Acta Scientific Pharmaceutical Sciences (ISSN: 2581-5423)

Volume 2 Issue 10 October 2018

Research Article

Antibiotic Use and resistance in the private sector in Namibia

Dawn Dineo Pereko*

School of Pharmacy, North-West University, South Africa

***Corresponding Author:** Dawn Dineo Pereko, School of Pharmacy, North-West University, South Africa.

Received: September 07, 2018; **Published:** September 21, 2018

Abstract

Background: Antibiotics resistance is a global concern. A considerable body of evidence has shown a direct association between antibiotic use and the development of resistance. The objective of this study was to ascertain susceptibility patterns in the private health sector and determine possible relationship between antibiotic usage and resistance in Namibia.

Methodology: A retrospective analysis of prescription claims data 2008 to 2011 and microbiological reports for 2005 to 2011 was conducted. Antibiotic use was expressed in defined daily dose per 1000 inhabitants per day in accordance with the anatomical therapeutic classification. Antibiotic resistance was expressed as sensitivity rates.

Results: Antibiotic consumption was high (27DDD/1000/day) and increased by 3.5% between 2008 and 2011. Beta- lactams were the highest used antibiotic class followed by macrolides. Antibiotic resistance showed very little change between 2010 and 2011. Overall, the greatest resistance was observed with chloramphenicol (18%). *E. coli* and *S. aureus* showed great resistance to amoxicillin (23% and 7% respectively). Overall, increasing resistance was observed in older antibiotic agents as compared with the newer agents. No association between antibiotic use and resistance was observed however statistical significance increased when correlating earlier antibiotic use with resistance of later years.

Conclusion: Antibiotic resistance profiles observed in this study are comparable to those in other African countries. The study could not establish a statistically significant correlation between antibiotic use and resistance. Continuous monitoring of antibiotic use and resistance in Namibia in the context of the WHO Global Action Plan is recommended.

Keywords: Antibiotics; Antibiotic Use; Antibiotic Resistance; Namibia

Introduction

Antibiotic resistance is a major public health problem globally with both clinical and financial consequences [1-3]. The European Commission estimates 250,000 deaths and cost of over 1,5 billion Euro due to antimicrobial resistance each year [4]. The Unites States on the other hand reports that two million people daily are infected with antibiotic resistant bacteria and at least 23,000 of these die [5]. Though there are no statistics in Africa, antibiotic resistance has been described as a growing problem that accounts for most of Africa's disease burden [6-8]. The WHO also reports that despite the limited availability of data, the African region shows worldwide trends of increasing antibiotic resistance [9].

Resistance is a result of antibiotic selection pressure as a result of antibiotic overuse, under-use of irrational or indiscriminate use [5,10,11]. In 1998, Finch suggested that antibiotic resistance is a function of time and use [12]. Since then, numerous studies have been conducted that show the relationship between antibiotic use and the development of resistance over time [13-15].

Knowledge of local sensitivity patterns is important in guiding optimal empiric treatment and rational use of antibiotics. These can be effectively monitored through the use of antibiograms [16-18]. In Namibia, a few studies were done to look into the sensitivity patterns of antimicrobials. However, these were done only in the public sector and do not look into the correlation of use and resistance pattern.

A combined strategy of surveillance for antibiotics, that is using both consumption and resistance data, provides a better understanding of the relationship between usage and resistance [19]. Accordingly, the objective of this study was to ascertain susceptibility patterns in the private health care setting and determine possible relationship between antibiotic use and resistance in Namibia.

Methodology

Ethical clearance for this study was obtained from the Research Ethics Committee (Human), Faculty of Health Sciences, North-West University (Ethical clearance number NWU-00028-13-s1). All analyses were conducted on anonymized, aggregated records therefore no individual patient consent was necessary. Additional permission was obtained from the medical aid administrators and the specific laboratory.

Antibiograms: antibiotic sensitivity data

Antibiograms for pathogens isolates were provided by the laboratory for the period 2001 to 2011.

Viable specimens were processed in accordance with in-house procedures. Methodology for pathogen identification was dependent on the source of the specimen, for example, uri-select is used for urine samples while blood agar and chalk plates were used for cerebrospinal fluid samples (CSF). Sensitivity testing was performed in accordance with the Clinical Laboratories Standard Institutions (CLSI) guidelines. The first line test for sensitivity testing is the Kirby-Bauer disk diffusion method whereby the discs containing antibiotics were placed over an agar plate inoculated with the organism. The size of the zone of inhibition was equated with whether or not the organism was sensitive or resistant to the antibiotic at standard doses. Antibiotic susceptibilities were then reported in qualitative recorded and entered onto Meditech® and stored by organism. Annual sensitivity reports were then drawn from these data.

From the antibiograms, the number of isolates tested and those testing susceptible were computed. Percentage susceptibility for each antibiotic was calculated by combining all species for which the antibiotic was indicated. The nature of the information provided did not allow for identification of information by source of specimen.

Antibiotic use data

Antibiotic use data covering a four (4) year period from 01 January 2008 to 31 December 2011 were collected from the medical aid claims data of a medical aid fund that covers 54% of the insured population. Only data related to antibiotics for systemic use (anatomical therapeutic classification (ACT) J01) were collected and analysed using the defined daily dosage (DDD) methodology. The ACT/DDD methodology was used to evaluate the consumption of antibiotics and each antibiotic was assigned a DDD obtained from the ACT/DDD index 2013 (www.whocc.no/act_ddd_index). The data were expressed as DDD/1000 population/day using the formula:

DDD/1000/day = (Total consumption in DDDs/Total population covered x Total days in the period of data collection) x 1000.

Statistical analysis

Microsoft Excel 2010 and SAS Version 9.1.3 (SAS Institute, Cary, NC) were used for analysis. Descriptive statistics were used to summarize frequencies and distribution of microbial isolates and their sensitivity to different antibiotics. All statistical significance was considered with probability of $p < 0.05$. The practical significance of the results was computed when the p-value was statistically significant (p 0.05). Chi-square test (χ^2) was used to determine if an association exists between proportions of two or more groups, The Cramer's V statistics was used to test practical significance of this association. Because of the non-linear nature of the data, Spearman's correlation coefficient was used to determine the relationship between antibiotic use and sensitivity.

Results

Antibiotic consumption

Overall antibiotic use measured in DDD/1000 population per day (DID) was high (27) and showed a 3.5% increase between 2008 and 2011. Most frequently used antibiotic class was beta-lactams followed by macrolides. The most frequently used antibiotic over the years was amoxicillin with clavulanic acid. A high increase in antibiotic use over the 4 year period was observed for macrolides especially clarithromycin and azithromycin. Table 1 shows antibiotic usage (including changes in usage over the 4 years) by pharmacological group.

Antibiotic resistance

Because of the gap in data between 2005 and 2010, only sensitivity data for 2010 and 2011 were used to allow for comparability with antibiotic usage data year on year from 2008 to 20011. A total of 3506 and 5037 isolates were reported for 2010 and 2011 respectively. Nine species were reported and *Escherichia coli* was the most commonly isolated organism (49%) followed by *Staphylococcus aureus* (16%). The other isolates reported were *Enterococcus* spp. (14%), *Streptococcus pyogenes* (2.7%), *Haemophilus influenza* (3.03%), *Pseudomonas aeruginosa* (8.45%), *Salmonella* spp. (3.57%) and *Shigella* spp. (1.09%).

Antibiotic Class	ATC	2008	2009	2010	2011	Diff	% Diff
Penicillin	J01C	13.64	10.44	9.53	10.22	-3.4	-25.07
Cephalosporin	J01D	4.5	4.7	5.2	6.3	1.8	40.00
Macrolides	J01F	1.97	4.65	5.09	5.67	3.7	187.82
Quinolones	J01M	2.6	2.6	2.7	2.8	0.2	7.69
Aminoglycosides	J01G	0.106	0.073	0.57	0.078	0.0	-26.42
Tetracyclines	J01A	2.3	2.1	1.8	3.4	1.1	47.83
Other	J01X	0.056	0.068	0.127	0.088	0.0	57.14
Other Beta Lactams		0.47	0.77	0.71	0.04	-0.4	-91.49

Table 1: Trends in antibiotic use by class expressed in DDD/1000/day.
*ATC denotes the anatomic therapeutic classification of the WHO.

Escherichia coli showed resistance to amoxicillin and co-trimoxazole. Decreasing sensitivity to amoxicillin/clavulanic acid and nalidixic acid by *E. coli* was also observed.

S. aureus showed the highest resistant of all the pathogens to amoxicillin.

S. pneumonia showed sensitivity to amoxicillin and 3rd generation cephalosporins. Decreased sensitivity to erythromycin and tetracycline was observed.

S. pyogenes showed sensitivity to all antibiotics tested and reduced sensitivity to tetracycline (84%). Not much change in sensitivity. *Haemophilus* spp. species showed sensitivity to all antibiotics except co-trimoxazole.

With regards to stool pathogens, *Shigella* spp. is resistant to ampicillin/amoxicillin, cotrimoxazole and chloramphenicol; while *Salmonella* spp. showed resistance to chloramphenicol and reduced sensitivity to cotrimoxazole and ampicillin.

Resistance between 2010 and 2011 for individual antibiotics for different isolates remained fairly stable. The table below shows percentage susceptibility of each antibiotic calculated by combining all species for which the antibiotic is indicated.

Antibiotic	2001	2002	2003	2004	2005	2010	2011
Ampicillin	67.62	69.37	65.62	64.25	65.5	62	61.88
Augmentin	95	96	93	92	93.5	88.33	88.33
Cloxacillin	95	95	95	93	96	89	92
Cotrimoxazole	54.8	56.8	56.16	47.83	43.33	52	53.4
Cephalosporins 2nd	99	99	98.5	98.5	97.5	88.5	91.67
Cephalosporins 3rd	99.2	98.2	98.8	99.4	95.8	95.57	96
Cephalosporins 4th	0	0	0	0	0	86.5	87.5
Gentamycin	97.5	96.5	93.5	94.5	90.5	76.75	82.5
Nalidixic Acid	97	93	83	85	85.5	84	82.83
Nitrofurantoin	91.5	99	97	92.5	96.5	96	97.5
Ofloxacin	96.8	99.4	98	95.8	95.8	95.5	92.5
Ciprofloxacin	99	98.4	98.2	97.4	96.2	89.86	89.86
Moxifloxacin	0	0	0	0	0	96.67	99.33
Erythromycin	91.25	90.5	89.5	85.5	86.5	86	83.67
Azithromycin	0	0	0	0	0	100	100
Tetracycline	87	90.5	92.5	88	86.25	66.75	84.5
Clindamycin	74.5	93.5	91.5	95	90	43.5	81.5
Fucidic acid	95	98	97	95	98	93	96
Chloramphenicol	76	50	71	63	74.5	18	18

Table 2: Percentage antibiotic sensitivity for all isolates.

Chloramphenicol showed the lowest sensitivity profile. A modest rise in resistance to ciprofloxacin, gentamycin, nalidixic acid and chloramphenicol over the 11 year period (2001 - 2011) was observed.

Comparing antibiotic use and resistance pairs for 2010 and 2011 respectively showed no association between antibiotic usage and resistance both at individual antibiotic level and at antibiotic class level.

Comparing earlier antibiotic use (2008) with later resistance (2010 and 2011 respectively) still showed no correlation but the p value decreased from p = 0.856 in 2010 to p = 0.056 in 2011. Same trends were seen when comparing antibiotic use in 2009 and 2010 with sensitivity data of 2010 and 2011 as seen on table 3 below.

	Antibiotic use year		
Sensitivity year	2008	2009	2010
2010	0.856	0.858	0.843
2011	0.056	0.058	0.153

Table 3: Comparing changes in significance of earlier antibiotic use with resistance in later years (p value).

Comparing earlier antibiotic use with resistance in later years shows a trend in decreasing p-value that is approaching significance ($p < 0.05$).

Discussion

This study reports on observed antibiotic resistance patterns in the private sector of Namibia and the association between these patterns and antibiotic use. Antibiotic use in Namibia is high and logically, an association is expected between such usage and resistance [13,20].

Over the 4 year period, an overall increasing trend in antibiotic use was observed. Generally, a decrease in beta-lactams was observed and an increase in the use on macrolides was observed over the 4 year period. On the other hand, despite the gap in data between 2005 and 2010 (when analysis was not recorded and reported), antibiotic resistance showed very little change between 2001 and 2011. This was observed across all organisms and all antibiotics. However increasing resistance has been observed in older antibiotic agents as compared with the newer agents.

Sensitivity profiles observed in the private sector of Namibia are similar to those reported elsewhere in Africa. Sensitivity profiles similar to those reported for *E. coli* were reported in Ethiopia and Ghana [21,22] and also in the Namibia public sector [23]. Similarly, sensitivity profiles similar to *S. aureus* were reported in Gabon, Ethiopia and other Sub-Saharan countries [22,24,25]. Decreased sensitivity to erythromycin and tetracycline by *S. pneumonia* was observed in South Africa [25].

When antibiotic use and prevalence of resistance were compared, no statistically significant correlation was found both at individual antibiotic level and at the level of the antibiotic class. However, comparing earlier antibiotic use (2008) with prevalence of resistance in later years (2010 and 2011), a decreasing trend in p-value was year on year, with the trend approaching significance. Correlating earlier antibiotic use with later resistance also showed that as the volume of antibiotic consumption increases, the time to reach the same strength of correlation is shorter. For example, in 2009 and 2010, the volume of antibiotics used were higher and the corresponding resistance a year later showed a lower p-value compared to earlier p-value. This shows that increasing the volume of antibiotic consumption increases the selection pressure for the development of resistance [26-28]. This finding suggests that resistance is a function of time and antibiotic use, findings that were previously reported by others [29-31]. This implies that prior antibiotic exposure can have an impact in future resistance.

The relationship between antibiotic use and resistance is complex. The lack of correlation between antibiotic use and resistance has not only been found in this study but has been reported by others and attests to the complex relationship between the two [1,14,32,33]. This has been attributed to confounding factors such as infection control, sample selection bias, susceptibility testing methods and patient's underlying illness.

Other methodological factors that have been cited as possible contributors to the lack of correlation between antibiotic use and resistance the fact that data used were aggregated data. Resistance selection pressure occurs at an individual level and DDD does not measure individual exposure [14,33,34]. In 2005, Hay., *et al*. [32] concluded that "associations at individual level were obscured by analysis of aggregate data".

There are several limitations to this study. Firstly, the laboratory data was only available for two years and could therefore not allow for 4 year comparison with the usage data. Secondly, aggregate data was used and as pointed out already, this could potentially obscure the associations that could be present at individual level. Thirdly, it is unlikely that every infection seen in the private sector actually engendered a sample for microbiological analysis. Finally, the laboratory serves a much smaller population as compared to the rest of the country therefore the sensitivity results do not show

the full picture of the country. All these suggest that the sensitivity data presented here could be an under-estimation of the actual sensitivity in the private sector. Equally, use data represent only a small fraction of the population (those accessing care in the private sector) and not a full picture of antibiotic usage in a country with dual health care system.

Conclusion

Understanding the relationship between antibiotic use and the prevalence of resistance is crucial to the fight against antimicrobial resistance. This was the first study in Namibia to ascertain susceptibility patterns in the private health sector and determine possible relationships between antibiotic use and resistance.

The study found an increasing trend in use of antibiotics especially broad spectrum antibiotics. While resistance trend remained stable over the observed period, greater resistance to older agents was observed. The study also found that while there was no obvious correlation between antibiotic use and resistance, trends showed that prior antibiotic use as well as the volume of antibiotics had a bearing on sensitivity in later years.

In line with the objectives 2 and 4 of the WHO Global Action Plan, a surveillance system should be established that will routinely monitor sensitivity profiles of common organisms from health care facilities and communities. This should be linked to monitoring of antibiotic consumption and together these data should be used to promote responsible use of antibiotics in order to extend their lifespan. Such a system should collect data from both the public and private health sectors. The results of this study and the methodology employed therefore could serve as a starting point [35].

Results of this surveillance should be shared with all health professionals and should be shared at regional and global fora.

Acknowledgment

The authors would like to thank the staff and management of the laboratory that provided the data specifically Dr Braam van Greunen and Mr Advance Manghonzo for their advice and support. The authors also wish to acknowledge the medical aid fund and administrators who provided the prescription claims data.

Bibliography

1. Essack SY., *et al*. "Antibiotic use and resistance in public sector hospitals in KwaZulu-Natal". *South African Medical Journal* 95.11 (2005): 865-870.

2. Shaban RZ., *et al*. "National surveillance and reporting of antimicrobial resistance and antibiotic usage in Australia". Australian Commission on quality and safety in health care. Sydney (2012).

3. van Bijnen Evelien ME., *et al*. "The appropriateness of prescribing antibiotics in the community in Europe: study design". *BMC Infectious Diseases* 11 (2011): 293- 297.

4. European Commission. Antimicrobial resistance policy document (2013).

5. Centre for Disease Control and Prevention (CDC). "Antibiotic resistance threats in the United States". US Department of Health and Human Services, Centre for Diseases Control and Prevention. Georgia, USA (2013).

6. Kimang'a AN. "A situational analysis of antimicrobial drug resistance in Africa: are we losing the battle?" *Ethiopian Journal of Health Sciences* 22.2 (2012): 135-143.

7. Laxminarayan R., *et al*. "Antibiotic resistance-the need for global solutions". *The Lancet* 13.12 (2013): 1057-1098.

8. Okeke IN., *et al*. "Growing problem of multi-drug resistant enteric pathogens in Africa". *Emerging Infectious Diseases* 13.11 (2007): 1640-1646.

9. WHO. "Antimicrobial resistance: global report on surveillance". World Health Organization, Geneva, Switzerland (2014).

10. Byarugaba DK. "A view of antimicrobial resistance in developing countries and responsible risk factors". *International Journal of Antimicrobial Agents* 24.2 (2004): 105-110.

11. Kotwani A., *et al*. "Methodology for surveillance of antimicrobial use among outpatient in Delhi". *Indian Journal of Medical Research* 129.5 (2009): 555-560.

12. Finch RG. "Antibiotic resistance". *Journal of Antimicrobial Chemotherapy* 42.2 (1998): 125-128.

13. Bergman M., *et al*. "Macrolides and azithromycin use are linked to increased macrolide resistance in *Streptococcus pneumoniae*". *Antimicrobial Agents and Chemotherapy* 50.11 (2006): 3646-3650.

14. Hsu L., *et al*. "Surveillance and correlation of antibiotic prescription and resistance of gram-negative bacteria in Singaporean hospitals". *Antimicrobial Agents and Chemotherapy* 54.3 (2010): 1173-1178.

15. Vernaz N., *et al*. "Modeling the impact of antibiotic use on antibiotic-resistant *Escherichia coli* using population-based data from a large hospital and its surrounding community". *Journal of Antimicrobial Chemotherapy* 66.4 (2011): 928-935.

16. Orsi GB., *et al*. "Surveillance of management of multidrug resistant microorganisms". *Medscape* (2011).

17. Stein C., *et al*. "Using hospital antibiogram data to assess regional pneumococcal resistance to antibiotics". *Emerging Infectious Diseases* 9.2 (2003): 211-216.

18. Van Beneden C., *et al*. "Aggregated antibiograms and monitoring of drug-resistant *Streptococcus pneumoniae"*. *Emerging Infectious Diseases* 9.9 (2003): 1089-1095.

19. World Health Organization (WHO). "The evolving threat on antimicrobial resistance: options for action". Geneva (2012).

20. Hsueh P., *et al*. "Relationship between antimicrobial use and antimicrobial resistance in gram-negative bacteria causing nosocomial infections from 1991-2003 at a university hospital in Taiwan". *International Journal of Antimicrobial Agents* 26.6 (2005): 463-472.

21. Ameko E., *et al*. "Effects of self-medication on the efficacy of four antibiotics commonly used in Ghana on clinically isolated micro-organisms". *International Journal of Pure and Applied Sciences and Technology* 10.2 (2012): 62-70.

22. Tirunneh M., *et al*. "Changing trends in prevalence and antibiotic resistance of uropathogens in patients attending Gondar University Hospital, Northwest Ethiopia". *International Journal of Bacteriology* (2014): 629424.

23. Mengistu A. "A review of empirical treatment of urinary tract infections based on national antimicrobial sensitivity data". *Pharmacovigilance and Drug Safety* 1.3 (2014): 6-12.

24. Alabi AS., *et al*. "Retrospective analysis of antimicrobial resistance and bacterial spectrum of infection in Gabon, Central Africa". *BMC Infectious Diseases* 13 (2013): 455-460.

25. Ashley EA., *et al*. "Antimicrobial susceptibility of bacterial isolates from community acquired infections in Sub-Sahara and Asian low and middle income countries". *Tropical Medicine and International Health* 16.9 (2011): 1167-1179.

26. Bell BG., *et al*. "A systemic review and meta-analysis on the effects of antibiotic consumption on antibiotic resistance". *Biomed Central Infectious Diseases* 14 (2014): 13.

27. Costelloe C., *et al*. "Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systemic review and meta-analysis". *British Medical Journal* 340 (2010): c2096.

28. Goosens H., *et al*. "Outpatient antibiotic use in Europe and associations with resistance: a cross-national database study". *The Lancet* 365.9459 (2005): 579-587.

29. Gallini A., *et al*. "Influence of fluoroquinolone consumption in inpatients and outpatients on ciprofloxacin-resistant *Escherichia coli* in a university hospital". *Journal of Antimicrobial Chemotherapy* 65.12 (2010): 2650-2657.

30. Kritsotakis EI., *et al*. "The dynamic relationship between antibiotic use and the incidence of vancomycin-resistant Enterococcus: time series modelling of 7 years surveillance data in a tertiary care hospital". *Clinical Microbiology and Infection* 14.8 (2008): 747-754.

31. Mahamat A., *et al*. "Evolution of fluoroquinolone resistance among Escherichia coli urinary tract isolates from a French university hospital: application of the dynamic regression model". *Clinical Microbiology and Infection* 11.4 (2005): 301-306.

32. Hay AD., *et al*. "The relationship between primary care antibiotic prescribing and bacterial resistance in adults in the community: a controlled observational study using inpatient data". *Journal of Antimicrobial Chemotherapy* 56.1 (2005): 143-156.

33. Lai C., *et al*. "Correlation between antibiotic use and resistance of gram-negative bacteria causing healthcare-associated infections at a university hospital in Taiwan from 2000-2009". *Journal of Antimicrobial Chemotherapy* 66.6 (2011): 1374-1382.

34. Schechner V., *et al*. "Epidemiological interpretation of studies examining the effect of antibiotic use on resistance". *Clinical Microbiology Reviews* 26.2 (2013): 289-307.

35. WHO. "Global Action Plan on antimicrobial resistance. Draft for consultation with member states". Geneva (2014).

Volume 2 Issue 10 October 2018