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Original Article

Improved use of antibiotics following implementation of antimicrobial stewardship in a neonatal intensive care unit

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Abstract

Introduction: Inappropriate antibiotic use in infants can have multiple adverse effects and contribute to the development of bacteria resistant to antimicrobials. Antimicrobial stewardship programs can reduce unnecessary antibiotic use in children. The aim of this study was to evaluate the effect of an antimicrobial stewardship program implemented in 2017 in the Neonatal Intensive Care Unit (NICU) at The Children's Hospital Iceland.

Materials and methods: The study included all infants who were admitted to the NICU during the study period (January 1st 2012–October 31st 2020). Data was collected from hospital records. Three periods were defined: preimplementation (2012–2014), peri-implementation (2015–2016) and postimplementation (2017–October 2020). Antibiotic use was quantified using days of therapy (DOT) per 1000 bed days (BD). For statistical analysis the pre- and postimplementation periods were compared.

Results: Antibiotics were administered in 38.6% (1372) of admissions to the NICU during the study period. Antimicrobial use per year decreased from 584.6 to 317.1 DOT/1000 BD per year ($P < 0.001$). Use of broad-spectrum antibiotics decreased significantly. The average number of BD per month decreased from 297.8 to 220.9 BD/month ($P = 0.0096$). There were no significant changes in the length of stay for each infant or the proportion of readmissions or retreatment.

Conclusion: Increased awareness of appropriate use of antimicrobials in the NICU led to shorter treatments and less use of broad-spectrum antibiotics. No increase in adverse effects such as readmissions or retreatment was observed.

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Introduction

Infectious diseases have historically been the leading cause of death worldwide in children under the age of five.[1] Therefore it is not surprising that antibiotics are the most commonly prescribed drugs to children.[2] It is however concerning that a large part of these prescriptions is unnecessary or inappropriate.[2,3]

Neonates are at an increased risk of suffering side effects from antibiotic treatment.[3] The use of unnecessary broad-spectrum antibiotics for empirical and guided treatment has not been shown to improve outcomes in neonates. Inappropriate systemic antibiotic use in neonates may lead to higher mortality rates due to increased risk of necrotizing enterocolitis, bronchopulmonary dysplasia, invasive fungal infections, and other adverse outcomes.[4–10] Moreover, administering antibiotics in neonates may cause various adverse health related conditions possibly mediated through altered microbiome[11,12] and disturbed immune maturation.[13–17] In addition, children and neonates with multiple exposures to antibiotics are at increased risk of colonization and infection with resistant microorganisms.[3,19–22] Importantly, implementation of antimicrobial stewardship in pediatric hospitals has been shown to reduce both overall antibiotic prescriptions and specific broad-spectrum antibiotics.[23–25] A multidisciplinary antimicrobial stewardship team has been operational at The Children's Hospital Iceland and its Neonatal Intensive Care Unit (NICU) since 2015. It utilizes a postprescription approach to stewardship, which does not involve restriction of antimicrobial prescribing, but rather consultations, reviews and feedback after treatment has been started.[26] Using clear guidelines and collaboration with the NICU team, the aim is for all prescriptions to start smart by choosing empiric treatment according to the most likely diagnosis and appropriate guidelines after obtaining necessary cultures and then focusing the treatment based on culture results and clinical development. Clinical diagnoses should be reviewed 36–72 hours after starting treatment and further treatment adjusted accordingly.[27] The team itself consists of a pediatric infectious disease specialist and a clinical pharmacist. The team reviews all patients receiving antibiotic treatment three times per week with a 1–2 hour person-to-person visit and is also available during other times for consultations. The clinical pharmacist prepares the round with printouts of all patients receiving antibiotics, including route and doses.

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The aim of the current study was to evaluate the effect of the antimicrobial stewardship program, started in the neonatal intensive care unit at The Children's Hospital Iceland in 2015 and fully implemented in 2017, compare the periods before and after implementation of the program and assess its impact on antibiotic use while also considering possible adverse effects such as undertreated infections and readmissions.

Methods

Setting and study design

This was a retrospective study conducted at the NICU at The Children's Hospital Iceland at Landspítali-University Hospital, Reykjavík, Iceland. Development of the antimicrobial stewardship program began in 2015 but was fully implemented in 2017.

Study sample

All infants admitted to the NICU from January 1st, 2012, until October 31st, 2020, who received systemic (oral or iv) antibacterial and/or antifungal medication from predefined anatomical therapeutic chemical (ATC) classes for more than one day were included in the study. The studied ATC classes were J01, J02, J04, J05, P01AB and A07AA09 and the specific antimicrobial agents studied were ampicillin, cloxacillin, cefotaxime, meropenem, gentamicin, vancomycin, metronidazole and fluconazole. The Children's Hospital's NICU is the only tertiary neonatal intensive care unit in Iceland and therefore all neonates and infants younger than three months of age in need of intensive care in Iceland are treated there. Infants with multiple admissions and treatments during the period were studied once for each admission, and readmission was defined as a second admission involving antimicrobial treatment within 30 days from discharge. Retreatment was defined as starting antibiotics within seven days of completing antimicrobial treatment during the same admission. The study group was divided in to sub-groups based on gestational age according to the CDC's definition; early preterm (<34 weeks gestation), late preterm (34–<37 weeks gestation) and full term (≥37 weeks gestation).[28]

Data collection

The NICU's registry and the National University Hospital of Iceland's electronic records were used to extract a list of all infants who required antimicrobial treatment for the study period. The data included sex, age, gestational age, antimicrobials administered and ATC class, route of admission, number of treatments and length of stay. Electronic records of prescribed medications were not available before 2017 and data was therefore collected manually from non-electronic records. All patient's personally identifiable information was removed from the data set before processing and study numbers were used for analysis. Information was also obtained about the total number of admissions to the NICU as well as bed days and whether antibiotics were administered or not, during the study period.

To quantify the extent of antimicrobial use, DOT was obtained by counting the total number of days for each patient receiving an antimicrobial agent, separately for every agent. If a patient received two antibiotic agents simultaneously for 5 days it was counted as 10 DOT. The number of bed days was calculated using the combined length of stay (LOS) of all admissions during the study period (Equation A). The DOT/1000 BD ratio was subsequently calculated (Equation B).

$$BD = number\ of\ admissions\ \times average\ LOS \tag{A}$$

$$\frac{DOT}{1000BD} = \frac{Number\ of\ days\ of\ antimicrobial\ treatment}{BD} \times \frac{1000}{1000} \tag{B}$$

Additionally, a treatment session was defined as the number of days receiving antimicrobial treatment, and the average duration of a treatment session was calculated using equation C.

$$\begin{aligned} Average\ duration\ of\ treatment\ session &= average \frac{DOT}{1000BD} per\ patient \\ &= \frac{\frac{DOT}{1000BD}}{number\ of\ patients\ treated} \end{aligned} \tag{C}$$

Period

The study period was divided into three periods that were defined as preimplementation (2012–2014), peri-implementation (2015–2016) and postimplementation (2017–October 2020). For the statistical analysis the preimplementation period was compared to the postimplementation period. For ITS analysis, 2015 was defined as the year of intervention.

Data processing and statistical analysis

Data was collected and sorted using Microsoft Excel and Rstudio (version 2022.12.0+353). Independent sample t tests were used to compare means for numerical variables between periods, before and after implementation of antimicrobial stewardship. Chi-squared tests were used to evaluate proportions. Segmental regression was used for interrupted time series analysis. The confidence interval used was 95% and results were considered statistically significant if $P < 0.05$.

Licensing

The study was approved by the National University Hospital of Iceland's ethics committee (37/2020) as well as the Scientific Research Committee (16/2020) of the hospital and the Icelandic Data Protection authority.

Results

During the study period, there were 3555 admissions to the NICU. Antimicrobial agents were administered in 1372 (38.6%) admissions of which 12 were readmissions. Of these admissions, 546 (39.8%) were female and 826 (60.2%) were male. Of these admissions, 789 (57.5%), were full term infants, 262 (19.1%) were late preterm and 321 (23.4%) were early preterm. The total number of NICU bed days (BD) was 39959, and of those, antimicrobial treatment was given in 25852 days (64.7%). Further demographic information can be seen in Table 1.

The number of bed days per month during the study period decreased from an average of 297.8 BD per month in the preimplementation period to 220.9 BD per month postimplementation ($P = 0.0096$). Over the study period, the mean length of stay for each infant per admission was 17.5 days preimplementation and 19.4 days in the postimplementation periods ($P = 0.24$).

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Table 1. Demographic information for the study cohort 2012–2020

	Total	2012	2013	2014	2015	2016	2017	2018	2019	2020*
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Children born in Iceland	38659 (100)	4533 (11.7)	4326 (11.1)	4375 (11.3)	4129 (10.6)	4034 (10.4)	4071 (10.5)	4228 (10.9)	4451 (11.5)	4512 (11.6)
Admissions	3555 (100)	393 (11.1)	416 (11.7)	449 (12.6)	378 (10.0)	357 (10.0)	314 (8.8)	386 (10.9)	482 (13.6)	380 (10.7)
Infants treated with AMAs**	1360 (100)	196 (14.4)	203 (14.9)	211 (15.5)	120 (8.8)	116 (8.5)	94 (6.9)	144 (10.6)	146 (10.7)	130 (9.6)
Admissions where AMAs were given	1372 (100)	196 (14.3)	204 (14.9)	212 (15.5)	120 (8.7)	116 (8.5)	94 (6.9)	150 (10.9)	147 (10.7)	133 (9.7)
Proportion of total admissions where AMAs were given	38%	49%	49%	47%	31%	32%	29%	38%	30%	35%
Gestational age of infants treated with AMAs										
Early preterm (< 34 weeks)	321 (23.4)	51 (26.0)	47 (23.0)	43 (20.3)	36 (30.0)	25 (21.6)	26 (27.7)	30 (20.0)	34 (23.1)	29 (21.8)
Late preterm (34–37 weeks)	262 (19.1)	47 (24.0)	41 (20.1)	38 (17.9)	25 (20.8)	25 (21.6)	12 (12.8)	29 (19.3)	30 (20.4)	15 (11.3)
Full term (> 37 weeks)	789 (57.5)	98 (50.0)	116 (56.9)	131 (61.8)	59 (49.2)	66 (56.9)	56 (59.6)	91 (60.7)	83 (56.5)	89 (66.9)
Bed days	39959 (100)	4952 (12.4)	4820 (12.1)	5060 (12.7)	4718 (11.8)	4114 (10.3)	4286 (10.7)	3838 (9.6)	4495 (11.2)	3676 (9.2)
Bed days in admissions where AMAs were given	25852 (64.7)	3578 (72.3)	3547 (73.6)	3595 (71.0)	2885 (61.1)	2100 (51.0)	2351 (54.9)	2463 (64.2)	3060 (68.1)	2273 (61.8)

*Study data includes infants born through October.
**Antimicrobial agents.

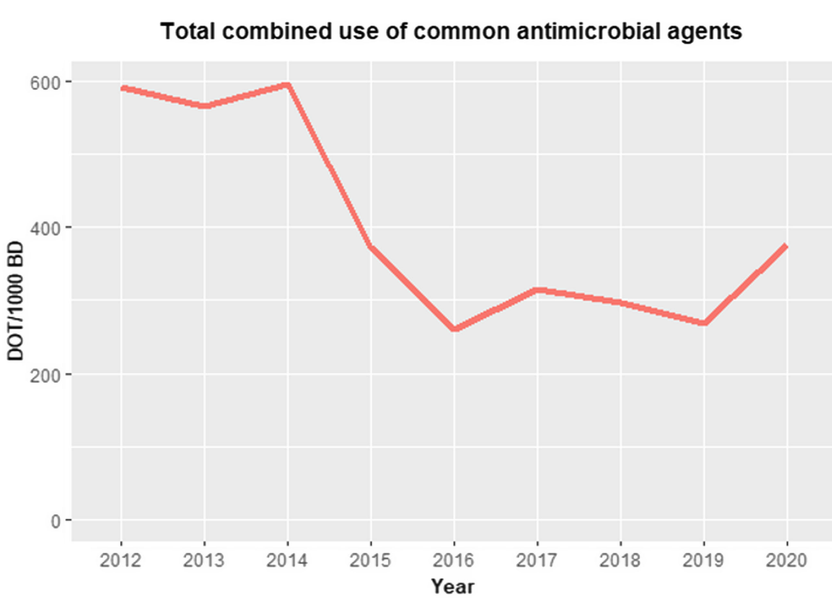

Figure 1. Total days of therapy (DOT) per 1000 bed days (BD) for every year of the study period, for the most frequently used agents (ampicillin, cloxacillin, cefotaxime, meropenem, gentamicin, vancomycin, metronidazole and fluconazole).

Antibiotic use

The combined total days of therapy per 1000 bed days (DOT/1000 BD) for the studied agents (ampicillin, cloxacillin, cefotaxime, meropenem, gentamicin, vancomycin, metronidazole and fluconazole) decreased from 592 DOT/1000 BD in 2012 to 376 DOT/1000 BD in 2020 (Figure 1). Other antibiotics were used during the study period, but combined accounted for only 18 DOT/1000 BD and were not included in the analysis of data.

The most frequently used antibiotics were ampicillin and gentamicin and changes of DOT/1000 BD for each individual microbial agent during the study period is shown in Figure 2.

Implementation of antimicrobial stewardship

The average DOT/1000 BD per year was 584.6 in the preimplementation period and was reduced by 45% to 317.1% in the postimplementation period ($P < 0.001$). A segmental

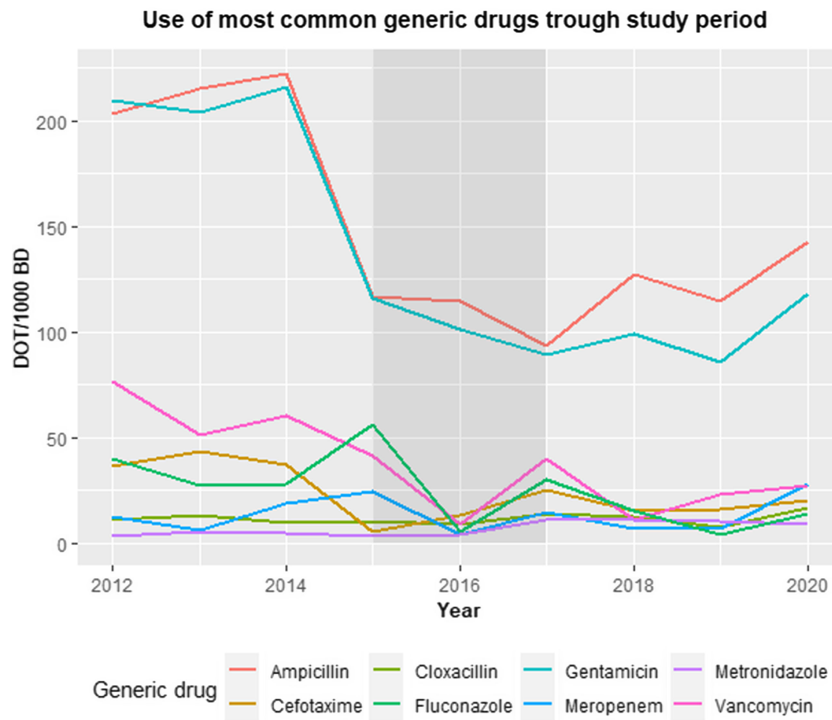

Figure 2. Number of days of therapy (DOT) per 1000 bed days (BD) for eight of the most used agents through the study period. The shaded area indicates the peri-implementation period.

regression analysis for the total use of antibiotics before and after 2015 showed no difference in slopes between the periods but a significant difference between the point of intersection on the y-axis ($P = 0.003$). This is illustrated in supplemental Figure S1.

A comparison of the two periods showed a significant reduction in the average DOT/1000 BD per year for ampicillin (44.1%), cefotaxime (50.6%) and gentamicin (53.4%) (Table 2). For metronidazole, the average DOT/1000 BD per year increased significantly (135.2%) but remained overall low (10.2 DOT/1000 BD).

The average DOT/1000 BD per year declined significantly for all three age groups. For early preterm it was reduced by 48.0% ($P = 0.011$), for late preterm by 51.1% ($P = 0.013$) and for full term by 43.3% ($P = 0.008$).

For intravenous antibiotics, the average DOT/1000 BD per year went from 592.87 in the preimplementation period to 325.42 in the postimplementation period ($P < 0.001$). For antibiotics given orally the average DOT/1000 BD per year increased from 10.81 to 18.87 DOT/1000 BD per year, although not statistically significant ($P = 0,11$).

The average duration for each treatment session is given in Table 3 showing a significant decrease for ampicillin, gentamicin and fluconazole. An upward but non-significant trend was observed for cloxacillin and metronidazole. Meropenem use remained stable with some fluctuations (4-20 DOT/1000 BD) and an upward trend in 2020 with a peak DOT/1000 BD of 28. For intravenous antibiotics specifically, the average duration of a treatment session decreased from 1.21 to 1.04 DOT/1000 BD ($P < 0.001$). There was no difference in the treatment session duration for antibiotics administered orally during the study period ($P = 0.49$).

The rate of readmissions during the preimplementation was similar compared to the postimplementation period (6.0% vs 7.2%, $P = 0.094$). The proportion of infants that were started on antibiotics within seven days from completing treatment was also unchanged between the two periods (4.8% vs 3.8%, $P = 0.39$).

Discussion

This study demonstrated a significant reduction in antibiotic use after implementation of antimicrobial stewardship in the NICU of The Children's Hospital Iceland. The percentage of admitted infants that received antibiotics decreased from around 50% at the start of the period to just over 30% at the end of the study. This is a lower proportion than reported in other studies and may reflect international cultural differences between NICU centers.[29–31] The overall >40% reduction in use is in line with a systematic review of stewardship programs, with even slightly greater reduction in our study.[32] Ampicillin and gentamicin were the most common agents administered through the entire study period which is in accordance with standards of care and the national guidelines.[33] The decrease in the use of these agents was very clear both in terms of overall use and duration of treatment.

This confirms what previous studies have shown, that a postprescription "hand-shake" approach to stewardship is an effective way to reduce antibiotic use, even if preauthorization of certain agents is not a feasible option.[29] Although it is time and labor consuming it provides the platform for debate and discussion between stakeholders and is more likely to be adhered to and sustained. The advantages of this approach include no delay in starting necessary treatment immediately and lower costs since preauthorization requires considerable human, technological and financial resources. However, a combination of both approaches has been shown to be most effective for reducing antibiotic use and should therefore be considered if the resources are available.[29]

The use of antimicrobial agents in the NICU started decreasing in 2015 and it can be postulated that the culture of judicious and more appropriate antibiotic use started changing alongside the

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Table 2. The difference in average days of therapy (DOT) per 1000 bed days (BD) per year between the preimplementation 2012–2014 and postimplementation 2017–2020 of antimicrobial stewardship, for the most frequently used antimicrobial agents

	Preimplementation 2012–2014		Postimplementation 2017–2020		
Generic drug	Average DOT/1000 BD	SD	Average DOT/1000 BD	SD	P^*
Ampicillin	213.7	97	119.5	21.1	**<0.001**
Cloxacillin	11.0	1.8	12.6	3.9	0.56
Cefotaxime	38.7	3.9	19.1	4.6	**0.0019**
Meropenem	12.5	6.5	14.1	9.9	0,83
Gentamicin	209.9	5.8	97.8	14.4	**<0.001**
Vancomycin	62.9	12.8	25.2	12.2	**0.011**
Metronidazole	4.3	1.2	10.2	0.9	**<0.001**
Fluconazole	31.8	7.1	15.7	10.8	0.078

SD, Standard deviation.
*Statistically significant *P* values in bold ($P < 0.05$).

Table 3. The difference in the average duration of a treatment session between the two periods, before and after implementation of antimicrobial stewardship, for the most frequently used antimicrobial agents

	Preimplementation 2012–2014		Postimplementation 2017–2020		
Generic drug	Treatment session duration**	SD	Treatment session duration**	SD	P^*
Ampicillin	1.12	0.44	1.03	0.54	**<0.001**
Cloxacillin	1.03	0.49	1.14	0.66	0.44
Cefotaxime	1.30	0.86	1.14	0.80	0.23
Meropenem	2.21	2.17	1.87	1.70	0.56
Gentamicin	1.09	0.64	0.86	0.62	**<0.001**
Vancomycin	2.14	2.33	1.83	1.94	0.41
Metronidazole	1.00	0.74	1.20	1.2	0.57
Fluconazole	3.28	2.57	1.85	1.65	**0.013**

SD, Standard deviation.
*Statistically significant *P* values in bold ($P < 0.05$).
**Average duration of a treatment session in DOT/1000 BD.

development of the antimicrobial stewardship program, which was fully implemented in 2017. The impressive reduction in the use of the most frequently used antimicrobials, ampicillin, gentamicin and cefotaxime along with moderate decrease in the use of vancomycin and fluconazole are noteworthy. Importantly, no adverse outcomes related to the program were observed as undertreatment of serious infections or failing to start antibiotics in blood stream infections is the most important, potential downside of stringent antimicrobial guidelines. This was however not the case in this study since the proportion of readmissions was not significantly different between periods, a finding others have also observed. Also, the rate of retreatment within seven days of completing antibiotic treatment was not increased. The approach of using person-to-person visits has the obvious advantage of clear communication and reasoning for advice on antibiotic treatment and is considered the preferred practice.[34] It furthermore has educational value for younger generations of doctors, imprinting the importance of sensible use of antimicrobials, not only for individual patients but for populations in general. The intervention was overall very welcomed and has led to increased awareness among the staff. While remote stewardship programs may be less labor intensive, they might be less well received and sustained.

In our data set, an increase in antibiotic use was observed in 2019–2020. Before 2019, some infants would finish their intravenous antibiotic treatment at home with the assistance of at home nursing of which no data was available. The apparent increase in the years after 2019 could therefore be explained by missing data from these infants in the years preceding that time point when all infants would finish their treatment in liaison with the ward. Despite this increase, the annual use of common antimicrobial agents was still considerably lower in the postimplementation period (317 DOT/1000 BD) than before implementation (585 DOT/1000 BD).

It is interesting that while DOT/1000 BD decreased for most agents, it increased considerably for metronidazole. The increase probably stems from the fact that in recent years the tradition in the NICU has changed towards it being used routinely when necrotizing enterocolitis (NEC) is suspected and it is now a part of the first line treatment for NEC according to our guidelines.[27] The increase could also partly be due to advancements in neonatal intensive care leading to the treatment of more premature infants, since NEC is most common in extremely premature infants[35] the prevalence might be higher later in the study period. Although unlikely, reduced use of antimicrobials during the period could be associated with higher risk of NEC.

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Our data set did not include clinical information or the indication for initiation antimicrobial treatment. We can therefore not speculate further on the reasons for the 2.5-fold increase in metronidazole use, but this warrants further study.

The use of meropenem remained constant and relatively low throughout the study period although an upward trend in 2015 and 2020 was observed. In a small population such as Iceland, fluctuations in rarely used drugs are to be expected.

The average number of bed days decreased between periods, from 297.8 bed days per month to 220.9 bed days per month. However, the average length of stay for each patient was not significantly different between periods, which is comparable to previous studies of antimicrobial stewardship[23,24] and therefore the decrease in the number of bed days is most likely explained by fewer admissions in the later period.

There are some limitations to the study. The population of Iceland is small so fluctuations in the number of newborns and premature infants could affect the results. However, the fact that the study period was long should counteract the possible effects of such fluctuations. The length of the study period could theoretically also impact the results since continuous advances in neonatal care have led to more extreme premature infants being treated. These infants need more intensive therapy, often including antibiotic treatment, but despite that, the use of antibiotics decreased in the postimplementation period. Also, no information on the rate of proven or probable infections was available in our data set. In addition, further collection of data during the years of the COVID pandemic would have been useful. This would give better insights into sustainability of the program during pressing conditions. Permission for data collection was however not available beyond our study period but could potentially be pursued in a follow up study.

A considerable strength worth mentioning is the fact that the study was conducted at the only NICU in Iceland. All data was therefore collected in one center with meticulous and coordinated registration. Any follow up and all readmissions would always be to this department or at least to The Children's Hospital Iceland so there is little risk of underestimating the possible adverse effects. Therefore, it can be concluded that the results are generalizable for other NICU settings, although the size of bigger centers could affect communication channels and success of implementation.

In conclusion, we maintain that the antimicrobial stewardship program improved the use of antimicrobial agents in the NICU with shorter treatment and reduced use of broad-spectrum agents and did not increase adverse effects. This hopefully adds to better antibiotic use for the individual patient, but also on a population level. Further studies could investigate the cost benefits of the program, the importance of the benefits of fewer side effects related to antimicrobial therapy for the patients as well as any changes in antimicrobial resistance.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/ice.2024.151.

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