A Collaborative Multicenter QI Initiative To Improve Antibiotic Stewardship in Newborns

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OBJECTIVES: To determine if NICU teams participating in a multicenter quality improvement (QI) collaborative achieve increased compliance with the Centers for Disease Control and Prevention (CDC) core elements for antibiotic stewardship and demonstrate reductions in antibiotic use (AU) among newborns.

METHODS: From January 2016 to December 2017, multidisciplinary teams from 146 NICUs participated in Choosing Antibiotics Wisely, an Internet-based national QI collaborative conducted by the Vermont Oxford Network consisting of interactive Web sessions, a series of 4 point-prevalence audits, and expert coaching designed to help teams test and implement the CDC core elements of antibiotic stewardship. The audits assessed unit-level adherence to the CDC core elements and collected patient-level data about AU. The AU rate was defined as the percentage of infants in the NICU receiving 1 or more antibiotics on the day of the audit.

RESULTS: The percentage of NICUs implementing the CDC core elements increased in each of the 7 domains (leadership: 15.4%–68.8%; accountability: 54.5%–95%; drug expertise: 61.5%–85.1%; actions: 21.7%–72.3%; tracking: 14.7%–78%; reporting: 6.3%–17.7%; education: 32.9%–87.2%; $P < .005$ for all measures). The median AU rate decreased from 16.7% to 12.1% (P for trend $< .0013$), a 34% relative risk reduction.

CONCLUSIONS: NICU teams participating in this QI collaborative increased adherence to the CDC core elements of antibiotic stewardship and achieved significant reductions in AU.

Unnecessary antibiotic use (AU) is a significant problem in health care across both the inpatient and outpatient settings. Antibiotic therapies provide potentially life-saving benefits to patients with bacterial infection, but these therapies have multiple, often dangerous, adverse effects that pose risk. Among very low birth weight preterm neonates, prolonged use of antibiotics has been associated with increased subsequent risk of necrotizing enterocolitis, bronchopulmonary dysplasia, retinopathy of prematurity, fungal infection, and mortality.[1–4] Authors of epidemiological studies have associated early antibiotic exposures among term infants with increased risks of atopic and allergic disorders as well as increases in early childhood weight gain.[5–8] Such adverse impacts of early

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antibiotic exposures may be mediated through effects on the developing neonatal gut microbiome. Antibiotic exposure at birth can cause prolonged changes in the developing microbiota,[9–11] and early life antibiotic exposures are associated with abnormal host development in preclinical animal models.[12–14]

Antibiotic overuse adversely impacts society as well as individual patients. A steady rise of antibiotic-resistant infections as a percent of total bacterial infections has been observed over the last 14 years, with associated excess mortality and cost.[15] Considerable practice variation in AU has been demonstrated among NICUs[16] and has been identified as a major source of health care waste in newborn medicine, particularly when used beyond 48 hours in infants with negative culture results.[17] Admissions to NICUs in the United States have been increasing in the last decade across all of the birth weight strata[18,19] without evidence of an increase in illness acuity.[20] One contributor to this may be variations in the practice of evaluating well-appearing newborns for early-onset sepsis on the basis of the maternal intrapartum diagnosis of chorioamnionitis.[21]

Over the past decade, multiple national[22] and international[23] campaigns have addressed antibiotic overuse and promoted antibiotic stewardship. In the United States in 2014, the Centers for Disease Control and Prevention (CDC) introduced 7 core elements of antibiotic stewardship for all inpatient facilities.[24] To help address the overuse and misuse of antibiotics in newborns, the Vermont Oxford Network (VON) partnered with the CDC in a multicenter, Internet-based quality improvement (QI) learning collaborative effort, Choosing Antibiotics Wisely.[25] Although single-center reports demonstrate successful reduction of unnecessary AU in newborns through the introduction of a sepsis risk calculator,[26,27] few have taken a systematic approach to antibiotic stewardship[28] and none on a national scale. In this report, we describe the impact of participation in the VON Choosing Antibiotics Wisely QI collaborative on antibiotic use rates (AURs) in 146 neonatal centers. Our objective of the current study was to assess the progress of the participating NICUs with respect to achieving the CDC core elements of antibiotic stewardship and measure the AUR over the 2 years of this collaborative.

TABLE 1 PBPs for Antibiotic Stewardship

PBPs Provided as Part of the Choosing Antibiotics Wisely iNICQ
Demonstrate an organizational commitment and promote an organizational culture that supports appropriate AU in the NICU as a critical priority
Develop, test, implement, and continually refine policies and protocols for appropriate AU in specific neonatal conditions including suspected early- and late-onset sepsis, necrotizing enterocolitis, and surgical conditions
Apply pharmacy-driven interventions designed to assure appropriate antibiotic treatment of newborn infants
Report regularly on AU and resistance in the NICU to doctors, nurses, and staff

METHODS

Program Description

Choosing Antibiotics Wisely was an Internet-based Neonatal Improvement Collaborative for Quality (iNICQ) launched by the VON in 2016[25] and concluded in 2018. This program engaged NICUs in a virtual learning network consisting of 6 to 9 webinars per year, supported by an evidence-based toolkit outlining 4 potentially better practices (PBPs). Webinars provided a review of current evidence with an emphasis on translating evidence into practice, testing PBPs, and sharing team data-driven improvement stories. The collaborative emphasized the rigorous use of QI methodology (the model for improvement[29]) to demonstrate measurable change. Centers were provided with a comprehensive toolkit that included PBPs,[30] with an emphasis on the importance of testing changes in their local context before wide-scale adoption. The PBPs (Table 1) encompassed CDC core elements of antibiotic stewardship as the foundation for QI work for the individual teams and entire collaborative. Although no single practice or bundle of care was prescribed to the NICUs, the teams self-selected key PBPs to guide local site-specific interventions. In Choosing Antibiotics Wisely, each participating center formed a multidisciplinary QI team, engaged clinical staff, and participated in 2 prospectively planned, cross-sectional, 1-day audits each year (February and November). The audits represent a uniform assessment of QI work across sites and included the following: compliance with key elements of antibiotic stewardship, standardization of 12 common clinical guidelines, measured AUR, and captured patient-level characteristics (eg, birth weight, gestational age at birth and at the time of audit, severity of illness, AU, and indications). After each audit, centers performed a gap analysis to target and further refine their ongoing QI initiatives. Teams were encouraged to develop SMART (specific, measurable, attainable, relevant, and timely) aim statements and to implement changes to local practices starting with small-scale rapid cycle improvement (ie, plan, do, study, act). The VON provided coaching and a sample table of measures (process, outcome, balancing, family-centered, and value [ie, cost needed to achieve desired

outcome and/or quality[31]]), and teams were asked to develop a local measurement plan to evaluate their ongoing tests of change. Choosing Antibiotics Wisely collaborative intentionally aligned the approach to reducing unnecessary AU with the CDC core elements of antibiotic stewardship to help develop infrastructure rather than choosing 1 specific strategy (eg, implementation of the early-onset sepsis risk calculator; see Fig 1).

Participants

A total of 262 individual centers (Supplement Table 4) participated in at least 1 year of this collaborative, with centers participating for 1, 2, or all 3 years. Of those, 221 NICUs participated in at least 1 of the first 2 years (eg, 2016–2017), and 146 participated in at least 1 audit during that time period. The intention of the third year was to encourage participation in a global sustainment strategy by the VON and CDC for continuing rigorous antibiotic stewardship in newborn care. Thus, only the first 2 years of the Choosing Antibiotics Wisely collaborative were selected for the audit analysis. In the third year, a number of new centers joined the collaborative, whereas multiple other centers completed their participation after 2 years as priorities shifted for the respective NICUs. Several statewide QI organizations and health systems formally joined the iNICQ collaborative, mobilized hospitals in their state and/or system, and provided additional support, coaching, and guidance to participating teams. These states received state-level VON Day Audit reports in addition to individual center reports to fuel their regional improvement efforts.

Audits

Audit details and baseline findings (February 2016) have been previously described,[25] including the core elements. The AUR was defined as the percentage of infants in a unit receiving 1 or more antibiotics on the day of the audit. In addition, we described individual NICUs' progress on management of disease-specific guidelines (eg, for early-onset sepsis). The audits took place on 1 day during a 2-week prescribed period. Each audit had 2 parallel assessments: (1) NICU-level questions that were focused on the 7 CDC core elements and general antibiotic stewardship program (ASP) practices (Supplemental Table 6 in Ho et al[25]), standardization around 12 key clinical or disease triggers for antibiotic prescribing, and the presence of specific policies, protocols or guidelines, as well as other unit-level variables relevant to the ASP; and (2) patient-level details, including the number of patients exposed to antibiotics on that day, the total unit census, and relevant clinical details about each of the patients treated with antibiotics. Not all centers participated in each audit. The reason for lack of participation was not tracked systematically, although some common reasons provided by individual centers included the lack of a timely institutional review board (IRB) waiver and personnel availability to perform the audit.

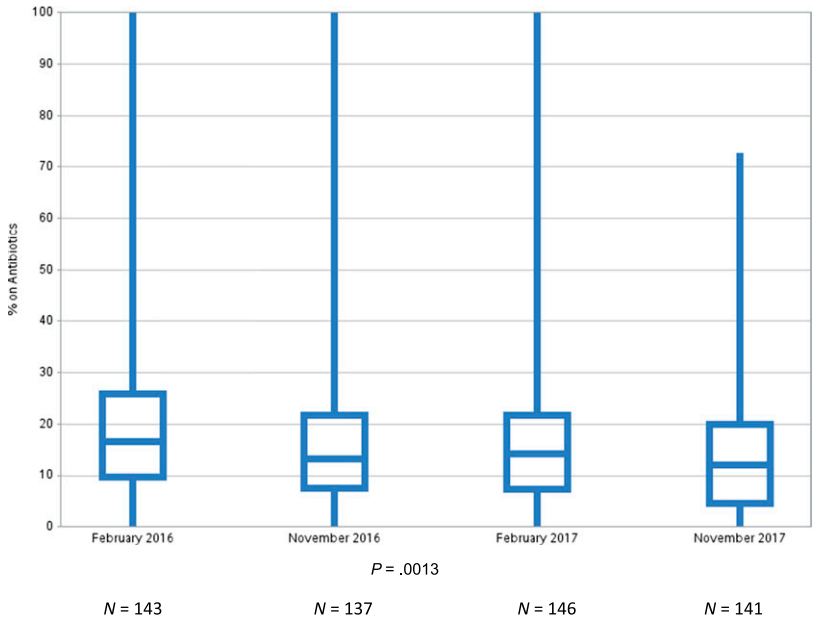

FIGURE 1
NICU AUR among participating NICUs across the 4 audits. The box and whiskers plot represents the median (solid line), interquartile range (box) and lowest to highest values for each of the four audits. The p-value represents the Cochrane-Armitage test for trend.

Statistical Approach

Our primary aims with this article were to describe progress toward the CDC core elements and changes in AUR from the first audit to the fourth audit. Cochran-Armitage trend tests were used to assess changes in the CDC core elements and in AUR over the 4 time points, with $P < .05$ considered significant. Descriptive analyses of disease-specific guidelines were presented without statistical testing. Primary analyses included centers that participated in any audit. A priori sensitivity analyses were planned to limit secondary analyses to only those centers that participated in all 4 audits (N = 85). Besides the AUR, additional patient-level elements described in the baseline publication[25] will be presented in a separate publication.

Human Subjects

The IRB at the University of Vermont determined that Choosing Antibiotics Wisely was not human subjects research. Each center was provided with sample materials to modify for their IRB or approving body and was responsible to obtain a local determination status.

RESULTS

Between 2016 and 2017, 146 centers participated in at least 1 of the 4 audits, with 122 centers participating in both of the years. Eighty-five of the eligible centers (69.7%) participated in all 4 audits, whereas 81.3% and 82.3% of the centers in years 1 and 2 participated in both of the audits for that year, respectively. Of these 146 centers, 92.8% were from the United States and 65.2% were teaching hospitals. Participating NICUs had variable levels of care: 29.7% had restrictions on ventilation or did not perform surgery; 51.1% had no restrictions on ventilation and performed surgery but not perform cardiac surgery requiring bypass; and 19.2% had no restrictions on ventilation and performed surgery including cardiac surgery requiring bypass.

The proportion of NICUs implementing 1 or more of the 7 CDC core elements of antibiotic stewardship (Table 2) increased over the 4 audit time points ($P < .005$ for all 7 elements). Whereas accountability, drug expertise, and ongoing education all reached >85% compliance by the fourth audit, elements relating to leadership commitment, action (eg, implementation of antibiotic time outs at 48–72 hours after initiation of antibiotics), and AUR tracking remained in the 68% to 78% range. The number of centers participating in National Healthcare Safety Network (NHSN) AU and antibiotic resistance (AR) modules improved but remained low at 17.7% (Table 2).

TABLE 2 CDC Core Elements of ASPs Among Participating NICUs Across the 4 Audits

	February 2016 (*N* = 143)	November 2016 (*N* = 137)	February 2017 (*N* = 146)	November 2017 (*N* = 141)	*P*
	%	%	%	%	
Leadership commitment	15.4	51.1	60.3	68.8	<.0001
Accountability	54.5	89.1	89.7	95.0	<.0001
Drug expertise	61.5	85.4	83.6	85.1	<.0001
Time out	21.7	56.9	61.6	72.3	<.0001
Tracking	14.7	68.6	63.7	78.0	<.0001
NHSN reporting	6.3	13.1	14.4	17.7	.0046
Ongoing education	32.9	73.0	75.3	87.2	<.0001
All of the above	0	5.8	5.5	9.9	.0005

The table shows the percent of NICUs that participated in 1 or more of the VON Day Audits that met each of the core CDC elements of antibiotic stewardship. *N* refers to the number of individual NICUs that participated in each audit.

Only 9.9% of participating centers met all 7 of the core CDC elements as defined here by audit 4.

At baseline assessment, there was substantial variation between centers (9.8%–53.1%) in the prevalence of disease-specific policies, protocols or guidelines to standardize diagnosis, and antibiotic treatment of 12 common neonatal conditions (Table 3). Among the disease-specific policy areas, guidance was most commonly found for maternal risk factors for evaluating risk of early-onset sepsis (53.1%), for addressing suspected or proven early-onset sepsis or meningitis (44.8%), and for identifying and managing methicillin-resistant *Staphylococcus aureus* (MRSA) colonization (43.4%).

Guidelines were least likely to be present for surgical site infection (9.8%), ventilator-associated pneumonia (13.3%), and urinary tract infection (14%). At the end of the 2-year period, the presence of disease-specific guidelines increased in all 12 categories (Table 3).

Hospital-specific factors included increases in financial support provided to the NICU and/or hospital for antibiotic stewardship (from 10.5% to 32.6% of centers) and increased awareness of local infection antibiograms (55.9% to 69.5%) as well as modest increases in NHSN reporting (6% to 17.7%). Provider-specific practices included improved monitoring and reporting of provider adherence to specific treatment

TABLE 3 Percent of NICUs With Policies, Protocols, or Guidelines To Standardize the Diagnosis and Antibiotic Treatment of Common Neonatal Conditions

	February 2016 (*N* = 143)	November 2017 (*N* = 141)
	%	%
Maternal risk factors, Suspected or proven	53.1	71.6
Early-onset sepsis or meningitis	44.8	73.8
Late-onset sepsis or meningitis	32.9	50.4
Ventilator-associated pneumonia	13.3	27.7
Central venous line infection	30.8	48.9
Urinary tract infection	14.0	34.0
Necrotizing enterocolitis	31.5	44.7
Surgical site infection	9.8	19.1
Prophylaxis for urinary tract infection	19.6	30.5
Prophylaxis for surgery	25.2	27.7
Prophylaxis for fungal sepsis	35.0	40.4
MRSA colonization	43.4	51.1

The table shows the percent of NICUs that participated in 1 or more of the VON Day Audits that had a policy, protocol, and/or guideline for 1 of the listed common neonatal conditions. *N* refers to the number of NICUs that participated in the respected audit.

recommendations (7% to 36.2%) as well as to documentation of 3 key components (dose, duration, and indication for treatment) of every antibiotic order and/or prescription (7% to 37.6%).

The audits also evaluated the cross-sectional point-prevalence AUR across the participating centers. The mean number of infants audited per center at each time point was 29, and the mean number of infants being treated with antibiotics at the time of the audit was 5. The median AUR decreased from 16.7% (interquartile range [IQR]: 9.7%–25.9%) in February 2016 to 12.1% (IQR: 4.5%–20.0%) in the November 2017 audit (Fig 1), which is a 34% relative risk reduction.

A priori sensitivity analyses limited to centers that participated in all 4 audits (N = 85) revealed similar findings for compliance with CDC core elements (Supplemental Table 5), the number of disease-specific guidelines (Supplemental Table 6), and AUR (Supplemental Fig 2). Despite improvement across all the participating centers, there was a large variability with respect to implementation of the CDC core elements and policies as well as the AUR.

DISCUSSION

Among the participating centers in the VON Choosing Antibiotics Wisely iNICQ, there was both a clinically meaningful and statistically significant increase in implementation of the CDC core elements of antibiotic stewardship that mirrored the reduction in AU over the 2-year time period. Improvement opportunities remain across the 7 categories, especially leadership commitment, as defined by having a written plan for antibiotic stewardship, and NHSN reporting.

The CDC core elements were designed for implementation at the hospital level; in this study, we examined their relevance, application, and potential impact at a unit level. There was large interhospital variation across the categories, with only 9.9% of centers achieving all core elements. Choosing Antibiotics Wisely set a high bar by recommending that the core elements be applied at the NICU level.

Participating NICUs made strides in increasing the number of standardized policies, protocols, and/or guidelines for some of the common conditions encountered in the neonatal setting. Progress in developing guidance was not seen across all disease-specific conditions, perhaps reflecting the need for NICUs to prioritize their time and resources and focus on the most frequently encountered conditions (ie, risk for early- and late-onset sepsis). The combination of increase in compliance with the CDC core elements along with the standardized guidelines likely contributed to statistically significant and clinically meaningful decrease in the AU.

Although it increased over the 2 years, the use of the CDC NHSN AU and AR modules remained 1 of the lowest categories in compliance. This intervention relies heavily on hospital-level technology and resources to facilitate automated reporting directly from the hospital's electronic data sources to the CDC. Low levels of awareness around the NHSN AU and/or AR modules, coupled with the significant technological infrastructure and resources required to accomplish this task, may have contributed to speed of adoption of this important national data set, which has the potential to provide a continuous source of ongoing high-quality data to fuel local QI work. In the future, as NHSN participation grows, these data will be a resource for benchmarking, risk adjustment, and standardized antimicrobial administration ratios (SAARs). The use of risk adjustment, such as SAARs, can help NICUs identify target areas for antimicrobial stewardship when observed use exceeds what is expected for similar units or populations. The VON and the CDC, along with other stakeholders, are currently developing SAAR measures that are specific to the newborn population.

The Choosing Antibiotics Wisely iNICQ results build on the previously reported baseline audit[25] and reveal that a multicenter national QI collaborative can improve ASP and AUR outcomes. Efforts to increase key domains of antibiotic stewardship practice provide a strong foundation for NICUs to maintain ongoing efforts that promote judicious antimicrobial use. In addition, this approach can help NICUs (as well as other individual units within a hospital) align their goals with center, state, and national priorities and demonstrate the value of investing in disciplined QI to achieve improved results.

Collaborative QI initiatives are used widely in health care and have demonstrated success, although the results are likely overestimated given the publication bias and in some cases limited use of standard QI reporting criteria.[32] Nonetheless, collaboration leads to greater opportunities to standardize care, share ideas, and benchmark to propagate progress. Recent data from the Sharing Antimicrobial Reports for Pediatric Stewardship collaborative revealed an increase in development of antibiotic stewardship interventions, including implementations of some of the CDC core elements across children's hospitals in the United States[33] (although individual metrics over time across the hospitals have yet to be reported). The case to support the success of the VON Choosing Antibiotics Wisely iNICQ as a collaborative QI effort includes 2 of multiple previously successful iNICQ initiatives on neonatal abstinence syndrome[34] and alarm safety[35] that

achieved meaningful outcomes. Some VON centers had the opportunity to participate in all 3 collaboratives and likely benefited from the exposure to disciplined QI science methods and learning from previous efforts. Furthermore, Choosing Antibiotics Wisely brought together several health systems and states to work alongside the iNICQ units. Although not evaluated here, it might be reasonable to hypothesize a potential dose response to collaborative QI in which the centers that engaged at local, regional, and global efforts had a potentially added benefit in their improvement compared to individual NICUs.

Although the results of Choosing Antibiotics Wisely iNICQ are promising, several limitations must be acknowledged. Selection bias is an important limitation that has been previously discussed.[25] The participating NICUs self-selected to participate in this iNICQ collaborative. Second, the estimate of both ASP and AUR was made at 4 discrete cross-sectional time periods, and not all of the centers participated in all 4 audits. We tested the validity of this analysis by comparing it to outcomes from the 85 centers that participated in all 4 audits and the findings were consistent. Furthermore, although there is undoubtedly daily, weekly, and monthly variation in AUR, the 4 cross-sectional assessments provide a consistent trend in AUR reduction, which is also supported by the observation of center-specific AURs submitted as abstracts to the VON Annual Quality Congress (VON, personal communication, 2018), as well as recent publications from centers participating in the collaborative.[36–38] Third, there is a lack of a balancing measure(s) at the collaborative level, although all of the NICUs were encouraged to develop one(s) as part of their local work, which reflected the local context of their project. Typical balancing measures for antibiotic stewardship can include increase in infections and mortality and other morbidities as a result of undertreatment. Neither was practical to obtain at the audit time points, given the additional factors on the causal pathway that would not be captured in a cross-sectional audit. In fact, one could hypothesize that given the established relationship between antibiotic overuse and infections and mortality,[1,2,4] both could decrease, as previously demonstrated for late-onset infections in the NICU.[28] Furthermore, with the relatively low incidence of mortality and infections in the NICU, there may be additional challenges with adequately assessing signal versus noise in the balancing measures. Finally, although the CDC core elements of antibiotic stewardship have demonstrated reductions in unnecessary antibiotic exposure[39] and associated reductions in resistant organisms,[40] Choosing Antibiotics Wisely iNICQ was not designed to demonstrate a causal relationship between adherence to CDC core elements and decrease in AUR. However, this raises important questions for future research that is focused on the impact of applying ASP elements at the unit level and to special populations like newborns.

Despite the limitations, the results of the Choosing Antibiotics Wisely iNICQ reveal successful implementation of the CDC core elements of antibiotic stewardship, as well as a meaningful reduction in AUR. This collaborative was built on the evidence for benefit of ASPs, including impact on decreased antibiotic-resistant organisms,[41] reduced unnecessary use, prescribing errors, and costs.[42] As in many collaborative QI initiatives, not all of the teams were able to achieve all of the goals (including the fact that only 9.9% of NICUs met all the CDC core elements), leaving further opportunities for improvement. In addition, the sustainment phase of antibiotic stewardship improvement will be critically important. Key lessons learned from the Choosing Antibiotics Wisely collaborative include the need for prioritization when there are multiple avenues for improvement within the same scope (ie, clinical guidelines, policies, and/or procedures), as well as capitalizing on the opportunity to collaborate with hospital support to successfully implement core elements such as those in place by the CDC for antibiotic stewardship. NICUs were encouraged to seek out pharmacy, information technology, and adult antibiotic stewardship resources at their respective facilities to be more efficient with their use of resources and time to implementation. Lastly, the importance of local QI efforts at the center level cannot be understated. Although a multicenter collaborative QI offers many aforementioned advantages, encouraging the individual NICUs to really dig in and understand their local processes contributed greatly to implementation and success of core elements and policies.

It is our hope that setting the foundation with the core stewardship principles will help ensure stability and sustainment of the work. In particular, core elements such as tracking and reporting AU will prompt continuous monitoring and awareness to help enable sustainment. Increased participation in the NHSN AU module from hospitals with NICUs is already demonstrating promise with 351 participants in the United States.[43] Such efforts should promote rapid cycle uptake and dissemination of national clinical reports and consensus guidelines, such as the recently published American Academy of Pediatrics reports on the management of neonates with suspected or proven early-onset sepsis.[44,45] As part of the next phase of this work, VON has

committed to the 2018 US Antimicrobial Resistance Challenge[46] with a goal of reducing antibiotics by 45% by 2022.

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ABBREVIATIONS

AR: antibiotic resistance
ASP: antibiotic stewardship program
AU: antibiotic use
AUR: antibiotic use rate
CDC: Centers for Disease Control and Prevention
iNICQ: Internet-based Neonatal Improvement Collaborative for Quality
IQR: interquartile range
IRB: institutional reviewboard
MRSA: methicillin-resistant *Staphylococcus aureus*
NHSN: National Healthcare Safety Network
PBP: potentially better practice
QI: quality improvement
SAAR: standardized antimicrobial administration ratio
VON: Vermont Oxford Network

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