.6	15.9	14.9
Organ dysfunction (%)				
Cardiovascular	30.0	24.7	42.6	34.6
Respiratory	27.4	41.1	40.7	43.0
Neurologic	11.4	9.9	10.5	10.6
Hematologic	17.8	15.4	16.6	15.5
Hepatic	1.8	1.5	5.1	4.3
Renal	47.9	41.4	48.7	62.0
Mean number of organ dysfunctions	1.38	1.36	1.68	1.89
Mean length of stay (d)	11.5	10.9	14.1	13.8

Angus et al (8) (905/100,000), Wang et al (12) (1,031/100,000), Dombrovskiy et al (13) (300/100,000), and Martin et al (14) (369/100,000). Yearly incidence varied as much as 3.5-fold depending on the method used. The total number of cases of severe sepsis nationally in 2009 ranged from 894,013 (13) to 3,110,630 (14). Regardless of method, there was a steady increase in the annual incidence (**Fig. 2*A***) and average annual percentage increase in the incidence was similar: 13.0% for both Angus et al (8) and Wang et al (12) and 13.3% for both Dombrovskiy et al (13) and Martin et al (14).

Mortality

We examined sepsis-associated mortality in two ways. We describe the total number of deaths from sepsis, as well as the case fatality rate. Mortality from severe sepsis varied two-fold depending on the definition, ranging from 14.7% (13) to 29.9% (14). Regardless of method used, there was an annual decrease in the case fatality rate over the 6-year period (Fig. 2*B*). A significant decrease in the relative mortality rate (27.2% and 31.1%) was found over the study period using the methods of Dombrovskiy et al (13) and Angus et al (8), respectively. Total mortality increased yearly from 2004 to 2008 regardless of method used (Fig. 2*C*).

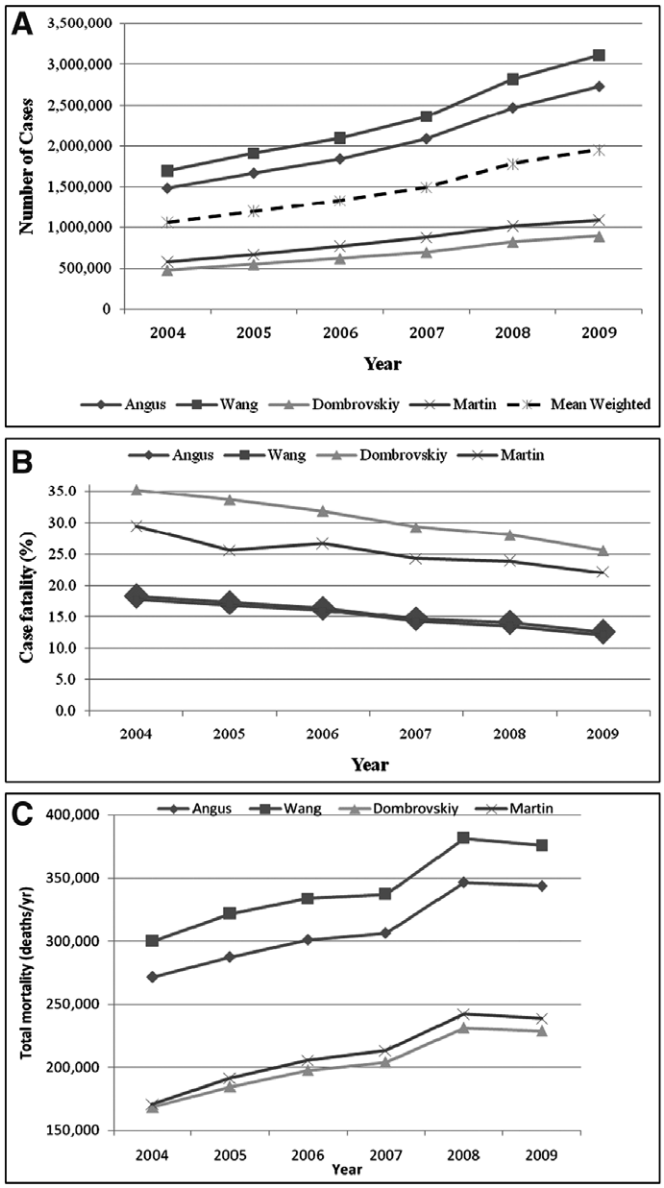

Figure 2. **A**, Incidence of severe sepsis by method over 6-year period. **B**, In-hospital case fatality of severe sepsis by method. **C**, Total mortality of severe sepsis by method.

Organ Dysfunction

It is possible that the four methods of ICD-9 abstraction identified cohorts of patients with different levels of illness severity. Cases identified using each ICD-9 method were compared by number of organ dysfunctions present. There was substantial variation in the percentage of patients with specific organ dysfunctions, including cardiovascular, pulmonary, and renal dysfunction depending upon capture technique. Regardless of technique used, a strikingly high percentage of patients had renal dysfunction (**Fig. 3**). Patients identified using the methods of Angus et al (8) and Wang et al (12) were more likely to have single-organ system involvement (72.4% and 71.9%, respectively) compared with cases found using the methods of Martin et al (14) and Dombrovskiy et al (13) (47.8% and 47.3%, respectively). Conversely, the methods by Martin et al (14) and Dombrovskiy et al (13) were more likely to identify patients with four or more organ system involvement (9.5% and 5.5%, respectively) compared with the alternative methods (2.1% [8], 1.9% [12]). There were a small percentage of patients in the cohort identified using Wang et al (12) and Dombrovskiy et al (13) (0.9% and 5.4%, respectively) that only received a new ICD-9 code for severe sepsis (995.92) and not a corresponding code for organ dysfunction.

Use of ICD-9 Codes for Sepsis, Severe Sepsis, and Septic Shock

Using the new ICD sepsis codes introduced in 2002–2003, we found an annual incidence of 231 cases of sepsis (995.91), 144 cases of severe sepsis (995.92), and 95 cases of septic shock (785.52) per 100,000 over the 6-year period. For all sepsis codes, an annual increase in use was observed (**Fig. 4**), the rate of which varied by ICD-9 code: 22.3% for sepsis, 25.3% for severe sepsis, and 18.2% for septic shock. In-hospital mortality rates were 10.6%, 36.9%, and 42.2%, respectively. A minority of patients with severe sepsis found using the four methods described above was assigned an ICD-9 specifically designated for severe sepsis (**Table 2**). Patients identified using the methods of Dombrovskiy et al (13) and Martin et al (14) were more likely to receive the ICD-9 code for severe sepsis (48.1% and 36.9%, respectively) compared with patients identified using the methods of Angus et al (8) and Wang et al (12) (14.4% and 14.0%, respectively). It would be expected that patients receiving the ICD-9 code for septic shock would also receive an ICD-9 code for severe sepsis, yet (depending on the severe sepsis methodology used) just between 51.4% and 56.6% of such patients identified received both codes.

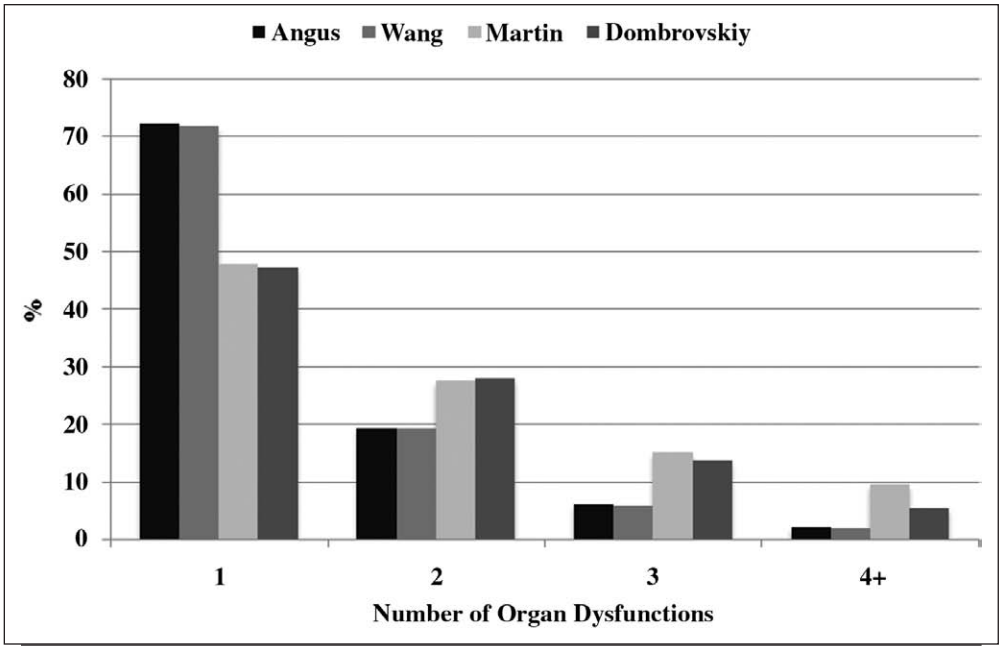

Figure 3. Number of organ dysfunctions by methods of *International Statistical Classification of Diseases*, 9th Edition (ICD-9), abstraction.

DISCUSSION

Accurate estimates of epidemiologic trends in severe sepsis and septic shock are vital for public health researchers, clinical investigators, and clinicians alike. In this study, we found that both incidence and mortality vary substantially using existing methods to identify severe sepsis. Previous prospective epidemiologic studies of severe sepsis were confined to academic settings and are not suitable for generating national estimates and trends (4, 22). Retrospective use of ICD-9 codes, although imperfect, has been shown to be highly sensitive for severe sepsis (23). Both the methods by Martin et al (14) and Angus et al (8) were validated using small groups of patients with documented cases of severe sepsis from within their own institution (Martin et al) or from hospitals included in the study (Angus et al). Because both methods were internally validated, an explanation of the large discrepancies in incidence and mortality reported is required. The difference, it appears, is how severe sepsis is defined. More inclusive definitions (Angus et al [8] and Wang et al [12]) capture more cases with lower severity; more exclusive definitions (Dombrovskiy et al [13], Martin et al [14]) capture fewer cases but with higher severity.

Our work needs to be put into context of two studies examining the incidence of severe sepsis in divergent populations. Wilhelms et al (21) used modified versions of the methods by Angus et al (8) and Martin et al (14) to estimate the incidence of severe sepsis in Sweden from 1987 to 2005. This study found an incidence of 35 cases per 100,000 (Angus et al) and 13 cases per 100,000 (Martin et al) in 2005 (8, 14). The incidence of severe sepsis reported in Sweden is strikingly lower than that reported in our U.S.-based study (8). Despite this, similar to our study, Wilhelms et al demonstrated a three-fold difference in cases captured depending upon the method used.

In a recent study, Lagu et al (7) used a modified version of the method by Dombrovskiy et al (13) to generate national estimates of severe sepsis incidence for the years 2003–2007. They found a very similar incidence (300 per 100,000) in 2007 as we report using the method by Dombrovskiy et al (13), lending support to the accuracy of our methodology. Our study expands these results using additional methods of patient capture and comparing variability between these methods.

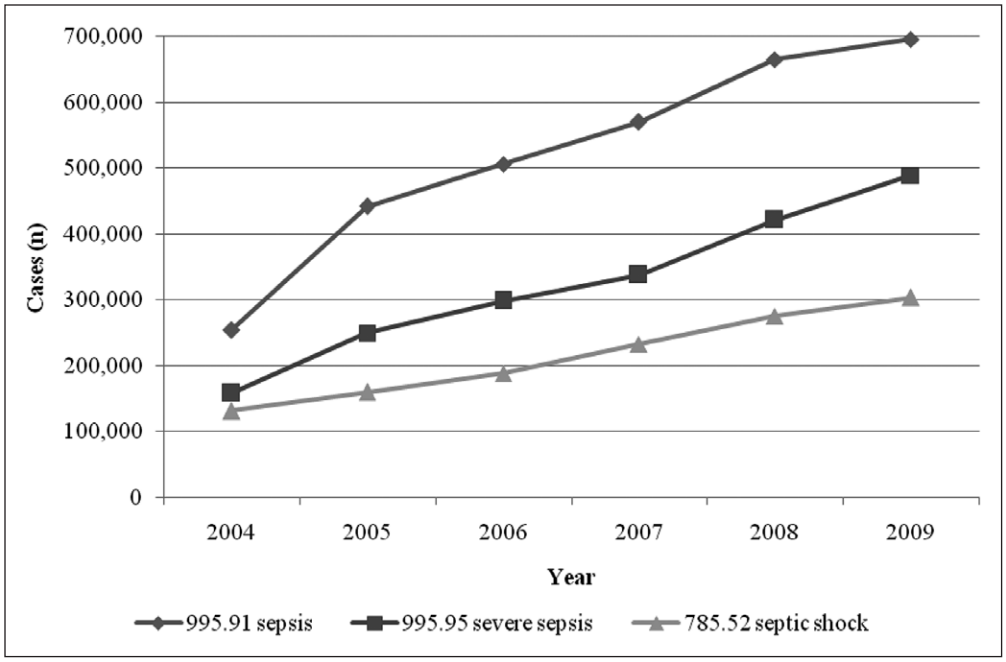

Figure 4. Use of *International Statistical Classification of Diseases*, 9th Edition, codes for sepsis (995.91), severe sepsis (995.92), and septic shock (785.52).

TABLE 2. Use of *International Statistical Classification of Diseases*, 9th Edition, Sepsis Codes by Method

	Severe Sepsis[a] (*n*)	995.92[b] (%)	785.52[c] (%)	785.52 Given 995.92[d] (%)
Angus et al (8)	12,267,065	14.4	10.4	56.6
Wang et al (12)	13,980,084	14.0	9.2	51.4
Dombrovskiy et al (13)	4,067,836	48.1	31.8	51.4
Martin et al (14)	5,001,750	36.9	25.0	53.6

[a]Total number of patients with severe sepsis from Nationwide Inpatient Sample database using respective author's method of *International Statistical Classification of Diseases*, 9th Edition (ICD-9), code abstraction over 6-yr period (2004–2009).

[b]Percentage of cases of severe sepsis using respective author's method of ICD-9 code abstraction, who also received new severe sepsis code (995.92).

[c]Percentage of cases of severe sepsis using respective author's method of ICD-9 code abstraction who also received new ICD-9 code for septic shock (785.52).

[d]Percentage of patients with ICD-9 code for septic shock, who also were assigned ICD-9 code for severe sepsis.

All four methods examined in our study utilized ICD-9 codes to pair patients with a diagnosis of infection to those with acute organ dysfunction (8, 12–14). Although small differences exist in the ICD-9 codes used in the four cohorts for organ dysfunction, there are large differences in the ICD-9 codes used for infection. Martin et al (14) and Dombrovskiy et al (13) used narrow criteria to define infection, including septicemia, bacteremia, and disseminated fungal infection. Both Angus et al (8) and Wang et al (12), however, employed a wider range of infectious ICD-9 codes including those potentially less severe such as pharyngitis, cholecystitis, pyelonephritis, and candidiasis.

According to Angus et al (8), the national incidence of severe sepsis in 1995 was estimated to be 751,000 cases, with an expected annual increase of 1.5%. Given these estimates, one would expect a national incidence of approximately 925,000 cases of severe sepsis in 2009, yet we found a incidence nearly three times that (2.7 million) using their methods. Moreover, a much higher percentage of annual increase was found using all four methods (13.0% to 13.3%). It is likely that multiple factors contribute to this rapid increase in incidence. First, the U.S. population is aging with an increasing burden of chronic disease. Second, initiatives such as the Surviving Sepsis Campaign (24) likely contribute to increased awareness among practicing clinicians, which led to a rise in diagnosis. Third, coding for organ dysfunction may have increased for financial reasons over the past decade. Finally, a recent study speculated that use of electronic records that automatically calculate clinical variables such as glomerular filtration rate may have contributed to increased coding (7).

A decrease in the case fatality rate was observed using all four abstraction methods. However, the actual number of deaths (total mortality) from severe sepsis (using any definition) increased over the study period. In fact, by our most conservative estimate, using the methods of Dombrovskiy et al (13), there were 229,044 deaths from severe sepsis in 2009, which would place severe sepsis as the third most common cause of death in the United States, after heart disease and malignant neoplasms (6).

As with our findings of increased incidence, we can only speculate about the cause of the simultaneous decrease in the case fatality rate. Improved recognition and coding of subtle and less-severe cases may have increased incidence, resulting in decreased mortality. It is also likely that clinical advances including early goal-directed therapy and prioritization of early, appropriate antimicrobials (25, 26), in addition to highly publicized mortality reduction campaigns, play a role (27). Finally, diagnostic "creep" in coding for sepsis has been recognized for decades (28) and likely contributes to the increasing incidence noted across capture methods in our study.

ICD-9 codes for sepsis including 991.91, 991.92, and 785.52 for sepsis, severe sepsis, and septic shock, respectively, were introduced in 2002 and 2003. To our knowledge, this is the first study to explore the ability of all of these codes to benchmark national incidence. Using existing methods to identify sepsis in administrative data, only a minority of cases of severe sepsis received the corresponding ICD-9 code. Cases identified using the criteria of Martin et al (14) and Dombrovskiy et al were more likely to receive proper ICD-9 coding, suggesting that patients with increasing severity of illness were more likely to have documentation by providers of severe sepsis. A patient in septic shock by definition must also have severe sepsis. Yet only 51.4% to 56.6% of patients given the septic shock code (785.52) were also assigned the severe sepsis code (991.92). This redundancy demonstrates the inherent confusion facing coders. We speculate that physicians may neglect to document severe sepsis in patients with septic shock.

Similarly, clinicians may fail to specifically document any form of sepsis in patients with the disease. Some cases may not receive ICD-9 codes necessary for capture by any of the four methods. In one study, the reproducibility of diagnoses assigned to ICU patients by the original clinicians vs. two external senior intensivists who reviewed the charts was found to be poor to moderate (kappa = 0.25–0.52) but increased to moderate to substantial (kappa = 0.49–0.77) when limited to the codes for septicemia and shock (29). We did observe an increased use of the sepsis-specific codes over the study period, likely reflecting a lag as coders became accustomed to their use along with a recognition that the new codes have a specificity that is lacking from other codes for infectious etiologies. Given the paucity of use of the new sepsis codes, our data suggest that they are at

present ill-suited to generate national estimates, unless coupled to ICD-9 codes for infection and organ dysfunction.

Our findings suggest the methods employed by Angus et al (8) and Wang et al (12) identify a group of patients with a wide spectrum of disease severity, which more accurately reflects clinical experience with severe sepsis patients. Both Angus et al (8) and Wang et al (12) employ a broader range of infectious etiologies, which we believe more closely follows the American College of Chest Physicians and Society for Critical Care Medicine consensus definition of severe sepsis (3). However, our data suggest that both Martin et al (14) and Dombrovskiy et al (13) have identified a sicker cohort of patients with over two-fold higher mortality, increased organ dysfunction, and longer hospital length of stay. The fundamental issue raised by these variations is the advantages and disadvantages of more or less inclusive capture strategies for cases of severe sepsis. It is informative that trends in the number of cases, the case fatality rate, and the yearly mean increase are almost identical regardless of search technique, providing internal validity to the capture strategies and suggesting that the differences are primarily in the inclusion or exclusion of less sick cases.

Increased recognition and novel therapeutic strategies have led to a renewed focus by hospitals to improve outcomes in patients with sepsis. There is considerable interest in sepsis pathways, treatment bundles, and other methods to reduce sepsis mortality. Many hospitals are implementing sepsis alerts in an attempt to lower their sepsis mortality (30). Pay for performance initiatives akin to time to antibiotics for patients with community-acquired pneumonia (31) could be developed to target clinical interventions for patients with severe sepsis. Yet central to these efforts is a uniform definition of the disease in question and a universal means by which to measure outcomes. Consistent use of an acceptable proxy definition in administrative databases would result in more reliable estimates of epidemiologic trends and the efficacy of clinical interventions. Without either a new data collection infrastructure or an agreed upon use of administrative data, facilities will not be able to uniformly report how many cases of sepsis are seen annually or measure the impact of efforts focused on reducing morbidity and mortality.

Although we provide the first national analysis benchmarking the incidence and case fatality rate of severe sepsis using all recognized definitions, our study has limitations. The NIS is the largest all-payer, publicly available inpatient database in the United States, but we are limited by our inability to independently verify accuracy of hospital codes. Factors such as preexisting organ dysfunction may be inappropriately attributed to new or hospital-acquired dysfunction. We are likewise unable to attribute in-hospital mortality to severe sepsis, as some patients likely expired of other causes, and the impact of do-not-resuscitate orders are not available in our data or considered in our analysis. We have excluded patients less than or equal to 18 years old, and our comparisons to previous epidemiologic work should be interpreted in that context, as Angus et al (8), Martin et al (14) and Dombrovskiy et al (13) included patients of all ages. Wang et al (12) used the clinical variables of ED triage temperature and systolic blood pressure to identify patients with severe sepsis. These variables are not available in the NIS, and their absence may have led us to underestimate the incidence of severe sepsis using their methods. Finally, although we were able to analyze the NIS using four well-recognized capture methodologies and to explore the use of newer sepsis-specific ICD-9 codes, none of these is the "gold standard" that can be used to analyze the sensitivity and specificity of each methodology. We have provided a mean incidence calculated from the four methodologies, which provides another estimate of annual incidence and reflects a balance between inclusivity and exclusivity of capture techniques. The increase in total number of patients captured using the sepsis-specific codes may reflect either a true increase in incidence or an incremental increase in use of the specific codes.

CONCLUSION

We show that national estimates of severe sepsis incidence and mortality are highly variable depending on the method used, and we offer the varying ranges of incidence and mortality in an effort to benchmark the true national incidence and impact of this life-threatening condition. Despite this variability, our work sheds light on some important trends. National rates of death from severe sepsis increased between 2004 and 2009 despite a decrease in the case fatality rate. We attribute this to increasing recognition, more inclusive coding, as well as the impact of novel interventions, on disease course. Further use of administrative databases utilizing ICD-9 codes should consider the differences between the methods described here. Finally, as new consensus definitions develop that will likely incorporate clinical variables, attention should be given to the development of a consensus definition of severe sepsis using administrative data for the purposes of national benchmarking and public reporting.

REFERENCES

1. Geroulanos S, Douka ET: Historical perspective of the word "sepsis". *Intensive Care Med* 2006; 32:2077
2. Bone RC: Sepsis, the sepsis syndrome, multi-organ failure: A plea for comparable definitions. *Ann Intern Med* 1991; 114:332–333
3. Bone RC, Balk RA, Cerra FB, et al: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992; 101:1644–1655
4. Rangel-Frausto MS, Pittet D, Costigan M, et al: The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study. *JAMA* 1995; 273:117–123
5. Bone RC: Sepsis, sepsis syndrome, and the systemic inflammatory response syndrome (SIRS). Gulliver in Laputa. *JAMA* 1995; 273:155–156
6. Kochanek KD, Xu J, Murphy SL, et al: Deaths: Preliminary data for 2009. *In:* National vital statistics reports. Volume 59, No 4. Hyattsville: National Center for Health Statistics, 2011

7. Lagu T, Rothberg MB, Shieh MS, et al: Hospitalizations, costs, and outcomes of severe sepsis in the United States 2003 to 2007. *Crit Care Med* 2012; 40:754–761
8. Angus DC, Linde-Zwirble WT, Lidicker J, et al: Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001; 29:1303–1310
9. Weycker D, Akhras KS, Edelsberg J, et al: Long-term mortality and medical care charges in patients with severe sepsis. *Crit Care Med* 2003; 31:2316–2323
10. McBean M, Rajamani S: Increasing rates of hospitalization due to septicemia in the US elderly population, 1986–1997. *J Infect Dis* 2001; 183:596–603
11. Melamed A, Sorvillo FJ. The burden of sepsis-associated mortality in the United States from 1999 to 2005: An analysis of multiple-cause-of-death data. *Crit Care* 2009; 13:R28
12. Wang HE, Shapiro NI, Angus DC, et al: National estimates of severe sepsis in United States emergency departments. *Crit Care Med* 2007; 35:1928–1936
13. Dombrovskiy VY, Martin AA, Sunderram J, et al: Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: A trend analysis from 1993 to 2003. *Crit Care Med* 2007; 35:1244–1250
14. Martin GS, Mannino DM, Eaton S, et al: The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003; 348:1546–1554
15. Powell ES, Khare RK, Courtney DM, et al: Volume of emergency department admissions for sepsis is related to inpatient mortality: Results of a nationwide cross-sectional analysis. *Crit Care Med* 2010; 38:2161–2168
16. Strehlow MC, Emond SD, Shapiro NI, et al: National study of emergency department visits for sepsis. *Ann Emerg Med*. 2006; 48:326–331
17. Dombrovskiy VY, Martin AA, Sunderram J, et al: Facing the challenge: Decreasing case fatality rates in severe sepsis despite increasing hospitalizations. *Crit Care Med* 2005; 33:2555–2562
18. Wang HE, Devereaux RS, Yealy DM, et al: National variation in United States sepsis mortality: A descriptive study. *Int J Health Geogr* 2010; 9:9
19. Wenzel RP, Edmond MB: Severe sepsis-national estimates. *Crit Care Med* 2001; 29:1472–1474
20. Linde-Zwirble WT, Angus DC: Severe sepsis epidemiology: Sampling, selection, and society. *Crit Care* 2004; 8:222–226
21. Wilhelms SB, Huss FR, Granath G, et al: Assessment of incidence of severe sepsis in Sweden using different ways of abstracting International Classification of Diseases codes: Difficulties with methods and interpretation of results. *Crit Care Med* 2010; 38:1442–1449
22. Sands KE, Bates DW, Lanken PN, et al: Academic Medical Center Consortium Sepsis Project Working Group: Epidemiology of sepsis syndrome in 8 academic medical centers. *JAMA* 1997; 278: 234–240
23. Ollendorf DA, Fendrick AM, Massey K, et al: Is sepsis accurately coded on hospital bills? *Value Health* 2002; 5:79–81
24. Townsend SR, Schorr C, Levy MM, et al: Reducing mortality in severe sepsis: The Surviving Sepsis Campaign. *Clin Chest Med* 2008; 29:721–733
25. Rivers E, Nguyen B, Havstad S, et al: Early Goal-Directed Therapy Collaborative Group: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345:1368–1377
26. Kumar A, Roberts D, Wood KE, et al: Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006; 34:1589–1596
27. Levy MM, Dellinger RP, Townsend SR, et al: Surviving Sepsis Campaign: The Surviving Sepsis Campaign: Results of an international guideline-based performance improvement program targeting severe sepsis. *Crit Care Med* 2010; 38:367–374
28. Helms CM: A pseudo-epidemic of septicemia among Medicare patients in Iowa. *Am J Public Health* 1987; 77:1331–1332
29. Misset B, Nakache D, Vesin A, et al: Outcomerea Database Investigators: Reliability of diagnostic coding in intensive care patients. *Crit Care* 2008; 12:R95
30. McGillicuddy DC, O'Connell FJ, Shapiro NI, et al: Emergency department abnormal vital sign "triggers" program improves time to therapy. *Acad Emerg Med* 2011; 18:483–487
31. Pines JM, Hollander JE, Datner EM, et al: Pay for performance for antibiotic timing in pneumonia: Caveat emptor. *Jt Comm J Qual Patient Saf* 2006; 32:531–535