

Online Appendix.

Table 1. Summary of antibiotics and measures[‡]

Antimicrobial (WHO ATC) and Age category	Reference dose in mg/kg	Reference frequency	Estimated daily use of vials for children(grams) [§]	Average daily vial requirements for age ((dose for age in mg/kg x 50th percentile weight for age, rounded to whole vials) x reference dosage frequency)	Age-adjusted daily use of vials [^] , mean (min, max)	Adult DDD
Amikacin (J01GB06)						
Neonate	n/a	24 hourly	n/a	≤ 7 years, 2 months: 1 vial per day	1.2 (1.1-1.4)	1g
Paediatric	1 month - 10 years 22.5 mg/kg	24 hourly	1 vial (0.5g)	≥ 7 years, 3 months: 2 vials per day		
	≥ 10 years 18 mg/kg (1.5g)	24 hourly	1 vial (0.5g)			
Ampicillin (J01CA01)						
Neonate	n/a	12 hourly	n/a	< 3 months: 2 vials per day	3.5 (3.0-3.8)	2g
Paediatric	25 mg/kg (1g)	6 hourly	4 vials daily (2 - 4g)	≥ 3 months: 4 vials per day		
Azithromycin (J01FA10)						
Neonate	n/a	24 hourly	n/a	All patients: 1 vial per day	n/a	0.5g
Paediatric	10 mg/kg (0.5g)	24 hourly	1 vial daily (0.5g)			
Aztreonam (J01DF01)						
Neonate	n/a	8 hourly	n/a	<10 years, 5 months: 3 vials per day	3.4 (3.1-3.9)	4g
Paediatric	30 mg/kg (2g)	8 hourly	3 vial daily (3g)	≥ 10 years, 6 months: 6 vials per day		
Benzathine penicillin (J01CE08)						
Neonate	Not used	n/a	n/a	All patients: 1 vial per month	n/a	3.6g
Paediatric	<20kg 450 mg or 0.6 million units	once	1 vial per month (0.9g)			
	>20kg 900 mg or 1.2 million units	once	1 vial per month (0.9g)			
Benzylpenicillin (J01CE01)						
Neonate	n/a	12 hourly	n/a	< 3 months: 2 vials per day	3.5 (3.0-3.8)	3.6g
Paediatric	30 mg/kg (1.2g)	6 hourly	4 vial daily (2.4 - 4.8g)	≥ 3 months: 4 vials per day		
Cefalotin (J01DB03)						
Neonate	n/a	n/a	n/a	All patients: 4 vials per day	n/a	4g
Paediatric	25 mg/kg (1g)	6 hourly	4 vials daily (4g)			
Cefazolin (J01DB04)						
Neonate	n/a	12 hourly	n/a	<1 month of age: 2 vials per day	2.9 (2.7-3.0)	3g
		8 hourly	n/a			
Paediatric	25mg/kg (1g)	6 hourly	3 vial daily (3g)	>1 month: 3 vials per day		
Cefepime (J01DE01)						
Neonate	n/a	8-12 hourly	n/a	All patients: 2 vials per day	n/a	2g
Paediatric	50mg/kg (2g)	12 hourly	2 vial daily (2 - 4g)			
Cefotaxime (J01DD01)[£]						
Neonate	n/a	8 hourly	n/a	< 3 months: 3 vials per day	3.7 (3.5-3.9)	4g
Paediatric	25mg/kg (1g)	6 hourly	4 vial daily (2 - 8g)	≥ 3 months: 4 vials per day		
Cefoxitin (J01DC01)						
Neonate	Not used	n/a	n/a	≤ 8 years, 2 months: 3 vials per day	3.9 (3.3-4.6)	6g
Paediatric	40mg/kg (2g)	8 hourly	3 vial daily (3g)	≥ 8 years, 4 months: 6 vials per day		
Ceftazidime (J01DD02)						
Neonate	n/a	12 hourly	n/a	<3 months: 2 vials per day	2.7 (2.5-2.9)	4g

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Ceftriaxone (J01DD04)						
Paediatric	25-50mg/kg (2g)	8 hourly	3 vial daily (3 - 6g)	≥ 3 months: 3 vials per day		
Neonate	Not used	n/a	n/a	≥ 5 months - ≤ 6 years, 3 months: 1 vial per day	1.3 (1.1-1.6)	2g
Paediatric	50mg/kg/day (2g)	24 hourly	1 vial daily (0.5 - 1g)	≥ 6 years 4 months: 2 vials per day		
Ciprofloxacin (J01MA02)						
Neonate	n/a	12 hourly	n/a	≤ 6 years, 3 months: 2 vials per day	2.5 (2.2-2.8)	0.5g
Paediatric	10mg/kg (0.4g)	12 hourly	2 vial daily (0.2 - 0.4g)	≥ 6 years 4 months: 4 vials per day		
Clindamycin (J01FF01)						
Neonate	n/a	8 hourly	n/a	All patients: 3 vials per day	n/a	1.8g
Paediatric	15mg/kg (0.6g)	8 hourly	3 vial daily (0.9 - 1.8g)			
Daptomycin (O1XX09)						
Neonate	Not used	n/a	n/a	All patients: 1 vial per day	n/a	0.28g
Paediatric	1 - 2 years 10mg/kg	24 hourly	1 vial daily (0.5g)			
	2 - 6 years 9mg/kg	24 hourly				
	7 - 11 years 7mg/kg	24 hourly				
	12 - 17 years 5mg/kg	24 hourly				
Flucloxacillin (J01CF05)						
Neonate	n/a	6-12 hourly	n/a	<1 month: 2 vials per day	3.7 (3.4-4.0)	2g
Paediatric	25mg/kg (1g)	6 hourly	4 vial daily (2 - 4g)	>1 month: 4 vials per day		
Imipenem (J01DH51)						
Neonate	Not used	n/a	n/a	All patients: 4 vials per day	n/a	2g
Paediatric	15 mg/kg (0.5g)	6 hourly	4 vial daily (2g)			
Lincomycin (J01FF02)						
Neonate	Not used	n/a	n/a	All patients (i.e., ≥ 5 months: 3 vials per day)	n/a	1.8g
Paediatric	15 mg/kg (0.6g)	8 hourly	3 vial daily (1.8g)			
Linezolid (J01XX08)						
Neonate	n/a	8-12 hourly	n/a	<12 years: 3 vials per day	2.9 (2.7-3.0)	1.2g
Paediatric	<12 years 10mg/kg (0.6g)	8 hourly	3 vial daily (1.8g)	≥ 12 years: 2 vials per day		
	>12 years 0.6g	12 hourly				
Meropenem (J01DH02)						
Neonate	n/a	8 hourly	n/a	All patients: 3 vials per day	n/a	2g
Paediatric	20mg/kg (1g)	8 hourly	3 vial daily (1.5 - 3g)			
Metronidazole (J01XD01)						
Neonate	n/a	12 hourly	n/a	< 1 month: 2 vials per day	2.9 (2.7-3.0)	1.5g
Paediatric	7.5mg/kg (0.5g)	8 hourly	3 vial daily (1.5g)	≥ 1 month: 3 vials per day		
Moxifloxacin (J01MA14)						
Neonate	Not used	n/a	n/a	All patients: 1 vial per day	n/a	0.4g
Paediatric	10 mg/kg (0.4g)	24 hourly	1 vial daily (0.4g)			
Piperacillin-Tazobactam (J01CR05) [#]						
Neonate	n/a	6 hourly	n/a	All patients: 3.5 vials per day	n/a	14g
Paediatric	100mg/kg (4g)	6-8 hourly	3.5 vial daily (14g)			
Rifampicin						

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(J04AB02)						
Neonate	Not used	n/a	n/a	All patients: 1 vial per day	n/a	0.6g
Paediatric	10-20mg/kg (0.6g)	24 hourly	1 vial daily (0.6g)			
Teicoplanin (J01XA02)						
Neonate	n/a	24 hourly	n/a	All patients: 1 vial per day		0.4g
Paediatric	10mg/kg (0.4g)	24 hourly	1 vial daily (0.4g)			
Ticarcillin-clavulanate (J01CR03) #						
Neonate	n/a	12 hourly	n/a	≤ 1 month: 2 vials per day	4.6 (4.2-5.0)	15g
Paediatric	50 mg/kg (3g)	4-6 hourly	5 vial daily (15g)	>1 month: 5 vials per day		15g
Tigecycline (J01AA12)						
Neonate	Not used	n/a	n/a	All patients: 2 vials per day	n/a	0.1g
Paediatric	1.2 mg/kg (0.05g)	12 hourly	2 vial daily (0.1g)			
Trimethoprim-sulfamethoxazole (J01EE01) #						
Neonate	Not used	n/a	n/a	≥ 5 months - ≤ 6 years, 3 months: 2 vials per day	2.7 (2.3-3.2)	20mL
Paediatric	4 mg/kg (160 mg, 10 mL)	12 hourly	2 vial daily (10 mL)	≥ 6 years, 4 months: 4 vials per day		
Vancomycin (J01XA01) ‡						
Neonate	15 mg/kg	8 - 12 hourly	n/a	< 3 months: 2 vials per day	4.0 (3.3-5.0)	2g
Paediatric	15 mg/kg (0.75g)	6 hourly	4 vial daily (2g)	≥ 10 years, 6 months - 18 years: 8 vials per day ≥ 3 months - ≤ 10 years, 5 months: 4 vials per day		

Abbreviations: DDD, World Health Organization defined daily dose; g, Grams; WHO ATC, World Health Organization Collaboration Centre for Drug Statistics Methodology Anatomical Therapeutic Chemical Classification

‡ Agents targeted by the hospital antimicrobial stewardship program appear in bold text

§ Estimated daily use of vials, reference frequency × 1 vial(grams of daily use obtained from vial sizes supplied during the study period).^ Age-adjusted daily use of vials derived from the proportion of monthly patient bed days for each age (in years, months) and the average daily vial requirements.€ Cefotaxime 0.5 g vial size available January 2010 to July 2012 and August 2014 to November 2015, cefotaxime 2g vial size supplied during cefotaxime shortage March 2013 -April 2013 and August 2013 to November 2013.#Dosage refers to piperacillin, ticarcillin or trimethoprim component only.± Vancomycin 1g vial size supplied 3/77 months (9 grams/77 months)was not incorporated into the daily measure.

Table 2. Differences and limits of agreement between defined daily doses and local measures to estimate days of injectable antibiotic use^{¥§}

Injectable antibiotic (n)	DDD vs Estimated daily use of vials						DDD vs Age-adjusted estimated daily use of vials						DDD vs Recommended daily doses					
	Mean difference = B ₀ + B ₁ Averages			Limits = Mean difference +/-2.46 (C ₀ + C ₁ Averages)			Mean difference= B ₀ + B ₁ Averages			Limits = Mean difference +/-2.46 (C ₀ + C ₁ Averages)			Mean difference= B ₀ + B ₁ Averages			Limits = Mean difference +/-2.46 (C ₀ + C ₁ Averages)		
	B ₀	B ₁	p*	C ₀	C ₁	p*	B ₀	B ₁	p*	C ₀	C ₁	p*	B ₀	B ₁	p*	C ₀	C ₁	p*
Amikacin (16)	0.0	-0.7	<0.001	0.0	0.0	0.818	0.1	-0.5	<0.001	0.2	0.0	0.075	-0.4	-1.1	<0.001	-0.2	0.1	0.046
Ampicillin (67)	-1.4	0.3	<0.001	2.1	0.1	0.026	-1.0	0.2	<0.001	2.0	0.1	0.003	3.5	-0.7	<0.001	2.1	0.1	0.004
Azithromycin (58)	0.0	0.0	n/a	0.0	0.0	n/a	0.0	0.0	n/a	0.0	0.0	n/a	2.0	-1.3	<0.001	1.6	0.0	0.013
Benzylpenicillin (60)	-1.4	0.1	0.072	0.4	0.1	<0.001	-1.2	-0.1	<0.001	0.6	0.1	<0.001	2.3	-1.1	<0.001	0.4	0.1	<0.001
Cefalotin (19)	0.0	0.0	n/a	0.0	0.0	n/a	0.0	0.0	n/a	0.0	0.0	n/a	0.2	-1.2	<0.001	0.7	0.0	0.541
Cefazolin (77)	0.0	0.0	n/a	0.0	0.0	n/a	-0.6	0.0	<0.001	0.0	0.0	<0.001	12.4	-1.3	<0.001	1.6	0.1	0.001
Cefotaxime (76)	-7.1	0.0	0.922	3.8	0.1	0.026	-6.5	-0.1	0.219	3.3	0.1	0.016	16.2	-1.3	<0.001	2.5	0.1	<0.001
Ceftazidime (39)	-0.3	-0.1	0.003	-0.1	0.2	<0.001	-0.3	-0.2	<0.001	0.0	0.1	<0.001	0.7	-1.0	<0.001	0.4	0.1	0.001
Ceftriaxone (48)	-0.5	-0.8	<0.001	0.6	0.1	<0.001	-0.4	-0.5	<0.001	0.4	0.1	<0.001	-0.3	-1.2	<0.001	0.1	0.1	<0.001
Ciprofloxacin (19)	-1.0	-0.3	0.001	0.7	0.1	0.034	-1.2	0.0	0.754	0.6	0.1	0.077	0.6	-0.9	<0.001	0.8	0.1	0.304
Clindamycin (39)	-1.0	-0.3	<0.001	1.0	0.1	0.001	-1.0	-0.3	<0.001	1.0	0.1	0.001	0.2	-1.1	<0.001	0.0	0.1	<0.001
Flucloxacillin (66)	-3.1	0.6	<0.001	2.3	0.0	<0.001	-3.0	0.5	<0.001	2.6	0.0	0.006	0.2	-0.6	<0.001	-0.8	0.1	<0.001
Lincomycin (53)	0.0	0.0	n/a	0.0	0.0	n/a	0.0	0.0	n/a	0.0	0.0	n/a	2.3	-1.2	<0.001	0.7	0.1	<0.001
Linezolid (18)	0.0	0.4	<0.001	0.0	0.0	<0.001	0.1	0.4	<0.001	0.1	0.0	0.065	0.0	-1.2	<0.001	1.8	0.0	0.811
Meropenem (69)	-2.8	0.3	<0.001	1.4	0.1	<0.001	-2.8	0.3	<0.001	1.4	0.1	<0.001	3.1	-1.1	<0.001	-0.3	0.1	<0.001
Metronidazole (76)	0.0	0.0	n/a	0.0	0.0	n/a	0.0	-0.1	<0.001	0.1	0.0	<0.001	2.1	-1.5	<0.001	1.2	0.0	<0.001
Piperacillin-Tazobactam (63)	0.0	0.0	n/a	0.0	0.0	n/a	0.0	0.0	n/a	0.0	0.0	n/a	7.9	-1.3	<0.001	4.0	0.1	0.002
Ticarcillin-Clavulanate (42)	0.0	0.0	n/a	0.0	0.0	n/a	-0.1	-0.1	<0.001	0.1	0.0	<0.001	4.0	-1.5	<0.001	0.8	0.1	<0.001
Trimethoprim-Sulfamethoxazole (14)	0.0	-0.7	<0.001	0.0	0.0	0.901	1.3	-0.5	<0.001	1.1	0.0	0.052	1.1	-1.2	<0.001	2.7	0.0	0.353
Vancomycin (77)	-0.1	0.0	0.059	-0.1	0.0	0.001	-1.2	0.1	0.070	0.6	0.1	<0.001	12.8	-1.2	<0.001	3.5	0.1	0.010

Abbreviations: DDD, Defined daily doses; Limits, Limits of Agreement; n, observations (months of use) n/a, Not applicable; PICU, Paediatric Intensive Care Unit;

¥ Linear regression for Bland-Altman plots DDD vs Estimated daily use of vials (Figure 2), DDD vs Age-adjusted estimated daily use of vials (Figure 3), DDD vs Recommended daily doses (Figure 4)

§ Shapiro Wilk test of differences p>0.05 for DDD vs Estimated daily vials (ceftazidime, ciprofloxacin), DDD vs age-adjusted estimated daily vials (linezolid, vancomycin), DDD vs recommended daily dose (amikacin, cefazolin, lincomycin).

*P value for the coefficient of the Averages (B₁ and C₁)