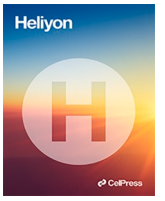
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Quality equivalence and in-vitro antibiotic activity test of different brands of amoxicillin/clavulanic acid tablets in Mwanza, Tanzania: A cross sectional study

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ABSTRACT

Background: Each film coated tablet of amoxicillin/clavulanic acid contains 500 mg of amoxicillin as an active pharmaceutical ingredient and 125 mg of clavulanic acid. Different brands have the same active ingredients but different excipients, which may cause differences in efficacy. With the emergence of generic antibiotics post-patent expiration, the antibiotic activity of generics is in question in comparison to the innovator. This study aims at determining the pharmaceutical quality and in-vitro antimicrobial activity of different brands of amoxicillin/clavulanate.
Method: ology: The study was a cross-sectional laboratory-based experimental study conducted at the TMDA (Tanzania Medicines and Medical Devices Authority) Lake Zone laboratory and the CUHAS Microbiology Laboratory from in May 2021. The study samples were four brands of amoxicillin/clavulanate and sixty archived isolates, thirty of which were *E. coli* and the remaining thirty *K. pneumoniae*. Determination of minimum inhibitory concentrations, assay and dissolution test results were used to make conclusions for the study.
Results: All tablets samples complied with the British pharmacopeia (BP) specifications, however sixty archived isolates which were tested in this study showed resistance towards the standard AMC disc (68 %). The innovator brand (AC1) showed significant mean difference from 2 out of 3 generics (p-values <0.05) while the first generic brand (AC2) showed significant superiority among the generics.
Conclusion: Thus, the four samples that were used all complied with the specifications according to BP on dissolution and assay tests but there was an overall resistance towards amoxicillin/clavulanate, and this was moreover seen by generic brands in comparison to the innovator which proved to be of superior activity.

1. Background

Amoxicillin is a broad-spectrum antibiotic belonging to the semi-synthetic group of aminopenicillin beta-lactams found in 1970s.

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The beta-lactam agents inhibit the synthesis of peptidoglycan in bacterial cell wall, however, some bacteria acquired to produce beta-lactamase which inactivates beta-lactam antibiotics. Clavulanic acid binds to bacterial beta-lactamase and enhances the effects of beta-lactam antibiotics. Combination of amoxicillin and clavulanic acid was patented, manufactured and marketed as Augmentin® in 1984 by Beecham which is now part of GlaxoSmithKline and still one of the most common antibiotics used as the first choice agent in different infections [1–3].

The growing market for pharmaceutical products led to increase of substandard and falsified drugs. The World Health Organization (WHO) estimated 10 % of medical products is either falsified or substandard in low and middle-income countries where standards of governance and technical capacity are limited [4,5]. Use of substandard and falsified antibiotics may have impact on treatment failure which increases mortality and mobility but also to drive antimicrobial resistance by exposing pathogens to subtherapeutic doses [6].

Generic medications are usually less expensive than patent medications and have approved they have the same therapeutic effect. However, despite formulation similarities but may use different excipients, many studies show that efficacy of generic drugs may be lower than their innovators [7,8]. Consumption of antibiotics are increased with more generics brands on the market resulting in growing resistance to antibiotics [9,10].

1.1. Amoxi-cluv indications

Amoxicillin formulation like amoxicillin/clavulanate is included in the treatment guidelines for the treatment of bacterial infections including sinusitis, acute otitis media, community acquired pneumonia, and acute exacerbations of chronic bronchitis [11]**.**

1.2. Amoxi-cluv in Tanzania

Due to the capacity limitation of pharmaceutical production, Tanzania depends on imported medications from different countries and bata-lactam antibiotics are the most imported antibiotics [12,13]. While in 2019, falsified Augmentin tables were found on the Tanzanian market [14].

Routine analysis on the quality and antimicrobial activity tests are necessary, therefore, this study aimed to determine the pharmaceutical quality and in-vitro antimicrobial activity of different brands of amoxicillin/clavulanate marketed in Mwanza, Tanzania.

2. Methodology

2.1. Material and reagents

Reagents that were used included; Water (Sigma-Aldrich, Milli-Q water purification system, United States), methanol (Sigma-Aldrich, HPLC grade, United States), orthophosphoric acid and sodium dihydrogen orthophosphate monohydrate (Sigma-Aldrich, analytical grade, United States), bleach reagent and MacConkey agar(Sigma-Aldrich, laboratory grade, United States). Apparatus that were used include; measuring cylinder(Pyrex Measuring Cylinder (Make: Pyrex, United States), volumetric flask (Class A Volumetric Flask (Make: Duran, Germany), beaker(Beaker: Pyrex Beaker (Make: Pyrex, United States), filter paper(Whatman Filter Paper (Make: Whatman, United Kingdom), thermometer(H–B Instrument Thermometer (Make: H–B Instrument, United States), analytical scale (Mettler Toledo Analytical Balance (Make: Mettler Toledo, Switzerland), mortar and pestle (Agate Mortar and Pestle (Make: Agate), petri dishes(Falcon Petri Dishes (Make: Falcon, United States), pipette (Eppendorf Pipette (Make: Eppendorf, Germany), cotton wool (Pharmco-AAPER Cotton Wool (Make: Pharmco-AAPER, United States), inoculation loop (Nichrome Inoculation Loop (Make: Various) and kerosene burner (Primus Kerosene Burner (Make: Primus, Sweden).

2.1.1. Commercial tablets used in this study

SN	Date of manufacture	Date of expire	Country of origin	Batch number
AC1	November 2019	November 2021	United Kingdom	3H5Y
AC2	June 2020	June 2022	China	687200601
AC3	July 2020	June 2022	India	ZA111
AC4	October 2019	September 2021	India	BTBUV0050

2.2. Equipment

HPLC machine (Model: Agilent 1260 Infinity II HPLC System: Agilent Technologies, United States) which was used for quantification of active pharmaceutical ingredients of samples collected. Dissolution tester (Erweka DT 820 Dissolution Tester, Germany) machine which was used to determine in vitro drug released. P^H meter (Mettler Toledo Seven Compact S220 pH Meter Make: Mettler Toledo, Switzerland) for measuring P^H, sonicator (Branson SFX150 Sonifier Make: Branson, United States) for sonication. Autoclave machine for sterilization of reagents and equipment. Electric stove for heating agar solutions. Incubator for the incubation of both

cultured and un-cultured agars.

2.3. Data collection procedure

Tablet samples were inspected to observe physical appearance and storage condition.

2.4. Antibacterial studies

2.4.1. Recovery of testing isolates, E. coli and K. Pneumoniae

Sixty Gram-negative bacteria, *E. coli* (n = 30) and *K. pneumoniae* (n = 30) were retrieved from previous studies databases, and sub-cultured on MacConkey agar (MCA; HiMedia, India) for recovery. MCA plates were incubated aerobically at 37 °C for 20 h. Fresh growth was used for further analysis.

2.4.2. Antibiotic susceptibility testing of standard AMC disk by disk diffusion method

Disk diffusion method by Kirby-Bauer technique as recommended by the Clinical and Laboratory Standards (CLSI) guidelines of 2020 [15]. One to two colonies of freshly growth of test bacteria were suspended into sterile 0.85 % normal saline and turbidity were adjusted equivalently to 0.5McFarland Standard solution. Then, using sterile bacteriological cotton swab, the entire surfaces of Mueller Hinton agar (MHA; HiMedia, India) plates were swabbed to obtain evenly lawns. Antibiotic disks of amoxicillin/clavulanic acid 30 μg (AMC; HiMedia, India) were seeded on each plate of MHA within 15 min. MHA plates were incubated at 37 °C in ambient air for 18 h. After incubation, zones of inhibitions around AMC disks were measured in millimetre using ruler and were interpreted to susceptible, intermediate and resistance as recommended by the CLSI, 2020.

2.4.3. Antibiotics susceptibility testing of AMC tablets by agar dilution method

AMC solutions were prepared by grinding 625 mg of AMC tablets of innovator (AC1) and generics (AC2, AC3 and AC4) into fine powder using motor and pestle and then dissolved into 25 ml of sterile distilled water. AMC solutions (AC1, AC2, AC3 and AC4) were sterilized by membrane filtration using filter paper (Whatman™, China). MHA plates were supplemented with AC1, AC2, AC3, and AC4 of increasing concentrations from 8 μg/ml (MIC of AMC by CLSI) to 16 μg/ml, 32 μg/ml and 64 μg/ml were prepared. Test bacterial suspensions equivalent to 0.5McFarland standard solution were inoculated on MHA 8 μg/ml, 16 μg/ml, 32 μg/ml and 64 μg/ml plates and then incubated in ambient air at 37 °C for 18 h. After incubation, the minimum concentrations that inhibited the growth of test bacteria were recorded as minimum inhibitory concentrations (MICs).

2.4.4. Quality control

E. coli (American Type Control Culture) ATCC 25922 and *K. pneumoniae* ATCC 700603 were used as control organisms.

2.5. Statistical analysis

The statistical analysis was conducted using SPSS to analyze the data obtained from the quality equivalence and in-vitro antibiotic activity test of different brands of amoxicillin/clavulanic acid tablets in Mwanza, Tanzania. Descriptive statistics were used to summarize the data, including mean, standard deviation, and percentage.

In addition to evaluating quality equivalence, the in-vitro antibiotic activity of the different brands was assessed. The minimum inhibitory concentration (MIC) values were determined for each brand using standard methods (e.g., broth microdilution method). The MIC values were compared using appropriate statistical tests, such as the *t*-test or Mann-Whitney *U* test.

3. Results

3.1. Specific results

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Table 1
Results on assay by HPLC machine.

Sample	Released%/tablet	SD	%RSD	Specification	Remark
AC1	93.0	3.6	0.2	90–105 % ± 5	Pass
AC2	109.3	1.0	0.0	90–105 % ± 5	Pass
AC3	107.6	5.5	0.3	90–105 % ± 5	Pass
AC4	101.2	2.5	0.1	90–105 % ± 5	Pass

4. Discussion

4.1. Assay test

Quantification of amoxicillin active pharmaceutical ingredient by using HPLC, results were 93 %, 109.3 %, 107.6 % and 101.2 % respectively as shown in Table 1. Compared to the specifications, sample AC1 and AC4 lies between the ranges but for the case of sample AC2 and AC3, they were found to be slightly out of the range. Since an error of not more than 5 % is acceptable, the small deviation observed in our results can be due to inaccurate measurements in pharmaceutical industry or during research study. Therefore, both samples passed the test and are of good quality that is they both contained acceptable amounts of the active pharmaceutical ingredients.

4.2. Dissolution test

According to BP, a tablet that after 45 min release more than 85 % of its active pharmaceutical ingredient will be of good quality. According to our study, sample AC1, AC2, AC3 and AC4 after 45 min released 108.9 %, 104.9 %, 105 % and 107.8 % respectively as presented in Table 2. This indicated that all tablets were of good quality since they all exceeded 85 %, the drugs can dissolve and reach to the systemic circulation for activity. According to the table presented above, sample AC1 which is the innovator released more of its active ingredient than the generic drugs, but all of the generic drugs also released their active ingredients in correct amounts.

4.4. Percentage resistance of isolates to AMC disc

The archived isolates tested in this study generally show high resistance towards the AMC disc (68.3 %) which was similar to other studies [16]. Resistance may be likely due to extensive use of this medication for first line treatment, prescription without prior microbial sensitivity results, non-adherence to dose and cheap availability over the counter. Results on the percentage resistance of isolates to AMC disc has presented on Table 3.

4.5. MIC comparison between innovator and generics

The proportion of isolates resistant (MIC $\geq$32 μg/ml) to amoxicillin/clavulanate innovator and generics were 83.3 %, 55 %, 76.7 %, 51.7 %, 80 %, 76.6 %, 100 % and 95 % as recommended by CLSI guideline (2020) [15] has presented on Table 4. Although, the innovator was found to be effective than generics, similar effects can be produced by the generics at higher doses i.e. they are dose dependent. The innovator shows significant superiority against AC4 at 32 μg/ml and 64 μg/ml, and AC3 at 64 μg/ml. It can thus be concluded that the innovator drug is superior in activity compared to both the second (AC3) and third (AC4) generic brand of amoxicillin/clavulanate. However, the second generic brand is superior in activity than the third generic brand. It should be kept in mind that differences in activity may induce the emergence of more resistant subpopulations [17].

The innovator's superiority may be due to several factors including lower availability compared to the generics making the intended bacteria less exposed to this drug [10,18,19]. The price of the innovator drug was eight times the price of each generic brand hence not easily accessible by the public. Formulation differences may also be a strong factor since it is unique and may not be available to other manufacturers. However, the absence of any significant difference in some of the parameters evaluated cannot be interpreted as evidence that the generics are equivalent to the innovator [7].

4.6. MIC comparison among generics

Data from the study shows that there was a significant superiority seen by AC2 compared to AC4 at 32 μg/ml, AC3 compared to AC4 at 32 μg/ml, AC2 compared to AC3 at 64 μg/ml, AC2 compared to AC4 at 64 μg/ml and AC3 compared to AC4 at 64 μg/ml. From these results shown in Table 5 it can be concluded that AC4 had the poorest activity among the other brands while AC2 was seen to be the superior of the three generic brands of amoxicillin/clavulanate. This is likely due to differences in formulations which may lead to alterations in activity [18,20,21]. It is well known that differences in excipients and production methods lead to different quality of medication [18]. It may also be due to transport and storage before and after being purchased for this study.

Table 2
Results on dissolution by HPLC machine.

Sample	Released%/tablet	SD	%RSD	Specification	Remark
AC1	108.9	5.4	4.9	>85 %	Pass
AC2	104.9	4.4	4.2	>85 %	Pass
AC3	105.0	3.1	3.0	>85 %	Pass
AC4	107.8	4.5	4.1	>85 %	Pass

Table 3
Isolates and percentage resistance to amoxicillin/clavulanic acid.

Antibiotic tested (μg/ml)	Overall Resistance			*E. coli*			*K. pneumoniae*		
	R	I	S	R	I	S	R	I	S
AC1-8	60 (100 %)	N/A	–	30 (100 %)	N/A	–	30 (100 %)	N/A	–
AC1-16	60 (100 %)	N/A	–	30 (100 %)	N/A	–	30 (100 %)	N/A	–
AC1-32	50 (83.3 %)	N/A	10 (16.6 %)	22 (73.3 %)	N/A	8 (26.7 %)	28 (93.3 %)	N/A	2 (6.75 %)
AC1-64	33 (55 %)	N/A	–	14 (46.7 %)	N/A	16 (53.3 %)	19 (63.3)	N/A	11 (36.7 %)
AC2-8	60 (100 %)	N/A	–	30 (100 %)	N/A	–	30 (100 %)	N/A	–
AC2-16	57 (95 %)	N/A	3 (5 %)	30 (100 %)	N/A	–	27 (90 %)	N/A	3 (5 %)
AC2-32	46 (76.7 %)	N/A	14 (23.3 %)	17 (56.7 %)	N/A	13 (43.3 %)	29 (96.7 %)	N/A	1 (3.3 %)
AC2-64	31 (51.7 %)	N/A	29 (48.3 %)	8 (26.7 %)	N/A	22 (73.3 %)	23 (76.7 %)	N/A	7 (23.3 %)
AC3-8	60 (100 %)	N/A	–	30 (100 %)	N/A	–	30 (100 %)	N/A	–
AC3-16	60 (100 %)	N/A	–	30 (100 %)	N/A	–	30 (100 %)	N/A	–
AC3-32	48 (80 %)	N/A	12 (20 %)	19 (63.3 %)	N/A	11 (36.7 %)	29 (96.7 %)	N/A	1 (3.3 %)
AC3-64	46 (76.6 %)	N/A	14 (23.3 %)	18 (60 %)	N/A	12 (40 %)	28 (93.3 %)	N/A	2 (6.7 %)
AC4-8	60 (100 %)	N/A	–	30 (100 %)	N/A	–	30 (100 %)	N/A	–
AC4-16	60 (100 %)	N/A	–	30 (100 %)	N/A	–	30 (100 %)	N/A	–
AC4-32	60 (100 %)	N/A	–	30 (100 %)	N/A	–	30 (100 %)	N/A	–
AC4-64	57 (95 %)	N/A	3 (5 %)	27 (90 %)	N/A	3 (10 %)	30 (100 %)	N/A	–
AMC	41 (68.3 %)	17 (28.3 %)	2 (3.3 %)	19 (63.3 %)	9 (30 %)	2 (3.3 %)	22 (73.3 %)	8 (26.7 %)	–

Key: AC1 = innovator; AC2 = generic 1; AC3 = generic 2; AC4 = generic 3 R=Resistant; I=Innovator; S=Susceptible; N/A = Not Available.

Table 4
Comparison between generics and innovator.

Antibiotic Mean (±SD) (μg/ml)		Mean (±SD) Difference	[95 % CI]	*P*-Value
AC1-32	0.17 (±0.37)	[-0.07 (±−0.006)]	[-0.21–0.08]	0.3655
AC2-32	0.23 (±0.43)			
AC1-32	0.17 (±0.37)	[-0.03 (±−0.03)]	[-0.17–0.11]	0.6404
AC3-32	0.2 (±0.40)			
AC1-32	0.17 (±0.37)	[0.17 (±0.37)]	[0.71–0.26]	0.0008
AC4-32	0 (±0)			
AC1-64	0.45 (±0.50)	[-0.03 (±0)]	[-0.21–0.15]	0.7172
AC2-64	0.50 (±0.50)			
AC1-64	0.45 (±0.50)	[0.22 (±0.07)]	[0.05–0.39]	0.0121
AC3-64	0.23 (±0.43)			
AC1-64	0.45 (±0.50)	[0.4 (±0.28)]	[0.26–0.54]	<0.001
AC4-64	0.05 (±0.22)			

Table 5
Comparison between generics.

Antibiotic Mean (±SD) (μg/ml)		Mean (±SD) Difference	[95 % CI]	*P*-Value
AC2-16	0.05 (±0.22)	0.05 (±0.22)	[-0.01–0.11]	0.0806
AC3-16	0 (±0)			
AC2-16	0.05 (±0.22)	0.05 (±0.22)	[-0.01–0.11]	0.0806
AC4-16	0 (±0)			
AC2-32	0.23 (±0.43)	0.03 (±0.03)	[-0.12–0.2]	0.6609
AC3-32	0.2 (±0.4)			
AC2-32	0.23 (±0.43)	0.23 (±0.43)	[0.12–0.34]	<0.001
AC4-32	0 (±0)			
AC3-32	0.2 (±0.4)	0.2 (±0.4)	[0.1–0.3]	0.0002
AC4-32	0 (±0)			
AC2-64	0.5 (±0.5)	0.25 (±0.1)	[0.1–0.4]	0.004
AC3-64	0.2 (±0.4)			
AC2-64	0.5 (±0.5)	0.43 (±0.28)	[0.3–0.6]	<0.001
AC4-64	0.05 (±0.22)			
AC3-64	0.23 (±0.43)	0.20 (±0.21)	[0.06–0.31]	0.0037
AC4-64	0.05 (±0.22)			

4.7. Comparison between quality and antimicrobial activity

From the above results, it can be noticed that there is a close link between the antimicrobial activity and the quality pharmaceutical parameters of each brand of amoxicillin/clavulanate. It has been seen that the innovator was superior in antimicrobial activity

compared to AC3 and AC4. This may be linked to the high dissolution rate of the innovator (108.9 %) compared to AC3 (105 %) and AC4 (107.8 %). Despite the dissolution rate of AC2 being less than the other generics (104.9 %), it showed superior antimicrobial activity since it contained a higher content of active pharmaceutical ingredient (109.3 %) than the other generics; AC3 (107.6 %) and AC2 (109.3 %).

At concentrations of 8 μg/ml and 16 μg/ml, all brands, including the innovator, exhibited resistance. This may be to a few factors, the first being the failure to test the pharmaceutical parameters of clavulanic acid. This missing information would be of great importance since clavulanic acid has the main role of preventing the destruction of the lactamase ring in the drug. Another factor may be the overall growing resistance seen by these isolates towards amoxicillin/clavulanate.

5. Conclusion

The findings of this study revealed a concerning trend of resistance towards amoxicillin/clavulanate across the tested brands. Notably, the resistance was more prominent among the generic brands in comparison to the innovator brand, which demonstrated superior activity.

These results suggest that the quality and efficacy of amoxicillin/clavulanate formulations can vary depending on the brand, with the innovator brand showing better performance in terms of antimicrobial activity. Further investigation into the specific factors contributing to this difference is warranted.

Possible factors influencing the observed resistance among generic brands could include variations in manufacturing processes, differences in the quality of raw materials, or variations in formulation stability. Additionally, variations in the dosage, dissolution profiles, or bioavailability of the active ingredients may also contribute to the observed differences in antimicrobial activity.

It is crucial for regulatory bodies and healthcare providers to be aware of these findings and consider the potential impact on treatment outcomes. Further studies and increased surveillance are necessary to better understand the reasons behind the observed resistance and ensure the availability of high-quality amoxicillin/clavulanate formulations in the market." Generics are an economic relief to many countries, however, this should not be at the expense of low-quality patient care.

6. Recommendations

1. We would like to recommend further studies to be done concerning amoxicillin/clavulanate with a larger sample size of clinical isolates and drugs to come up with a more generalized study.
2. We would also recommend further studies to investigate the presence of resistant genes that may be harboured by these bacteria with resistance against amoxicillin/clavulanate.
3. Further study should be done on clavulanic acid so as to rule out on the belief that Amoxicillin/clavulanic acid can be of the correct amount on active pharmaceutical ingredient, but less amount of clavulanic acid that cannot inhibit the lactamase enzyme and cause degradation of the active ingredient and lead to therapeutic failure.

Ethical approval and consent to participate

The current study does not involve human participants or animals so ethical approval and consent to participate are not applicable on this case. But study was given ethical clearance by Joint BMC-CUHAS ethics and Review Committee.

Consent for publication

Not applicable.

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Data availability statement

Unfortunately, due to privacy and confidentiality considerations, the authors do not possess the necessary permissions to share the dataset used in this study.

CRediT authorship contribution statement

Emmanuel Kimaro: Writing - review & editing, Writing - original draft, Supervision, Conceptualization. **Erica Yusto:** Methodology, Data curation. **Annin Mohamed:** Methodology, Formal analysis. **Vitus Silago:** Writing - review & editing, Investigation. **Prisca Damiano:** Methodology, Investigation. **Kayo Hamasaki:** Writing - review & editing, Investigation. **Eliangiringa Kaale:** Project administration, Methodology.

Declaration of competing interest

The authors declare that they have no competing interests.

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List of Abbreviation

AC1-AC4 Code name "Generic names" of different Amoxyclav tablets
AMC- disks Amoxyclav disks
CLSI Clinical and Laboratory standards (CLSI)
CUHAS Catholic University of Health and Allied Science
HPLC High performance liquid chromatography
MHA Mueller Hinton agar
MCA MacConkey agar
MIC Minimum Inhibitory Concentration
MUHAS Muhimbili University of Health and Allied Science
SPSS Statistical Package for the Social Sciences
WHO World Health Organization

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