Supplementary material: Pharmacokinetics of clavulanic acid in the pediatric population: a systematic literature review

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Journal: Clinical Pharmacokinetics

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S1: Prisma checklist
S2: Search strategy
S3: Quality assessment ClinPK tool
S4: Additional data

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Suppl material
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 6-7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 6-7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Not applicable
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Not applicable
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Not applicable
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Not applicable
Reporting bias	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Not

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			applicable
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not applicable
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 8
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Suppl material
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 2
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Not applicable
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Not applicable
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Not applicable
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not applicable
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Not applicable
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not applicable
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 9-12
	23b	Discuss any limitations of the evidence included in the review.	Page 9-12
	23c	Discuss any limitations of the review processes used.	Page 17
	23d	Discuss implications of the results for practice, policy, and future research.	Page 17
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 6 & abstract
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 6
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Not applicable
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 18

Section and Topic	Item #	Checklist item	Location where item is reported
Competing interests	26	Declare any competing interests of review authors.	Page 18
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Extracted data: table 1&2 and suppl material

S2_Search Strategy

Database searched	Platform	Years of coverage	Records	Records after duplicates removed
Embase	Embase.com	1971 - Present	2292	2273
Medline ALL	Ovid	1946 - Present	601	172
Web of Science Core Collection*	Web of Knowledge	1975 - Present	458	137
Cochrane Central Register of Controlled Trials	Wiley	1992 - Present	332	75
Additional Search Engines: Google Scholar			200	111
Total			**3883**	**2768**

*Science Citation Index Expanded (1975-present) ; Social Sciences Citation Index (1975-present) ; Arts & Humanities Citation Index (1975-present) ; Conference Proceedings Citation Index- Science (1990-present) ; Conference Proceedings Citation Index- Social Science & Humanities (1990-present) ; Emerging Sources Citation Index (2005-present)

Embase.com

('amoxicillin plus clavulanic acid'/de OR 'clavulanate potassium'/de OR 'clavulanic acid'/de OR (clavulan*):ab,ti,kw) **AND** ('pharmacokinetics'/exp OR 'drug concentration'/exp OR 'urine level'/de OR 'saliva level'/exp OR 'pharmacokinetics':lnk OR 'safety'/de OR 'drug safety'/exp OR 'pharmacokinetic parameters'/exp OR 'area under the curve'/exp OR 'blood level'/de OR 'peak-trough fluctuation'/de OR (pharmacokinetic* OR ((drug* OR pharma* OR clavulan*) NEAR/3 (kinetic* OR dynamic*)) OR absorpt* OR distribut* OR biotransform* OR bio-transform* OR eliminat* OR bioavailab* OR clearance* OR excret* OR half-life* OR metabolism* OR ((drug* OR pharma* OR clavulan* OR plasma* OR blood* OR serum* OR urine* OR saliva* OR peak* OR trough*) NEAR/3 (concentration* OR level*)) OR pharmacodynamic* OR safe* OR ((area*) NEAR/3 (curve*)) OR AUC* OR PK-PD):ab,ti,kw) **AND** (child/exp OR adolescent/exp OR adolescence/exp OR 'child behavior'/de OR 'child parent relation'/de OR pediatrics/exp OR childhood/exp OR 'child nutrition'/de OR 'infant nutrition'/exp OR 'child welfare'/de OR 'child abuse'/de OR 'child advocacy'/de OR 'child development'/de OR 'child growth'/de OR 'child health'/de OR 'child health care'/exp OR 'child care'/exp OR 'childhood disease'/exp OR 'child death'/de OR 'child psychiatry'/de OR 'child psychology'/de OR 'pediatric ward'/de OR 'pediatric hospital'/de OR 'pediatric anesthesia'/de OR 'pediatric intensive care unit'/de OR 'neonatal intensive care unit'/de OR 'prematurity'/de OR (adolescen* OR preadolescen* OR infan* OR newborn* OR (new NEXT/1 born*) OR baby OR babies OR neonat* OR prematur* OR pre-matur* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEXT/1 (age* OR aging OR ageing)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool* OR suckling* OR PICU OR NICU OR PICUs OR NICUs):ab,ti,kw) **NOT** ([animals]/lim NOT [humans]/lim)

Medline (Ovid)

(exp Clavulanic Acids/ OR (clavulan*).ab,ti,kf.) **AND** (exp Pharmacokinetics/ OR pharmacokinetics.fs. OR Safety/ OR Area Under Curve/ OR (pharmacokinetic* OR ((drug* OR pharma* OR clavulan*) ADJ3 (kinetic* OR dynamic*)) OR absorpt* OR distribut* OR biotransform* OR bio-transform* OR eliminat* OR bioavailab* OR clearance* OR excret* OR half-life* OR metabolism* OR ((drug* OR pharma* OR clavulan* OR plasma* OR blood* OR serum* OR urine* OR saliva* OR peak* OR trough*) ADJ3 (concentration* OR level*)) OR pharmacodynamic* OR safe* OR ((area*) ADJ3 (curve*)) OR AUC* OR PK-PD).ab,ti,kf.) **AND** (exp Child/ OR exp Infant/ OR exp Adolescent/ OR exp "Child Behavior"/ OR exp "Parent Child Relations"/ OR exp "Pediatrics"/ OR "Child Nutrition Sciences"/ OR "Infant nutritional physiological phenomena"/ OR exp "Child Welfare"/ OR "Child Development"/ OR exp "Child Health Services"/ OR exp "Child Care"/ OR "Child Rearing"/ OR exp "Child development Disorders, Pervasive"/ OR "Child Psychiatry"/ OR "Child Psychology"/ OR "Hospitals, Pediatric"/ OR exp "Intensive Care Units, Pediatric"/ OR (adolescen* OR infan* OR newborn* OR (new ADJ born*) OR baby OR babies OR neonat* OR prematur* OR pre-matur* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under ADJ1 (age* OR aging OR ageing)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool* OR suckling* OR PICU OR NICU OR PICUs OR NICUs).ab,ti,kf.) **NOT** (exp animals/ NOT humans/)

Web of Science

TS=(((clavulan*)) **AND** ((pharmacokinetic* OR ((drug* OR pharma* OR clavulan*) NEAR/2 (kinetic* OR dynamic*)) OR absorpt* OR distribut* OR biotransform* OR bio-transform* OR eliminat* OR bioavailab* OR clearance* OR excret* OR half-life* OR metabolism* OR ((drug* OR pharma* OR clavulan* OR plasma* OR blood* OR serum* OR urine* OR saliva* OR peak* OR trough*) NEAR/2 (concentration* OR level*)) OR pharmacodynamic* OR safe* OR ((area*) NEAR/2 (curve*)) OR AUC* OR PK-PD)) **AND** ((adolescen* OR preadolescen* OR infan* OR newborn* OR (new NEAR/1 born*) OR baby OR babies OR neonat* OR prematur* OR pre-matur* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEAR/1 (age* OR aging OR ageing)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool* OR suckling* OR PICU OR NICU OR PICUs OR NICUs)) **NOT** ((animal* OR rat OR rats OR mouse OR mice OR murine OR dog OR dogs OR canine OR cat OR cats OR feline OR rabbit OR cow OR cows OR bovine OR rodent* OR sheep OR ovine OR pig OR swine OR porcine OR veterinar* OR chick* OR zebrafish* OR baboon* OR nonhuman* OR primate* OR cattle* OR goose OR geese OR duck OR macaque* OR avian* OR bird* OR fish*) NOT (human* OR patient* OR women OR woman OR men OR man)))

Cochrane CENTRAL

((clavulan*):ab,ti,kw) **AND** ((pharmacokinetic* OR ((drug* OR pharma* OR clavulan*) NEAR/3 (kinetic* OR dynamic*)) OR absorpt* OR distribut* OR biotransform* OR bio NEXT transform* OR eliminat* OR bioavailab* OR clearance* OR excret* OR half NEXT life* OR metabolism* OR ((drug* OR pharma* OR clavulan* OR plasma* OR blood* OR serum* OR urine* OR saliva* OR peak* OR trough*) NEAR/3 (concentration* OR level*)) OR pharmacodynamic* OR safe* OR ((area*) NEAR/3 (curve*)) OR AUC* OR

PK NEXT PD):ab,ti,kw) **AND** ((adolescen* OR preadolescen* OR infan* OR newborn* OR (new NEXT/1 born*) OR baby OR babies OR neonat* OR prematur* OR pre NEXT matur* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEXT/1 (age* OR aging OR ageing)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool* OR suckling* OR PICU OR NICU OR PICUs OR NICUs):ab,ti,kw)

Google Scholar *Top 200 relevant references*

Clavulanate|clavulanic pharmacokinetics|'drug|clavulanic|clavulanate kinetics|absorption|distribution|elimination|clearance|excretion|half-life|metabolism' infants|newborns|babies|neonates|prematurity|children|kids|toddlers|boys|girls|PICU|NICU

S3_Quality assesment

	Checklist Item
	Title/Abstract
1.	The title identifies the drug(s) and patient population(s) studied.
2.	The abstract minimally includes the name of the drug(s) studied, the route of administration, the population in whom it was studied, and the results of the primary objective and major clinical pharmacokinetic findings.
	Background
3.	Pharmacokinetic data (i.e., absorption, distribution, metabolism, excretion) that [are] known and relevant to the drugs being studied [are] described.
4.	An explanation of the study rationale is provided.
5.	Specific objectives or hypotheses [are] provided.
	Methods
6	Eligibility criteria of study participants are described.
7.	Co-administration (or lack thereof) of study drug(s) with other potentially interacting drugs or food within this study is described.
8.	Drug preparation and administration characteristics including dose, route, formulation, infusion duration (if applicable), and frequency are described.
9.	Body fluid or tissue sampling (timing, frequency, and storage) for quantitative drug measurement is described.
10.	Validation of quantitative bioanalytical methods used in the study [is] referenced or described if applicable.
11.	Pharmacokinetic modeling methods and software used are described, including assumptions made regarding the number of compartments and order of kinetics (zero, first, or mixed order).
12.	For population pharmacokinetic studies, covariates incorporated into pharmacokinetic models are identified and described.
13.	Formulas for calculated variables (such as creatinine clearance, body surface area, AUC, and adjusted body weight) are provided or referenced.
14.	The specific body weight used in drug dosing and pharmacokinetic calculations [is] reported (i.e., ideal body weight versus actual body weight versus adjusted body weight).
15.	Statistical methods including software used are described.
	Results
16.	Study withdrawals or subjects lost to follow-up (or lack thereof) are reported.
17.	Quantification of missing or excluded data is provided if applicable.
18.	All relevant variables that may explain inter- and intra-patient pharmacokinetic variability (including: age, sex, end-organ function, ethnicity, weight or BMI, health status or severity of illness, and pertinent co-morbidities) are provided with appropriate measures of variance.
19.	Results of pharmacokinetic analyses are reported with appropriate measures of precision (such as range or 95% confidence intervals).
20.	Studies in patients receiving extracorporeal drug removal (i.e., dialysis) should report the mode of drug removal, type of filters used, duration of therapy, and relevant flow rates.
21.	In studies of drug bioavailability comparing two formulations of the same drug, F (bioavailability), AUC, Cmax (maximal concentration), and Tmax (time to maximal concentration) should be reported.
	Discussion/Conclusion
22.	Study limitations describing potential sources of bias and imprecision where relevant should be described.
23.	The relevance of study findings (applicability, external validity) is described.
	Other Information
24.	Funding sources and conflicts of interest for the authors are disclosed.

Table. ClinPK and checklist results

	Al Roomi 1984	Begue 1982	Begue 1986	Burstein 1994	de Cock 2015	Fayed 1987	Feldman 1985	Fricke 1989	Hoberman 1989	Jacobs 1985
1.	Yes, population was not specified but paper published pediatric journal	yes	Yes	yes	yes	yes	yes	yes	yes	yes
2.	No	Yes	Yes	Yes	Yes	Yes	No	yes	yes	yes
3.	No	Yes	No	Yes	Yes	yes	Yes	yes	yes	yes
4.	Yes	Yes	Yes	Yes	Yes	yes	yes	yes	yes	yes
5.	Yes	Yes	Yes	Yes	Yes	yes	yes	yes	yes	yes
6.	Yes	Yes	Yes	Yes	Yes	Yes	yes	yes	yes	yes
7.	Yes, food reported, co-medication not	Yes, food reported, co-medication not	Yes, co-medication reported, food not applicable	Yes, co-medication reported, food not applicable	Yes, co-medication reported, food not applicable	No, co-medication not reported, food not applicable	yes	No, co-medication not reported, food not applicable	yes	yes
8.	Yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
9.	Yes, serum and urine	yes	Yes, serum and urine	yes	yes	Yes, serum and urine	yes	yes	yes, middle ear	yes
10.	Agar plate method	Agar plate method	Agar plate method	Agar plate method	UPLC MS/MS	Agar plate method	HPLC	Agar plate method	not reported	HPLC
11.	n.a.	n.a.	n.a.	yes, adapt 2	yes, NONMEM 7.3	n.a.	Lagran AUC	ad hoc software	n.a.	ESTRIP/KINONITE
12.	n.a.	n.a.	n.a.	n.a.	yes	n.a.	n.a.	n.a.	n.a.	n.a.
13.	n.a.	n.a.	n.a.	n.a.	yes	n.a.	n.a.	n.a.	n.a.	n.a.
14.	No weight provided	No	Yes	yes	yes	Yes	no	Yes	No	yes
15.	n.a.	n.a.	n.a.	n.a.	yes R version 7.3	n.a.	n.a.	n.a.	n.a.	n.a.
16.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
17.	n.a.	n.a.	n.a.	n.a.	yes	n.a.	n.a.	n.a.	n.a.	n.a.
18.	no, only average age	no, only average age	yes, raw data are provided	yes	yes	no, average	no, average	yes, raw data provided	no, average	no, average
19.	n.a. concentrations reported (mean + SD)	n.a. serum concentrations reported (mean + SEM); $T_{1/2}$	n.a. individual concentrations are reported, $T_{1/2}$, Vd	yes	yes	n.a.	n.a.	n.a. individual concentrations are reported $T_{1/2}$, Vd, AUC	n.a. mean concentrations are reported $T_{1/2}$, Vd, AUC	n.a. mean concentrations are reported $T_{1/2}$, Vd, AUC, Cl
20.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
21.	n.a.	n.a.	n.a.	n.a.	n.a.		n.a.	n.a.	n.a.	n.a.
22.	Partial	Partial	Partial	yes	yes	Partial	yes	yes	yes	yes
23.	Yes	yes	yes	yes	yes	Yes	yes	yes	yes	yes
24.	Yes	No	No	Yes	yes	no	no	Yes	Yes	no

	Jehl 2003	Jones 1990	Miall Allen 1988	Nelson 1982	van Niekerk 1985	Reed 1995	Schaad 1983	Schaad 1986
1.	yes	yes	yes	yes	yes	yes	yes	yes
2.	yes	yes	yes	yes	yes	yes	yes	yes
3.	yes	yes	yes	Yes, but not in clear paragraphs	yes	yes	yes	yes
4.	yes	yes	yes	yes	yes	yes	yes	yes
5.	yes	yes	yes	yes	yes	yes	yes	yes
6.	yes	yes	yes	yes	yes	yes	yes	yes
7.	yes	Yes, co-medication reported, food not applicable	Yes, co-medication reported, food not applicable	Yes, co-medication reported, food not reported	Yes, co-medication reported, food not reported	Yes, co-medication reported, food not reported	Yes, co-medication reported, food not applicable	Yes, co-medication and food reported
8.	yes	yes	yes	yes	yes	yes	yes	yes
9.	yes, serum and middle ear fluid	yes	yes	yes	yes	Yes, serum and urine	Yes, serum and urine	Yes, serum and urine
10.	HPLC	Agar plate method	Agar plate method	agar plate method	Agar plate method	HPLC	Agar plate method	Agar plate method
11.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
12.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
13.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
14.	Yes	yes	yes	no	n.a.	n.a.	No weight provided	No weight provided
15.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
16.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
17.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
18.	no, average	no, average	no, average	no, average	no, average	no, average	no, average	no, average
19.	n.a.	n.a. mean concentrations are reported, AUC, k, $T_{1/2}$	n.a. mean concentrations + SD are reported	n.a. mean concentrations + SEM are reported	n.a. mean concentrations + SEM are reported	n.a. mean concentrations, Cl, AUC, Vd are reported	n.a. mean concentrations, Cl, AUC, Vd are reported	n.a. mean concentrations, Cl, AUC, Vd are reported
20.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
21.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
22.	yes	yes	yes	yes	yes	yes	yes	yes
23.	yes	yes	yes	yes	yes	yes	yes	yes
24.	no	no	yes	yes	yes	yes	no	no

S4_ Additional data

Reference	population	Dosing regimen	Cmax (mg/L)	Tmax (h)	Vd (L)	Bioavailability (%)	Cl	AUC (mg·h/L)
Carlier et al (2013)	ICU patients > 18 years	Amoxicillin/clavulanic acid 100-200 mg/dose	-	-	19.2	-	6.8 L/h	-
De Velde et al (2018)	Healthy males > 18 years	Amoxicilin/clavulanic acid *oral* varying dosing regimens	2.21±0.78 (0.21-4.35)	1.29±0.32	-	-	First order elimination: 24.6 L/h (26.7% between subject variability)	4.82±1.53 (0.44-8.31 (0-8hrs)
Vree et al (2003)	Healthy subjects >18 years	Amoxicillin/clavulanic acid *oral* varying amoxicillin dosing + 125 mg clavulanic acid	1.15-3.79	0.7-1.78		-	-	1.5-8
Kaye et al (2001)	Healthy males and females > 18 years	Amoxicillin/clavulanic acid *oral; single dose* (2000/125 mg)	2.05±0.80	1.03 (0.75-3.0)	-	-	-	5.29 ± 1.55
Bolton et al (1986)	Healthy subjects >18 years	Clavulanic acid *intravenous and oral* 125 mg/dose	-	Oral: 0.75 Iv: -	Oral: - Iv: 12.01 (10/1-14.3)	64 (51-75)	Oral: 6.6 L/h Iv: 6 L/h	Oral: 7.7 iv: 10.6
Nilsson-Ehle et al (1985)	10 healthy man > 18 years	Amoxicillin/clavulanic acid *intravenous and oral* Single dose 125 mg	oral: 2.3±0.88 mg/L	1.3 h (1.0-2.0)	-	60.0 ± 23.1 (31.4 - 98.8)	14.88±3.3 L/h x 1.73	oral: 4.6±1.6 mg*h/Lx1.73^2 iv: 7.1 ±1.6 mg·h/Lx1.73^2

Table 1. Pharmacokinetics of clavulanic acid in adults reported in literature Cmax: maximum concentration; T: time; Vd: volume of distribution; Cl: clearance; AUC: area under the curve; ICU: intensive care; iv; intravenous

Reference	Population	Ratio	Clavulanic acid (mg/kg)	Dosing frequency	Daily dose clavulanic acid (mg/kg/day)
IV clavulanic acid, co-administered with ticarcillin					
Burstein	Preterm	30:1	2.5	Every 8 hours	7.5
Fayed	Preterm/term	15:1	5	Every 12 hours	10
Fricke	Neonates < 36 wks Neonates > 36 wks	25:1 25:1	3.3 4	Every 8 hours	9.9 12
Miall-Allen	Neonates	15:1	5	< 2 kg every 12 hrs > 2 kg every 8 hrs	10 15
Bégué (1)	Neonates	25:1	2.25	Every 6 hours	9
	Children	25:1	4	Every 6 hours	16
Reed	Children	30:1	1.7	Every 4 hours	6.8
Jacobs	Children & adolescents	15:1 30:1	5 2.5	Single dose	- -
Feldman	Adolescents	30:1	1.7	Every 4 hours	6.8
Oral clavulanic acid, co-administered with amoxicillin					
Al Roomi	Children	4:1 2:1	<1 month: 4.76 mg/dose* 1-3 month: 6.35 mg/dose* 3-9 month: 7.9 mg/dose* 9 mnd-2 yr: 15.9 mg/dose* 2.5 yr: 31.75 mg/dose* > 5 yr: 62.5 mg/dose*	Every 8 hours	<1 month: 14.28 mg/day* 1-3 month: 19.05 mg/day 3-9 month: 23.7 mg/day 9 mnd-2 yr: 47.7 mg/day 2.5 yr: 95.25 mg/day > 5 yr: 187.5 mg/day
Bégué (2)	Children	4:1	2.5 5	Single dose	-
Nelson	Children	4:1	1.7 3.3	Single dose	- -
van Niekerk	Children	4:1	2-5 yrs: 31.25mg/dose* 6-10 yrs: 62.5 mg/dose*	Every 8 hours	93.75 mg/day* 187.5/mg/day
Schaad	Children	4:1	5	Single dose	-
Jehl	Children	8:1	3.3	Every 8 hours	10
Hoberman	Children	28:1	1.6 1.425	Every 12 hours	9.9 12
iv clavulanic acid, co-administered with amoxicillin					
Jones	Children	10:1	5 mg	Single dose	-
de Cock	Children	10:1 5:1	3.5-7	Every 6 hours	14-28
Schaad	Children	5:1	5 mg/kg	Single dose	-

Table 2: dosing regimens of included studies

* fixed dosage based on age ranges, not dosed on kg bodyweight.

Reference	Sample management	Analysis technique	Additional details
Al Roomi	Not specified	Agar plate diffusion method *Klebsiella pneumoniae*	-
Bégué (1)	Not specified	Agar plate diffusion method *Klebsiella aerogenes*	-
Bégué (2)	Immediately centrifuged, stored at -80°C for max 3 days	Agar plate diffusion method *Klebsiella aerogenes*	-
Burstein	Immediately centrifuged, stored at -70°C	Agar plate diffusion method *Klebsiella pneumoniae*	Linear assay from 0.08 to 5 mg/L LLOQ: 0.078 mg/L
de Cock	Immediately centrifuged, stored at -80°C for max 3 months	UPLC- tandem mass spectometry	LLOQ: 0.5 mg/L
Fayed	Not specified	Agar plate diffusion method *Klebsiella pneumoniae*	-
Feldman	Immediately centrifuged, stored at -70°C	HPLC method	Linear assay from 0.25 to 5 µg/mL
Fricke	Immediately centrifuged, stored at -70°C	Agar plate diffusion method	LLOQ: 0.16 mg/L
Hoberman	Not specified	Not specified	-
Jacobs	Immediately centrifuged, stored at -70°C for max 60 days	HPLC method	Only provided for ticarcillin assay
Jehl	Immediately centrifuged, stored at -80°C	HPLC method	-
Jones	Immediately centrifuged, stored at -70°C	Agar plate diffusion method *Klebsiella pneumoniae*	LLOQ: 0.08 mg/L
Miall-Allen	Immediately centrifuged, stored at -70°C	Agar plate diffusion method Bacteria not mentioned	-
Nelson	Immediately centrifuged, stored at -70°C for max 72 hours	Agar plate diffusion method *Klebsiella pneumoniae*	Linear assay CV between 0.3 and 50 mg/L was 1.8-2.2%
van Niekerk	Immediately centrifuged, stored at -70°C for max 7 days	Agar plate diffusion method *Klebsiella aerogenes*	-
Reed	Immediately centrifuged, addition of morpholinopropane sulfonic acid to stabilize, stored at -70°C for max 45 days	HPLC method	Doubling dilutions from 1.6 to 0.1 µg/mL
Schaad	Mixed with sodium citrate, centrifuged, stored at -70°C for max 7 days	Agar plate diffusion method *Klebsiella aerogenes*	-
Schaad	Mixed with sodium citrate, centrifuged, stored at -70°C for max 96 hours	Agar plate diffusion method *Klebsiella aerogenes*	-

Table 3. overview of sample management and used method of analysis.
LLOQ: lower limit of quantification; CV: coefficient of variation

Reference	Reported adverse events/side effects/adverse reactions
Burstein	Treatment well tolerated, no adverse events or laboratory abnormalities reported
Fayed	Treatment well tolerated, no biochemical or hematological abnormalities, no adverse reactions reported
Fricke	Treatment well tolerated, no laboratory abnormalities or adverse reactions reported
Miall-Allen	No adverse local or generalized reactions to ticarcillin/clavulanic acid reported
Bégué (1)	Intravenous administration was well tolerated. 1 case of erythema at injection site. 2 cases of allergic-type rash. 2 cases of moderate eosinophilia and 3 cases of neutropenia
Reed	No clinical or laboratory abnormalities were associated with treatment administration
Jacobs	Patients responded well to therapy, no further details provided
Feldman	Adverse reactions in 2 cases. 1 case of mild pruritic rash, 1 case of transient eosinophilia. Patients received other antimicrobials next to ticarcillin/clavulanic acid. No cessation of therapy needed
Al Roomi	1 case of severe diarrhea (withdrawal), 3 cases of vulvitis, 2 cases of loose stool. No biochemical or hematological abnormalities reported
Bégué (2)	Not reported
Nelson	Not reported
Van Niekerk	1 case of transient drop in white cell count, no other biochemical or hematological abnormalities reported
Schaad	Well tolerated, no local or systemic reactions reported
Jehl	Not reported
Hoberman	Diarrhea 17-25%, diaper dermatitis 22-33%
Jones	Well tolerated, no drug related adverse events
De Cock	Not reported
Schaad	3 cases of mild nausea without vomiting 1 hour after ingestion

Table 4. Reported side effects, adverse events and reactions from included studies.