Antimicrobial utilisation patterns between 2013 and 2022 in Canadian neonates born at less than 33 weeks gestation: a retrospective cohort study

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Summary

Background Excessive antimicrobial exposure is associated with an increase in neonatal mortality, morbidities and adverse neurodevelopment. Canadian Neonatal Network has been promoting judicious antimicrobial use through the Evidence-based Practice for Improving Quality processes. Our objective was to evaluate the antimicrobial consumption among neonates in tertiary neonatal intensive care units (NICU) in Canada in the recent decade.

Methods This is a retrospective cohort study including data from very preterm infants (born at <33 weeks gestational age) admitted to all NICUs in Canada between January 1, 2013, and December 31, 2022. Nationwide antimicrobial utilization rate (AUR) benchmarking started in 2016, and quality improvement initiatives were continued in the subsequent years to promote judicious use of antimicrobials across the network. AUR is defined as the number of days with ≥1 antimicrobial divided by the total patient days (PD). Culture-proven sepsis refers to a neonate with positive culture of pathogens in blood and/or cerebrospinal fluid. The outcomes were evaluated during pre- (2013–2017) and post-intervention periods (2018–2022). Interrupted time-series analysis was used, and comparison of AUR calculated per each 3-month time block and the slope changes were conducted across the pre- and post-intervention periods regarding total patients and subgroups.

Findings A total of 41,253 infants were included, with 22,644 (55%) being male. The AUR was significantly lower among infants from the post- vs. those from the pre-intervention periods (152 vs. 184, $p < 0.0001$). Among 35,670 infants without culture-proven sepsis or necrotizing enterocolitis ≥ Stage 2, AUR was significantly lower in the post-intervention group vs. the pre-intervention group (110 vs. 136, $p < 0.0001$). Interrupted time-series showed significant reduction in AUR during both pre- and post-intervention periods among all infants with and without culture proven sepsis or necrotizing enterocolitis ≥ Stage 2 (all $p < 0.0001$), as well as those born at <29 weeks gestational age.

Interpretation A comprehensive, network-wide quality improvement initiatives led to a significant and sustained reduction in antimicrobial use among preterm infants born at <33 weeks gestational age with and without culture-proven sepsis or necrotizing enterocolitis ≥ Stage 2.

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Research in context

Evidence before this study

In the Neonatal Intensive Care Units (NICU), antimicrobials are often used to mitigate risks associated with neonatal sepsis. However, prolonged exposure of antimicrobials in neonates are associated with increased adverse outcomes. Antimicrobial stewardship program (ASP) has been shown to be effective in decreasing antimicrobial exposure.

We searched PubMed for literature on ASP in the NICU in September 2023. We used the following search terms: ("neonatal intensive care unit" OR "NICU" or "preterm" or "neonates") AND ("antimicrobial stewardship" OR "antibiotic stewardship"). Our search identified only a couple of single-centre studies reporting NICU-specific ASP interventions to reduce the overall antimicrobial consumption in the preterm populations.

Added value of this study

This study uses a nationwide database of tertiary NICUs over a 10-year period to evaluate the time trends of antimicrobial utilisation before and after enhanced ASP interventions. Over the decade, there is a one-fifth reduction in antimicrobial utilization rate (AUR) among infants with or without culture-proven sepsis or necrotising enterocolitis ≥ Stage 2.

Implications of all the available evidence

This study serves as an inaugural step in devising NICU-specific ASP strategies. A nationwide enhanced benchmarking coupled with the continuous quality improvement initiatives not only sustained the low AUR but also facilitated a further diminution. Upcoming endeavors should incorporate a thorough analysis of ASP's influence on antimicrobial resistance, while also crafting strategies that cater to sites with diverse needs.

Introduction

Antimicrobials are commonly used medications in the Neonatal Intensive Care Units (NICU).[1] Neonatal sepsis frequently presents with nonspecific clinical features, often mirroring other non-infectious pathologies, complicating their differential diagnoses. The limitations of current diagnostic markers for sepsis, which lack sufficient sensitivity and specificity for routine bedside use, necessitate pre-emptive treatment strategies.[2] Consequently, potent antimicrobials are commonly administered early in the NICU context to mitigate risks associated with sepsis.

It has been shown that prolonged neonatal antimicrobial exposure among those without sepsis was associated with increased morbidities, mortality, and/or adverse neuro-developmental outcomes.[3,4] In addition to fostering antimicrobial resistance, extended antimicrobial use is correlated with early-life gut dysbiosis, which can impact the infant's health and contribute to heightened disease susceptibility in subsequent life stages.[5]

Antimicrobial stewardship strategies aim to optimize antimicrobial use. Since 2010, an increasing number of studies have reported the effectiveness of NICU-specific stewardship interventions.[6] Antimicrobial stewardship program (ASP) was found to be particularly challenging among the most preterm infants, attributed to the difficulties in differentiating clinical features of sepsis from non-infective aetiologies.[7] Cantey et al. illustrated that diligent evaluation of antimicrobial usage and collective interventions yielded 27% reduction in antimicrobial use over 14 months in their NICU, with no discernible disparity in safety outcomes during the intervention compared to baseline periods.[8] Ting et al. reported a significant 34% reduction in the overall days of therapy after initiating a NICU-specific ASP spanning over a decade.[9] Present literature on the impact of ASP interventions is primarily derived from single-centre studies, with a dearth of multi-centre or collaborative network research.[6]

In Canada, a national Evidence-based Practice for Improving Quality (EPIQ) program within the Canadian Neonatal Network has been implemented since 2003, aiming at improving neonatal outcomes, with emphasis on national benchmarking and self-learning systems within individual units.[10] As part of this process, antimicrobial use was targeted as a potential practice to be improved in year 2016. Our objective was to evaluate the time trends of antimicrobial utilization before and after enhanced ASP interventions across the network and in different subgroups of patients over a decade.

Methods

Setting and population

We conducted a multicentre, national, retrospective cohort study. We included data from infants born at <33 weeks gestational age admitted to participating 31–33 Canadian NICUs between January 1, 2013, and December 31, 2022. Infants who had a major congenital anomaly or were moribund on admission were excluded. The Canadian Neonatal Network database

captures >85% of tertiary-level NICU admissions in Canada and has been shown to have high consistency and reliability.[11] Data on the variables and outcomes, in accordance with the standard of clinical care, were extracted from infants' medical records. Data collection and transmission to the Canadian Neonatal Network Coordinating Centre in Toronto, Ontario from each site were approved by either research ethics boards or hospital quality improvement committees.[12] Specific institutional review board approval for this study was obtained from the Children's and Women's Research Ethics Board at the University of Alberta (Pro00126559) and the Executive Committee of the Canadian Neonatal Network.

Data collection

Gestational age was calculated from best estimate based on the date of early prenatal ultra-sonography, last menstrual period, in vitro fertilization, obstetric estimate, and pediatric estimate. An infant was considered small for gestational age if the birth weight was <10th percentile for gestational age.[13] The Score for Neonatal Acute Physiology II (SNAP-II) is a validated measure of newborn severity of illness that captures physiologic derangements within the first 12 h of admission to the NICU.[14] Early onset sepsis and late onset sepsis were indicated by positive bacterial, viral, or fungal culture results in blood or cerebrospinal fluid from birth to age 2 days and beyond 2 calendar days, respectively.

Antimicrobials included agents prescribed to actively inhibit or kill infecting pathogens according to the Canadian Neonatal Network drug classification list in the Canadian Neonatal Network Abstractor's Manual.[12] Prophylactic administration of trimethoprim or amoxicillin for the prevention of urinary tract infections in patients with a suspected renal anomaly were not included.

Interventions

Canadian Neonatal Network has pioneered the EPIQ method, a strategy for ongoing quality enhancement that underscores the use of empirical data, collaboration, interactivity, targeted interventions, and sustainability. It is a proven Knowledge Translation strategy derived from the "Promoting Action on Research Implementation in Health Services" (PARiHS) framework, which examines the interaction between evidence, context, and facilitation for implementation of research into practice.[10,15–17] The EPIQ approach has proven effective in curbing nosocomial infections and ameliorating infant outcomes in the past.[10,15] The following outlines the strategies implemented to enhance the judicious antimicrobial use and infection prevention among our NICUs.

- As initial step to develop ASP, we first identified antimicrobial utilisation pattern in each individual units in 2016 and reported the result to each unit in 2017. At the same time, units were encouraged to develop local ASP that suits their need based the availability of staff and support. Every year, data on antimicrobial utilization rate (AUR) and documented sepsis, and AUR in infants who did not have sepsis or necrotizing enterocolitis were then fed to all units which allowed them to identify pattern of use and areas to improve.
- The EPIQ Nosocomial Infection subgroup spearheaded numerous initiatives that encourage best practices concerning prudent antimicrobial use and infection prevention. These initiatives included the development of best practices to guide the antimicrobial use in commonly encountered neonatal conditions (early onset sepsis, late onset sepsis, necrotizing enterocolitis, ventilator-associated pneumonia, urinary tract infection, and surgical site infection),[18] the conduction of a national survey for developing ASP targets,[19] the implementation of the Central-line Associated Blood Stream Infection (CLABSI) care bundle with graded evidence, the development of a nationwide NICU-specific ASP,[20] virtual grand rounds with open discussion on judicious use of antibiotics and infection prevention, and regular virtual meetings with frontline healthcare workers to review commonly encountered topics including, but not limited to management of outbreak related to resistant organisms. These activities foster collaboration and exchange of experiences, where professionals can discuss emerging topics and shared challenges. Additionally, team members from various NICUs convene annually at the Canadian Neonatal Network/EPIQ conference to engage in face-to-face discussions, sharing insights and strategies for reducing nosocomial infections and enhancing ASP.

Outcomes

Our primary outcome was the antimicrobial use assessed as AUR, which is defined as the number of days with ≥1 antimicrobial divided by the total patient days during the study period. Secondary outcomes included: (1) the AUR among those who did not have any culture-proven sepsis (both early onset sepsis and late onset sepsis) or necrotizing enterocolitis stage II or above, per Bell's staging criteria[21]; (2) the AUR among those who were born at <29 weeks gestational age, (3) the combination of criteria I and II, and; (4) the episodes of clinical sepsis per 1000-patient days.

To understand the change in prescription practices, further analyses were also conducted to understand any potential changes in antimicrobial prescription practices in terms of (1) change in the number of clinical sepsis, defined as negative blood culture or absence of necrotizing enterocolitis, yet receiving ≥5 days of antimicrobials; (2) total number of days of antimicrobials within the first week among those without culture-proven sepsis, intestinal perforation, or ≥ Stage II necrotizing enterocolitis.

Statistical analysis

The population was divided into two periods: pre- (2013–2017), and post- (2018–2022) intervention groups. Demographic characteristics of the population in the two groups were compared via Pearson Chi-square test for dichotomous data and Student's test/Mann–Whitney U-test for continuous data, as appropriate.

Poisson regression models were conducted to evaluate the AUR changes in the pre- and post-intervention periods, with three models included: (1) adjusted for gestational age, sex, and SNAP II-score; (2) adjusted for gestational age, sex, SNAP-II score and site, with site as a fixed effect and (3) adjusted for gestational age, sex, and SNAP II-score. A generalized estimating equation applied on site to account for within-site correlation.

Interrupted time-series models were constructed to study the trend of change in AUR. We used linear regression to model the slope of the AUR over time, AUR over 3-month time period as the unit of analysis. AUR for each time period was calculated by total number of days exposed to at least one antimicrobial agent over 3 months divided by the total hospital stay days over the same 3 months x 1000. This represented the antimicrobials days per 1000 patient days in each of the 3 months period. Sub-group analyses were conducted accordingly by the same statistical approaches. All statistical analyses were conducted using a software program (SAS, version 9.3; SAS Institute), with statistical significance evaluated using 2-sided p-values at the 5% testing level.

	Pre-intervention (2013–2017)	Post-intervention (2018–2022)	p-value
	N = 20,735	N = 20,518	
Maternal characteristics			
Suspected or confirmed chorioamnionitis, n (%) (6301 missing)	1669/15,734 (11%)	4555/19,218 (24%)	<0.0001
Diabetes, n (%) (1832 missing)	2795/19,838 (14%)	3532/19,583 (18%)	<0.0001
Caesarean section, n (%) (101 missing)	12,514/20,675 (61%)	13,221/20,477 (65%)	<0.0001
PROM ≥24 h, n (%) (2269 missing)	4415/19,821 (22%)	4941/19,163 (26%)	<0.0001
Neonatal characteristics			
GA, weeks, mean (SD)	29.0 (2.6)	28.9 (2.7)	0.07
BW, grams, mean (SD)	1322 (457)	1322 (263)	0.90
SNAP-II score >20, n (%) (455 missing)	3033/20,501 (15%)	2738/20,297 (13%)	0.0002
Male sex, n (%) (46 missing)	11,379/20,702 (55%)	11,265/20,505 (55%)	0.95
SGA, n (%) (52 missing)	2049/20,698 (10%)	2132/20,503 (10%)	0.09
5 min Apgar score <3, n (%) (1587 missing)	713/19,928 (4%)	750/19,738 (4%)	0.24
Mechanical ventilation on day 1, n (%)	6905/20,735 (33%)	7084/20,518 (35%)	0.009

BW, birth weight; GA, gestational age; N, number; PROM, prolonged rupture of membrane; SD, standard deviation; SGA, small for gestational age; SNAP, Score for neonatal acute physiology.

Table 1: **Demographic characteristics of infants born at <33 weeks GA.**

Funding source

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Results

There were 41,253 infants fulfilling the study criteria during 2013–2022, with a mean birth weight and gestational age of 1322 g (standard deviation: 460) and 29 weeks (standard deviation: 2.6), respectively. In the post-intervention period, there were more infants born through Caesarean Section, with prolonged rupture of membrane for 24 h or above, with suspected or confirmed chorioamnionitis, maternal diabetes, and had mechanical ventilation on day 1 (Table 1). Compared to the pre-intervention period (2013–2017), less infants developed necrotizing enterocolitis ≥ Stage II and late onset sepsis in the post-intervention period (2018–2022) (Table 2).

Among infants born at <33 weeks gestational age, the AUR per 1000 patient days was significantly lower among infants in the post-intervention cohort vs. those in the pre-intervention cohort (152 vs. 184, $p < 0.0001$) (Table 3). Among the 35,670 infants without early onset sepsis/late onset sepsis/necrotizing enterocolitis ≥ Stage 2, the AUR per 1000 patient days was also significantly lower in the post-intervention group (110 vs. 136, $p < 0.0001$). The same trend of AUR was noted after adjusted for gestational age, sex, and SNAP II-score. Subgroup analyses among infants born at <29 weeks gestational age revealed similar trends of decrease in the adjusted AUR over time (Table 3).

The number of clinical sepsis per 1000 patient-days were significantly lower among infants in the post-intervention period vs those in the pre-intervention period (Table 4).

The proportion of inborn infants born at <33 weeks gestational age and without culture-proven sepsis or any intestinal perforation or necrotizing enterocolitis within the first 7 days of life who have received prolonged antimicrobials of 4–7 days was significant lower in the post-intervention period vs. those in the pre-intervention period (4063/13,607 [30%] vs. 2783/13,866 [20%], $p < 0.0001$). Subgroup analysis among those born at <29 weeks gestational age revealed similar findings (2097/4507 [47%] vs. 1570/4603 [34%], $p < 0.0001$).

Among infants born at <33 weeks gestational age (Fig. 1) per each 3-month time block, there was statistically significant non-zero downward slopes in both pre- ($p < 0.0001$) and post-intervention periods ($p = 0.005$). A similar trend was observed among infants born at <29 weeks gestational age (Fig. 2). Among infants without culture proven sepsis or necrotizing enterocolitis ≥ Stage 2, interrupted time-series was conducted among infants born at <33 weeks gestational age [Fig. 3] and <29 weeks gestational age [Fig. 4] per each 3-month time block. Statistically significant non-zero downward slopes were seen in both figures.

Discussion

In this 10-year review, we reported an approximate 20% reduction in AUR among infants born at <33 weeks gestational age. Similar reduction in antimicrobial exposure was also accomplished among infants without culture-proven sepsis or necrotizing enterocolitis ≥ Stage 2, as well as those born at <29 weeks. To the best of our knowledge, this is the first reported multi-centre study to demonstrate a considerable decrease in antimicrobial use through collaborative efforts across a national neonatal network.

It is not uncommon in NICUs to commence broad-spectrum antimicrobials, and to frequently continue its use in circumstances where the benefits or indications remain largely indistinct.[22] Emerging evidences reveal that prolonged antimicrobial exposure is associated with emergence of antimicrobial resistant organisms, neonatal mortality, or major morbidities like severe neurologic injury, retinopathy of prematurity, necrotizing enterocolitis, and bronchopulmonary dysplasia.[23] Moreover, the stage of early life is acknowledged as a crucial period for the colonisation of gut microbiota, and antimicrobial exposure has the potential to fundamentally alter its developmental trajectory.[24] An emerging body of evidence accentuates a complex interplay between microbiota, necrotizing enterocolitis, and cerebral development, incorporating the brain-gut axis in premature infants.[25] Such evidence suggests that gut dysbiosis possesses the potential to detrimentally impact neurodevelopment, whether directly or via inflammation, and augment future risk of obesity and inflammatory bowel diseases.[26] The knowledge gleaned from population-based studies and bench research underscores the significance of advocating for judicious antimicrobial utilisation.[23]

With growing recognition of the complications associated with excessive antimicrobial use, there has been an increasing number of ASP aiming to control their use and ensure appropriate prescriptions. These programs usually evaluate the trend of defined daily doses or days of therapy per 1000 patient days of overall or specific antimicrobials, prolonged antimicrobial use (e.g. >36 h or >5 days), or proportion of inappropriate antimicrobial-days.[27] Nzegwu et al. published a quasi-experimental, interrupted time-series study including more than 4500 infants in a level 4 NICU to evaluate the

	Pre-intervention (2013–2017)	Post-intervention (2018–2022)	p-value
	N = 20,735	N = 20,518	
EOS, n (%)	252 (1.2%)	328 (1.6%)	0.0009
LOS, n (%)	2122 (10.2%)	1955 (9.5%)	0.016
NEC ≥ Stage II, n (%)	860 (4.1%)	749 (3.7%)	0.009

BW, birth weight; GA, gestational age; EOS, early-onset sepsis; LOS, late-onset sepsis; NEC, necrotizing enterocolitis.

Table 2: **Incidences of LOS or NEC ≥ Stage II of infants born at <33 weeks GA.**

	Pre-intervention (2013–2017)	Post-intervention (2018–2022)	p-value
Infants born at <33 weeks GA			
ALL eligible infants (N)	N = 20,735	N = 20,518	–
Total patient days	929,472	971,149	–
Total antibiotic-day	171,193	147,343	–
AUR per 1000 patient days	184	152	<0.0001
Adjusted AUR[a] (95% CI)	167 (166, 168)	136 (135, 137)	<0.0001
Adjusted AUR[b] (95% CI)	163 (161, 165)	133 (132, 135)	<0.0001
Adjusted AUR[c] (95% CI)	167 (150, 185)	136 (121, 153)	<0.0001
Infants without EOS/LOS/ NEC ≥ Stage 2 (number)	N = 17,839	N = 17,831	–
Total patient days	705,817	749,337	–
Total antibiotic-day	95,863	82,500	–
AUR per 1000 patient days	136	110	<0.0001
Adjusted AUR[a] (95% CI)	136 (134, 137)	110 (109, 111)	<0.0001
Adjusted AUR[b] (95% CI)	129 (128, 131)	106 (104, 107)	<0.0001
Adjusted AUR[c] (95% CI)	136 (120, 154)	110 (95, 126)	<0.0001
Infants born at <29 weeks GA			
ALL infants (number)	N = 7967	N = 7921	–
Total patient days	565,097	594,533	–
Total antibiotic-day	119,098	104,169	–
AUR per 1000 patient days	211	175	<0.0001
Adjusted AUR[a] (95% CI)	202 (201, 204)	165 (164, 166)	<0.0001
Adjusted AUR[b] (95% CI)	207 (201, 212)	168 (164, 173)	<0.0001
Adjusted AUR[c] (95% CI)	202 (188, 218)	165 (150, 182)	<0.0001
Infants without EOS/LOS/ NEC ≥ Stage 2 (number)	N = 5787	N = 5833	–
Total patient days	376,002	401,710	–
Total antibiotic-day	56,082	49,297	–
AUR per 1000 patient days	149	123	<0.0001
Adjusted AUR[a] (95% CI)	146 (144, 147)	119 (118, 120)	<0.0001
Adjusted AUR[b] (95% CI)	146 (142, 151)	119 (116, 123)	<0.0001
Adjusted AUR[c] (95% CI)	146 (132, 160)	119 (107, 133)	<0.0001

p-value is from Poisson regression model and tested for "time period" effect. AUR, antimicrobial utilisation rate; CI, confidence interval; EOS, early-onset sepsis; GA, gestational age; GEE, Generalized estimating equation; LOS, late-onset sepsis; N, number; NEC, necrotising enterocolitis; SNAP, Score for neonatal acute physiology. [a]Adjusted AUR: adjusted for GA, sex, and SNAP II-score. [b]Adjusted AUR: adjusted for GA, sex, SNAP II-score, and site (site as a fixed effect). [c]Adjusted AUR: adjusted for GA, sex, and SNAP II-score. GEE applied on site to account for within-site correlation.

Table 3: **Antimicrobial usage across the study period.**

	Pre-intervention (2013–2017)	Post-intervention (2018–2022)	Post- vs. Pre- intervention			
			RR (95% CI)	Adjusted RR[b] (95% CI)	Adjusted RR[c] (95% CI)	Adjusted RR[d] (95% CI)
Infants born at <33 weeks GA						
Number of clinical sepsis	6032	4870	–	–		
Total patient days	688,352	734,229	–	–		
Clinical sepsis/1000 patient days[a]	8.76	6.63	0.79 (0.76, 0.82)	0.78 (0.75, 0.81)	0.79 (0.76, 0.82)	0.78 (0.70, 0.87)
Infants born at <29 weeks GA						
Number of clinical sepsis	3872	3313	–	–		
Total patient days	365,308	390,467	–	–		
Clinical sepsis/1000 patient days[a]	10.60	8.48	0.82 (0.78, 0.86)	0.81 (0.78, 0.85)	0.81 (0.77, 0.85)	0.81 (0.73, 0.90)

Infants with any of the following condition were excluded: culture-proven sepsis, NEC ≥ Stage 2, any intestinal perforation, death within 7 days during hospital stay. GA, Gestational age; GEE, Generalized estimating equation; RR, Risk ratio. [a]Defined as administration of antimicrobials for ≥5 consecutive days in the absence of a positive blood or cerebrospinal fluid culture. [b]Adjusted for GA, sex, and SNAP II-score. [c]Adjusted RR: adjusted for GA, sex, SNAP II-score, and site (site as a fixed effect). [d]Adjusted RR: adjusted for GA, sex, and SNAP II-score. GEE applied on site to account for within-site correlation.

Table 4: **Episodes of clinical sepsis per 1000-patient days.**

antimicrobial utilisation and prescription practices after convening a multidisciplinary team and developing guidelines for common infections. They found no significant decrease in the primary outcome of overall days of therapy, but the prescription of ampicillin, the most commonly prescribed antimicrobial, declined significantly by 22.5 days of therapy per 1000 days over a five-year period.[28] Tolia reported a retrospective cohort study of 674 very-low-birth-weight (birth weight <1500 g) infants to understand the impact of an ASP, including the 48-h automatic stop order and health staff education, which resulted in observed reduced median antimicrobial exposure (6.5 vs. 4 days of therapy; $p < 0.001$), and a lower percentage of infants with antimicrobial use more than 48 h (63.4% vs. 41.3%; $p < 0.001$), while there were no differences in mortality, early mortality, or other reported morbidities.[29]

Canadian Neonatal Network includes all tertiary NICUs across Canada, with 360,000 annual births served by regionalized perinatal care systems of maternity units and tertiary-level NICUs.[10] EPIQ method, a proven Knowledge Translation strategy, has a long-standing history of nationwide strategies in improving neonatal outcomes by successfully achieving a 25% increase in survival without major morbidity among very preterm infants and reductions in specific morbidities, including bronchopulmonary dysplasia, retinopathy of prematurity, and necrotizing enterocolitis.[10] Our findings of the decrease in AUR may also contribute to certain extent to the reduction of late onset sepsis and necrotizing enterocolitis across the study period. It is noteworthy that in the pre-intervention period, the average AUR among neonates without early onset sepsis/late onset sepsis/necrotizing enterocolitis ≥ Stage 2 was remarkably low at

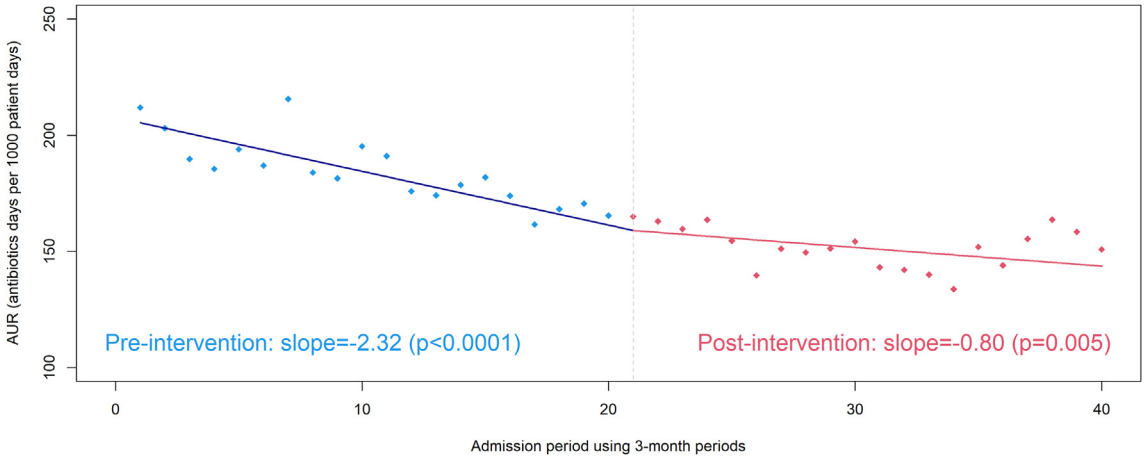

Fig. 1: Change in AUR (antibiotics days per 1000 patient days) among all infants born at <33 weeks' gestation from linear model. AUR for each time period was calculated by total number of days exposed to at least one antimicrobial agent over 3 months divided by the total hospital stay days over the same 3 months x 1000. This represented the antimicrobials days per 1000 patient days in each of the 3 months period. Within each period, statistically significant non-zero downward slope was observed. There was a statistically significant difference between the two slopes ($p = 0.004$).

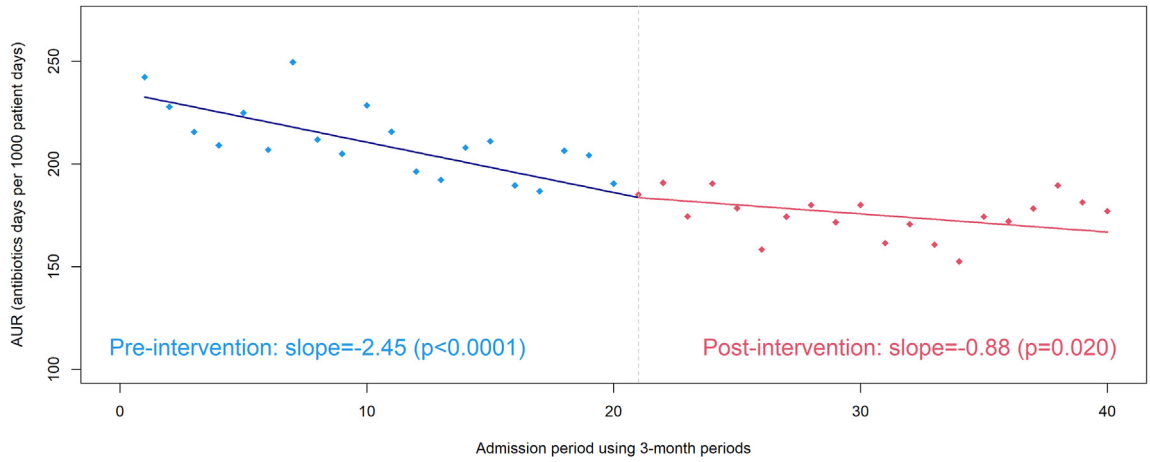

Fig. 2: Change in AUR (antibiotics days per 1000 patient days) among all infants born at <29 weeks' gestation from linear model. AUR for each time period was calculated by total number of days exposed to at least one antimicrobial agent over 3 months divided by the total hospital stay days over the same 3 months x 1000. This represented the antimicrobials days per 1000 patient days in each of the 3 months period. Within each period, statistically significant non-zero downward slope was observed. There was a statistically significant difference between the two slopes (p = 0.024).

136 and 149 per 1000 patient days, for infants born at <33 weeks and <29 weeks gestational age, respectively. The nationwide enhanced benchmarking coupled with our continuous quality improvement initiatives not only sustained these low rates of AUR but also facilitated a further diminution, evidenced by the significant non-zero downwards slopes observed in both pre- and post-intervention periods.

While the promotion of optimal antimicrobial use necessitates consideration of the unique antimicrobial susceptibility profiles, prescription practices, and staff culture of individual centres, our study suggests that strategies such as nationwide benchmarking and collaborative educational initiatives are likely to be effective in promoting the best practices of antimicrobial usage. Our findings underscore the significance of these interventions, as evidenced by the observed decrement in (1) clinical sepsis episodes and (2) the prolonged empirical antimicrobial administration during the neonate's first week of life. The observed reduction in clinical sepsis episodes may indicate a decrease in the frequency of sepsis evaluations or, more plausibly, a reduction in extended antimicrobial exposure (≥5 days) in instances where blood cultures yield negative results.

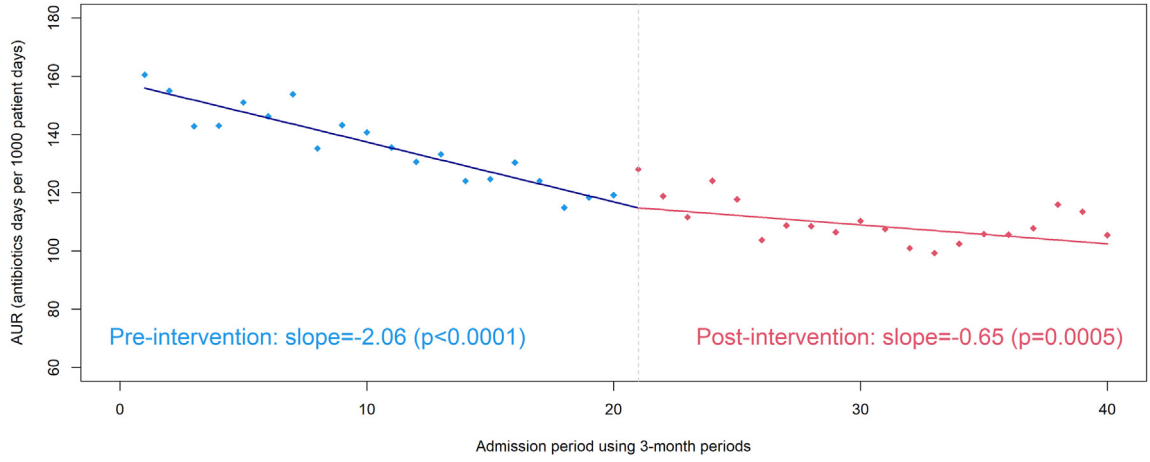

Fig. 3: Change in AUR (antibiotics days per 1000 patient days) among all infants born at <33 weeks' gestation without culture-proven sepsis or necrotising enterocolitis ≥ Stage II. AUR for each time period was calculated by total number of days exposed to at least one antimicrobial agent over 3 months divided by the total hospital stay days over the same 3 months x 1000. This represented the antimicrobials days per 1000 patient days in each of the 3 months period. Each of the two periods shows a significant non-zero downward slope. There was a statistically significant difference between the two slopes (p < 0.001).

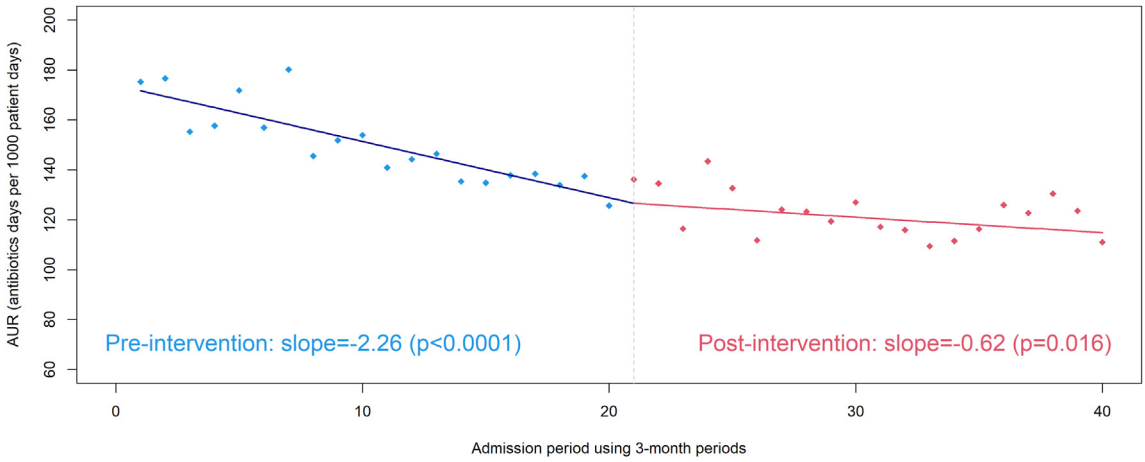

Fig. 4: Change in AUR (antibiotics days per 1000 patient days) among all infants born at <29 weeks' gestation without culture-proven sepsis or necrotising enterocolitis ≥ Stage II. AUR for each time period was calculated by total number of days exposed to at least one antimicrobial agent over 3 months divided by the total hospital stay days over the same 3 months x 1000. This represented the antimicrobials days per 1000 patient days in each of the 3 months period. Each of the two phases shows a significant non-zero downward slope. There was a statistically significant difference between the two slopes ($p < 0.001$).

Through the educational activities, we have been promoting the importance of obtaining adequate blood culture volumes to enhance its negative predictive value, as well as the imperative to restrictive unnecessary early antimicrobial exposure. This awareness follows our previous findings that elucidate the correlation between extended antimicrobial administration (>3 days during the initial week of life) in neonates lacking definitive clinical indications and an increase in mortality and/or morbidities.[30]

Our study has several limitations. In our current Canadian Neonatal Network database, we did not capture the identity of individual antimicrobials. Likewise, drug dose and intervals were not recorded. We were unable to understand the change in the days of therapy of individual antimicrobial or calculate the antimicrobial spectrum index. There were substantial variability in terms of antimicrobial prescription practices across all the NICUs.[18,19] The resources available (e.g. ASP funding) in individual centres varied as well, such that the effectiveness of our intervention strategies could differ across the network.[19] When evaluating antimicrobial use among infants without culture-proven sepsis or necrotizing enterocolitis, we might have included infants with other potential infections like ventilator-associated pneumonia, urinary tract infection, conjunctivitis, omphalitis and surgical site infection in the analyses. These infections have heterogeneous definitions in preterm neonatal populations, making it difficult to estimate the true burden.[15] These clinical sepsis cases might also have included instances of false-negative blood cultures due to insufficient blood volume drawn. Our database did not record the ethnicity or sociodemographic background of individual patients, limiting our ability to assess whether these factors influence antimicrobial prescribing.

This study serves as an inaugural step in devising nationwide, NICU-specific ASP strategies. Our recent meta-analysis including 44 cohort and 26 observational studies reveals that neonatal ASP interventions are associated with reduction in the initiation and duration of antimicrobial use, without an increase in adverse events.[31] Upcoming endeavors should incorporate a thorough analysis of ASP's influence on antimicrobial resistance, while also crafting strategies that cater to sites with diverse needs (for example, a high prevalence of third generation cephalosporin use or resistant gram-positive organisms). We are also engaged in the roll-out of a nationwide ASP plan across Canada, scheduled to span until 2025 and beyond.[20]

Conclusion

We demonstrated that comprehensive, network-wide quality improvement initiatives can effectively yield a significant reduction in AUR among preterm infants born at <33 weeks gestational age with and without culture-proven sepsis or necrotizing enterocolitis ≥ Stage 2 in tertiary NICUs across Canada.

Contributors

Conceptualisation: JYT, PSS; Data curation: JYT, SGB, RS, JT, GE, MB, PSS; Formal analysis: EY, PSS; Funding acquisition: JYT, PSS; Investigation: JYT, PSS; Methodology: JYT, PSS; Project administration: JYT, MB, PSS; Resources: JYT, PSS; Software: EY; Supervision: PSS; Validation: EY, MB, PSS; Visualisation: JYT, EY, PSS; Writing—original draft: JYT; Writing—review & editing (all authors—JYT, SGB, JC, EY, GE, RS, JT, PSS). PS and EY have full access to all the data in the study. JT, PS have the final responsibility for the decision to submit for publication.

Data sharing statements

This is a retrospective study based on retrospective data, collected per standard of clinical care. Individual de-identified participant data will not be shared.

Declaration of interests

The funding agency has no role in the study design, analysis or interpretation of data, or preparation of this manuscript. None of the authors have been paid to write this article by a pharmaceutical company or other agency.

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