An assessment of the prevalence and treatment outcomes of multiple antibiotic prescribing *vis-à-vis* the appropriateness of antibiotic prescriptions in the empirical treatment of infections: A cross-sectional study from Lesotho

Matthias Adorka[1]*, Kabwebwe H. Mitonga[2]†, Kirk Allen[3]

[1]School of Pharmacy, FOHS, University of Namibia, Windhoek

[2]School of Medicine, FOHS, University of Namibia, Windhoek

[3]Faculty of Health & Medicine, Lancaster University, Lancaster, England.

Received: 22nd August, 2015. Accepted: 23rd May, 2016. Published: 15th August, 2016.

Abstract

Purpose: The study had the objective of evaluating the prevalence and effectiveness of healthcare providers' use of multiple antibiotics in the empiric treatment of infections. *Methods*: Three hundred and seven (307) antibiotic prescriptions from inpatient departments of five selected hospitals in Lesotho were assessed for their appropriateness. Antibiotic treatment success rates among patient groups and subgroups treated with antibiotic prescription categories considered appropriate and inappropriate and with specified numbers of antibiotics were determined. Correlations or associations of numbers of antibiotics per prescription and relevant variables were determined and used to evaluate the effects of multiple antibiotic prescribing on treatment outcomes. *Results*: Single antibiotics were most prescribed for clinical conditions where prescribers had not absolutely identified bacteria pathogens as aetiologies of treated infections. Greater numbers of prescribed antibiotics were associated with inappropriate use of the agents in the empiric treatment of infections. Appropriateness of antibiotic prescriptions rather than numbers of prescribed antibiotics correlated positively with treatment outcomes.

*Deceased

†Corresponding author: honoremitonga@gmail.com; Tel: +264 856056256; Fax: +264 61 254130

Conclusion: No categorical relationship appears to exist between the number of antibiotics prescribed and treatment outcomes. Prescribing higher numbers of antibiotics did not produce higher favourable treatment outcomes as compared with prescribing antibiotics appropriately.

Keywords: Prescriptions; antibiotics; numbers; appropriateness; treatment outcome.

ISTJN 2016; 8:3-14.

1 Introduction

Multiple antibiotic prescribing in the empiric treatment of infections is common in medical practice. Reasons healthcare providers often give in support of such antibiotic prescribing practices center around their desire to cover all possible bacterial pathogens that normally would be associated with the infections they treat [1]. As rational as this may sound, multiple antibiotic prescribing is frowned upon by some schools of thought in the antibiotic prescribing world [1]. Expressing his reservations about the appropriateness of this mode of antibiotic prescribing, Chambers, for example, indicated that care providers' frequent use of antibiotic combinations or their use of antibiotics with the broadest spectrum in treating infections is a cover up for their diagnostic imprecision. Prescribers' use of multiple antibiotics in the treatment of infections, he asserted, is more of habit than for specific indications [1]. Chambers' comments and that of schools of thought like him do recognise that multiple antibiotic prescribing can be useful provided they are indicated in infections requiring their use.

In mixed infections where bacterial pathogens with varied morphological and sensitivity characteristics are implicated, the use of multiple antibiotics indeed may become the only means of effecting a cure. The recommendation of the multiple prescribing of an aminopenicillin and gentamicin in treating severe illnesses of complicated urinary tract infections, for example, recognises the presence of *Enterobacteriaciae, Pseudomonas, Serratia*, and *enterococci* as most probable causative agents for which the combined use of the antibiotics would be appropriate [2]. Prescribed appropriately, multiple antibiotic prescribing would undeniably be the only means of achieving positive treatment outcomes in certain *types* of infections. This said, however, the debate continues as to how appropriate or even beneficial many of these prescriptions are to justify their entrenchment in clinical practice. Rampant use of multiple antibiotics in the empiric treatment of infections leads to antibiotic overuse, the development of antibiotic resistance and increased incidences of adverse drug effects (ADE) [3,4].

It is doubtlessly a source of inappropriate prescribing and the problem deserving redress

amidst global concerns of antibiotic resistance development [3]. In spite of having this knowledge, healthcare providers nevertheless cling to practices of multiple antibiotic prescribing in treating infections empirically. One may genuinely wonder what the motivating reasons for the habit could be among healthcare providers. Could it be their conviction of associations of such antibiotic prescribing practices with good treatment outcomes in comparison with a judicious selection and use of the agents? This and similar questions motivated us to undertake this study. In accordance with our objective, we assessed the prevalence and the effects of multiple antibiotic prescribing on treatment outcomes in the empiric treatment of infections within a cohort of clinical practitioners. The results of our study, we believe, will provide some education on multiple antibiotic prescribing that may influence perceptions of clinicians generally in regard to the practice.

2 Experimental set-up

2.1 Study design and data collection

This was an observational cross-sectional study in which relevant data from case notes of inpatients admitted for infections in five public hospitals in Lesotho were prospectively collected and analysed. Specifically data on diagnosed infections, prescribed antibiotics, patients' demographic characteristics and recovery status were collected. The hospitals included the country's referral hospital, the Queen Elizabeth II Hospital and the Motebang, Berea, Maluti and Scott hospitals. Data collection was done in 2009 for a period of one month from 15th June to 15th July. The total number of antibiotic prescription data records collected and analysed was 307. The cohort of healthcare providers responsible for prescribing the antibiotic prescriptions studied were all medical practitioners engaged by the hospitals at the time of data collection.

2.2 Prescription records and study subjects categorisation

Antibiotic prescription records were assessed and categorised into seven predefined groups of appropriateness according to a methodology previously developed and described [5]. The prescription categories ranged from A1 and A2 through B, C, D, E and F. A1 and A2 prescription categories were appropriate and were respectively used in the empirical treatment of infections with absolute and suspected bacterial aetiologies. Prescription category B had antibiotics that were inappropriately prescribed for the empirical treatment of infections. Antibiotic prescriptions used in the definitive treatment of patients were categorised as prescription category C. Antibiotics in prescription categories D and E were appropriately and

inappropriately prescribed for the prophylactic treatment of infections while those in prescription category F were prescribed in clinical conditions for which antibiotic use were not justified.

Study subjects were categorised into groups according to prescription categories used for their management. We limited results of our investigations to the effects of multiple antibiotic prescribing in the empiric treatment of infections by considering only patients who were treated empirically with antibiotic prescriptions. We also excluded patient groups who either received antibiotic prescriptions for prophylaxis or received such treatments for clinical conditions we considered not justified for antibiotic use. We grouped study subjects according to antibiotic prescription categories used in treating them. Patient treated with prescription categories A1, A2 and B satisfied our inclusion and exclusion criteria and hence were the three major patient groups investigated. We classified these three major patient groups further into subgroups according to the number of antibiotics prescribed per prescription for the treatment of their infections.

2.3 Data analysis

We used SPSS version 21 for our statistical analysis. We analysed our data to determine the demographic characteristics of our total study group. We determined treatment success rates (TSRs) for patient groups treated with antibiotic prescriptions categorised as appropriate and inappropriate. We also determined in each group relative treatment success rates (RTSRs) for subgroups of patients treated with one, two, three and more than three antibiotics stratified by prescription categories, appropriate and inappropriate. In our TSR and RTSR calculations, if 100 patients for example, received one type of appropriate prescription with n number of antibiotics and 75 of these patients improved, then the TSR for that patient group is 75%. If the overall TSR of all patients treated with appropriate prescriptions is 90%, then the RTSR is 75% / 90% = 0.83. We excluded deaths from the number of patients we used in TSR determinations as deaths of patients on hospital admission can be due to other factors other than non-response to drug treatment. In their study of mortality from invasive pneumococcal pneumonia Feikin et al. similarly excluded from their analysis, deaths after 30 days in hospital to improve their chances that deaths attributed to invasive pneumonia were indeed due to pneumococcal infection rather than other causes [6].

We determined associations of numbers of antibiotics per prescription with diagnosed infections, patients' recovery status and the appropriateness of antibiotic prescriptions. We interpreted the results of these determinations to establish effects of multiple antibiotic use *vis-à-vis* the appropriateness of antibiotic prescriptions in the empiric treatment of infections.

2.4 Ethical considerations

Ethical permissions for the conduct of this research were obtained from both the Ministry of Health of Lesotho through its ethics committee and the individual hospitals where the study was carried out.

3 Results

3.1 Subject demographic characteristics and patterns of multiple antibiotic prescribing with infection types

Of the total 188 antibiotic prescription records that met our inclusion criteria, 56.4% and 43.6% were for female and male patients respectively. About 70% similarly were for adults and 30% for children (Table 1). Table 2 reports percentage distribution of prescriptions according to infection types, the number of antibiotics prescribed per each prescription and prescription appropriateness. Healthcare providers showed higher rates of prescribing fewer antibiotics (one or two antibiotics per prescription) in infections of the respiratory and gastrointestinal tracts and also in cases of fevers of unknown origin (FUO). They prescribed two or three antibiotics most commonly in infections of the central nervous system (CNS) and in cases of multiple infections. One, two, three and greater than three antibiotics were prescribed nearly at the same rates in skin and soft tissue infections (SSIs). Inappropriate prescribing of antibiotics was most dominant in infections of the CNS (87.5%), bones (75%), skin and soft tissues (62.1%) and the genitourinary tract (53.3%) where higher numbers of antibiotics per prescription were most predominantly prescribed (Table 2).

Table 1: Frequency distributions of subjects according to gender and age.

Demographic variable	**Categories**	**Frequencies** N	**Percentage** %
Gender	Female	106	56.4
	Male	82	43.6
	Total	188	100
Age	Adult	131	69.7
	Children	57	30.3
	Total	188	100

Nearly three quarters of total prescriptions analysed were composed of prescriptions with one (44.0%) and two (33.0%) antibiotics. About one quarter of prescriptions similarly had

Table 2: Frequency distributions of infection types according to numbers of antibiotics per prescription and prescription appropriateness.

Infection (inf) Type	**Numbers of antibiotics per prescription**										**Prescription appropriateness**			
	1		2		3		> 3		Total		Appropriate (Prescription) (categories) (A1 and A2)		Inappropriate (Prescription) (categories B)	
	n	n%	n	n%	n	n%	n	n%	n	N%	n	n%	n	n%
Respiratory tract inf	39	52.7 (54.2)	21	28.4 (35.0)	9	12.2 (23.7)	5	6.8 (27.8)	74	100 (39.4)	44	59.5	30	40.5
Gastrointestinal inf	13	43.3 (18.1)	13	43.3 (21.7)	2	6.7 (5.3)	2	6.7 (11.1)	30	100 (16.0)	18	60	12	40
Genitourinary tract inf	4	26.7 (5.6)	3	20.0 (5.0)	5	33.3 (13.2)	3	20.0 (16.7)	15	100 (8.0)	7	46.7	8	53.3
Skin and soft tissue inf	7	24.1 (9.7)	9	31.0 (15.0)	8	27.6 (21.1)	5	17.2 (27.8)	29	100 (15.4)	11	37.9	18	62.1
Bone inf	1	25.0 (1.4)	0	0 (0.0)	3	75.0 (7.9)	0	0 (0.0)	4	100 (2.1)	1	25.0	3	75.0
Central nervous system Inf	1	12.5 (1.4)	4	50.0 (6.7)	3	37.5 (7.9)	0	0 (0.0)	8	100 (4.3)	1	12.5	7	87.5
Blood inf	0	0 (0.0)	1	100 (1.7)	0	0 (0.0)	0	0 (0.0)	1	100 (0.5)	1	100	0	0
Fevers of unknown origin	3	75.0 (4.2)	1	25.0 (1.7)	0	0 (0.0)	0	0 (0.0)	4	100 (2.1)	4	100	0	0
Multiple infections	4	17.4 (5.6)	8	34.8 (13.3)	8	34.8 (21.1)	3	13.0 (16.7)	23	100 (12.2)	11	47.8	12	52.2
Total	72	38.3 (100)	60	31.9 (100)	38	20.2 (100)	18	9.5 (100)	188	100 (100)	98	52.1	90	47.9

‡n% value determinations in brackets based on column totals; n% value determinations not in brackets based on row totals.

three (16.0%), four (6.2%) and greater than four (0.65%) antibiotics. The lowest and highest percentage frequencies of prescribing one and three antibiotics per prescription were both observed at the Queen II hospital, the biggest study site hospital with referral status (Fig. 1).

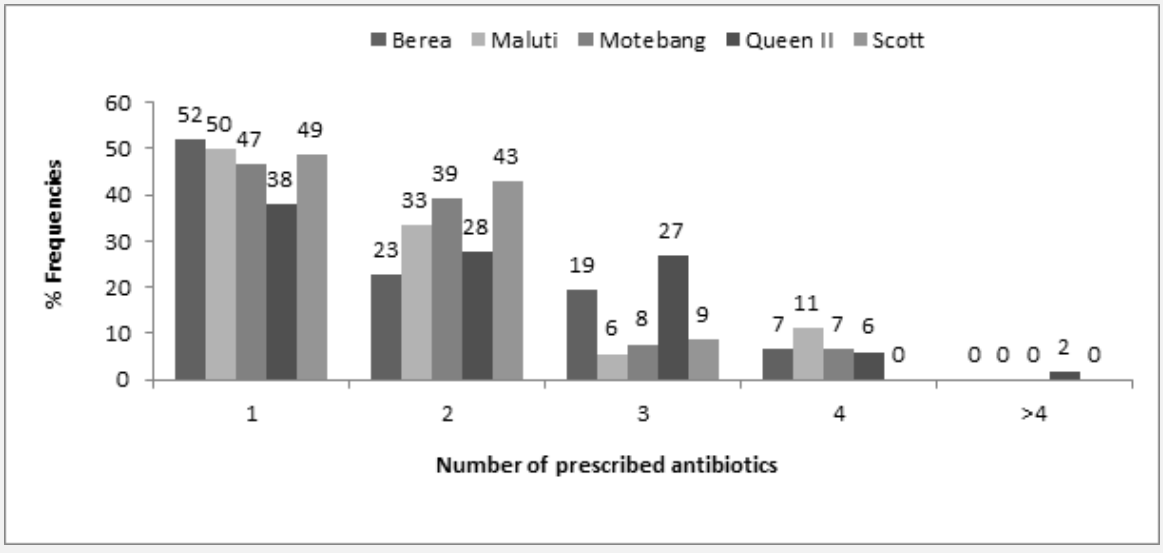

Figure 1: Percentage frequencies of numbers of prescribed antibiotics per prescription for study site hospitals.

3.2 Associations of number of antibiotics per prescription with appropriateness of antibiotic prescriptions

Of all patients diagnosed with infections and consequently treated with antibiotics empirically, nearly half (49%) were treated with inappropriately prescribed antibiotics (category B). Nearly a third (29%) and a quarter (22%) were treated with prescription categories considered appropriate for absolute (category A1) and suspected (category A2) bacterial infections. The frequency of inappropriate prescriptions increased as the number of antibiotics prescribed per prescription increased from 28% when only one antibiotic was prescribed, to 82% - 90% when three or more antibiotics were prescribed (Figure 2). There was a corresponding decrease in the frequency of appropriate prescriptions, such that only 18% (13% A1, 5% A2) were appropriate when three antibiotics were prescribed and 11% (A1 only) when more than three antibiotics were prescribed.

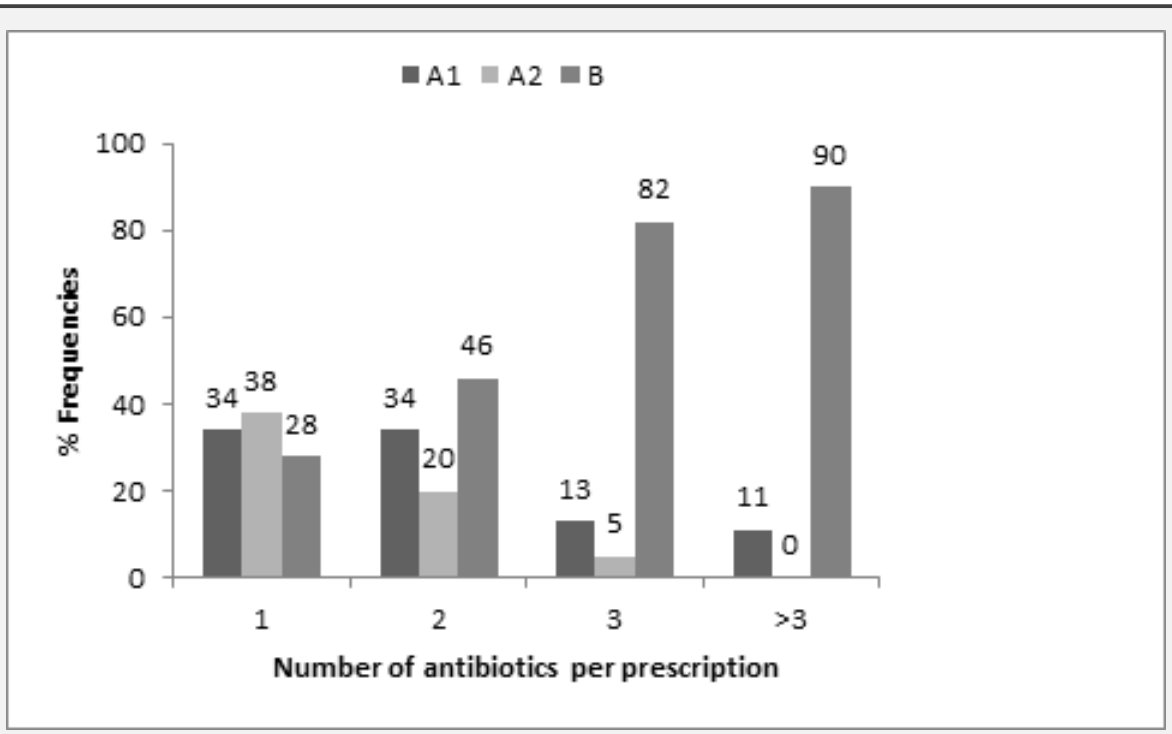

Figure 2: Percentage frequencies of antibiotics categories with numbers of antibiotics per prescription.

3.3 Effects of single and multiple antibiotic therapies on antibiotic treatment outcomes: A comparative assessment with appropriateness of antibiotic prescriptions

In patient subgroups treated with antibiotic prescriptions considered appropriate (prescription categories A1 and A2), calculated RTSRs were nearly constant regardless of the number of antibiotics prescribed per prescription in treating patient subgroups (Table 3). For patient subgroups treated with antibiotic prescriptions classified as inappropriate (category B) RTSR was lowest in the patient subgroups treated with only one antibiotic (Table 3).

Table 3: Treatment success rates of patient subgroups receiving given numbers of antibiotics in patient groups treated with appropriate and inappropriate antibiotic prescriptions.

Number of antibiotics per prescription	PRESCRIPTION CATEGORY A1 + A2 (APPROPRIATE)				PRESCRIPTION CATEGORY B (INAPPROPRIATE)			
	Frequency distribution of prescriptions by treatment response		TSR	RTSR	Frequency distribution of prescriptions by treatment response		TSR	RTSR
	Improved	Not Improved			Improved	Not Improved		
1	40	8	83	1.0	7	5	58	0.8
2	21	5	81	1.0	18	7	72	1.0
3 or more	7	1	88	1.1	32	11	74	1.0
Total	68	14	–	–	57	23	–	–
	Patient group treatment success rate: 83				Patient group treatment success rate: 71			

‡Abbreviations: TSR: Treatment success rate; RTSR: Relative treatment rate

3.4 Statistical associations and correlations of numbers of prescribed antibiotics with other study variables

No association was found between number of antibiotics prescribed per prescription and patients' recovery status. A linear chi-squared test of association produced a p-value 0.13, which was > 0.05. Results of further Linear test for the trend between number of antibiotics prescribed per prescription and infection types showed the two variables to be to be associated (p-value $= 0.001$ which was < 0.05).

4 Discussion

4.1 Patterns of multiple antibiotic prescribing

Of the total number of prescriptions studied, more than three quarters had one (44%) and two (39%) antibiotics. By comparison only 16% and 6.9% were prescriptions with three and more than three antibiotics, respectively. These results differ from results of similar studies carried out by other researchers. Aparna et al. in an intensive care unit (ICU) in Northern India and Mohager et al. in a paediatric emergency setting in central Saudi Arabia studied antibiotic prescribing patterns with objectives similar to our study [8,9]. The results of the Aparna et al. study showed no difference between numbers of prescriptions with one to two and three or more than three antibiotics as were prescribed in the empiric treatment of infections [7]. Mohager et al. similarly found that almost equal percentages of prescriptions with three antibiotics (41.7%) and less than three antibiotics (37.7%) were used in the empiric treatment of patients [8]. The two studies were conducted within intensive care and emergency units of study site hospitals where more severe illnesses were treated. In our study, most prescriptions with three or more antibiotics came from the Queen II Hospital, the study site hospital with referral status to which more severe illnesses from other hospitals were referred. It is probable by these observations that the prescribing of higher numbers of antibiotics per prescription in the empiric treatment of infections may somehow be related to the severity of the infections treated.

The multiple antibiotic prescribing patterns we established showed antibiotic prescribing practices in which the number of antibiotics prescribed per prescription appeared to depend on type of infections treated. While fewer (one or two) rather than greater (three or more) numbers of antibiotics per prescription were used in the presumptuous treatment of RTIs and FUOs, the reverse was seen to be true for such infections as genitourinary tract and skin and soft tissue infections. Frequency distributions of prescription categories according to numbers of antibiotics prescribed per prescription had shown that fewer numbers of antibiotics, particularly single antibiotics, were prescribed mostly for patient groups that had not been diagnosed for infections with absolute bacterial aetiologies (Figure 2). This observation suggested care providers' inclination to prescribing "some antibiotic at least" in events of diagnostic uncertainties. Our results also showed that incidences of inappropriate prescribing of antibiotics occurred mainly in cases of multiple antibiotic prescribing involving higher numbers (three or more) of antibiotics per prescription (Figure 2). By these results, care providers appear to demonstrate high tendencies of prescribing antibiotics inappropriately in the empiric treatment of infections irrespective of how many antibiotics they prescribed per prescription. The situation has the propensity of leading to antibiotic overuse and the orchestration of the stage for resistance development [9]. That incidences of inappropriate prescribing of antibiotics were most associated with higher numbers of pre-

scribed antibiotics per prescription, showed an inability of healthcare providers to prescribe antibiotic combinations appropriately. This could be attributed to care providers' lack of adequate knowledge in the bacteriology of infections and principles of antibiotic prescribing. Care providers' knowledge in prevailing bacterial pathogen sensitivity patterns or the synergistic interactions of antibacterial agents for example can be deemed necessary in making choices of antibiotics appropriate for effective multiple antibiotic therapy.

4.2 Effects of multiple antibiotic prescribing on treatment outcomes

All subgroups of patients treated with one, two, three and more than three antibiotics per prescription in patient groups treated with appropriate (category A1+A2) and inappropriate (category B) prescriptions demonstrated RTSRs that were similar. We did not expect to find such similarities in RTSR trends within the two patient groupings. Inappropriate prescriptions with higher numbers of antibiotics, we believed, combined for most of the times one or more than one effective antibiotics with others deemed inappropriate. This may be due mainly to diagnostic imprecision. The lack of differences in RTSR trends among the patient subgroups in the two patient categories is a noteworthy finding. It showed that multiple antibiotic therapies may produce similar treatment outcomes irrespective of the appropriateness of the prescribed antibiotics. The situation in our opinion blinds healthcare providers from appreciating the ill effects of unnecessary multiple antibiotic therapy and could largely be a reason why multiple and hence inappropriate prescribing of antibiotics is perpetuated in clinical practice. Generally, our observed trends in RTSRs can be interpreted as not showing any convincing link between treatment outcomes and numbers of antibiotics used in treating infections.

Results of our statistical analysis did not show an association between categories of numbers of antibiotics and patients' recovery status (Linear chi square test p-value = $0.130 > 0.05$). Types and hence numbers of antibiotics required to achieve adequate treatment outcomes in the empiric treatment of infections may depend on the type of infection diagnosed in a patient. Results of linear chi-squared test for variable associations proved this to be true (p-value = 0.001). Infections at various anatomic sites are associated with specific types of bacterial pathogens and most often may be mixed infections of such pathogens, particularly in hospital settings [10]. Depending on the spectra of activity of antibiotics selected for prescribing, empiric treatments of infections may indeed require the use of more than one antibacterial agent. It is realistic to assume that the number of prescribed antibiotics may count in producing positive treatment outcomes in the presumptuous treatment of infections. This would mean an association between number of antibiotics prescribed per prescription and study subjects' recovery status which rather had not been shown by results of our statistical analysis as reported above. This finding suggested that numbers of antibi-

otics as prescribed in our study were mostly prescribed injudiciously. It also confirmed to a large extent Chambers' assertion that healthcare providers' use of multiple antibiotics in the treatment of infections is more of habit than for specific indications justifying this manner of antibiotic prescribing [1]. For the number of prescribed antibiotics to count in producing positive treatment outcomes it is imperative that they are judiciously selected on the basis of their unique activities against bacterial pathogens causing the infections. Each prescribed antibiotic in multiple antibiotic therapy must have a unique antibacterial effect that complements the effects of others in eradicating target causative pathogens of the infection. A single antibiotic in certain instances can have a spectrum of activity similar to the spectra of activities of all antibiotics used in a specified multiple antibiotic therapy. Prescribing such an antibiotic will expectedly have the same treatment outcome as the multiple therapy, all other factors determining the effectiveness of both treatments being equal. This partly may explain the non-correlation of numbers of antibiotics with treatment outcomes.

5 Conclusion

The results of the study did not show a categorical relationship between numbers of antibiotics prescribed and treatment outcomes though it did suggest that prescribing higher numbers of antibiotics per prescription may produce similar treatment outcomes as appropriately prescribed antibiotics. This situation most likely blinds healthcare providers' judgement on the appropriateness of their antibiotic prescriptions and could largely be a reason why multiple prescribing of antibiotics is entrenched in clinical practice.

Acknowledgements

We acknowledge and appreciate contributions made by Prof M. Lubbe of Northwest University and Prof Jan Serfontein (retired) in the conduct of this research.

Editor's Comment: Dr. Mathias Adorka died in December 2015.

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