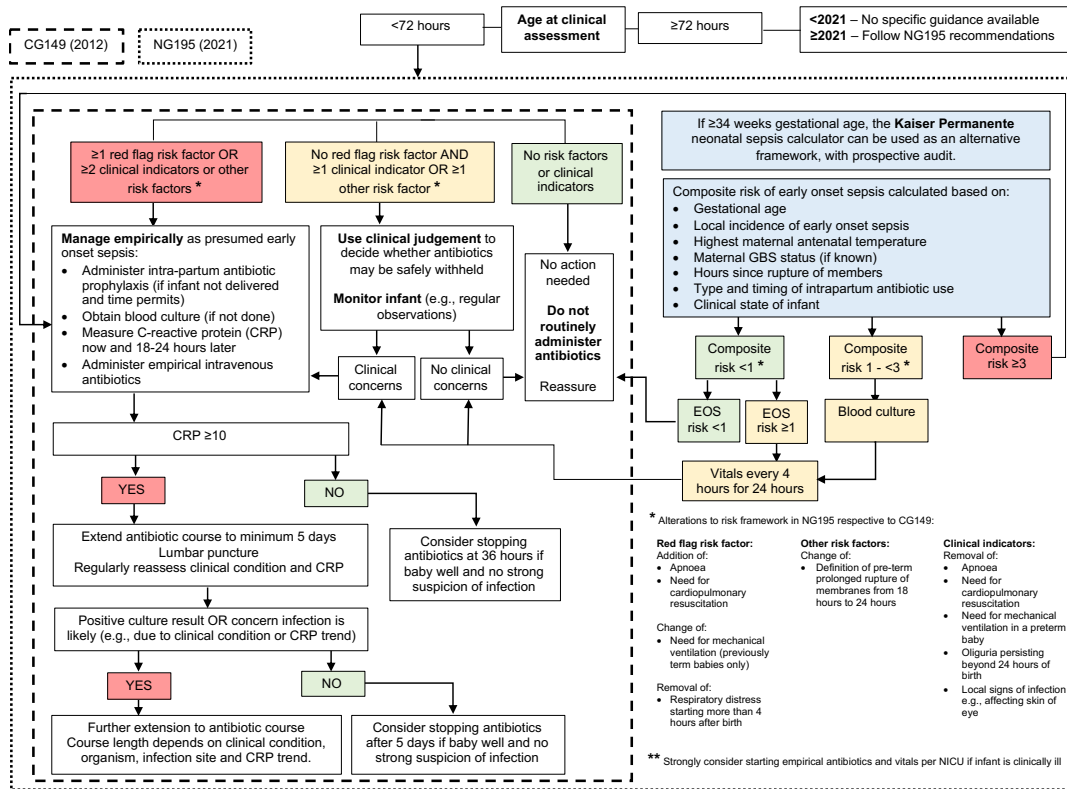


# The impact of NICE clinical guidelines for prevention and treatment of neonatal infections on antibiotic use in very preterm infants in England and Wales: an interrupted time series analysis

## Supplementary Figure 1: Summary of antibiotic prescribing guidelines for early onset infection



Supplementary Table 1: Exclusions due to congenital anomalies

Anomaly	Number <sup>a</sup>
Anencephaly and similar malformations	<5
Holoprosencephaly	20
Bilateral renal agenesis/Potter Syndrome	11
Trisomy 13 (Patau Syndrome) and/or Trisomy 18 (Edward Syndrome)	59
Triploidy/tetraploidy/polyploidy	8
Thanatophoric Dysplasia	<5

<sup>a</sup> Counts <5 suppressed for statistical disclosure control; some infants excluded with >1 anomaly.

### Supplementary Table 2: Search terms for antibiotics with neonatal intravenous preparations

Antibiotic name	Alternative names and spellings
amikacin	
ampicillin	
amoxicillin	amoxycillin
ampicillin	
aztreonam	
benzylpenicillin	benzyl penicillin
cefotaxime	
ceftazidime	
ceftriaxone	
cefuroxime	
ciprofloxacin	
clarithromycin	
clindamycin	
co-amoxiclav	augmentin; coamoxiclav
colistin	colistimethate sodium; colomycin
co-trimoxazole	cotrimoxazole; cotramoxazole
daptomycin	
ertapenem	
erythromycin	erthromycin
flucloxacillin	
fosfomycin	
fusidic acid	sodium fusidate
gentamicin	gentamycin
imipenem	primaxin
linezolid	
meropenem	meropenum; meropenam
metronidazole	
rifampicin	
tazocin	piperacillin; piptazocin; tazobactam
teicoplanin	
tobramycin	
vancomycin	

### Supplementary Table 3: Search terms, identify bacterial infection, clearly pathogenic bacterial organisms, isolation of an antibiotic resistant organism, and necrotising enterocolitis

BACTERIAL INFECTION	
Search term	Related search terms
acute lower respiratory tract infection- bacterial	
alpha haemolytic streptococci	
anaerobic sepsis	
bacterial meningitis	
bacterial pneumonia	
bacterial sepsis	bacterial sepsis / septicaemia (other); confirmed bacterial sepsis
bacteriuria	
catheter associated blood stream infection	
septicaemia	septicaemia (post operative)

congenital pneumonia due, escherichia coli	
congenital pneumonia due, other bacterial agents	
congenital pneumonia due, pseudomonas	
congenital pneumonia due, staphylococcus	
congenital pneumonia due, streptococcus	
e. coli	e. coli sepsis; infection – e. coli; sepsis – e. coli
enterobacter	infection – enterobacter sp.; sepsis / septicaemia – specified – enterobacter sp.
enterococcus	infection – enterococcus
extended beta lactamase coliform	extended beta lactamase coliform infection/sepsis
gram negative septicaemia	
group b streptococcal sepsis / septicaemia (gbs)	sepsis – group b streptococcus (gbs); umbilical sepsis / septicaemia – group b streptococcus
haemophilus influenzae	hemophilus influenzae; infection – hemophilus influenzae
infection - bacterium	
klebsiella	infection – klebsiella; klebsiella pneumonia; sepsis / septicaemia – specified – klebsiella sp.; sepsis – klebsiella sp.
listeria	listeria sepsis / septicaemia / disseminated
meningitis - bacterial	meningitis – bacterial (specific organism); meningitis – bacterial (unknown); meningitis – bacterial (unknown or unspecified cause); meningitis – bacterial (unknown or unspecified cause) organism; meningitis – bacterial (unknown or unspecified cause) organism
mrsa	methicillin resistant staph aureus (mrsa); mrsa colon; mrsa colonization; multi-resistant staph aureus (mrsa)
mycoplasma	mycoplasma infection; mycoplasma pneumoniae; infection – pneumococcus
pneumococcus	infection – pneumococcus
pseudomonas aeruginosa	sepsis / septicaemia – specified - pseudomonas
sepsis - confirmed	sepsis – confirmed bacterial (gram negative); sepsis – confirmed bacterial (gram negative); sepsis – confirmed bacterial (gram positive); sepsis – confirmed bacterial (streptococci b positive); sepsis – confirmed bacterial (streptococci positive); sepsis / septicaemia – confirmed with +ve microbiology
staph aureus	sepsis – staph aureus; staph. aureus sepsis / septicaemia
urinary tract infection	lower urinary tract infection; urinary tract infection (uti); neonatal urinary tract infection; uti; uti-proven; infection of urinary tract

**CLEARLY PATHOGENIC BACTERIAL ORGANISMS**

From: Royal College of Paediatrics and Child Health. 2022. National Neonatal Audit Programme (NNAP) Annual Report on 2020 Data, Appendix A – NNAP 2020 data results and methods. <https://www.rcpch.ac.uk/resources/national-neonatal-audit-programme-annual-report-2020>

acinetobacter baumannii	enterococcus sp	salmonella brandenburg
acinetobacter baumannii	escherichia	salmonella colindale
aeromonas caviae	escherichia sp	salmonella cotham
aeromonas hydrophila	escherichia vulneris	salmonella cubana

aeromonas salmonicida	escherichia hermannii	salmonella djugu
aeromonas sobria	escherichia coli	salmonella dublin
aeromonas sp	fusobacterium necrophorum	salmonella enteritidis
anaerococcus prevotii	fusobacterium nucleatum	salmonella gold-coast
b haemolytic streptococci	fusobacterium sp	salmonella hadar
bacteroides capillosus	gardnerella	salmonella heidelberg
bacteroides distasonis	gardnerella vaginalis	salmonella hofit
bacteroides fragilis	gbs	salmonella hull
bacteroides ovatus	group b streptococcus	salmonella infantis
bacteroides sp	group g streptococcus	salmonella kedougou
bacteroides uniformis	haemophilus influenzae	salmonella kiambu
bacteroides vulgatus	hafnia alvei	salmonella kibusi
c. koseri	klebsiella	salmonella kintambo
campylobacter ureolyticus	klebsiella aerogenes	salmonella kisarawe
campylobacter fetus	klebsiella oxytoca	salmonella matopeni
campylobacter jejuni	klebsiella ornitholytica	salmonella mississippi
campylobacter sp	klebsiella planticola	salmonella monschau
cedecea lapagei	klebsiella pneumoniae (or klebsiella pneumoniae subsp ozenae)	salmonella montevideo
citrobacter	klebsiella pneumoniae	salmonella muenchen
citrobacter amalonaticus	klebsiella sp	salmonella muenster
citrobacter braakii	kluuvera sp	salmonella newport
citrobacter diversus	leclercia adecarboxylata	salmonella oranienburg
citrobacter farmeri	listeria monocytogenes	salmonella poona
citrobacter freundii	listeria sp	salmonella reading
citrobacter koseri	mrsa	salmonella saphra
citrobacter sp	morganella morgani	salmonella senftenberg
clostridium paraputrificum	neisseria meningitidis	salmonella sinstorff
clostridium beijerinckii	pantoea septica	salmonella sp
clostridium bifermentans	pantoea sp	salmonella stanley
clostridium butyricum	pantoea agglomerans	salmonella tel-el-kebir
clostridium perfringens	pasteurella	salmonella typhi (or salmonella paratyphi)
clostridium septicum	pasteurella sp	salmonella typhimurium
clostridium sordelli	pasteurella haemolytica	salmonella unnamed
clostridium sp	pasteurella multocida	salmonella virchow
clostridium sporogenes	pasteurella pneumotropica	salmonella vitkin
clostridium tertium	peptostreptococcus	salmonella wichita
coccidioides sp.	peptostreptococcus asaccharolyticus	serratia liquefaciens
coliform	peptostreptococcus magnus	serratia marcescens
e.coli	prevotella bivia	serratia odorifera
enterobacter agglomerans	prevotella buccalis	serratia plymuthica
enterobacter aerogenes	prevotella oralis	serratia proteamaculas
enterobacter agglomerans (or pantoea agglomerans)	proteus mirabilis	serratia rubidaea
enterobacter amnigenus	proteus penneri	serratia sp
enterobacter asburiae	proteus sp	shigella flexneri
enterobacter cloacae	proteus vulgaris	shigella soneri
enterobacter cloacaecomplex	providencia alcalifaciens	staphylococcus aureus (or s. aureus)
enterobacter gergoviae	providencia stuartii	stellatoidea
enterobacter hormaechei	pseudomonas aeruginosa	streptococcus agalactiae
enterobacter intermedius (or enterobacter intermedium)	raoultella planticola (or klebsiella planticola)	streptococcus anaerobic
enterobacter kobei	raoultella sp	streptococcus anginosus
enterobacter other named	raoultella terrigena	streptococcus bovis

enterobacter sakazakii	salmonella aba	streptococcus constellatus
enterobacter sp	salmonella agama	streptococcus faecalis
enterococcus avium	salmonella ajobo	Streptococcus pneumoniae
Enterococcus casseliflavus	salmonella apapa	streptococcus group a stem
enterococcus durans	salmonella arizonae	streptococcus group b stem
enterococcus faecalis (or streptococcus faecalis)	salmonella ajobo	streptococcus group c stem
enterococcus faecalis	salmonella apapa	streptococcus group d stem
enterococcus faecium	salmonella arizonae	streptococcus group g stem
enterococcus gallinarum	salmonella brandenburg	streptococcus milleri (or streptococcus milleri group)
enterococcus hirae	salmonella colindale	Streptococcus pyogenes
enterococcus raffinosus	salmonella cotham	veillonella atypica (or veillonella named)
		yersinia enterocolitica

ANTIBIOTIC RESISTANT ORGANISMS	
Search term	Related search terms
extended beta lactamase coliform	esbl
mrsa	methicillin resistant staph aureus (mrsa); mrsa colon; mrsa colonization; multi-resistant staph aureus (mrsa)
antibiotic resistance	antibiotic resistant
carbapenemase	carbapenemase producing Enterobacteriaceae; cpe
multi resistant	multi-resistant

NECROTISING ENTEROCOLITIS	
Search term	Related search terms
necrotising enterocolitis	necrotising enterocolitis – suspected; necrotising enterocolitis – confirmed; necrotising enterocolitis – perforated; necrotising enterocolitis – proven (on xray or at surgery)
necrotizing enterocolitis	necrotizing enterocolitis – confirmed

**Supplementary Table 4: Counts of exclusions**

<b>Variable</b>	<b>Missing, n (%)</b>
Total exclusions	12,761 (13.1)
Missing sex	94 (0.1)
Missing birthweight	14 (0.0)
Birthweight for age z-score >+4SD or <-	122 (0.1)
Admitted >24hrs after birth	567 (0.6)
Lethal congenital anomaly	101 (0.1)
Missing records for 1+ episodes of care	390 (0.4)
Final discharge destination unknown	167 (0.2)
Final discharge, specialist continuing care	3,085 (3.2)
Died	8,761 (9.0)

**Supplementary Table 5: Month-on-month absolute percentage changes in antibiotic use before and after the publication of NICE CG149 and NG195, by subgroup**

Outcome	Jan 2010 - Jul 2012 (Period 1; pre-CG149)	Aug 2012 - Mar 2021 (Period 2; post-publication of CG149)			Apr 2021 – Dec 2022 (Period 3; post-publication of NG195)		
	Trend pre-CG149	Immediate change in level compared, pre-CG149	Change in trend compared, pre-CG149	Absolute trend Aug 2012-Mar 2021	Immediate change in level compared, Aug 2012-Mar 2021	Change in trend compared, Aug 2012-Mar 2021	Absolute trend Apr 2021-Dec 2022
<b>Antibiotic use rate</b>							
GA <28 weeks	n/a	-1.35 (-1.97, -0.73)	-0.02 (-0.02, -0.01)	-0.02 (-0.02, -0.01)	n/a	-0.06 (-0.11, -0.01)	-0.08 (-0.13, -0.03)
GA 28-31 weeks	0.04 (0.01, 0.07)	-0.76 (-1.38, -0.13)	-0.07 (-0.10, -0.04)	-0.03 (-0.03, -0.02)	n/a	n/a	-0.03 (-0.03, -0.02)
Bacterial infection	n/a	-1.42 (-1.96, -0.87)	n/a	n/a	n/a	n/a	n/a
No bacterial infection	0.05 (0.02, 0.08)	-0.92 (-1.51, -0.33)	-0.07 (-0.10, -0.04)	-0.02 (-0.03, -0.02)	n/a	n/a	-0.02 (-0.03, -0.02)
Recorded indication(s)	n/a	-1.55 (-1.99, -1.10)	n/a	n/a	n/a	-0.05 (-0.09, -0.00)	-0.05 (-0.09, 0.00)
No recorded indication	0.03 (0.00, 0.06)	-1.00 (-1.55, -0.44)	-0.06 (-0.08, -0.03)	-0.02 (-0.03, -0.02)	n/a	n/a	-0.02 (-0.03, -0.02)
<b>Received ≥1 day of antibiotics for EOI</b>							
GA <28 weeks	n/a	n/a	n/a	n/a	n/a	-0.25 (-0.34, -0.17)	-0.25 (-0.34, -0.17)
GA 28-31 weeks	n/a	n/a	-0.01 (-0.02, 0.00)	-0.01 (-0.02, 0.00)	n/a	-0.13 (-0.21, -0.06)	-0.14 (-0.21, -0.07)
Bacterial infection	-0.10 (-0.21, 0.00)	-2.62 (-4.68, -0.56)	0.14 (0.04, 0.25)	0.04 (0.02, 0.05)	n/a	-0.27 (-0.39, -0.15)	-0.23 (-0.34, -0.12)
No bacterial infection	n/a	2.65 (1.67, 3.62)	-0.03 (-0.04, -0.02)	-0.03 (-0.04, -0.02)	n/a	-0.11 (-0.20, -0.03)	-0.14 (-0.22, -0.06)
Recorded indication(s)	-0.15 (-0.21, -0.10)	n/a	0.17 (0.11, 0.23)	0.02 (0.01, 0.03)	n/a	-0.22 (-0.31, -0.12)	-0.20 (-0.29, -0.11)
No recorded indication	n/a	n/a	n/a	n/a	n/a	-0.20 (-0.26, -0.14)	-0.20 (-0.26, -0.14)
<b>Received ≥1 day of antibiotics for LOI</b>							
GA <28 weeks	0.02 (0.01, 0.03)	n/a	n/a	0.02 (0.01, 0.03)	n/a	-0.42 (-0.55, -0.29)	-0.40 (-0.53, -0.28)
GA 28-31 weeks	n/a	n/a	n/a	n/a	n/a	-0.14 (-0.24, -0.03)	-0.14 (-0.24, -0.03)
Bacterial infection	0.08 (0.04, 0.10)	-3.18 (-5.80, -0.56)	n/a	0.08 (0.04, 0.10)	n/a	-0.22 (-0.42, -0.01)	-0.14 (-0.33, 0.05)
No bacterial infection	0.03 (0.02, 0.05)	n/a	n/a	0.03 (0.02, 0.05)	n/a	-0.26 (-0.39, -0.13)	-0.23 (-0.35, -0.11)
Recorded indication(s)	0.08 (0.06, 0.10)	-2.95 (-5.11, -0.79)	n/a	0.08 (0.06, 0.10)	n/a	-0.27 (-0.44, -0.10)	-0.19 (-0.35, -0.03)
No recorded indication	0.02 (0.01, 0.03)	n/a	n/a	0.02 (0.01, 0.03)	n/a	-0.25 (-0.36, -0.14)	-0.23 (-0.34, -0.13)
<b>Received ≥1 prolonged course of antibiotics for EOI</b>							
GA <28 weeks	n/a	-3.30 (-5.61, -1.00)	-0.07 (-0.09, -0.04)	-0.07 (-0.09, -0.04)	n/a	n/a	-0.07 (-0.09, -0.04)
GA 28-31 weeks	n/a	-1.41 (-2.56, -0.26)	-0.09 (-0.10, -0.08)	-0.09 (-0.10, -0.08)	n/a	n/a	-0.09 (-0.10, -0.08)
Bacterial infection	n/a	-3.17 (-5.59, -0.76)	-0.04 (-0.06, -0.02)	-0.04 (-0.06, -0.02)	n/a	n/a	-0.04 (-0.06, -0.02)
No bacterial infection	n/a	-1.68 (-2.86, -0.49)	-0.08 (-0.09, -0.07)	-0.08 (-0.09, -0.07)	n/a	n/a	-0.08 (-0.09, -0.07)
Recorded indication(s)	n/a	-3.86 (-5.97, -1.75)	-0.05 (-0.07, -0.03)	-0.05 (-0.07, -0.03)	n/a	n/a	-0.05 (-0.07, -0.03)
No recorded indication	n/a	-1.81 (-2.90, -0.72)	-0.08 (-0.09, -0.07)	-0.08 (-0.09, -0.07)	n/a	n/a	-0.08 (-0.09, -0.07)
<b>Received ≥1 prolonged course of antibiotics for LOI</b>							
GA <28 weeks	n/a	-1.94 (-3.55, -0.34)	n/a	n/a	-5.46 (-7.34, -3.58)	n/a	n/a
GA 28-31 weeks	n/a	n/a	-0.04 (-0.05, -0.03)	-0.04 (-0.05, -0.03)	n/a	n/a	-0.04 (-0.05, -0.03)
Bacterial infection	0.26 (0.06, 0.45)	-6.68 (-10.5, -2.84)	-0.21 (-0.41, -0.01)	0.05 (0.02, 0.07)	n/a	n/a	0.05 (0.02, 0.07)
No bacterial infection	n/a	-1.17 (-2.13, -0.20)	n/a	n/a	-1.91 (-3.03, -0.78)	n/a	n/a
Recorded indication(s)	0.06 (0.04, 0.09)	-4.29 (-6.71, -1.88)	n/a	0.06 (0.04, 0.09)	-3.39 (-5.92, -0.86)	n/a	0.06 (0.04, 0.09)
No recorded indication	0.13 (0.04, 0.21)	-2.90 (-4.60, -1.20)	-0.15 (-0.24, -0.06)	-0.02 (-0.03, -0.01)	n/a	-0.13 (-0.23, -0.03)	-0.15 (-0.24, -0.06)

n/a – variable not included in parsimonious model

**Supplementary Table 6: Antibiotics prescribed on the first day of prescribing for a) early onset infection b) late onset infection (combinations received by <10 infants suppressed)**

**a) Early onset infection**

Antibiotic(s)	Frequency	% of infants
benzylpenicillin + gentamicin	63,341	80.17
amikacin + benzylpenicillin	3,743	4.74
cefotaxime	3,040	3.85
amoxicillin + gentamicin	1,983	2.51
benzylpenicillin + cefotaxime	1,454	1.84
amoxicillin + cefotaxime	1,242	1.57
benzylpenicillin	1,146	1.45
amoxicillin + benzylpenicillin + gentamicin	475	0.6
co-amoxiclav	426	0.54
benzylpenicillin + cefotaxime + gentamicin	364	0.46
gentamicin	316	0.4
amoxicillin + benzylpenicillin + cefotaxime + gentamicin	115	0.15
benzylpenicillin + cefuroxime	109	0.14
benzylpenicillin + gentamicin + metronidazole	105	0.13
amikacin + benzylpenicillin + gentamicin	71	0.09
flucloxacillin + gentamicin	71	0.09
benzylpenicillin + flucloxacillin + gentamicin	66	0.08
cefotaxime + gentamicin	56	0.07
amoxicillin + benzylpenicillin	51	0.06
benzylpenicillin + gentamicin + meropenem	51	0.06
amikacin + amoxicillin	40	0.05
amoxicillin	39	0.05
amikacin	36	0.05
benzylpenicillin + tobramycin	35	0.04
amoxicillin + cefotaxime + gentamicin	34	0.04
amoxicillin + gentamicin + metronidazole	34	0.04
benzylpenicillin + gentamicin + teicoplanin	34	0.04
amikacin + amoxicillin + benzylpenicillin	28	0.04
benzylpenicillin + co-amoxiclav + gentamicin	25	0.03
cefotaxime + vancomycin	24	0.03
benzylpenicillin + gentamicin + vancomycin	21	0.03
tazocin + vancomycin	21	0.03
amoxicillin + benzylpenicillin + cefotaxime	18	0.02
gentamicin + teicoplanin	17	0.02
ceftazidime + vancomycin	16	0.02
benzylpenicillin + flucloxacillin	15	0.02
cefotaxime + teicoplanin	13	0.02
meropenem	13	0.02
benzylpenicillin + ceftazidime + gentamicin	11	0.01
flucloxacillin	10	0.01



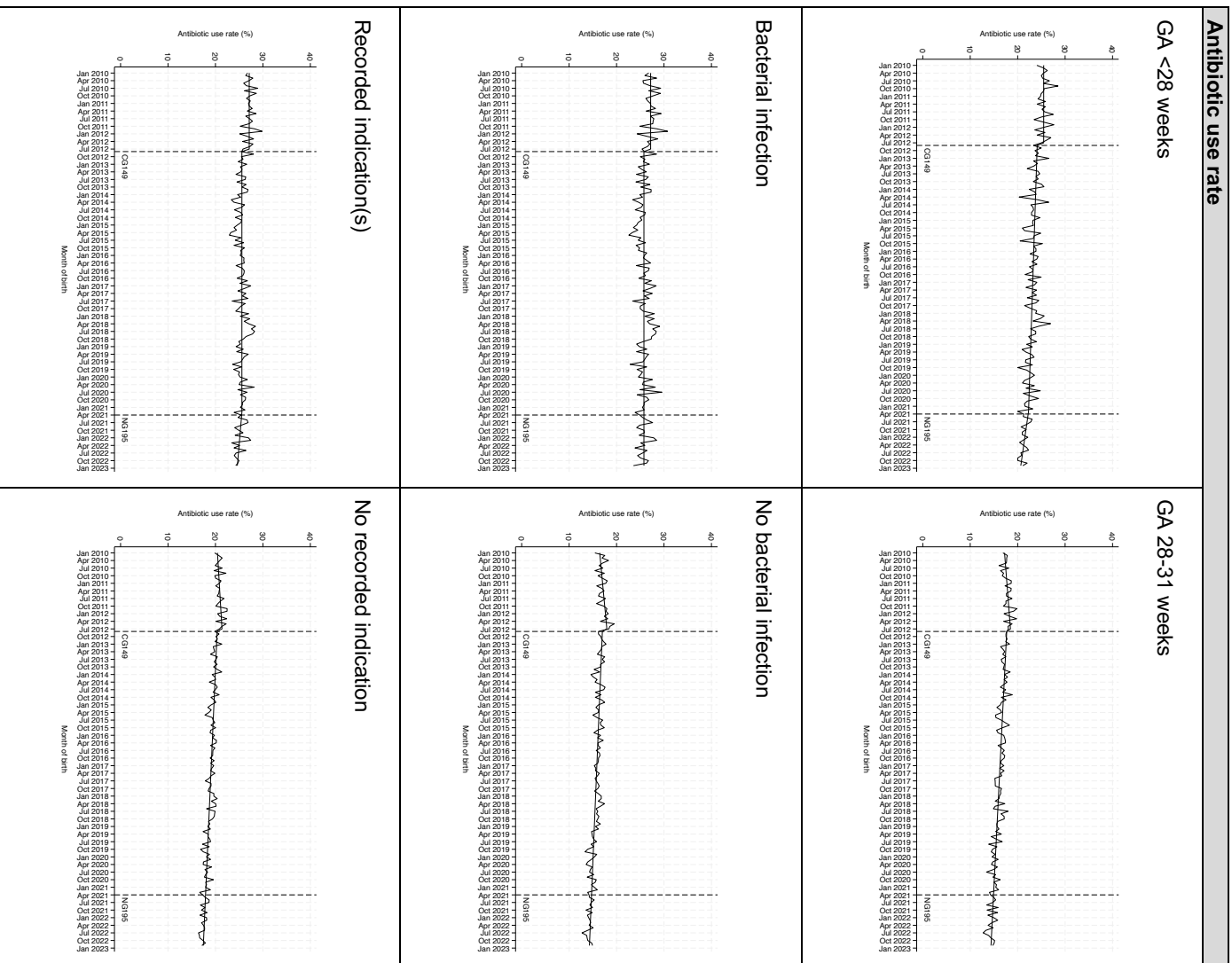
**b) Late onset infection**

<b>Antibiotic(s)</b>	<b>Frequency</b>	<b>% of infants</b>
flucloxacillin + gentamicin	12,868	28.17
cefotaxime + vancomycin	3,492	7.64
ceftazidime + vancomycin	1,988	4.35
tazocin + vancomycin	1,908	4.18
benzylpenicillin + gentamicin	1,879	4.11
flucloxacillin	1,812	3.97
cefotaxime + teicoplanin	1,568	3.43
gentamicin + vancomycin	1,510	3.31
gentamicin + teicoplanin	1,487	3.25
cefotaxime	1,356	2.97
erythromycin	1,269	2.78
cefotaxime + flucloxacillin	1,238	2.71
flucloxacillin + gentamicin + metronidazole	1,185	2.59
cefotaxime + gentamicin	894	1.96
amikacin + flucloxacillin	833	1.82
co-amoxiclav + gentamicin	805	1.76
vancomycin	653	1.43
ceftazidime + teicoplanin	478	1.05
amoxicillin + cefotaxime	450	0.99
cefotaxime + metronidazole + vancomycin	400	0.88
meropenem + vancomycin	388	0.85
amoxicillin + flucloxacillin + gentamicin	344	0.75
amoxicillin + gentamicin + metronidazole	327	0.72
meropenem	294	0.64
benzylpenicillin + gentamicin + metronidazole	285	0.62
co-amoxiclav	276	0.6
cefotaxime + metronidazole + teicoplanin	232	0.51
ceftazidime + metronidazole + vancomycin	219	0.48
meropenem + teicoplanin	198	0.43
benzylpenicillin	180	0.39
gentamicin	180	0.39
teicoplanin	171	0.37
tazocin	163	0.36
cefotaxime + metronidazole	162	0.35
cefotaxime + gentamicin + metronidazole	156	0.34
cefotaxime + flucloxacillin + metronidazole	154	0.34
gentamicin + metronidazole + teicoplanin	148	0.32
amoxicillin + gentamicin	144	0.32
gentamicin + metronidazole + vancomycin	136	0.3
cefotaxime + gentamicin + vancomycin	133	0.29
amikacin + tazocin	126	0.28
amoxicillin	115	0.25
amikacin + benzylpenicillin	102	0.22
amoxicillin + cefotaxime + metronidazole	90	0.2

cefotaxime + flucloxacillin + gentamicin	82	0.18
benzylpenicillin + cefotaxime	81	0.18
flucloxacillin + gentamicin + vancomycin	80	0.18
ceftazidime	77	0.17
ceftazidime + flucloxacillin	68	0.15
amikacin + flucloxacillin + metronidazole	67	0.15
gentamicin + meropenem	66	0.14
benzylpenicillin + flucloxacillin + gentamicin	65	0.14
ceftazidime + metronidazole + teicoplanin	64	0.14
flucloxacillin + metronidazole	63	0.14
tazocin + teicoplanin	63	0.14
benzylpenicillin + flucloxacillin	61	0.13
amoxicillin + flucloxacillin + gentamicin + metronidazole	48	0.11
co-amoxiclav + gentamicin + metronidazole	48	0.11
amikacin	44	0.1
ciprofloxacin	42	0.09
flucloxacillin + vancomycin	39	0.09
cefotaxime + flucloxacillin + gentamicin + vancomycin	37	0.08
cefuroxime	37	0.08
Fusidic acid	36	0.08
benzylpenicillin + cefuroxime	35	0.08
metronidazole	35	0.08
benzylpenicillin + cefotaxime + gentamicin	33	0.07
amikacin + co-amoxiclav	32	0.07
flucloxacillin + gentamicin + teicoplanin	32	0.07
amikacin + meropenem	30	0.07
amikacin + vancomycin	30	0.07
amikacin + amoxicillin + metronidazole	29	0.06
gentamicin + tazocin + vancomycin	28	0.06
co-trimoxazole	26	0.06
gentamicin + tazocin	26	0.06
cefotaxime + flucloxacillin + vancomycin	25	0.05
cefotaxime + flucloxacillin + gentamicin + metronidazole	23	0.05
flucloxacillin + gentamicin + meropenem	23	0.05
amoxicillin + flucloxacillin	22	0.05
cefotaxime + gentamicin + teicoplanin	22	0.05
ceftazidime + gentamicin	22	0.05
flucloxacillin + gentamicin + tazocin + vancomycin	22	0.05
gentamicin + metronidazole	21	0.05
clarithromycin	20	0.04
amikacin + cefotaxime	19	0.04
benzylpenicillin + metronidazole	19	0.04
gentamicin + meropenem + vancomycin	18	0.04
amikacin + teicoplanin	17	0.04
meropenem + metronidazole + vancomycin	17	0.04
metronidazole + vancomycin	17	0.04
amoxicillin + metronidazole	16	0.04

cefotaxime + flucloxacillin + gentamicin + metronidazole + vancomycin	16	0.04
amoxicillin + cefotaxime + teicoplanin	15	0.03
benzylpenicillin + flucloxacillin + gentamicin + metronidazole	15	0.03
cefotaxime + meropenem + vancomycin	15	0.03
metronidazole + teicoplanin	15	0.03
amoxicillin + cefotaxime + flucloxacillin + gentamicin	14	0.03
amikacin + benzylpenicillin + metronidazole	13	0.03
erythromycin + flucloxacillin + gentamicin	13	0.03
benzylpenicillin + cefotaxime + metronidazole	12	0.03
benzylpenicillin + gentamicin + teicoplanin	12	0.03
benzylpenicillin + gentamicin + vancomycin	12	0.03
cefotaxime + erythromycin + vancomycin	12	0.03
cefotaxime + gentamicin + metronidazole + vancomycin	12	0.03
metronidazole + tazocin + vancomycin	12	0.03
erythromycin + gentamicin + vancomycin	11	0.02
meropenem + tazocin + vancomycin	11	0.02
amoxicillin + cefotaxime + gentamicin	10	0.02
benzylpenicillin + vancomycin	10	0.02
cefotaxime + meropenem + teicoplanin	10	0.02
ceftazidime + erythromycin + vancomycin	10	0.02
ceftazidime + flucloxacillin + metronidazole	10	0.02
ceftazidime + flucloxacillin + vancomycin	10	0.02
co-amoxiclav + flucloxacillin + gentamicin	10	0.02
flucloxacillin + gentamicin + metronidazole + vancomycin	10	0.02
flucloxacillin + meropenem	10	0.02
gentamicin + meropenem + teicoplanin	10	0.02

Supplementary Figure 2: Fitted regression lines, by subgroup, with vertical lines indicating the publication of CG149 and NG195



Recorded indication(s)

Bacterial infection

GA <28 weeks

Antibiotic use rate

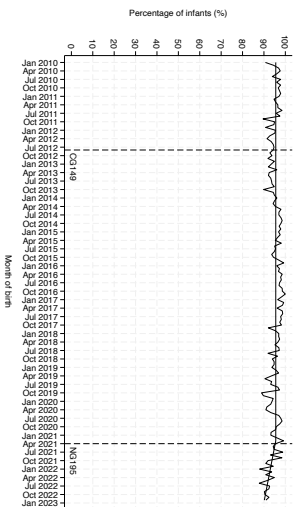
No recorded indication

No bacterial infection

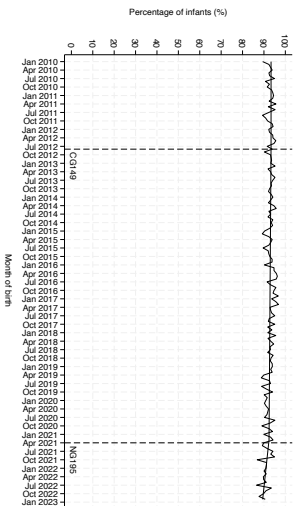
GA 28-31 weeks

Received  $\geq$ 1 day of antibiotics for EOI

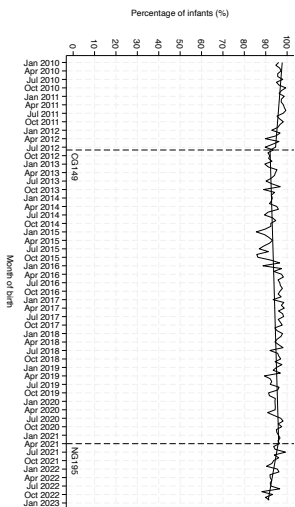
GA <28 weeks



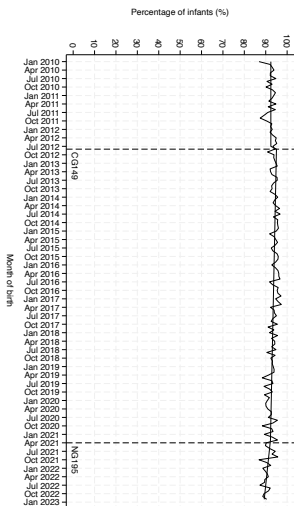
GA 28-31 weeks



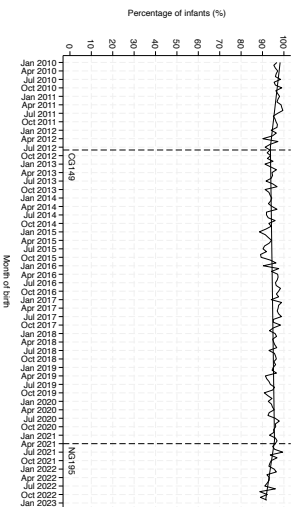
Bacterial infection



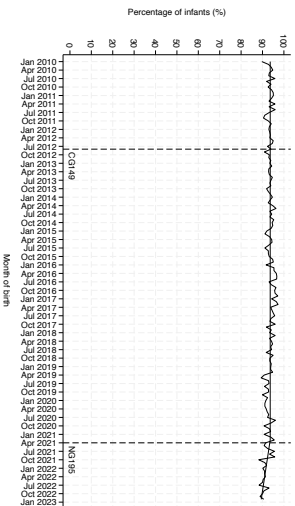
No bacterial infection



Recorded indication(s)

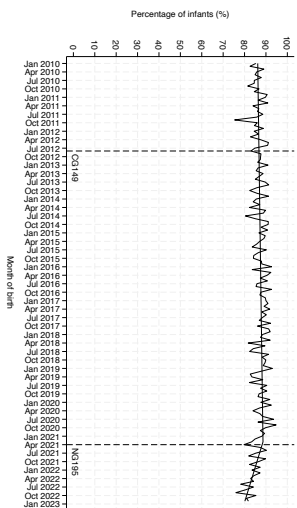


No recorded indication

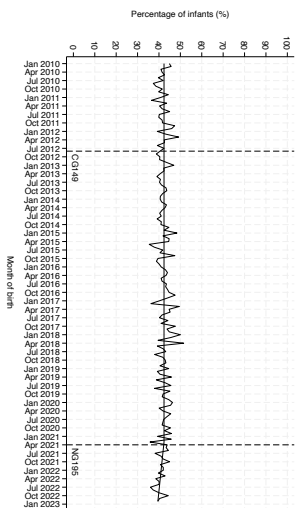


**Received  $\geq 1$  day of antibiotics for LOI**

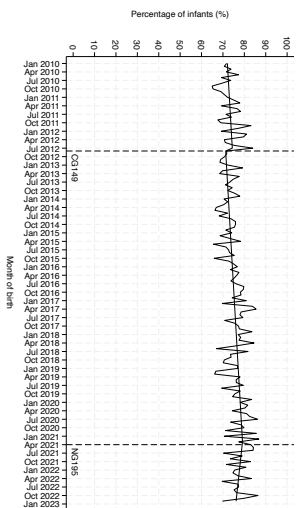
**GA <28 weeks**



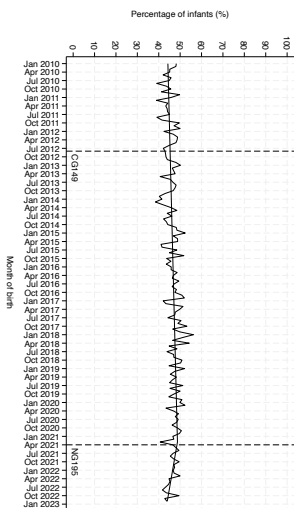
**GA 28-31 weeks**



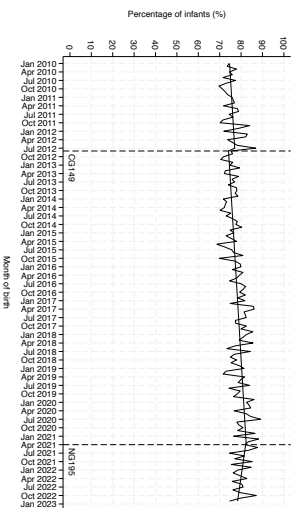
**Bacterial infection**



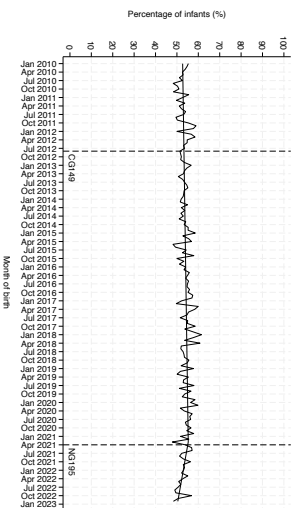
**No bacterial infection**



**Recorded indication(s)**

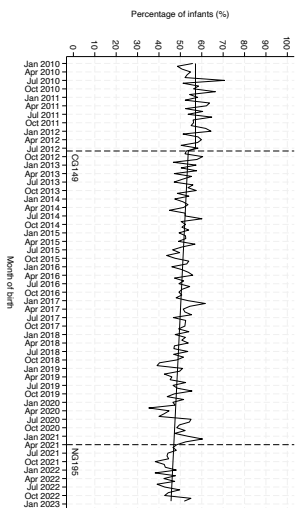


**No recorded indication**

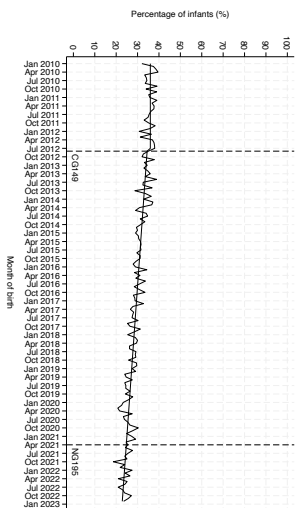


**Received  $\geq 1$  prolonged course of antibiotics for EOI**

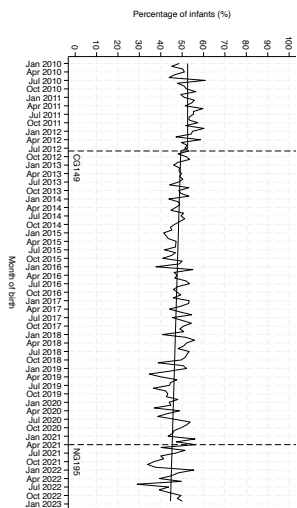
**GA <28 weeks**



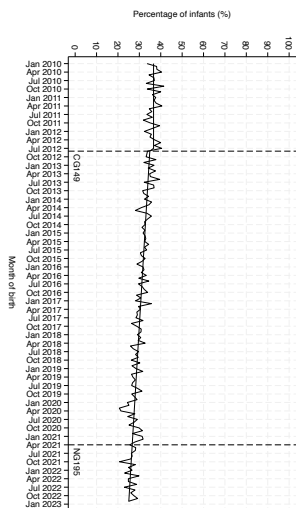
**GA 28-31 weeks**



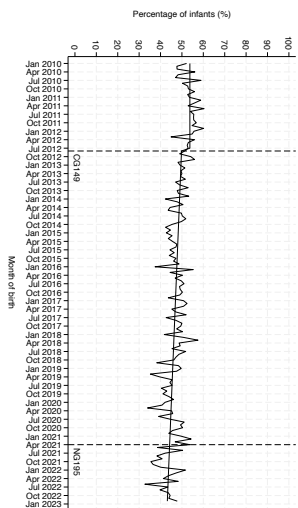
**Bacterial infection**



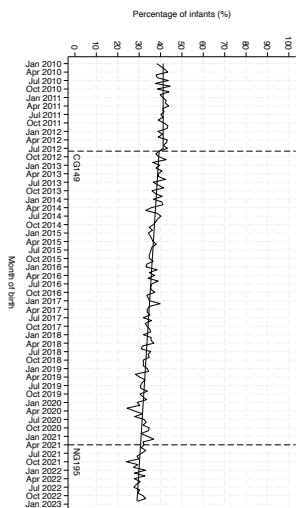
**No bacterial infection**



**Recorded indication(s)**

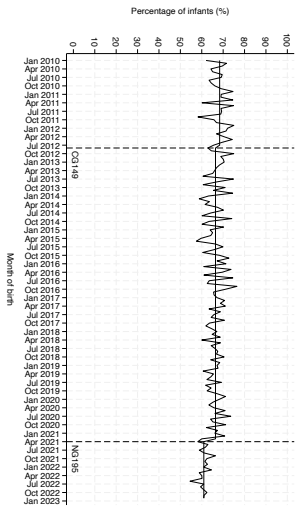


**No recorded indication**

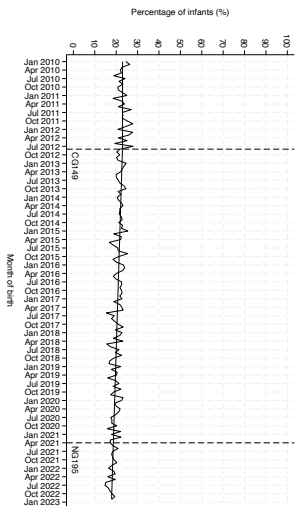


**Received  $\geq 1$  prolonged course of antibiotics for LOI**

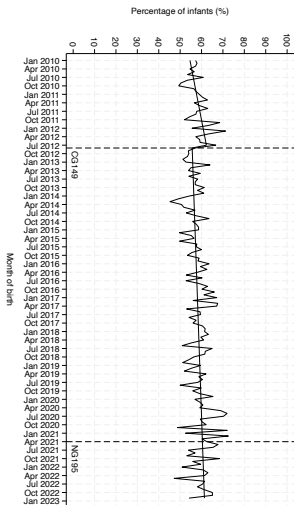
**GA <28 weeks**



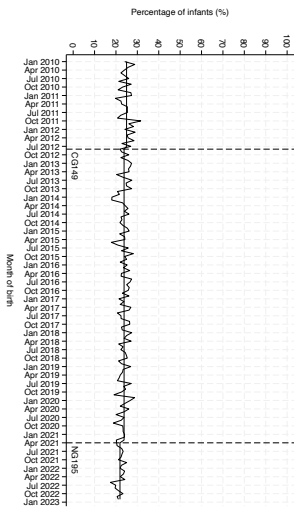
**GA 28-31 weeks**



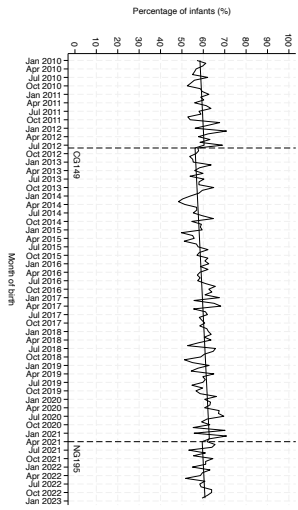
**Bacterial infection**



**No bacterial infection**



**Recorded indication(s)**



**No recorded indication**

