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A Quality Improvement Intervention to Reduce Necrotizing Enterocolitis in premature infants with Probiotic Supplementation

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Abstract

Background: Necrotizing Enterocolitis (NEC) is a severe intestinal inflammatory disease due to multifactorial causes that present in preterm infants. Compared with similar neonatal intensive care units, our NEC rate was increasing and prompted reduction by a quality improvement (QI) intervention. **Methods:** We aimed to reduce NEC rate by 30% by the end of 2016. We used the Institute of Healthcare Improvement model and typical QI tools, including teamwork, process organizing tools, and evidence-based review, to assist in our selection of supplementation of *Lactobacillus reuteri* probiotic. We used education, process mapping, process control statistics, and forcing mechanism to implement the changes. In addition to reducing NEC rates, our additional outcome measures were sepsis, mortality, sepsis evaluations, feeding intolerance, growth, days of both antimicrobials, and parenteral nutrition use. Process measures were compliance with probiotics supplementation policy and balancing measures were sepsis rates and feeding intolerance. **Results:** NEC rates decreased from 4.4% to the current 1.7%, and in a pre/post-intervention analysis, the results were significant in all patient subcategories. We did not demonstrate a reduction in mortality. No adverse events occurred. Feeding intolerance episodes and days nil-per-os decreased with no differences in growth at discharge. These results continued over 2 years, and this practice has already spread to several neonatal intensive care units in Ontario, Canada. **Conclusions:** We utilized QI methods and tools to implement a successful practice change of routine probiotic supplementation to reduce NEC rates in preterm infants. We suggest considering this intervention as a successful means to prevent this serious illness. *(Pediatr Qual Saf 2019;4:e201; doi: 10.1097/pq9.0000000000000201; Published online September, 9 2019.)*

INTRODUCTION

Necrotizing enterocolitis (NEC) is a severe inflammatory intestinal disease affecting preterm infants and is a cause of preterm mortality and morbidity in neonatal intensive care units (NICU).[1] NEC incidence peaks around 6–8 weeks of life or 31 weeks of corrected gestation.[2] NEC is a cause of increased mortality, prolonged hospitalization, intestinal surgery, chronic complications, and developmental sequelae.[3,4] NEC is a multifactorial condition, with current knowledge suggesting concurrent gut immaturity, under-perfusion, infections, genetic and metabolic predisposition, and changes in intestinal microbiota as contributors to its pathogenesis.[5–7] The role of the microbiome in NEC has been explored extensively in the last 2 decades[8,9] and has led to proposed interventions that promote a more stable and less pathogenic intestinal microbiome. These interventions include a reduction of antimicrobial exposure,[10–13] better feeding practices,[14] and supplementation of probiotics to preterm infants.[15–25] Indeed, multiple randomized, controlled trials and multiple meta-analyses have supported the use of probiotics to prevent NEC.[26,27] Although we still have a limited understanding of the pathogenesis of NEC, and limited data on the most effective strains of probiotics, doses required, or the target population, meta-analyses demonstrate typical 40% risk reduction in NEC with an excellent safety profile in babies treated with probiotic products.[28]

Rationale

Several clusters of severe NEC cases in 2014 prompted us to develop a quality improvement (QI) intervention.

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Given the multitude of evidence supporting the use of probiotics, we decided to explore the use of probiotics as the intervention of choice. This QI intervention aimed to reduce the NEC rates in our NICU by 30%, from 4.5% to 3%, within 12 months in all infants younger than 33 weeks gestation utilizing the Institute of Healthcare Improvement (IHI) as our general framework.

METHODS

Sunnybrook Health Sciences Centre is a perinatal center, and our NICU is a tertiary level, 42-bed unit, that cares for ~300 very-low-birthweight infants a year, of which 80 infants are <26 weeks of gestation. Outborn infants admitted to our unit are transferred via the provincial transfer coordination services on the first day of life. Between the years 2003 and 2014, our NEC rates in very-low-birthweight infants average 5.02% (SD = 1.2%).

For this QI intervention, we used the IHI model for improvement[29] as a framework. We built a multi-professional team to target modifiable factors associated with NEC and to develop the potential intervention. Our team included a QI-trained staff neonatologist, a dietitian, a nurse practitioner, a pharmacist, a parent representative, and a safety manager. We had team discussions to review cases; performed a literature review for potential evidence-based interventions; surveyed other units in our NICU collaboration (Vermont Oxford Network homeroom) for benchmarking; and created a PICK (PICK: Possible, Implement, Challenging, Kill) chart (Supplemental Digital Content at http://links.lww.com/PQ9/A133) for potential interventions. Five team members participated in the PICK analysis by estimating the feasibility and potential impact of each potential intervention. The team discussion led us to select probiotics supplementation as the potentially most effective intervention. We decided that our target population is all preterm infants born <33 weeks of gestation. Subjects were to receive probiotic supplementation from the first day of life or the first day of admission if an outborn patient. Our recognized drivers for change were staff education, orders standardization, and compliance with supplementation policy. Some other interventions (eg, donor milk, feeding protocol) were in routine use in our unit.

For both compliance with hospital policy, and to improve buy-in, we liaised with the hospital's Infection Prevention and Control team regarding acceptable characteristics of a probiotics product, and risk management regarding licensing and product use. This collaboration narrowed our search to a liquid form, Health Canada-registered, infant-approved product. We chose *Lactobacillus reuteri* DSM 17938 suspension (BioGaia, Ferring, Stockholm, Sweden).

To ensure safety, we consulted with our microbiology lab to ensure identification of *L. reuteri* as a pathogen and not a contaminant if isolated in a culture specimen.

We developed a process map to optimize ways to prepare, distribute, and deliver the probiotic. We then conducted dry-practice runs to explore best administration methods for our smallest babies. The steering team decided timelines for review of safety, technical difficulties, and compliance.

When all steps of the process were clear to the team, we wrote a unit policy document "Routine supplementation of probiotics to reduce NEC in preterm infants." This policy listed all the above steps for future staff reference. We then performed pod-by-pod (NICU subunits) education to the team in 3 shifts, to ensure education for all staff members, and published the information on the computer screensavers that are visible continuously.

We provided parents with verbal information and written handouts on probiotics. Our NICU parent QI team representative assisted with parental engagement and acceptance of a newly implemented standard of care.

As a forcing mechanism, we revised the NICU standard admission orders sheet for preterm infants <33 weeks to add an order for probiotics. We expected this intervention would increase compliance with the new probiotic policy and ensure consistent behavior of the patient care team.

The intervention commenced in February 2015, after we experienced a cluster of severe NEC cases, 2 of whom died. That cluster created a "burning platform" and enabled the team to begin the intervention with little resistance from the staff. In the first month post-intervention, we conducted Plan-Do-Study-Act (PDSA) cycle no. 1, rolling out the project. We reviewed compliance in all charts in week 1 and later sampled day admissions' charts and audited admission orders. We addressed comments regarding technical issues (such as administration and storage) during PDSA no.1. We conducted additional spot audits to assure continued compliance throughout the year.

We conducted PDSA no. 2 in summer 2016 when reeducation and tightening of compliance were encouraged and measured. There were no changes in the policies on antibiotic usage or feeding protocols during the project. Maternal or human donor milk is the exclusive nutrition source for this population in our NICU. Moreover, none of the babies were exposed to infant formula, H2 blockers, nor proton-pump inhibitors.

Measures

Our primary outcome measures were as follows:

1. Severe NEC rates in infants <33 weeks: for a definition, we used radiologic diagnosis or surgical diagnosis at laparotomy of Bell's stage 2 or above.[30] In unclear cases, 2 independent neonatologists adjudicated the diagnosis.
2. Sepsis rates: we defined as any positive blood culture. We selected this metric to monitor for invasive *L. reuteri* infection and to assess the possible beneficial role of probiotics on late-onset sepsis, as reported in previous studies.
3. Death before discharge home: we defined as mortality in our center or the surgical referral center.

Secondary outcome measures were as follows:

1. Total days NPO, defined as holding feeding for >15 hours, per patient.
2. Growth—weight change per week, as calculated at NICU discharge.
3. Days on antibiotics after the initial 48 hours—total days for a patient.
4. Days on intravenous parenteral nutrition (TPN)—total days for a patient on at least partial intravenous nutrition.

Balancing measures were as follows:

1. Sepsis workups: we defined as the drawing of a blood culture after the second day of life. We tracked the number of workups per patient.
2. Feeding intolerance: we defined as an event leading to a failure to advance or maintain the unit's feeding protocol (including skipped feed, changes in feeding advancements, or reduction of feed volume). We monitored the number of episodes per patient and sepsis rates, as defined above.
3. *L. reuteri* infections for specific detection of the probiotic agent.

Our process measures were as follows:

1. Probiotic supplementation compliance rates—percent of patients who received probiotics from the first day of life or admission.
2. Days on probiotics: percent of hospital stay when the infants received the probiotic product.

Analysis

We selected a combined approach to data analysis, both to satisfy the QI methods and to compare between the exposure groups. We plotted time-sensitive and process-related measures in statistical-process-control charts, and estimated the means every month, defining new process after the 2 main changes. These charts also produced a visible display for success and further compliance with the NICU team. For binomially distributed, attribute measures (eg, NEC-yes/no, sepsis, compliance-yes/no), we used P control charts. For non-time-sensitive (days on TPN, number of sepsis workups, continuous measures), we used χ^2 tests comparing to a cohort of the year 2014 patients. As the number of infants was large, sensitivity to special cause variation was noticed quickly, and processes were adjusted accordingly. We confirmed our results with a G chart, a control chart sensitive for time or events between rare events (characterized by geometric distribution). We also confirmed the results with a generalized linear model measuring NEC rates in probiotics versus no-probiotics groups, accounting for gestational age, birth weight, maternal chorioamnionitis, or hypertensive disorders. This model is flexible for different data types in common statistical software (R and SPSS). For special cause-defining rules in control charts, we used the IHI rules.

Ethics

None of our team have conflicts of interests, and we received no funding for this intervention. We consulted with parent representatives and hospital stakeholder as part of the process acceptance. Hospital Research Ethics Board assessed this intervention as a QI initiative and approved chart and data analyses (Sunnybrook Research Ethics Board #102–217). The data deidentified master chart is kept on the main hospital server on an encrypted, password protected file as required by hospital policy.

RESULTS

During the intervention period, from February 1, 2015, to March 31, 2018, there were 1,357 infants of <33 weeks of gestation at birth admitted and cared for in the NICU. Of these, 1,027 infants were given the probiotic preparation according to the protocol. Figure 1 shows our main driver, compliance with supplementation of *L. reuteri* on the first day of life. The initial compliance rate was high, (94.2%), typical of adoption and enforcement of a new policy. After 2 babies had NEC over a short period during the intervention period, we reiterated the policy and the required process in summer 2016, which resulted in an increase of compliance further to 99.5% ($P < 0.001$). Of note, some clinicians began prescribing the product to selected patients before the full policy implementation.

Our primary outcome, NEC rates for all <33wk infants are plotted in a P control chart (for binomially distributed, attribute class data) in Figure 2. While the p chart can demonstrate clustering of cases, a typical poorly explained phenomenon in NEC epidemiology,[31] the clusters are less frequent and affect fewer patients. A G-chart (Fig. 3, for the number of events between geometrically distributed rare events) presents the number of <33wk infants between NEC cases and shows an increase in numbers between events in the 3 periods of the process.

Table 1 depicts the baseline characteristics of the population and the secondary outcomes in a before and after analysis. Table 2 depicts the NEC rates in a before and after analysis, with subcategories. There were no differences in patients' baseline characteristics. The NEC rates were significantly lower in the probiotics cohort, in all subcategories of patients. We validated our results with general linear model analysis and confirmed that NEC rates were associated with probiotics exposure after correction for gestational age, birth weight, maternal hypertension, and chorioamnionitis. In all <33-week infants NEC rates reduced from 4.4% to 2.1% (adjusted odds ratio = 0.4, 95% CI 0.2–0.8, $p = 0.01$). We also demonstrate a reduction in feeding intolerance episodes, and in days NPO. There were no increases in sepsis rates, sepsis evaluations, growth, antibiotic days, or mortality. There were no *L. reuteri* infections, and we had no safety events.

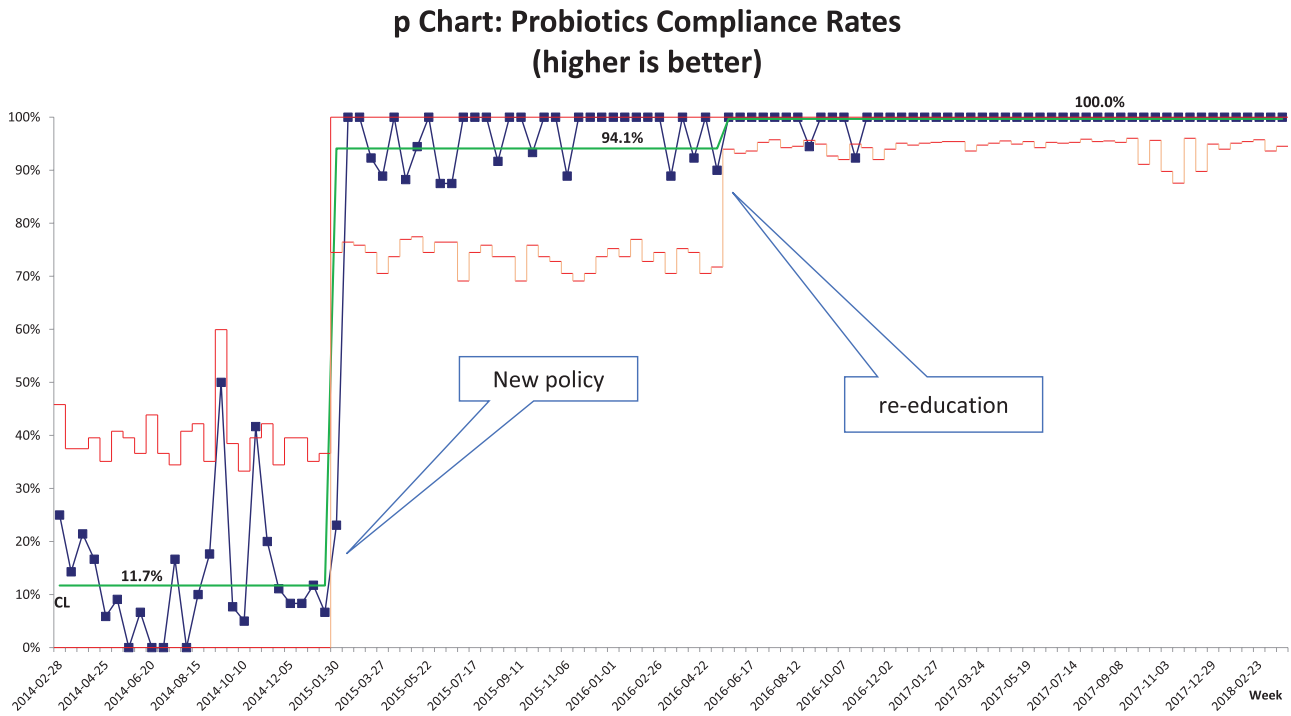

Fig. 1. P chart: compliance with probiotic supplementation on the first day of NICU hospitalization. The blue (or red, when indicating special causes signal) dots represent the percent of patients born a week that received our probiotic intervention. Green line—CL, central line (mean), pale red lines—upper and lower control limits.

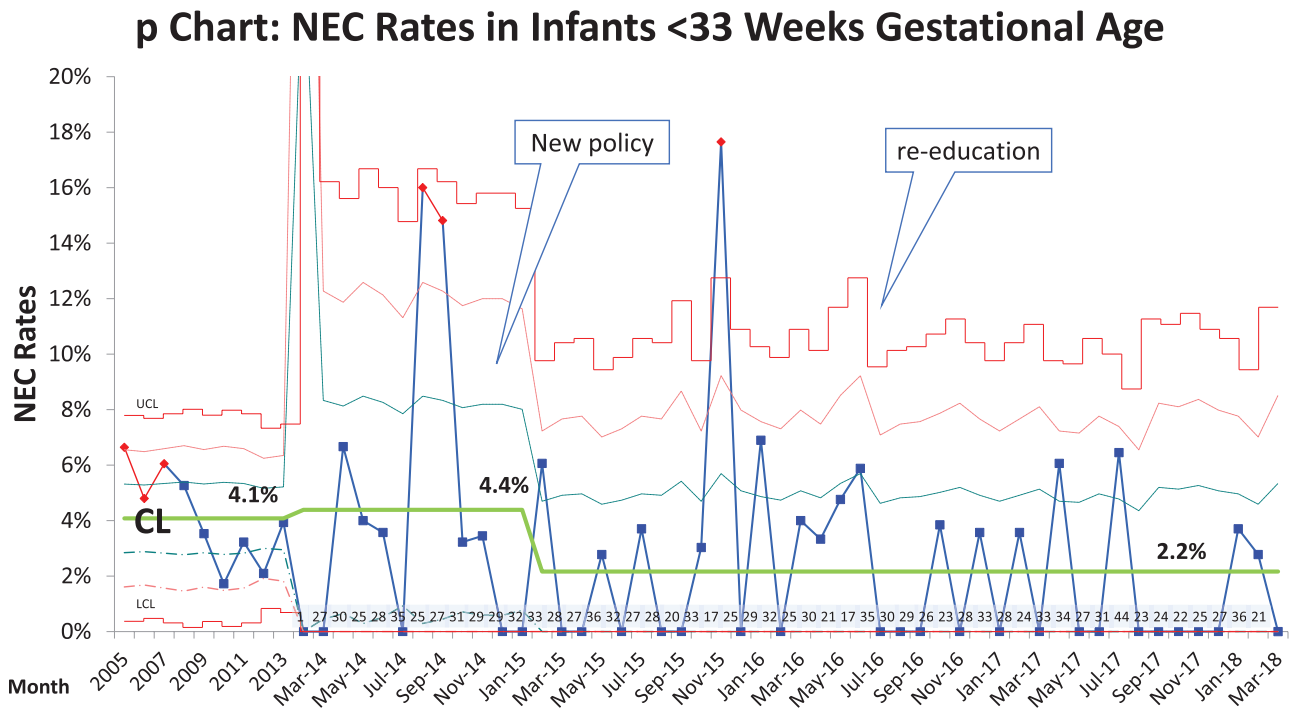

Fig. 2. P chart: monthly NEC rates in infants born before 33 weeks of gestation with historical yearly rates. Blue lines (or red, when indicating a special cause signal) represent the percentage of infants who had NEC by a week of birth. Green line—CL, central line (mean), pale lines—upper control limits. Lower control limit (0%) are not shown. Pale blue—sample size, number of admitted infants <33weeks.

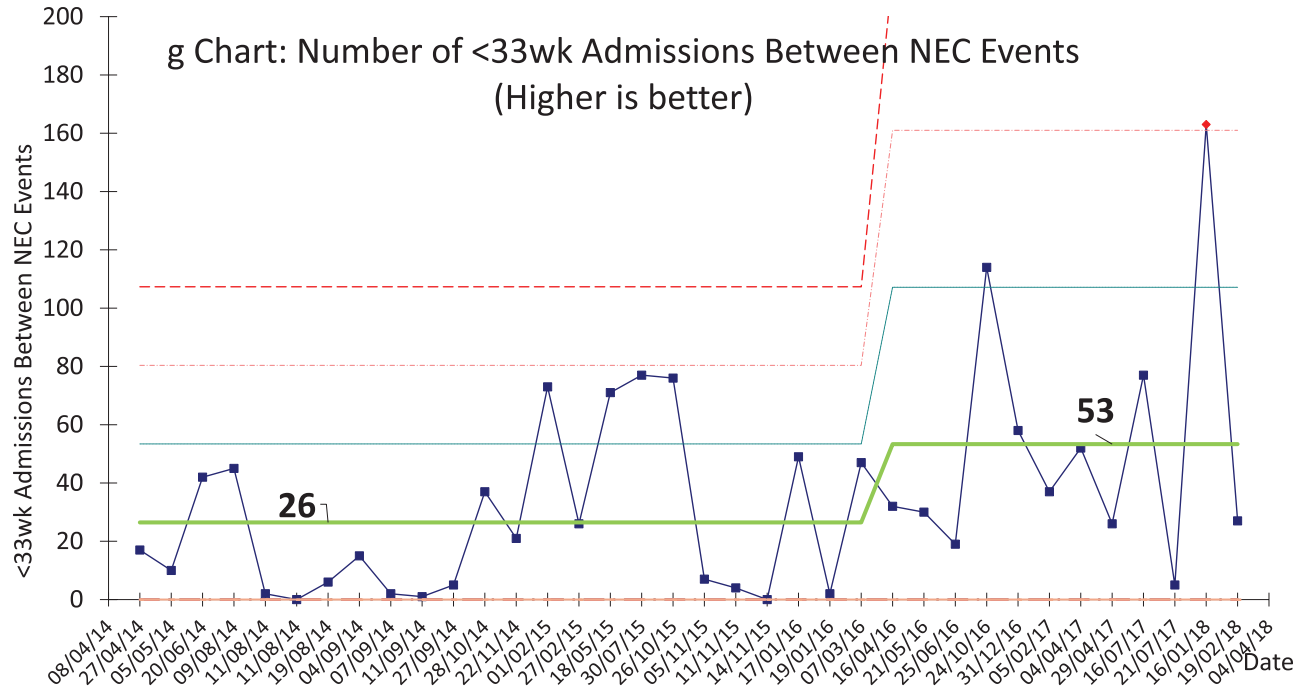

Fig. 3. G chart, for included patients admitted between NEC episodes, the green line represents the mean. The broken line represents the upper process control limit.

Table 1. Baseline and Secondary Outcomes Analysis: Infections and Growth/Nutrition Parameters

		Pre-probiotic n = 330			Post-probiotic n = 1,027			
		Mean	SD	% (n)	Mean	SD	% (n)	*P*
Infant characteristics	Gestational age (wk)	28.1	2.6		28	2.6		>0.05
	Females			46.7 (154)			47.6 (489)	>0.05
	Small for gestational age			10 (33)			9.9 (101)	>0.05
	Maternal hypertension			16.9 (55)			19.1 (196)	>0.05
	Chorioamnionitis			5.8 (19)			5.6 (57)	>0.05
	Outborn status			14.6 (48)			13.5 (138)	>0.05
Secondary oucomes	Days on antibiotics	4	5.2		4.6	6.4		>0.05
	Sepsis			12 (39)		10% (103)		>0.05
	Sepsis workups	0.41	0.9		0.44	0.85		>0.05
	Line sepsis			4.9 (16)			4 (41)	>0.05
	Average growth /wk	42.8	117		59.9	217		>0.05
	Parenteral nutrition days	9.6	6.4		10.6	8		>0.05
	Day of life at 160 ml/kg/d	12.7	6.2		13.6	7.3		>0.05
	Age diagnosed with NEC (days)	13.2	8.2		21.4	14.6		>0.05
	Mortality			6.7 (22)			6 (62)	>0.05
	Feeding intolerance episodes	0.66	1.04		0.32	0.72		<0.01
	Days NPO	1.34	2.2		0.8	1.9		<0.01

Table 2. NEC Outcomes

		Pre-Probiotic		Post-Probiotic				
	NEC results	n	%	n	%	aOR	95% CI	*P*
Primary outcome	Severe NEC—all <33wk	15	4.4	22	2.1	0.4	0.2–0.8	0.01
	Severe NEC in <29wk	15	8.9	19	3.6	0.32	0.16–0.67	0.002
	Severe NEC in <26wk	10	14.3	10	5.0	0.28	0.11–0.7	0.009
	Severe NEC in VLBW	15	6.0	22	2.7	0.4	0.2–0.81	0.01
	Severe NEC in ELBW	14	11.3	17	4.4	0.34	0.16–0.71	0.004
	Surgical NEC	8	53.3	11	50.0	0.88	0.32–4.09	>0.05

The primary outcomes of NEC by subgroups.
VLBW, very-low birthweight, ELBW, extremely low birthweight; aOR, adjusted odds ratio.
Surgical NEC rates are calculated from the NEC cases in the cohort.

DISCUSSION

Our QI intervention aimed to reduce NEC rates in preterm infants by 30%. Implementation and maintenance of routine supplementation of a probiotic product to our patients led to a successful and sustained reduction in NEC rates, without adverse effects. We also demonstrated a beneficial effect on feeding intolerance in this fragile population and a significant reduction in days NPO.

Our study involved QI methods and tools that when implemented, sequentially led to successfully reaching our aim. The tools were the IHI model for improvement, teamwork, process mapping, PICK chart, team engagement, education, forcing mechanisms, PDSA, and process control statistics. The length of the measurements and the robustness of the intervention effect strengthens the results.

This work is consistent with much of the previously published studies on probiotics effect on NEC, typically showing 40% reductions.[32–34] Our intervention shows a reduction of the rates from 4.4% to 1.7% that persists for over 2 years. While some studies suggest a beneficial effect of probiotics on invasive infections, we have not demonstrated this in our patients, presumably because of low rates of infections in the first place, or a probiotic strain that is less effective in this regard.

Our work was a source of interest in other NICUs across Ontario, and we valued spread as an important outcome of this QI intervention. We presented the project to the other tertiary centers in our city, and several NICUs in the province adopted it, some with other products. We have not advocated for a specific strain of product, but we hypothesize that an introduction of a probiotic as part of a QI project like this may be beneficial and unlikely to be harmful.

The benefits of this QI work are a reduction in NEC, a severe disease with high mortality, prolonged hospital stay, and very high costs, reduction in the number of days the babies did not feed, and reduction in feeding intolerance episodes, although without changes in TPN usage or growth rates at discharge.

The calculated number needed to treat is 42 babies to supplement with probiotics to prevent 1 case of NEC. At the retail cost of one BioGaia bottle of 30 Canadian Dollars that suffices for a month of treatment, with an average of 2 bottles per patient, and an estimated cost of 100,000 Canadian Dollars per NEC case (personal communication), this intervention is highly cost-effective.

This work has some potential limitations that warrant discussion. First, it is a QI intervention; thus, its results are dependent on layers of system functions that are different between units. However, we believe that the current evidence supports the use of probiotics to prevent NEC, and this is where any QI initiative should start. Second, NEC tends to occur in clusters. While the intervention clearly shows fewer cases and longer time intervals between cases, confirmed with a G chart (for geometrically distributed events-between rare events), we cannot ensure the elimination of larger clusters in the future. We think that the length of the observation so far is robust enough to support the effectiveness of this work. For comparison, our NEC rates have been monitored for 27 years and have been stable, by statistical-process-control definitions; our median NEC rates since 2000 were 3.52%, interquartile range = 1.93%. Lastly, potential confounders may exist for which we did not account. To minimize such bias, we have compared a large cohort before the beginning of the intervention and after the intervention and have demonstrated no significant differences in the baseline characteristics to explain differences in NEC incidence. The process control charts show special cause variations that support significant, persistent changes in NEC rates. We also performed a general linear model analysis that showed that NEC rates were associated with probiotics exposure even after correction for gestational age, birth weight, maternal hypertension, small for gestational age, and chorioamnionitis. Lastly, while we cannot prove a direct correlation between the compliance rate and the NEC rates, there were differences between the compliance rates before and after PDSA no. 2 that were significant ($P = 0.003$). We believe that better compliance with what we consider our main driver of change is an important step to achieve our aim.

In conclusion, this intervention used QI tools to implement a change in an aim to reduce NEC rates by routine supplementation of a probiotic product and was successful in doing so. We sustained our results throughout 3 years and spread the practice to other units. NEC is a devastating condition that carries a high mortality and long-term complications in survivors, and the benefit of this intervention is significant, both in morbidity and in cost. Potential better probiotic products may demonstrate better effects or may show a reduction in invasive infection, as previously mentioned. Our planned next steps are to continue auditing compliance and measuring NEC rates. We may consider changing our policy to a multistrain probiotic product or consider adding lactoferrin supplements in the future.

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The authors have no financial interest to declare in relation to the content of this article.

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