The Impact of Centers for Medicare & Medicaid Services SEP-1 Core Measure Implementation on Antibacterial Utilization: A Retrospective Multicenter Longitudinal Cohort Study With Interrupted Time-Series Analysis

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Background. The impact of the US Centers for Medicare & Medicaid Services (CMS) Severe Sepsis and Septic Shock: Management Bundle (SEP-1) core measure on overall antibacterial utilization is unknown.

Methods. We performed a retrospective multicenter longitudinal cohort study with interrupted time-series analysis to determine the impact of SEP-1 implementation on antibacterial utilization and patient outcomes. All adult patients admitted to 26 hospitals between 1 October 2014 and 30 September 2015 (SEP-1 preparation period) and between 1 November 2015 and 31 October 2016 (SEP-1 implementation period) were evaluated for inclusion. The primary outcome was total antibacterial utilization, measured as days of therapy (DOT) per 1000 patient-days.

Results. The study cohort included 701,055 eligible patient admissions and 4.2 million patient-days. Overall antibacterial utilization increased 2% each month during SEP-1 preparation (relative rate [RR], 1.02 per month [95% confidence interval {CI}, 1.00–1.04]; P = .02). Cumulatively, the mean monthly DOT per 1000 patient-days increased 24.4% (95% CI, 18.0%–38.8%) over the entire study period (October 2014–October 2016). The rate of sepsis diagnosis/1000 patients increased 2% each month during SEP-1 preparation (RR, 1.02 per month [95% CI, 1.00–1.04]; P = .04). The rate of all-cause mortality rate per 1000 patients decreased during the study period (RR for SEP-1 preparation, 0.95 [95% CI, .92–.98; P = .001]; RR for SEP-1 implementation, .98 [.97–1.00; P = .01]). Cumulatively, the monthly mean all-cause mortality rate/1000 patients declined 38.5% (95% CI, 25.9%–48.0%) over the study period.

Conclusions. Announcement and implementation of the CMS SEP-1 process measure was associated with increased diagnosis of sepsis and antibacterial utilization and decreased mortality rate among hospitalized patients.

Keywords. antimicrobial utilization; sepsis; patient outcomes.

Severe sepsis leads to increased mortality rates [1, 2] and is the leading cause of infection-related death in hospitalized patients. The Surviving Sepsis Campaign (SSC) was launched as an international consensus group in 2002, with a goal of reducing sepsis-related mortality rates [3]. For almost 20 years, the SSC has promoted and updated evidence-based guidelines that include protocol-driven, goal-oriented resuscitation within the first 6 hours of sepsis onset [4, 5]. Adherence to interventions and activities promoted by the SSC can lead to decreased mortality rate [6]. In particular, early administration of effective antimicrobial therapy has been associated with decreased mortality rate in sepsis [7, 8].

As a result, the Centers for Medicare & Medicaid Services (CMS) amended its Core Measures program to mandate a National Quality Forum–endorsed measure that included specific elements from the SSC guidelines [9]. Announced in October 2014 and required as of 1 October 2015, all US hospitals began reporting specific data for the Severe Sepsis and Septic Shock: Management Bundle (SEP-1) core measure to receive full CMS reimbursement. Among other requirements, hospitals must administer broad-spectrum antibacterial agents within 3 hours of sepsis onset. However, the SEP-1 measure and most hospital sepsis bundle processes do not include important follow-up care outlined in SSC guidelines: a daily review of antibacterial therapy to deescalate or discontinue treatment in appropriate patients.

Although the SEP-1 core measure was designed to improve sepsis care, it could have the unintended consequence...
of increasing unnecessary antibiotic use in patients who do not have sepsis, leading to unintended adverse events [10]. In fact, the Infectious Disease Society of America (IDSA) recently released suggested changes to the SEP-1 measure to decrease this risk [11]; editorialists countered that the IDSA had not adequately demonstrated that the SEP-1 measure increased antibiotic utilization [12]. Thus, the objective of the current study was to determine the impact of CMS SEP-1 core measure on antibacterial utilization in hospitalized patients.

METHODS

Study Design
We performed a retrospective multicenter longitudinal cohort with interrupted time series segmented regression analysis. Our analysis included 3 distinct time periods: 1 October 2014 through 30 September 2015, the 12 months following the announcement of the SEP-1 requirement before implementation, hereafter the “SEP-1 preparation period”; 1 October 2015 through 31 October 2015, the first month of SEP-1 implementation, hereafter the “wash-in period”; and 1 November 2015 through 31 October 2016, hereafter the “SEP-1 implementation period.” The “study period” was defined as the period from 1 October 2014 to 31 October 2016.

Our study was designed to test the hypothesis that implementation of the SEP-1 core measure led to increased utilization of antibacterial agents. To evaluate this hypothesis, we compared antibacterial use during 12 months of SEP-1 preparation, at the time of transition from SEP-1 preparation to implementation, and during 12 months of SEP-1 implementation.

Participating Hospitals
A total of 26 hospitals participated in the study, including 3 academic medical centers and 23 community hospitals (Supplementary [Appendix] Table 1).

Inclusion and Exclusion Criteria—Patient Selection
All adult patients (aged ≥18 years) admitted to study hospitals during the study period were evaluated for inclusion. If patients had multiple admissions, only the first admission during each study period was included. Patients were excluded if they spent <24 hours in the hospital, spent >120 days in the hospital (consistent with the SEP-1 rule), or spent any time in pediatric units or obstetrics units. Nonantibacterial antibiotics and antibacterial agents given through unknown or miscellaneous routes were excluded.

Data Collection
All participating hospitals provided data sets for all patients who received antibacterial therapy, including antibacterial utilization data (agent, date/time of administration, route [eg, intravenous, oral], and hospital unit where the antibacterial agent was administered), age, sex, and race. When available, hospitals provided mortality data, administrative data (International Classification of Disease, Ninth Revision, Clinical Modification [ICD-9]/International Classification of Disease, Tenth Revision, Clinical Modification [ICD-10-CM] codes) for comorbid conditions, and microbiology data.

Definitions
Days of therapy (DOT) was defined as any amount of a specific antibacterial agent administered in a calendar day to a particular patient (eg, if a patient receives 3 antibiotics for 3 days, the patient has received 9 DOT) [13]. Length of therapy (LOT) was defined as the number of calendar days the patient received any antibacterial agents, regardless of the number of antibiotics received during any given day (eg, if a patient receives 3 antibiotics for 3 days, the patient’s LOT is 3). A patient-day was defined as any day a patient was present in the location of interest (ie, hospital or unit) for any portion of the day. Antibiotic classes and agents were defined according to Appendix B of the Antimicrobial Use Option of the National Healthcare Safety Network [13].

Broad-spectrum antibacterial agents were defined using previously defined criteria [14]. Sepsis diagnosis, Charlson score, venous thromboembolism, and acute kidney injury with hemodialysis were derived using ICD-9-CM and ICD-10-CM codes (Supplementary Table 2) [15–17]. Healthcare facility–associated Clostridioides difficile infection was defined using National Healthcare Safety Network criteria [18]. New intensive care unit (ICU) admissions within 30 days were determined using bed flow data. Relapse of suspected infection included readmission within 30 days of index admission and initiation of a new antibacterial course after a period of >2 days with no antibacterials. For a subgroup analysis, we defined “suspected sepsis” as a patient with ≥1 blood culture who was still receiving broad-spectrum antibacterial agents 48–72 hours after blood culture collection.

Outcomes
The primary outcome was total antibacterial utilization measured as DOT per 1000 patient-days. Several predetermined secondary outcomes were evaluated, including LOT per 1000 patient-days, DOT for intravenous agents per 1000 patient-days, DOT for specific agents and classes of therapy per 1000 patient-days, sepsis incidence per 1000 patients, all-cause mortality rate per 1000 patients, ICU transfer per 1000 patients, length of hospitalization, and incidence of healthcare facility–associated C. difficile infection within 28 days of discharge per 10 000 patient-days.

Statistical Analysis
Standard descriptive statistics were used throughout. Summary statistics were compared using χ 2 tests for categorical and
Wilcoxon rank sum for continuous variables. To answer the question of interest, we modeled the outcome trajectories over time using segmented regression models, assuming that (1) the trajectories were linear before and after first implementation of SEP-1 (October 2015), (2) there could have been an immediate change in the outcome after SEP-1 implementation, and (3) the slope of the outcome trajectory may have changed after SEP-1 implementation. Hospital was the unit of analysis; mean monthly antibacterial use and monthly adverse event rates were aggregated by hospital and by month. We created a generalized estimating equation model with a log link and negative binomial distribution to determine changes in level or trend in DOT during the SEP-1 preparation period and after SEP-1 implementation.

The model included an offset term of log patient-days per 1000; mean age and mean Charlson score (both averaged across the patients admitted in a hospital in a given month) were included as adjustment covariates. An autoregressive [1] correlation structure was used to account for autocorrelation between months for observations from the same hospital. This same modeling approach was used for all models. For ease of interpretation of the primary outcome, contrasts were calculated to compare changes at 3 time points corresponding to before (month 1), during (month 13), and after (month 25) SEP-1 implementation. Ninety-five percent confidence intervals for these contrasts were estimated using the bias-corrected-and-accelerated bootstrap method [19].

All analyses were performed using SAS Institute software, version 9.4. All statistical tests were 2 sided with an α level of 0.05. No formal adjustment for multiplicity of analyses was performed.

Ethics Statement
The Duke University Health System Institutional Review Board (IRB) served as the IRB of record for the study. The study was approved with expedited review and waiver of informed consent. All study hospitals ceded authority to the Duke University Health System IRB.

RESULTS
Patient Population
In total, 701,055 patient admissions met all inclusion and exclusion criteria during the study period. Patient characteristics were similar in the SEP-1 preparation and implementation periods (Table 1). The number of patients with a sepsis diagnosis code increased from 16,934 (4.8%) during the SEP-1 preparation period to 19,807 (5.7%) during the SEP-1 implementation period. Study hospitals accrued a total of 4.2 million patient-days during the study. More than 1.9 million antibiotic DOT were administered during the study (Supplementary Table 3). The majority were administered intravenously (Supplementary Table 4).

Antibacterial Utilization During the SEP-1 Preparation and Implementation Periods
The proportion of patients receiving any antibacterial agent increased from the SEP-1 preparation to the SEP-1 implementation periods (47% vs 52%; Table 1). The proportion of patients receiving ≥1 day of intravenous therapy also increased from the SEP-1 preparation to the SEP-1 implementation period (42% vs 47%). The unadjusted median monthly antibacterial DOT per 1000 patient-days increased from the SEP-1 preparation period to the SEP-1 implementation period (545.6 [interquartile range, 394.9–661.2] vs 605.2 [471.2–714]; Table 2).

Trends and Changes in Utilization Estimated From Models
Antibacterial utilization changed during the SEP-1 preparation period (Table 3 and Figure 1). Overall antibacterial utilization increased 2% each month during SEP-1 preparation (relative rate [RR], 1.02 per month [95% confidence interval (CI)], 1.00–1.04; P = .02). While the slope of the utilization trend differed between the SEP-1 implementation phase and preparation phases (RR, 0.98 [95% CI, 0.96–0.99]; P = .003), the slope did not change after SEP 1 implementation (implementation phase trend RR, 1.00 [95% CI, 0.99–1.00]; P = .10). Cumulatively, the mean monthly DOT per 1000 patient-days increased 32.5% (5% CI, 23.6%–45.8%) during the 12 months of SEP-1 preparation (Supplementary Table 5). The overall use of antibacterials increased 24.4% (95% CI, 18.0%–38.8%) over the entire study period (October 2014 to October 2016; Supplementary Table 5). Similar trends were seen with LOT per 1000 patient-days (Table 3 and Supplementary Figure 1).

A similar increase in intravenous antibacterial use categories (RR, 1.02 [95% CI, 1.01–1.04]; P = .005) and anti–methicillin-resistant Staphylococcus aureus (MRSA) agents (1.02 [1.00–1.04]; P = .02) was observed during SEP-1 preparation. Increased utilization of vancomycin (RR, 1.03 [95% CI, 1.01–1.04]; P = .003) was likely responsible for the increase in use of anti-MRSA agents.

Observed increases in antibacterial utilization during the SEP-1 preparation period were likely driven by changes observed in community hospitals (RR, 1.02 per month [95% CI, 1.00–1.04]; P = .02). In contrast, antibacterial utilization increased 12% at the time of SEP-1 implementation (RR, 1.12 [95% CI, 1.02–1.23], P = .02) in tertiary care hospitals (Supplementary Figures 2 and 3).

Adverse Events
Descriptive statistics for adverse events are provided in Supplementary Table 7. The rate of sepsis diagnoses per 1000 patients increased 2% each month during SEP-1 preparation (RR, 1.02 per month [95% CI, 1.00–1.04]; P = .04). Cumulatively, the rate of sepsis diagnosis increased 32.9% (95% CI, 25.0–52.2) during the study period (Table 3 and Supplementary Figure 4). The all-cause mortality rate declined during the study period (Table 3 and Figure 2). The mortality rate per 1000 patients...
decreased 5% each month during SEP-1 preparation (RR, 0.95 [95% CI, 0.92–0.98]; \( P =.001 \)), increased 19% at the transition to SEP-1 implementation (1.19 [1.02–1.40]; \( P =.03 \)), and then declined 2% each month during SEP-1 implementation (0.98 [0.97–1.00]; \( P =.01 \)). Cumulatively, the monthly mean all-cause mortality rate per 1000 patients declined 21.7% (95% CI, ...
1.0%–30.6%) during the 12 months of SEP-1 preparation and 38.5% (25.9%–48.0%) over the study period (Supplementary Table 5).

Additional analyses and sensitivity analyses regarding hospital trends, adverse events, and methodological assumptions and decisions are provided in the appendix. Results from an analysis of patients with suspected sepsis from a subgroup of 10 study hospitals with complete microbiology data are provided in the Supplement and Supplementary Table 9.

**DISCUSSION**

To our knowledge, our multicenter study is the largest to describe the impact of CMS's SEP-1 process measure...
implementation on antibacterial utilization and adverse events. Preparation and implementation of SEP-1 in our cohort of hospitals led to mixed results. The SEP-1 requirement was associated with an increase in antibacterial utilization during the 12-month SEP-1 preparation period; antibacterial utilization remained elevated by 24% at the end of the first 12 months of SEP-1 implementation. In addition, we observed a significant decline in all-cause mortality, which declined 39% over the entire study period.

Several other observations support the association between SEP-1 requirements and increased antibacterial utilization: the proportion of patients who received any antibacterial agent and the proportion who received any intravenous agent increased in the SEP-1 implementation period; the utilization rates of overall and anti-MRSA agents increased in the SEP-1 implementation period; the overall LOT increased during the study period; and the proportion of patients with suspected sepsis increased in the SEP-1 implementation period.

The SSC provides evidence-based practices for patients with sepsis and septic shock [4]. Adherence to interventions and activities promoted by the SSC can lead to a decreased mortality rate [6]. In particular, early administration of effective antimicrobial therapy has been associated with decreased mortality rate in sepsis [7], particularly in patients with septic shock [20, 21]. As a result, it is plausible that the observed decline in mortality rate was related to improved and prompt antibacterial therapy for patients with sepsis. However, we did not observe changes in mortality rate in our subanalysis of patients with suspected sepsis. Furthermore, the decline in observed all-cause mortality rate was out of proportion to the increased number of patients with diagnosed sepsis and increased antibacterial utilization. Additional analyses will be required to confirm our population-level observation of improved mortality rate. Interventions recommended by the SSC, however, can lead to additional risks, for both the patient (eg, adverse drug events, C. difficile infection, and antibiotic resistance) and the healthcare

### Table 3. Changes in Antibacterial Utilization and Adverse Events in the SEP-1 Preparation and Implementation Periods, Estimated From Generalized Estimated Equation Models

<table>
<thead>
<tr>
<th>Cohort and Outcome</th>
<th>Admissions, No.</th>
<th>Value (95% CI); P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AU Models (Hospitals)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOT/100 patient-days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All hospitals (n = 26)</td>
<td>701 055</td>
<td></td>
</tr>
<tr>
<td>Overall AU</td>
<td>1.02 (1.00–1.04); .02</td>
<td>0.99 (.92–1.07); .81</td>
</tr>
<tr>
<td>Intravenous antibacterial</td>
<td>1.02 (1.01–1.04); .005</td>
<td>0.96 (.89–1.04); .28</td>
</tr>
<tr>
<td>Anti-MRSA</td>
<td>1.02 (1.00–1.04); .02</td>
<td>0.96 (.84–1.10); .56</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1.03 (1.01–1.04); .003</td>
<td>0.93 (.82–1.05); .23</td>
</tr>
<tr>
<td>Antipseudomonal</td>
<td>1.02 (1.00–1.03); .07</td>
<td>1.03 (.95–1.11); .53</td>
</tr>
<tr>
<td>Carbapenem</td>
<td>1.00 (.98–1.03); .81</td>
<td>0.91 (.69–1.19); .48</td>
</tr>
<tr>
<td>P/T</td>
<td>1.02 (1.00–1.04); .12</td>
<td>0.92 (.81–1.04); .18</td>
</tr>
<tr>
<td>Community hospitals (n = 23)</td>
<td>545 498</td>
<td></td>
</tr>
<tr>
<td>Tertiary care hospitals (n = 3)</td>
<td>155 557</td>
<td></td>
</tr>
<tr>
<td>Patients with suspected sepsis (n = 10)</td>
<td>31 013</td>
<td></td>
</tr>
<tr>
<td>LOT/1000 patient-days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All hospitals (n = 26)</td>
<td>701 055</td>
<td></td>
</tr>
<tr>
<td>AE Models (n = 26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE rate/1000 patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis rate</td>
<td>701 055</td>
<td>1.02 (1.00–1.04); .01</td>
</tr>
<tr>
<td>Mortality rate</td>
<td>701 055</td>
<td>0.95 (.92–.98); .001</td>
</tr>
<tr>
<td>ICU transfer rate</td>
<td>616 508</td>
<td>1.07 (1.04–1.09); &lt;.001</td>
</tr>
<tr>
<td>Length of hospitalization</td>
<td>701 055</td>
<td>0.97 (.95–.99); .007</td>
</tr>
<tr>
<td>CDI</td>
<td>285 149</td>
<td>0.97 (.91–1.03); .32</td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse event; AU, antimicrobial utilization; CDI, Clostridioides difficile infection; CI, confidence interval; DOT, days of therapy; ICU, intensive care unit; LOT, length of therapy; MRSA, methicillin-resistant Staphylococcus aureus; P/T, piperacillin-tazobactam; SEP-1, Severe Sepsis and Septic Shock: Management Bundle.

*All models were adjusted for mean age and mean Charlson score, averaged across the patients admitted in a hospital in a given month.

*Defined as the number of calendar days a patient received any antibacterial agent.

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*Nine hospitals had microbiological data available; rate summarized as CDIs/10,000 patient-days.
population (eg, antibiotic resistance). Thus, mandates for prompt, aggressive empiric antibacterial therapy in a broad population must be scrutinized for unintended consequences.

In fact, prior federal mandates for process measures requiring prompt treatment with antibiotics have led to unintended consequences. For example, the CMS CAP core measure required administration of antibacterials to patients with community-acquired pneumonia (CAP) within 4 hours of their arrival [22]. This measure led to an alarming proportion of patients who unnecessarily received antibacterials in the emergency department despite no subsequent evidence for a diagnosis of CAP [23] and increased rates of *C. difficile* infection [24]. These findings led many experts to conclude that the CAP core measure directly led to unnecessary antibiotic use and patient harm, leading to subsequent adjustment of the measure. Similar concerns have been raised regarding the SEP-1 core measure [10, 25]. While patients with septic shock are likely to benefit from rapid, aggressive antibacterial therapy [20, 21], the benefit is unclear for patients with sepsis but without shock [7, 26]. These concerns were reiterated more emphatically in a 2020 IDSA statement calling for SEP-1 to be restricted to septic shock [11].

Our data largely support findings from other studies. Miller and colleagues [27] evaluated 400 patients admitted to the emergency department with suspected sepsis and concluded that the proportion of patients receiving appropriate broad-spectrum antibacterial combination therapy declined 12% after implementation of SEP-1. Hiensch and colleagues [28] implemented an electronic sepsis initiative to quickly identify patients with suspected sepsis in a large, tertiary care hospital. Once prompted by the electronic system, clinicians used a protocolized order set to administer care. Implementation of the electronic sepsis screening tool and treatment protocol led to statistically significant increases in antibacterial utilization and hospital-onset *C. difficile* infection.

In contrast, we observed a significant decline in mortality rate that occurred simultaneously with the increase in antibacterial therapy. This finding must be evaluated in context of other studies suggesting that aggressive use of empiric antibacterial therapy and prolonged treatment duration have been associated with increased mortality risk. For example, Hranjec and colleagues [29] implemented a protocol for aggressive antibacterial therapy (ie, at the first clinical suspicion of infection) for 12 months in a tertiary care surgical ICU, followed by a protocol for conservative antibacterial therapy (ie, therapy only after objective evidence of infection). The mortality rate was lower and the length of stay shorter among the 721 patients in the conservative treatment arm compared with the 762 in the aggressive treatment arm. Furthermore, our finding is in contrast to results from a systematic review of 20 studies evaluating the impact of SEP-1 implementation on patient outcomes. Authors of this systematic review concluded that SEP-1 implementation did not improve survival in adults with sepsis [30]. At the very least, we believe that results from our analysis point to opportunities for improving deescalation (ie, stopping empiric antibacterial agents when...

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**Figure 1.** Changes in antibacterial utilization (days of therapy [DOT] per 1000 patient-days) in the Severe Sepsis and Septic Shock: Management Bundle (SEP-1) preparation, transition, and implementation periods. Solid lines represent averages of the monthly hospital rates, calculated for each month and year. Dashed lines represent expected rates calculated from the fitted generalized estimating equation models reported in Table 3. Expected rates were calculated for a hypothetical hospital with the values of age and Charlson score covariates equal to the averages across the hospitals.

**Figure 2.** Changes in all-cause mortality rate (per 1000 patients) in the Severe Sepsis and Septic Shock: Management Bundle (SEP-1) preparation, transition, and implementation periods. Solid lines represent averages of the monthly hospital rates, calculated for each month and year. Dashed lines represent expected rates calculated from the fitted generalized estimating equation models reported in Table 3. Expected rates were calculated for a hypothetical hospital with the values of age and Charlson score covariates equal to the averages across the hospitals.
no longer needed) and the need for evaluation of ongoing therapy.

Our study has limitations. First, it was retrospective, which should limit interpretation of the results to association and not causality. Second, study outcomes were based on antibacterial utilization rates; no assessment of appropriateness was performed. Third, our study was performed in hospitals, health systems, and networks that emphasized improvement in sepsis care as well as antibiotic stewardship during the study period. Our results may not be generalizable to other settings and may represent an understimation of the potential impact of SEP-1 implementation on antibacterial utilization. The study included 26 hospitals in 3 regions of the United States and included a large number of community hospitals, where the majority of healthcare in the United States is provided [31, 32]. Fourth, coding data were used to summarize comorbid conditions and adverse events; microbiological data were not available to determine the impact of SEP-1 on the incidence of multidrug-resistant organisms. Fifth, we were not able to analyze antimicrobial utilization trends before the study period to confirm that the trends observed in the SEP-1 preparation phase were novel. Finally, given the observational nature of the study, we cannot exclude the possibility of an unmeasured confounder that could have affected the results.

In summary, implementation of the CMS SEP-1 process measure was associated with important changes in antibacterial utilization and patient outcomes in our cohort of hospitals. Utilization increased, particularly in broad-spectrum antibacterial agents typically used for treatment of sepsis. In contrast, the mortality rate declined. Our analysis does not demonstrate a causal association between implementation of SEP-1 and changes in antibacterial use or mortality, but it strongly suggests that additional investigation into the value and potential adverse events of mandated antibiotic therapy is required. Any benefits provided by the prompt and broad application of antibacterial therapy for patients with suspected sepsis may be quickly outweighed by adverse events.

Supplementary Data
Supplementary materials are available at Clinical Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyrighted and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes
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