Antimicrobial prescribing in South Africa using a large pharmacy database: A drug utilisation study
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Abstract
The primary aim was to determine the general prescribing trends of antimicrobial drugs to patients whose prescriptions were dispensed by community pharmacies. A retrospective, cross-sectional drug utilization study was conducted on 2010 data of a national community pharmacy group in South Africa. A total of 660,500 patients received 1,576,593 antimicrobial products during 2010. The average age of patients was 34.23 (SD=19.92) years. Most patients were female (58.32%). Patients between 40 and 49 years received the highest average of 3.22 antimicrobial prescriptions during the year. Beta-lactams were the most often prescribed (34.56% of antimicrobial prescriptions), followed by antiviral agents (20.92%) and quinolones (11.12%). Differences were observed between females and males with respect to the prescribing frequency of different antimicrobial classes ($\chi^2=12763; \text{d.f.}=11; p<0.0001$), especially between antifungal agents and beta-lactam antibiotics. Within the beta-lactam class, penicillins accounted for 76.47% of products and cephalosporins for 23.44%. The most frequently prescribed trade name product was a generic combination of amoxicillin and clavulanic acid. Antiviral agents were the most expensive (R195.67), followed by aminoglycosides (R188.42). Prescribing peaked during the winter months. This study provides a general overview of antimicrobial prescribing that can be used for comparative studies with other population groups, African countries and for more specific investigations.

Introduction
Antibiotic prescribing in primary care rose steadily world-wide during the last decade. There are concerns about some common infections which are becoming increasingly difficult to treat. Several studies have demonstrated that patterns of antibiotic usage greatly affect the development of resistant organisms. Excessive and irrational prescribing and use of antibiotics remain important contributing factors to the development of antibiotic resistance. Nearly 80% of prescriptions for systemic antibiotics are issued in primary care, with respiratory tract infections being the most frequent indication. Many antibiotic drugs are therefore prescribed for respiratory tract infections even though these infections are known to be predominantly viral. Some studies report that respiratory infections account for 60% of general practitioners’ antibiotic prescriptions. Antimicrobial resistance is currently the greatest challenge for effective treatment of infections globally. Resistance to antimicrobial drugs is increasingly being reported in the medical literature in South Africa, as in many other countries. The burden of infectious diseases is greater in developing countries and is exacerbated by limited access to, and availability and affordability of antimicrobials required to treat infections. Problems of increased morbidity, costs of extended hospitalisation and mortality are extremely serious in terms of their impact on the quality of life of patients as well as their economic impact. The problem of susceptibility to and spread of infections caused by multidrug-resistant (MDR) infectious agents is fuelled by factors such as limited access to clean water and sanitation to ensure personal hygiene, malnutrition, and the HIV/TB epidemic. The consequences of resistance on clinical outcomes, through either treatment failures or the development of more virulent infections, are poorly understood. The full impact of antibiotic resistance on health in South Africa is therefore not known. In addition, South Africa faces a quadruple burden of disease, as a result of the HIV/AIDS epidemic, other infectious diseases, injuries, and non-communicable diseases. It is therefore important to know the general pattern of antimicrobial prescribing and how this pattern compares to other countries.

The European Surveillance of Antimicrobial Consumption (ESAC) project is an international network of surveillance systems, aimed at collecting comparable and reliable data on antibiotic use in Europe. The ESAC...
project has for the first time established a credible alternative to industry sources for the collection of internationally comparable data on antibiotic use in Europe, based on cooperation between regulatory authorities, scientific societies, health insurers and professional organisations.12 The ESAC project has provided a tool for assessing public health strategies to optimise antibiotic prescribing.

Information on antibiotic consumption in the private sector in South Africa comes primarily from IMS Health. According to Essack and colleagues, based on IMS private sector sales data, unit sales of broad-spectrum penicillins, fluoroquinolones, carbapenems and penems, carbacephems and glycopeptides have increased annually.13 The use of chloramphenicol has decreased, while cephalosporins, trimethoprim combinations, aminoglycosides and monobactams have fluctuated.13 From a market share perspective, the top three classes of antibiotics used in the private sector are oral broad-spectrum penicillins (18.3%), penems and carbapenems (14%) and macrolides (11.1%).13

A limited number of drug utilisation or pharmacoepidemiological studies focusing specifically on antimicrobial prescribing in South Africa from a general perspective could be found in the literature. One such study was conducted by Katende-Kyenda and colleagues on 2001 data from nine private primary healthcare clinics in South Africa.14,15 The antimicrobials that were most often prescribed were penicillins (38.17%), sulphonamides (22.49%), antiprotozoals (9.88%) and tetracyclines (9.34%).14,15 The antibiotics were often prescribed for diagnoses such as viral-influenza, upper-respiratory infections, acute-bronchitis and acute-sinusitis, which indicated inappropriate use because these infections are usually caused by non-bacterial agents, and are thus self-limiting.14 Due to the absence of comprehensive pharmacoepidemiological studies on antimicrobial prescribing and use in South Africa, the current study was conducted on a large claims database of a retail pharmacy group in order to identify antimicrobial prescribing patterns in general. The aim of the study was therefore to determine the general prescribing patterns and cost of antimicrobial drugs to primary care patients in South Africa in 2010 whose prescriptions were dispensed by community pharmacies.

Methods

Study design and setting

A retrospective, cross-sectional drug utilization study was conducted on prescription data of a national community pharmacy group in South Africa for 2010. The pharmacy group has more than 300 pharmacies in all nine provinces of South Africa and can be considered as representative of community pharmacy in South Africa.

Data analysis

All records for antimicrobial products (total of 1 576 593 products) were extracted and analysed. Each medication record contained information on the age and gender of the patient, with a unique number to identify each patient, the date of the prescription, detailed information on the dispensed drug (name, package size, formulation, strength and quantity) and sales value. The database did not contain information on consultations (by doctors/specialists). It only contained data on medication (products dispensed and paid for).

The Anatomical Therapeutic Chemical (ATC) Classification System16, MIMS17 and the South African Medicines Formulary18 were used to identify the medicines that were prescribed. Microsoft Access® and Excel® were used to analyse the data. Descriptive statistics were calculated. The costs indicated in the study were the amount paid by the respective medical aid insurance schemes and may have differed from the Single Exit Price (SEP)19 that is used in South Africa, as not all medical insurance schemes cover the full costs of these products and co-payments may have to be made by patients. One Euro (€1.00) was equal to R9.38 (South African Rand), one US Dollar ($1.00) was equal to R7.64 and one British Pound (£1.00) was equal to R11.48 at the time of the study (30 June 2010).

Ethical approval

Ethical approval to conduct studies on prescription databases was obtained from the Research Ethics Committee (Human) of the Nelson Mandela Metropolitan University (ethics clearance number: H08-HEA-PHA-005).

Limitations of the Study

Limitations of the study were that no clinical information was available in the database. ICD-10 Codes for diagnoses were used, but were not specific. Code Z (factors influencing health status and contact with health services) accounted for 88.03% of prescriptions, followed by code J (diseases of the respiratory system).

Results

Demographic information of patients

A total of 660 500 patients received 1 576 593 antimicrobial products at a cost of R191 875 007.00 during 2010. The age and gender distribution of patients is given in Figure 1. The average age of patients was 34.23 (SD=19.92) years (the average age of female patients was 35.21 (SD=19.24) years compared to 32.86 (SD=20.75) years for males). Significant differences were observed between the number of females and males in the different age groups ($\chi^2 = 10060; d.f. = 9; p < 0.0001$).

Figure 1: Age and gender distribution of patients ($n=660500$)
p < 0.0001). Nearly 60% of patients were females (58.32%), and they were prescribed 60.12% of antimicrobial products.

**General prescribing frequency and cost of antimicrobial products**

The average number of antimicrobial products per patient over the year was determined. Patients between 40 and 49 years of age received the highest average number of antimicrobial products per patient (3.22) over the year (females: average of 3.23 antimicrobial products per patient over the year; males: average of 3.21 antimicrobial products per patient over the year). Nearly a fifth (18.46% or 290 989) of the 1 576 593 antimicrobial prescriptions accounted for repeat prescriptions. Most of the 1 576 593 antimicrobial products were tablets (61.80%), followed by capsules (16.25%) and suspensions (14.39%). The prescribing frequency for females and males over the 12 months was analysed and a clear peak in prescribing during the winter months in South Africa (May to August) was observed for both gender groups.

Of the 1 576 593 products dispensed, 63.43% were generic products and 36.57% were originator products. Generic products contributed 48.40% of the total cost and originator products contributed 51.60%.

**Prescribing frequency of antimicrobial classes**

The prescribing frequency of the different antimicrobial classes for females and males is given in Table 1. Beta-lactam antibiotics was the most frequently prescribed class accounting for 34.56% of all antimicrobial prescriptions, followed by anti-viral agents (20.92%) and quinolones (11.12%). Significant differences were observed between females and males with respect to the prescribing frequency of the different antimicrobial classes ($\chi^2 = 12763; \text{d.f.} = 11; p < 0.0001$), especially between anti-fungal agents and beta-lactam antibiotics.

<table>
<thead>
<tr>
<th>Antimicrobial class</th>
<th>Percentage of products</th>
<th>Both genders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females (N=947 811)</td>
<td>Males (N=628 782)</td>
</tr>
<tr>
<td>Beta-lactams</td>
<td>32.52</td>
<td>37.64</td>
</tr>
<tr>
<td>Anti-viral agents</td>
<td>20.54</td>
<td>21.48</td>
</tr>
<tr>
<td>Quinolones</td>
<td>11.86</td>
<td>9.99</td>
</tr>
<tr>
<td>Erythromycin &amp; Macrolides</td>
<td>10.68</td>
<td>10.77</td>
</tr>
<tr>
<td>Anti-fungal agents</td>
<td>8.82</td>
<td>5.31</td>
</tr>
<tr>
<td>Anti-protozoal agents</td>
<td>5.95</td>
<td>4.93</td>
</tr>
<tr>
<td>Sulphonamides &amp; combinations</td>
<td>4.29</td>
<td>5.02</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>3.10</td>
<td>3.20</td>
</tr>
<tr>
<td>Other anti-bacterial agents</td>
<td>1.98</td>
<td>1.30</td>
</tr>
<tr>
<td>Mycobacteria</td>
<td>0.26</td>
<td>0.35</td>
</tr>
<tr>
<td>Chloramphenicolics</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>0.01</td>
<td>0.00</td>
</tr>
<tr>
<td>TOTAL</td>
<td>100.00</td>
<td>100.00</td>
</tr>
</tbody>
</table>

* $\chi^2 = 12763; \text{d.f.} = 11; p < 0.0001$.

Of the anti-viral products, acyclovir was the most frequently prescribed (31.36% of all anti-viral products) at an average cost of R39.64 per prescription. Acyclovir was followed by efavirenz at 20.51%. A wide variety of anti-viral, especially HIV/AIDS, medicines were prescribed. Oseltamivir (a neuraminidase inhibitor) accounted for 1.52% of anti-viral prescriptions (5 020 products). The average cost per oseltamivir prescription was R236.17. Ciprofloxacin accounted for nearly a half of all quinolone prescriptions (MIMS class 18.7). Mycobacteria (MIMS class 18.8) consisted of 37.74% anti-leprotic products (1 780 prescriptions) and 62.26% tuberculostatics (2 903).

As indicated, 18.46% of antimicrobial products were repeat prescriptions. The highest percentage of repeat prescriptions was for sulphonamides and combinations (64.02% of all products dispensed in this class were repeat prescriptions), followed by mycobacteria (58.65%) and anti-viral agents (54.66%). Beta-lactams (1.06%), erythromycin and other macrolides (2.52%), and quinolones (2.23%) had the lowest repeat prescription rate.

The variation in prescribing frequency of antimicrobial classes over the 12 months is shown in Figure 2. Noteworthy was the clear peak of the beta-lactam antibiotics over the winter months, as well as the steady increase in the prescribing frequency of anti-viral agents over the year.

The male population younger than 20 years received a high percentage of beta-lactams (especially penicillin) and erythromycin and macrolides. Boys in the age group 2- to 5-year old were dispensed 40.12% of all the antimicrobial agents to patients in the age group from birth to 19 years, mostly in the form of suspensions. There was a clear peak in the dispensing of these products during the winter months (May to August).

**Prescribing cost of antimicrobial classes**

The average cost per antimicrobial product was R121.70 (SD=R158.21). The average cost per product in each antimicrobial class is given in Figure 3. The average cost per over-the-counter product (Schedule 1 and Schedule 2) was R32.75, compared to R158.21 for prescription-only (Schedule 3 and higher) antimicrobial products. Per prescription...
dispensed, injections were the most expensive (average of R343.85 per prescription), followed by ampoules (R324.56) and solutions (R267.33). Creams were on average the least expensive (R31.24).

**Trade name products prescribed**

A total of 751 different trade names and dosage strengths of antimicrobials were prescribed. Roughly 30% of the products were originator products. The 10 most frequently prescribed trade name products accounted for 24.92% of antimicrobial prescribing and the 10 trade names with the highest sales value accounted for 36.51% of total antimicrobial cost. The single most often prescribed trade name product was a generic combination product of amoxicillin and clavulanic acid accounting for 31.8% of all antimicrobial products prescribed. Generics clearly led to cost savings.

**Prescribing frequency and cost of beta-lactam antibiotics**

Beta-lactam antibiotics were the most frequently prescribed class. Within the beta-lactam class, penicillins accounted for 76.47% of products and cephalosporins for 23.44% (see Table 2). “Others” consisted of 478 prescriptions for loracarbef. Overall, the penicillins accounted for 24.92% of total antimicrobial cost. The most prescribed outpatient antibiotics in all 25 European Medical Schemes in South Africa, the average age of members of all registered medical schemes for the period ended 30 September 2011 was 31.8 years and the proportion of pensioners was 6.8%. No information on the gender distribution of members could be found. The demographic details of patients in this study were therefore roughly comparable to that of all medical aid scheme members in South Africa. Patients received an average of 2.39 antimicrobial products over the year at an average cost of R121.70 per product. Of the total number of products dispensed, 63.43% were for generics (representing 48.40% of total cost) and 36.57% were originator products (representing 51.60% of total cost).

**Table 2: Prescribing frequency and cost of beta-lactam antibiotics**

The most frequently prescribed beta-lactam antibiotic was the combination of amoxicillin and clavulanic acid (54.69%), followed by amoxicillin (18.15%), cefpodoxime (11.4%) and cefuroxime (9.1%). The combination of amoxicillin and clavulanic acid constituted 71.87% of all penicillin prescriptions, followed by amoxicillin (23.74%). More than 95% (95.61%) of the penicillin prescriptions therefore contained amoxicillin.

**Discussion**

Antimicrobial drugs deserve their place as one of the most powerful pillars of modern medical care, but the development of antibiotic resistance appears to be emerging faster than the availability of new antibiotics, and this is widely recognised as a major threat to public health. Antibiotic resistance is driven by many factors, many of which are associated with inappropriate antibiotic and irrational management and consumption. To prevent irrational prescribing and possible over-prescribing, country-specific detailed data on antimicrobial utilization should be available.

In this study, the average age of patients was 34.23 (SD=19.92) years. Most patients were females (58.32%). According to the Council on Medical Schemes in South Africa, the average age of members of all registered medical schemes for the period ended 30 September 2011 was 31.8 years and the proportion of pensioners was 6.8%. No information on the gender distribution of members could be found. The demographic details of patients in this study were therefore roughly comparable to that of all medical aid scheme members in South Africa. Patients received an average of 2.39 antimicrobial products over the year at an average cost of R121.70 per product. Of the total number of products dispensed, 63.43% were for generics (representing 48.40% of total cost) and 36.57% were originator products (representing 51.60% of total cost). Generics clearly led to cost savings.

Beta-lactam antibiotics were the most frequently prescribed antimicrobial class in this study, accounting for 34.56% of prescriptions. This high prescribing rate is in agreement with several other international studies. The combination of amoxicillin and clavulanic acid accounted for 54.96% of all beta-lactam prescriptions. More than 95% of penicillin prescriptions contained amoxicillin as active ingredient. A study conducted in Catalonia, Spain in 2007 also showed that the combination of amoxicillin and clavulanic acid was the most prescribed (showing an increase of 84.4% since 2002), followed by amoxicillin. The average cost for a beta-lactam prescription in this study was R99.63. Overall, the penicillins accounted for 24.92% of all antimicrobial products prescribed. The previous South African study also found that penicillins were the most frequently prescribed class accounting for 38.17% of all prescriptions, and most prescriptions for antimicrobials were also to female patients (59.50%).

Anti-viral agents were the most expensive (average cost of R195.67 per product), followed by aminoglycosides (R188.42). The least expensive products were chloramphenicol (R17.25) and sulphonamides and combinations (R22.68). The chloramphenicol prescriptions were all for generic chloramphenicol 250 mg capsules (Schedule 4). The sulphonamides and combinations were exclusively for co-trimoxazole (mostly tablet formulations, but also suspensions, ampoules and injections).

In the ESAC study on outpatient antibiotic use in Europe, penicillins were the most prescribed outpatient antibiotics in all 25 European Medical Schemes in South Africa.
countries where they increased their leading position between 1997 and 2003. Similarly, the use of quinolones surged, while the use of another two major classes of antibiotics, tetracyclines and sulphonamides, stagnated or decreased in most European countries as newer antibiotics superseded them.12 Geographical variations were observed in the use of various antibiotic classes. For instance, the narrow-spectrum penicillins and the first-generation cephalosporins were widely prescribed for the treatment of community-acquired infections in many Nordic countries, while they almost disappeared in most Southern European countries.12 Geographical variations were not investigated in this study, but it will be possible to describe variations between provinces in future papers.

The current study showed a clear increase in prescribing during the winter months (May to August), the time period in South Africa when respiratory conditions usually peak. The usefulness of antibiotics in upper respiratory tract infections has been questioned in many published studies. In the ESAC study12, seasonality of outpatient antibiotic use was observed in all countries and it seems to be a general phenomenon related to an increased incidence of respiratory tract infections during winter months, resulting in higher prescriptions rates for antibiotics during this period. Since the vast majority of respiratory tract infections are of viral origin and self-limiting, the increase in antibiotic consumption in winter months should theoretically be finite.13 Excessive winter consumption of antibiotics suggests their inappropriate prescribing for respiratory tract infections, such as the common cold, influenza and bronchitis. This was also one of the findings of the previous South African study.14 The absence of complete and specific diagnoses in this study was a serious limitation preventing any definite conclusions regarding irrational use or overprescribing to be made.

Conclusion
Worldwide, research on antimicrobial prescribing and use is growing. This study provided a general overview of antimicrobial prescribing and cost in a South African primary care patient population. The findings were generally in agreement with other studies. Costs varied widely depending on originator or generic prescribing and should be further investigated. Similarly, variations in prescribing between the nine provinces in South Africa may yield interesting results. Further studies with other population groups, comparative studies with other African countries and more specific investigations are also recommended.

Conflict of interest
The author does not have a commercial or other association that may pose a conflict of interest.

Declaration
This work is based upon research supported by the National Research Foundation (NRF). Any opinion, findings and conclusions or recommendations expressed in this paper are those of the author and therefore the NRF do not accept any liability in regard thereto.

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Condensed versions of this manuscript have been presented as posters as:


References