QUALITY IMPROVEMENT ARTICLE

Managing antibiotics wisely in a neonatal intensive care unit in a low resource setting

Juan M. Graus[1,2], Cecilia Herbozo[1,2]✉, Roger Hernandez[1,2], Alfonso Francisco Pantoja[1,3] and Jaime Zegarra[1,2]

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BACKGROUND AND OBJECTIVES: Unnecessary early antibiotic exposure is deleterious, it may induce the selection of multi-drug-resistant organisms. The objective of this project was to decrease antibiotic exposure of newborns admitted to the neonatal intensive care unit at Hospital Cayetano Heredia, a level 3 unit in Lima, Peru.
METHODS: Quality improvement project in which we implemented an antibiotic stewardship program for early onset sepsis in the neonatal intensive care unit. Primary outcome measure was antibiotic usage rate, total number of days infants were exposed to antibacterial agents divided by 1000 patient-days.
RESULTS: Antibiotic usage rate declined from 291/1000 patient-days to 82/1000 patient-days during the last months of 2020, representing a total decrease of 65.1%.
CONCLUSIONS: Antibiotic stewardship for early-onset sepsis implemented in a perinatal center like ours is effective, appears to be safe and results in a sustained and significant decrease in the use of antibiotics for early-onset sepsis.

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INTRODUCTION

Antibiotics are the most commonly prescribed medication in the neonatal intensive care unit (NICU) [1–4]. Treatment with antimicrobials might be life-saving in cases with bacterial infection, nonetheless, antibiotic overuse can be detrimental. It may condition adverse patient outcomes, and pose a threat to the NICU as well as a public health problem, due to the emergence of multidrug resistant organisms, especially when there is antibiotic overuse in the community [5, 6].

Early antibiotic exposure might disrupt the developing neonatal gut microbiome and may cause substantial changes in the developing microbiota [7–9]. Prolonged use of antibiotics has been associated with increased mortality, major morbidities such as late onset sepsis, necrotizing enterocolitis, bronchopulmonary dysplasia, retinopathy of prematurity and neurodevelopment impairment in very low birth weight (VLBW) infants [10–19]. Other consequences related to antibiotic overuse include an increase in antimicrobial resistance and the appearance of fungal infections, as well as higher health care costs. The emergence of multidrug resistance bacteria not only affects each unit, but also society as a whole [20, 21]. Antibiotic exposure also presents long term consequences. It has been associated with an increase in wheezing, atopic and allergic disorders, bowel inflammatory disease as well as childhood obesity [22–25].

Antibiotic use varies widely among different NICUs [26]. Even in the absence of a positive culture to prove infection, many physicians continue to treat patients with a presumptive diagnosis of "culture-negative sepsis", resulting in unnecessary overuse of antibiotics [4, 27].

Antibiotic stewardship programs (ASP) have been successful in decreasing inappropriate use of antibiotics in NICUs. In a point prevalence study in 84 NICUs in 29 countries, Prusakov et al. [26] showed that NICUs with ASPs had significantly lower rates of antibiotic use compared to NICUs without ASPs.

In the last decade, there have been various international campaigns addressing the need of antibiotic stewardship in order to rationalize and safely reduce the use of antibiotics [28]. In 2014, the Center for Disease Control and Prevention (CDC) presented the 7 core elements for antibiotic stewardship, which was updated recently [29]. Starting in 2015, the Vermont Oxford Network partnered with the CDC in a collaborative effort, "Choosing antibiotics wisely" and successfully reduced the misuse of antibiotics in NICUs that voluntarily enrolled in the collaborative [30].

In this study, we show our experience developing a quality improvement (QI) initiative to rationalize and reduce the use of antibiotics in a level 3 neonatal unit in a middle income country, through the introduction of an antibiotic stewardship program.

METHODS

Setting

This single-center quality improvement (QI) project was conducted in a 25-bed level 3 NICU in Lima, Peru, at Hospital Cayetano Heredia. This NICU has nearly 500 admissions per year and approximately 75 VLBW infants per year. Our Hospital has all pediatric subspecialties and pediatric surgery. Only patients with congenital heart disease or neurological conditions that require surgery are transferred to a level 4 referral center.

Ethical Considerations: Our Institutional Review Board determined that this study qualified as a QI project therefore did not require its oversight.

[1]Universidad Peruana Cayetano Heredia, School of Medicine, Lima, Peru. [2]Hospital Cayetano Heredia, Lima, Peru. [3]St Joseph Hospital, Denver, CO, United States.
✉email: Cecilia.herbozo.n@upch.pe

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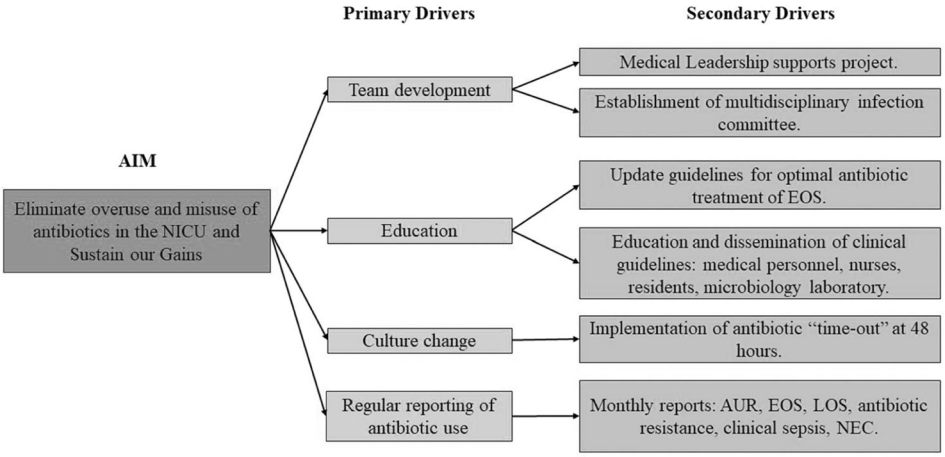

Fig. 1 Key driver diagram.

Program design

The design of this project began in May 2018. A multidisciplinary team was formed, which included neonatologists, neonatology fellows, a pediatric infectious diseases physician, NICU registered nurses and microbiology laboratory technicians. It was established as the Neonatal Infections Committee. Our team did not include a pharmacist since we do not have a pharmacist assigned to our Unit. Our project had support from the NICU director, the department of Epidemiology and the Hospital Medical Direction. Participation was voluntary and there was no funding for this program. Members of the committee had no conflict of interest in relation to this program.

Education sessions were held weekly in order to complete training on principles of antibiotic stewardship and quality improvement.

The team reviewed baseline data and designed a key driver diagram (Fig. 1), which served as a guide for project implementation and to organize our approach to reduce antibiotic use in the NICU. Our primary drivers were: team development, education, culture change, regular reporting of antibiotic use.

Intervention

The project began in July 2018. Baseline data of antibiotic usage rate (AUR) was obtained in July and August 2018. AUR was defined as the total number of days that infants were exposed to antibacterial agents, given intravenously or intramuscularly, divided by 1000 patient-days [31].

Over the next 24 months, we sequentially implemented seven Plan-Do-Study-Act (PDSA) cycles following the model of improvement [32].

PDSA 1: Blood culture collection standardization and reporting

In August 2018, blood culture sampling was standardized in the NICU, with a volume of at least 1 ml drawn for every blood culture. Staff were reeducated on the desired blood volume for cultures. A registry was created to gather data from all blood, urine, cerebrospinal fluid cultures in a standardized manner. There was a mandatory field created to document blood volume drawn for cultures, so that all health providers knew how much volume had been obtained. Also, daily communication was established with the microbiology laboratory, which allowed for a timely information regarding culture results.

PDSA 2: Optimal use of antibiotics

On September 2018, education sessions were held with NICU personnel in order to disseminate guidelines of antibiotic optimal use. Education sessions included discussion of cases, capacity development in prevention and management of infections, training in adequate antibiotic prescription and rationale for stewardship. The standard empiric antibiotic regime for an infant with a suspected diagnosis of early-onset sepsis (EOS) in our NICU is ampicillin and gentamicin. For babies with suspected EOS with meningoencephalitis, ampicillin and cefotaxime.

PDSA 3: Discontinuation of antibiotics at 48 h

Since our hospital does not have an electronic medical record, starting in October 2018, two neonatologists (J.Z and J.G), members of the team, standardized a routine daily communication with the microbiology laboratory to check the results of the blood cultures of patients in the NICU in order to establish a timeout for antibiotic use. The results were then communicated to the attending neonatologist. This prompted a discussion with the health care team to decide whether antibiotics should be discontinued if the blood culture was negative by 48 h. If the decision was to continue antibiotics, entertaining the diagnosis of "culture negative sepsis", the rationale for that decision was documented in the medical record. With positive culture results, the team selected an appropriate antibiotic coverage.

PDSA 4: Monthly monitoring and review of AUR

On January 2019, monthly meetings were started in order to review data of AUR and discuss further change ideas. Information regarding AUR and its monthly tendency was posted in a main location in the entrance to the NICU in order to provide a visual display of changes occurring overtime.

PDSA 5: Education for new residents and fellows

On July 2019 and July 2020 new residents and fellows were incorporated in our department, so educational sessions on neonatal sepsis, optimal antibiotic use and antibiotic stewardship were held.

PDSA 6: Evidence based medicine (EBM) journal club meetings

On November 2019, a weekly EBM journal club was started in order to review current evidence regarding the best approach to infants born to mothers with intrauterine infection, the approach to EOS, the use of biomarkers for the diagnosis of sepsis, etc.

PDSA 7: Introduction of the observational method for diagnosis of EOS

On August 2020 our clinical practice guideline (CPG) for EOS was updated. We introduced the observational method for diagnosis of EOS. With the new CPG, newborns with risk factors are observed and a structured serial physical examination is done every 6 h in order to be able to identify any clinical symptoms or signs of infection. No antibiotics are started unless the infant presents with signs or symptoms suggesting sepsis. This CPG excluded extremely low birth weight infants. One of the aims of this CPG was to reduce antibiotic use in preterm infants and to avoid treating the healthy appearing term or near term newborn with a maternal diagnosis of chorioamnionitis. We standardized which clinical signs and laboratory findings would be taken into consideration in order to diagnose culture-negative sepsis. The duration of antibiotic treatment for confirmed sepsis was standardized according to the causing microorganism. Treatment for culture-negative sepsis was standardized to 7 days.

Table 1 shows the timeline of the interventions.

Measures

The primary outcome measure was the AUR. Antibiotic data was obtained from a manual review of the medical charts done on a daily basis and NICU patient-days were obtained from the hospital daily census. Throughout the implementation of our interventions, we registered all EOS cases and readmissions of newborns after discharge as a safety measure.

Ethical considerations

This project is a quality improvement project; therefore it was considered exempt from ethical approval and consent process.

RESULTS

During the period of time studied, between July 2018 and December 2020, there were 12051 births at Hospital Cayetano

Table 1. Timeline of interventions.

Date	Description of intervention
August 2018	Blood culture collection standardization
September 2018	Dissemination of guidelines of optimal use of antibiotics
October 2018	Discontinuation of antibiotics at 48 h
January 2019	Monthly monitoring and review of AUR
July 2019	Education for new residents and fellows
November 2019	Evidence based journal club meetings
July 2020	Education for new residents and fellows
August 2020	Introduction of the updated CPG for diagnosis of early-onset sepsis

Heredia. 858 newborns were admitted to our NICU (7.1% of live births). 325 newborns (37.9% of infants admitted) were admitted with a rule/out EOS diagnosis. There were 15 cases of EOS confirmed with a positive blood culture (4.6%). Table 2 shows the demographic characteristics of our population of newborns admitted for suspected EOS.

Baseline data of antibiotic use was gathered in July and August 2018 with an AUR of 291 and 335/1000 patient days respectively. Our initial aim was to diminish AUR in 20%. Baseline and ongoing AUR values were plotted in a Statistical Process Control Chart (SPCC) (Fig. 2). The first significant drop in AUR occurred after successful implementation of the first 3 PDSA cycles. When antibiotic time-out was established at 48 h, there was a continued drop in AUR. Monthly monitoring and review of AUR also prompted a further decrease in AUR. By May 2019, we had accomplished a decrease of 57% in our AUR, to 118/1000 patient days.

A sudden increase in AUR occurred in July 2019. This coincided with new personnel, residents and fellows, working in the NICU. As part of our plan of quality improvement, PDSA cycle number 5 was implemented, with frequent education sessions to new residents and fellows, accomplishing a decrease in AUR in the following months.

In November 2019, a weekly EBM journal club was established in order to update our CPG on EOS. In August 2020, we started following the updated CPG for EOS (PDSA cycle 7) which furthered the decrease of AUR, reaching a total decrease of 65.1% from baseline. (Fig. 2).

Figure 3 shows a Statistical Process Control Chart (SPCC), p-chart displaying the use of empirical antibiotic therapy in VLBW infants. Initially, there was a great variability in the use of empirical antibiotic therapy in these infants, with a mean of 78.8% of VLBW infants receiving antibiotics empirically since birth. In June 2020, a downward shift in the use of empirical antibiotics was noted, which became greater after August 2020, after successful implementation of the new CPG for EOS, with a mean of 44.4% of VLBW infants receiving empirical antibiotic therapy. This represents a relative decrease of 43.7%. As seen in Fig. 3, use of antibiotics continued to decrease in the following months.

Figure 4 shows a p-chart displaying the percent of infants discharged each month without ever receiving antibiotics. After implementing our QI project we noticed an increase in the number of patients who were admitted in the NICU and were discharged without ever receiving antibiotics to 64.3%. There was no increase in the cases of EOS following the antibiotic discontinuation nor infants readmitted for sepsis after discharge, nor mortality.

DISCUSSION

Our study describes a comprehensive, sequential approach conducted in a level 3 NICU in Peru that safely decreased unnecessary antibiotic use in our NICU. Our multidisciplinary team applied core QI principles, and through a sequential approach we were able to lower the AUR by 65.1% over a 30 month period, through the establishment of 4 primary drivers: team development, education, culture change and regular reporting of antibiotic use to all NICU personnel. We exceeded our initial project´s aim which was to diminish AUR by 20%. In the first 9 months, we accomplished a decrease of 57% in AUR, and this decrease was sustained and even surpassed in the following 19 months.

We believe the interventions we have described in our study can be easily replicated in other centers and therefore are likely to be of interest for neonatologists in middle income countries such as ours. An interesting aspect is that two members of the team communicated blood culture results to the attending physicians every day of the week, which shows that units without EMRs can achieve judicious antibiotic use in settings with low resources. Recent antibiotic stewardship QI projects published in the literature, such as Meyers et al. [33] in the USA or Makri et al. [34] in UK developed in high resource settings showed similar or more modest success. Our project, despite being developed in a hospital with limited resources, was able to demonstrate a successful approach to safely diminish antibiotic use in our patients, an approach that could be applicable to most, if not all NICUs. There was no increase in the cases of EOS following the antibiotic discontinuation nor infants readmitted for sepsis after discharge, nor mortality.

We believe the decline in the AUR was mostly due to the sequential implementation of the planned interventions, particularly the first 4 interventions: standardizing blood culture sampling, education in terms of judicious antibiotic use, the 48 h "time-out" in antibiotic orders, which prompted a discussion with the treating team about the recommended best practice to discontinue antibiotics if culture was negative, and monthly monitoring and regular reporting of AUR. As mentioned earlier, the order to discontinue antibiotics if the cultures were negative had to be hand written in the baby´s medical chart. The definition

Table 2. Demographic characteristics.

Demographic characteristics	Total (%)
Total number of births	12051
Newborns admitted to the NICU	858 (7.1%)
Suspected EOS episodes	325 (37.9%)
EOS episodes with positive culture	15 (4.6%)
Culture negative EOS	128 (39.4%)
Ruled out EOS	182 (56%)
Male	168 (51.7%)
Female	157 (48.3%)
Gestational age (weeks)	
<25	12 (3.7%)
25–30	115 (35.4%)
31–35	109 (33.5%)
36–40	80 (24.6%)
>40	9 (2.8%)
Weight (grams)	
<500	3 (1%)
500–999	55 (17%)
1000–1499	76 (23%)
1500–1999	57 (18%)
2000–2499	46 (14%)
>2500	88 (27%)

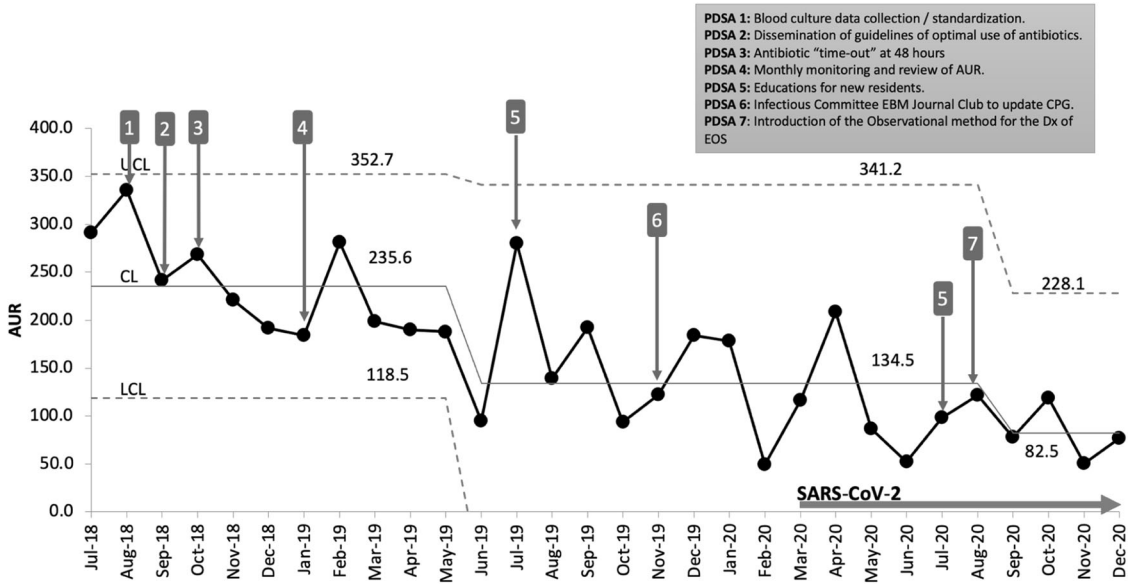

Fig. 2 SPCC for EOS AUR and PDSA cycles.

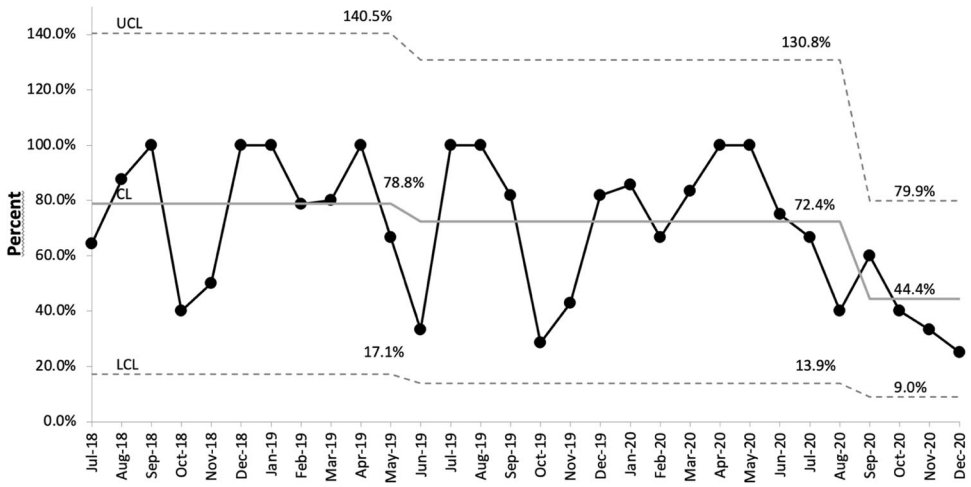

Fig. 3 P-chart displaying the percent of VLBW infants receiving empirical antibiotics after birth.

of culture negative sepsis is very challenging and before this study, there was some mistrust in blood cultures in our hospital, given that some practitioners believed that their sensitivity was extremely low. To believe in the results of a negative blood culture in the context of a baby showing clinical improvement, represented a significant change in our culture. Initially this was done at 48 h, but after 1 year, we decided to discontinue antibiotics at 36 h, given our own experience and the strong evidence of the literature showing that bacterial growth in blood cultures occurs in the initial 24 to 36 h [35, 36]. Also, regular reporting and visual display of changes in AUR in the "quality board" of our Unit, starting in January 2019 (PDSA cycle 4) prompted a further decrease in AUR. We believe visual display was important, given that it gives continued feedback to our team and all NICU health care givers, and helps achieve a culture change, which we believe was instrumental to achieving and sustaining our goal. We also believe that the evidence-based journal club started in November 2019, facilitated compliance of neonatologists to our initiative given that they were made part of the decision making process for the development of the CPG.

Even though there was a sustained decrease in AUR between September 2018 and June 2019, there was a spike in the AUR in February 2019, as noted in Fig. 2. This coincided with an outbreak of extended-spectrum-beta-lactamase organisms in our unit which caused late onset sepsis, in the context of an increase in our average daily census (overcrowded unit), which also led to an increase in mortality in our population. In this context, physicians were reluctant to discontinue antibiotics given the high rate of mortality attributable to those infections at that point.

There was also an increase in AUR in July 2019. It is important to consider that the presence of new personnel, such as new residents and fellows working in the NICU, could compromise the achievements reached; therefore it is recommended to assure adequate training and sufficient supervision.

Figure 2 also shows that in spite of the COVID-19 pandemic which started in March 2020 in our country, the decrease in AUR continued to decrease over the following months, revealing that this world-wide health emergency did not have an effect on our QI project, even though we had a higher census in our Unit given the admission of babies born to mothers with COVID-19.

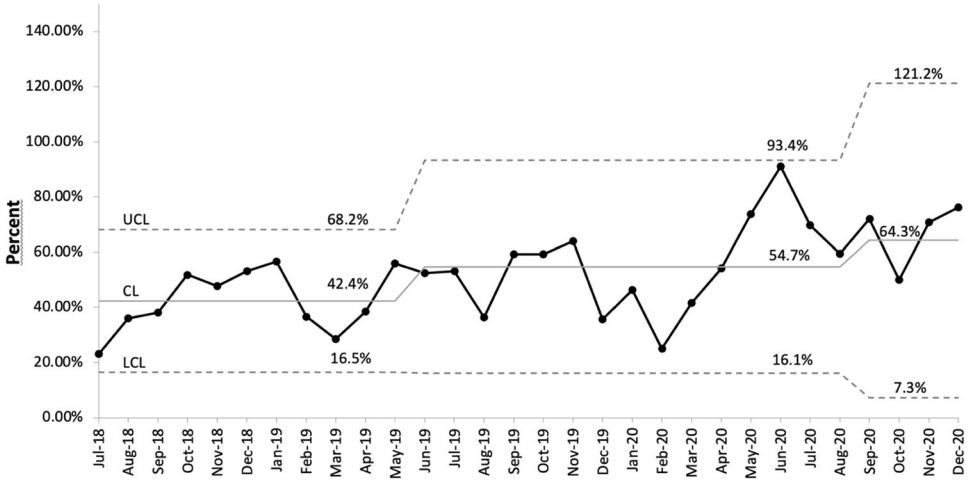

Fig. 4 P-chart displaying the percent of infants discharged without ever receiving antibiotics.

At baseline, 78.8% of VLBW infants received empiric antibiotics (Fig. 3). This number was very variable in the first few months. Premature VLBW infants have a higher risk of developing EOS. Published data has shown that premature infants who are delivered without risk factors, such as preterm labor, premature rupture of membranes or chorioamnionitis, and who are delivered for maternal indications are at lower risk for infections [10, 11, 37, 38]. The American Academy of Pediatrics Committee on Fetus and Newborn recently published management guidelines for infants below 34 + 6/7 weeks of gestation at risk for EOS in 2018 [39]. The decision to withhold antibiotic treatment in VLBW infants with respiratory distress, is challenging. Initially, the majority of these infants received antibiotics after admission in our unit. However, in August 2020, after a thorough review of the literature, our team decided to follow the recommendations of the AAP Committee of Fetus and Newborn for EOS for premature infants [39]. Figure 3 shows an important decrease in the prescription of empiric antibiotics in VLBW infants from 78.8% to 44.4% after the introduction of our new CPG.

Future directions of our initiative are now centered in diminishing AUR in late-onset sepsis (LOS). We are currently updating our CPG on LOS and are working on standardization of the clinical and laboratory findings that will help providers to entertain the diagnosis of LOS and also on establishing a new QI project in order in order to diminish center line associated blood infections.

CONCLUSIONS

Through a quality improvement initiative encompassing a comprehensive approach that included team development, education, culture change and regular reporting of antibiotic use, we were able to lower the antibiotic usage rate by 65.1%. We safely and successfully reduced unnecessary antibiotic use. We believe all NICUs should address antibiotic stewardship as it can be successfully achieved even in low resource settings such as ours.

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AUTHOR CONTRIBUTIONS

JMG conceptualized and designed the study, designed the data collection instrument, collected data, carried out the analyses and reviewed and revised the manuscript. CH collected data, carried out the analyses, drafted the initial manuscript and reviewed and revised the manuscript. RH and AFP carried out the analyses and reviewed and revised the manuscript. JZ conceptualized and designed the study, collected data and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Cecilia Herbozo.

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