REDACTED Ampicillin Safety in Hospitalized Infants (Analysis of the Pediatrix Database)

Investigational Product:	Ampicillin
Design:	Multi-Center, Retrospective Cohort – Database Review Safety Study
Report Version:	Version 4.0
Date of Report:	November 24, 2014
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1. Ethics

Informed Consent

A waiver of Informed consent and HIPAA was obtained from the IRB for the study investigators to perform data analysis on the limited datasets of the Pediatrix database. No direct participant interaction was involved in this data analysis study.

Participant Confidentiality

Data obtained from the Pediatrix database are considered limited data. No information concerning the study or the data will be released to any third party without prior written approval of the sponsor.

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2. Study Objectives

The objective of the study was to evaluate the safety profile of ampicillin administered to infants per standard of care by their treating caregiver.

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3. Overall Design and Plan Description

This was a multi-center retrospective cohort study conducted using the Pediatrix Medical Group administrative database. The Pediatrix Medical Group database is prospectively created from electronic health records of infants admitted to >300 neonatal intensive care units (NICU) in the United States. It is one of the largest repositories of data for neonatal medicine. The database includes approximately 20% of all NICU patients in the United States and >90,000 NICU admissions annually.

Study Population

Inclusion Criteria

1. Infants ≤28 days of life
2. Admitted to one of 348 NICUs managed by the Pediatrix Medical Group
3. Discharged from 1997-2012
4. Exposed to ampicillin with daily dose for at least one day of treatment recorded in the Pediatrix Medical Group administrative database

Exclusion Criteria

1. None

Classification of Participants

Infants were classified by gestational age (GA) and postnatal age (PNA) at the time of first antibiotic exposure as the following: Group 1 GA ≤34 weeks and PNA ≤7 days, Group 2 ≤34 weeks and PNA 8-28 days, Group 3 GA >34 weeks and PNA ≤28 days.

Study Medication

Administration of ampicillin was not part of the protocol but information was captured for infants exposed to ampicillin on all days during the hospitalization up to 28 days of life.

Definitions

The primary objective was to evaluate the safety of ampicillin. The safety of both ampicillin dosing and ampicillin exposure were evaluated.

Infection – An episode of infection was defined as all positive blood cultures obtained within 21 days of each other. Infant-days of infection were defined as days from the first to the last positive culture within a single episode.

Seizures - Each new diagnosis of seizure was considered as a separate AE. Seizures were considered to be present if they were documented in the infant's record. Electroencephalography was not required.

Laboratory adverse events - A laboratory adverse event (AE) was attributed to ampicillin if it occurred on a day with ampicillin exposure. Laboratory AEs were categorized as adverse events (AE) or severe adverse events (SvAE) based on pre-specified laboratory cut-off values (Table 1).

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Table 1. Laboratory values categorized as adverse events or severe adverse events

Laboratory Values	Adverse event	Severe adverse event
Elevated AST	>600 U/L	>1200 U/L
Leukopenia	<5000/mm^3	<2000/mm^3
Neutropenia	<500/mm^3	<100/mm^3
Thrombocytopenia	<100,000/mm^3	<30,000/mm^3

Statistical and Analytic Plan

Demographic Characteristics - The number of participants and demographic variables including GA, birth weight, PNA at first ampicillin exposure, race/ethnicity and gender are summarized using count, percentages, medians, 25th and 75th percentiles.

Ampicillin Dosing and Exposure - Doses and dosing intervals were determined for each group of infants. Ideal ampicillin dosing was defined by the results from the attached pharmacokinetic analysis. We considered ideal dosing to be 50 mg/kg every 12 hours for Group 1, 75 mg/kg every 12 hours for Group 2 and 50 mg/kg every 8 hours for Group 3. We defined ampicillin exposure as maximum concentration at steady state (Cmaxss), estimated from a previously described population PK model in neonates: V (L) = 0.399 * WTKG and CL (L/hr) = 0.078 * WTKG * (0.6/SCR)$^{0.428}$ * (PMA/37), combined with clinical characteristics and dosing information[1,34]. To allow ampicillin to reach steady state, Cmaxss was not estimated on the first day of each new ampicillin course. Standard descriptive statistics were used to summarize Cmaxss on days of ampicillin exposure with and without adverse events, excluding the first day of each new course.

Adverse Events - The percentage of days with each adverse event was determined for each dose and dosing interval. The median ampicillin exposure on days with and without each AE and SvAE was determined. The percentage of infant days with each AE and SvAE were determined for each decile of ampicillin exposure. These analyses were performed for all infants and for all infants by group. They were also performed with the analysis limited to all infants with infection and infected infants by group. Adverse events occurring at the calculated ideal dosing are highlighted in red. AEs and SvAEs were chosen based on their relevance to the use of beta-lactam antibiotics and their ability to be identified in the database.

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4. Tables

Table 2. Demographics

	All Infants N=199,883	Group 1* N=84,787 (42%)	Group 2 N=1140 (1%)	Group 3 N=113,956 (57%)
Gestational age, weeks†	35 (32, 38)	32 (29, 33)	30 (27, 32)	38 (36, 39)
PNA at first exposure, days	1 (1, 1)	1 (1, 1)	15 (11, 21)	1 (1, 2)
Birth weight, g†	2515 (1780, 3206)	1675 (1175, 2080)	1340 (935, 1790)	3105 (2690, 3526)
5 minute Apgar score				
0-3	4219 (2.2)	2358 (2.8)	31 (2.8)	1830 (1.6)
4-6	16,073 (8.2)	9185 (11.0)	151 (13.6)	6737 (6.0)
7-10	176,154 (89.7)	72,122 (86.2)	925 (83.6)	103,107 (92.3)
Race/ethnicity				
White	109,217 (56.1)	47,271 (56.9)	616 (57.3)	61,330 (55.5)
African-American	31,347 (16.1)	16,972 (20.4)	213 (19.8)	14,162 (12.8)
Hispanic	46,040 (23.7)	15,584 (18.8)	191 (17.8)	30,265 (27.4)
Other	8020 (4.1)	3218 (3.9)	55 (5.1)	4747 (4.3)
Male	114,556 (57.3)	46,569 (54.9)	645 (56.6)	67,342 (59.1)
Inborn	168,034 (84.6)	73,985 (87.9)	866 (77.2)	93,183 (82.4)
Cesarean section	102,343 (51.8)	49,912 (59.4)	761 (67.5)	51,670 (46.0)
Small for gestational age	18,759 (9.4)	8303 (9.8)	202 (17.8)	10,254 (9.0)
Died	4946 (2.7)	4185 (5.4)	62 (6.2)	699 (0.7)
Infected‡	2791 (1.4)	790 (0.9)	151 (13.3)	1850 (1.6)

*Infants grouped by gestational age and postnatal age. Group 1: gestational ≤34 weeks and postnatal age <7 days; Group 2: gestational age ≤34 weeks and postnatal age >7 days but ≤28 days; Group 3: gestational age >34 weeks and postnatal and postnatal age ≤28 days
†Median (25th, 75th percentile)
‡Infected: bacterial culture of urine, blood or cerebrospinal fluid positive during ampicillin course

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Dose and safety relationship

A variety of doses and intervals are used for administration of ampicillin to infants. Dosing could be determined for 946,723/1,163,928 (84%) of days with ampicillin exposure. Relatively few infants received the dose predicted to be most appropriate for their gestational and postnatal ages (bold/red).

Dosing regimens by gestational age and postnatal age for infants with infection

Table 3. Ampicillin dosing for all infants with infection, days

	Frequency				
Dose (mg/kg)	**Q 4H**	**Q 6H**	**Q 8H**	**Q 12H**	**Total**
25		74	118	181	373
50		273	1944	3499	5716
75		193	856	724	1707
100		277	1611	10,361	12,249
125		11	95	143	249
150		4	65	182	251
175			14	26	40
200		15	310	268	593
225				22	22
250				19	18
275				56	56
300				117	117
Total		847	5013	15,597	21,457

Table 4. Ampicillin dosing for Group 1 infants with infection, days

	Frequency				
Dose (mg/kg)	**Q 4H**	**Q 6H**	**Q 8H**	**Q 12H**	**Total**
25		6		44	50
50		17	81	**877**	975
75		14	75	198	287
100		9	81	2203	2293
125				57	57
150				58	58
175				12	12
200			1	48	49
225				7	7
250				3	3
275					
300					
Total		46	238	3507	3791

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Table 5. Ampicillin dosing in Group 2 infants with infection, days

	Frequency				
Dose (mg/kg)	**Q 4H**	**Q 6H**	**Q 8H**	**Q 12H**	**Total**
25		23	21	58	102
50		16	190	591	797
75		66	132	**168**	366
100		30	308	1408	1746
125			21	21	42
150			30	36	66
175			5	1	6
200			2	42	44
225				4	4
250				7	7
275					
300					
Total		135	709	2336	3180

Table 6. Ampicillin dosing in Group 3 infants with infection, days

	Frequency				
Dose (mg/kg)	**Q 4H**	**Q 6H**	**Q 8H**	**Q 12H**	**Total**
25		37	54	22	113
50		219	**1628**	1963	3810
75		77	619	357	1053
100		191	1097	6601	7889
125		11	63	65	139
150		4	25	85	114
175			3	13	16
200		13	307	162	482
225				11	11
250				8	8
275				56	56
300				117	117
Total		552	3796	9460	13,808

Ampicillin dosing by gestational age and postnatal age for all infants exposed to ampicillin

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Table 7. Ampicillin dosing in all infants, days

	Frequency				
Dose (mg/kg)	**Q 4H**	**Q 6H**	**Q 8H**	**Q 12H**	**Total**
25		304	2841	6190	9335
50	4	1491	58,637	245,065	305,197
75	23	479	18,377	38,472	57,351
100	18	516	9156	536,160	545,850
125		11	394	5585	5990
150		21	2737	3633	6391
175		28	224	1453	1705
200		96	2936	6233	9265
225				994	994
250				1483	1483
275				1126	1126
300				2036	2036
Total	45	2946	95,302	848,430	946,723

Table 8. Ampicillin dosing in all Group 1 infants, days

	Frequency				
Dose (mg/kg)	**Q 4H**	**Q 6H**	**Q 8H**	**Q 12H**	**Total**
25		7	593	3833	4433
50	1	64	8896	**105,443**	114,404
75		40	4519	18134	22,693
100	8	54	1074	203,313	204,449
125			108	3316	3424
150		5	284	1434	1723
175			16	711	727
200		6	181	2159	2346
225				427	427
250				256	256
275				80	80
300				53	53
Total	9	176	15,671	339,159	355,015

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Table 9. Ampicillin dosing in all Group 2 infants, days

	Frequency				
Dose (mg/kg)	**Q 4H**	**Q 6H**	**Q 8H**	**Q 12H**	**Total**
25		66	237	982	1285
50		116	2325	13,428	15,869
75		76	1121	**2244**	3441
100		53	1627	23,656	25,326
125			77	560	637
150		12	144	313	469
175			21	122	143
200		11	86	412	509
225				46	46
250				42	42
275				2	2
300				12	12
Total		334	5638	41,809	47,781

Table 10. Ampicillin dosing in all Group 3 infants, days

	Frequency				
Dose (mg/kg)	**Q 4H**	**Q 6H**	**Q 8H**	**Q 12H**	**Total**
25		231	2011	1375	3617
50	3	1311	**47,416**	126,194	174,924
75	23	363	12,737	18,094	31,217
100	10	409	6455	309,201	316,217
125		11	209	1709	1929
150		4	2309	1886	4199
175		28	187	620	835
200		79	2669	3662	6410
225				521	521
250				1185	1185
275				1044	1044
300				1971	1971
Total	36	2436	73,993	467,462	543,927

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Adverse events in infants exposed to ampicillin with infection

Seizures

In infants with infection, seizure occurred most often at doses of 125 mg/kg/dose for Group 3 infants (3.6% of infant-days) and at doses of 150 mg/kg/dose for Group 1 infants (3.4% of infant-days). A dosing interval of 6 hours was associated with the highest incidence of seizures for all groups: 4.3% for Group 1, 2.2% for Group 2 and 2.2% for Group 3.

AST Elevation

AST elevation was rare in infected infants with Group 1 infants most frequently affected. Dose did not appear to be related to AST elevation or severe AST elevation. A dosing interval of 6 hours was associated with the highest incidence of AST elevation (4.3% of infant-days) and severe AST elevation (2.0% of infant-days) in Group 1 infants. There was no AST elevation or severe elevation in infected Group 2 infants.

Leukopenia

Leukopenia occurred most often in Group 1 infants (10.9% of infant-days). There was not a clear relationship between ampicillin dose or dosing interval and leukopenia for any group.

Neutropenia

Neutropenia was associated with higher doses in Group 1 and Group 2 infants. There did not appear to be a relationship between the dosing interval and neutropenia. Severe neutropenia was seen most frequently in Group 1 infants (0.9% of infant-days) and appeared to occur more frequently at increasing doses of ampicillin. There did not appear to be a relationship between dosing interval and the incidence of severe neutropenia.

Thrombocytopenia

Thrombocytopenia was the most common of the studied adverse events in infected infants occurring on 6.4% of infant-days. Group 1 (13.0%) and Group 2 (11.8%) developed thrombocytopenia more often than Group 3 infants (3.3%). Thrombocytopenia occurred at many doses but occurred on >20% of Group 1 infant-days at doses of 25 mg/kg/dose, 150 mg/kg/dose and 200 mg/kg/dose. Thrombocytopenia occurred more often at shorter dosing intervals (6 hours) for Group 1 infants. There did not appear to be a relationship between dosing interval and thrombocytopenia for Group 2 and 3 infants. Severe thrombocytopenia was less common and was most commonly seen in Group 2 infants at doses of 125 mg/kg/dose (9.5%).

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REDACTED Table 11. Adverse events and severe adverse events for all infant-days at each dose and frequency of ampicillin for all infants with infection.

	Seizure	AST AE	AST SvAE	Leukopenia AE	Leukopenia SvAE	Neutropenia AE	Neutropenia SvAE	Thrombocytopenia AE	Thrombocytopenia SvAE
N=21,457	N=126 (0.6%)	N=12 (0.1%)	N=5 (<0.1%)	N=968 (4.6%)	N=153 (0.7%)	N=249 (1.2%)	N=54 (0.3%)	N=1336 (6.4%)	N=181 (0.9%)
Dose (mg/kg)									
25 n=373 (0%)	1 (0.4)	0 (0)	0 (0)	14 (5.1)	6 (2.2)	2 (0.7)	0 (0)	40 (14.7)	9 (3.3)
50 n=5716 (32%)	29 (0.5)	9 (0.2)	5 (0.1)	198 (3.5)	21 (0.4)	47 (0.8)	8 (0.1)	314 (5.6)	32 (0.6)
75 n=1707 (6%)	12 (0.7)	0 (0)	0 (0)	74 (4.3)	14 (0.8)	18 (1.0)	3 (0.2)	135 (7.9)	28 (1.6)
100 n=12,249 (57%)	71 (0.6)	3 (<0.1)	0 (0)	635 (5.3)	104 (0.9)	169 (1.4)	39 (0.3)	752 (6.3)	98 (0.8)
125 n=249 (0%)	5 (2.1)	0 (0)	0 (0)	11 (4.6)	0 (0)	2 (0.8)	0 (0)	26 (10.8)	5 (2.1)
150 n=251 (0%)	3 (1.2)	0 (0)	0 (0)	10 (4.1)	2 (0.8)	4 (1.7)	2 (0.8)	29 (12.0)	5 (2.1)
175 n=40 (0%)	0 (0)	0 (0)	0 (0)	1 (2.9)	1 (2.9)	1 (2.9)	0 (0)	3 (8.6)	0 (0)
200 n=593 (0%)	4 (0.7)	0 (0)	0 (0)	21 (3.6)	4 (0.7)	6 (1.0)	2 (0.3)	31 (5.4)	4 (0.7)
225 n=22 (0%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
250 n= 18 (0%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (11.1)	0 (0)
275 n=56 (0%)	0 (0)	0 (0)	0 (0)	1 (1.8)	1 (1.8)	0 (0)	0 (0)	3 (5.4)	0(0)
300 n=117 (0%)	1 0.9)	0 (0)	0 (0)	3 (2.6)	0 (0)	0 (0)	0 (0)	1 (0.9)	0 (0)
Frequency									
q4h n=0 (0%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
q6 n=847 (0%)	17 (2.3)	2 (0.3)	1 (0.1)	29 (3.9)	4 (0.5)	7 (0.9)	1 (0.1)	52 (6.9)	8 (1.1)
q8 n=5013 (10%)	28 (0.6)	0 (0)	0 (0)	152 (3.2)	27 (0.6)	37 (0.8)	5 (0.1)	248 (5.2)	29 (0.6)
q12 n=15,597(89%)	81 (0.5)	10 (0.1)	4 (<0.1)	787 (5.1)	122 (0.8)	205 (1.3)	48 (0.3)	1036 (6.8)	144 (0.9)

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REDACTED Table 12. Adverse events and severe adverse events for infant-days at each dose and frequency of ampicillin for Group 1 infants with infection.

	Seizure	AST AE	AST SvAE	Leukopenia AE	Leukopenia SvAE	Neutropenia AE	Neutropenia SvAE	Thrombocytopenia AE	Thrombocytopenia SvAE
N=3791	N=29 (0.8%)	N=5 (0.1%)	N=1 (<0.1%)	N=414 (10.9%)	N=66 (1.7%)	N=127 (3.4%)	N=36 (0.9%)	N=493 (13.0%)	N=56 (1.5%)
Dose (mg/kg)									
25 n=50 (1%)	1 (2.0)	0 (0)	0 (0)	6 (12.0)	2 (4.0)	1 (2.0)	0 (0)	11 (22.0)	3 (6.0)
50 n=975 (25%)	8 (0.8)	4 (0.4)	1 (<0.1)	93 (9.5)	11 (1.1)	27 (2.8)	4 (0.4)	108 (11.1)	6 (0.6)
75 n=287 (7%)	4 (1.4)	0 (0)	0 (0)	34 (11.8)	5 (1.7)	9 (3.1)	3 (1.0)	47 (16.4)	4 (1.4)
100 n=2293 (60%)	13 (0.6)	1 (<0.1)	0 (0)	267 (11.6)	45 (2.0)	82 (3.6)	0 (0)	290 (12.6)	39 (1.7)
125 n=57 (1%)	0 (0)	0 (0)	0 (0)	5 (8.8)	0 (0)	2 (3.5)	0 (0)	9 (15.8)	1 (1.8)
150 n=58 (1%)	2 (3.4)	0 (0)	0 (0)	5 (8.6)	1 (1.7)	3 (5.2)	2 (3.4)	14 (24.1)	2 (3.4)
175 n=12 (<0.1%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (16.7)	0 (0)
200 n=49 (1%)	1 (2.0)	0 (0)	0 (0)	4 (8.2)	2 (4.1)	3 (6.1)	2 (4.1)	12 (24.5)	1 (2.0)
225 n=7 (<0.1%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
250 n=3 (<0.1%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
275 n=0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
300 n=0 (0%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Frequency									
q4h n=0 (0%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
q6 n=46 (1%)	2 (4.3)	2 (4.3)	1 (2.0)	1 (2.2)	0 (0)	1 (2.2)	0 (0)	12 (26.1)	2 (4.3)
q8 n=238 (6%)	0 (0)	0 (0)	0 (0)	18 (7.6)	4 (1.7)	7 (2.9)	2 (1.0)	27 (11.3)	8 (3.4)
q12 n=3507 (92%)	27 (0.8)	3 (0.1)	0 (0)	395 (11.3)	62 (1.8)	119 (3.4)	34 (0.9)	454 (12.9)	46 (1.3)

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REDACTED Table 13. Adverse events and severe adverse events for infant-days at each dose and frequency of ampicillin for Group 2 infants with infection.

	Seizure	AST AE	AST SvAE	Leukopenia AE	Leukopenia SvAE	Neutropenia AE	Neutropenia SvAE	Thrombocytopenia AE	Thrombocytopenia SvAE
N=3180	N=16 (0.5%)	N=0 (0%)	N=0 (0%)	N=83 (2.6%)	N=14 (0.4%)	N=17 (0.5%)	N=5 (0.2%)	N=374 (11.8%)	N=68 (2.1%)
Dose (mg/kg)									
25 n=102 (3%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	20 (19.6)	5 (4.9)
50 n=797 (25%)	4 (0.5)	0 (0)	0 (0)	17 (2.1)	1 (0.1)	1 (0.1)	0 (0)	89 (11.2)	14 (1.8)
75 n=366 (11%)	2 (0.5)	0 (0)	0 (0)	12 (3.3)	4 (1.1)	2 (0.5)	0 (0)	53 (14.5)	12 (3.3)
100 n=1746 (54%)	10 (0.6)	0 (0)	0 (0)	53 (3.0)	8 (0.5)	13 (0.7)	5 (0.3)	188 (10.8)	33 (1.9)
125 n=42 (1%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	8 (19.0)	4 (9.5)
150 n=66 (2%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	5 (7.6)	0 (0)
175 n=6 (<1%)	0 (0)	0 (0)	0 (0)	1 (16.7)	1 (16.7)	1 (16.7)	0 (0)	1 (16.7)	0 (0)
200 n=44 (1%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	8 (18.2)	0 (0)
225 n=4 (<1%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
250 n=7 (<1%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (28.6)	0 (0)
275 n=0 (0%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
300 n=0 (0%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Frequency									
q4h n=0 (0%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
q6 n=135 (4%)	3 (2.2)	0 (0)	0 (0)	2 (1.5)	1 (0.7)	0 (0)	0 (0)	24 (17.8)	3 (2.2)
q8 n=709 (22%)	2 (0.3)	0 (0)	0 (0)	24 (3.4)	5 (0.7)	5 (0.7)	0 (0)	86 (12.1)	14 (2.0)
q12 n=2336 (73%)	11 (0.5)	0 (0)	0 (0)	57 (2.4)	8 (0.3)	12 (0.5)	5 (0.2)	264 (11.3)	51 (2.2)

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REDACTED Table 14. Adverse events and severe adverse events for infant-days at each dose and frequency of ampicillin for Group 3 infants with infection.

	Seizure	AST AE	AST SvAE	Leukopenia AE	Leukopenia SvAE	Neutropenia AE	Neutropenia SvAE	Thrombocytopenia AE	Thrombocytopenia SvAE
N=3791	N=81 (0.6%)	N=7 (0.1%)	N=4 (<0.1%)	N=466 (3.4%)	N=72 (0.5%)	N=104 (0.8%)	N=12 (0.1%)	N=457 (3.3%)	N=56 (0.4%)
Dose (mg/kg)									
25 n=113	0 (0)	0 (0)	0 (0)	8 (7.1)	4 (3.5)	1 (0.9)	0 (0)	7 (6.2)	1 (0.9)
50 n=3810	17 (0.4)	5 (0.1)	4 (0.1)	87 (2.3)	9 (0.2)	19 (0.5)	4 (0.1)	115 (3.0)	12 (0.3)
75 n=1053	6 (0.6)	0 (0)	0 (0)	28 (2.7)	5 (0.5)	7 (0.7)	0 (0)	35 (3.3)	12 (1.1)
100 n=7889	48 (0.6)	2 (<0.1)	0 (0)	311 (3.9)	50 (0.6)	73 (0.9)	8 (0.1)	266 (3.4)	25 (0.3)
125 n=139	5 (3.6)	0 (0)	0 (0)	6 (4.3)	0 (0)	0 (0)	0 (0)	9 (6.5)	0 (0)
150 n=114	1 (0.9)	0 (0)	0 (0)	5 (4.4)	1 (0.9)	1 (0.9)	0 (0)	10 (8.8)	3 (2.6)
175 n=16	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
200 n=482	3 (0.6)	0 (0)	0 (0)	17 (3.5)	2 (0.4)	3 (0.6)	0 (0)	11 (2.3)	3 (0.6)
225 n=11	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
250 n=8	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
275 n=56	0 (0)	0 (0)	0 (0)	1 (1.8)	1 (1.8)	0 (0)	0 (0)	3 (5.4)	0 (0)
300 n=117	1 (0.9)	0 (0)	0 (0)	3 (2.6)	0 (0)	0 (0)	0 (0)	1 (0.9)	0 (0)
Frequency									
q4h n=0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
q6 n=552	12 (2.2)	0 (0)	0 (0)	26 (4.7)	3 (0.5)	6 (1.1)	1 (0.2)	16 (2.9)	3 (0.5)
q8 n=3796	26 (0.7)	0 (0)	0 (0)	108 (2.8)	17 (0.4)	24 (0.6)	2 (0.1)	132 (3.5)	7 (0.2)
q12 n=9460	43 (0.5)	7 (0.1)	4 (<0.1)	332 (3.5)	52 (0.5)	74 (0.8)	9 (0.1)	309 (3.3)	46 (0.5)

REDACTED

REDACTED Adverse events in all infants exposed to ampicillin

Seizures

Seizures occurred more frequently with higher doses and shorter dosing intervals. The highest proportion of seizures occurred in Group 3 infants receiving 125 mg/kg/dose. Seizures occurred most frequently at Q4 hour dosing intervals. However, relatively few infants received Q4 hour dosing and most of these infants were older (Group 3). Of those with Q4 hour dosing, a seizure occurred on 2.2% of infant-days. Every 6 hour dosing gave higher incidences of seizure than 8 and 12 hour dosing interval for all groups.

AST Elevation

AST elevation and severe AST elevation appeared to occur sporadically with no obvious relationship to ampicillin dose or dosing interval. Higher doses were not associated with increased incidence of AST elevation; all but 2 cases of AST elevation occurred at doses ≤150mg/kg/dose. Group 1 infants dosed every 6 hours had the most days of AST elevation (1.1% of infant-days) and severe AST elevation (0.6% of infant-days).

Leukopenia

Leukopenia occurred most often in Group 1 infants receiving 25 mg/kg/dose (12.0% of infant-days). Group1 infants developed leukopenia more often than Group 2 or 3 infants at all doses. Leukopenia occurred more frequently at shorter dosing intervals and was more common in Group 1 infants at all dosing intervals. Severe leukopenia was uncommon but occurred most often in Group 1 infants at doses of 25 mg/kg/dose.

Neutropenia

Neutropenia occurred most often in Group 1 infants receiving 25 mg/kg/dose (1.7% of infant-days). There was not a clear relationship between ampicillin dose and neutropenia for Group 2 or 3 infants. Neutropenia occurred more frequently at shorter dosing intervals. Severe neutropenia was uncommon occurring on <0.2% of infant-days for all groups at all doses and dosing intervals.

Thrombocytopenia

Thrombocytopenia occurred more frequently at shorter dosing intervals. Thrombocytopenia occurred in 11.1% of Group 1 infant-days and 8.3% of Group 3 infant-days receiving ampicillin at 4 hour dosing intervals. Doses of 25mg/kg/dose gave the highest incidence of thrombocytopenia for all groups. Group 1 infants who received 300 mg/kg/dose also frequently developed thrombocytopenia (13.2% of infant-days). Other doses did not suggest a relationship between increasing dose and increased risk of thrombocytopenia. Severe thrombocytopenia occurred most often in Group 1 infants at doses of 300 mg/kg/dose and for all groups at a dosing interval of 6 hours.

REDACTED

REDACTED Table 15. Adverse events and severe adverse events for all infant-days at each dose and frequency of ampicillin.

	Seizure	AST AE	AST SvAE	Leukopenia AE	Leukopenia SvAE	Neutropenia AE	Neutropenia SvAE	Thrombocytopenia AE	Thrombocytopenia SvAE
N=946,723	N=3291 (0.3%)	N=436 (<0.1%)	N=198 (<0.1%)	N=22,122 (2.3%)	N=1411 (0.1%)	N=3022 (0.3%)	N=430 (<0.1%)	N=32,268 (3.4%)	N=2565 (0.3%)
Dose (mg/kg)									
25 n=9335 (0%)	34 (0.4)	5 (0.1)	2 (<0.1)	570 (6.1)	59 (0.6)	87 (0.9)	10 (0.1)	705 (7.5)	40 (0.4)
50 n=305,197 (32%)	949 (0.3)	111 (<0.1)	46 (<0.1)	6613 (2.2)	367 (0.1)	849 (0.3)	103 (<0.1)	9920 (3.2)	797 (0.3)
75 n=57,351 (6%)	240 (0.4)	44 (0.1)	23 (<0.1)	1634 (2.8)	123 (0.2)	242 (0.4)	33 (0.1)	2580 (4.5)	253 (0.4)
100 n=545,850 (57%)	1973 (0.4)	270 (<0.1)	125 (<0.1)	12724 (2.3)	827 (0.2)	1784 (0.3)	273 (<0.1)	18137 (3.3)	1409 (0.3)
125 n=5990 (<1%)	22 (0.4)	1 (<0.1)	1 (<0.1)	237 (3.9)	13 (0.2)	24 (0.4)	4 (0.1)	342 (5.7)	15 (0.2)
150 n=6391 (<1%)	22 (0.3)	3 (<0.1)	1 (<0.1)	130 (2.0)	7 (0.1)	19 (0.3)	3 (<0.1)	184 (2.9)	15 (0.2)
175 n=1705 (<1%)	5 (0.3)	1 (0.1)	0 (<0.1)	28 (1.6)	2 (0.1)	2 (0.1)	0 (0)	53 (3.1)	1 (0.1)
200 n=9265 (<1%)	26 (0.3)	0 (0)	0 (<0.1)	142 (1.5)	9 (0.1)	14 (0.2)	3 (<0.1)	225 (2.4)	22 (0.2)
225 n=225 (<1%)	2(0.2)	0 (0)	0 (<0.1)	6 (0.6)	0 (0)	0 (0)	0 (0)	16 (1.6)	1 (0.1)
250 n=1483 (<1%)	6 (0.4)	0 (0)	0 (<0.1)	12 (0.8)	1 (0.1)	0 (0)	0 (0)	42 (2.8)	6 (0.4)
275 n=1126 (<1%)	2 (0.2)	0 (0)	0 (<0.1)	4 (0.4)	2 (0.2)	0 (0)	0 (0)	25 (2.2)	4 (0.4)
300 n=2036 (<1%)	10 (0.5)	1 (<0.1)	0 (<0.1)	22 (1.1)	1 (<0.1)	1 (<0.1)	1(<0.1)	39 (1.9)	2 (0.1)
Frequency									
q4h n=45 (<1%)	1 (2.2)	0 (0)	0 (<0.1)	2 (4.3)	0 (0)	0 (0)	0 (0)	4 (8.7)	0 (0)
q6 n=2946 (<1%)	35 (1.2)	3 (0.1)	2 (0.1)	60 (2.0)	6 (0.2)	10 (0.3)	1 (<0.1)	109 (3.6)	14 (0.5)
q8 n=95,302 (10%)	326 (0.3)	22 (<0.1)	12 (<0.1)	1002 (1.0)	90 (0.1)	194 (0.2)	41 (<0.1)	2313 (2.4)	238 (0.2)
q12 n=848,430 (89%)	2929 (0.3)	411 (<0.1)	184 (<0.1)	21058 (2.5)	1315 (0.2)	2818 (0.3)	388 (<0.1)	29842 (3.5)	2313 (0.3)

REDACTED

REDACTED Table 16. Adverse events and severe adverse events for infant-days at each dose and frequency of ampicillin for Group 1 infants.

	Seizure	AST AE	AST SvAE	Leukopenia AE	Leukopenia SvAE	Neutropenia AE	Neutropenia SvAE	Thrombocytopenia AE	Thrombocytopenia SvAE
N=355,015	N=565 (0.2%)	N=143 (<0.1%)	N=60 (<0.1%)	N=17,901 (5.0%)	N=1032 (0.3%)	N=2295 (0.6%)	N=276 (0.1%)	N=14,952 (1.2%)	N=927 (0.3%)
Dose (mg/kg)									
25 n=4433 (1%)	11 (0.2)	1 (<0.1)	0 (0)	531 (12.0)	51 (1.2)	75 (1.7)	6 (0.1)	460 (10.4)	14 (0.3)
50 n=114,404 (32%)	163 (0.1)	41 (<0.1)	13 (<0.1)	5515 (4.8)	291 (0.3)	676 (0.6)	65 (0.1)	4835 (4.2)	292 (0.3)
75 n= 22,693 (6%)	48 (0.2)	18 (0.1)	12 (0.1)	1317 (5.8)	99 (0.4)	189 (0.8)	24 (0.1)	1158 (5.1)	83 (0.4)
100 n=204,449 (57%)	325 (0.2)	82 (<0.1)	34 (<0.1)	10132 (5.0)	571 (0.3)	1314 (0.6)	172 (0.1)	8084 (4.0)	518 (0.3)
125 n=3424 (<1%)	3 (0.1)	1 (<0.1)	1 (<0.1)	208 (6.1)	10 (0.3)	21 (0.6)	3 (0.1)	209 (6.1)	9 (0.3)
150 n=1723 (<1%)	5 (0.1)	0 (0)	0 (0)	89 (5.2)	5 (0.3)	13 (0.8)	3 (0.2)	76 (4.4)	6 (0.3)
175 n=727(<1%)	1 (0.3)	0 (0)	0 (0)	24 (3.3)	1 (0.1)	0 (0)	0 (0)	12 (1.6)	0 (0)
200 n=2346 (<1%)	6 (0.3)	0 (0)	0 (0)	75 (3.2)	4 (0.2)	7 (0.3)	3 (0.1)	90 (3.8)	3 (0.1)
225 n=427 (<1%)	1 (0.2)	0 (0)	0 (0)	3 (0.7)	0 (0)	0 (0)	0 (0)	9 (2.1)	1 (0.2)
250 n=256 (<1%)	2 (0.8)	0 (0)	0 (0)	3 (1.2)	0 (0)	0 (0)	0 (0)	7 (2.7)	0 (0)
275 n=80 (<1%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	5 (6.3)	0 (0)
300 n=53 (<1%)	0 (0)	0 (0)	0 (0)	4 (7.5)	0 (0)	0 (0)	0 (0)	7 (13.2)	1 (1.9)
Frequency									
q4h n=9 (<1%)	0 (0)	0 (0)	0 (0)	2 (22.2)	0 (0)	0 (0)	0 (0)	1 (11.1)	0 (0)
q6 n=176 (<1%)	3 (1.7)	2 (1.1)	1 (0.6)	13 (7.3)	1 (0.6)	2 (1.1)	0 (0)	20 (11.3)	2 (1.1)
q8 n=15,671 (4%)	11 (0.1)	0 (0)	0 (0)	415 (2.6)	32 (0.2)	68 (0.4)	11 (0.1)	396 (2.5)	37 (0.2)
q12 n=339,159 (95%)	551 (0.2)	141 (<0.1)	59 (<0.1)	17471 (5.2)	999 (0.3)	2225 (0.3)	265 (0.1)	14535 (4.3)	888 (0.3)

REDACTED

REDACTED Table 17. Adverse events and severe adverse events for infant-days at each dose and frequency of ampicillin for Group 2 infants.

	Seizure	AST AE	AST SvAE	Leukopenia AE	Leukopenia SvAE	Neutropenia AE	Neutropenia SvAE	Thrombocytopenia AE	Thrombocytopenia SvAE
N=47,781	N=69 (0.1%)	N=6 (<0.1%)	N=3 (<0.1%)	N=443 (0.9%)	N=48 (0.1%)	N=112 (0.2%)	N=29 (0.1%)	N=2434 (5.1%)	N=213 (0.4%)
Dose (mg/kg)									
25 n=1285 (2%)	1 (0.1)	0 (0)	0 (0)	11 (0.9)	1 (0.1)	4 (0.3)	1 (0.1)	141 (11.0)	14 (1.1)
50 n=15,869 (33%)	14 (0.1)	0 (0)	0 (0)	124 (0.8)	7 (<0.1)	29 (0.2)	7 (<0.1)	807 (5.1)	69 (0.4)
75 n=3441 (7%)	4 (0.1)	1 (<0.1)	0 (0)	40 (1.2)	6 (0.2)	12 (0.3)	1 (<0.1)	252 (7.3)	40 (1.2)
100 n=25,326 (52%)	47 (0.2)	5 (<0.1)	3 (<0.1)	254 (1.0)	33 (0.1)	62 (0.2)	20 (0.1)	1122 (4.4)	81 (0.3)
125 n=637 (1%)	1 (0.2)	0 (0)	0 (0)	3 (0.5)	0 (0)	0 (0)	0 (0)	59 (9.3)	5 (0.8)
150 n=469 (<1%)	1 (0.2)	0 (0)	0 (0)	4 (0.9)	0 (0)	3 (0.6)	0 (0)	19 (4.1)	0 (0)
175 n=143 (<1%)	0 (0)	0 (0)	0 (0)	1 (0.7)	1 (0.7)	1 (0.7)	0 (0)	1 (0.7)	0 (0)
200 n=509 (1%)	1 (0.2)	0 (0)	0 (0)	6 (1.2)	0 (0)	1 (0.2)	0 (0)	31 (6.1)	4 (0.8)
225 n=46 (<1%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
250 n=42 (<1%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4.8)	0 (0)
275 n=2 (<1%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
300 n=12 (<1%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Frequency									
q4h n=0 (0%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
q6 n=334 (<1%)	3 (0.9)	0 (0)	0 (0)	6 (1.8)	1 (0.3)	0 (0)	0 (0)	38 (11.3)	5 (1.5)
q8 n=5638 (11%)	11 (0.2)	4 (0.1)	3 (0.1)	69 (1.2)	10 (0.2)	25 (0.4)	2 (<0.1)	224 (4.0)	27 (0.5)
q12 n=41,809 (87%)	55 (0.1)	2 (<0.1)	0 (0)	368 (0.9)	37 (0.1)	87 (0.2)	27 (0.1)	2172 (5.2)	181 (0.4)

REDACTED

REDACTED Table 18. Adverse events and severe adverse events for infant-days at each dose and frequency of ampicillin for Group 3 infants.

	Seizure	AST AE	AST SvAE	Leukopenia AE	Leukopenia SvAE	Neutropenia AE	Neutropenia SvAE	Thrombocytopenia AE	Thrombocytopenia SvAE
N=543,927	N=2657 (0.5%)	N=287 (0.1%)	N=135 (<1%)	N=3764 (0.7%)	N=329 (0.1%)	N=612 (0.1%)	N=124 (<0.1%)	N=14,835 (2.7%)	N=1421 (0.3%)
Dose (mg/kg)									
25 n=3617 (<1%)	22 (0.6)	4 (0.1)	2 (0.1)	28 (0.8)	7 (0.2)	8 (0.2)	3 (0.1)	99 (2.7)	12 (0.3)
50 n=174,924 (32%)	772 (0.4)	70 (<0.1)	33 (<0.1)	972 (0.6)	69 (<0.1)	144 (0.1)	31 (<0.1)	4266 (2.4)	436 (0.2)
75 n=31,217 (5%)	188 (0.6)	25 (0.1)	11 (<0.1)	277 (0.9)	18 (0.1)	41 (0.1)	8 (<0.1)	1163 (3.7)	129 (0.4)
100 n=316,217 (58%)	1601 (0.5)	183 (0.1)	88 (<0.1)	2326 (0.7)	221 (0.1)	405 (0.1)	80 (<0.1)	8911 (2.8)	808 (0.3)
125 n=1929 (<1%)	18 (0.9)	0 (0)	0 (0)	26 (1.3)	3 (0.2)	3 (0.2)	1 (0.1)	74 (3.8)	1 (0.1)
150 n=4199 (<1%)	16 (0.4)	3 (0.1)	1 (<0.1)	37 (0.9)	2 (<0.1)	3 (0.1)	0 (0)	86 (2.0)	8 (0.2)
175 n=835 (<1%)	4 (0.5)	1 (0.1)	0 (0)	3 (0.4)	0 (0)	1 (0.1)	0 (0)	40 (4.8)	1 (0.1)
200 n=6410 (1%)	19 (0.3)	0 (0)	0 (0)	61 (1.0)	5 (0.1)	6 (0.1)	0 (0)	104 (1.6)	15 (0.2)
225 n=521 (<1%)	1 (0.2)	0 (0)	0 (0)	3 (0.6)	0 (0)	0 (0)	0 (0)	7 (1.3)	0 (0)
250 n=1185 (<1%)	4 (0.3)	0 (0)	0 (0)	9 (0.8)	1 (0.1)	0 (0)	0 (0)	33 (2.8)	6 (0.5)
275 n=1044 (<1%)	2 (0.2)	0 (0)	0 (0)	4 (0.4)	2 (0.2)	0 (0)	0 (0)	20 (1.9)	4 (0.4)
300 n=1971 (<1%)	10 (0.5)	1 (0.1)	0 (0)	18 (0.9)	1 (0.1)	1 (0.1)	1 (0.1)	32 (1.6)	1 (0.1)
Frequency									
q4h n=36 (<1%)	1 (2.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (8.3)	0 (0)
q6 n=2436 (<1%)	29 (1.2)	1 (<0.1)	1 (<0.1)	41 (1.7)	4 (0.2)	8 (0.3)	1 (<0.1)	50 (2.1)	7 (0.3)
q8 n=73,993 (13%)	304 (0.4)	18 (<0.1)	9 (<0.1)	512 (0.7)	47 (0.1)	100 (0.1)	2 (<0.1)	1675 (2.3)	171 (0.2)
q12 n=467,462 (85%)	2323 (0.5)	268 (0.1)	125 (<0.1)	3211 (0.7)	278 (0.1)	504 (0.1)	96 (<0.1)	13107 (2.8)	1243 (0.3)

REDACTED

5. Figures

Exposure-safety relationship for infants with infection

Seizure

The incidence of seizures did not appear to be related to exposure to ampicillin. Seizures were seen at typical exposures and did not occur at high exposures. This was true for all gestational and postnatal age groups.

Figure 1. Cmax (steady state) concentrations on days with and without seizure for all infants with infection

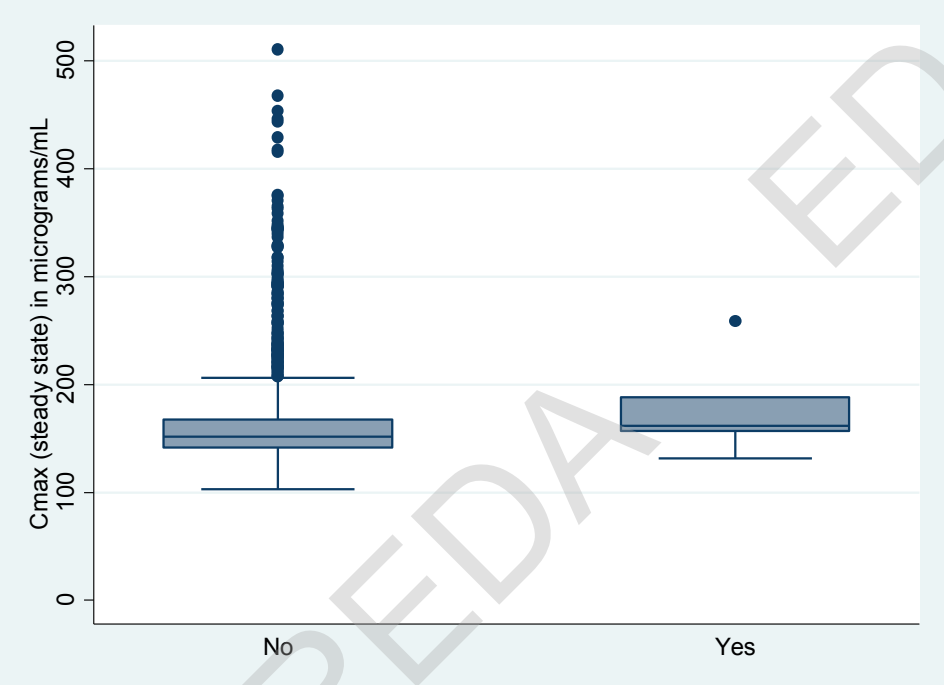

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Figure 2. Percentage of infant days with seizure for each decile of ampicillin exposure (Cmax (steady state)) for all infants with infection

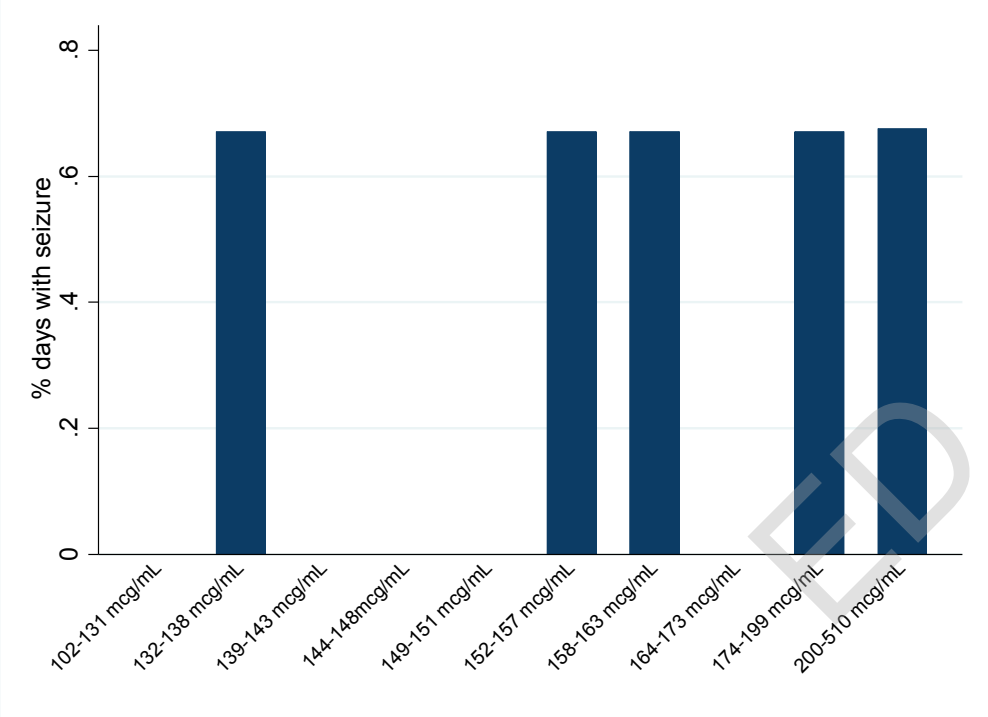

Figure 3. Cmax (steady state) concentration on days with and without seizure for Group 1 infants with infection

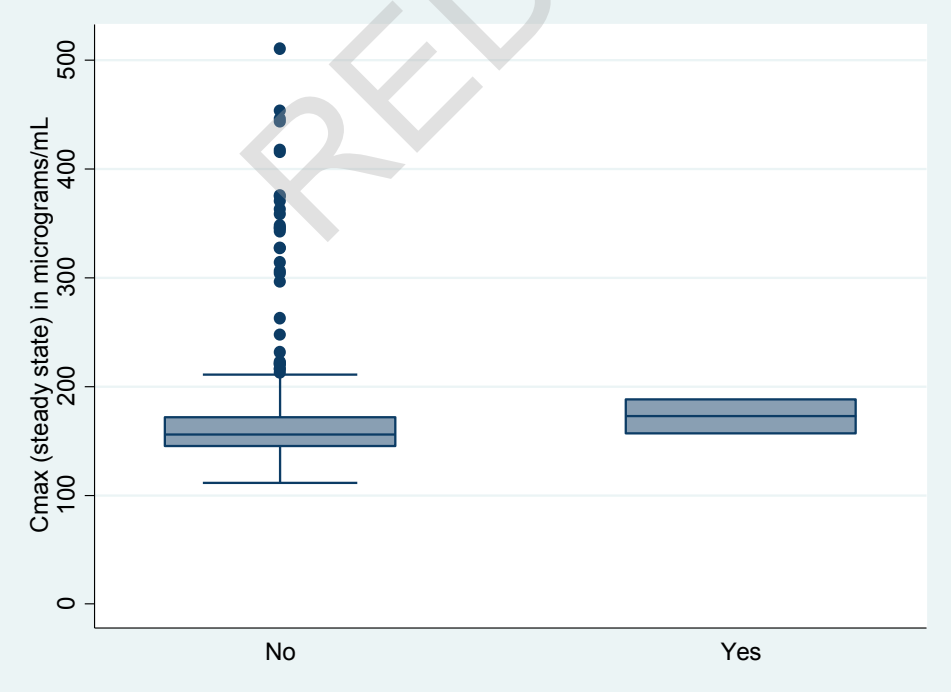

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Figure 4. Percentage of infant days with seizure for each decile of ampicillin exposure (Cmax (steady state)) in Group 1 infants with infection

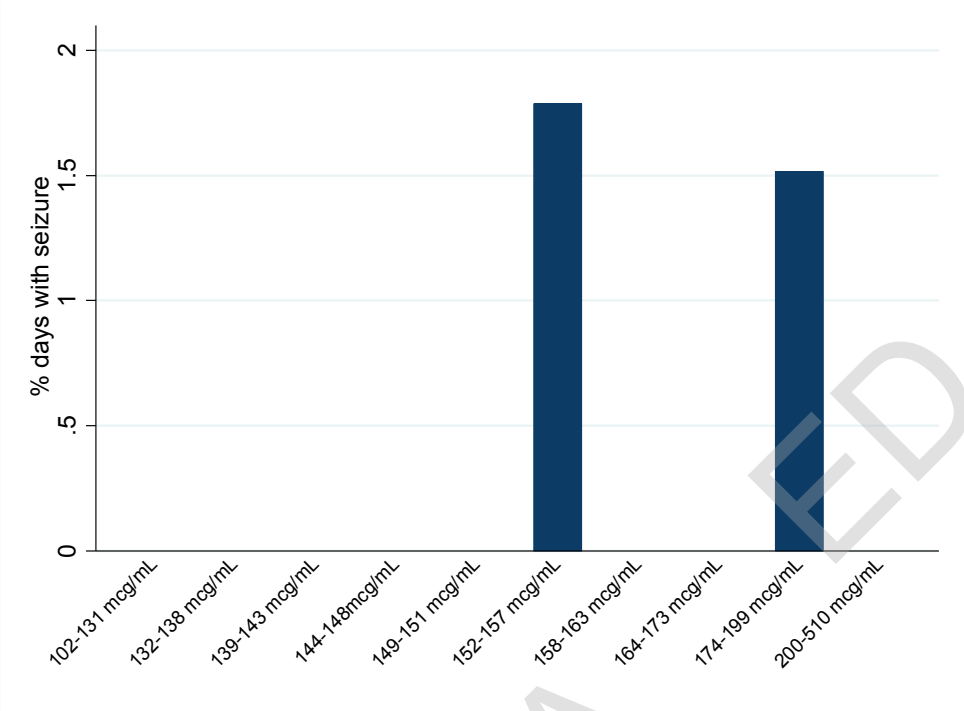

Figure 5. Cmax (steady state) concentration on days with and without seizure in Group 2 infants with infection

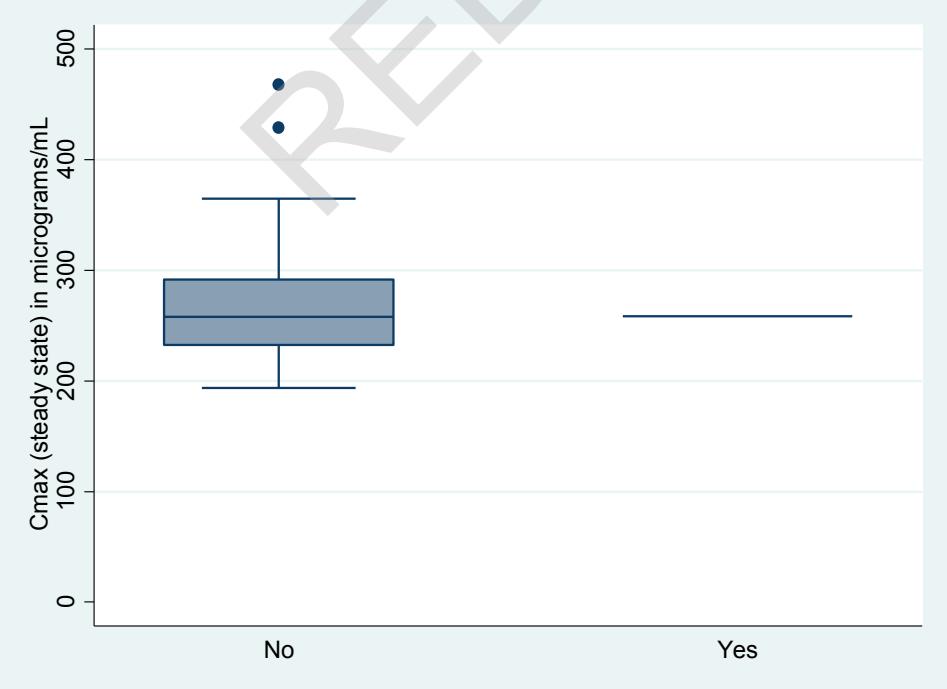

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Figure 6. Percentage of infant days with seizure for each decile of ampicillin exposure (Cmax (steady state)) in Group 2 infants with infection

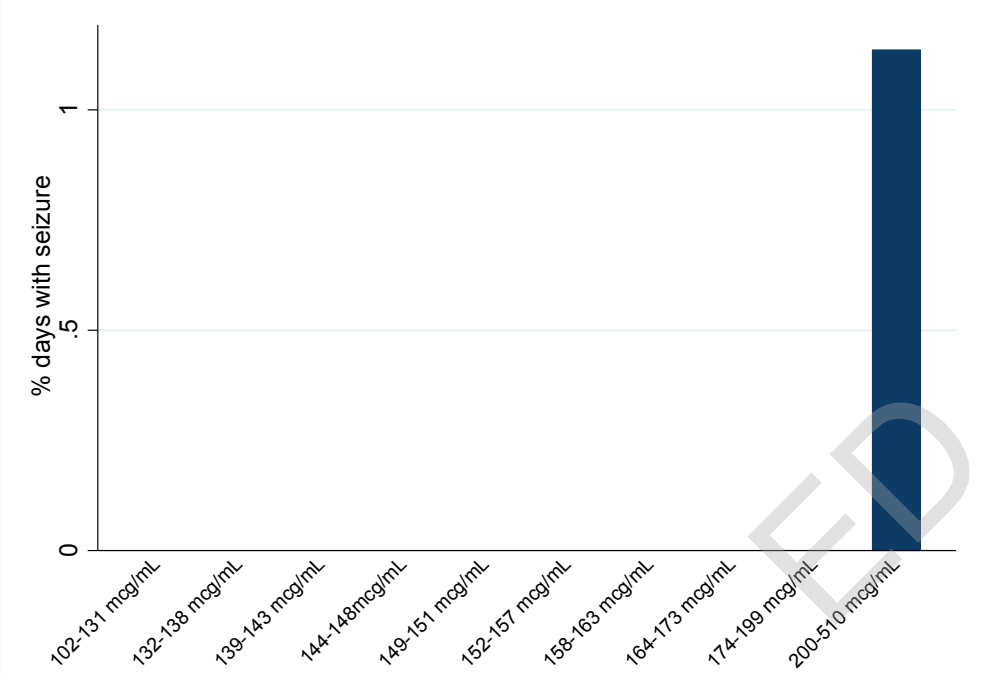
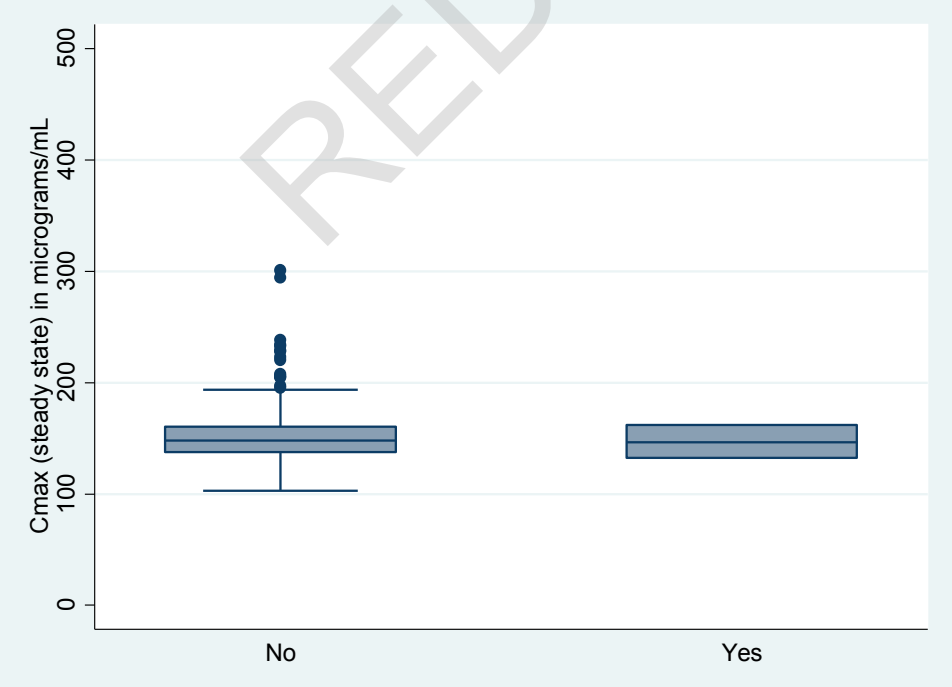
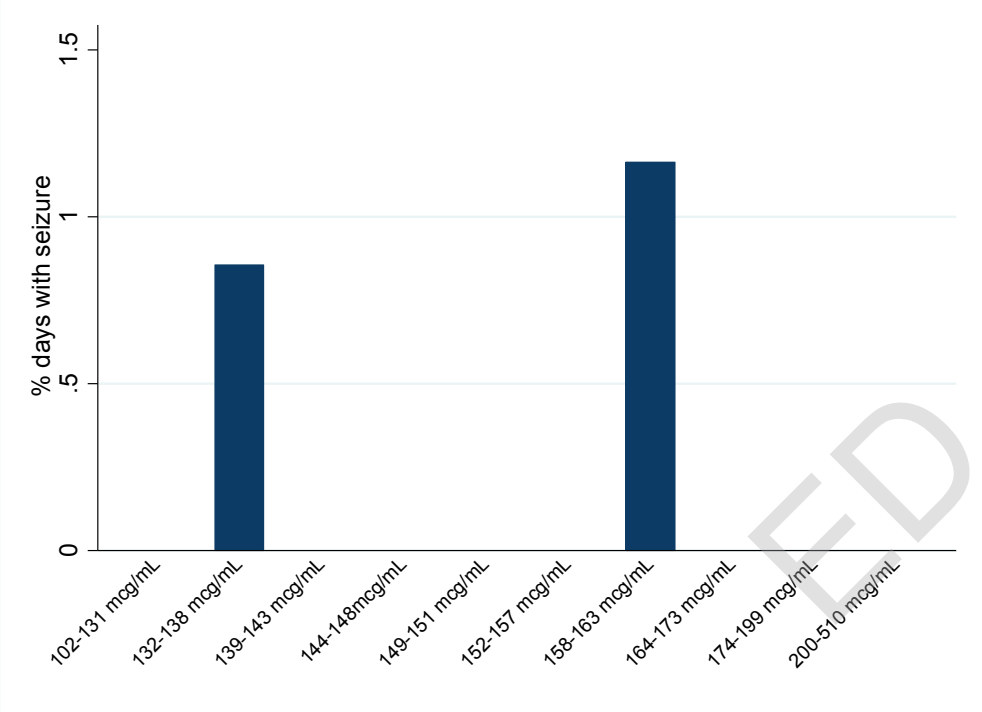


Figure 7. Cmax (steady state) concentration on days with and without seizure in infants Group 3 infants with infection



REDACTED

Figure 8. Percentage of infant days with seizure for each decile of ampicillin exposure (Cmax (steady state)) in Infants Group 3 infants with infection



AST Elevation

AST elevation did not occur with ampicillin exposure in infants with infection of any gestational or postnatal age group.

REDACTED

Figure 9. Cmax (steady state) concentration on days with and without AST elevation in all infants with Infection

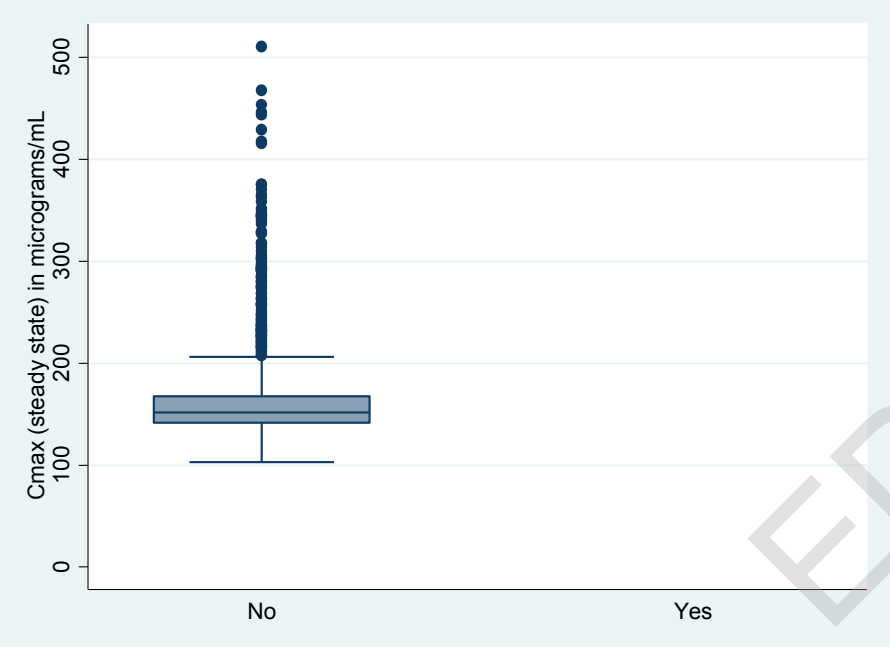


Figure 10. Cmax (steady state) concentration on days with and without AST elevation in Group 1 infants with infection

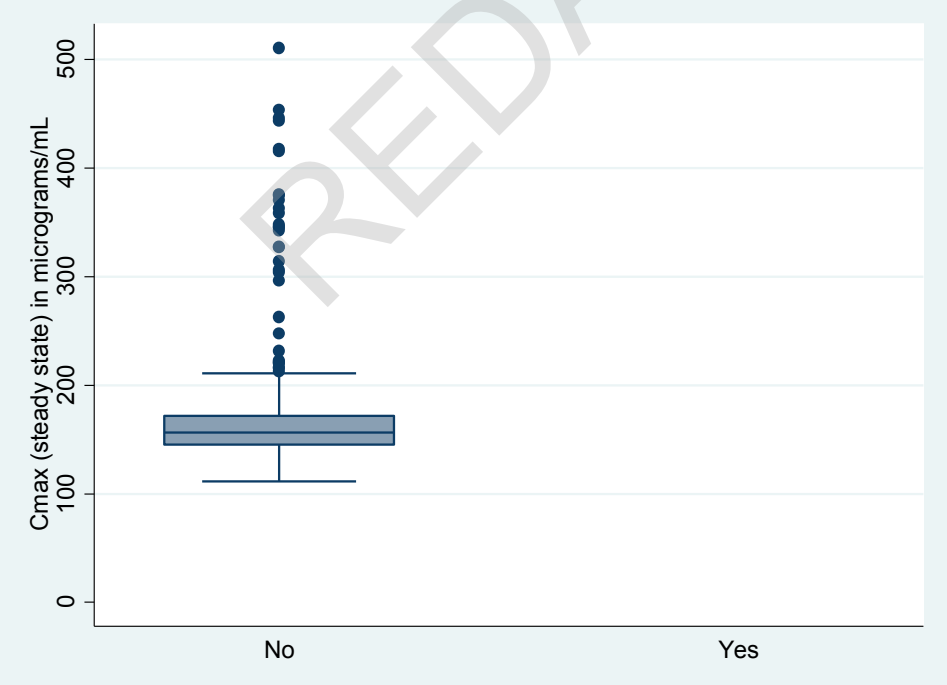


Figure 11. Cmax (steady state) concentration on days with and without AST elevation in Group 2 infants with infection

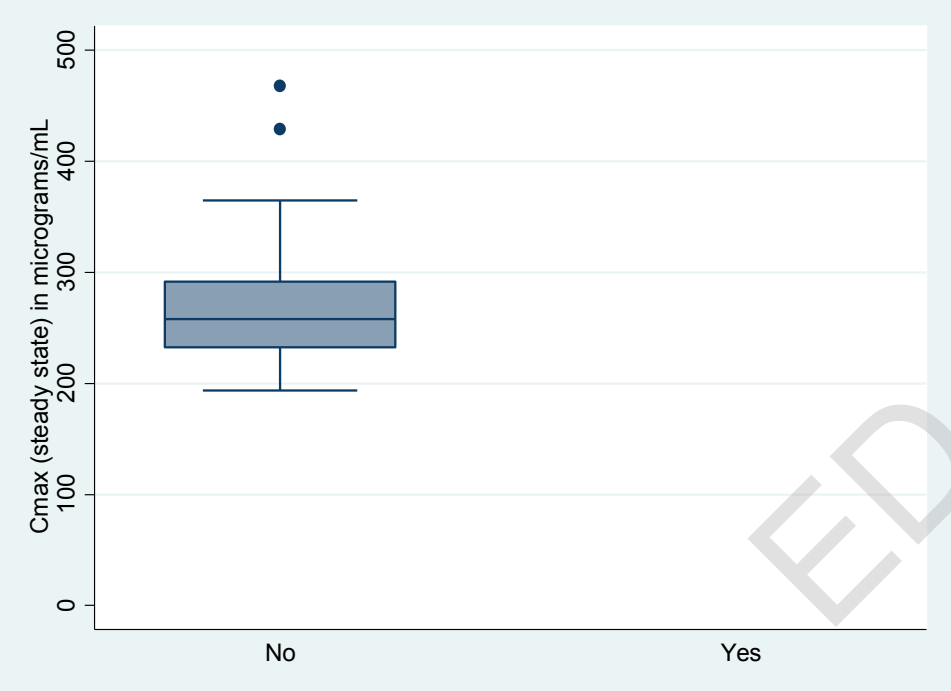
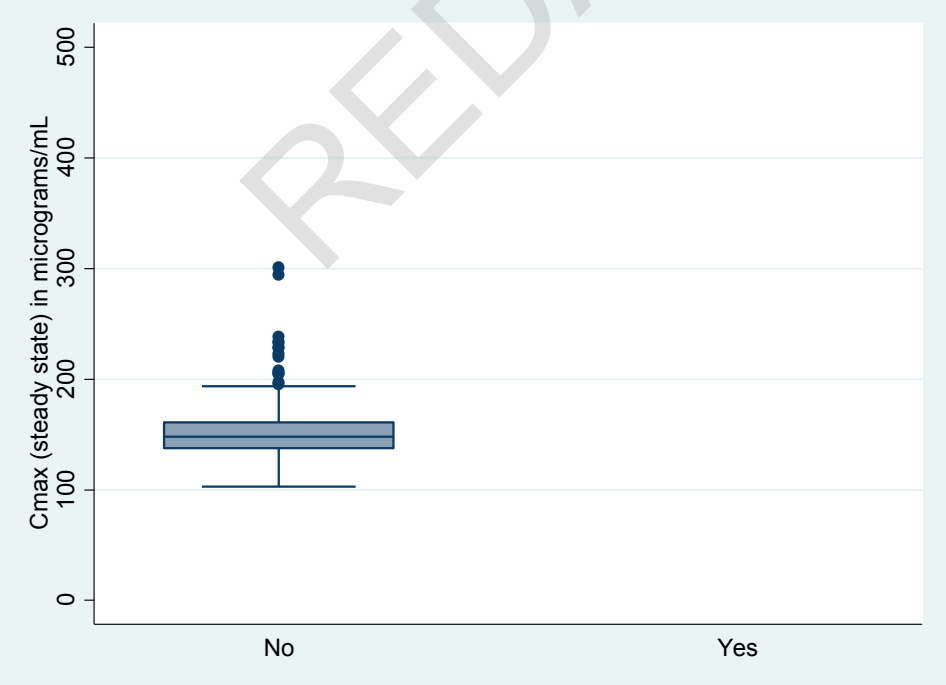


Figure 12. Cmax (steady state) concentration on days with and without AST elevation in infants Group 3 infants with infection



Severe AST Elevation

Figure 13. Cmax (steady state) concentration on days with and without severe AST elevation in all infants with infection

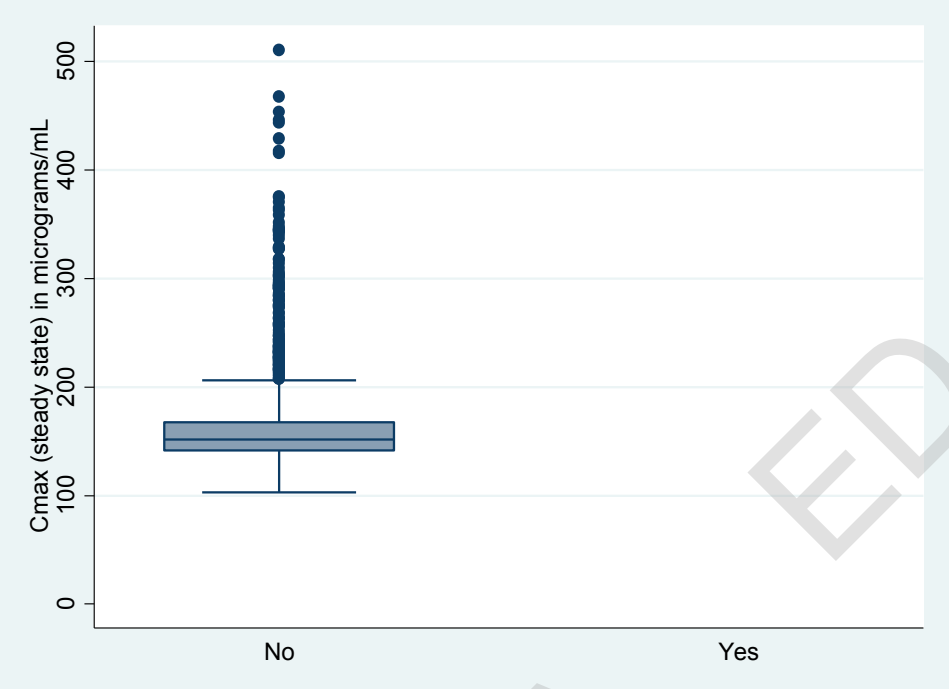
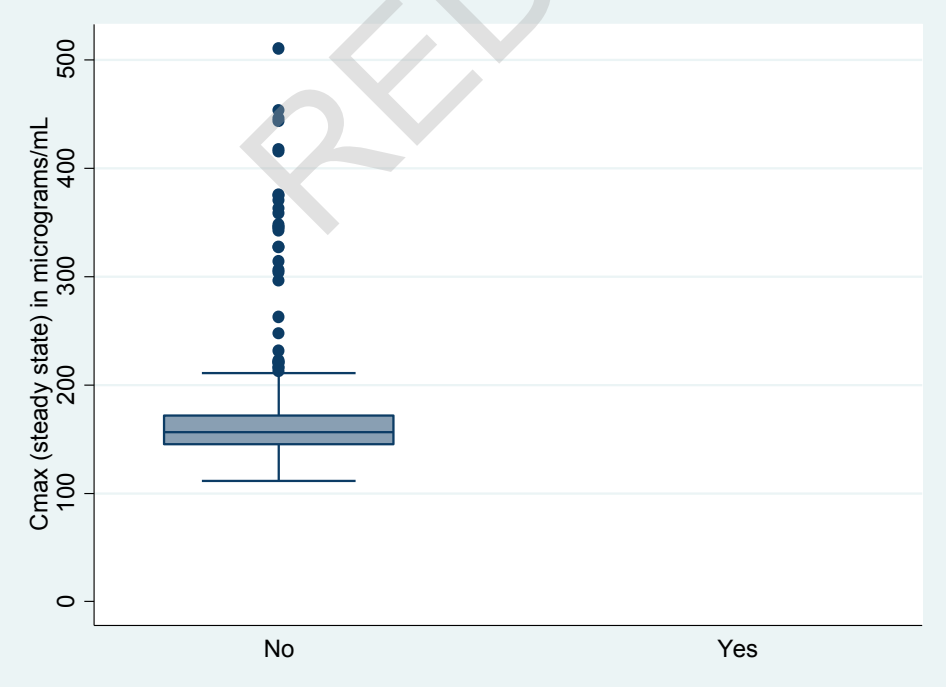
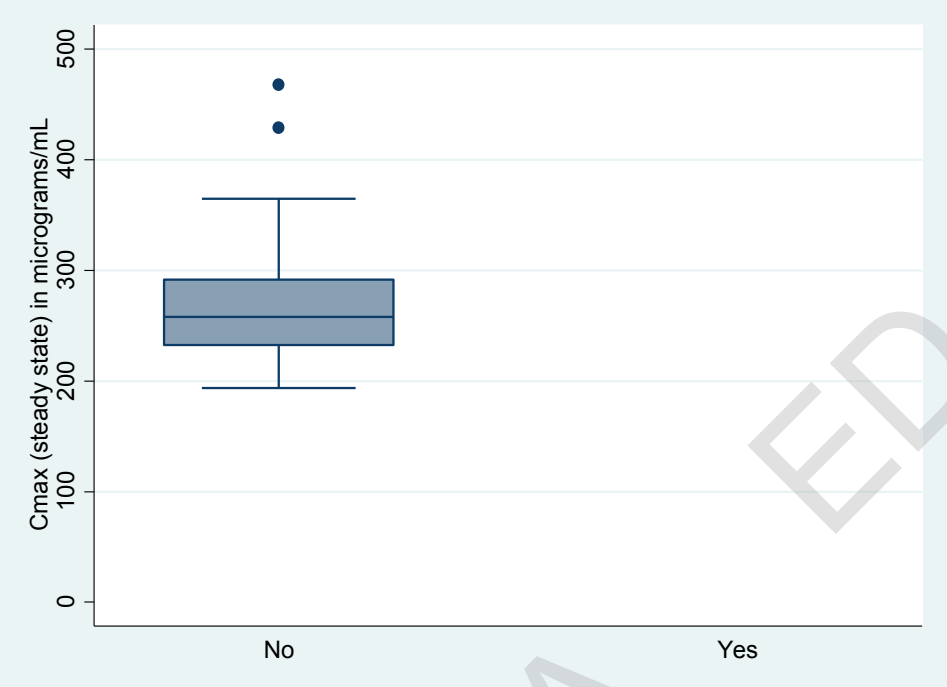


Figure 14. Cmax (steady state) concentration on days with and without severe AST elevation Group 1 infants with infection



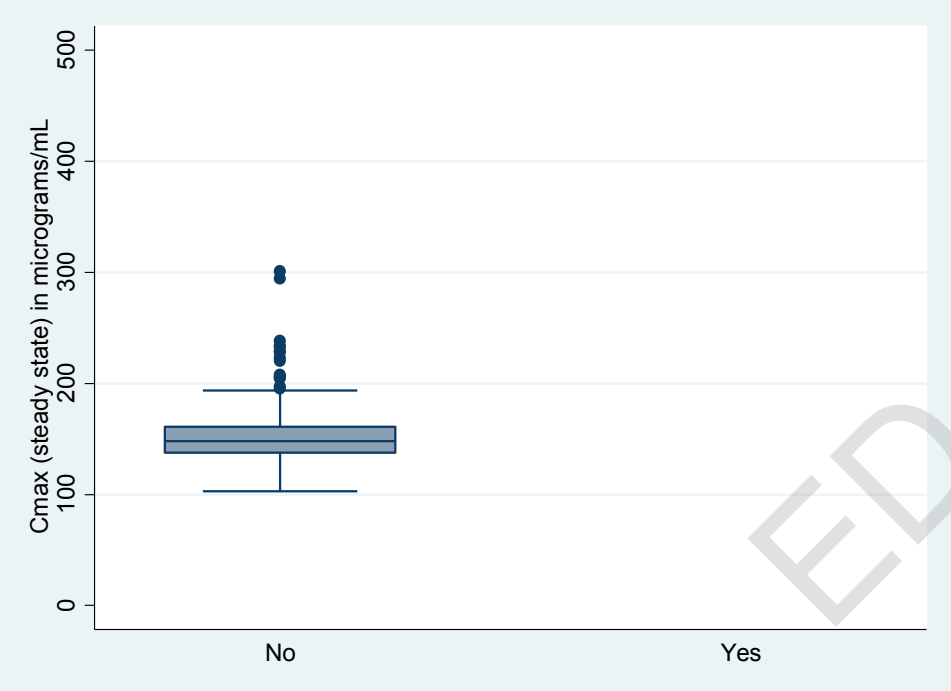
REDACTED

Figure 15. Cmax (steady state) concentration on days with and without severe AST elevation in Group 2 infants with infection



REDACTED

Figure 16. Cmax (steady state) concentration on days with and without severe AST elevation in Group 3 infants with infection



Thrombocytopenia

Thrombocytopenia appeared to occur slightly more often at higher exposures of ampicillin.

REDACTED

Figure 17. Cmax (steady state) concentration on days with and without thrombocytopenia in all infants with infection

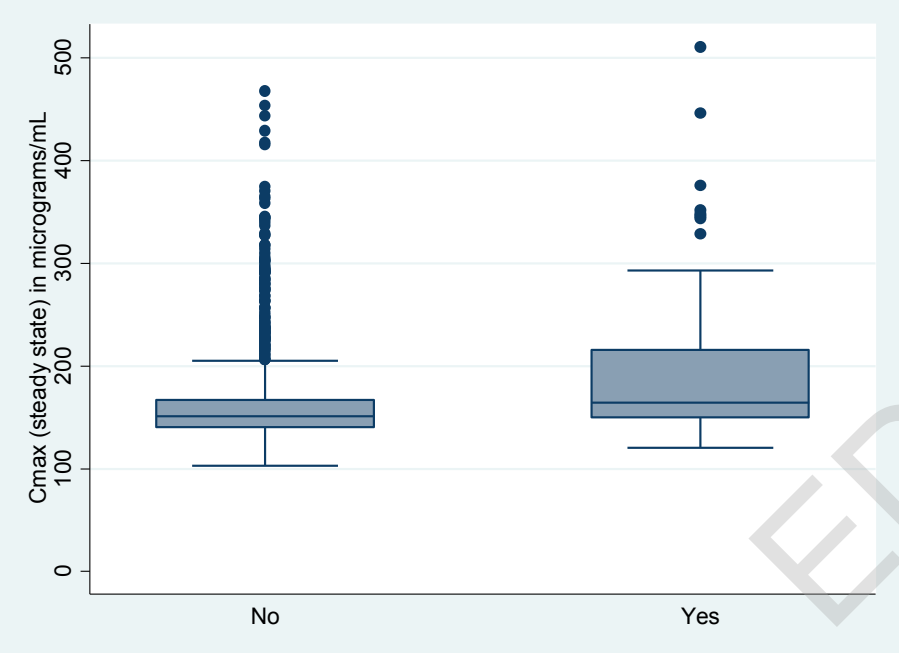


Figure 18. Percentage of infant days with thrombocytopenia for each decile of ampicillin exposure (Cmax (steady state)) in all infants with infection

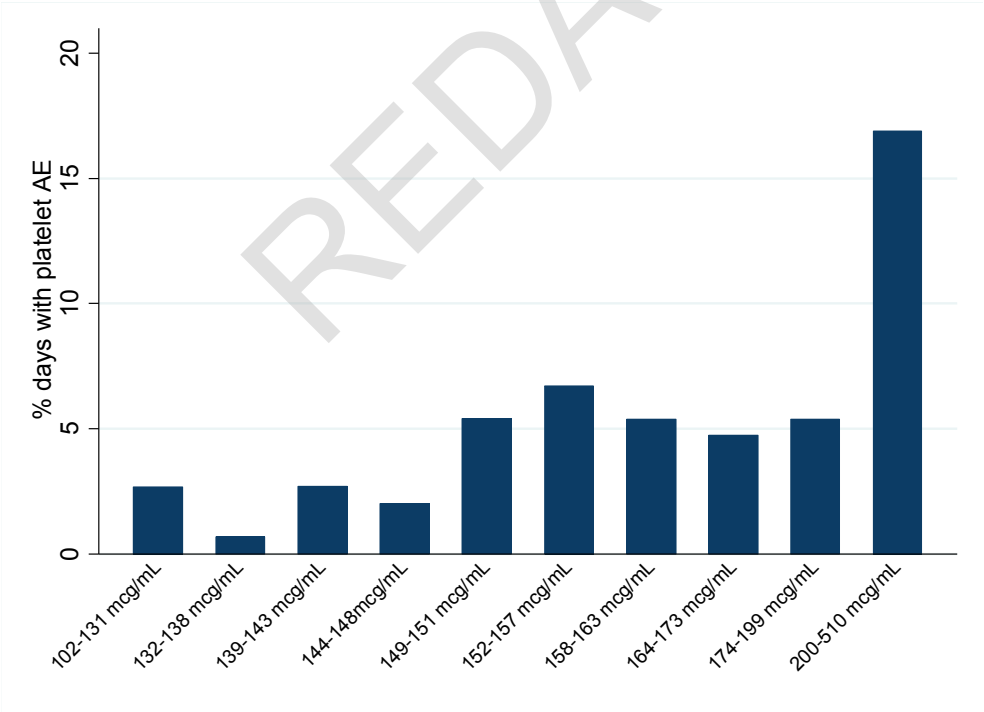


Figure 19. Cmax (steady state) concentration on days with and without thrombocytopenia in Group 1 infants with infection

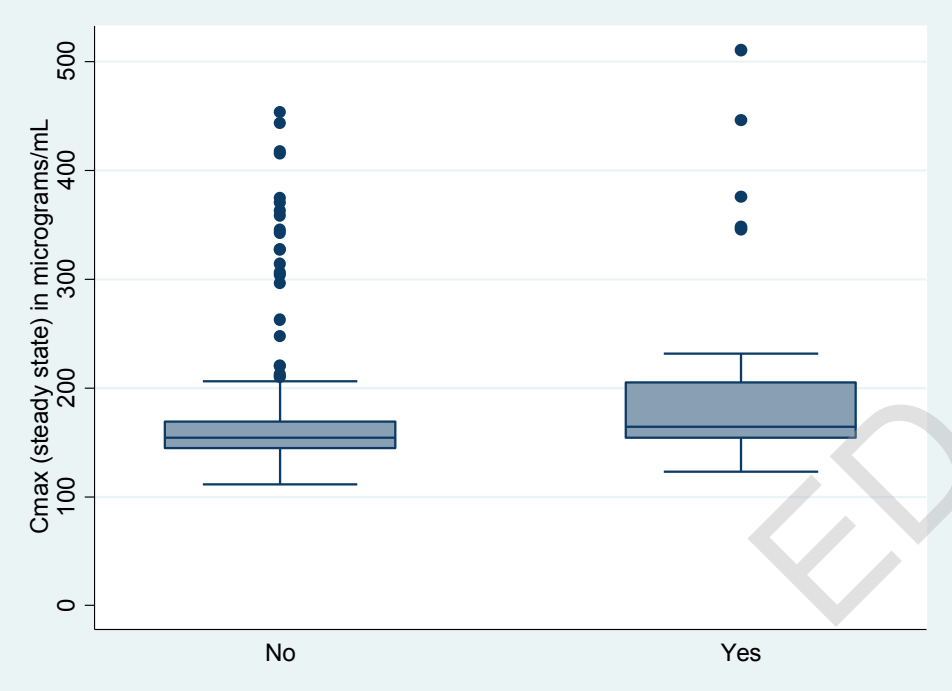


Figure 20. Percentage of infant days with thrombocytopenia for each decile of ampicillin exposure (Cmax (steady state)) in Group 1 infants with infection

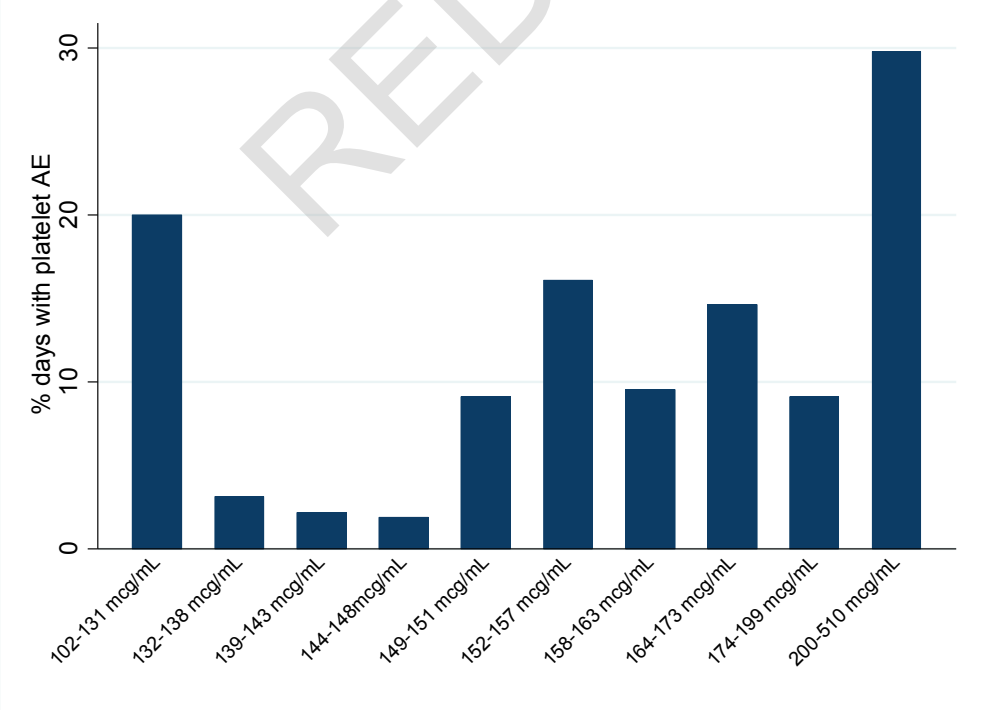


Figure 21. Cmax (steady state) concentration on days with and without thrombocytopenia in Group 2 infants with infection

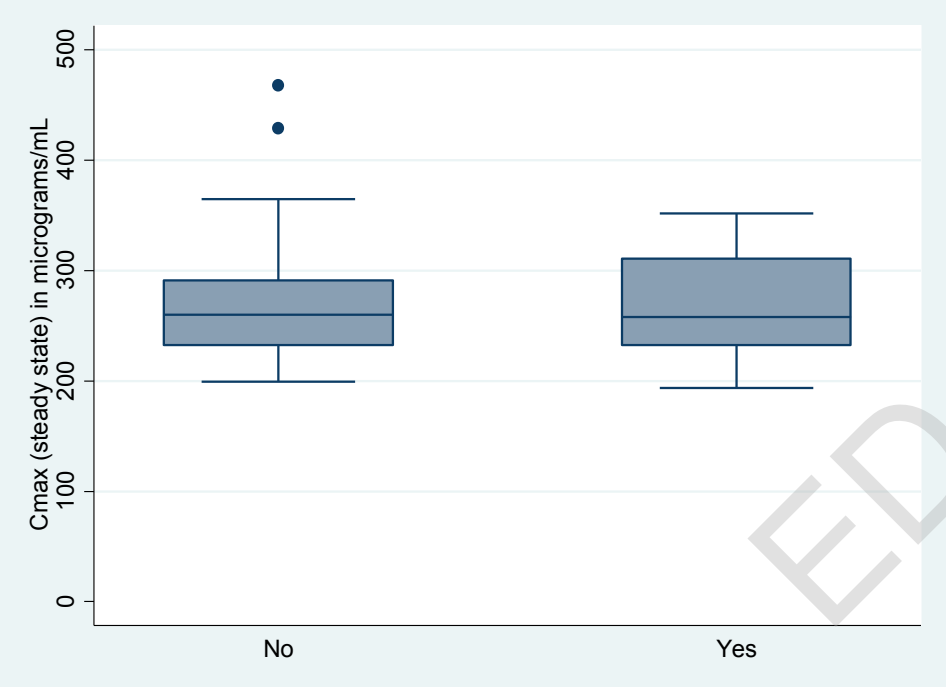


Figure 22. Percentage of infant days with thrombocytopenia for each decile of ampicillin exposure (Cmax (steady state)) in Group 2 infants with infection

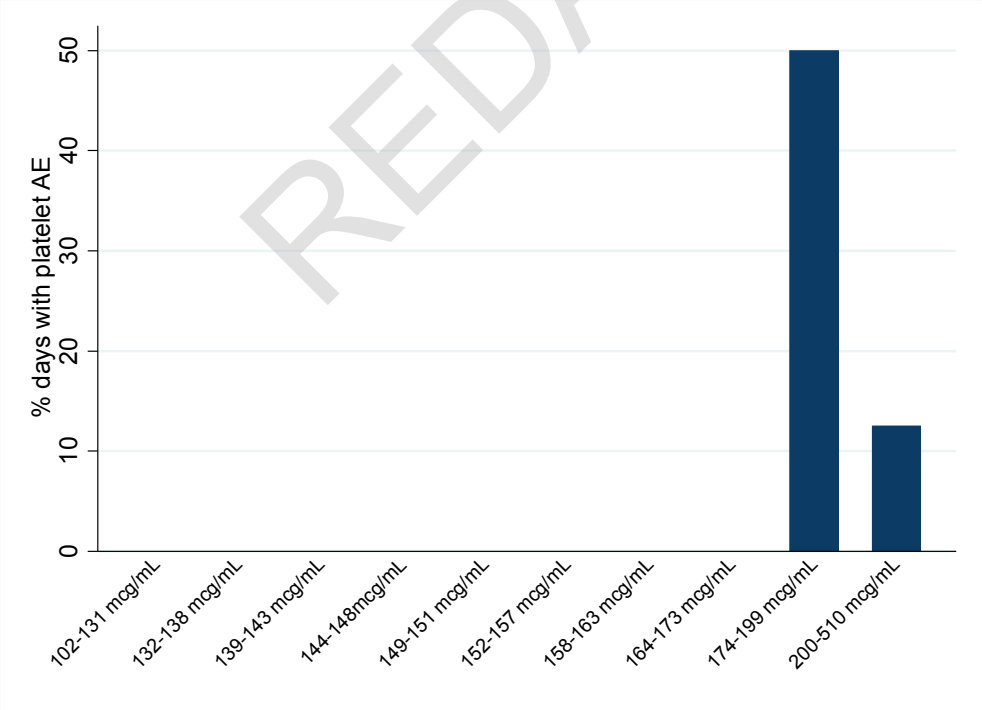
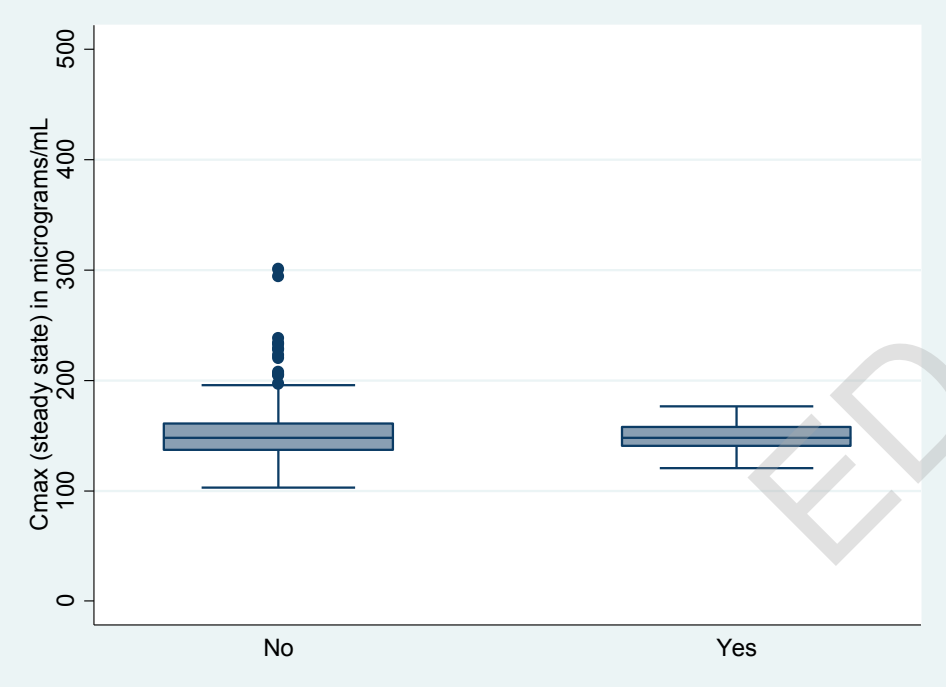
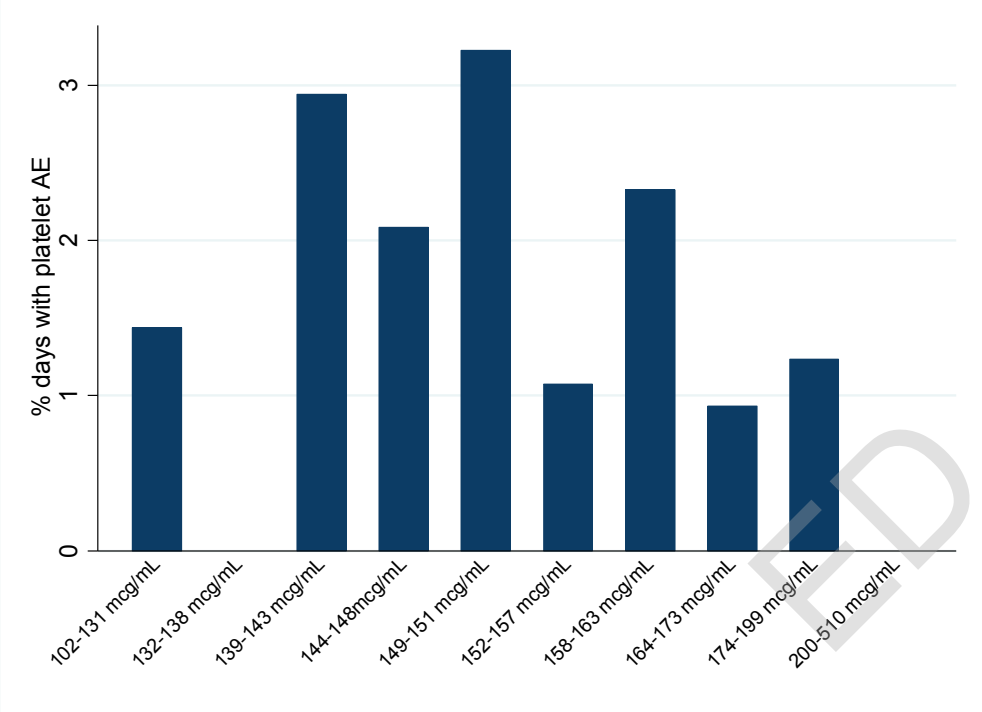


Figure 23. Cmax (steady state) concentration on days with and without thrombocytopenia in Group 3 infants with infection



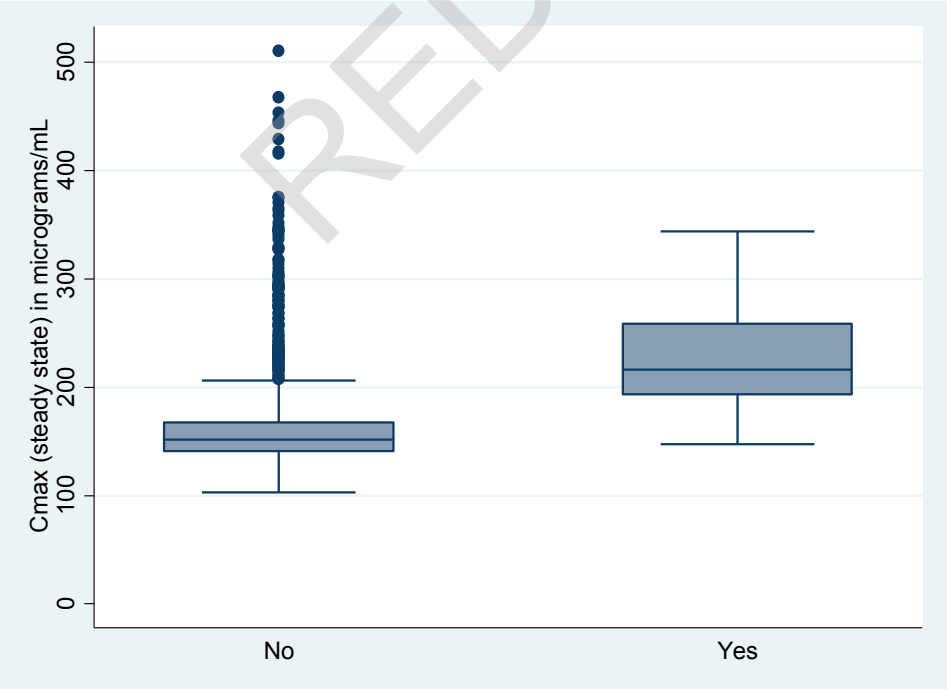
REDACTED

Figure 24. Percentage of infant days with thrombocytopenia for each decile of ampicillin exposure (Cmax (steady state)) in Group 3 infants with infection



Severe Thrombocytopenia

Figure 25. Cmax (steady state) concentration on days with and without severe thrombocytopenia in all infants with infection



REDACTED

Figure 26. Percentage of infant days with severe thrombocytopenia for each decile of ampicillin exposure (Cmax (steady state)) in all infants with infection

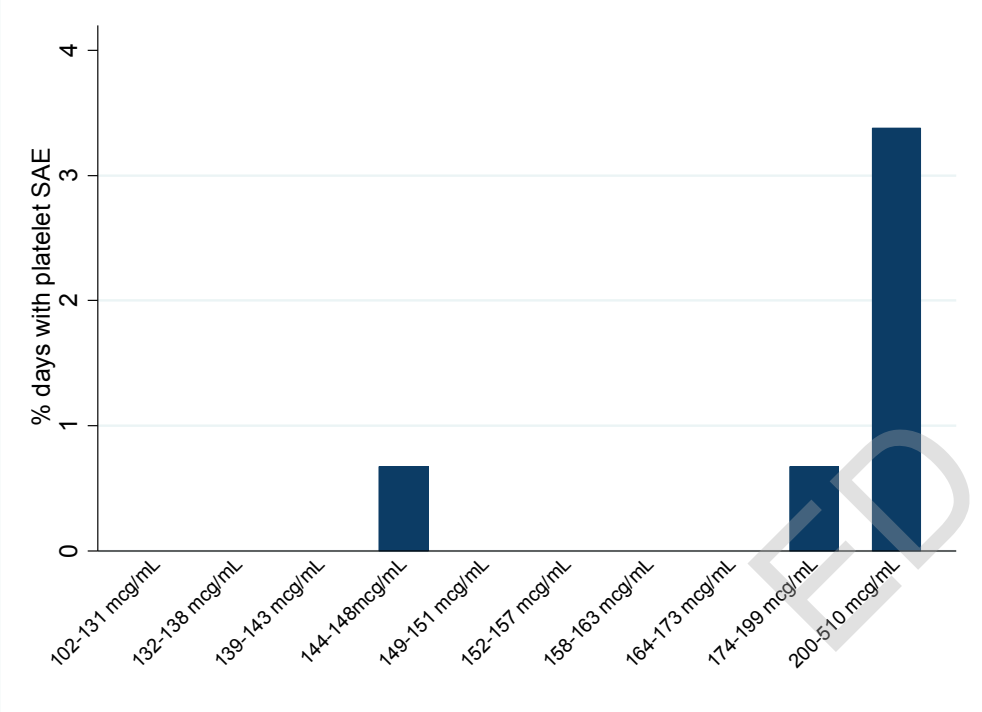
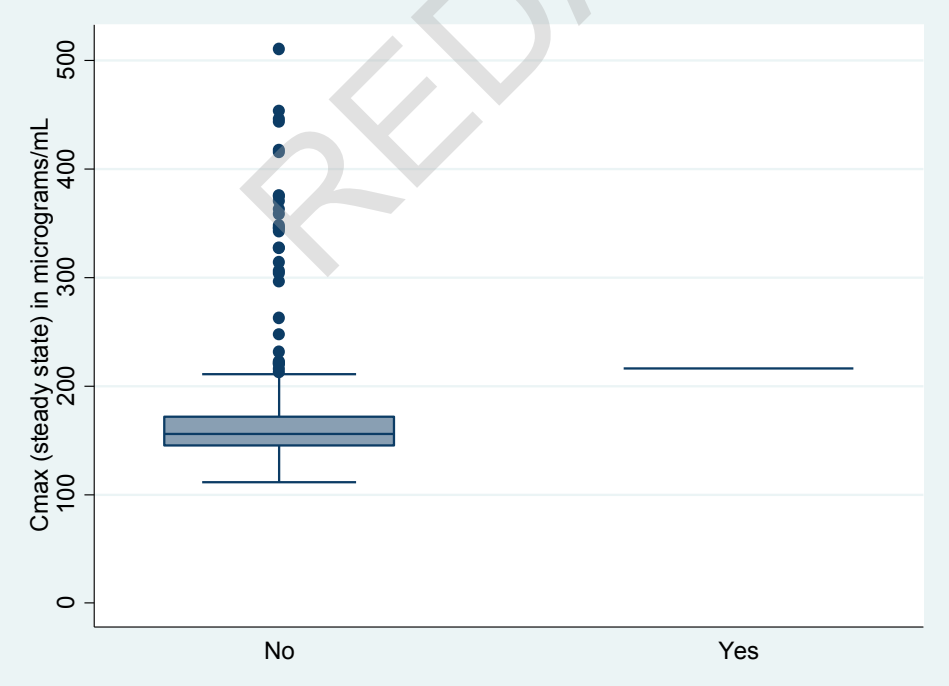


Figure 27. Cmax (steady state) concentration on days with and without severe thrombocytopenia in Group 1 infants with infection



REDACTED

Figure 28. Percentage of infant days with severe thrombocytopenia for each decile of ampicillin exposure (Cmax (steady state)) in Group 1 infants with infection

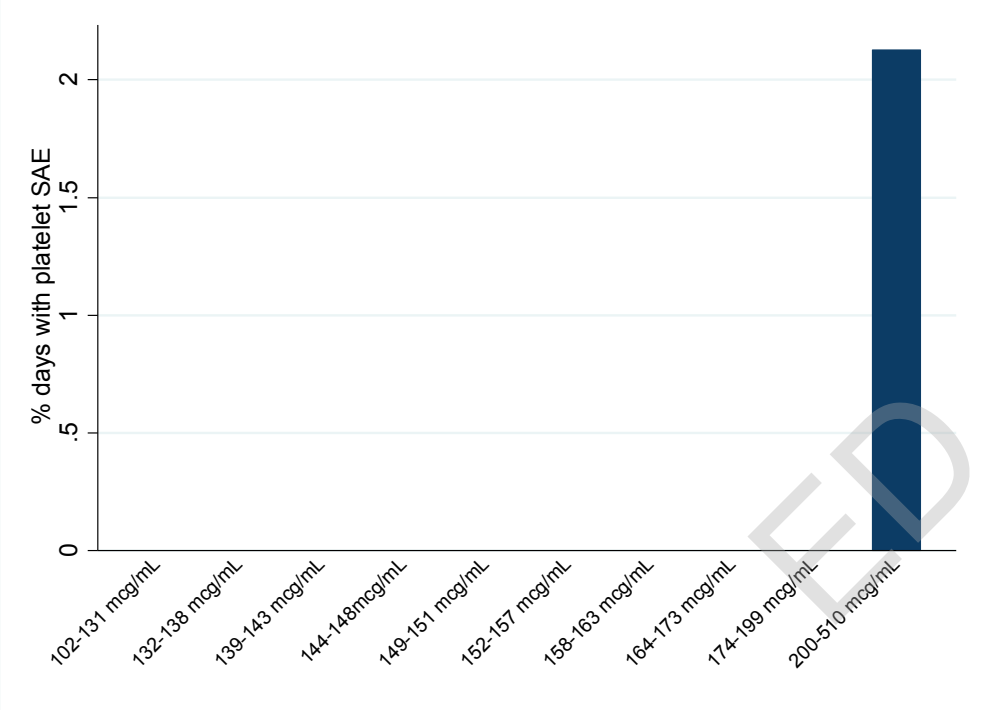
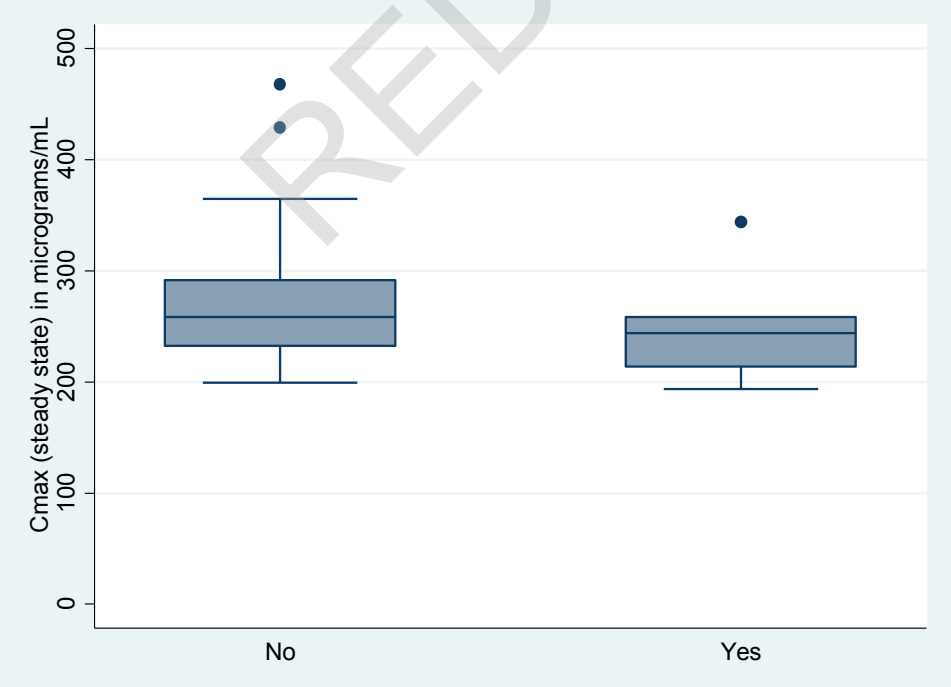


Figure 29. Cmax (steady state) concentration on days with and without severe thrombocytopenia Group 2 infants with infection



REDACTED

Figure 30. Percentage of infant days with severe thrombocytopenia for each decile of ampicillin exposure (Cmax (steady state)) in Group 2 infants with infection

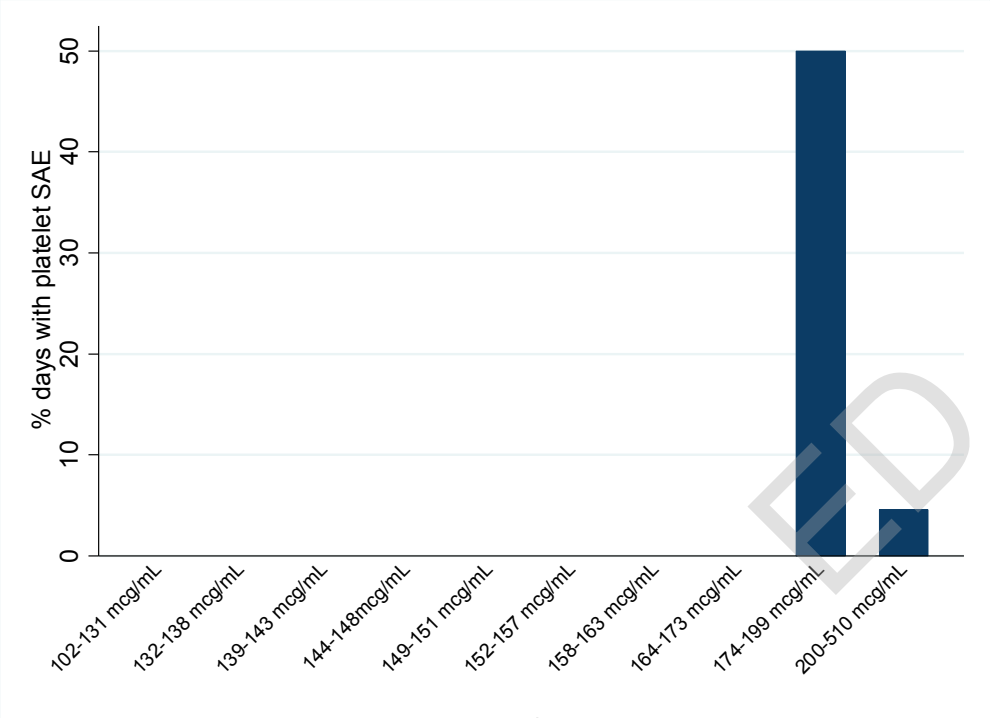
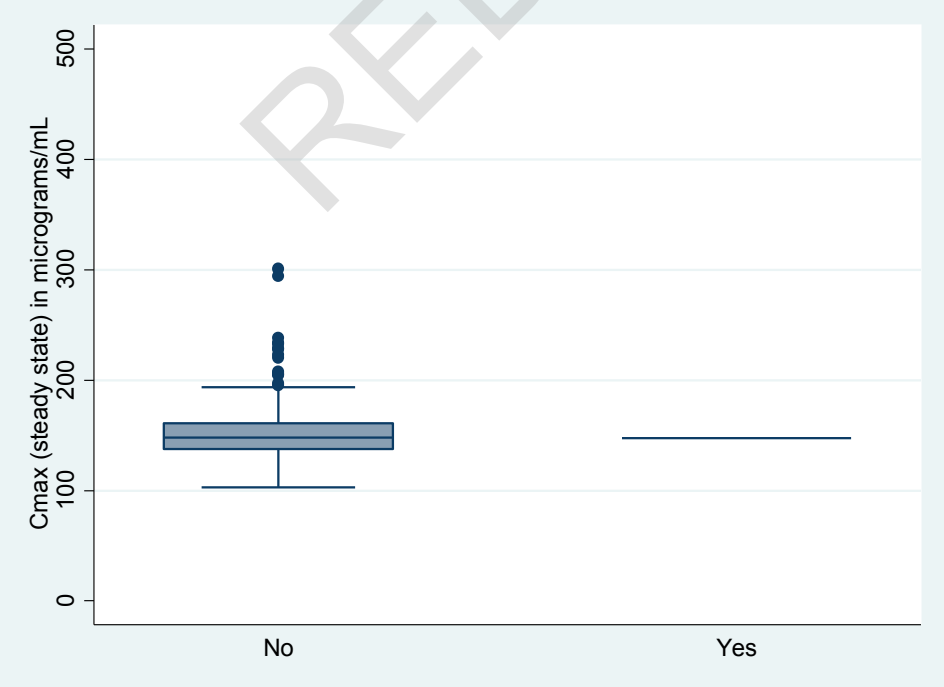
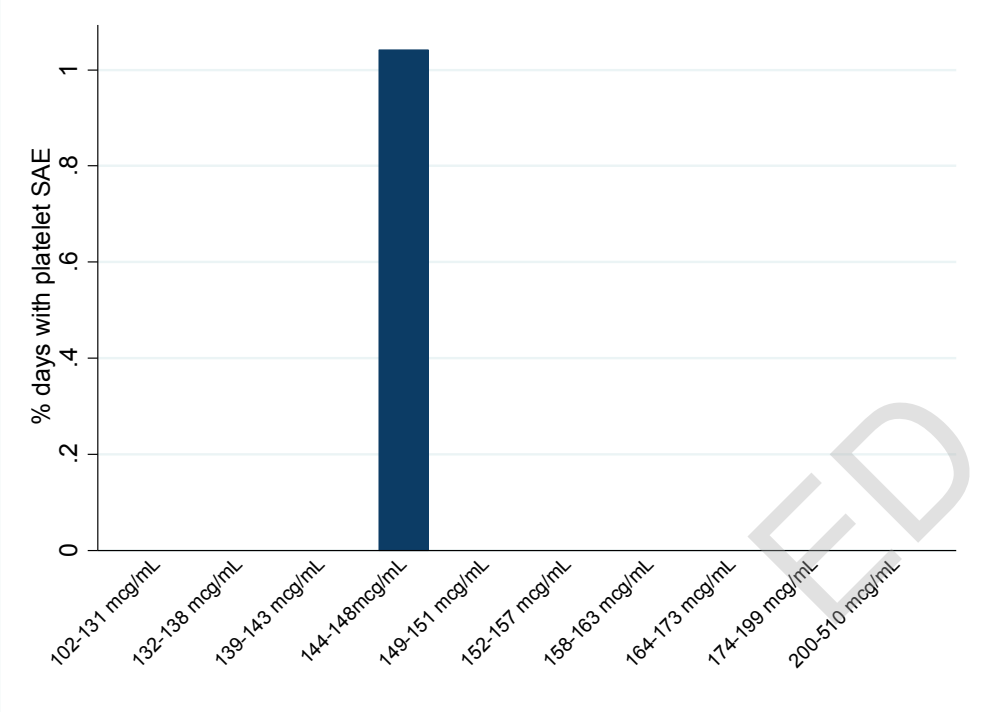


Figure 31. Cmax (steady state) concentration on days with and without severe thrombocytopenia in infants Group 3 infants with infection



REDACTED

Figure 32. Percentage of infant days with severe thrombocytopenia for each decile of ampicillin exposure (Cmax (steady state)) in Group 3 infants with infection



Leukopenia

The relationship between ampicillin exposure and leukopenia was unclear. Leukopenia did not occur at the highest exposures but did sometimes occur at typical exposures.

REDACTED

Figure 33. Cmax (steady state) concentration on days with and without leukopenia in all infants with infection

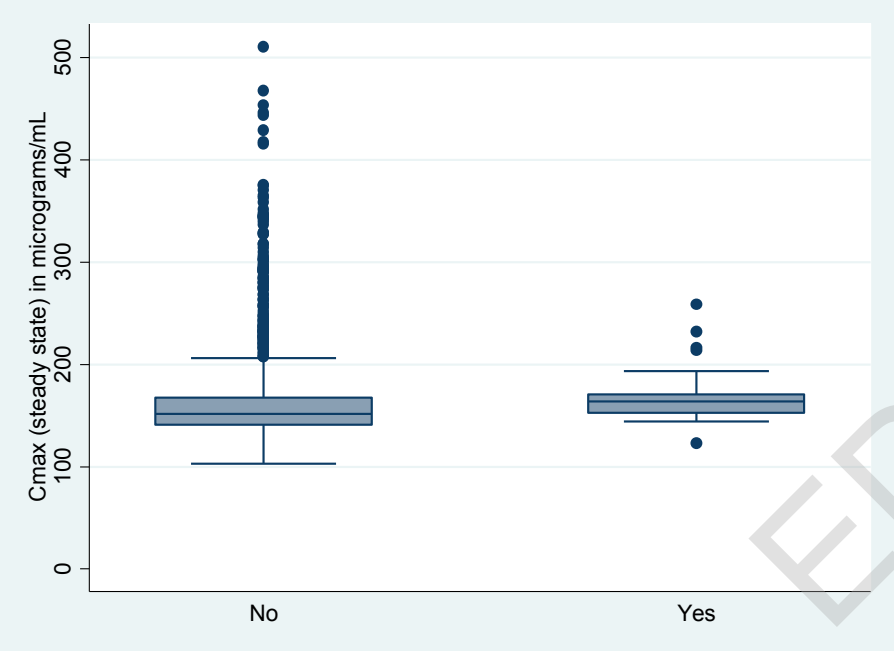
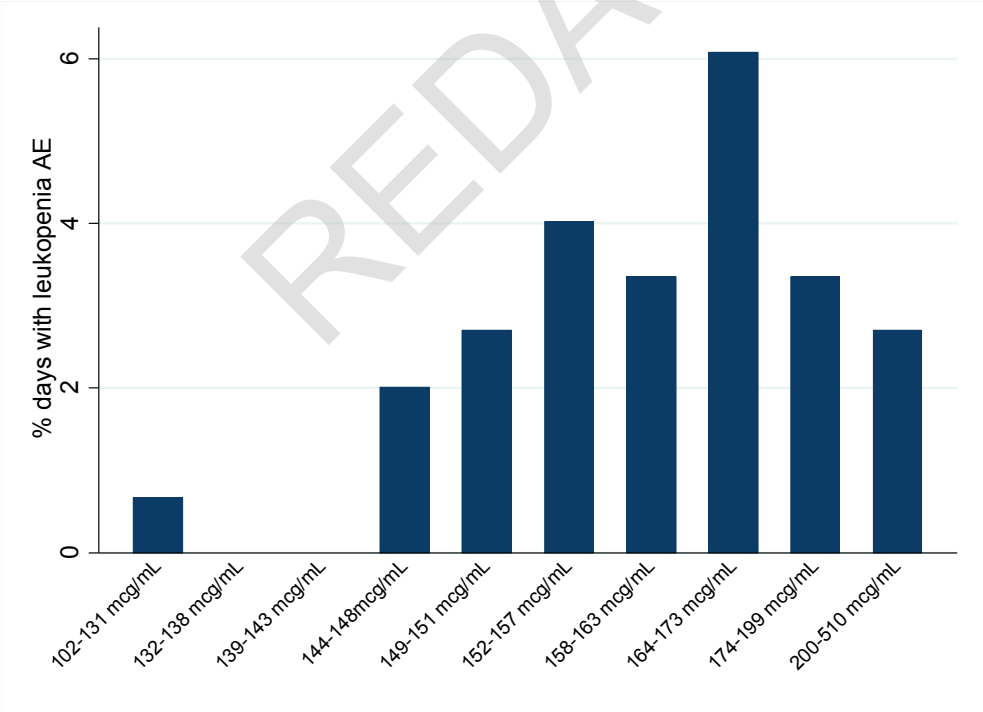


Figure 34. Percentage of infant days with leukopenia for each decile of ampicillin exposure (Cmax (steady state)) in all infants with infection



REDACTED

Figure 35. Cmax (steady state) concentration on days with and without leukopenia in infants Group 1 infants with infection

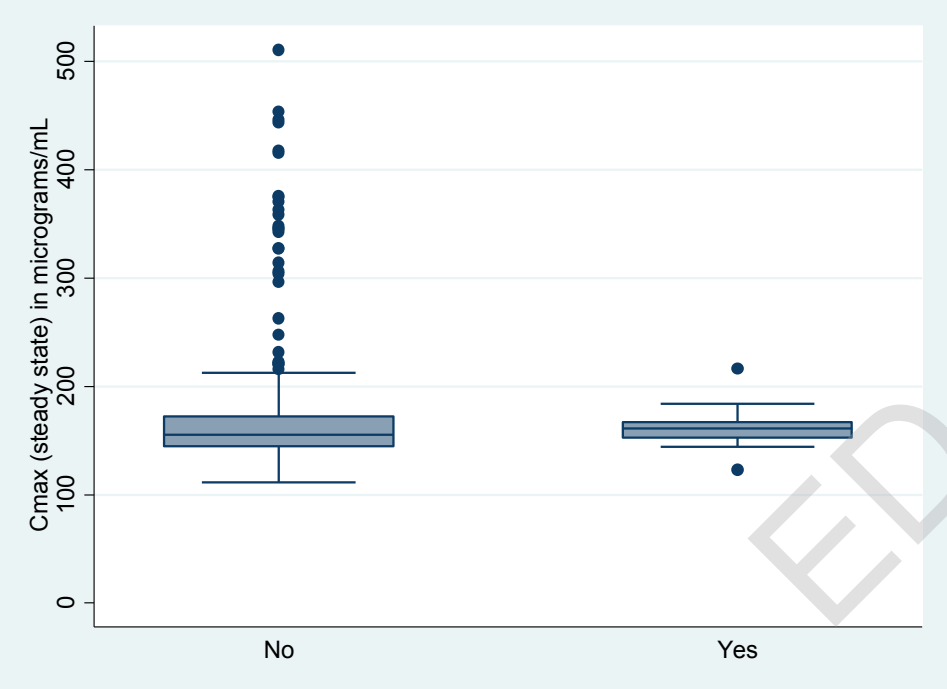


Figure 36. Percentage of infant days with leukopenia for each decile of ampicillin exposure (Cmax (steady state)) in Group 1 infants with infection

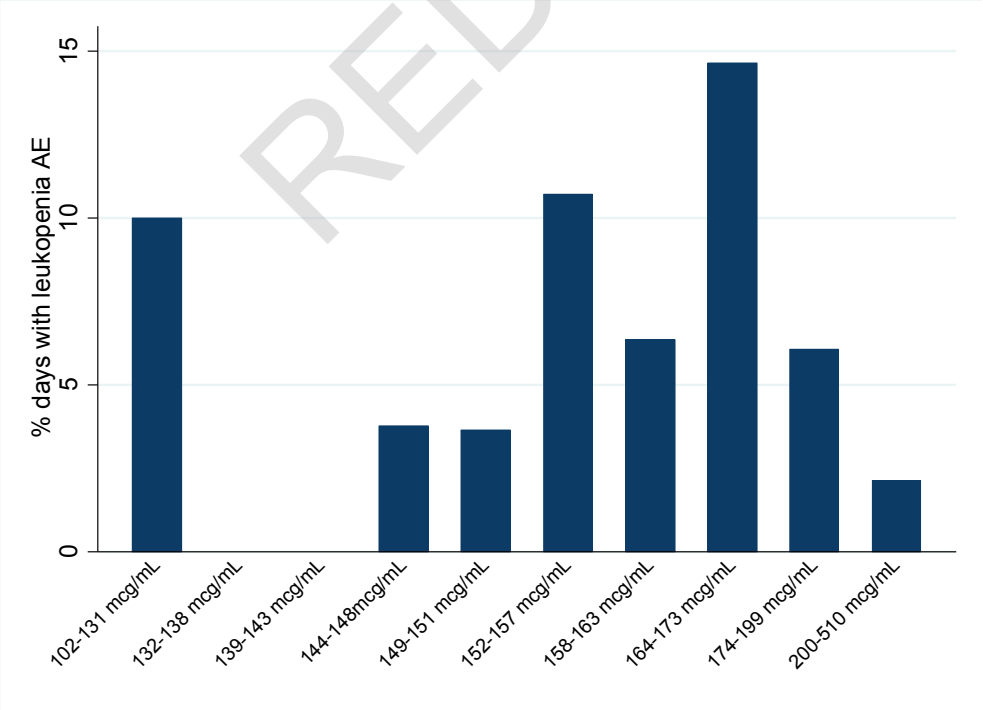


Figure 37. Cmax (steady state) concentration on days with and without leukopenia in Group 2 infants with infection

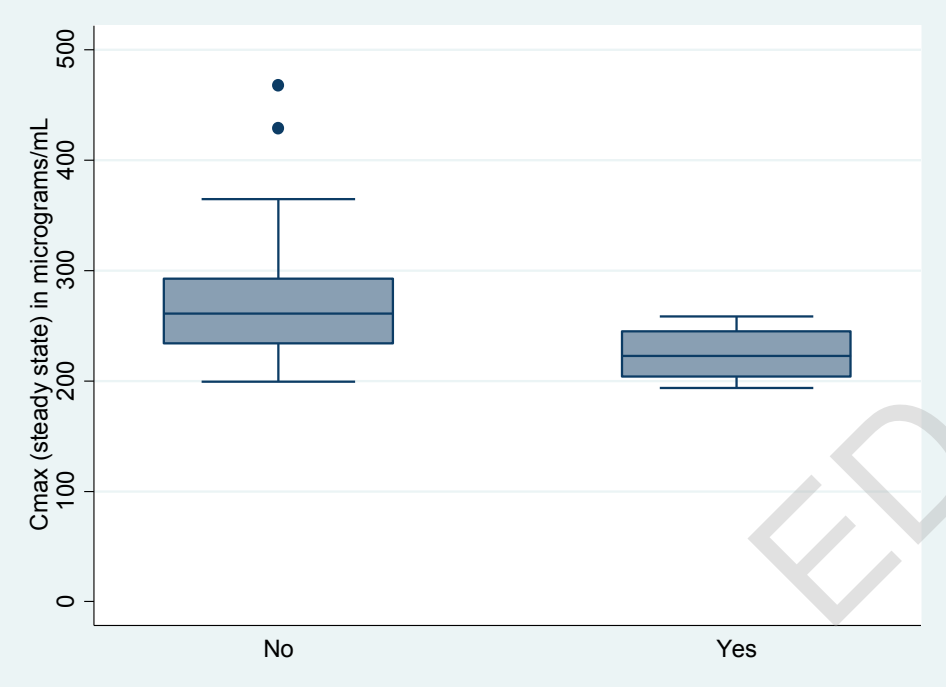


Figure 38. Percentage of infant days with leukopenia for each decile of ampicillin exposure (Cmax (steady state)) in Group 2 infants with infection

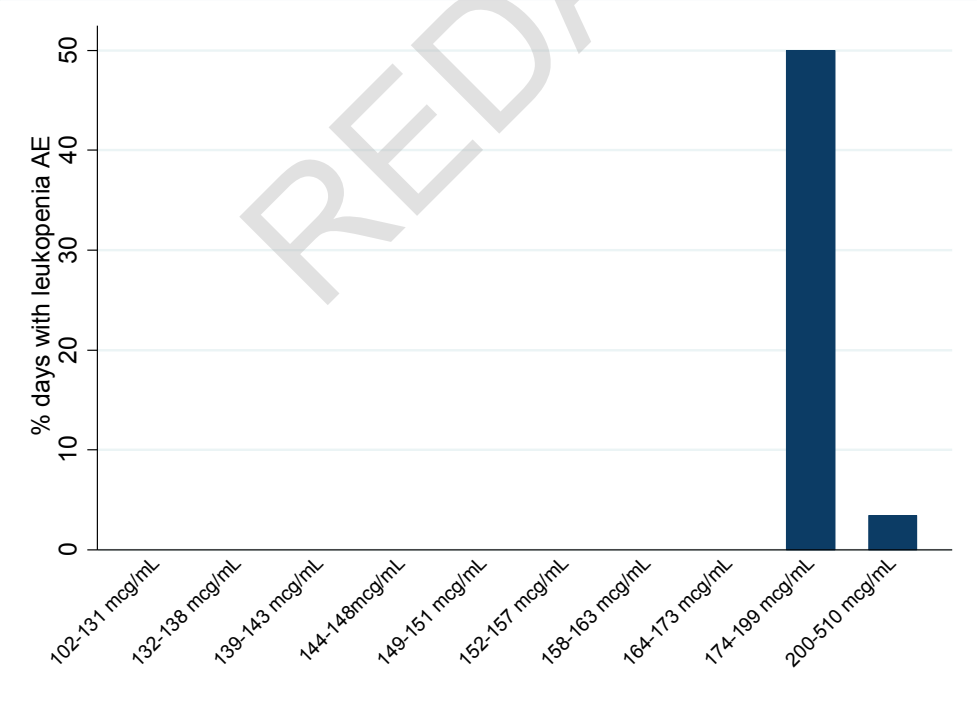


Figure 39. Cmax (steady state) concentration on days with and without leukopenia in infants Group 3 infants with infection

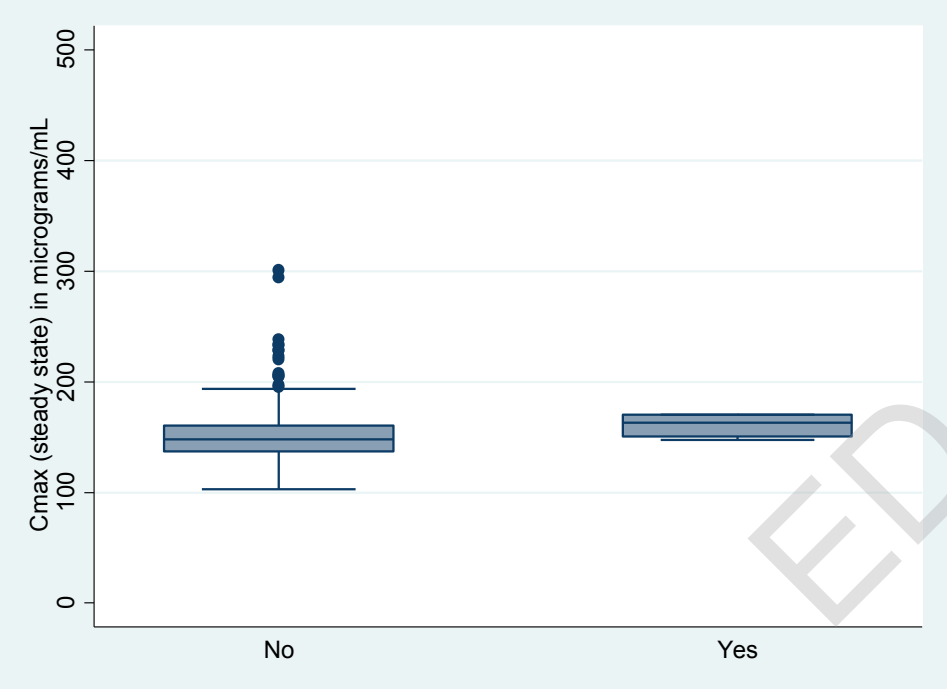
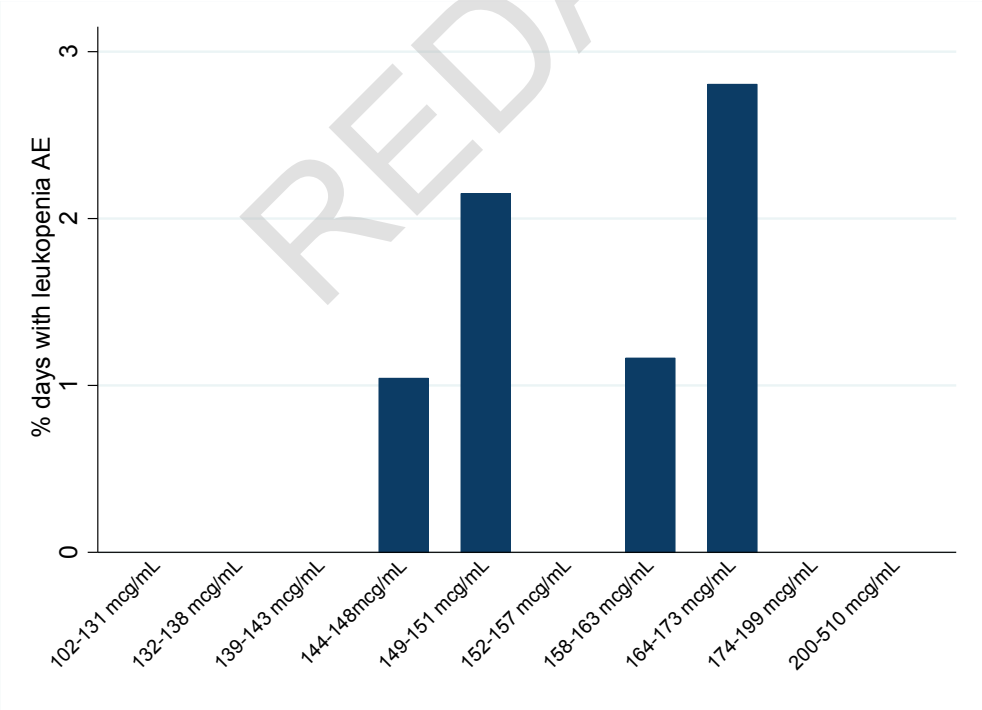


Figure 40. Percentage of infant days with leukopenia for each decile of ampicillin exposure (Cmax (steady state)) in Group 3 infants with infection



Severe Leukopenia

Figure 41. Cmax (steady state) concentration on days with and without severe leukopenia in all infants with infection

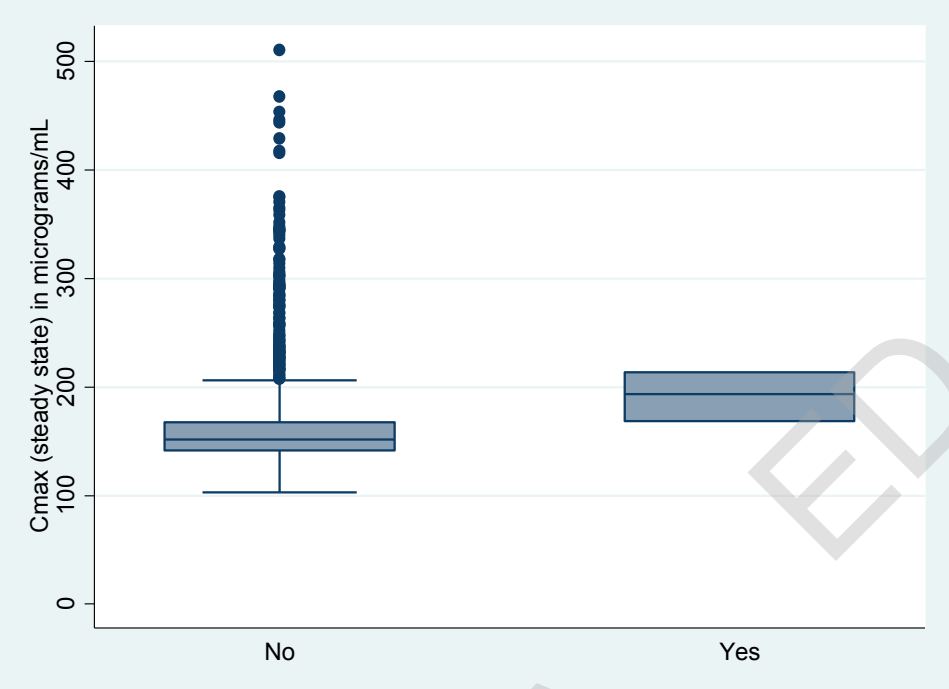
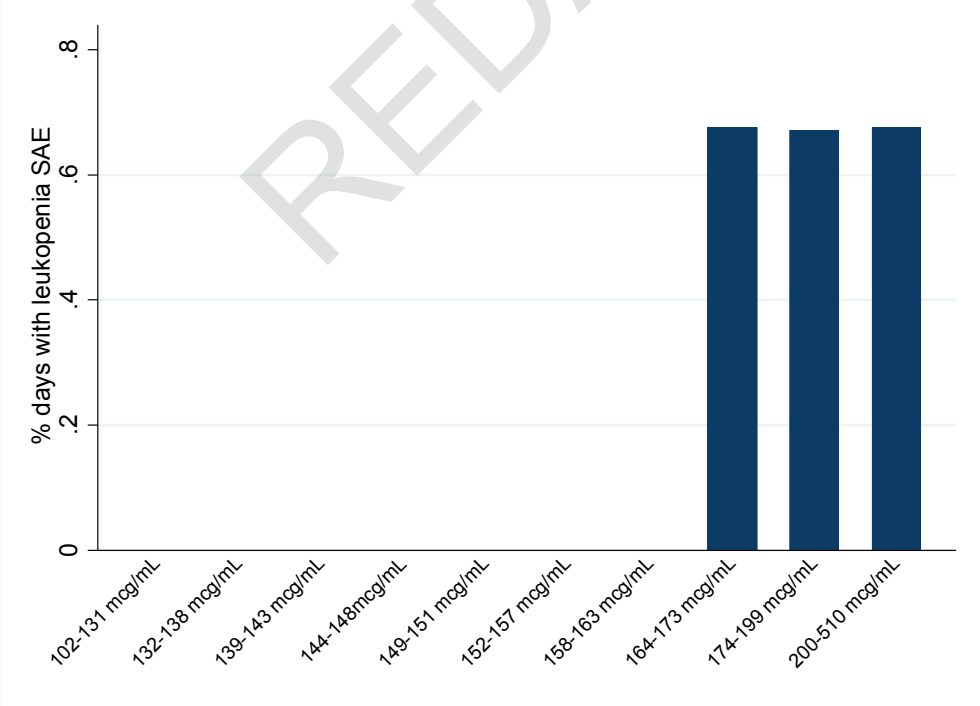


Figure 42. Percentage of infant days with severe leukopenia for each decile of ampicillin exposure (Cmax (steady state)) in all infants with infection



REDACTED

Figure 43. Cmax (steady state) concentration on days with and without severe leukopenia in Group 1 infants with infection

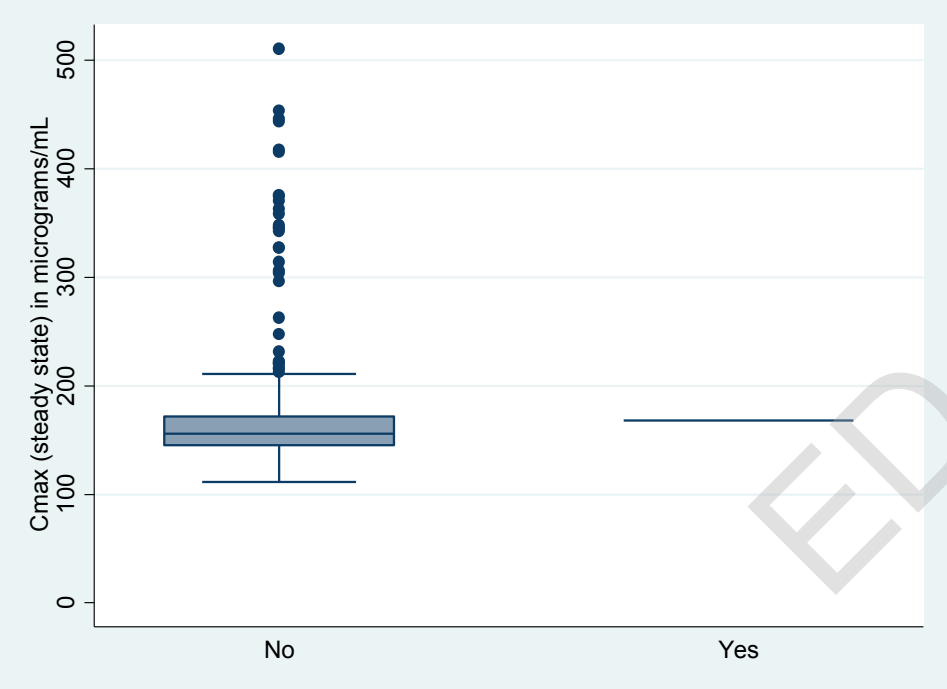


Figure 44. Percentage of infant days with severe leukopenia for each decile of ampicillin exposure (Cmax (steady state)) in Group 1 infants with infection

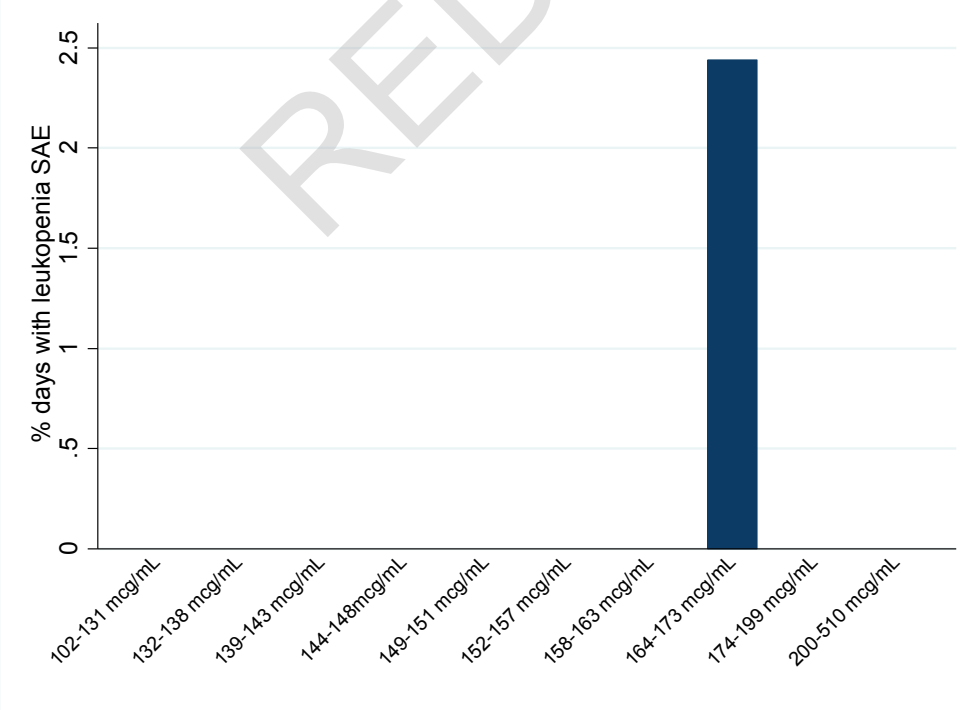


Figure 45. Cmax (steady state) concentration on days with and without severe leukopenia in Group 2 infants with infection

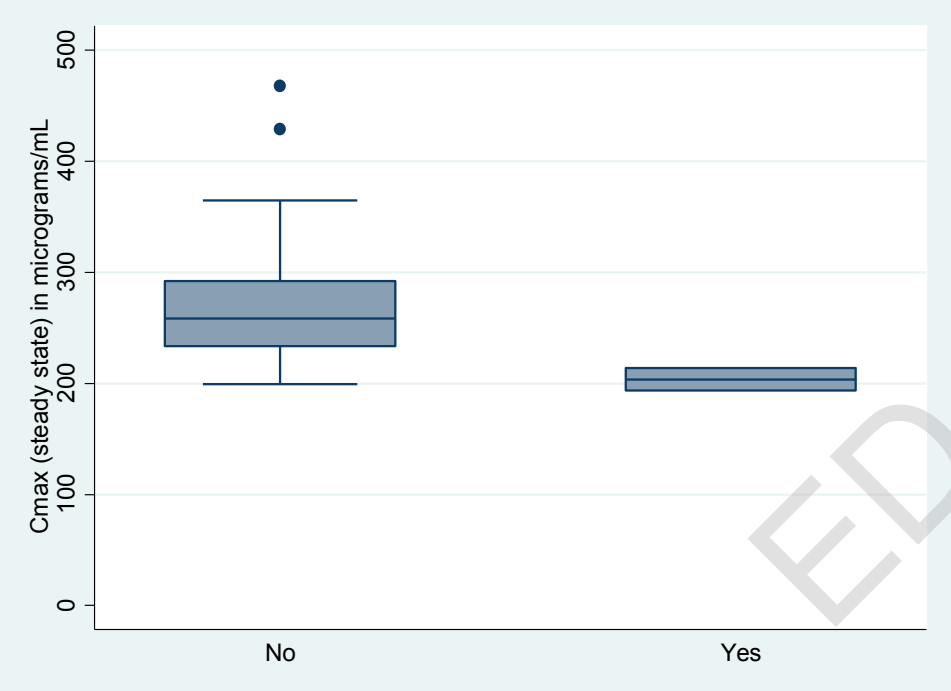


Figure 46. Percentage of infant days with severe leukopenia for each decile of ampicillin exposure (Cmax (steady state)) in Group 2 infants with infection

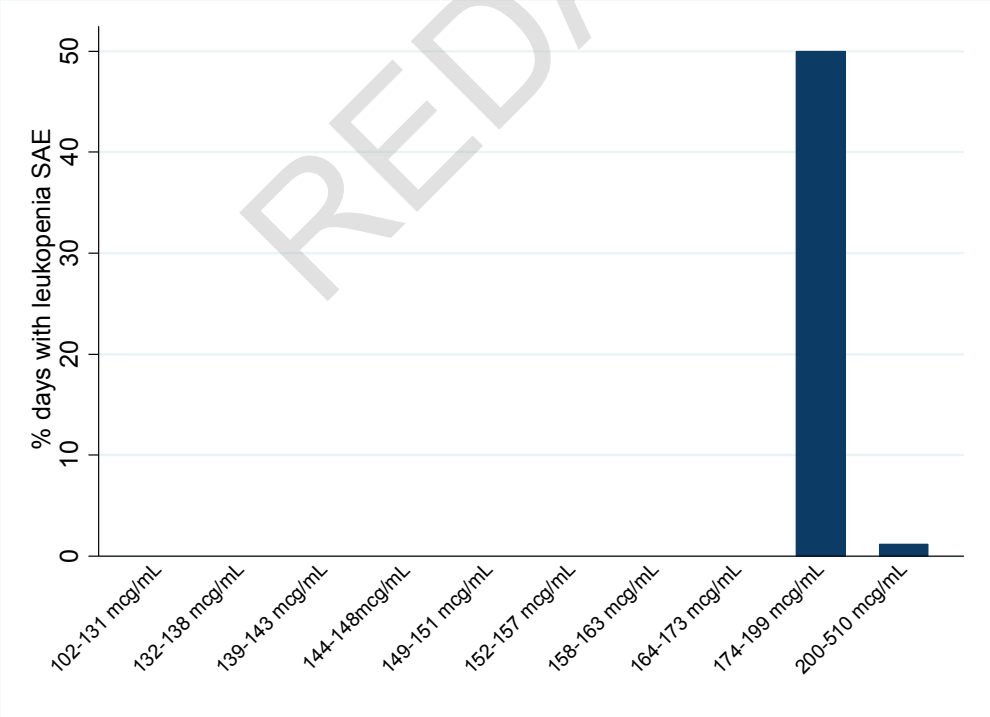
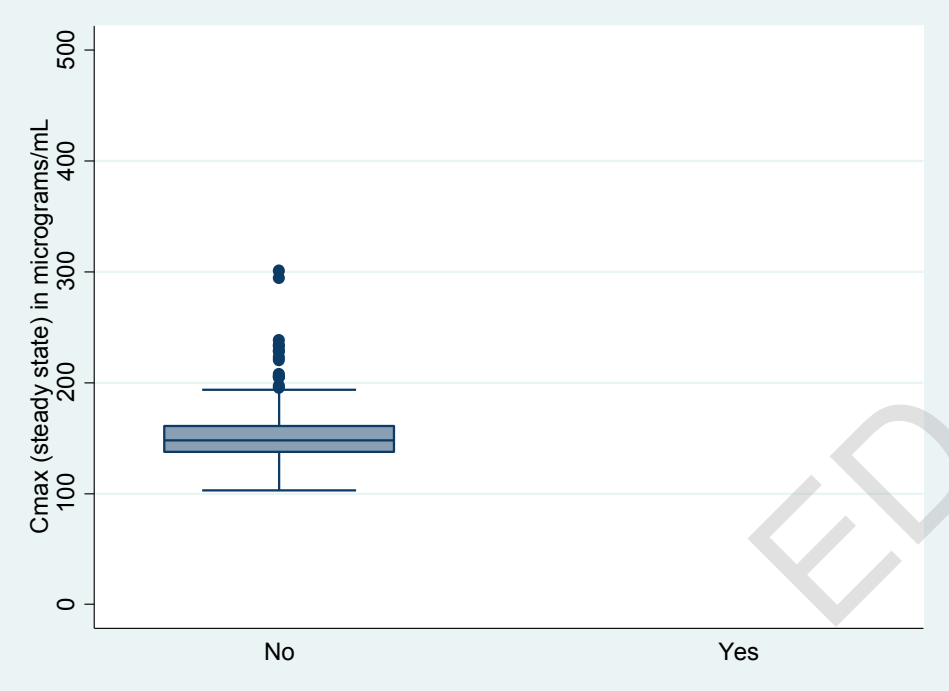


Figure 47. Cmax (steady state) concentration on days with and without severe leukopenia in Group 3 infants with infection



REDACTED

Neutropenia

There did not appear to be a relationship between ampicillin exposure and neutropenia. Neutropenia did not occur at the highest exposures but did occasionally occur at typical exposures.

Figure 48. Cmax (steady state) concentration on days with and without neutropenia in all infants with infection

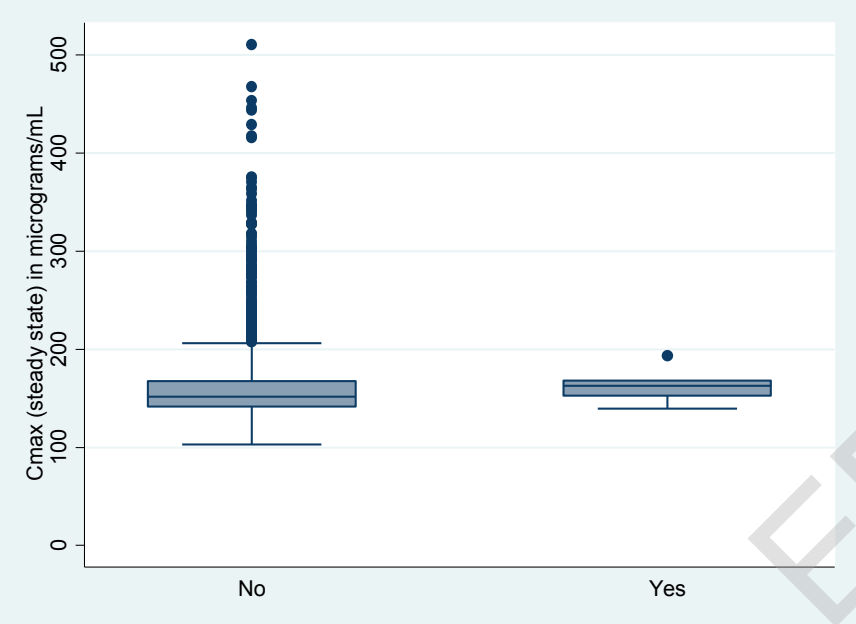


Figure 49. Percentage of infant days with neutropenia for each decile of ampicillin exposure (Cmax (steady state)) in all infants with infection

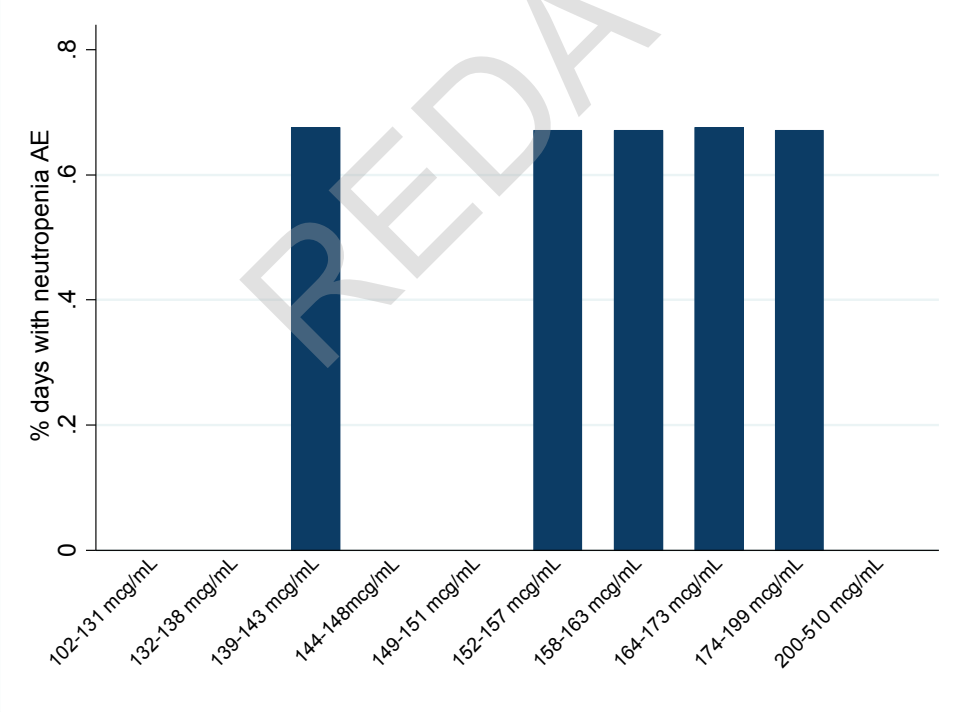


Figure 50. Cmax (steady state) concentration on days with and without neutropenia in Group 1 infants with infection

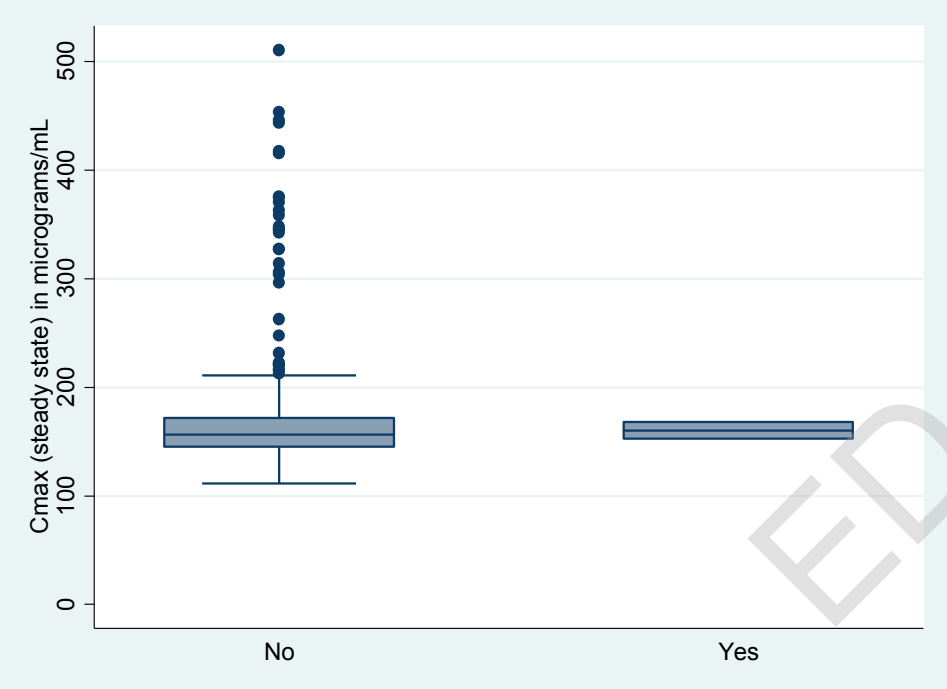


Figure 51. Percentage of infant days with neutropenia for each decile of ampicillin exposure (Cmax (steady state)) in Group 1 infants with infection

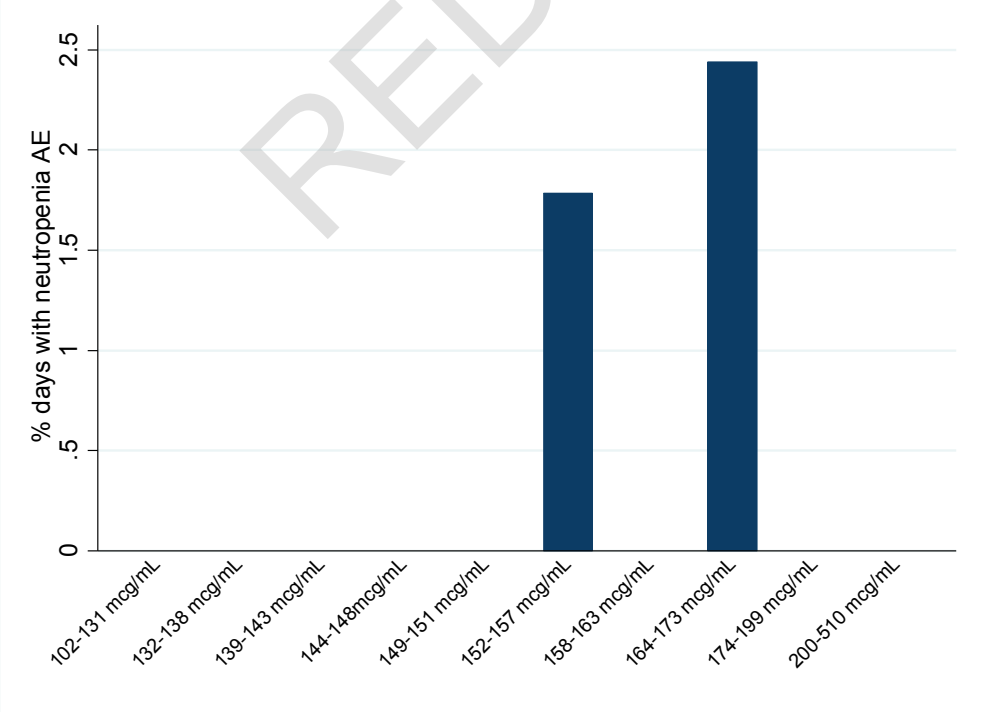


Figure 52. Cmax (steady state) concentration on days with and without neutropenia in Group 2 infants with infection

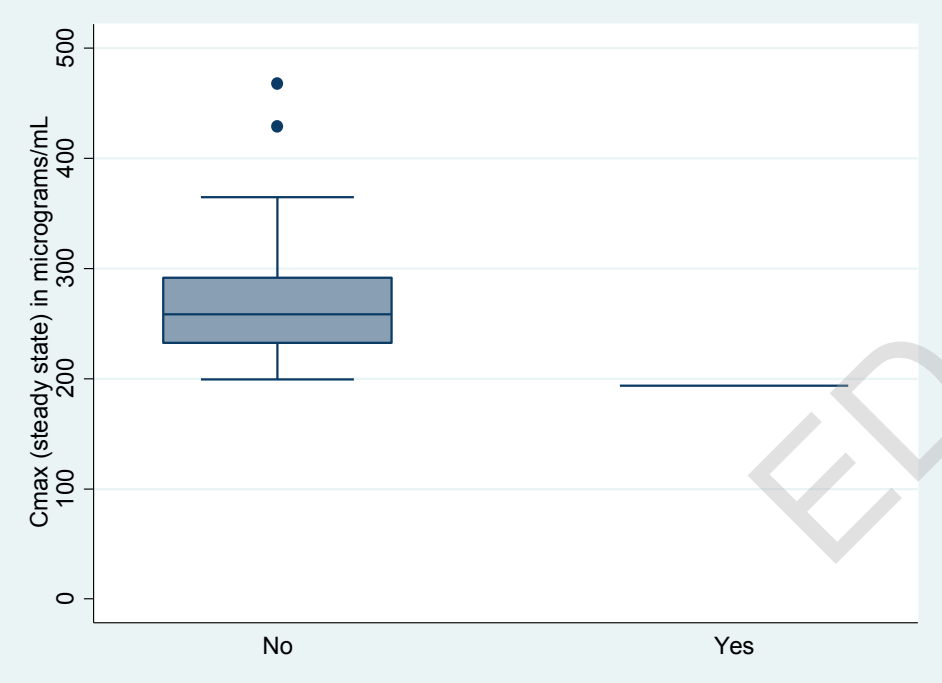
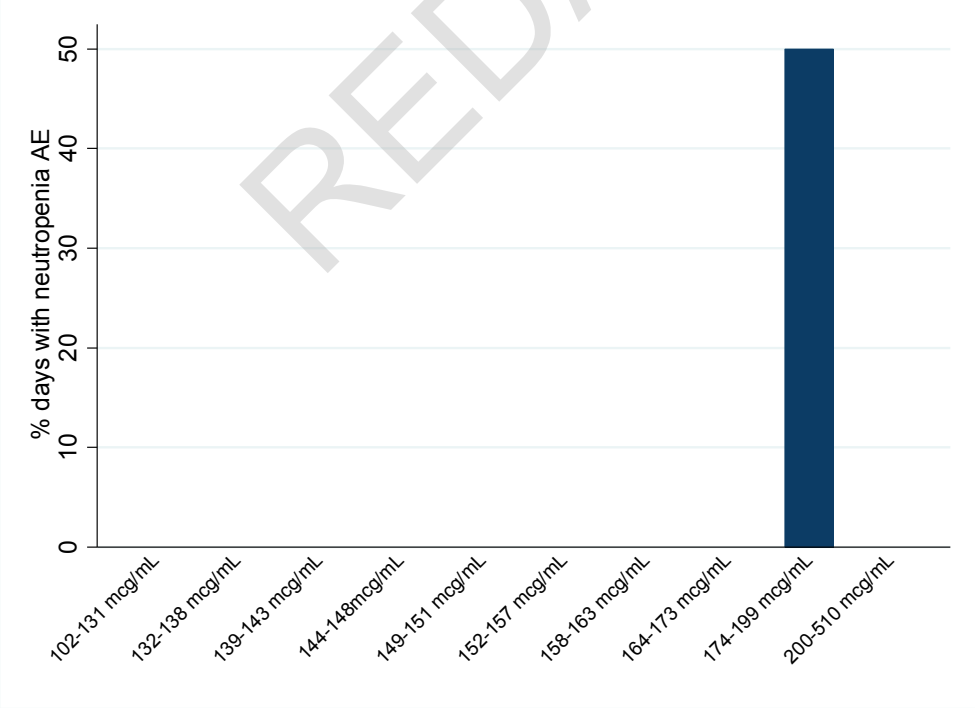


Figure 53. Percentage of infant days with neutropenia for each decile of ampicillin exposure (Cmax (steady state)) in Group 2 infants with infection



REDACTED

Figure 54. Cmax (steady state) concentration of ampicillin on days with and without neutropenia in Group 3 infants with infection

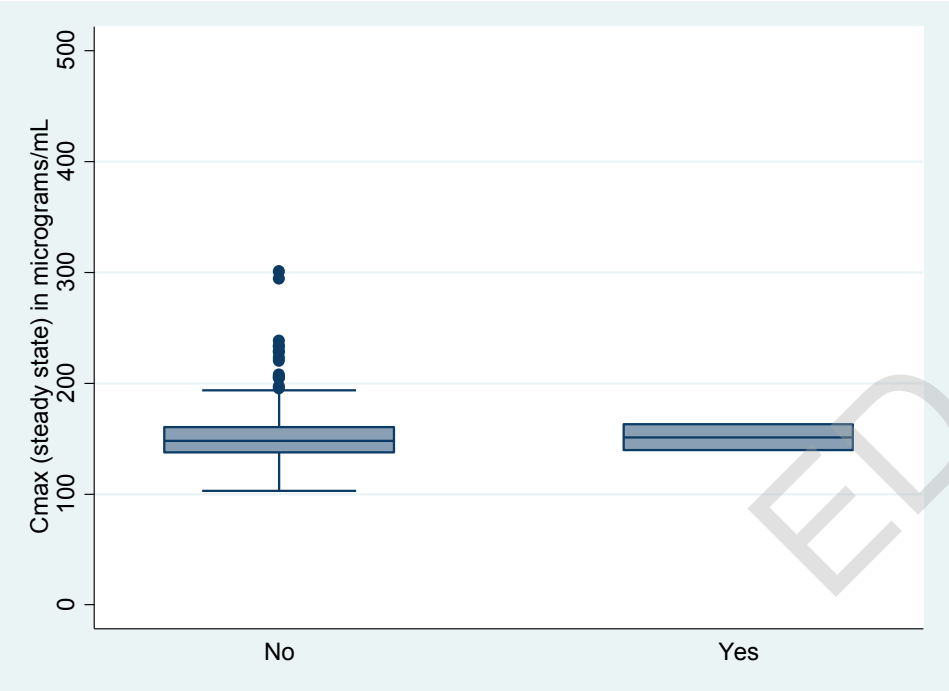
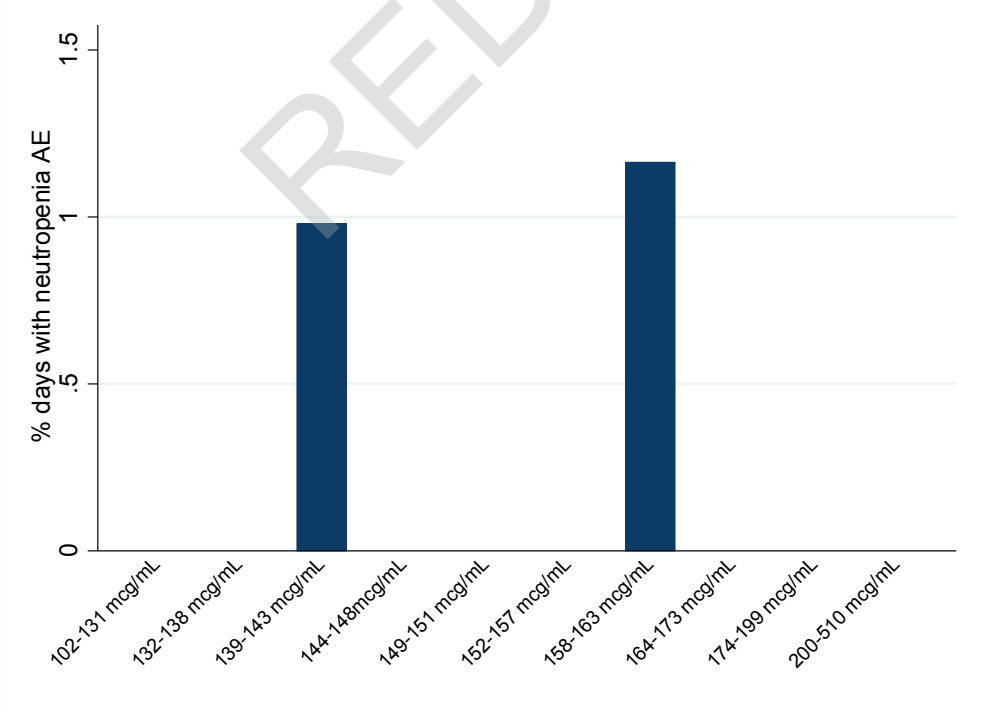


Figure 55. Percentage of infant days with neutropenia for each decile of ampicillin exposure (Cmax (steady state)) in Group 3 infants with infection

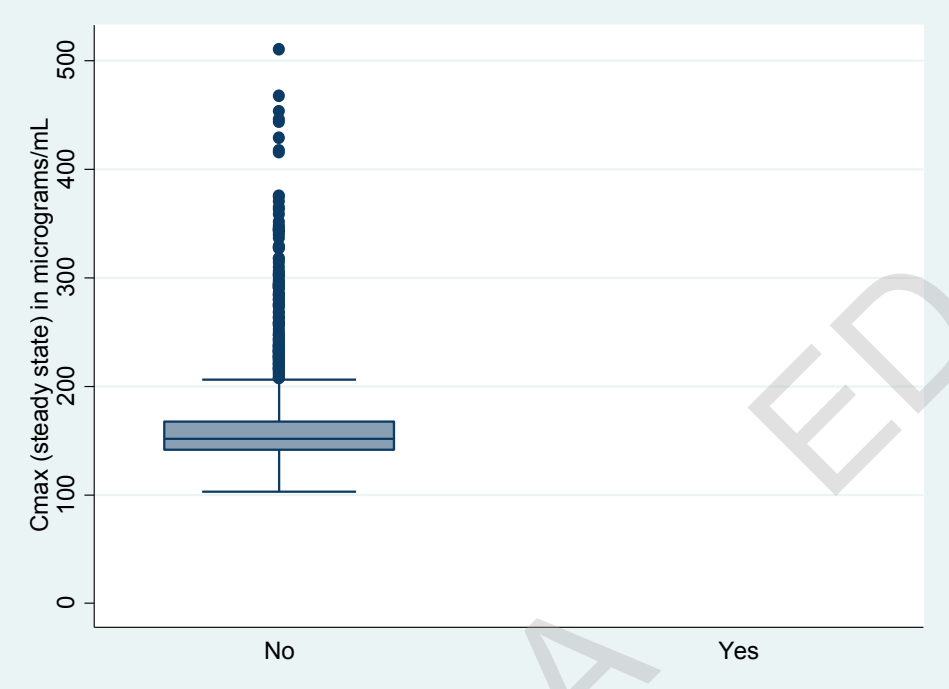


REDACTED

Severe Neutropenia

Severe neutropenia did not occur in infants with infection during exposure to ampicillin.

Figure 56. Cmax (steady state) concentration on days with and without severe neutropenia in all infants with infection



REDACTED

Figure 57. Cmax (steady state) concentration on days with and without severe neutropenia in Group 1 infants with infection

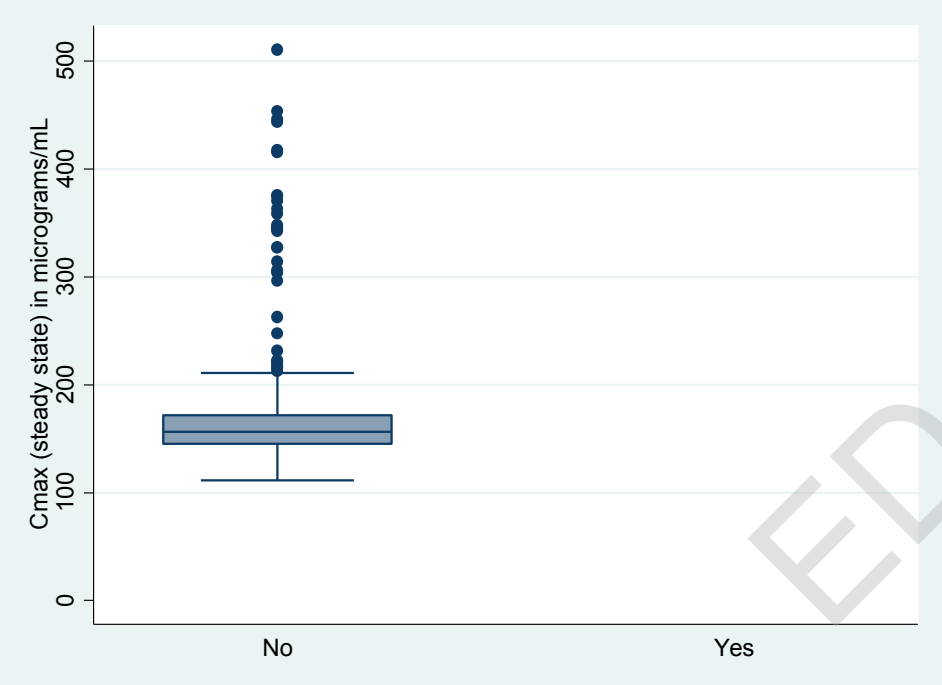


Figure 58. Cmax (steady state) concentration on days with and without severe neutropenia in Group 2 infants with infection

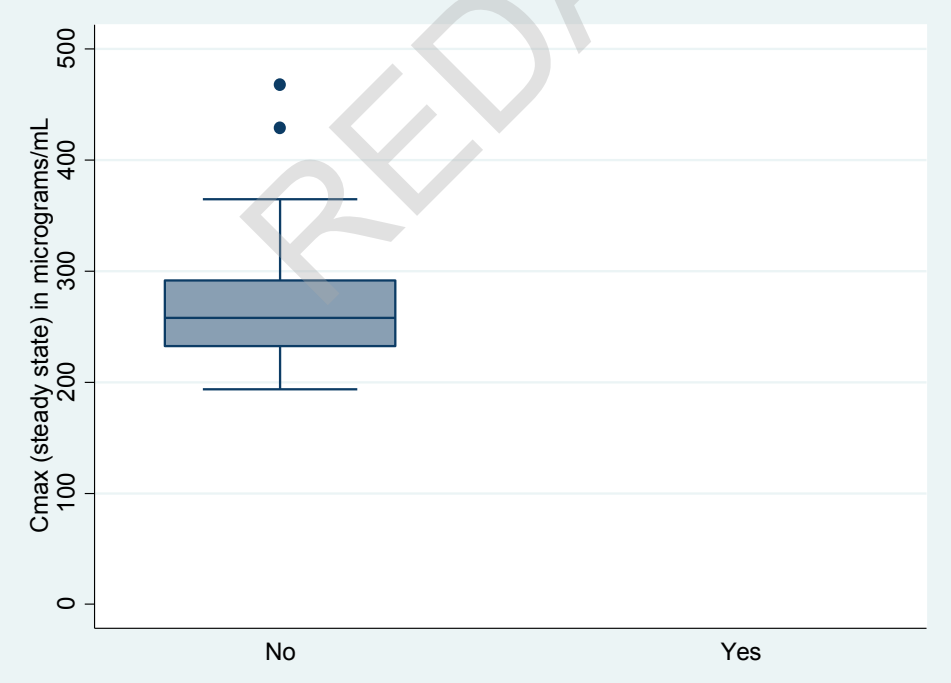
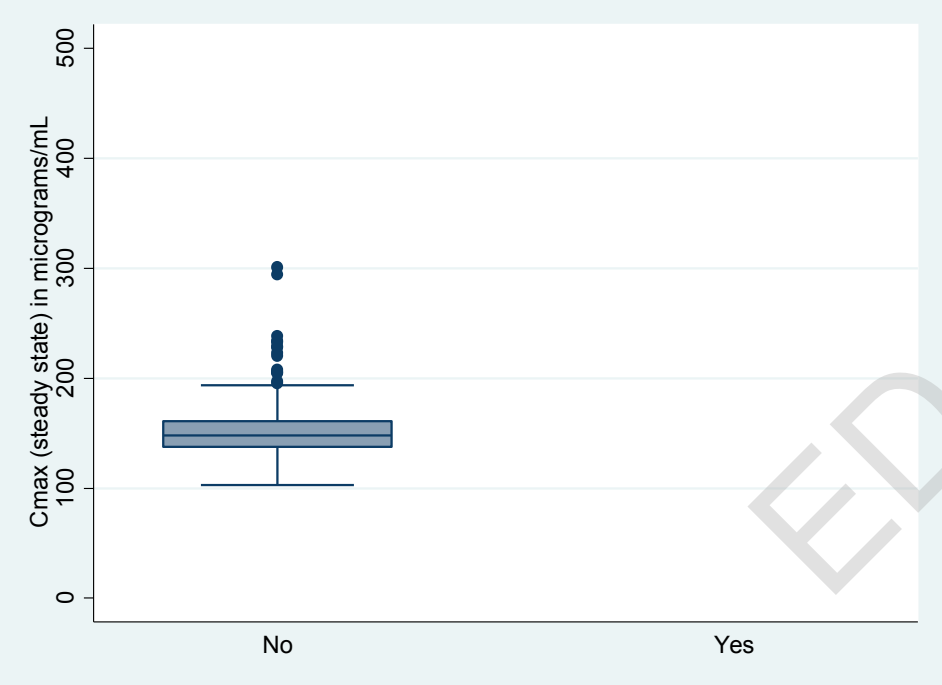


Figure 59. Cmax (steady state) concentration on days with and without severe neutropenia in Group 3 infants with infection



Exposure safety relationship for all infants

Seizure

The relationship between ampicillin exposure and seizure was unclear. For days with a seizure, exposure to ampicillin tended to be higher. However, infants with the highest exposures often had no seizures.

REDACTED

Figure 60. Cmax (steady state) concentration on days with and without seizure for all infants.

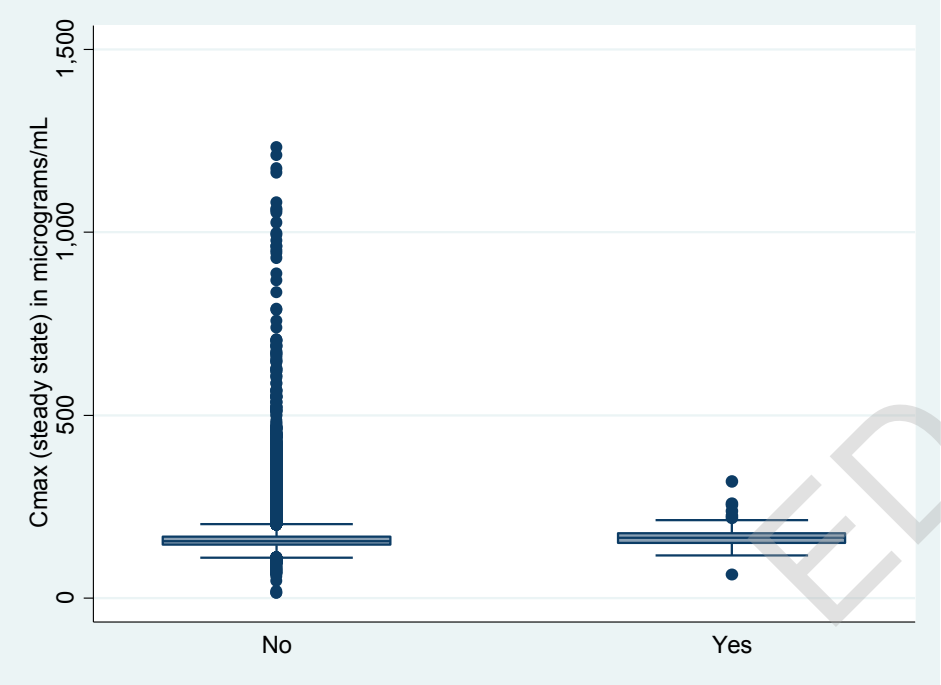


Figure 61. Percentage of infant days with seizure for each decile of ampicillin exposure (Cmax (steady state)) for all infants

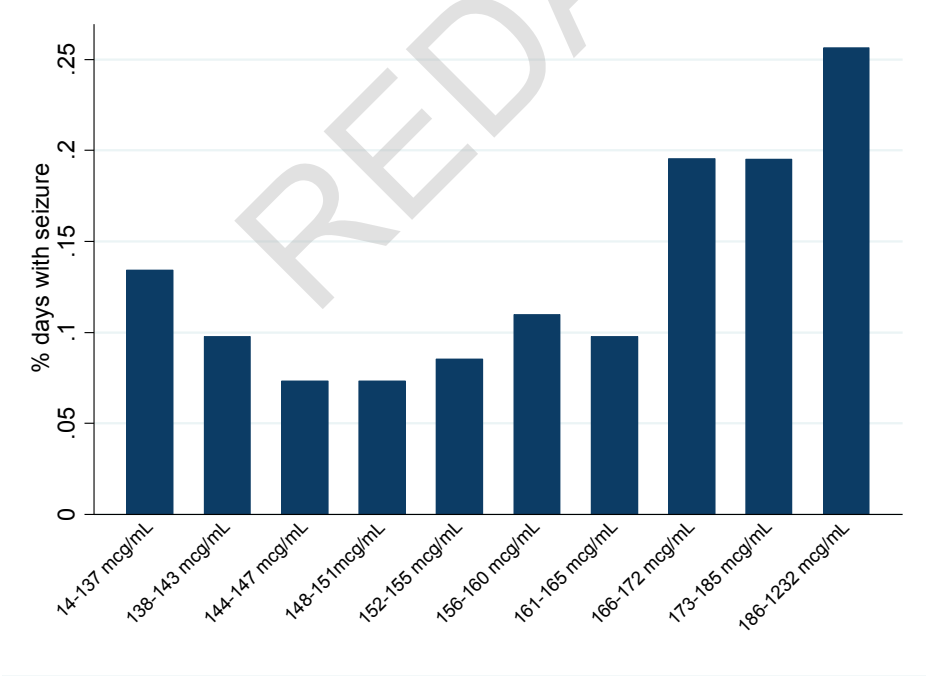


Figure 62. Cmax (steady state) concentration on days with and without seizure for all Group 1 infants

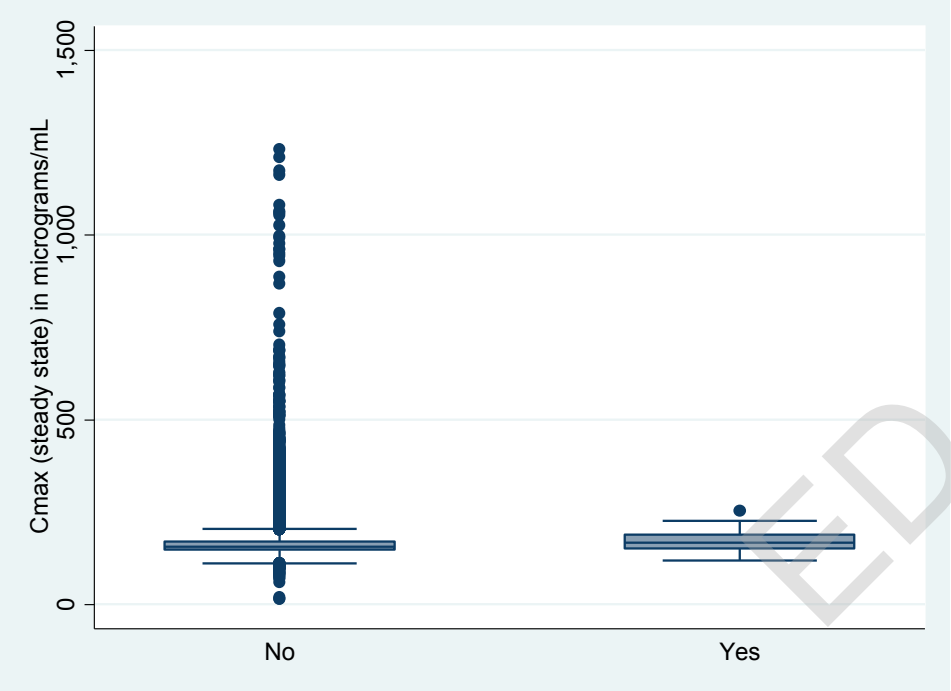


Figure 63. Percentage of infant days with seizure for each decile of ampicillin exposure (Cmax (steady state)) in all Group 1 infants

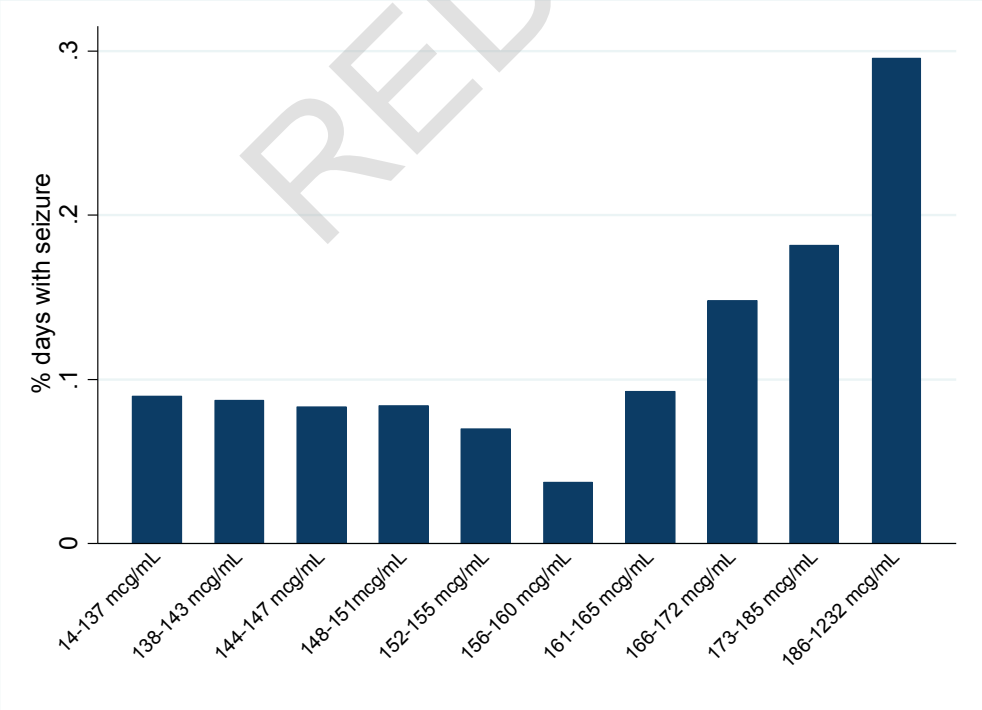


Figure 64. Cmax (steady state) concentration on days with and without seizure in all Group 2 infants

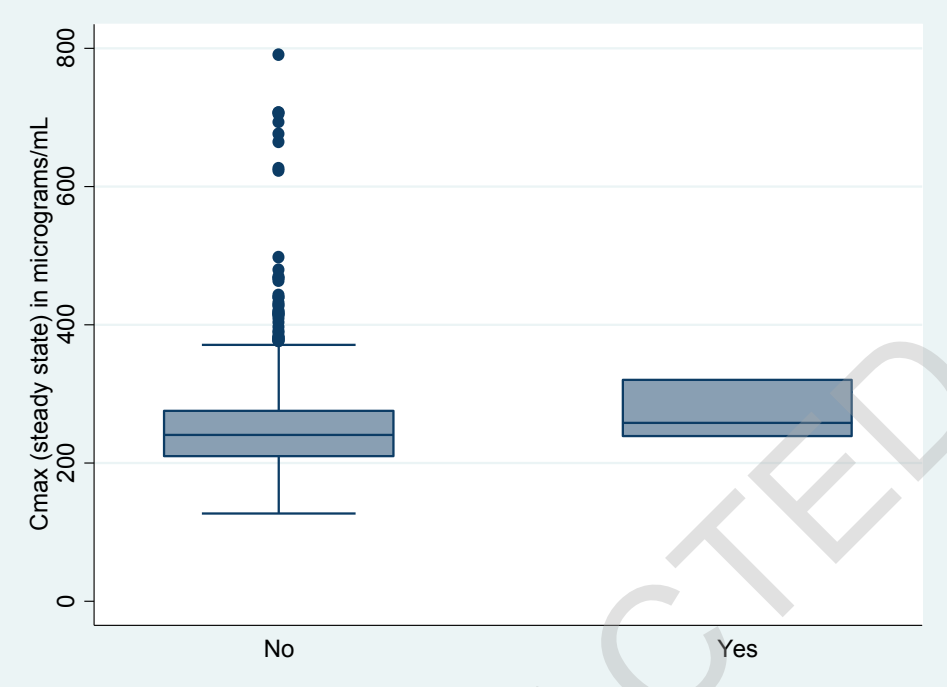
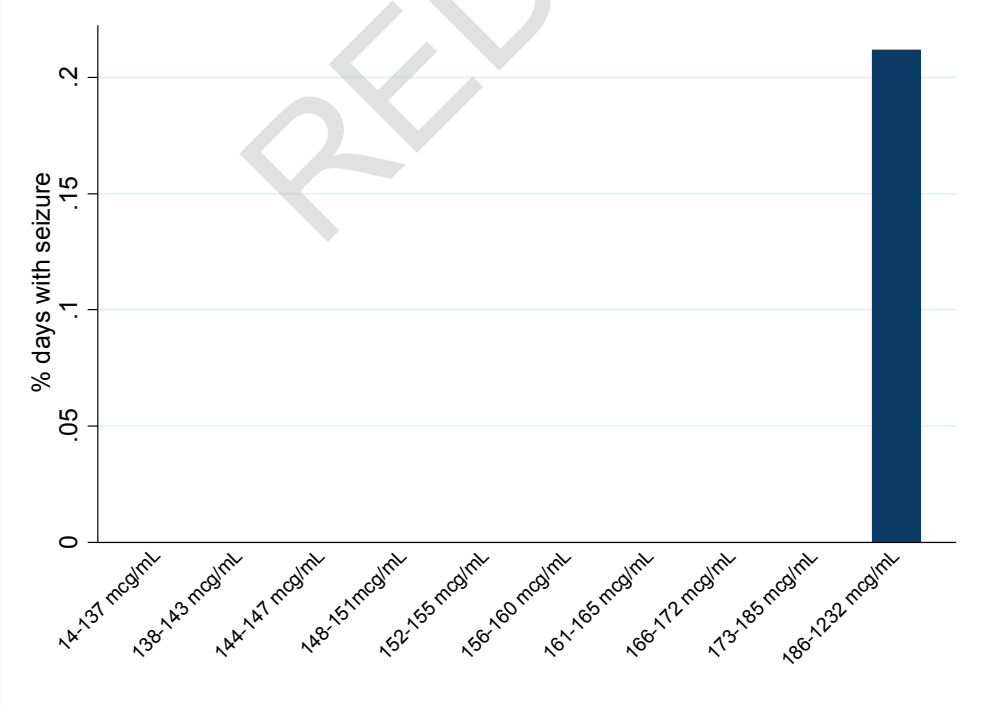


Figure 65. Percentage of infant days with seizure for each decile of ampicillin exposure (Cmax (steady state)) in all Group 2 infants



REDACTED

Figure 66. Cmax (steady state) concentration on days with and without seizure in all Group 3 infants

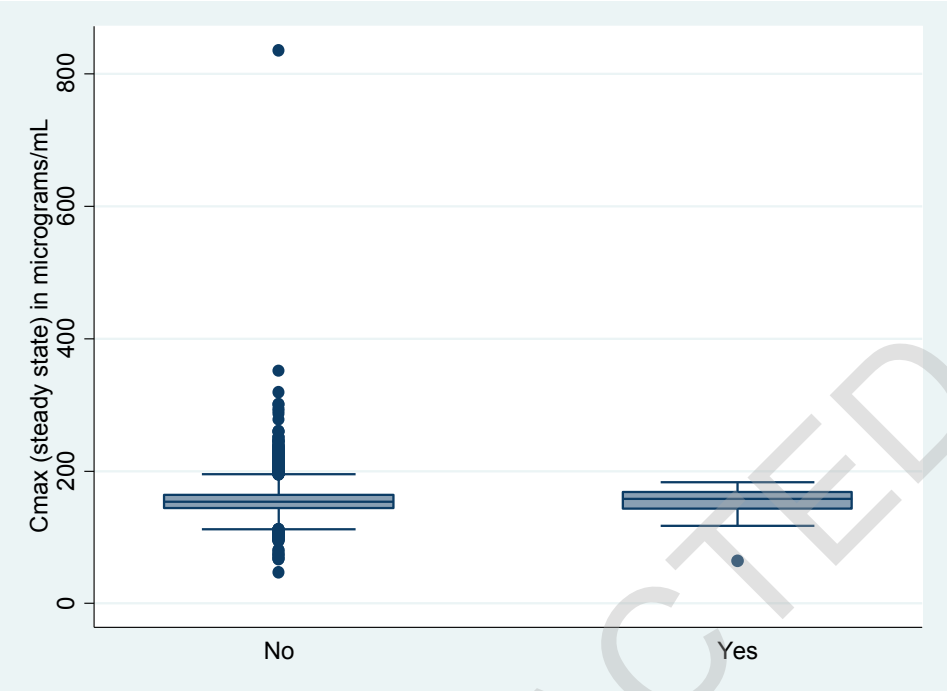
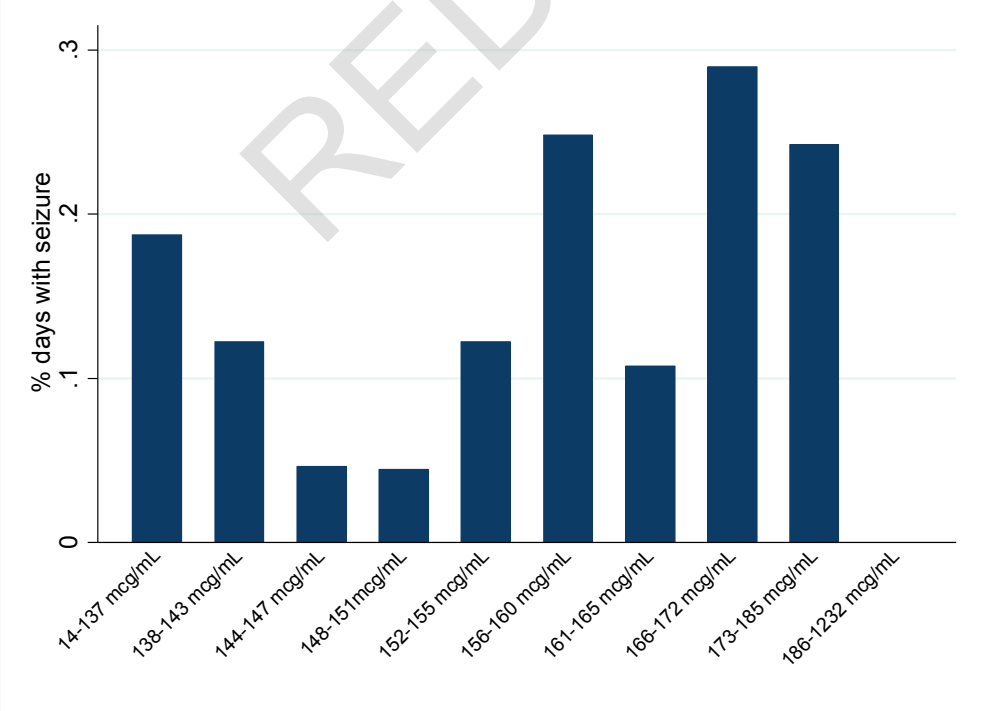


Figure 67. Percentage of infant days with seizure for each decile of ampicillin exposure (Cmax (steady state)) in all Group 3 infants



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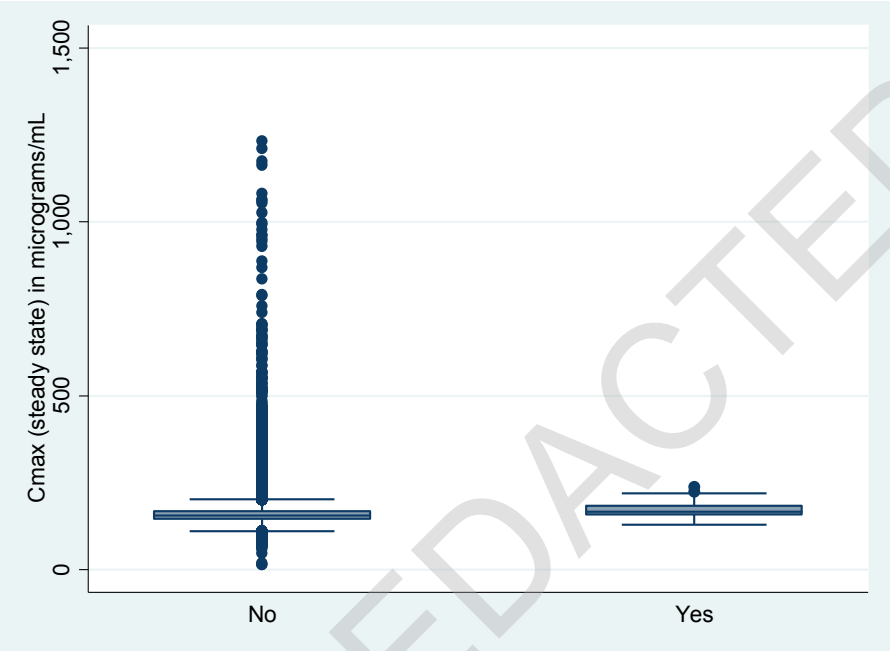
AST Elevation

Days on which there was AST elevation or severe AST elevation tended to have higher ampicillin exposures. However, infants with the highest exposures did not have AST elevation or severe AST elevation. There were no cases of AST elevation or severe AST elevation on days with ampicillin exposure for Group 2 infants. Severe AST elevation did not occur on days with ampicillin exposure for Group 3 infants.

Figure 68. Cmax (steady state) concentration on days with and without AST elevation in all infants



REDACTED

Figure 69. Percentage of infant days with AST elevation for each decile of ampicillin exposure (Cmax (steady state)) in all infants

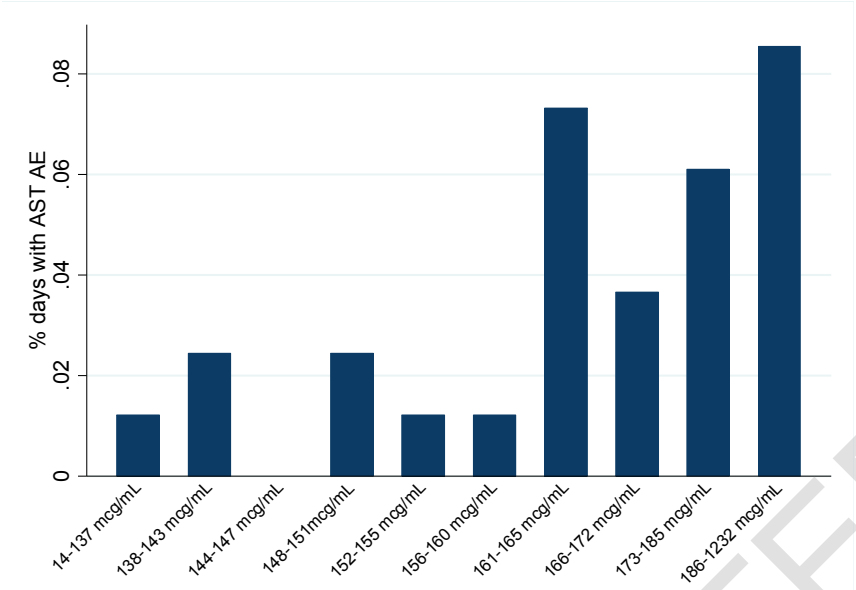
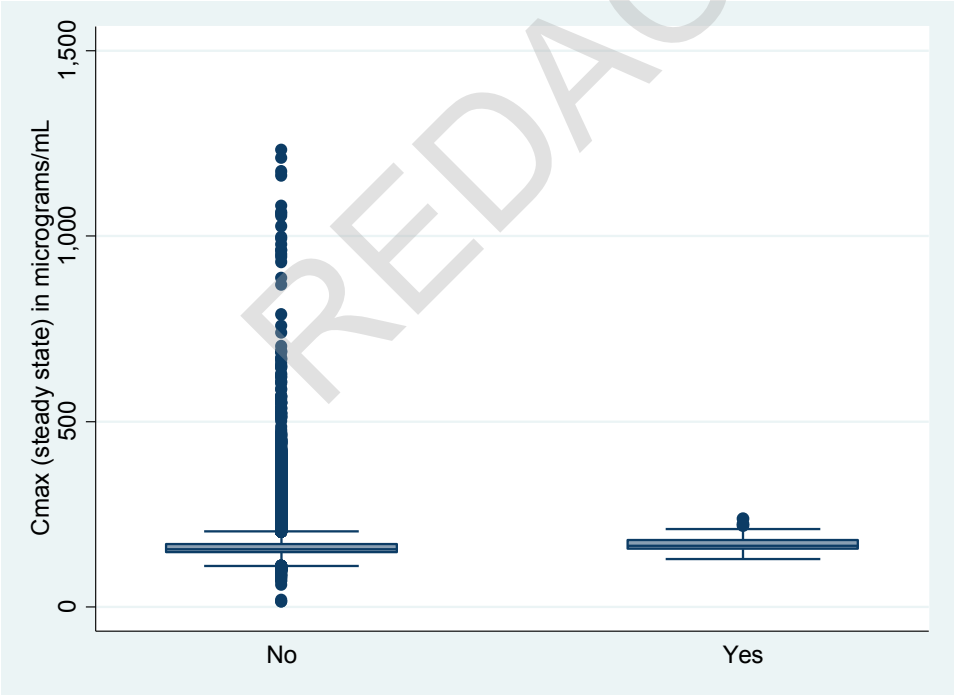


Figure 70. Cmax (steady state) concentration on days with and without AST elevation in all Group 1 infants



REDACTED

Figure 71. Percentage of infant days with AST elevation for each decile of ampicillin exposure (Cmax (steady state)) in all Group 1 infants

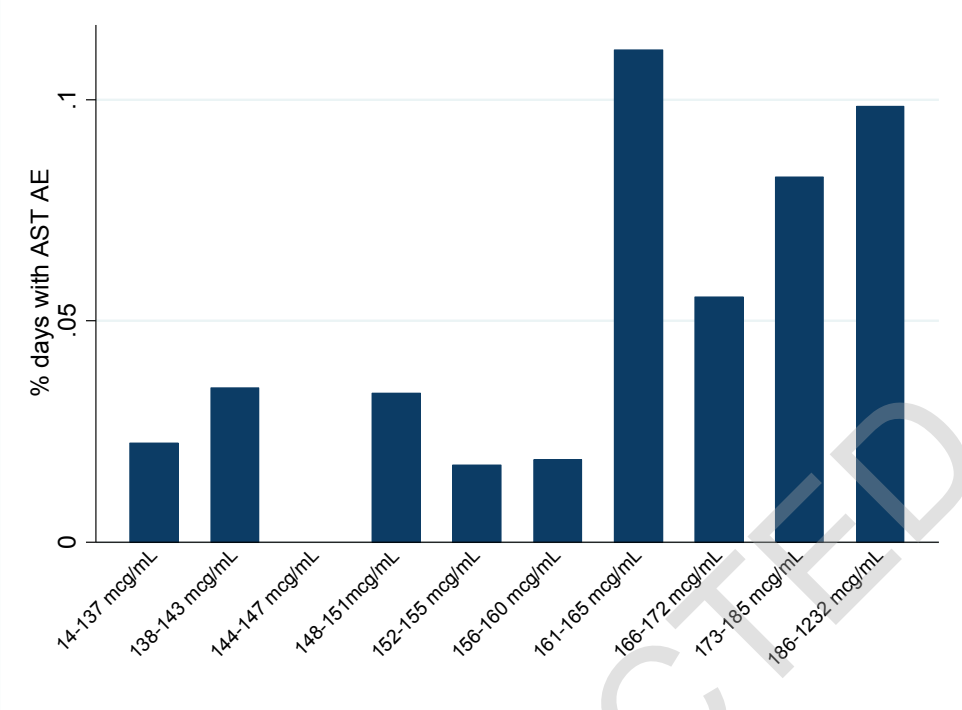
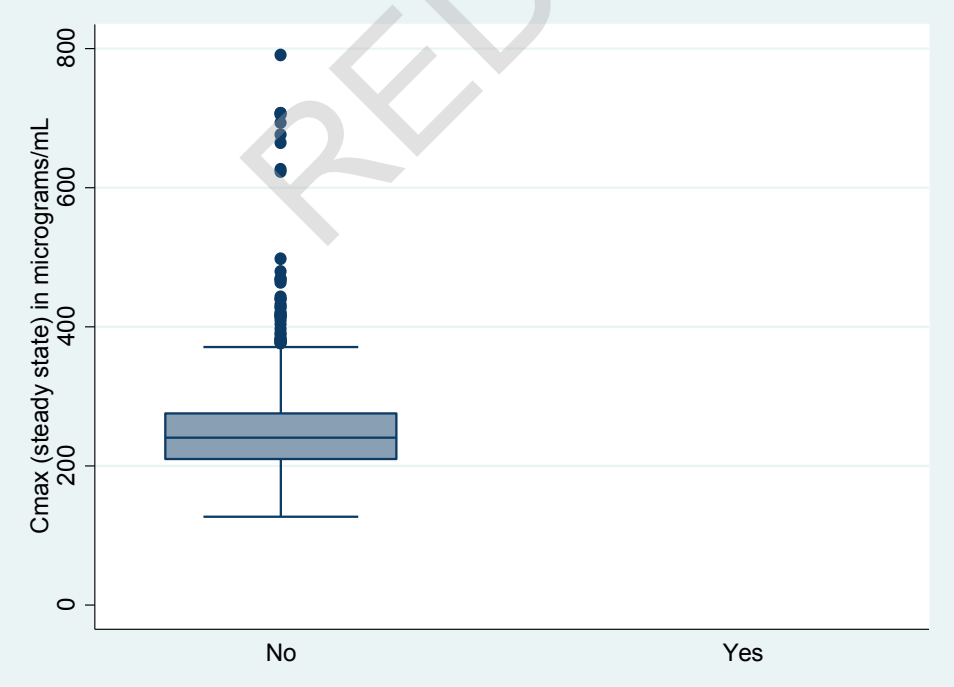
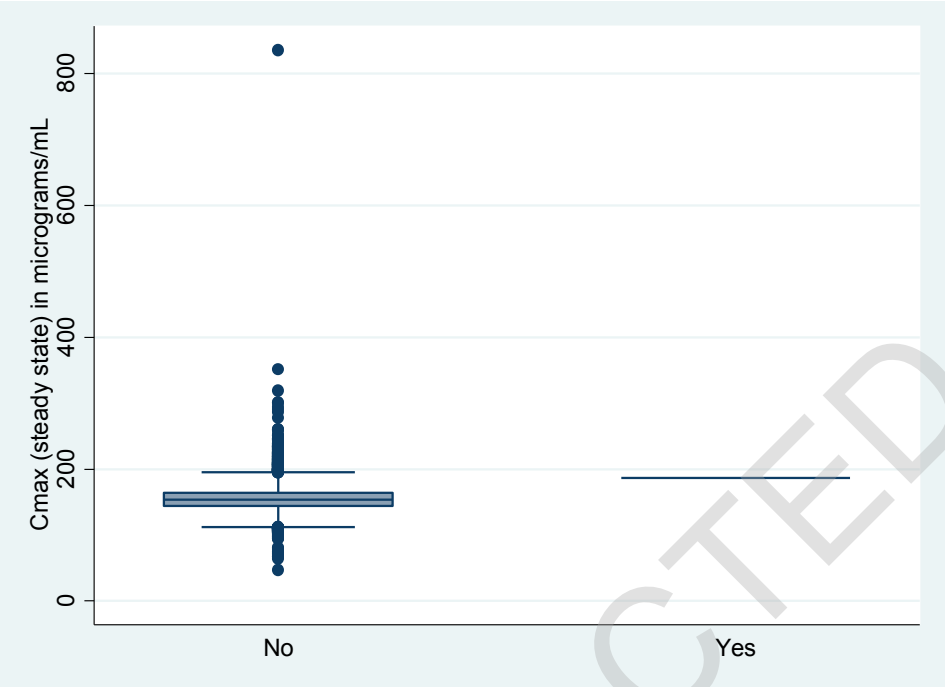


Figure 72. Cmax (steady state) concentration on days with and without AST elevation in all Group 2 infants



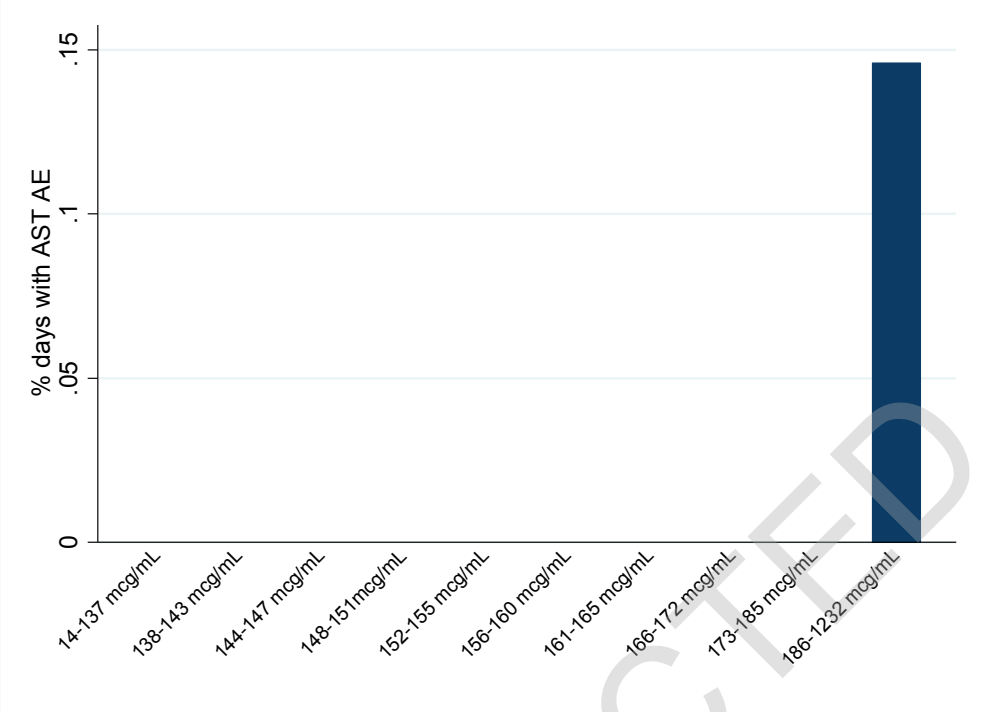
REDACTED

Figure 73. Cmax (steady state) concentration on days with and without AST elevation in all Group 3 infants



REDACTED

Figure 74. Percentage of infant days with AST elevation for each decile of ampicillin exposure (Cmax (steady state)) in all Group 3 infants



REDACTED

Severe AST Elevation

Figure 75. Cmax (steady state) concentration on days with and without severe AST elevation in all infants

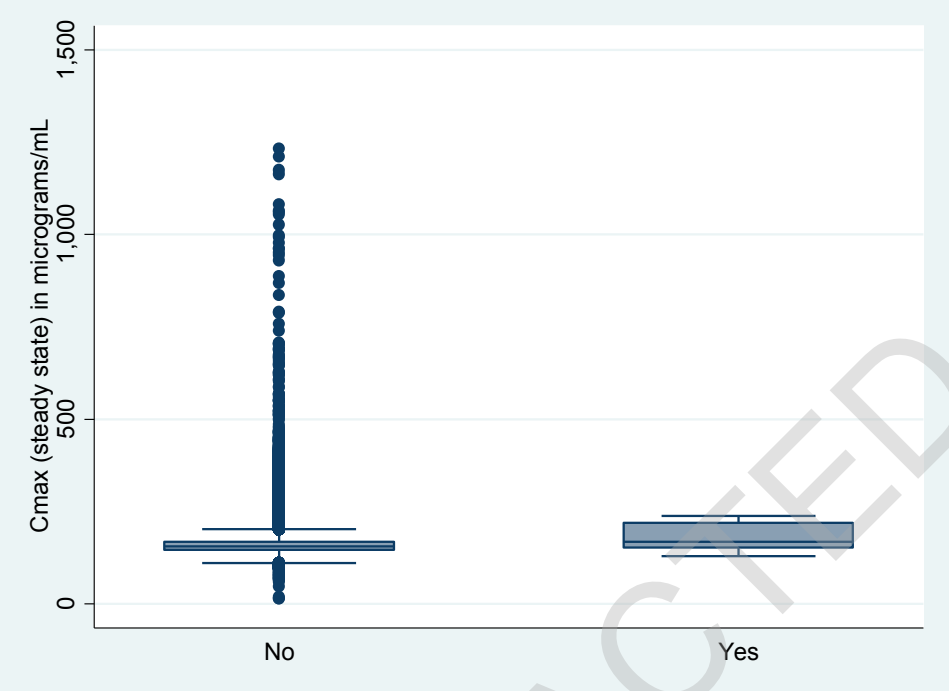
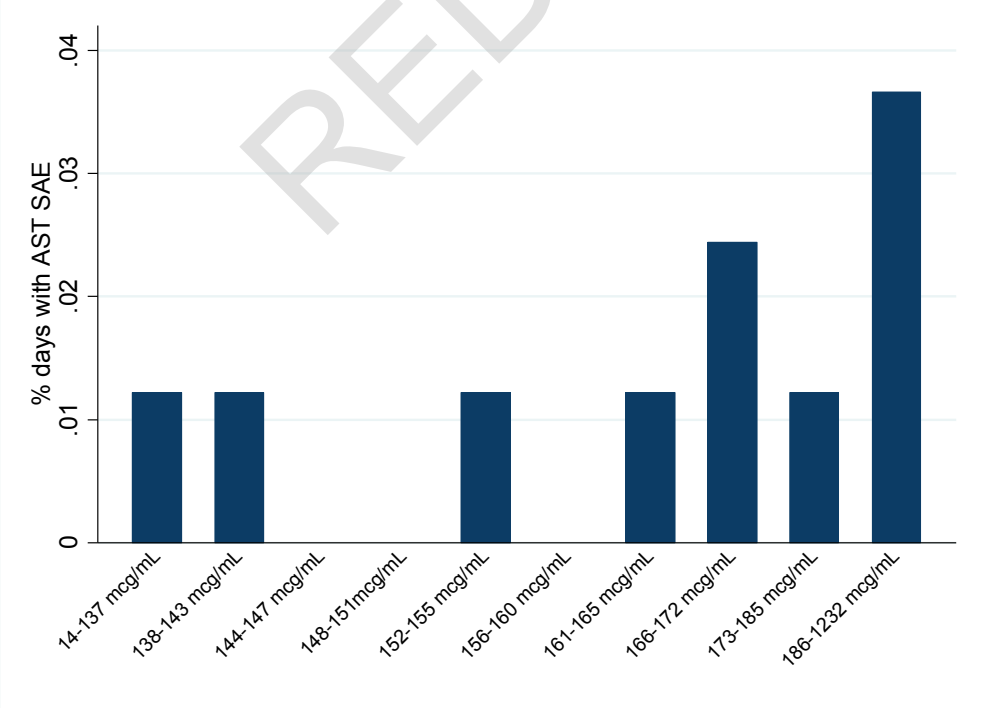
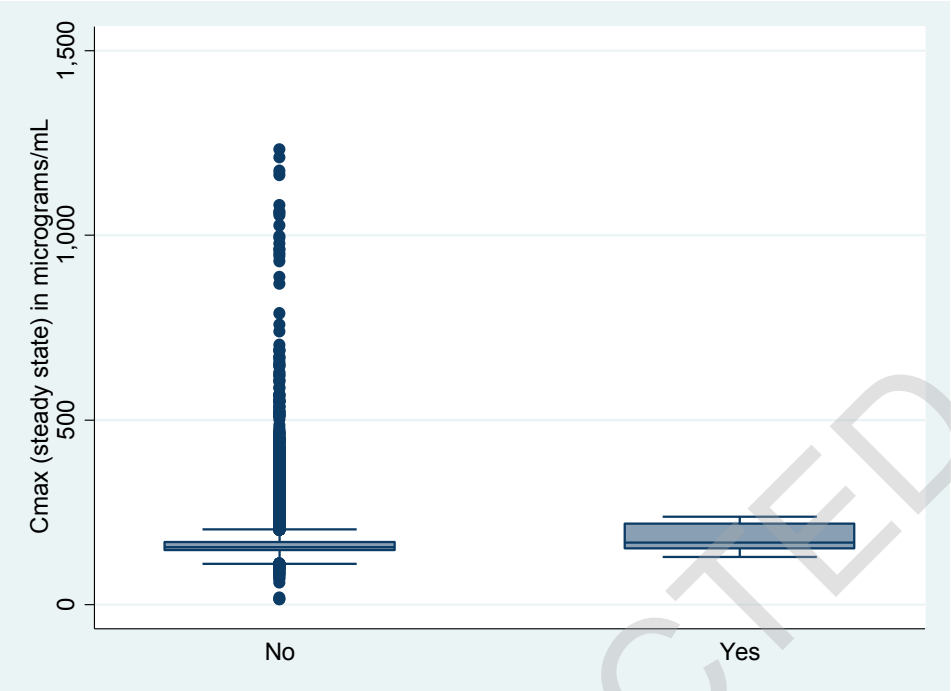


Figure 76. Percentage of infant days with severe AST elevation for each decile of ampicillin exposure (Cmax (steady state)) in all infants



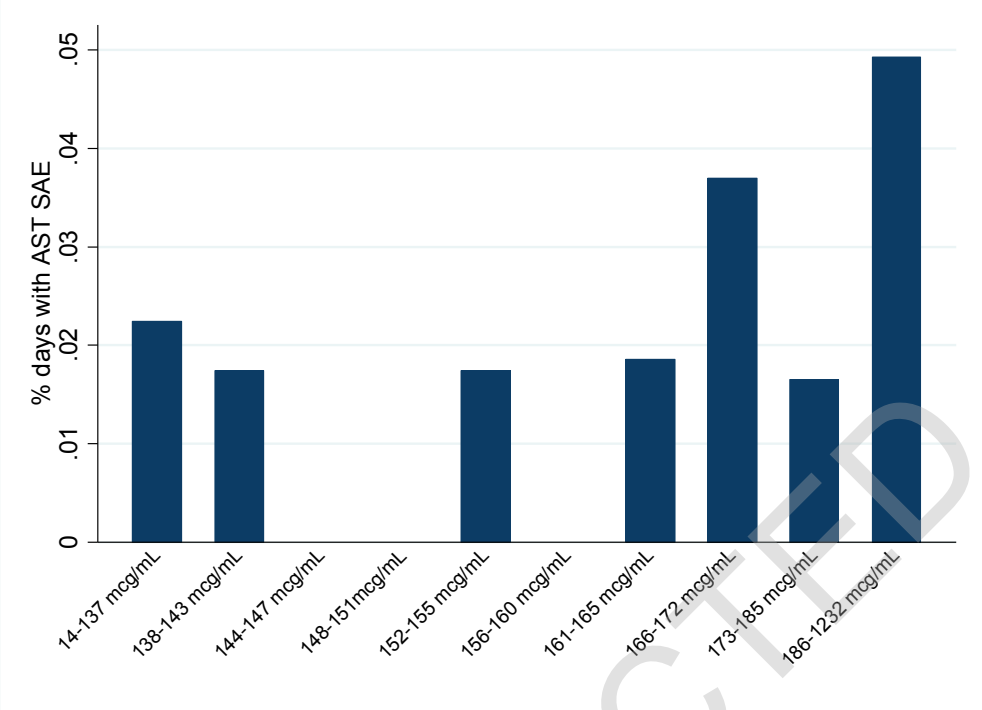
REDACTED

Figure 77. Cmax (steady state) concentration on days with and without severe AST elevation in all Group 1 infants



REDACTED

Figure 78. Percentage of infant days with severe AST elevation for each decile of ampicillin exposure (Cmax (steady state)) in all Group 1 infants



REDACTED

Figure 79. Cmax (steady state) concentration on days with and without severe AST elevation in all Group 2 infants

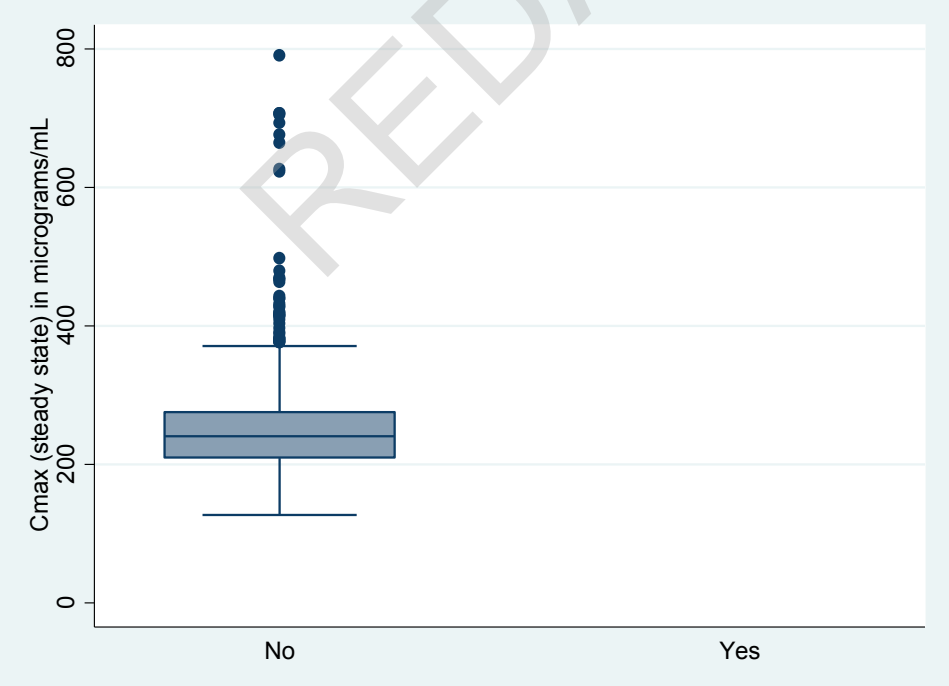
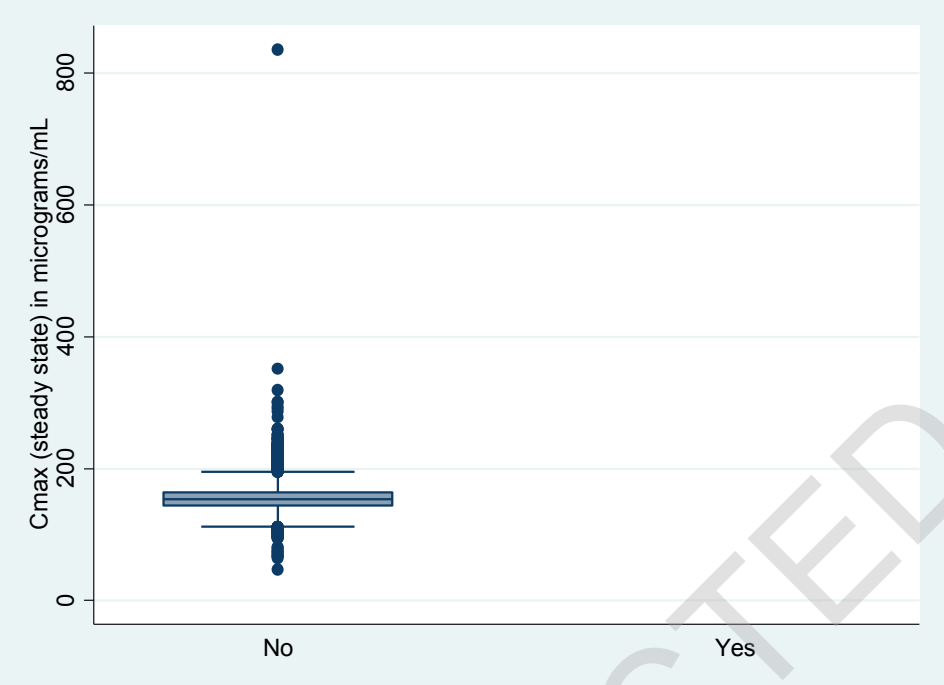
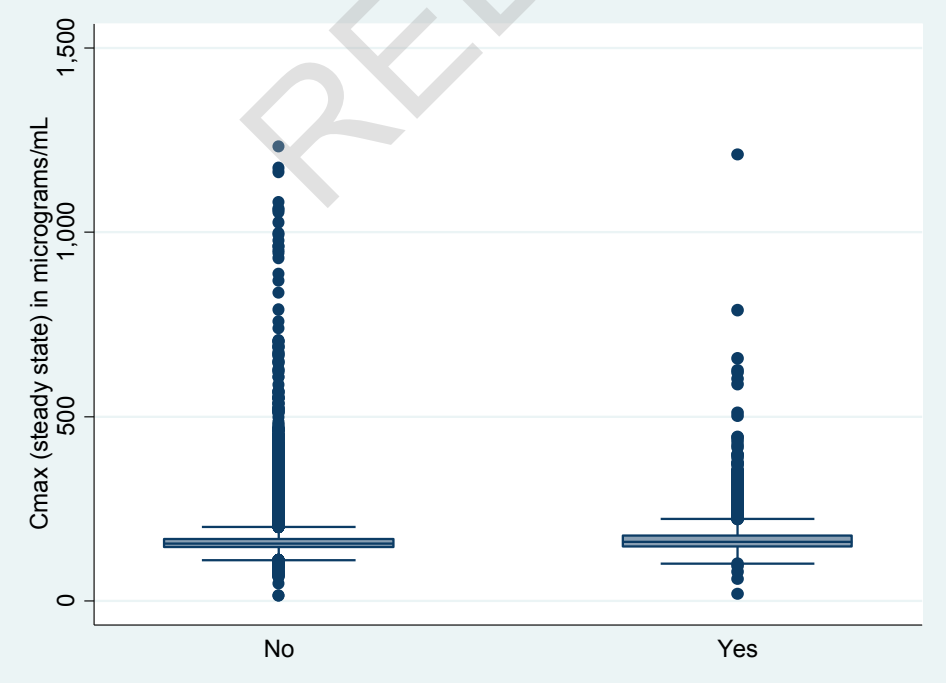


Figure 80. Cmax (steady state) concentration on days with and without severe AST elevation in all Group 3 infants



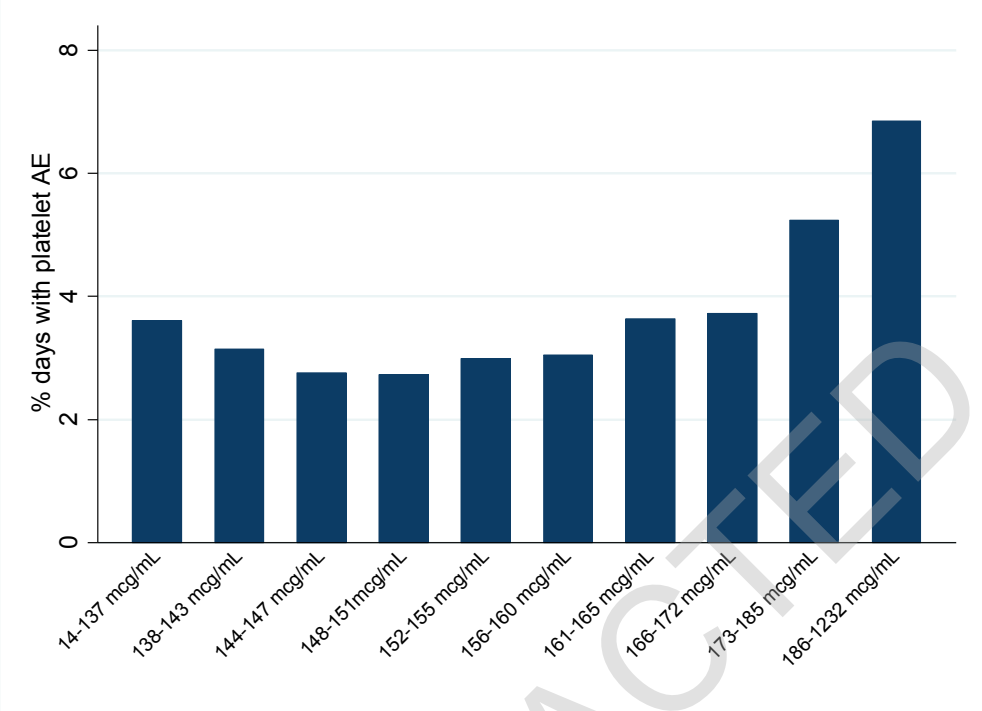
Thrombocytopenia

Figure 81. Cmax (steady state) concentration on days with and without thrombocytopenia in all infants



REDACTED

Figure 82. Percentage of infant days with thrombocytopenia for each decile of ampicillin exposure (Cmax (steady state)) in all infants



REDACTED

Figure 83. Cmax (steady state) concentration on days with and without thrombocytopenia all Group 1 infants

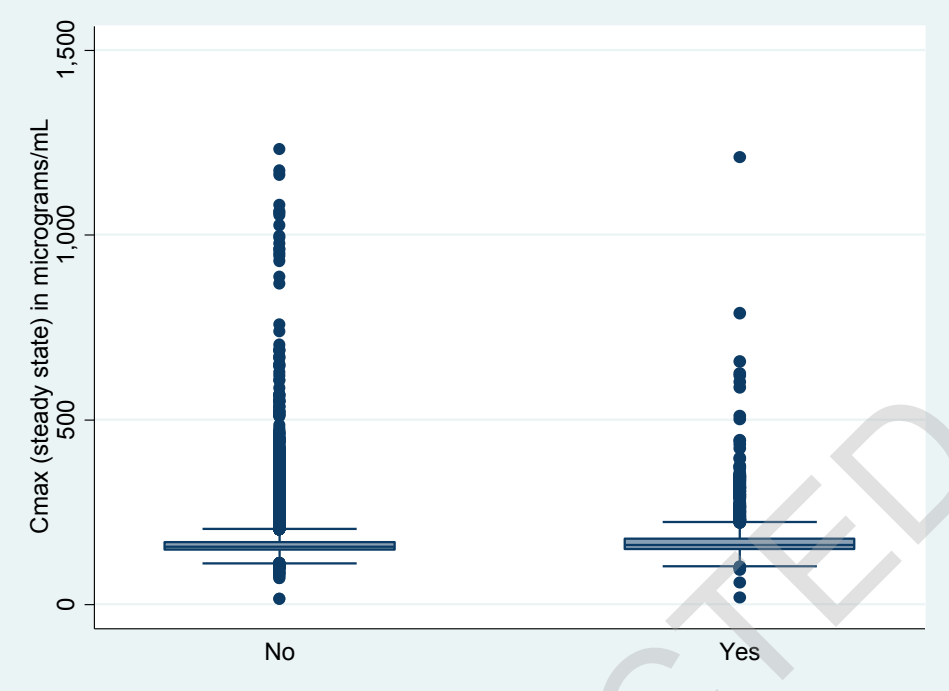
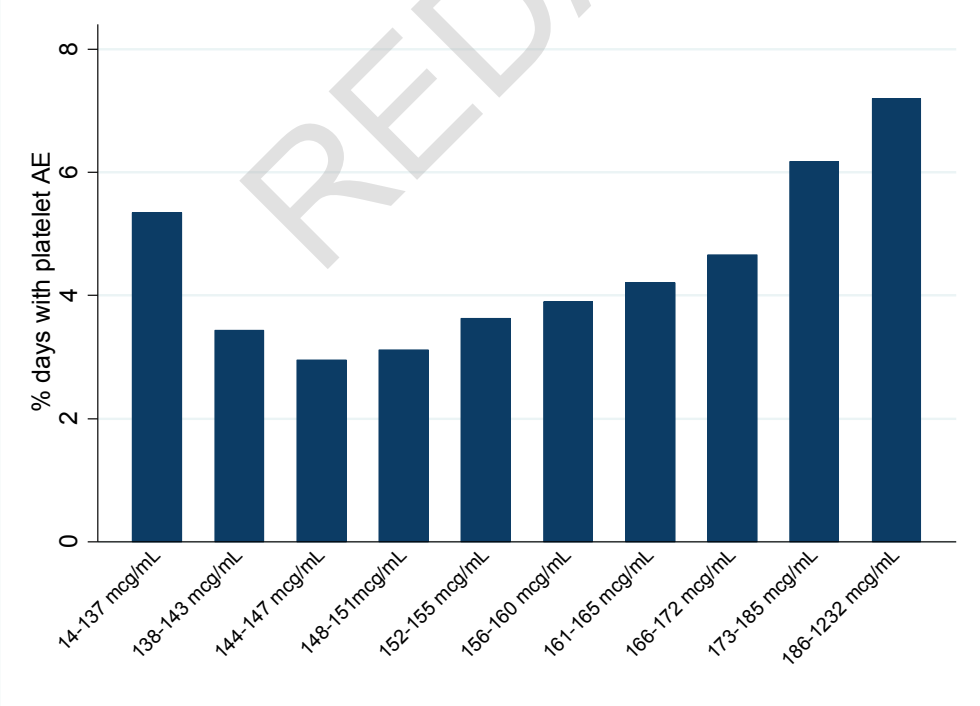
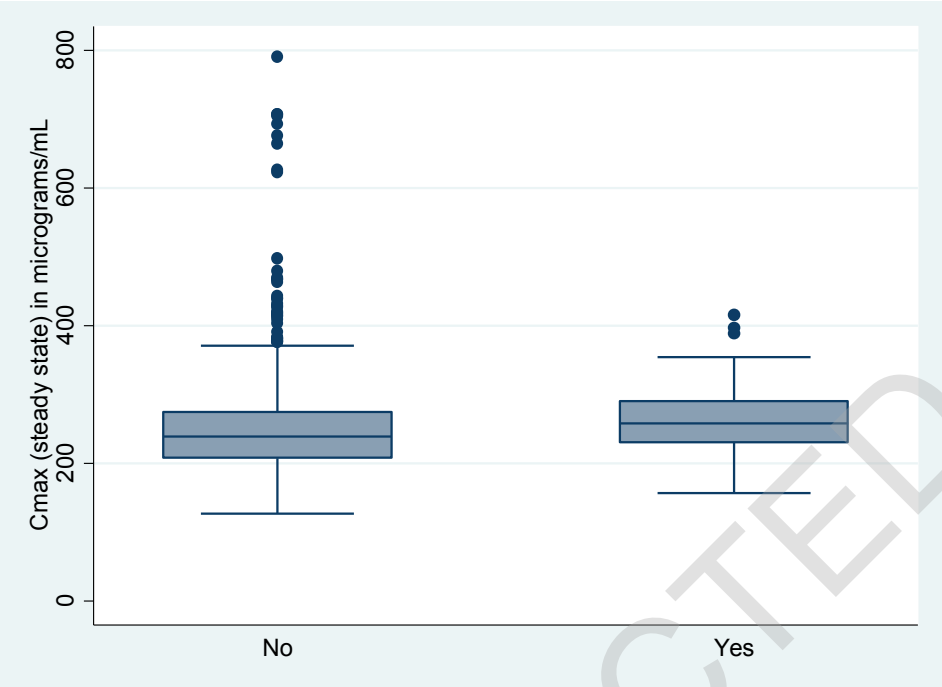


Figure 84. Percentage of infant days with thrombocytopenia for each decile of ampicillin exposure (Cmax (steady state)) in all Group 1 infants



REDACTED

Figure 85. Cmax (steady state) concentration on days with and without thrombocytopenia in all Group 2 infants



REDACTED

Figure 86. Percentage of infant days with thrombocytopenia for each decile of ampicillin exposure (Cmax (steady state)) in all Group 2 infants

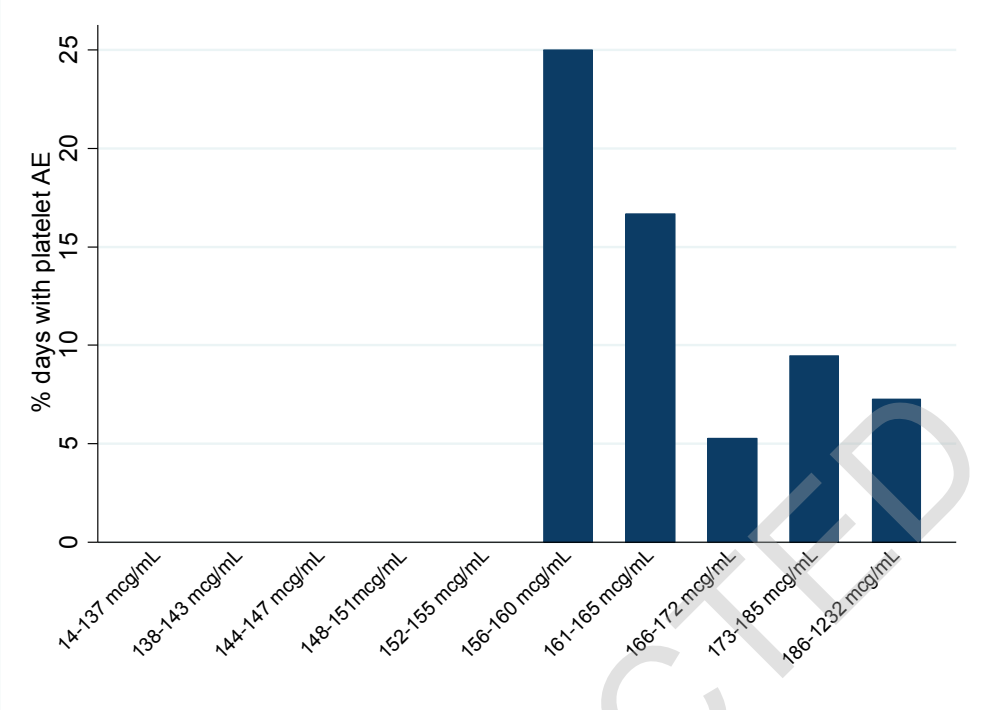
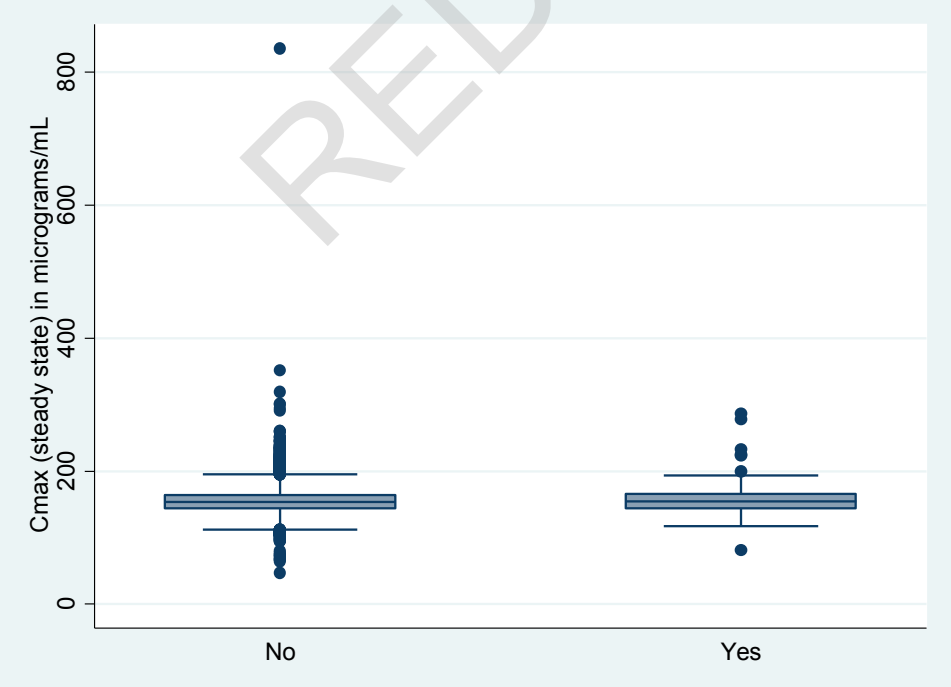
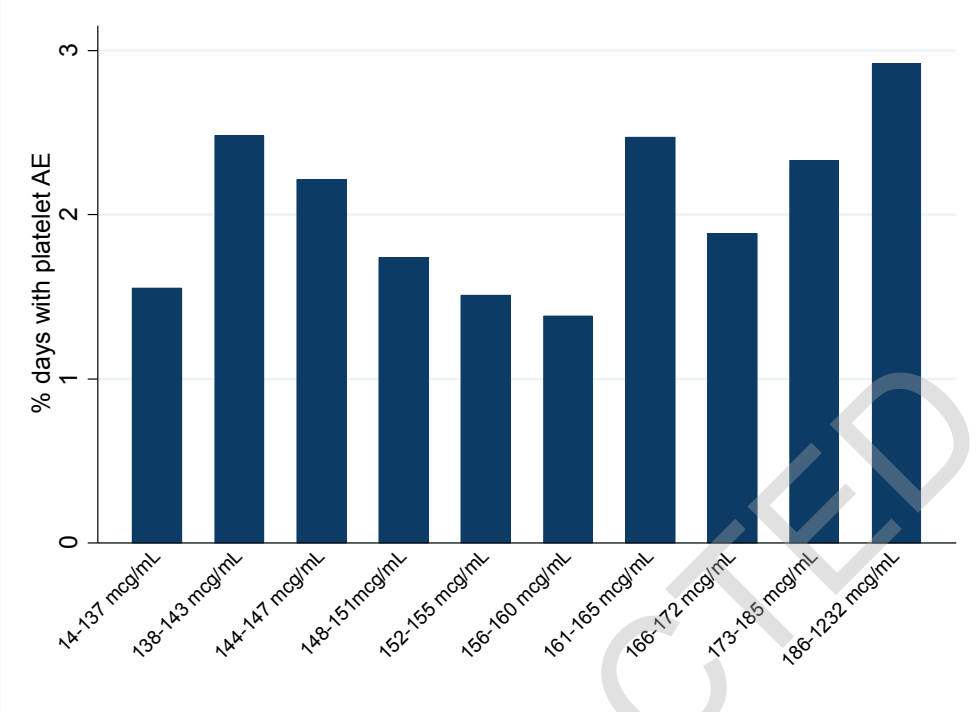


Figure 87. Cmax (steady state) concentration on days with and without thrombocytopenia in all Group 3 infants



REDACTED

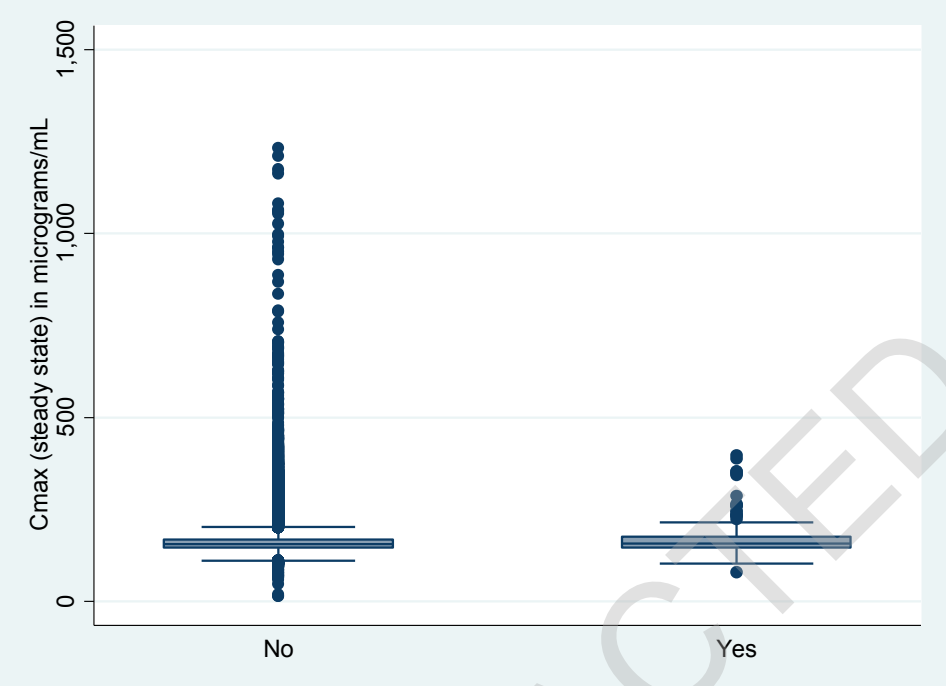
Figure 88. Percentage of infant days with thrombocytopenia for each decile of ampicillin exposure (Cmax (steady state)) in all Group 3 infants



REDACTED

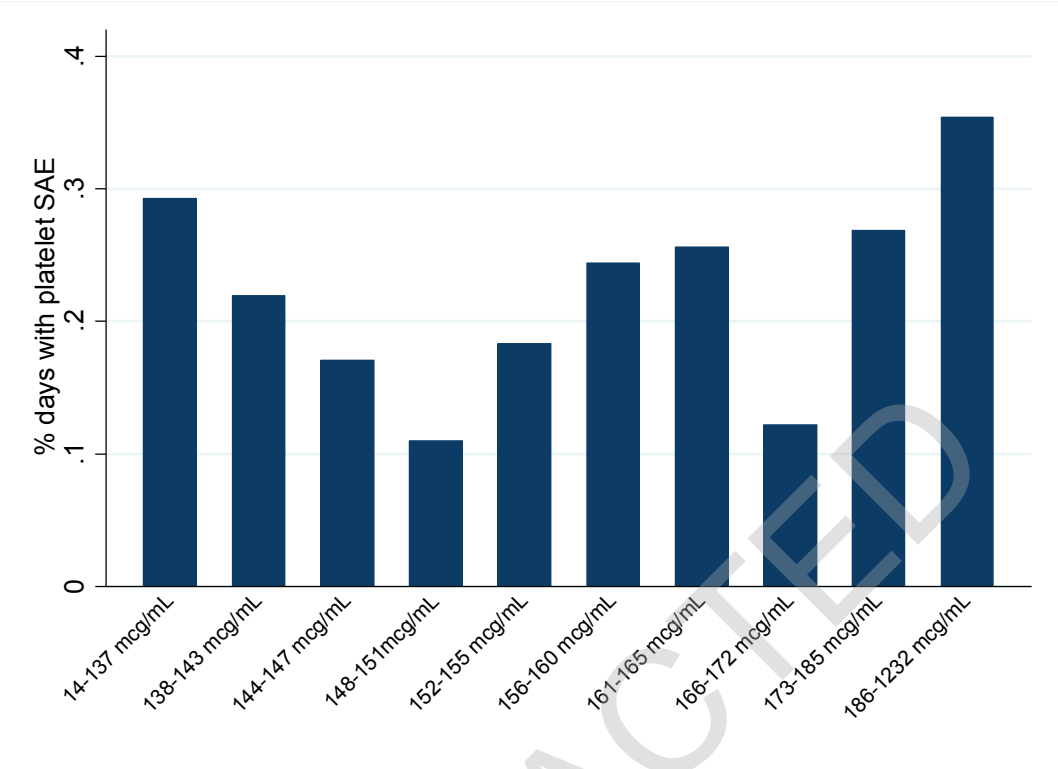
Severe Thrombocytopenia

Figure 89. Cmax (steady state) concentration on days with and without severe thrombocytopenia in all infants



REDACTED

Figure 90. Percentage of infant days with severe thrombocytopenia for each decile of ampicillin exposure (Cmax (steady state)) in all infants



REDACTED

Figure 91. Cmax (steady state) concentration on days with and without severe thrombocytopenia in all Group 1 infants

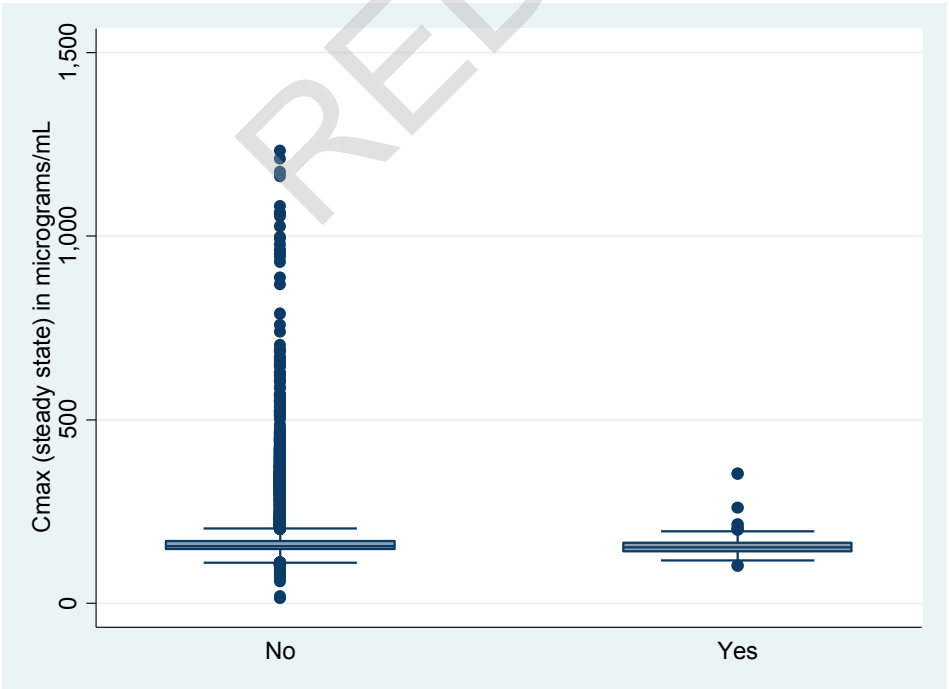


Figure 92. Percentage of infant days with severe thrombocytopenia for each decile of ampicillin exposure (Cmax (steady state)) in all Group 1 infants

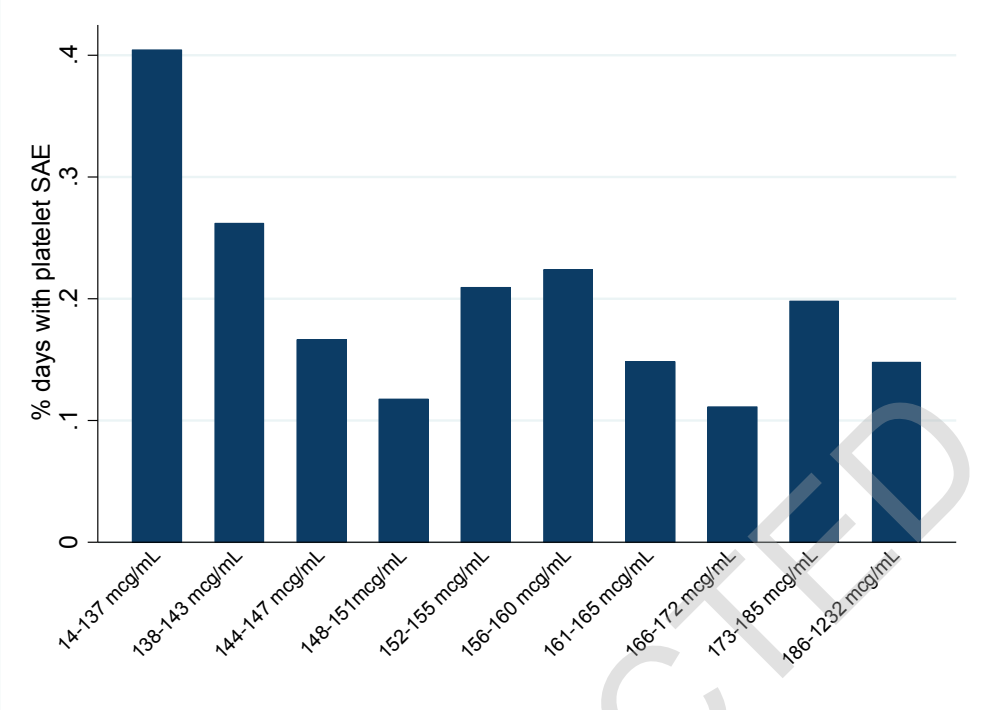
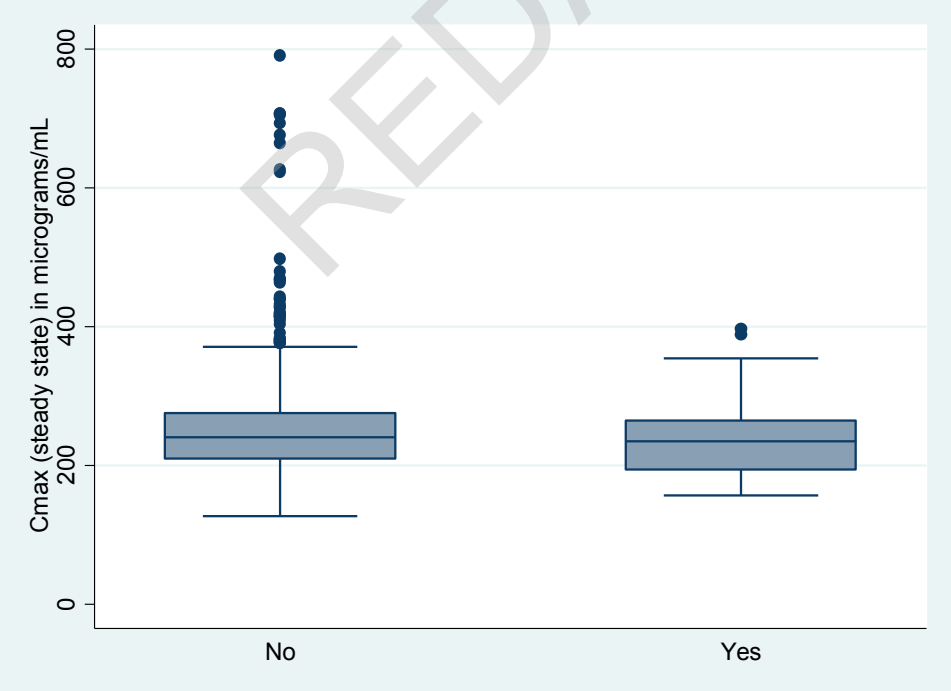


Figure 93. Cmax (steady state) concentration on days with and without severe thrombocytopenia in infants all Group 2 infants



REDACTED

Figure 94. Percentage of infant days with severe thrombocytopenia for each decile of ampicillin exposure (Cmax (steady state)) in all Group 2 infants

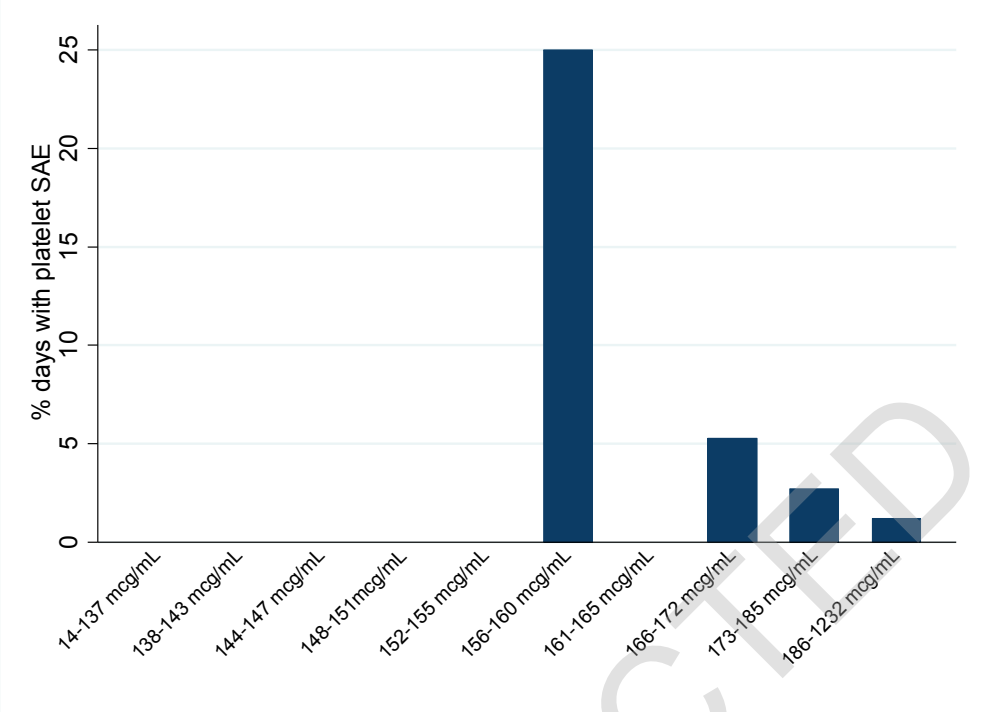


Figure 95. Cmax (steady state) concentration on days with and without severe thrombocytopenia in all Group 3 infants

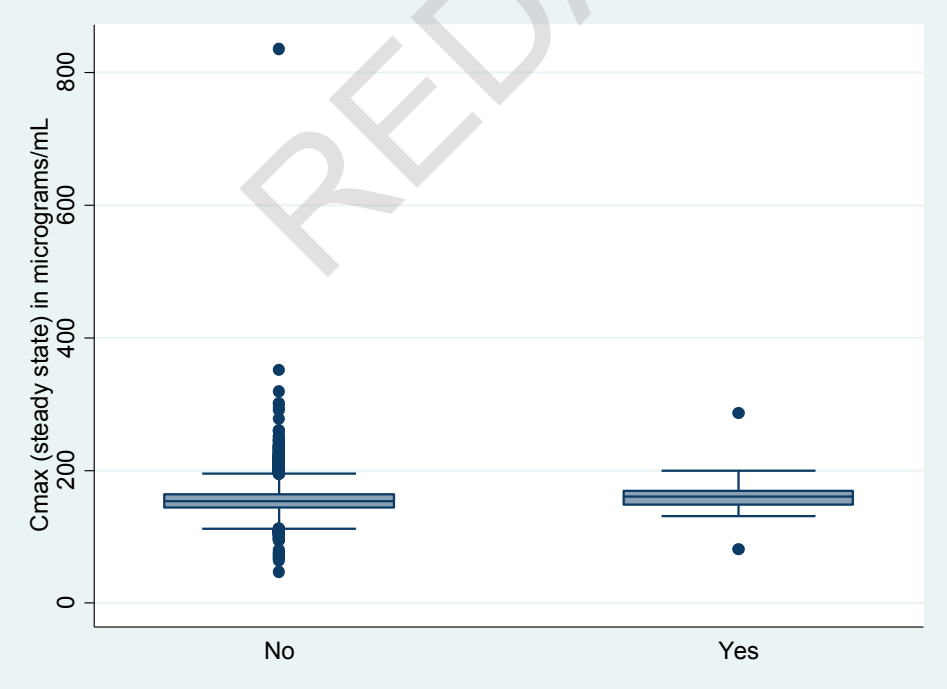


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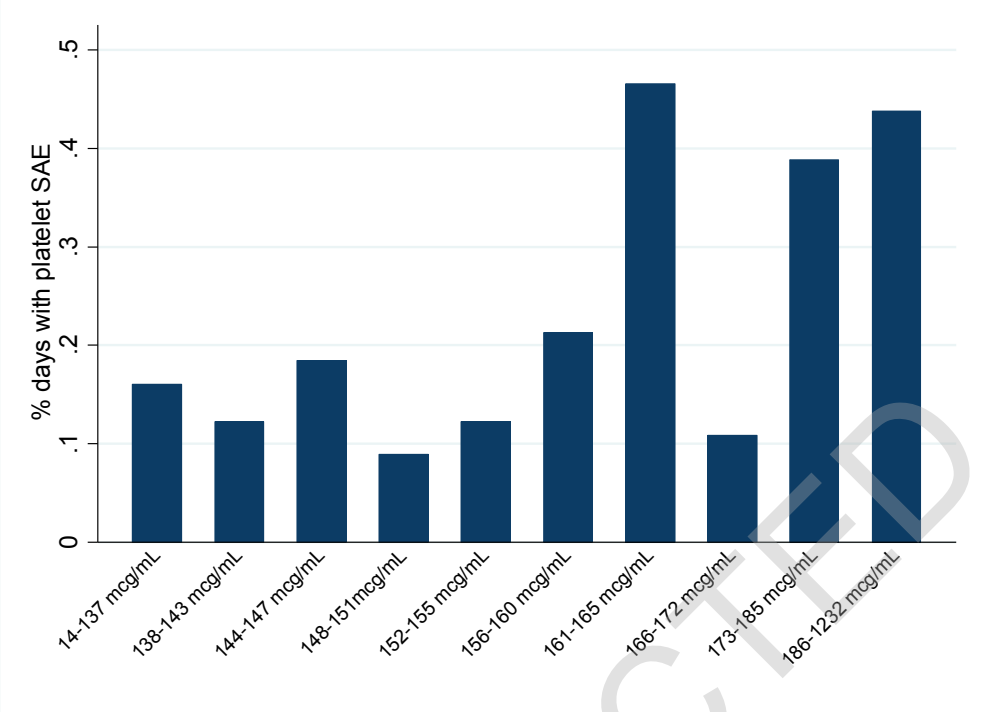
Figure 96. Percentage of infant days with severe thrombocytopenia for each decile of ampicillin exposure (Cmax (steady state)) in all Group 3 infants



Leukopenia

Leukopenia and severe leukopenia occurred more frequently with higher ampicillin exposures overall and for infants in Group 1. This relationship was less clear for infants of higher gestational and postnatal ages.

REDACTED

Figure 97. Cmax (steady state) concentration on days with and without leukopenia in all infants

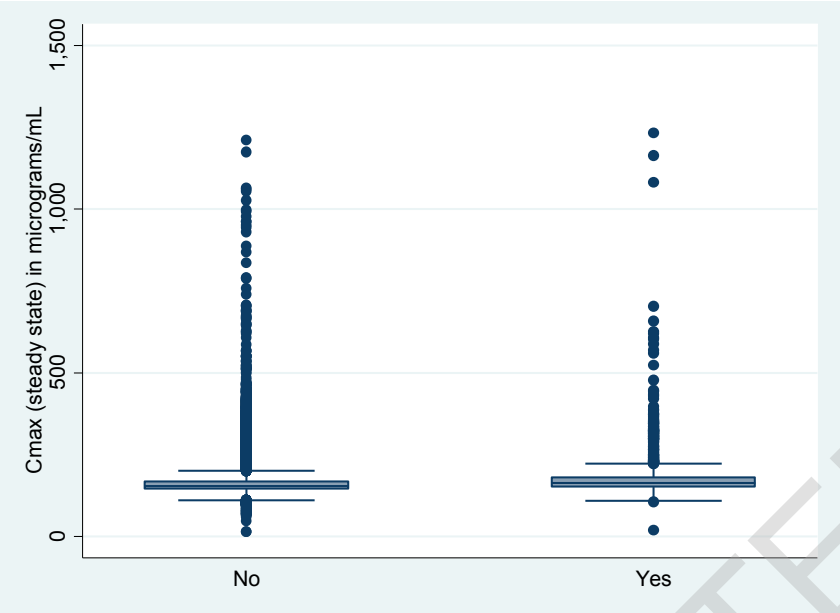
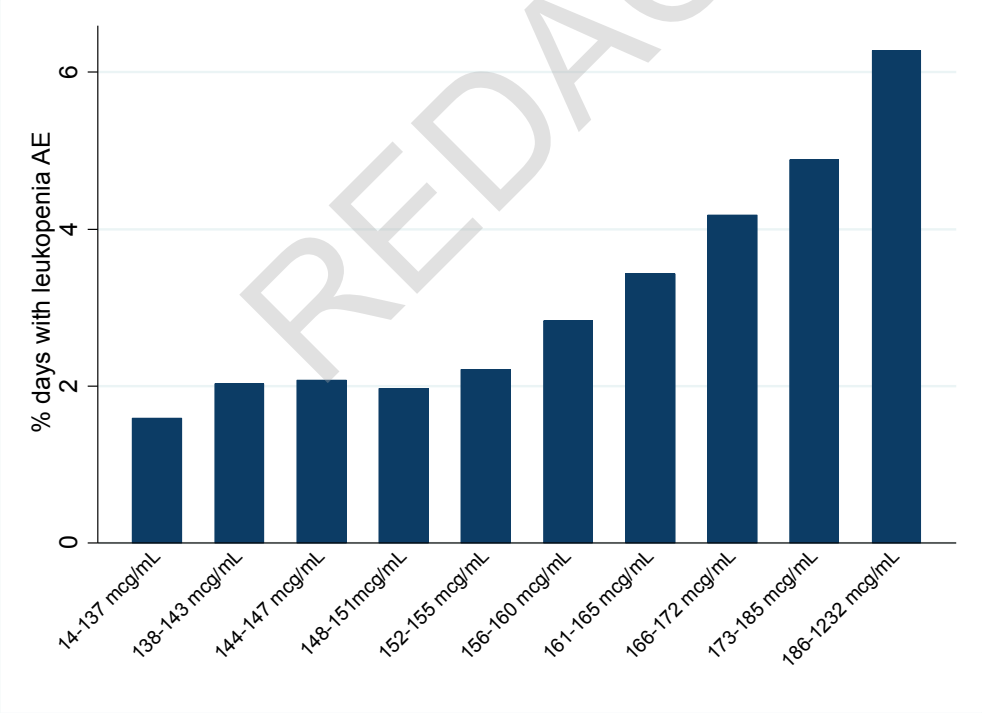


Figure 98. Percentage of infant days with leukopenia for each decile of ampicillin exposure (Cmax (steady state)) in all infants



REDACTED

Figure 99. Cmax (steady state) concentration on days with and without leukopenia in all Group 1 infants

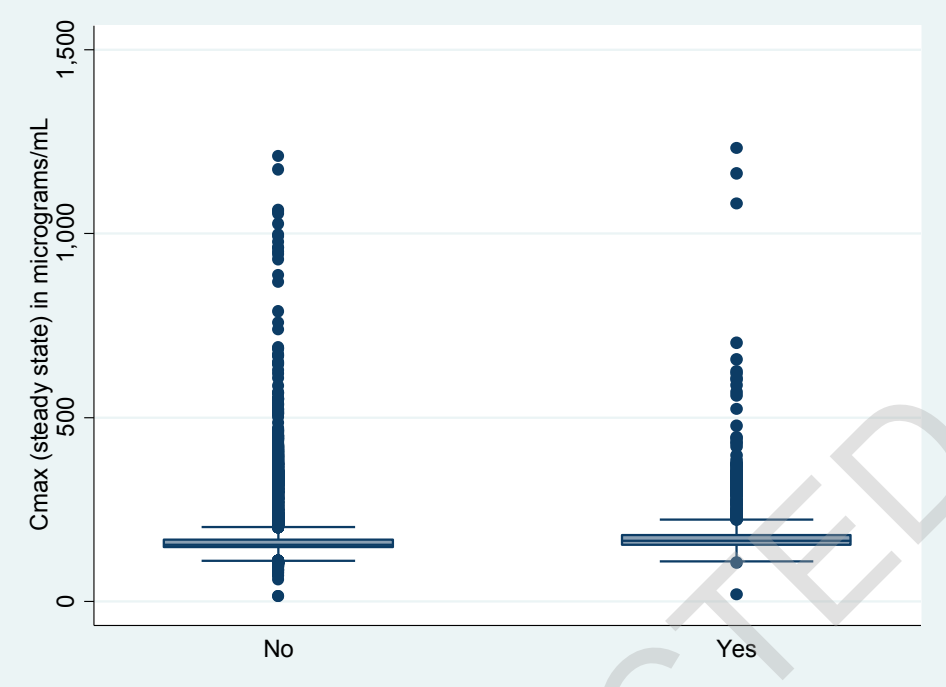
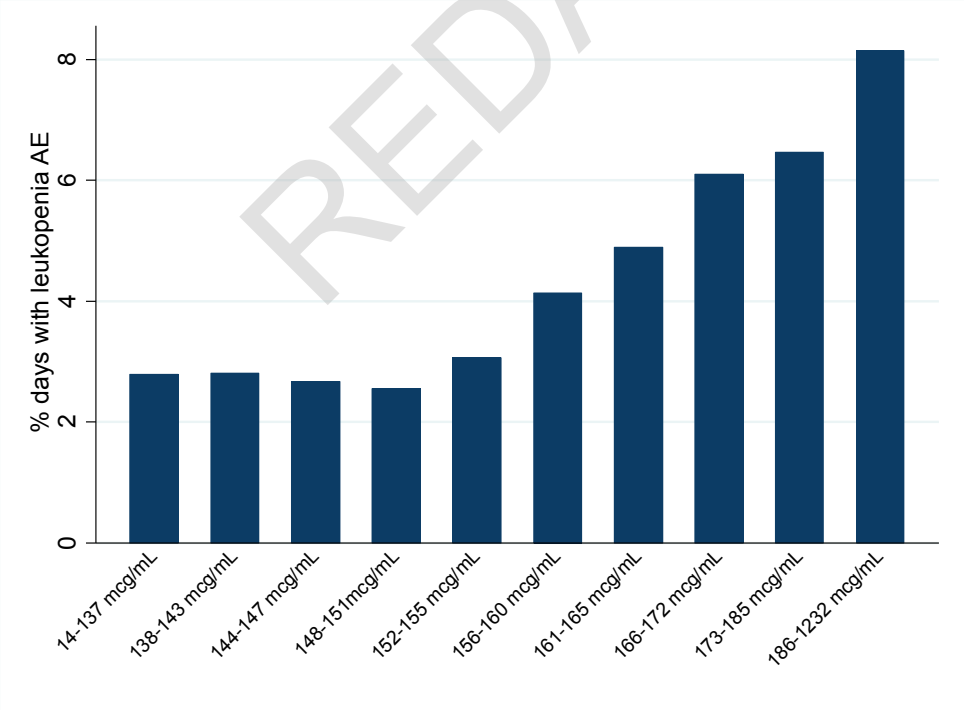


Figure 100. Percentage of infant days with leukopenia for each decile of ampicillin exposure (Cmax (steady state)) in all Group 1 infants



REDACTED

Figure 101. Cmax (steady state) concentration on days with and without leukopenia in all Group 2 infants

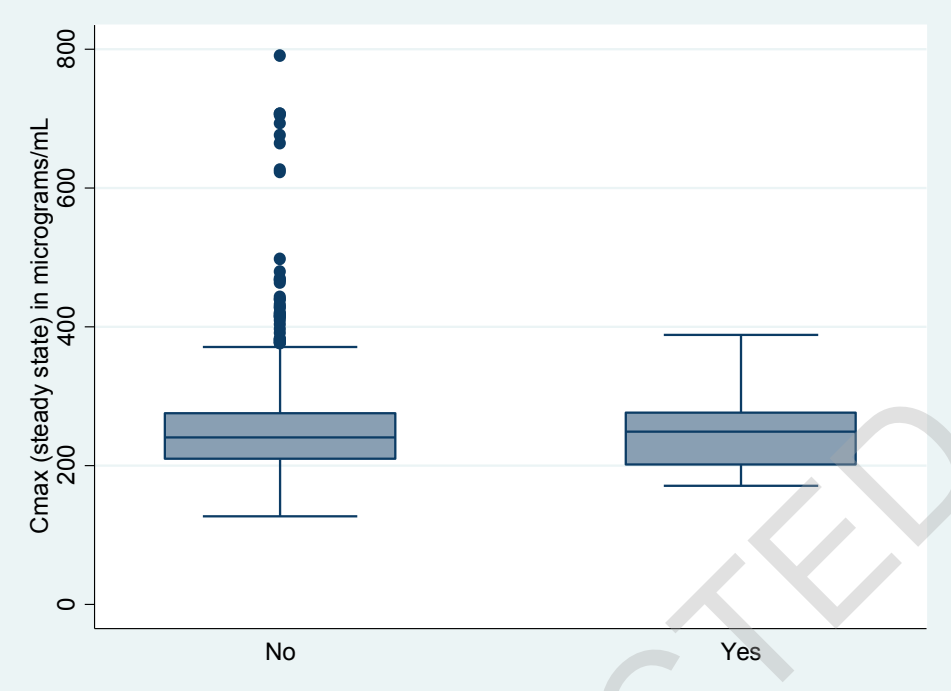
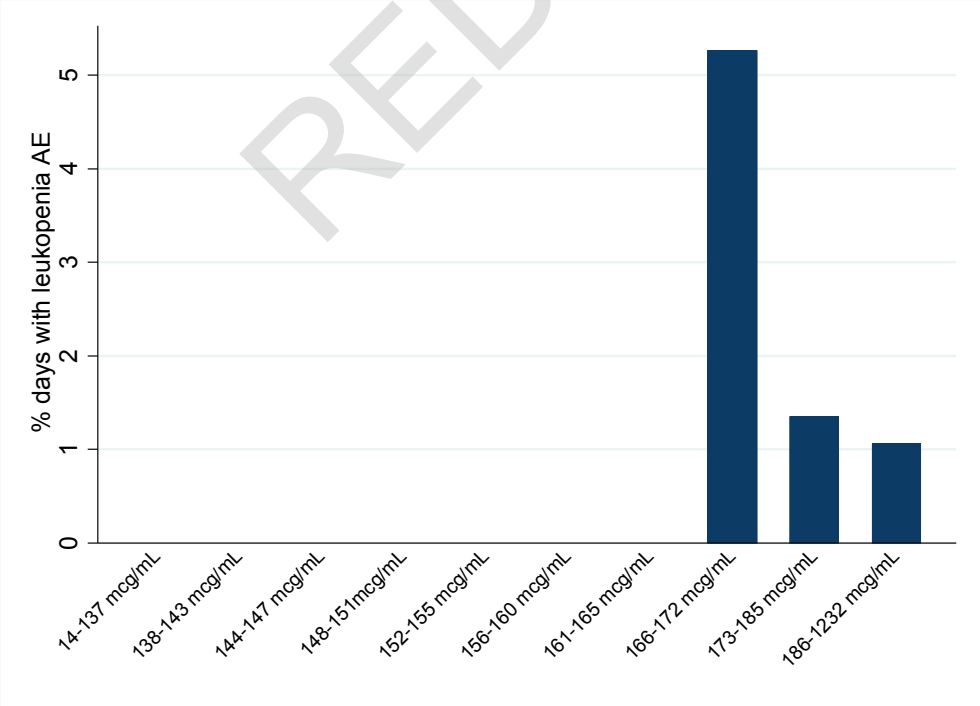
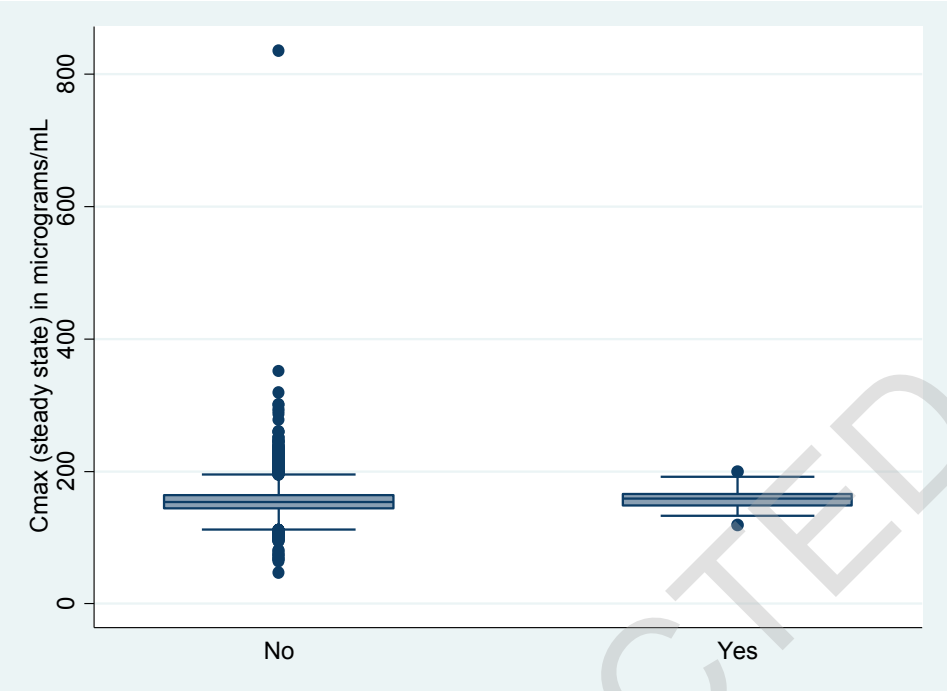


Figure 102. Percentage of infant days with leukopenia for each decile of ampicillin exposure (Cmax (steady state)) in all Group 2 infants



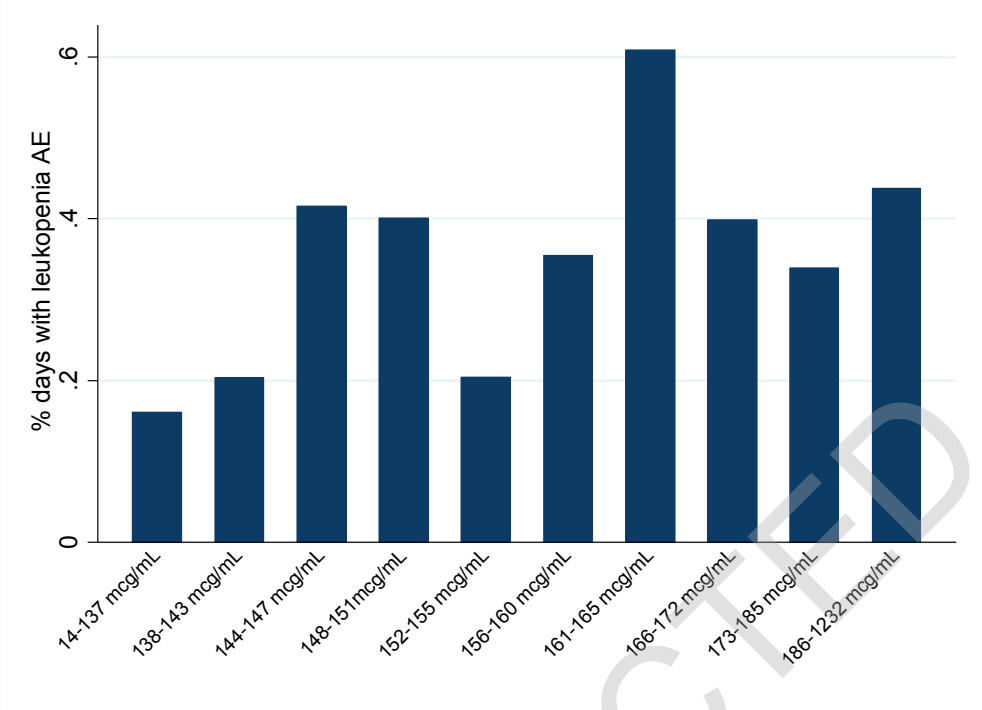
REDACTED

Figure 103. Cmax (steady state) concentration on days with and without leukopenia in all Group 3 infants



REDACTED

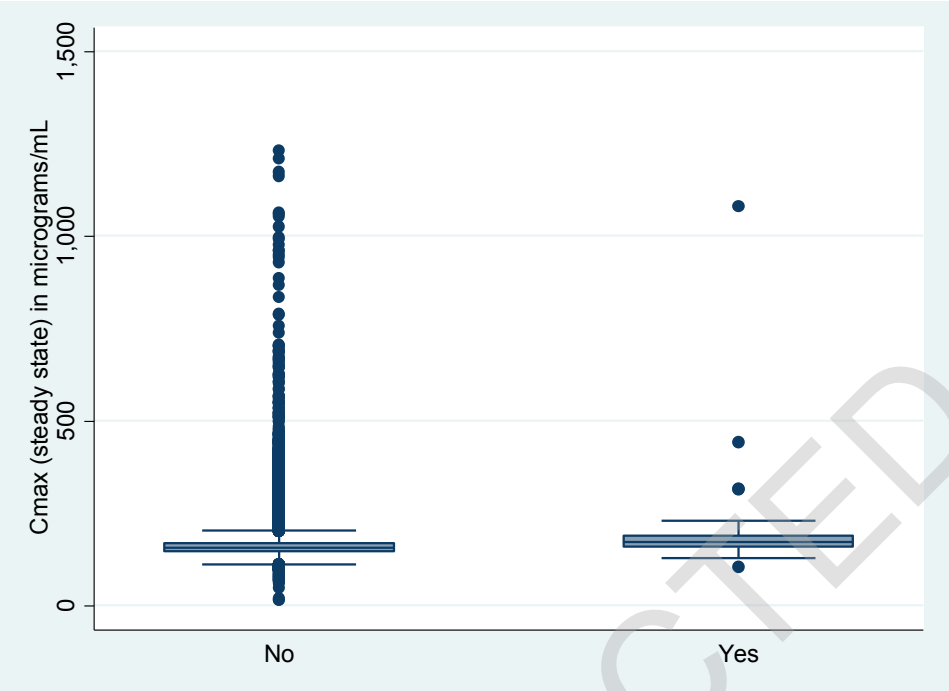
Figure 104. Percentage of infant days with leukopenia for each decile of ampicillin exposure (Cmax (steady state)) in all Group 3 infants



REDACTED

Severe Leukopenia

Figure 105. Cmax (steady state) concentration on days with and without severe leukopenia in all infants



REDACTED

Figure 106. Percentage of infant days with severe leukopenia for each decile of ampicillin exposure (Cmax (steady state)) in all infants

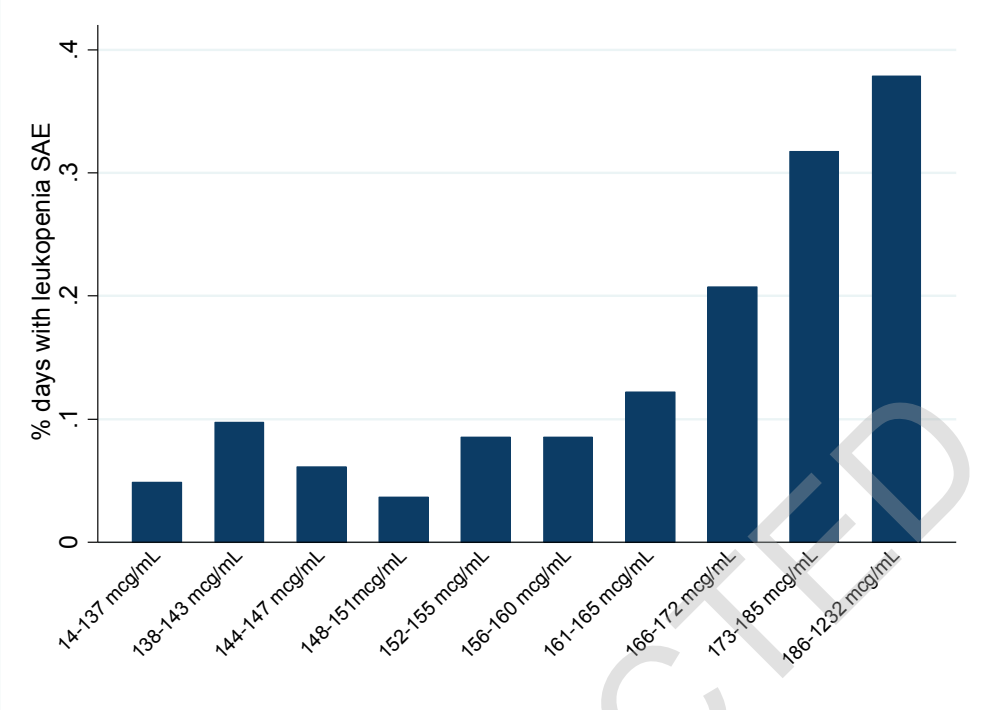
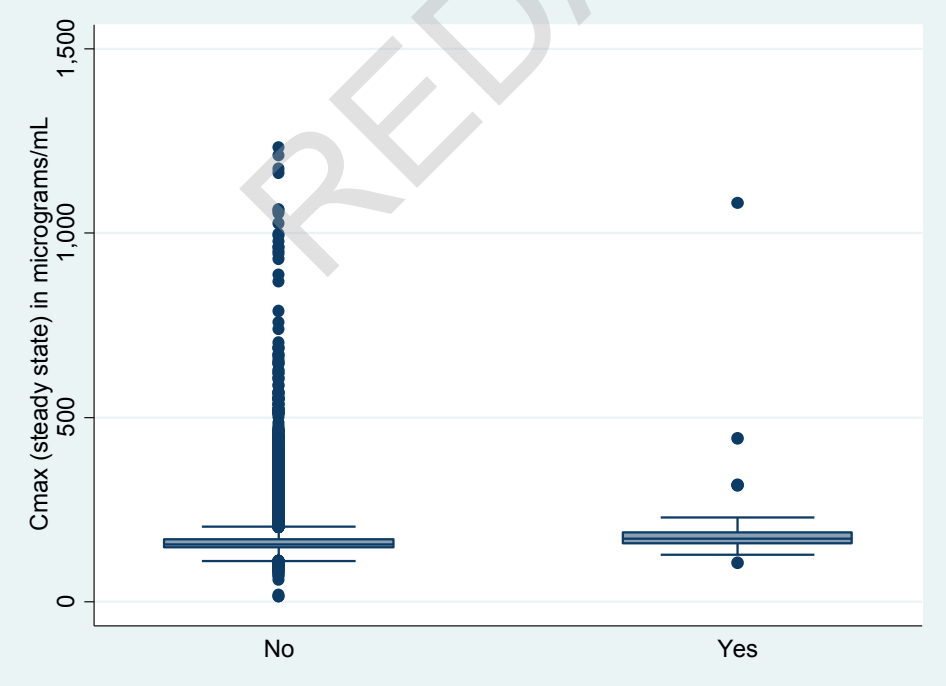


Figure 107. Cmax (steady state) concentration on days with and without severe leukopenia in all Group 1 infants



REDACTED

Figure 108. Percentage of infant days with severe leukopenia for each decile of ampicillin exposure (Cmax (steady state)) in all Group 1 infants

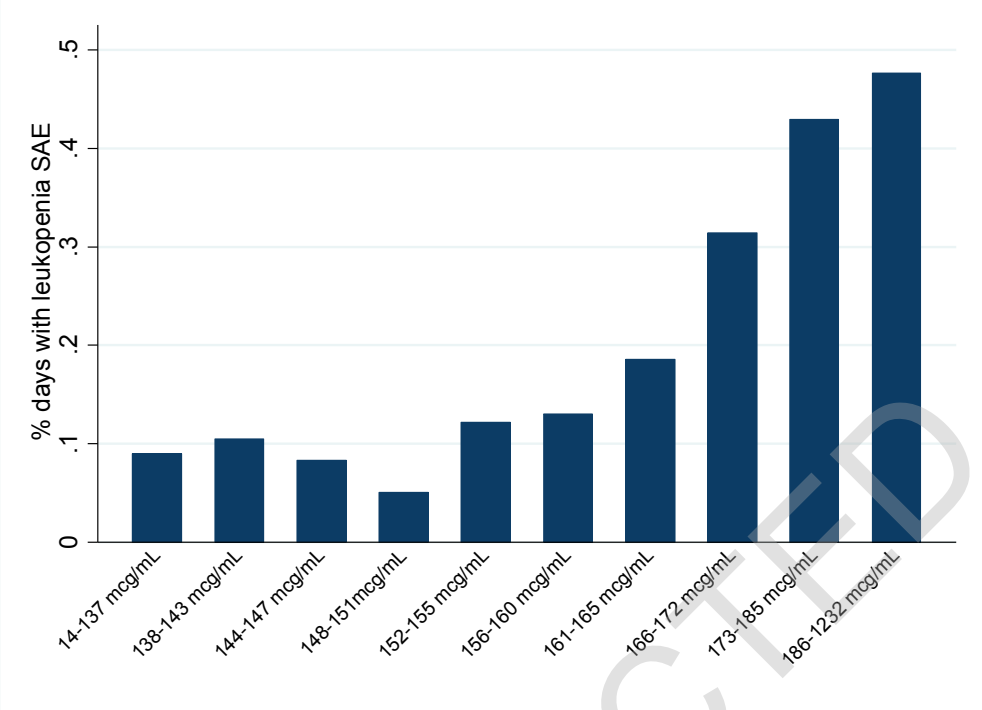
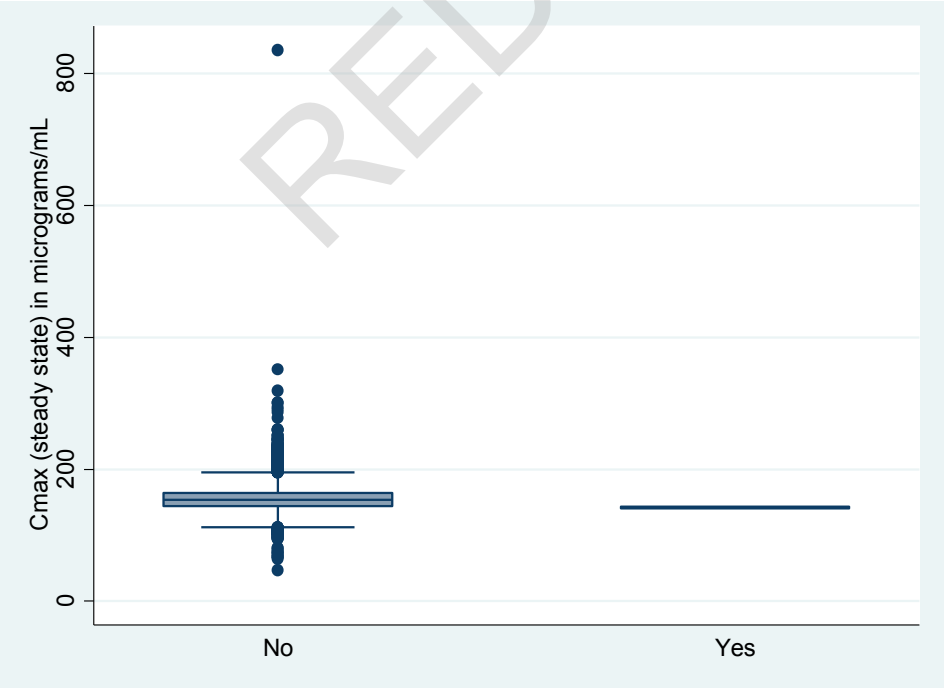


Figure 109. Cmax (steady state) concentration on days with and without severe leukopenia in all Group 2 infants



REDACTED

Figure 110. Percentage of infant days with severe leukopenia for each decile of ampicillin exposure (Cmax (steady state)) in Group 2 infants

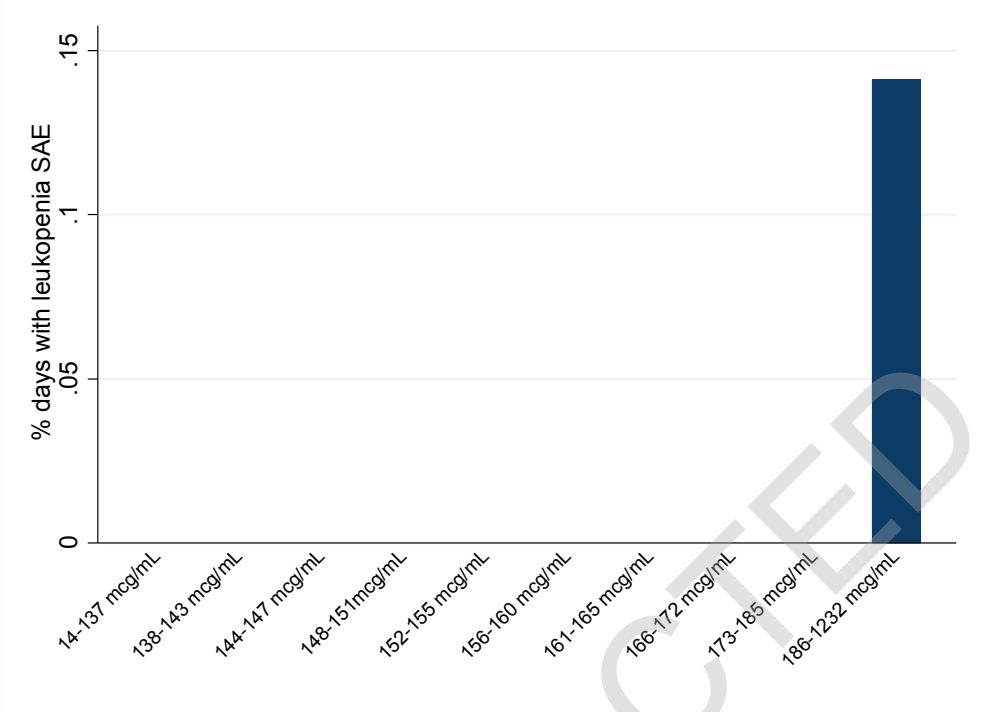
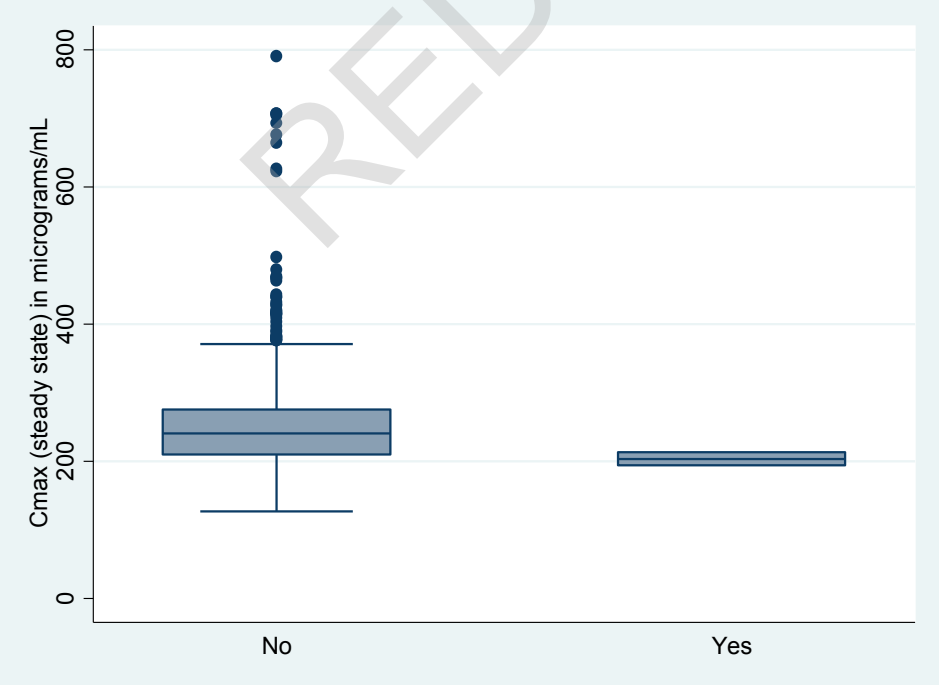
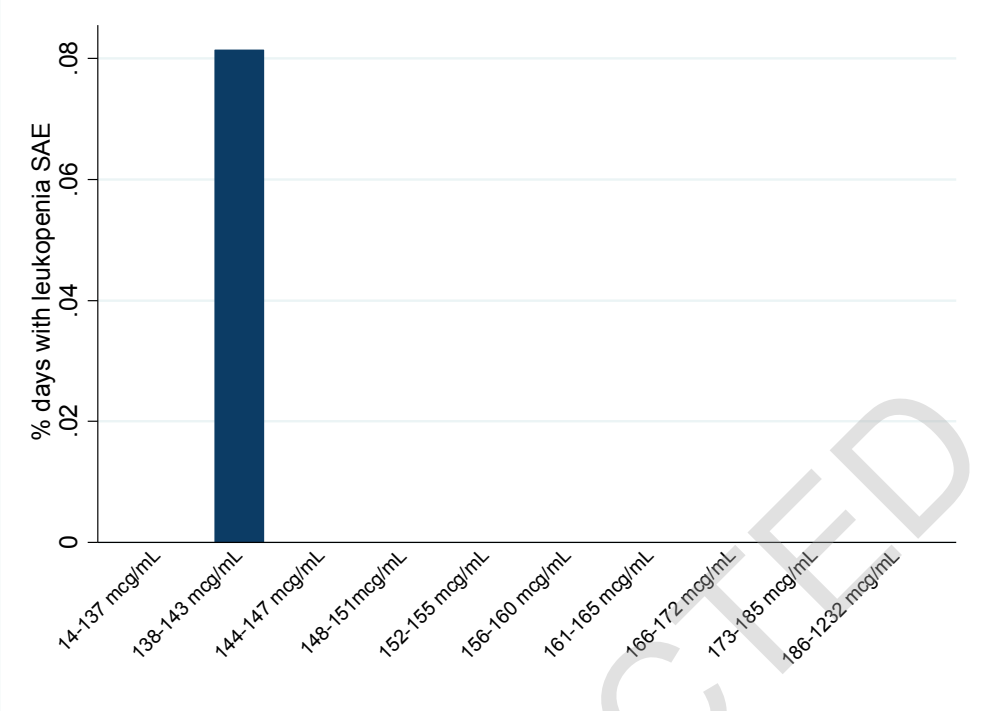


Figure 111. Cmax (steady state) concentration on days with and without severe leukopenia in all Group 3 infants



REDACTED

Figure 112. Percentage of infant days with severe leukopenia for each decile of ampicillin exposure (Cmax (steady state)) in infants Group 3 infants



REDACTED

Neutropenia

The relationship of leukopenia and severe leukopenia ampicillin exposure was unclear. A higher percentage of days with leukopenia in infants in Group 1 had higher ampicillin exposures. This was not seen in infants of higher gestational and postnatal ages or for severe neutropenia.

Figure 113. Cmax (steady state) concentration on days with and without neutropenia in all infants

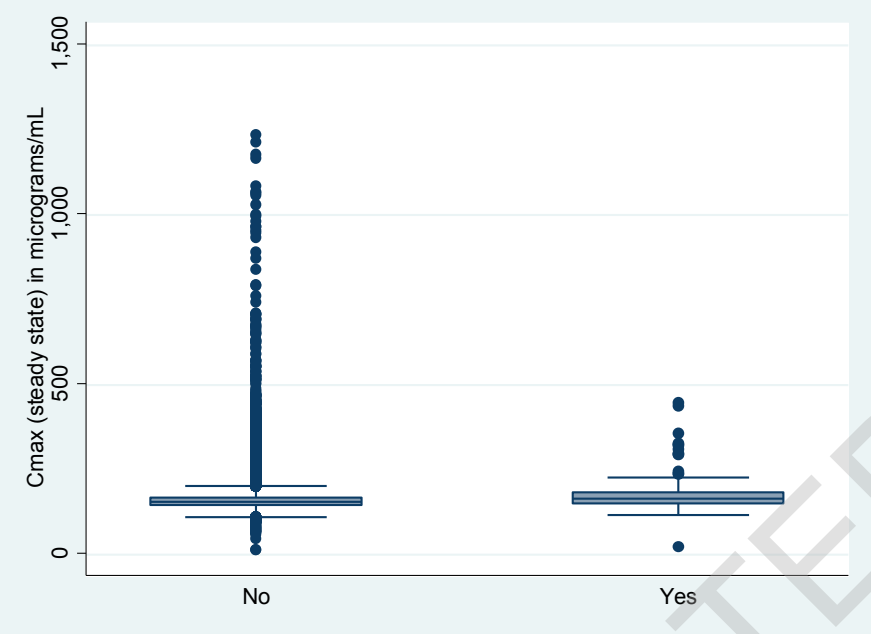
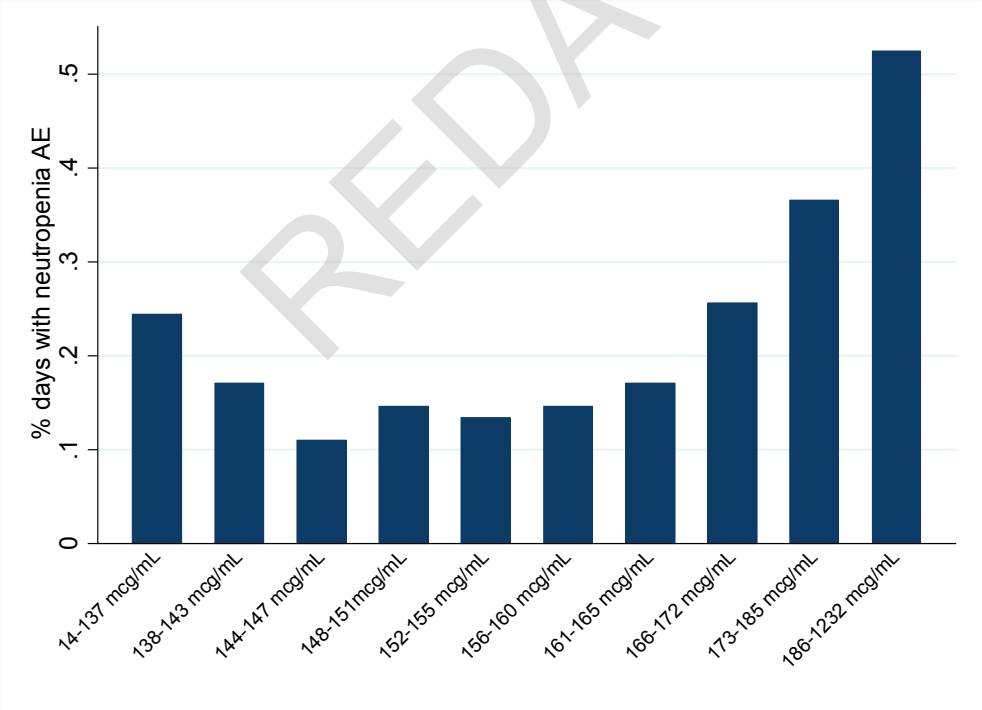


Figure 114. Percentage of infant days with neutropenia for each decile of ampicillin exposure (Cmax (steady state)) in all infants



REDACTED

Figure 115. Cmax (steady state) concentration on days with and without neutropenia in all Group 1 infants

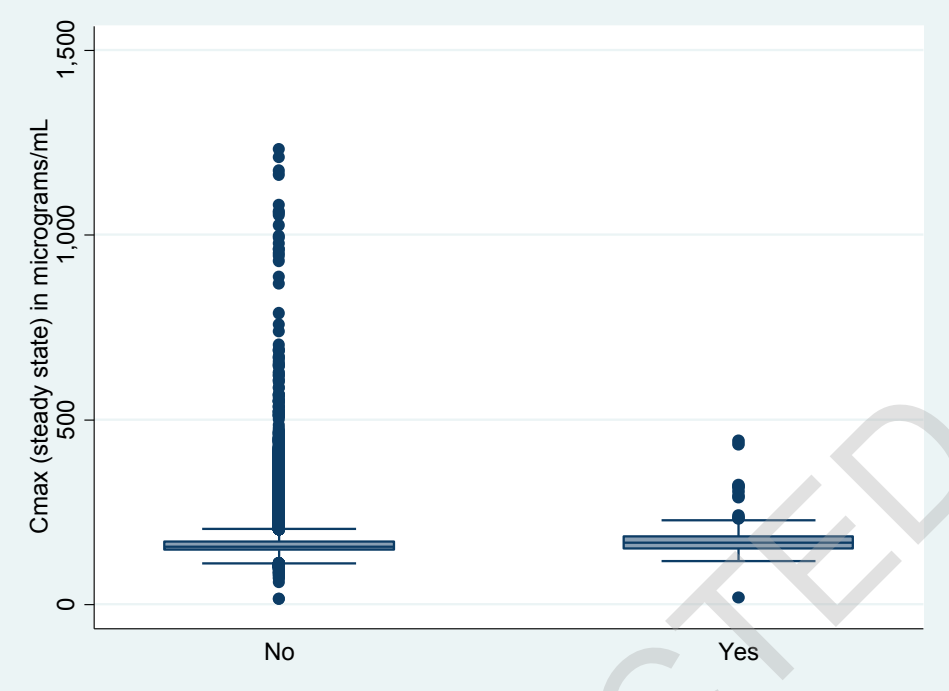
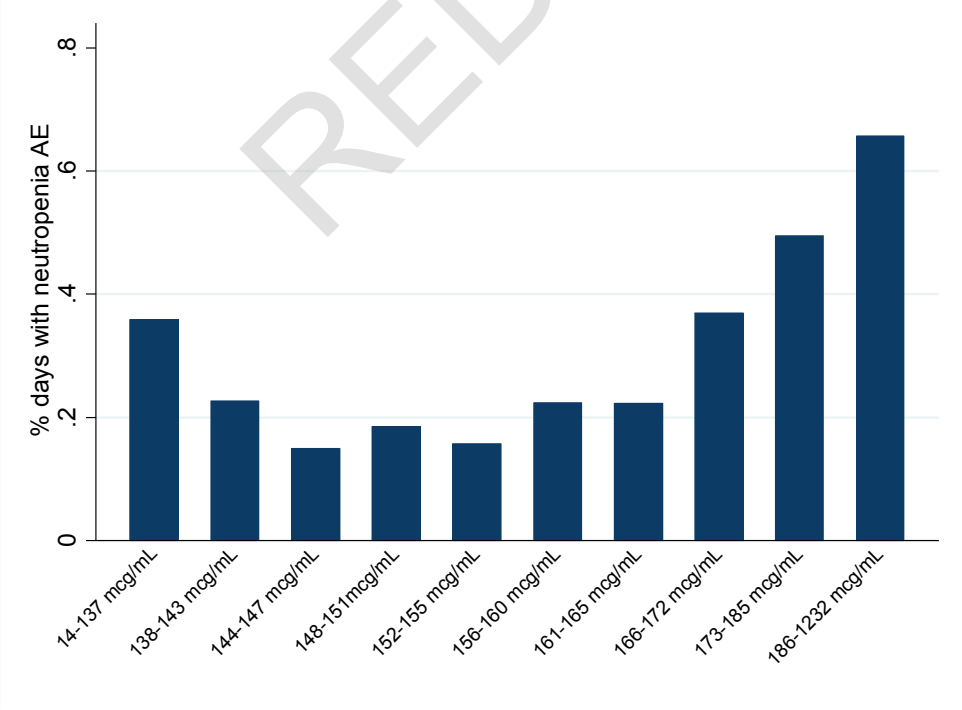
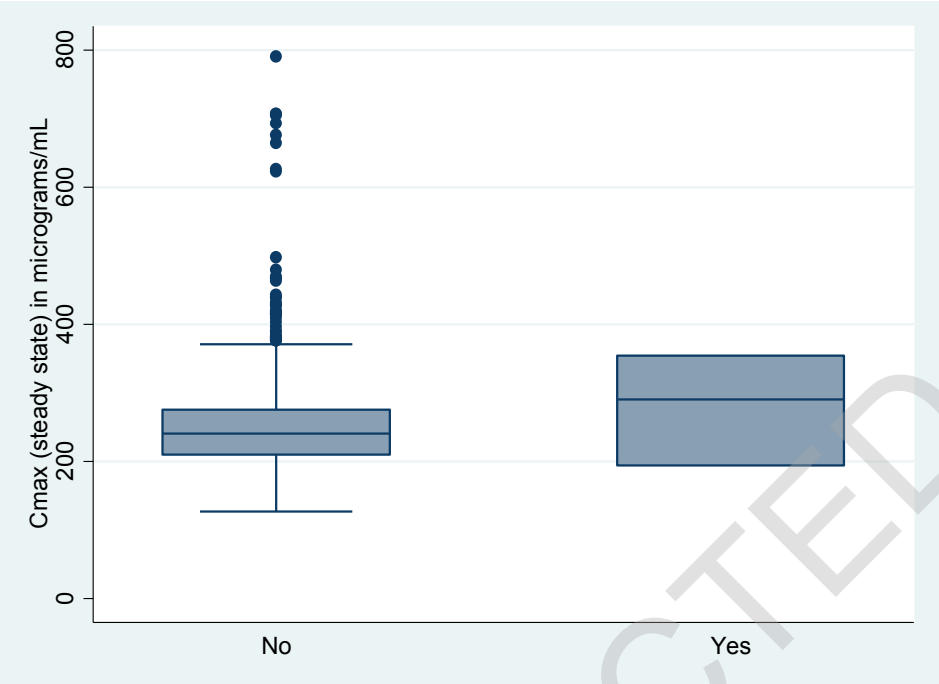


Figure 116. Percentage of infant days with neutropenia for each decile of ampicillin exposure (Cmax (steady state)) in all Group 1 infants



REDACTED

Figure 117. Cmax (steady state) concentration on days with and without neutropenia in all Group 2 infants



REDACTED

Figure 118. Percentage of infant days with neutropenia for each decile of ampicillin exposure (Cmax (steady state)) in all Group 2 infants

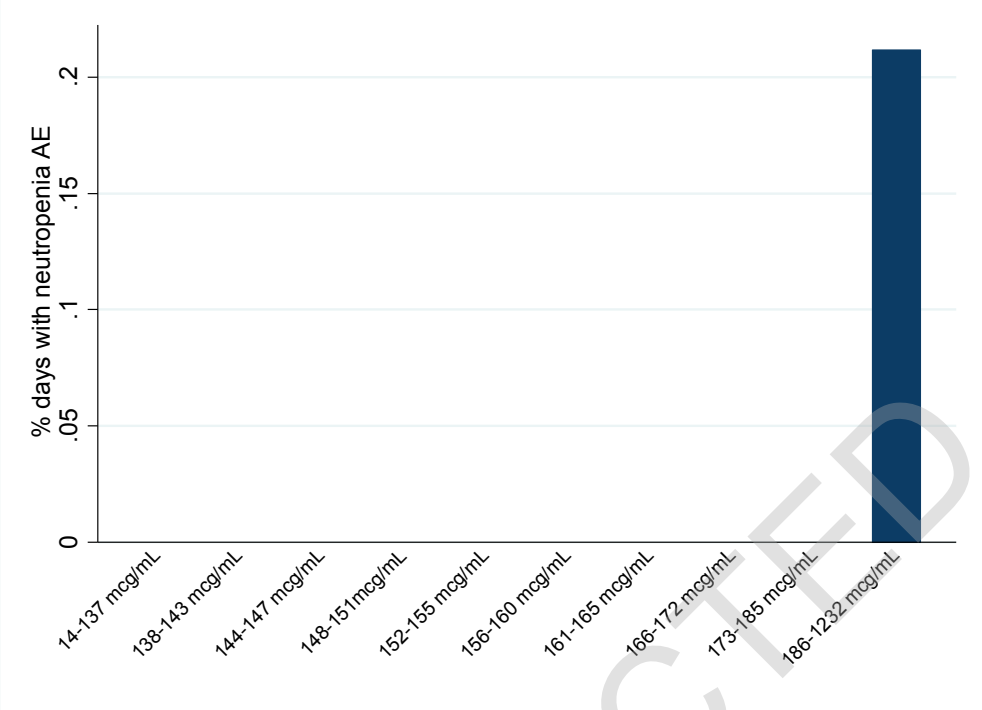
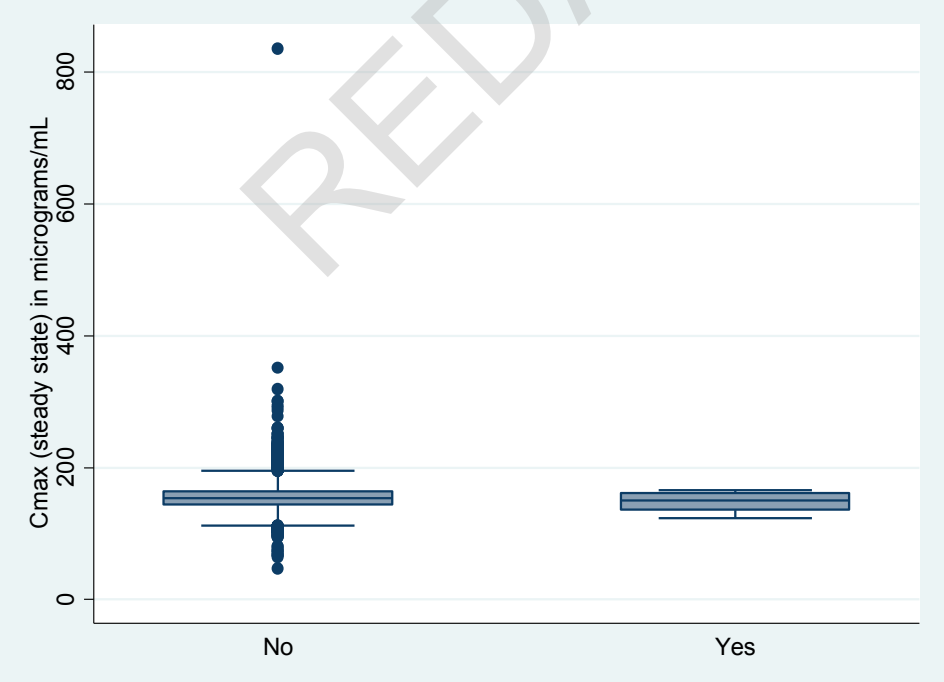
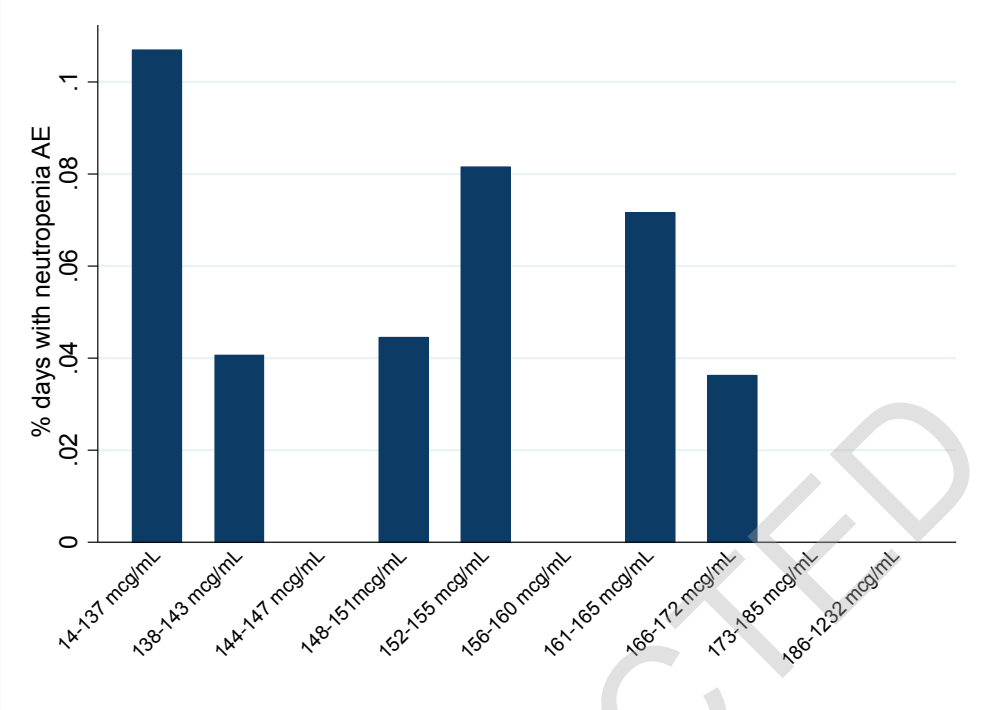


Figure 119. Cmax (steady state) concentration of ampicillin on days with and without neutropenia in all Group 3 infants



REDACTED

Figure 120. Percentage of infant days with neutropenia for each decile of ampicillin exposure (Cmax (steady state)) in all Group 3 infants



REDACTED

Severe Neutropenia

Figure 121. Cmax (steady state) concentration on days with and without severe neutropenia in all infants

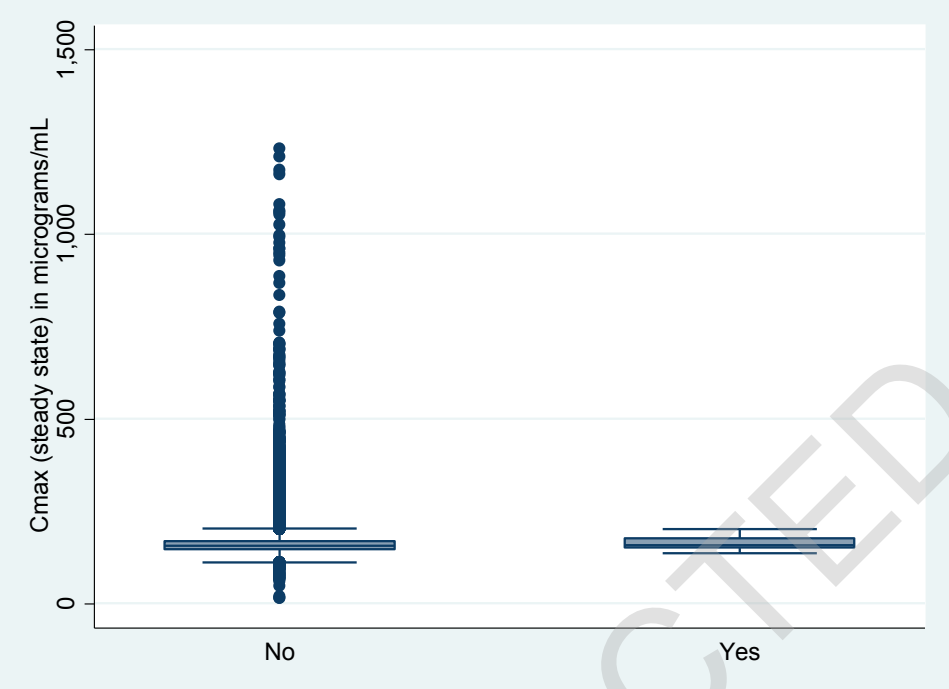
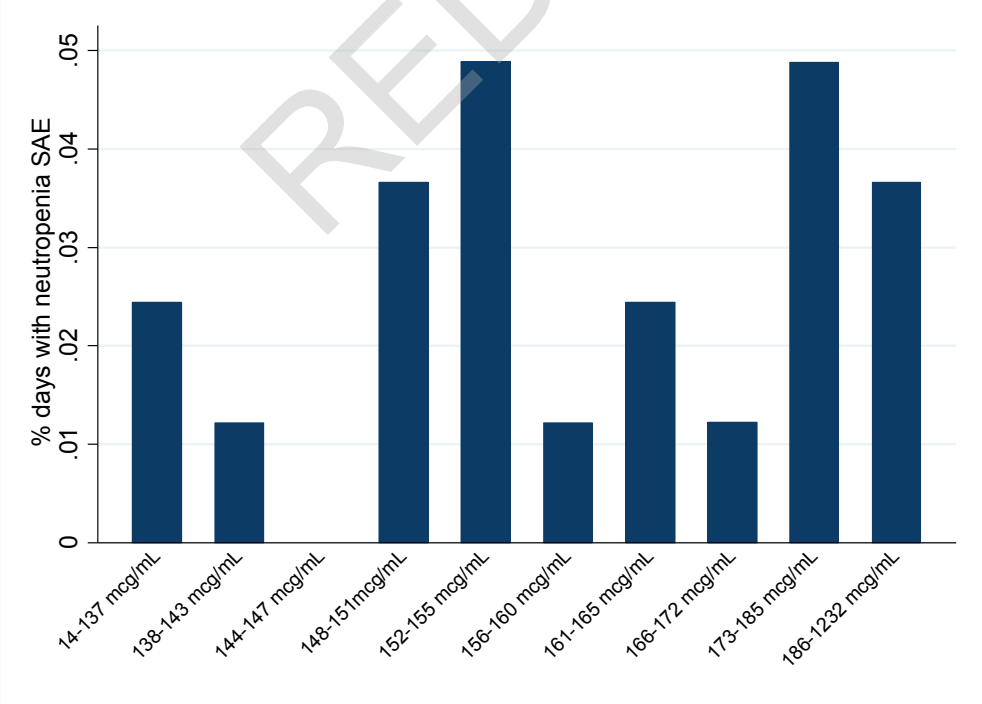
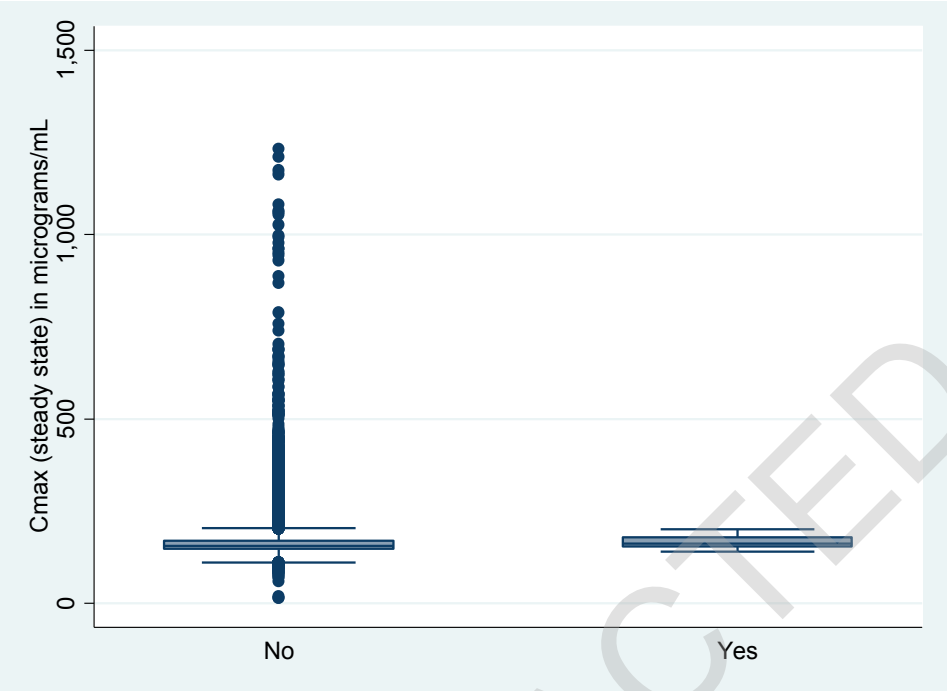


Figure 122. Percentage of infant days with severe neutropenia for each decile of ampicillin exposure (Cmax (steady state)) in all infants



REDACTED

Figure 123. Cmax (steady state) concentration on days with and without severe neutropenia in all Group 1 infants



REDACTED

Figure 124. Percentage of infant days with severe neutropenia for each decile of ampicillin exposure (Cmax (steady state)) in all Group 1 infants

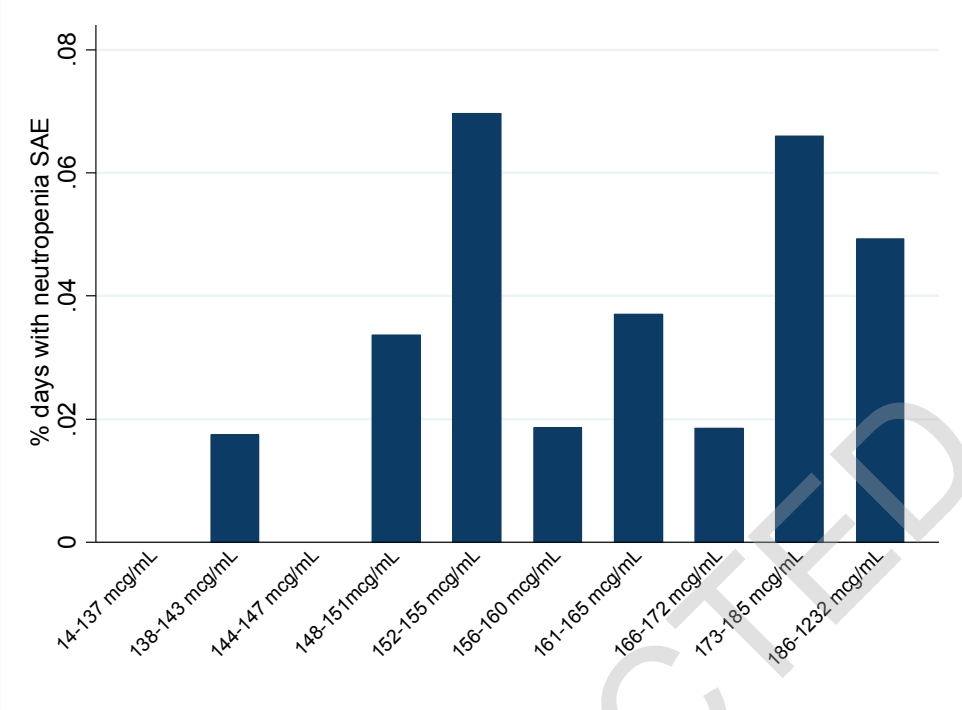
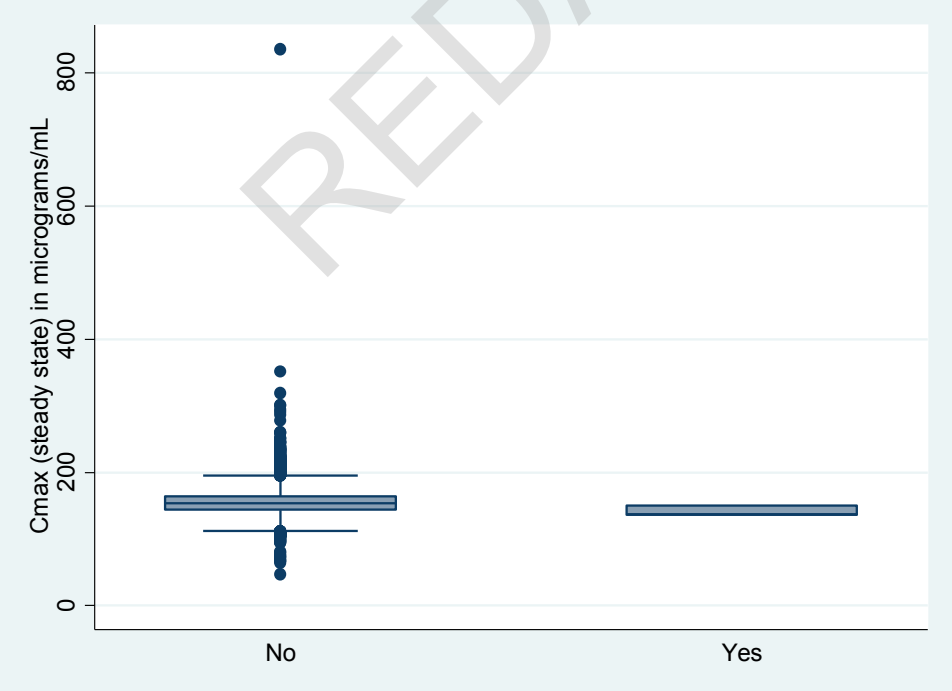
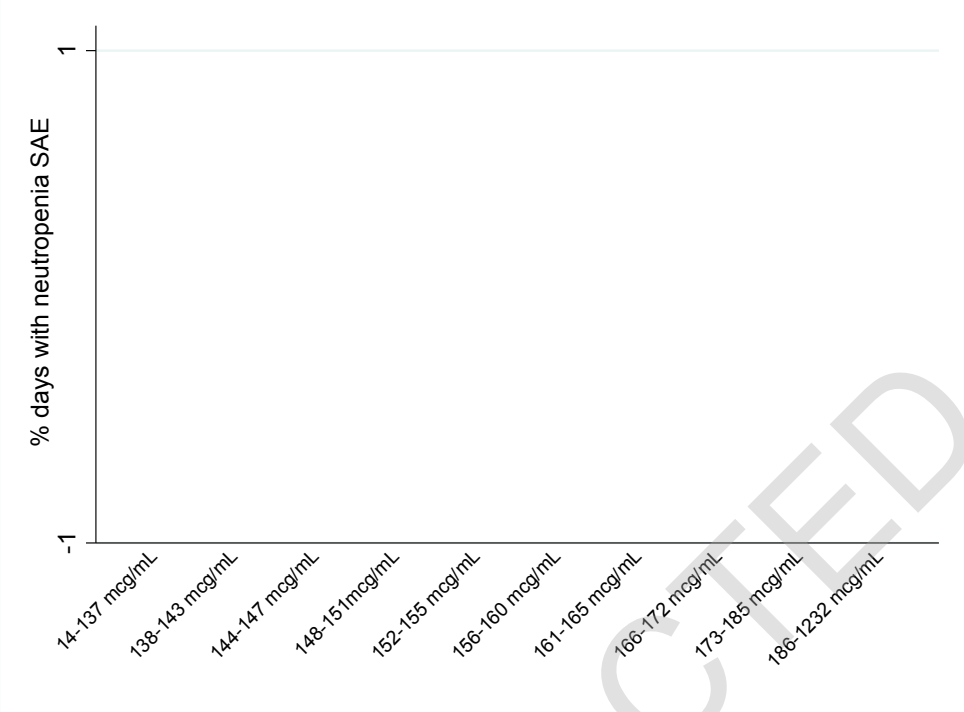


Figure 125. Cmax (steady state) concentration on days with and without severe neutropenia in all Group 2 infants



REDACTED

Figure 126. Percentage of infant days with severe neutropenia for each decile of ampicillin exposure (Cmax (steady state)) in all Group 2 infants



REDACTED

Figure 127. Cmax (steady state) concentration on days with and without severe neutropenia in all Group 3 infants

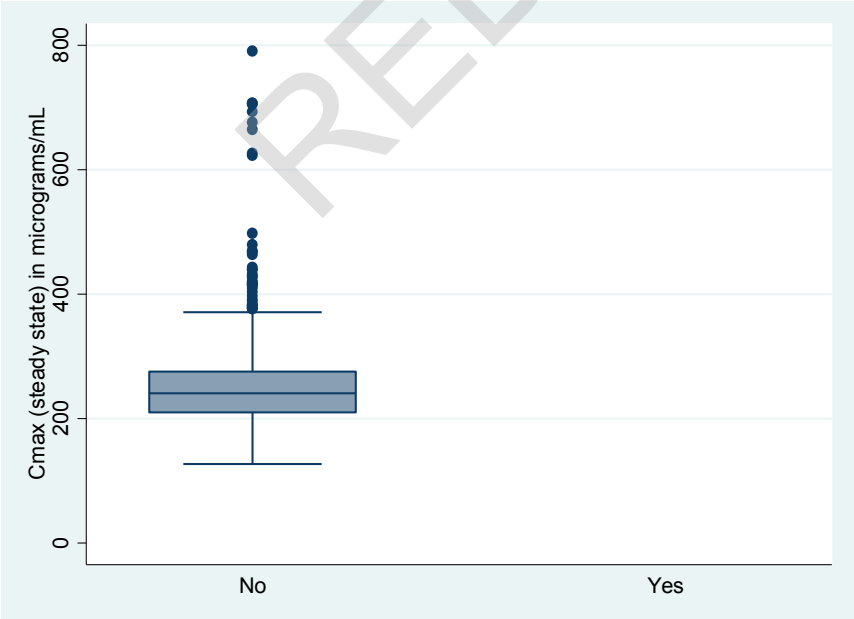
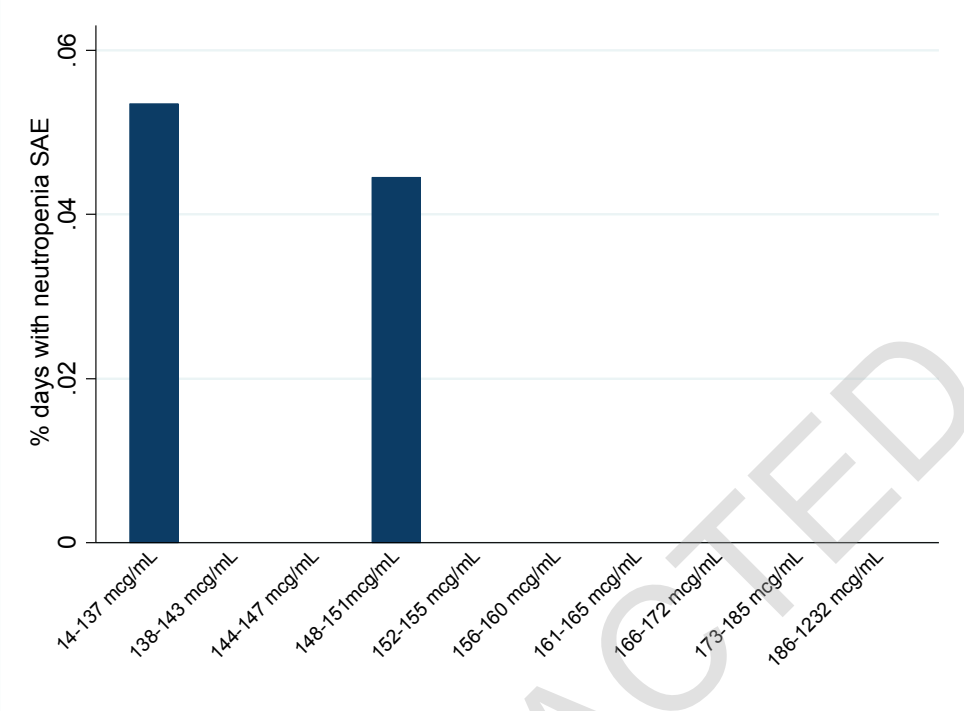


Figure 128. Percentage of infant days with severe neutropenia for each decile of ampicillin exposure (Cmax (steady state)) all Group 3 infants



REDACTED

6. Conclusion

Ampicillin dosing and dosing interval are not standardized and a variety of doses and dosing intervals are used for infants of all gestational and postnatal age groups. Adverse events occurred more frequently in infants with infection. Group 1 infants tended to have more adverse and severe adverse events than Group 2 and 3 infants. Thrombocytopenia was the most common adverse event.

Seizures occurred more frequently with higher doses and shorter dosing intervals. The highest proportion of seizures occurred in Group 3 infants receiving 125mg/kg/dose. Seizures occurred most frequently at Q4 hour dosing intervals. A 6 hour dosing interval gave higher incidences of seizure than 8 and 12 hour dosing interval for all groups. The incidence of seizures did not appear to be related to exposure to ampicillin. Seizures were seen at typical exposures and did not occur at high exposures for all gestational and postnatal age groups.

AST elevation and severe AST elevation appeared to occur sporadically with no obvious relationship to ampicillin dose or dosing interval. Higher doses were not associated with increased incidence of AST elevation; most cases of AST elevation occurred at doses ≤150mg/kg/dose. Days on which there was AST elevation or severe AST elevation tended to have higher ampicillin exposures. However, infants with the highest exposures did not have AST elevation or severe AST elevation. No Group 2 infants with known ampicillin exposure had AST elevation or severe AST elevation. Severe AST elevation did not occur on days with ampicillin exposure for Group 3 infants. AST elevation did not occur with ampicillin exposure in infected infants who had measurable ampicillin exposures of any gestational or postnatal age group.

Leukopenia occurred most often in Group 1 infants receiving 25mg/kg/dose. Group1 infants developed leukopenia more often than Group 2 or 3 infants at all doses. Leukopenia occurred more frequently at shorter dosing intervals and was more common in Group 1 infants at all dosing intervals. Severe leukopenia was uncommon but occurred most often in Group 1 infants at doses of 25mg/kg/dose. The relationship of leukopenia and severe leukopenia with ampicillin exposure was unclear. A higher percentage of days with leukopenia in infants in Group 1 had higher ampicillin exposures. For older infants, leukopenia did not occur at the highest exposures but did sometimes occur at typical exposures.

Neutropenia occurred most often in Group 1 infants receiving 25mg/kg/dose. There was not a clear relationship between ampicillin dose and neutropenia for Group 2 or 3 infants. Neutropenia occurred more frequently at shorter dosing intervals. There did not appear to be a relationship between ampicillin exposure and neutropenia. Neutropenia did not occur at the highest exposures but did occasionally occur at typical exposures.

Thrombocytopenia occurred more frequently at shorter dosing intervals. Thrombocytopenia occurred more often at shorter dosing intervals (4 and 6 hours). Doses of 25mg/kg/dose gave the highest incidence of thrombocytopenia for all groups. Group 1 infants given doses of 300mg/kg/dose had the highest incidence of thrombocytopenia. Higher ampicillin exposures were associated with slightly more frequent thrombocytopenia.

REDACTED