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Impact of NICE clinical guidelines for prevention and treatment of neonatal infections on antibiotic use in very preterm infants in England and Wales: an interrupted time series analysis

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ABSTRACT

Objective To assess the impact of publication of UK National Institute for Health and Care Excellence (NICE) guidelines on the prevention and treatment of early-onset infections (EOIs) in neonates (clinical guideline 149 (CG149), published in 2012, and its 2021 update (NG195) on antibiotic use in very preterm infants.

Design Interrupted time series analysis using data from the National Neonatal Research Database.

Setting Neonatal units in England and Wales.

Participants Infants born at 22–31 weeks' gestation from 1 January 2010 to 31 December 2022 and survived to discharge.

Interventions Publication of CG149 (August 2012) and NG195 (April 2021).

Main outcome measures Measures of antibiotic use, aggregated by month of birth: antibiotic use rate (AUR), the proportion of care days in receipt of at least one antibiotic; percentage of infants who received ≥1 day of antibiotics on days 1–3 for EOI and after day 3 for late-onset infection (LOI); percentage who received ≥1 prolonged antibiotic course ≥5 days for EOI and LOI.

Results 96% of infants received an antibiotic during inpatient stay. AUR declined at publication of CG149, without further impact at NG195 publication. There was no impact of CG149 on the underlying trend in infants receiving ≥1 day antibiotics for EOI or LOI, but post-NG195 the monthly trend began to decline for EOI (−0.20%, −0.26 to −0.14) and LOI (−0.23%, −0.33 to −0.12). Use of prolonged antibiotic courses for EOI and LOI declined at publication of CG149 and for LOI this trend accelerated post-NG195.

Conclusions Publications of NICE guidance were associated with reductions in antibiotic use; however neonatal antibiotic exposure remains extremely high.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Antibiotics are very often prescribed to preterm infants, though irrational use is associated with harm. The National Institute for Health and Care Excellence published clinical guideline 149 (CG149) in 2012 and updated guidance in 2021 (NG195), with recommendations for neonatal antibiotic prescribing. The national impact of CG149 and NG195 on antibiotic use has not been studied.

WHAT THIS STUDY ADDS

⇒ Interrupted time series analysis quantified the impact of publication of CG149 and NG195 on measures of antibiotic initiation and prolonged use. Publication of CG149 was associated with decreases in the proportion of care days infants received at least one antibiotic and exposure to a prolonged antibiotic course, though with smaller or no change for extremely premature infants and those with bacterial infection or recorded indication(s) for antibiotics. Publication of NG195 was associated with decreases in antibiotic use for late onset infection. Over 95% of preterm infants studied were exposed to antibiotics.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study finds that publication of national guidance CG149 and NG195 was associated with reductions in neonatal antibiotic use, possibly through more conservative and consistent antibiotic prescribing. However, antibiotic use remains extremely high among preterm infants. Further research is required to find evidence-based approaches to empiric antibiotic prescribing in newborn infants to identify reliable and safe means of optimising and safely reducing avoidable antibiotic exposure.

INTRODUCTION

Neonatal infection is common and burdensome.[1 2] Clinical manifestations can be non-specific and difficult to distinguish from other pathology.[3] Preterm infants have higher incidence and mortality of early-onset infection (EOI, within 72 hours of birth) and late-onset infection (LOI, ≥72 hours from birth) than term infants[2 4 5] and have prolonged hospital stays which carry risk of healthcare-associated infection.

Neonatal antibiotic use is empirical (given prior to confirmation of infection) and based on risk and clinical assessment,[4] as investigations may yield false negative results[3] and delay could risk deterioration.[6] Antibiotics are very commonly prescribed in neonatal units[7–9] and save lives but use risks drug toxicity, side effects[4] and antibiotic resistance. Prolonged antibiotic use is associated with harm, including necrotising enterocolitis (NEC),

neurological injury, LOI,[8 10–12] invasive fungal diseases[13] and disruption of gut microbiota.[3]

The National Institute for Health and Care Excellence (NICE) produces and publishes evidence-based clinical guidelines in the UK. Before 2012, there was no UK national guidance on preventing and treating neonatal infections. NICE published a consensus-based clinical guideline (CG149) in August 2012[2] with recommendations for intrapartum antibiotic prophylaxis, risk factors for and possible clinical signs of EOI, and indications for investigation and empirical treatment of EOI.

CG149 had potential limitations. Preterm birth after spontaneous labour with prolonged preterm rupture of membranes necessitated antibiotic use, meaning many premature babies receive antibiotics as default. Additionally, in practice a low threshold is used to manage maternal perinatal fever as sepsis[14] which obligated neonatal antibiotic prescribing. Clinical indicators of neonatal sepsis were non-specific,[1] based on low-quality evidence[2] and risked subjective interpretation. Additionally, antibiotic course length recommendations were unclear, the impact of intrapartum antibiotic prophylaxis on neonatal management was not described, and there were no recommendations for LOI.

New guidance (NG195) superseded CG149 in April 2021,[15] which introduced recommendations for managing LOI. The main recommendations in this revision were again introduced without any evidence-base or evaluation of impact of antibiotic exposure on babies. Based on evidence from the USA, NG195 permits the alternative of using the Kaiser Permanente neonatal sepsis risk calculator[16] (KP-SRC) to inform clinical decisions on EOI management. The KP-SRC, however, is only applicable to babies born at ≥34 weeks' gestation and the recommendations for most preterm babies therefore remained consensus based.

It is not known whether the introduction of NICE CG149 and NG195 (summarised in online supplemental figure 1) altered antibiotic prescribing patterns. This is pertinent to ensure antibiotics are used wisely and prevent avoidable harms. This study aims to assess their impact on measures of antibiotic use in very and extremely preterm infants admitted to neonatal units in England and Wales.

METHODS

Data management and analysis were conducted using R V.4.3.2[17] and Stata V.18 (Stata, College Station, Texas, USA).

Data source and study population

We used data from the UK National Neonatal Research Database (NNRD),[18] derived from the electronic patient records of all infants admitted to NHS neonatal units in England and Wales, for very preterm infants (born at 28–31 weeks gestational age, GA) and extremely preterm infants (22–27 weeks GA) born from 1 January 2010 to 31 December 2022. Infants were excluded if missing data on sex, birth weight, final discharge destination, episodes of care; died; or were discharged for ongoing care. We also excluded infants with implausible birth weight for GA z-scores >4 SD above or below the mean, admitted >24 hours after birth or born with a lethal congenital anomaly (online supplemental table 1).

Outcome measures

NNRD data on antibiotic exposure in the first 14 days are accurate.[18] Antibiotic use was identified by searching the NNRD daily drugs field for character strings matching antibiotic names with intravenous preparations (online supplemental table 2), identified from the British National Formulary for Children (version September 2021).[19] Prophylactic, oral and topical preparations were excluded.

We calculated several measures of antibiotic use aggregated by month of birth. The antibiotic use rate (AUR) was the aggregate percentage of inpatient days in receipt of at least one antibiotic. We calculated the percentage of infants exposed to one or more days of antibiotics initiated day 1–3 (presumed to be for EOI) and initiated day 4 or later (presumed to be for LOI), with day of birth defined as day 1. We identified the percentage of infants who received a prolonged antibiotic course (≥5 consecutive days) for EOI or LOI. LOI antibiotic prescribing was defined using a 'washout' period of 2 days without antibiotics to exclude a continuing EOI antibiotic course. Finally, for the first day of antibiotic prescription for EOI and LOI, we identified which antibiotic(s) were prescribed.

Statistical methods

The study period is divided into three periods: (1) before CG149 publication (January 2010–July 2012); (2) between publication of CG149 and NG195 (August 2012–March 2021); (3) after NG195 publication (April 2021–December 2022). Characteristics of the study population by period were described.

We used segmented regression to investigate the impact of publications on the outcomes.[20] The regression models estimate (1) the monthly trend in each outcome in period 1; (2) any immediate absolute change in magnitude or trend in period 2 relative to period 1 and (3) any immediate absolute change in magnitude or trend in period 3 relative to period 2.

We built a parsimonious model for each outcome through backwards elimination of non-statistically significant variables, based on a significance level of 0.05. The autocorrelation function, partial autocorrelation function and Ljung-Box test demonstrated no significant autocorrelation of model residuals.

Subgroup analysis

We conducted prespecified subgroup analyses to investigate variations in impact defined by characteristics considered likely to influence antibiotic use: (1) very versus extremely preterm infants; (2) infants with versus without evidence of bacterial infection; (3) infants with versus without a recorded antibiotic indication(s) (based on presence of diagnosis codes for bacterial infection, isolation of an antibiotic-resistant organism or NEC). We identified characteristics for subgroup analyses 2 and 3 by searching for character strings in daily and episodic diagnoses records matching a list of diagnoses (online supplemental table 3). We excluded diagnoses indicating risk of infection, suspected but unconfirmed infection and infections not specific to a bacterial cause.

Type(s) of antibiotic prescribed

We plotted the most frequently prescribed antibiotic monotherapy and combinations for EOI and LOI by birth year to illustrate changes over time. We present the top seven most frequently prescribed antibiotic(s) with the remainder categorised as 'other'.

RESULTS

Data were available for 97 387 infants born at 22–31 weeks GA during the study period and admitted to neonatal units in England and Wales. After exclusions (online supplemental table

Table 1 Description of characteristics of study population

		Month of birth		
	All infants	January 2010–July 2012 (period 1; pre-CG149)	August 2012–March 2021 (period 2)	April 2021–December 2022 (period 3; post-NG195)
Number of infants	84 626	16 391	57 426	10 809
Births per month, median (IQR)	546 (517, 569)	536 (504, 560)	557 (535, 581)	512 (497, 543)
Gestational age in weeks, median (IQR)	29 (27, 31)	29 (27, 31)	29 (27, 31)	29 (27, 31)
Birth weight in grams, median (IQR)	1240 (960, 1515)	1246 (977, 1520)	1240 (960, 1511)	1232 (950, 1510)
Birth weight z-score, median (IQR)	0.03 (–0.62, 0.60)	0.05 (–0.60, 0.61)	0.02 (–0.62, 0.59)	0.03 (–0.66, 0.61)
Female sex, n (%)	38 858 (45.9)	7583 (46.3)	26 370 (45.9)	4905 (45.4)
Neonatal intensive care unit	44 586 (52.7)	8147 (49.7)	30 612 (53.3)	5827 (53.9)
Local neonatal unit	32 606 (38.5)	6707 (40.9)	21 873 (38.1)	4026 (37.3)
Special care baby unit	6531 (7.7)	1364 (8.3)	4340 (7.6)	827 (7.7)
Missing	903 (1.07)	173 (1.1)	601 (1.1)	129 (1.2)
Length of hospital stay in days, median (IQR)	53 (38, 78)	52 (37, 77)	53 (38, 78)	54 (38, 80)

CG149, clinical guideline 149; NG195, NICE guideline 195.

4), 84 626 infants were included. Table 1 describes the population by time period.

On average, 546 infants were born each month, with relatively fewer per month in period 3. The proportion of infants first admitted to a neonatal intensive care unit increased over time but there were no clinically relevant differences in median GA, birth weight, birth weight for GA z-score and length of stay.

Table 2 describes overall use of antibiotics and indications for use. Almost all infants (96.0%, n=81 278) received at least one antibiotic during their stay. The percentage of infants who had a recorded antibiotic indication, evidence of bacterial infection or NEC declined over time, but there was little difference in the percentage with an antibiotic-resistant organism.

Table 3 shows the results of the interrupted time series analysis, and figures 1 and 2 show the fitted regression lines from the parsimonious models.

The median (IQR) AUR across the study period was 19.5% (18.5–20.2) of total care days per month. In period 1, AUR was increasing by 0.03% per month. This immediately declined by 1.02% in period 2 and the trend reversed, resulting in an absolute decrease of 0.02% per month, which did not change during period 3. Over the study period, the AUR declined from 20.5% to 17.5% of total care days, which equates to approximately 1000 fewer days of antibiotic use per month (approximately 2 fewer days of antibiotics per infant) on average.

Almost all (93.4%, n=79 006) infants received antibiotics for EOI. The prevalence was stable in periods 1 and 2, though declined in period 3 by 0.20% per month. Just over half (54.0%, n=45 684) received antibiotics for LOI. Prevalence was increasing by 0.02% per month in period 1 and did not change until period 3, where it declined by 0.23% per month.

Approximately one-third (35.7%, n=30 201) of infants received a prolonged EOI antibiotic course. The prevalence dropped by 1.87% in period 2 and continued to decline by 0.08% per month thereafter. Similarly, one-third (32.9%, n=27 796) were exposed to a prolonged LOI antibiotic course. Prevalence initially increased by 0.12% per month but immediately declined by 0.02% per month in period 2, accelerating to a decline of 0.14% per month in period 3.

Subgroup analysis

Online supplemental table 5 and online supplemental figure 2 show the subgroup analyses. The number of infants born per month in some subgroups was small, resulting in greater monthly outcome variability and reduced power to detect small changes.

Table 2 Antibiotic use and indications for use by study period

		Month of birth		
	All infants	January 2010–July 2012 (period 1; pre-CG149)	August 2012–March 2021 (period 2)	April 2021–December 2022 (period 3; post-NG195)
Number of infants				
Exposed to ≥1 antibiotic, n (%)	81 278 (96.0)	15 726 (95.9)	55 322 (96.3)	10 230 (94.6)
Any recorded antibiotic indication, n (%)	29 929 (35.4)	6228 (38.0)	20 471 (35.7)	3230 (29.9)
Evidence of bacterial infection, n (%)	22 273 (26.3)	4825 (29.4)	15 125 (26.3)	2323 (21.5)
Record of an antibiotic-resistant organism, n (%)	1325 (1.6)	257 (1.6)	877 (1.5)	191 (1.8)
Necrotising enterocolitis, n (%)	14 149 (16.7)	2837 (17.3)	9723 (16.9)	1589 (14.7)

CG149, clinical guideline 149; NG195, NICE guideline 195.

Table 3 Month-on-month absolute percentage changes (with 95% CIs) in antibiotic use before and after the publication of CG149 and NG195

Outcome	January 2010–July 2012 (period 1; pre-CG149)	August 2012–March 2021 (period 2; postpublication of CG149)			April 2021–December 2022 (period 3; postpublication of NG195)			Magnitude at start and end of study period (%) and reduction in number of days/infants with outcome per month*
	Trend pre-CG149	Immediate change in level compared with pre-CG149	Change in trend compared with pre-CG149	Absolute trend August 2012–March 2021	Immediate change in level compared with August 2012–March 2021	Change in trend compared with August 2012–March 2021	Absolute trend April 2021–December 2022	
Antibiotic use rate	0.03 (0.00 to 0.06)	−1.02 (−1.57 to −0.47)	−0.05 (−0.08 to −0.03)	−0.02 (−0.03 to −0.02)	n/a	n/a	−0.02 (−0.03 to −0.02)	20.5, 17.5; 1000 fewer days per month
Received ≥1 day of antibiotics for EOI	n/a	n/a	n/a	n/a	n/a	−0.20 (−0.26 to −0.14)	−0.20 (−0.26 to −0.14)	93.6, 89.5; 22 fewer infants per month
Received ≥1 day of antibiotics for LOI	0.02 (0.01 to 0.03)	n/a	n/a	0.02 (0.01 to 0.03)	n/a	−0.25 (−0.36 to −0.14)	−0.23 (−0.33 to −0.12)	52.9, 50.7; 12 fewer infants per month
Received ≥1 prolonged course of antibiotics for EOI	n/a	−1.87 (−2.97 to −0.78)	−0.08 (−0.09 to −0.07)	−0.08 (−0.09 to −0.07)	n/a	n/a	−0.08 (−0.09 to −0.07)	41.3, 29.1; 66 fewer infants per month
Received ≥1 prolonged course of antibiotics for LOI	0.12 (0.04 to 0.21)	−2.85 (−0.54 to −0.15)	−0.14 (−0.23 to −0.06)	−0.02 (−0.03 to −0.01)	n/a	−0.12 (−0.22 to −0.03)	−0.14 (−0.24 to −0.05)	33.0, 28.7; 23 fewer infants per month

n/a, variable not included in parsimonious model.
*Magnitude of effect calculated assuming a constant population size and expressed as the reduction in the number of days/infants with antibiotics in the last month of the study period compared with the first month.
CG149, clinical guideline 149; NG195, NICE guideline 195.

Extreme prematurity, bacterial infection and a recorded antibiotic indication were associated with a higher AUR and exposure to antibiotic(s) for ≥1 day, or ≥1 prolonged course, than the respective comparison subgroup.

Very premature infants observed a greater reduction in AUR, EOI antibiotic exposure and prolonged LOI exposure than extremely premature infants in period 2. During period 3, extremely premature babies observed greater reductions in AUR and EOI and LOI antibiotic exposure than very premature babies.

In period 2, the trend in AUR reduced for infants without bacterial infection, and EOI and LOI antibiotic use immediately reduced for infants with evidence of bacterial infection, but without a change in trend. Over the same period, infants without infection saw a temporary increase in EOI antibiotic use with a reduction in trend and no changes in LOI antibiotic use.

Type(s) of antibiotic prescribed

Figure 3 shows changes over time in the type of antibiotics prescribed on the first day of prescribing for EOI and LOI (full data in online supplemental table 6). For EOI, the percentage of infants receiving benzylpenicillin plus gentamicin increased from 72.3% in 2010 to 83.0% in 2014, remaining relatively stable since. Prescribing for LOI was more variable. Flucloxacillin plus gentamicin was the most frequent combination, received by 28.2% of infants, followed by cefotaxime and vancomycin (7.6%).

DISCUSSION

We found that publication of NICE guidance in 2012 (CG149) and its update in 2021 (NG195) were associated with some reductions in antibiotic use for extremely and very preterm infants in England and Wales, resulting in more consistent antibiotic use, with defined course lengths. This may explain the temporary changes in antibiotic prescribing for LOI seen in 2012, with sustained decreasing trends only seen following the update of the guidance in 2021 when recommendations on antibiotic use for LOI were first introduced.

Choice of antibiotics for EOI has become increasingly consistent with NICE guidance. However, choice for LOI continues to vary substantially, perhaps due to omission of recommendations for LOI in 2012 and only a broad recommendation to use 'a combination of narrow-spectrum antibiotics' in 2021.[15]

This is the first national evaluation of the impact of NICE guidelines on antibiotic use in preterms, though other studies have investigated the impact on term and near-term infants.[21 22] Almost all extremely and very preterm infants received antibiotics, reiterating that neonatal units are a priority setting to reduce avoidable antibiotic use.

For EOI antibiotic use in term and near-term infants, NICE now recommends an alternative approach, the KP-SRC.[16] While NICE standard recommendations are largely opinion based, the KP-SRC is based on a multivariable risk prediction model using data from large cohorts of infants born at ≥35 weeks' gestation in California, USA.[16] The KP-SRC and other strategies

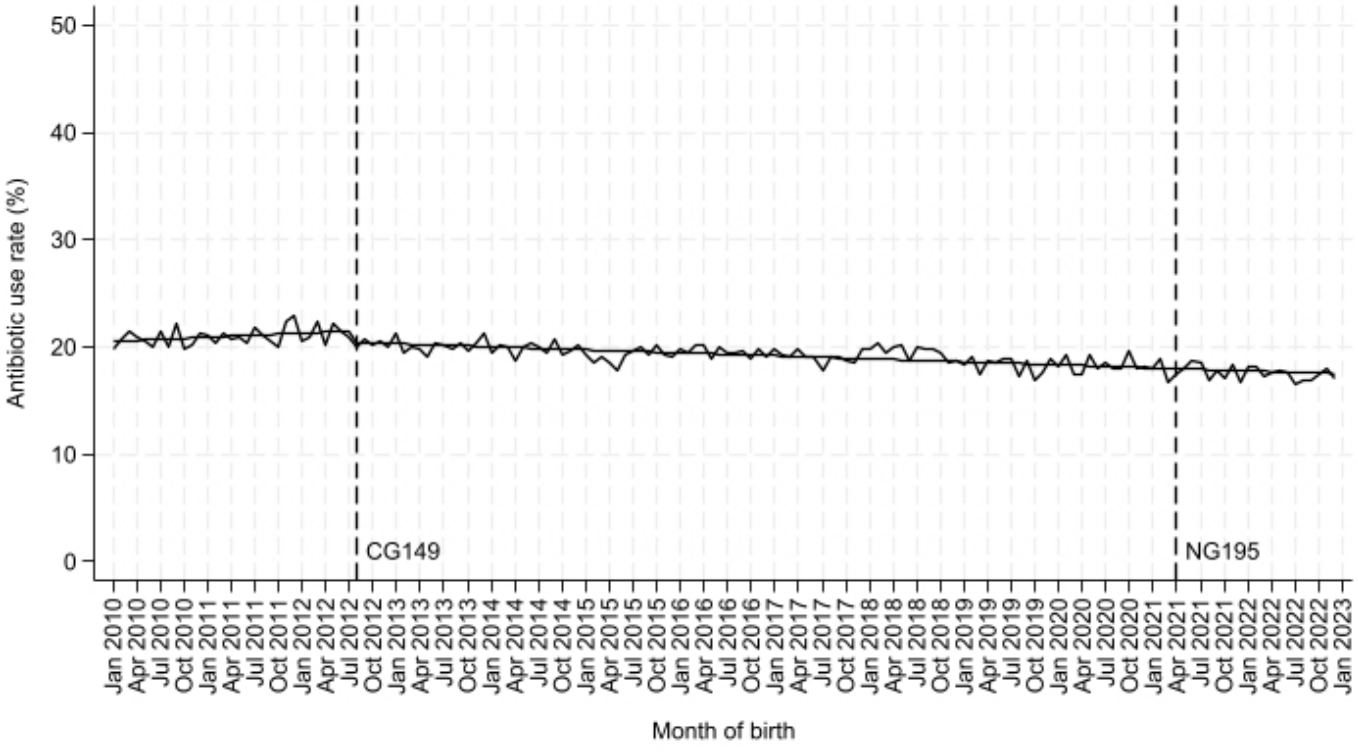

Figure 1 Changes in the overall antibiotic use rate before and after the publication of CG149 and NG195. CG149, clinical guideline 149; NG195, NICE guideline 195.

recommended by the US American Academy of Paediatics,[23] similar to NICE, identify risk factors for EOI and clinical indicators of illness and need for repeat observations. The KP-SRC has been widely adopted in the UK and observational studies show large reductions in antibiotic use and laboratory testing compared with NICE 2012 (Goel[24]) but there is a concern that more conservative use of antibiotics and fewer babies screened for EOI incurs a risk of missing a significant number of infants with infection.[25] Use of the KP-SRC has been subjected to numerous observational studies in the UK, but there is no randomised comparison with NICE 2021, although an ongoing trial is comparing a similar approach to NICE 2021 with the

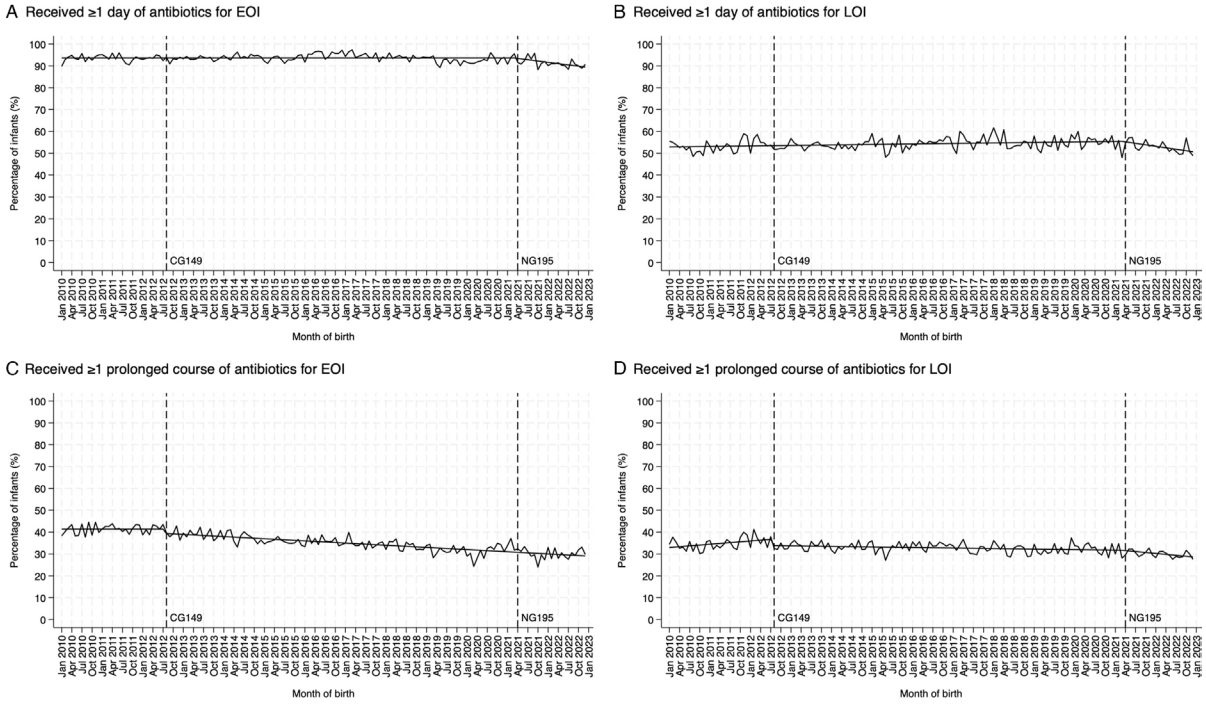

Figure 2 Changes in the percentage of infants who received ≥1 day, and ≥1 prolonged course, of antibiotics for EOI (A and C) and LOI (B and D). CG149, clinical guideline 149; NG195, NICE guideline 195; EOI, early-onset infection; LOI, late-onset infection.

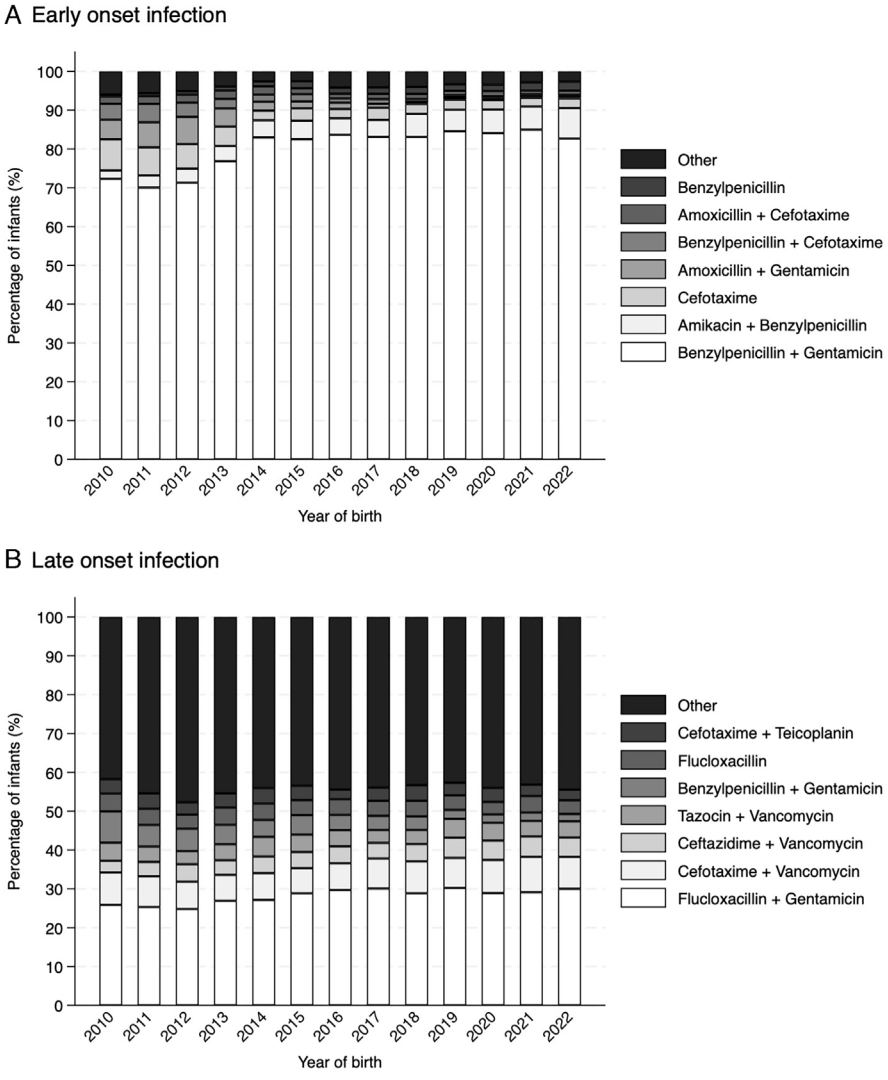

Figure 3 Type and combination of antibiotics prescribed on the first day of prescribing for EOI (A) and LOI (B), by year of birth. EOI, early-onset infection; LOI, late-onset infection.

KP-SRC in the Netherlands.[26] It remains a strong priority to compare the approaches, to reduce antibiotic use without risk of delayed treatment leading to harm. Furthermore, the KP-SRC is designed for ≥35 weeks' gestation and most premature infants, who are both at a higher risk of infection and disproportionately affected by antibiotic associated harm, are excluded. The only guidance in the UK for this population is the NICE recommendations, highlighting the need for developing an evidence-based approach to rationalise antibiotic use in this group.

Preterm infants often have clinical indicators of possible EOI as listed in the 2021 NICE guidance (eg, apnoea, feeding difficulty, temperature instability) due to prematurity and related comorbidities. Both iterations of NICE guidance combine recommendations for mature and preterm infants, overlooking the impact of prematurity on clinical presentation. Consequently, almost all very and extremely preterm infants receive antibiotics which may cause harm in the short term, such as increased risk of NEC, and via alterations in gut microbiome, impact long-term health of survivors of prematurity.

Interrupted time series analysis is the strongest quasi-experimental study design to evaluate the impact of national guidance over time.[20] There were few substantial changes in the study population case-mix over time, reducing the likelihood of confounding. This analysis assumed an instantaneous impact of guidance on antibiotic use, though this may not reflect reality. Anticipatory and lag effects were not assessed given the absence of literature to inform a defined time period of potential effect. It is also unclear to what extent NICE guidance is consistently implemented. An attempt to assess guidance compliance in did not specifically assess antibiotic prescribing.[27] Adherence to a similar guideline in the Netherlands was low,[28] especially non-prescribing. Similarly, German neonatal units also found gaps between national guidance and practice.[29]

While our findings demonstrate a temporal association between guidance publication and antibiotic use, we cannot infer causality. This segmented regression approach assumes preintervention trends would have continued without intervention, which cannot be verified. Changes in trends may be alternatively explained by other contemporaneous changes in practice or interventions, such as local quality improvement projects.

From NNRD data, it is challenging to distinguish suspected from confirmed infection, and indications for prescribing are not recorded. Excluding infants who died, who may have had very high AURs which would have skewed the overall measure, likely under-reports the full extent of neonatal antibiotic prescribing.

Reducing avoidable antibiotic prescribing can prevent antibiotic-associated harm, antibiotic resistance and health system costs.[30] Future guidance must consider the impact of prematurity on presentation and treatment to avoid antibiotic prescribing in preterm infants in situations where risk exceeds benefit. We corroborate international findings of overall reductions in antibiotic use though neonatal antibiotic use remains extremely high. It will be essential to monitor the impact of NG195 on antibiotic prescribing and apply findings to guidance development.

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Patient consent for publication Not applicable.

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