

Review**Evaluation of in-vivo and in-vitro microbiological methods for testing the efficacy of parenteral antibiotics: A Review**BAG Chaturanga¹, DMBT Dissanayake², SSN Fernando², CA Wanigatunge³*Sri Lankan Journal of Infectious Diseases 2020 Vol.10(2):86-97*DOI: <http://dx.doi.org/10.4038/sljid.v10i2.8275>**Abstract**

Antibiotics are available as innovators and generics. An innovator or branded drug is a medicine that is discovered, developed and marketed by a pharmaceutical company which also holds the patent for that drug. Generics only become available after the patent on the innovator expires. Generic drugs are required to have the same active ingredient, strength, dosage form, and route of administration as the innovator product. Generics should be bioequivalent to the innovator and when used, should have the same efficacy and safety profile. This is crucial for parenteral antibiotics because according to the World Health Organization and U.S. Food and Drug Administration criteria, parenteral generic products do not need to provide evidence for in-vivo bioavailability or bioequivalence before they can be marketed. Published evidence shows that there is a disparity in the efficacy of different generic antibiotic products. In-vitro microbiological methods of efficacy testing have been recognized as a standardized and cost-effective approach to clarify doubts regarding the efficacy of generic parenteral antibiotics. However, in-vitro methods used alone, might not be a good measurement of antibiotic efficacy as several studies have shown disparities between in-vitro and in-vivo efficacy of parenteral antibiotics.

Key words: *efficacy, generic drugs, innovator products, parenteral antibiotics, in-vitro*

Introduction

Antibiotics, the choice of treatment for bacterial infections, have greatly reduced illness and death from infectious diseases and helped to improve life expectancy. Antibiotics have become one of the most frequently used medicinal drugs for both treatment and prophylaxis. The global antibiotic consumption has increased by 65%, i.e. from 21.1 to 34.8 billion defined daily doses, between

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2000 and 2015. This was primarily driven by increased consumption in lower and middle income countries.¹

Antibiotics are available both as innovator products and generics. An innovator product is a medicine that is discovered, developed and marketed by a pharmaceutical company which also holds the patent for that drug, while a generic is a product that is comparable to an innovator/branded/reference listed product in dosage, form, strength, route of administration, quality and performance characteristics and intended use.² Generics only become available after the patent and/or data protection period expires on an innovator drug. Generic products are typically sold at lower costs, primarily because they do not have to bear expenses for drug discovery studies and also as a result of the competition in the market. Introduction of generics have resulted in significant reduction in prices of antibiotics.³

A major concern for healthcare delivery systems in developing countries is finding ways to limit increasing costs without compromising quality. To address this issue, their governments have encouraged the use of generic medicines. Medical practitioners in Sri Lanka are legally required to write the generic name of the medicine in every prescription.⁴ The prescriber may also write a brand name of the drug in addition to the generic name if desired. To effectively implement this policy, the generic drugs must be bioequivalent and pharmaceutically equivalent to the innovator/branded counterpart. To be pharmaceutically equivalent, a similar dosage form of a generic product must contain identical amounts of active ingredients and be identical in strength/concentration to the innovator. A generic product is considered bioequivalent to an innovator when there is no significant difference between the generic and the innovator in the rate and extent to which the active ingredient becomes available at the site of drug action when administered at the same dose under similar conditions.⁵

In most low and middle-income countries such as Sri Lanka, infrastructure facilities related to drug registration are not optimal. Laboratory facilities are not adequate to provide complete quality checks of generic products and are mostly limited to paper-based assessments at registration and when complaints are received. This factor might influence the medical practitioners in the selection of generic products for treatment. A survey conducted among physicians in the United States of America revealed that the majority showed concern about the quality and efficacy of generic drugs and this perception was a barrier to increase their use of generic drugs.⁶ Evidence based studies are required in developing countries to ensure that generics have the same efficacy and safety profile as innovator drugs which will then promote the prescription of generics to achieve the expected economic benefits. This general review was conducted to determine whether the existing literature supports the use of generic parenteral antibiotics and to analyze published data regarding the in-vitro assessment of parenteral antibiotic efficacy by microbiological methods.

Search strategy and selection of publications

As this is a general review, a broad search strategy was adopted. A literature search was performed in MEDLINE and PUBMED, without limits for publication date but with limits for English language publications. All articles published until August 2018 that were within the inclusion criteria were selected. The following keywords were used in various combinations for the literature search: 'generics,' 'generic products,' 'parenteral antibiotics,' 'brand name antibiotics,' 'in-vitro

efficacy testing,' 'microbiological methods,' 'minimal inhibitory concentration,' 'efficacy' and 'innovator products'.

Selection of appropriate studies

All authors independently reviewed abstracts to identify articles that required a full-text review. Final decision regarding the inclusion of an article was reached through consensus. Reference lists of the selected articles were searched for additional articles.

Two main categories of published data were selected for the review.

1. Studies that assessed therapeutic equivalence or non-equivalence of generic and branded drugs.
2. Comparative microbiological studies of the efficacy of parenteral antibiotics

Studies were selected, if they reported on a comparative assessment of at least two different commercial products of the same parenteral antibiotic. Comparative evaluation had to be done by microbiological methods.

Qualitative analyses of efficacy, clinical trials and pharmaco-economic evaluations were excluded.

Results

We identified 21 original research articles that fall under the above two categories for detailed analysis: There were 16 studies where the efficacy of parenteral antibiotics was compared by in-vitro methods. Of these, five (5) assessed both in-vivo and the in-vitro efficacy simultaneously. Two (2) studies showed therapeutic failures when using generic antibiotics and three (3) studies focused on increased antimicrobial resistance following the use of generic antibiotics.

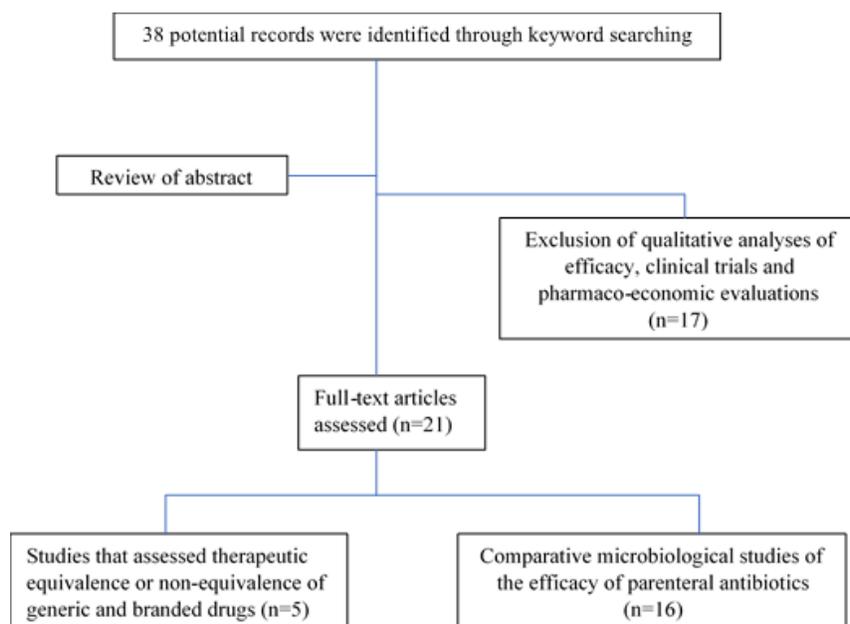


Figure 1: Summarized search strategy

Evidence for therapeutic failures and increased antimicrobial resistance following the use of generic antibiotics.

Therapeutic failures as a result of using suboptimal antibacterial therapy will lead to increased morbidity, mortality and dissatisfaction among prescribers regarding the generic antibiotics. Galleli et al⁷ reported a case series in which therapeutic failures were observed during treatment with generic products of ciprofloxacin and levofloxacin. Switching from generics to innovator formulations resulted in clinical improvement. The findings suggest that the use of generic drugs could lead to increased duration of the disease or therapeutic failure. In another case study, a patient developed methicillin resistant *Staphylococcus aureus* (MRSA) bacteremia following liver transplantation and was given a generic vancomycin product for 10 days without improvement of the condition.⁸ When the patient was switched to an identical regimen using the innovator product, clinical improvement was rapidly evident with sterility in blood cultures taken 24 hours after the infusion of the innovator product.⁸

Use of commercial products with low level of antibacterial efficacy results in therapeutic failures and might also promote the selection of resistant bacterial subpopulations.⁹ Such resistant bacterial infections would require broad spectrum antibiotics. An increase in the demand for broad spectrum antibiotics was noted after the introduction of generic products to the German pharmaceutical market after the year 2000.¹⁰ Generic norfloxacin was introduced to the German market in 1999 and the resistance rate increased by nearly 3 fold (26.4% in 2007) after the introduction of generics.¹⁰ In Denmark, a significant increase was observed in ciprofloxacin resistance in urine isolates of *Escherichia coli* after the introduction of generic ciprofloxacin.³ These data show the importance of establishing monitoring mechanisms to evaluate the quality of generic drugs.

The situation becomes more critical for parenteral antibiotics as both WHO and FDA criteria do not require parenteral generic products to provide evidence of in-vivo bioavailability or bioequivalence for approval.^{11,12} These authorities assume that the two products are therapeutically equivalent if they are pharmaceutically equivalent. This criterion of assessing therapeutic equivalence of generic drugs has been challenged by various researchers.^{7,8} Quality and efficacy testing therefore play a vital role to clear doubts among patients, healthcare personnel and prescribers regarding parenteral generic antibiotics.

Assessment of the efficacy of generic parenteral products by microbiological methods

Antibiotic efficacy can be assessed by different methodologies including analytical chemistry, in-vitro susceptibility studies, in-vivo animal experiments, and clinical studies in humans.¹³ In-vitro methods of efficacy testing have been recognized as a standardized and cost effective approach and thus recommended for parenteral antibiotics as their bioequivalence is considered as “self-evident”.¹⁴

Various in-vitro techniques have been used to compare the efficacy of different brands of antibiotics. Of the 16 studies considered in this review, Minimal Inhibitory Concentration (MIC) was used for efficacy testing in 13 studies. MIC is the lowest concentration of an antimicrobial agent that prevents visible growth of a microorganism in an agar or broth dilution susceptibility test.¹⁵ Seven studies (n=7) used Minimal Bactericidal Concentration (MBC) alongside the MIC

for efficacy testing. MBC is the minimal concentration of drug needed to kill most ($\geq 99.9\%$) of the viable organisms after incubation for a fixed length of time (generally 24 hours) under a given set of conditions.¹⁶ One study used MBC on its own without the MIC. Agar diffusion technique was used in three studies to assess efficacy instead of MIC or MBC. A summary of the in-vitro studies conducted to test the efficacy of parenteral antibiotics is given in Table 1.

In some studies (n=5), in-vitro efficacy was determined as a preliminary investigation prior to in-vivo efficacy tests. These studies have shown contradictory results where in-vitro studies show no difference in efficacy among different brands as opposed to in-vivo studies.¹⁷⁻¹⁹ All these researchers have used MIC as the in-vitro testing method and neutropenic mouse thigh infection model as the in-vivo testing method (Table 2). Zuluaga et al¹⁷ compared the in-vitro efficacy of 19 generics and one innovator product of intravenous gentamicin with the reference powder. Only one generic product demonstrated a statistically significant low level of efficacy in this study. Ten products, including the gentamicin reference powder, showed significantly low efficacy in the in-vivo testing. According to Vesga et al¹⁸ three generics and the innovator product of intravenous vancomycin showed no difference in efficacy in the in-vitro test whereas all three generics failed in-vivo. Only the innovator has shown the expected level of efficacy in the in-vivo testing. Similar observations were made by Rodriguez et al¹⁹ when they tested 11 generics and one innovator of oxacillin. No significant difference was observed in the in-vitro test, but all generics failed to achieve innovator's maximum effect in the in-vivo test. These studies highlight the importance of testing the in-vivo efficacy of parenteral antibiotics although this is not required by drug regulatory authorities.

Rodriguez et al²⁰ have compared the in-vitro activity of an innovator and a generic piperacillin-tazobactam in a study aimed to determine the impact of therapeutically non-equivalent generics on bacterial resistance. Though there was no significant difference in MIC value for both innovator and generic products, therapeutic non-equivalence was observed in the in-vivo assessment and higher enrichment of resistant sub-populations when exposed to the generic products. The same group of researchers have also studied an innovator and five generics of ciprofloxacin.²¹ All those products were identical in pharmaceutical and therapeutic equivalence, in terms of in-vitro activity and in-vivo pharmacodynamics. No differences were observed regarding the magnitude and mechanisms of resistance selection. These two studies have shown that the therapeutic non-equivalence of generics promote antibiotic resistance, whereas generics with equivalent efficacy as efficient as the innovator in preventing resistance.

Three in-vitro studies adopted the agar diffusion test as an alternative to MIC and MBC. These researchers compared the diameters of the zone of inhibition between different brands of antibiotics to determine efficacy. Gunasekaran et al²² tested seven parenteral ceftriaxone brands using this technique. Diluted test antibiotic solutions were added to wells punched in the agar inoculated with the control bacterial strains and allowed to diffuse. Significant difference was not observed in the diameter of the zone of inhibition for different brands and the authors recommended the use of cheaper generic products to reduce the health care cost. Pathak et al and Nkang et al used a different technique where they absorbed the diluted test antibiotics onto filter paper disks which were placed on the inoculated agar. Six products of amoxicillin-clavulanic acid were tested by Pathak et al²³ who noted a significantly lesser zone of inhibition for one product against *E. coli* ATCC 25922. Nkang et al²⁴ used two brands each from ampicillin,

chloramphenicol, erythromycin, co-trimoxazole and vancomycin to test efficacy. No significant difference was observed in the zone of inhibition of the tested brands. These three studies were conducted in low and middle-income countries (Ethiopia, India and Nigeria). They may have adopted this technique due to the unavailability of resources to carry out MIC and MBC.

The majority of the studies used standard bacterial strains as the test organism to determine efficacy. Fujimura et al^{25,26} performed two studies using clinical isolates as the test organisms. In one of the studies 80 clinical isolates of MRSA were used to test one innovator and five generics of parenteral vancomycin.²⁵ The MIC value of a generic product was higher than that of the other products and the content in each vial also varied between the branded and generic vancomycin products. 147 clinical isolates of MRSA were used to test the efficacy of one innovator and seven generics of teicoplanin. There was no difference in the in-vitro susceptibility between the innovator and the generic products.²⁶

Only a few authors have observed differences in efficacy between various brands of parenteral antibiotics by in-vitro testing methods. Jones et al²⁷ tested 12 generics formulations and one innovator product of piperacillin/tazobactam with four standard bacterial strains. They observed the highest activity with the innovator product, while one generic showed a significantly decreased activity. Zuluaga et al¹⁷ have also noted a low level of efficacy in one of 20 pharmaceutically equivalent generics of gentamicin. Other authors have reported similar MIC/MBC values for innovator and generic products and thus concluded that there was no difference in efficacy according to the in-vitro test results.

The majority of published data does not show significant pharmacokinetic differences when in-vitro and in-vivo efficacy comparisons were done simultaneously.¹³ While the in-vitro efficacy (MIC and MBC) was comparable, the therapeutic efficacy of generic and innovator products showed variability. The pharmaceutical equivalence may not therefore always imply therapeutic equivalence. These results suggest that in-vitro methods may not be very effective in detecting differences among therapeutically inequivalent generics.

Table 1: Summary of the in-vitro microbiological studies on parenteral antibiotic efficacy

Authors & year of publication	Evaluated antibiotics	Used in-vitro technique	Test organism	Main findings	Comments
Zuluaga et al ¹⁷ Colombia, 2010	Innovator product, 19 generics and the reference powder of gentamicin	MIC by micro broth dilution & MBC	Clinically isolated <i>E. coli</i> and <i>Pseudomonas aeruginosa</i> - ATCC 27853.	One generic showed significantly higher MIC and MBC values whereas all other gentamicin generic products were not different to that of the innovator	In-vivo efficacy tests were also carried out
Vesga et al ¹⁸ Colombia, 2010	Innovator and 3 generic products of vancomycin	MIC by micro broth dilution, MBC & Time kill curves	<i>Staphylococcus aureus</i> - a clinical isolate and ATCC 29213	No difference was observed in MIC, MBC and MIC/MBC ratio between tested products	In-vivo efficacy tests were also carried out
Rodriguez et al ¹⁹ Colombia, 2010	Innovator and 9 generic products of oxacillin	MIC by micro broth dilution & MBC	<i>Staphylococcus aureus</i> - a clinical isolate and ATCC 29213	There were no differences in the MIC, MBC and MIC/MBC ratio in the innovator and 9 generic products	In-vivo efficacy tests were also carried out
Rodriguez et al ²⁰ Colombia, 2016	Innovator and four generic product of piperacillin-tazobactam	MIC by CLSI method and Jones-modified arithmetic dilution method	<i>E. coli</i> ATCC 35218, <i>E. coli</i> 35218R and <i>E. coli</i> 35218Δbla	No significant difference was observed in MIC	In-vivo efficacy tests were also carried out
Rodriguez et al ²¹ Colombia, 2014	Innovator and five generics of ciprofloxacin	MIC by micro broth dilution and MBC	<i>Pseudomonas aeruginosa</i> PAOI	No significant difference was observed in MIC and MBC	In-vivo efficacy tests were also carried out.
Gunasekaran et al ²² Ethiopia, 2015	7 generic products of ceftriaxone	Agar well plate diffusion method	<i>Escherichia coli</i> ATCC 10536, <i>Staphylococcus aureus</i> ATCC 29737, <i>Pseudomonas aeruginosa</i> ATCC 25619, and <i>Salmonella typhi</i> ATCC 06775	No significant difference was observed in the zone of inhibition for all seven products of ceftriaxone	All generics showed sufficient inhibitory activity against all four microorganisms
Pathak et al ²³ India, 2016	1 generic and 5 "brand preparations" of amoxicillin-clavulanic acid	Antibiotic impregnated paper disk diffusion method	<i>Escherichia coli</i> ATCC 25922 and <i>Staphylococcus aureus</i> ATCC 25923	One brand has shown a statistically significant less zone of inhibition compared to other used products	
Nkang et al ²⁴ Nigeria, 2010	2 "brand-name" products each from ampicillin, chloramphenicol, erythromycin, cotrimoxazole and vancomycin were tested	Antibiotic impregnated paper disk diffusion method	Clinically isolated <i>Escherichia coli</i> , <i>Staphylococcus aureus</i> , <i>Pseudomonas aeruginosa</i> , <i>Klebsiella pneumoniae</i> and <i>Streptococcus pyogenes</i>	Significant difference was not observed in the diameter of the zone of inhibition between test drugs and the standard antibiotic disks for <i>E. coli</i> , <i>S. aureus</i> & <i>S. pyogenes</i> . For <i>P. aeruginosa</i> , the two brands of ampicillin and erythromycin and for <i>K. pneumoniae</i> , the two brands of chloramphenicol and erythromycin were significantly less effective compared to the standard disks	
Fujimura et al ²⁵ Japan, 2008	1 brand and 5 generic products of vancomycin	MIC by micro broth dilution	80 clinical isolates of MRSA	MIC of one generic product was slightly higher than the others	The content of vancomycin per vial varied from 91.0% to 103.4% for generic products. The generic which produced the highest MIC accounted for the lowest content.
Fujimura et al ²⁶ Japan, 2011	1 brand and 7 generic products of teicoplanin	MIC by micro broth dilution	147 clinical isolates of MRSA	MIC of the brand and all the generic products were similar	Potency equivalent of each generic teicoplanin tended to be lower than that of the branded drug
Jones et al ²⁷ USA, 2008	14 generic and 1 branded products of Piperacillin /Tazobactam	MIC by micro broth dilution	<i>Escherichia coli</i> - ATCC 25922 & ATCC 35218, <i>Pseudomonas aeruginosa</i> - ATCC 27853, <i>Staphylococcus aureus</i> - ATCC 29213	One generic product showed equal MIC value to the branded product. All the other products (22 sampled lots from 13 manufacturers) exhibited decreased activity in MIC that varied from the branded product by -5% to -35%	The branded (Zosyn®) formulation is used as a reference material to compare the MIC values

Table 2 (ct): Summary of the in-vitro microbiological studies on parenteral antibiotic efficacy

Authors & year of publication	Evaluated antibiotics	Used in-vitro technique	Test organism	Main findings	Comments
Jones et al ²⁷ USA, 2008	14 generic and 1 branded products of Piperacillin /Tazobactam	MIC by micro broth dilution	<i>Escherichia coli</i> - ATCC 25922 & ATCC 35218, <i>Pseudomonas aeruginosa</i> - ATCC 27853, <i>Staphylococcus aureus</i> - ATCC 29213	One generic product showed equal MIC value to the branded product. All the other products (22 sampled lots from 13 manufacturers) exhibited decreased activity in MIC that varied from the branded product by -5% to -35%	The branded (Zosyn®) formulation is used as a reference material to compare the MIC values
Tank et al ²⁸ India, 2016	1 generic and 3 brands of Ceftriaxime	MIC by macro broth dilution technique and MBC	<i>Pseudomonas aeruginosa</i> (ATCC 27853)	No significant difference in MIC/MBC values of the evaluated products	Cost of the branded drugs were approximately 5 times to 8 times higher than the generic product
Silva et al ²⁹ Colombia, 2010	Innovator (MERONEM®, TAZOCIN®), trademark products and generic products of Meropenem and Piperacillin /Tazobactam available in Colombia	MIC by micro broth dilution and MBC, Critical concentration, Production of spontaneous mutation	<i>Acinetobacter baumannii</i> - 4 strains, vancomycin-resistant <i>Enterococcus gallinarum</i> , <i>Streptococcus faecalis</i> ATCC 29212 and vancomycin-sensitive strain, <i>E. coli</i> - 3 strains, <i>Klebsiella pneumoniae</i> - 4 strains, <i>Pseudomonas aeruginosa</i> - 4 strains, and <i>Staphylococcus aureus</i> - 2 clinical strains & ATCC 25923	MIC and MBC results obtained with different Pathogenic and control strains showed no differences among samples, No significant difference in critical concentration among samples, All the samples behaved similarly in spontaneous mutant production	All the evaluated generic products have fulfilled the requirements to be considered for clinical use
Diaz et al ³⁰ Colombia, 2011	Trademarked and generic products of vancomycin available in Colombia	MIC by micro broth dilution and MBC, Critical concentration, Production of spontaneous mutation	<i>Acinetobacter baumannii</i> - 4 strains, vancomycin-resistant <i>Enterococcus gallinarum</i> , <i>Streptococcus faecalis</i> ATCC 29212 and vancomycin-sensitive strain, <i>E. coli</i> - 3 strains, <i>Klebsiella pneumoniae</i> - 5 strains, <i>Pseudomonas aeruginosa</i> - 4 strains, and <i>Staphylococcus aureus</i> - 2 clinical strains & ATCC 25923, <i>Morganella morganii</i> HE2	No significant difference was observed in MIC, MBC, Critical concentration and in the spontaneous mutant production	All the evaluated generic products have fulfilled the requirements to be considered for clinical use
Moet et al ³¹ USA, 2009	14 generic products of Piperacillin /Tazobactam	MIC by micro broth dilution	<i>Escherichia coli</i> - ATCC 25922 & ATCC 35218, <i>Pseudomonas aeruginosa</i> - ATCC 27853, <i>Staphylococcus aureus</i> - ATCC 29213	2 generics showed MIC values greater than the branded product. Other products (23 sampled lots from 14 manufacturers) exhibited decreased activity in MIC that varied from the branded product by -3% to -42%	This study was performed to expand the findings of Jones et al ²⁷ and has used 14 generics that were not studied by Jones et al.
Naimi et al ³² Afghanistan, 2016	40 generic products of ceftriaxone	MBC	<i>Staphylococcus aureus</i> - ATCC 29213	MBC difference among the products were not statistically significant	Efficacy had no relationship with the price of the product

Abbreviations: MIC, Minimal Inhibitory Concentration; MBC, Minimal Bactericidal Concentration; ATCC, American Type Culture Collection

Table 3: Summary of the studies where the efficacy is assessed by both in-vitro and in-vivo techniques

Authors & year of publication	Tested antibiotic/s and test organism/s	Used in-vitro & in-vivo techniques	Main in-vitro finding	Main in-vivo finding	Comment
Zuluaga et al ¹⁷ , 2010	Gentamicin – innovator, 19 generics & the reference powder Test organism: <i>E. coli</i> – clinical isolate <i>P. aeruginosa</i> ATCC 27853	In-vitro: MIC & MBC In-vivo: neutropenic mouse thigh infection model	Only one generic showed significantly higher MIC and MBC (lower efficacy) compared with the innovator	Reference powder & nine generics displayed significantly lower efficacy from the innovator	Reference powder & eight generics failed in-vivo despite being equivalent by in-vitro methods
Vesga et al ¹⁸ , 2010	Vancomycin – innovator & three generics Test organism: <i>S. aureus</i> – a clinical isolate and ATCC 29213	In-vitro: MIC, MBC & time-kill curves (TKC) In-vivo: neutropenic mouse thigh infection model	Vancomycin products did not differ in MIC, MBC, MBC/MIC and TKC	Only the innovator displayed the expected bactericidal efficacy (maximum antibacterial effect - E _{max})	All generics failed in-vivo despite being equivalent by in-vitro methods
Rodriguez et al ¹⁹ , 2010	Oxacillin – innovator & 11 generics Test organism: <i>S. aureus</i> – a clinical isolate and ATCC 29213	In-vitro: MIC & MBC In-vivo: neutropenic mouse thigh infection model	Only 9 generics & the innovator were tested in-vitro. No differences were observed.	All generics (n=11) failed to demonstrate therapeutic equivalence with the innovator	Microbiological assay was done to determine the concentration of active pharmaceutical ingredient of innovator & 9 generics. Four generics did differ in potency.
Rodriguez et al ²⁰ , 2016	Piperacillin-tazobactam – innovator & 4 generics Test organism: <i>E. coli</i> /ATCC 35218, 35218R and 35218Δbla	In-vitro: MIC In-vivo: neutropenic mouse thigh infection model.	No difference was observed in MIC	Only two generics and the innovator were tested in-vivo. One generic failed to demonstrate therapeutic equivalence with the innovator	Further tests were done with the failed generic to determine the selection of resistant bacterial sub-populations. The generic amplified the resistant sub-population up to 20-times compared with the innovator.
Rodriguez et al ²¹ , 2014	Ciprofloxacin – Innovator and five generics Test organism: <i>P. aeruginosa</i> ATCC 27853 & clinical strain	In-vitro: MIC & MBC In-vivo: neutropenic mouse thigh infection model.	There were no differences in the MIC or MBC for all products.	No difference in therapeutic equivalence with the innovator	Selection of resistant bacterial sub-populations were same magnitude for the innovator & generics.

Conclusion

It is important to maintain both pharmaceutical equivalence and bioequivalence between innovator products and their generics. Eleven of the sixteen studies in this review (68.8%) have shown no significant differences in the efficacy between generic and innovator antibiotics. However, in studies where in-vivo and in-vitro tests were done simultaneously on the same drugs, significant differences in efficacy were observed with in-vivo results. This is probably because the different brands were pharmaceutically equivalent, but not therapeutically equivalent. Thus the implication of in-vitro results alone to determine the efficacy of parenteral antibiotics may not yield optimum results. In-vitro methods such as MIC and MBC can be applied as a preliminary tool in the efficacy assessment. In low-income countries where optimal laboratory facilities are not available, in-vitro efficacy testing will serve as a presumptive method to identify sub-optimal generic parenteral antibiotics. Since the literature shows a discrepancy between in-vitro and in-vivo efficacy of different brands of parenteral antibiotics, policy makers in these countries should strive to implement in-vivo efficacy testing as a more standard tool for drug efficacy evaluation.

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