Volume 5 Issue 1 July 2012
ISSN 1174-2704

Southern Med Review

An International Journal to Promote Pharmaceutical Policy Research

Pharmacy practice: Is the gap between the North and South widening?

Should the C in CME Stand for Commercial?

Adverse drug events and drug resistant tuberculosis in Namibia

Medical supply system in Vanuatu

Generic medicines in Pakistan

Medicine registration in African countries

Medicines discounts and rebates in Europe

Medicines zero mark-up policy in Beijing

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Context: In developing countries where health systems and health policy are constantly evolving, there is a great need to publish informative research. However, there are few avenues to do so. Also, some of the other challenges are inexperienced or untrained researchers, topics out of the scope of current mainstream journals and limited funding.

Objectives: Southern Med Review provides a platform for researchers to disseminate commentary and empirical research findings, with a view to improve the rational use of and access to essential medicines.

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The Editor and Publisher of Southern Med Review is Zaheer Babar PhD, School of Pharmacy, University of Auckland. Auckland, New Zealand. The journal's financial transactions are managed by Auckland UniServiced Ltd, Auckland, New Zealand. The present issue of the journal has been produced with a partial funding support from the University of Auckland. The "Southern Med Review" can be distributed freely; however no part can be copied without the permission of the Editor. The opinions and interpretations expressed herein by the authors are their own and do not necessarily reflect those of the publisher, editors, or organizations with which they are affiliated. Southern Med Review(ISSN: 1174-2704) All rights reserved, copyright 2012.

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Designing & Online Publication: DEVNET Informatics.

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Contents

Pharmacy practice: Is the gap between the North and South widening?

Citation: Babar ZU, Vaughan C, Scahill S. Pharmacy practice: Is the gap between the North and South widening? Southern Med Review (2012) 5; 1:1-2

The aim and objective of good pharmacy practice and optimal clinical pharmacy is to promote the appropriate use of medicines. However, the improvement in medicines use is very much dependent on health systems and has greatly benefited from the advances in science, technology, innovation and from those public policy measures, which support public health. Developed economies have been at the forefront of innovation and as a result, their health systems have become stable and more advanced. The quality of service provision within pharmacy and across the system as a whole has contributed significantly to medicines-related patient care.

With the advantages of innovation and the changing pace of technology come changes in pharmacy practice which are transforming very quickly. This change is driven by influences within two domains. One is the development of new technologies in medicines, for example better drug delivery methods or the use of robotics to dispense medicines. The other domain relates to the changes that are driven by demographics, disease prevalence, mortality rates and the aging population.

An example of a policy change which has been influenced by the aging population in the 'North' is the expansion in roles of non-medical prescribers. Policy-makers have been instrumental in shifting workloads in chronic care management to other healthcare professionals including pharmacists and nurses [1]. The opportunity for pharmacists to prescribe medicines independently or under the supervision of an experienced physician has released physician time and helped to meet the demand of an aging population with diminishing numbers of doctors through facilitating improved access to care. One other example of change in western developed countries is the argument that pharmacy practice must move away from "supply and distribution" as a main focus and should direct its attention to optimising medicines related health outcomes through clinical activity [1]. Pharmacists' time can then be better utilised within specialised clinical roles such as palliative care and care of the elderly [1].

The above-mentioned changes in developed economies have been policy-driven and designed after consideration of the opportunities to better utilise pharmacists skills and to reconfigure services as applicable to the context of each country. In this Editorial we pose the question "to what extent can such change be implemented in low and middle income countries and what might be the challenges to achieving this?"

For example, there have been calls to promote pharmacist prescribing within developing countries. However, this does not equate to the developed world as the majority of pharmacies in low and middle income countries are manned by non-qualified personnel and prescription medicines can be purchased over-the-counter, without the need for a prescription.

Currently, under the western developed model in the 'North', non-pharmacist technicians are being utilised in order to release the pharmacist from more technical duties of procurement and supply, to undertake more clinically oriented services. Future developments in western pharmacy practice may also include drug stores operated by non-pharmacists. However, in the South, where counterfeit medicines and assuring the quality of medicines is a big challenge [2] placing pharmacists in procurement may have a positive impact on the successful supply and distribution of good quality medicines [3]. In the South, "pharmacists within the pharmacy" as a concept has just started to emerge, and significant analysis and direction will be required in order for successful adoption of the western concept.

The difference in emphasis and the practice of pharmacy in the North and South paint a stark contrast. The question we seek answers to is to what extent can the policy-driven and somewhat theoretical advances in pharmacy practice in the North be applied to the South? Authors in developed countries write about the potential for improvement in pharmacy practice at a global level; however they fail to both realise, and articulate the differences between the health systems and how pharmacy is positioned within these systems [4]. Returning to consider the two domains pertinent to change in the pharmacy sector and its practice, we believe that technological advances in drug delivery such as new methods of injecting vaccines and insulin could be safely implemented within developing countries. However, concepts such as pharmacist prescribing and the utilisation of non-pharmacists in procurement and supply roles requires careful regulation and planning to reduce the widening gap between pharmacy service provision in the North and South.

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An International Journal to Promote Pharmaceutical Policy Research

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Should the C in CME Stand for Commercial?

Citation: Lexchin J, Vitry A. Should the C in CME Stand for Commercial? Southern Med Review (2012) 5;1:3-5

Imagine you are on trial for a serious crime and that if convicted you will be sentenced to serve time in a prison run by a for-profit corporation. (There are such prisons in the United States (US).) Now, imagine that your lawyer, who is supposed to represent your best interests, has had her continuing legal education paid for by the same for-profit corporation that runs the prison. How confident are you that your lawyer will actually represent your best interests? This is essentially the situation that patients face when doctors have their continuing medical education (CME) paid for by pharmaceutical companies. The latest figures on company sponsorship give some cause for hope – in 2010 in the US, industry funded 31% of CME compared to 48% in 2007 [1] – but we should not feel complacent about the situation. Industry continues to fund thousands of events for doctors around the world. In Australia from April 1 to September 30, 2011 companies represented by Medicines Australia, the organization for the brand-name industry, spent over $40 million (AUS) on 18,000 events attended by 423,000 people, primarily doctors, with over $18 million of the total going on hospitality [2].

Concerns about company funded CME are not something new. They have their roots as far back as the late 1950s and early 1960s when over 4000 new drugs were brought onto the American market and an estimated 70 cents of every dollar spent on prescription medicines was going for drugs that had not existed 10 years previously [3]. The CME required to keep pace with this enormous increase in the number of new drugs came with a significant cost and pharmaceutical companies were willing to fill the void despite caution from editorials in journals such as JAMA: "The principal source of financial support must come from within the medical profession. Financing often determines control, and control must remain in the hands of the profession" [4] . A more contemporary editorial in the CMAJ echoed this same message. "It is time to stop the pharma-driven 'free lunch' approach and place our continuing medical education system firmly in the hands of unbiased and qualified people, not corporations whose main concern is the bottom line" [5].

However, this message of caution does not seem to have been heard by many doctors. Surveys have generally shown that they have a positive attitude towards commercially sponsored CME. Seventy percent of Norwegian general practitioners agreed completely that commercial courses kept high standards [6]. Similarly, industry meetings in Australia were judged to be of good to excellent quality by 81% of generalists, 79% of internists and 87% of psychiatrists [7]. Although many doctors recognize that there might be a conflict of interest (COI) in attending CME paid for by industry most naively think that they will not be affected by that COI [8]. A before and after study of hospital doctors' prescribing showed just how naive doctors can be. It found a dramatic increase in the use of drugs featured at pharmaceutical company symposia despite the fact that before going off to attend the conference the doctors involved did not believe that their prescribing practices would be influenced by their attendance [9].

It also appears that commercial sponsorship has a significant limiting effect on the number of topics covered in CME events. One paper compared talks developed by Harvard Medical School independent of any commercial influence and pharmaceutical company-funded symposia [10]. The 221 Harvard talks covered 133 topics while the 103 symposia focused on 30 topics, most of which were linked to recently approved new therapeutic agents sold by the funders. Drug therapy was the central topic in 27% of the Harvard talks compared to 66% of the symposia. Both types of courses were highly rated by attendees.

Bowman analyzed the content of two CME events in relation to their source of funding [11]. Both courses were given at a university that had policy guidelines that required the course content to be controlled by the institution. Despite this requirement, in both courses there was a bias in favour of the drug made by the sponsoring company as compared to equally effective drugs made by other companies and more importantly prescribing patterns were influenced by this bias [12]. Content advertised as independent of industry influence may in fact be heavily influenced by industry. A series of leaked e mails from HealthEd, a popular Australian provider of CME, showed the company asking Sanofi-Aventis "Could you please suggest a couple of speakers for our scientific committee's approval?" In another case a company representative asks HealthEd to "determine the speaker's opinion re: Tramal as I would like to ensure he positions it appropriately" [13].

As bad as things may be in developed countries, they are much worse in the developing world where independent medical information is hard to come by and companies provide most of the CME that doctors get. The chief pharmacist at the Kenyatta National Hospital in Nairobi described how companies organize CME courses in his country: "Sponsorship of CMEs at institutional/professional organizational level (they get a guest speaker, topic of their choice, pay for coffee/tea and snacks) this partnering with an institution/professional association endorses the company. Development of resource centres (rent for space, purchase of computers and necessary software, subscriptions

for journals) for professional association – quite a noble idea, but…?"[14]. A Nepalese medical student observed that "medical conferences … are strongly dominated by the pharmaceutical industry. Often, companies organize parties for doctors in which a continuing medical education topic is followed by a lavish cocktail dinner—but often the educational part is absent … Pharmaceutical companies also sponsor the activities of medical students (such sponsoring can take the form of sports matches, publications, and parties)" [15].

Out of all of the professions medicine is unique in that its practitioners actively ask for-profit corporations to pay for their education. It appears that doctors feel a sense of entitlement for this support, a hypothesis that was tested in an elegant trial designed to elicit how doctors rationalize their behavior. When residents (registrars) were reminded about the "sacrifices" that they made in order to become doctors their acceptance of industry-sponsored gifts increased and it increased even further when it was suggested to them that their sacrifices were an appropriate rational for accepting gifts [16]. A recent survey in the US showed that, although 88% of 770 US health professionals believed that commercial support introduces bias, 58% of them would not be willing to pay higher fees to decrease or eliminate commercial support [17].

The occasional company seems willing to cut back on its sponsorship of CME [18] but the head of Medicines Australia defends the practice of companies offering suggestions for speakers at CME events [13]. The Code of Practice from the International Federation of Pharmaceutical Manufacturers & Associations, the de facto marketing code in many developing countries, is hardly reassuring about CME. The 2012 revision to the code does not ban companies from suggesting speakers or supplying them with slides and does not require the disclosure of commercial sponsorship [19].

The situation in developed countries is changing, albeit slowly. A survey in 6 European countries showed that industry sponsorship of CME is allowed in all countries but Norway. Although limits are imposed on promotion during the CME events it is not clear what controls are placed on industry influence on the content [20]. In the US, the Oregon Academy of Family Physicians no longer accepts any type of pharmaceutical industry grants for its CME activities [21] and the House of Delegates of the American Medical Association voted that "when possible," CME activities should be free of industry sponsorship [1]. In developing countries progress will be even more difficult but with the help of the international community it should be possible. The World Medical Association (WMA) has a policy about the relationship between physicians and commercial enterprises [22] and should work with national medical associations to ensure that their policies are at least as stringent as the one from the WMA.

The Criteria for Medicinal Drug Promotion from the World Health Organization (WHO) has three clauses covering symposia and other scientific meetings [23]. Unfortunately, at present WHO is doing little to encourage drug regulatory authorities to use these criteria but various non-governmental organizations are pushing WHO to engage with national authorities to use the criteria as a model template in the same way that the Model List of Essential Medicines is used. Finally, some journal publishers are already making their publications available at a reduced cost or free to practitioners in low income countries. This practice should be expanded to help practitioners reduce their dependency on the pharmaceutical industry for current information about therapeutics.

The reliance of health professionals on industry-funded CME is more likely to happen in the absence of the provision of independent CME and medicines information. Some governments are funding independent CME and may also provide incentives to general practitioners to participate in independent educational activities. In Australia, the National Prescribing Service (NPS) provides educational activities that bring continuing professional development (CPD) points. These activities also qualify for the Quality Prescribing Initiative (QPI) of the Practice Incentives Program run by Australian Medicare. QPI provides financial rewards to general practices for participation in NPS educational activities. In many countries, there are bulletins and journals on drugs and therapeutics that are financially and intellectually independent of the pharmaceutical industry and are grouped under the umbrella of the International Society of Drug Bulletins (ISDB) (http://www.isdbweb.org/).

ISDB currently has 54 full and 24 associated members spread over all continents. Some of the educational activities organised by these journals can qualify for CPD points such as the monthly reading test and thematic educational activities organised by the French independent journal, la Revue Prescrire. Academic detailing that aims to provide noncommercial information through face to face meetings with prescribers has been utilized in Australia, France, Canada, the United Kingdom and several states of the US (http://www.rxfacts.org/). Unfortunately, the provision of independent CME is less likely to happen in developing countries because of the lack of resources.

As the father of Canadian national health insurance used to say "Courage; my friends, 'tis not too late to build a better world."

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Research Article

Southern Med Review

The burden of adverse events during treatment of drug-resistant tuberculosis in Namibia

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Citation: Sagwa E, Mantel-Teeuwisse A, Ruswa N, Musasa JP, Pal S, Dhliwayo P, van Wyk B. The burden of adverse events during treatment of drug-resistant tuberculosis in Namibia. Southern Med Review (2012) 5;1: 6-13

Received: 6th February 2012
Accepted: 6th June 2012
Published Online: 23rd July 2012

Abstract

Objective: Namibia faces a dual burden of HIV/AIDS and tuberculosis (TB). In 2010, HIV prevalence was 18.8%, the TB case notification rate was 634 cases per 100,000 population and the TB/HIV co-infection rate was 58%. There were 372 cases of drug-resistant TB (DR-TB) in 2009. The objective of this study was to assess the prevalence, profile and outcome of adverse events (AEs) associated with treatment of DR-TB and to explore possible influences of HIV disease on the occurrence of adverse events.

Methods: This was a cross-sectional descriptive study. After ethical approval, data were collected from treatment records of all patients treated for DR-TB at the study facility between January 2008 and February 2010 using a structured data collection form.

Results: A total of 141 adverse events of varying severity were experienced in 90% (53/59) of patients.The TB/HIV co-infection rate was 53% (n=31). The prevalence of gastrointestinal tract adverse events (abdominal pains, constipation, diarrhea, nausea and vomiting) was 64%, tinnitus 45%, joint pain 28%and decreased hearing 25%. Abdominal pains, rash, nausea, decreased hearing and joint pain were more common in HIV infected than in HIV uninfected patients.

Conclusions: Adverse events of varying severity are common during treatment of DR-TB, particularly in the intensive phase of therapy. Some adverse events were more prevalent in DR-TB patients co-infected with HIV. The study concludes that the characteristics and risk factors of serious adverse events should be further examined.

Keywords: tuberculosis, drug resistance, second-line drugs, adverse events, Namibia

Introduction

Tuberculosis (TB) exerts a huge burden of disease in Namibia, with a case notification rate (CNR) of 634 cases per 100,000 population in 2009 [1]. This is one of the highest tuberculosis CNRs in Africa. The TB/HIV co-infection rate was 58% in 2009 [1, 2]. Resistance to first-line regimens is a growing issue and could be due to various factors, including sub-optimal patient adherence to treatment schedules and defaulting in treatment [3]. Namibia reported 372 cases of drug resistant TB (DR-TB) in 2009, of which 74% of cases were`multi-drug resistant TB (MDR-TB), 22% poly-drug resistant TB and 5% were extensively drug resistant TB (XDR-TB) [1].

Although a number of studies [4-15] have examined the occurrence and characteristics of adverse events among patients

on second-line anti-TB medicines, very few have specifically examined occurrence of adverse events in sub-Saharan Africa [16], especially in the context of high HIV prevalence and high TB/HIV co-infection rates. Most reviewed studies have mainly focused on adverse events of either one or two anti-TB medicines, but not on the entire treatment regimen [4-16].

This study describes the epidemiology of adverse events associated with treatment of DR-TB in a sub-Saharan country with a dual burden of TB and HIV. It further explores possible influences of HIV disease and antiretroviral treatment on the occurrence of adverse events.

The study thereby contributes to the existing body of epidemiologic and public health knowledge about treatment of DR-TB, focusing on a sub-Saharan country. This will assist managers of tuberculosis control programs, clinicians, and patients in similar socio-economic and epidemiologic settings in making evidence-based decisions for optimizing treatment outcomes for DR-TB patients, particularly in HIV co-infected patients. In this context, we aimed at assessing the profile, frequency and outcomes of adverse events associated with the use of second-line anti-TB medicines. The specific objectives of the study were:

1) To determine the types and frequency of adverse events associated with the use of second-line anti-TB medicines in a selected DR-TB treatment facility in Namibia.

2) To describe the characteristics, duration and outcomes of the adverse events, focusing on differences in adverse event occurrence between HIV infected and HIV uninfected persons.

Methods

Settings

The study was conducted in a 25-bed district hospital DR-TB ward with the second largest number of patients on DR-TB treatment in Namibia. Patients diagnosed with DR-TB are hospitalized in this TB ward, which is physically isolated from the rest of the wards in the hospital. This isolation is part of the infection control measures put in place at the facility to minimize nosocomial transmission of *Mycobacteria tuberculosis*. The patients with DR-TB infection are initiated on second-line treatment for about six months of intensive chemotherapy that includes injectable agents (amikacin, kanamycin or capreomycin). Until 2008, amikacin was the preferred aminoglycoside but this was later changed to kanamycin from 2009 onwards. The daily patient doses for each medicine used in the regimen were calculated and individualized according to the recommended World Health Organisation (WHO) body weight-based dosing scheme for anti-TB drugs (Table 3). Continuation therapy using oral anti-TB agents that includes a fluoroquinolone is maintained through an outpatient directly observed treatment short-course (DOTS)-plus programme. This DOTS-plus treatment is implemented through the health center closest to the patient. Patients on continuation therapy visit the health facility every day (Monday - Friday) for daily doses of second-line anti-tuberculosis medicines. Doctors and nurses elicit information on adverse events from patients and record them on a structured, pre-printed DR-TB treatment side effects monitoring form.

Study participants and data collection

For this cross-sectional descriptive study, the study population included all patients treated with second-line anti-TB medicines at the DR-TB treatment facility from 01 January 2008 to 24 February 2010. Treatment records were reviewed for all the patients treated for DR-TB during this period. Further, data on patient demographics, *Mycobacterium tuberculosis* drug resistance, medications and other clinical variables, including occurrence of adverse events and the characteristics of the adverse events, were collected from patient records using a structured data collection form. Since the present study did not involve direct contact with patients, informed patient consent was not required. Ethical approval of the study protocol was obtained from the research unit of the Ministry of Health and Social Services of Namibia (MoHSS) and the Higher Degrees Committee of the University of the Western Cape, South Africa.

Occurrence of adverse events and the analysis of data

The main outcome variable was the occurrence of adverse events. Further, a detailed characterization of the adverse events was conducted, which included: the adverse event description, time to onset of the adverse event, grading of severity of the adverse event, duration of the adverse event, actions taken to clinically manage the adverse event, and the outcome of the adverse event. Data were single-entered into Epi Info version 3.5.3 and the accuracy of entry verified against the original paper forms. The data were further checked for any errors and then analyzed using descriptive statistics. Absolute and relative frequency counts and measures of central tendency (mean, median and mode) were calculated. Measures of dispersion including range, interquartile range and standard deviation were also calculated.Student's T-tests were used to assess differences in age and weight between the genders. A P-value of less than 0.05 was considered to be statistically significant. All statistical analyses were performed using Epi Info version 3.5.3.,while Microsoft Excel® (2010) was used to draw charts.

Results

Fifty-nine (59) patients were treated for DR-TB during the study period. There were more male patients than females (66% vs. 34%). The mean patient age was 34.7 ± 9.4 (SD) years (Table 1). Males were slightly older than females (36.9 versus 31 years;P=0.02). The mean baseline weight was 52.5 ± 11.3 (SD) kilograms (kg), with no statistically significant gender difference (53.6 ± 7.8 kg males, versus 49.8 ± 16.4 kg females; P=0.23). About one-third of patients were unemployed.

Table 1: Demographic and clinical characteristics of the 59 patients treated with DR-TB therapy

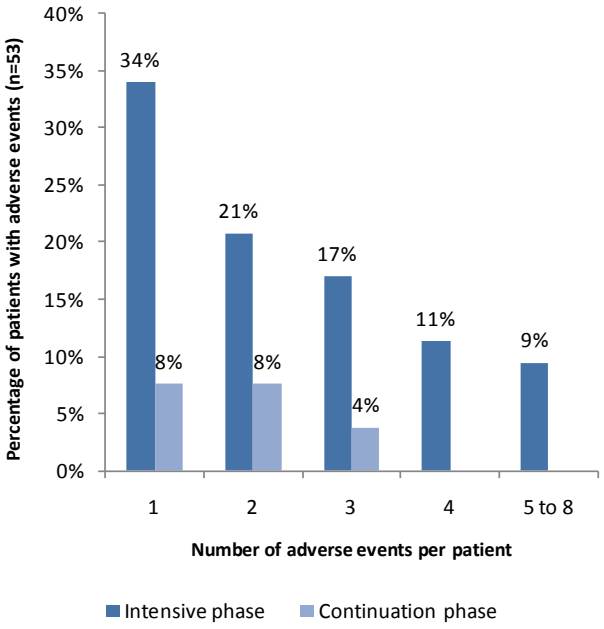
Characteristic	n (%)
Gender	
Male	38 (64%)
Female	20 (34%)
Missing	1 (2%)
Age (years), SD	**34.7 ± 9.4**
Male	36.9 ± 8.4
Female	31.0 ± 10.2
Weight (kg), SD	**52.5 ± 11.3**
Male	53.6 ± 7.8
Female	49.8 ± 16.4
Occupation	
Unemployed	18 (31%)
Employed	20 (34%)
Student	1 (2%)
Missing	20 (34%)
Type of TB	
PTB smear +	55 (93%)
PTB smear -	3 (5%)
EPTB	1 (2%)
Diagnostic category of DR-TB	
Previously treated with 1st line medicines	46 (78%)
Previously treated with 2nd line medicines	8 (14%)
New patient, never treated for TB	5 (8%)
TB drug resistance pattern	
MDR	36 (61%)
Poly resistant	18 (28%)
XDR	1 (2%)
Missing	4 (6%)
Number of medicines in anti-TB regimen; median (range)	
Intensive phase regimens	5 (4-7)
Continuation phase regimens	3 (3-5)
Days on intensive phase treatment; Median (IQR) n=53	
Male	182 (154-186)
Female	184 (165-211)
Days on continuation phase treatment; Median (IQR) n=49	
Male	389 (185-503)
Female	522 (451-584)
HIV co-infection	
Male	19 (32%)
Female	12 (20%)
Unknown	3 (5%)
Proportion of HIV positive persons on HAART*	**13 (42%)**
D4T/3TC/EFV	5 (16%)
AZT/3TC/EFV	3 (10%)
AZT/3TC/NVP	2 (6%)
TDF/3TC/EFV	2 (6%)
D4T/3TC/NVP	1 (3%)

Almost all (92%) of the 59 patients had a prior history of treatment with either first-line or second-line anti-tuberculosis medicines. Approximately half of the patients (31/ 59 or 53%) were co-infected with the human immuno deficiency virus (HIV). Of the 31 HIV co-infected TB patients,13 (42%) were on highly active antiretroviral treatment (HAART).

In total, there were fifteen different anti-tuberculosis medicines that were used by the patients included in this study (Table 3). Most of the patients were treated with DR-TB regimens containing pyrazinamide (93%) and ethionamide (92%). All patients were treated with an injectable anti-tuberculous agent (amikacin, kanamycin or capreomycin) during the intensive phase of treatment,with kanamycin being the most frequently used aminoglycoside in 54% of the patients. Fluoroquinolones (ciprofloxacin and levofloxacin) were used in almost all of the patients (98%), of which levofloxacin was used twice as much as ciprofloxacin (66% versus 32%). There were 30 individualized regimens that were used in the intensive phase of treatment and 18 in the continuation phase of treatment. These individualized regimens were determined according to the drug sensitivity patterns of the infecting *Mycobacterium tuberculosis* strain.

Fifty-three of the 59 patients experienced at least one adverse event of varying severity grading (90% prevalence). A total of 141 adverse events were reported by these patients. The number of adverse events experienced by an individual patient ranged from one to eight. The proportion of patients experiencing a given number of adverse events dramatically reduced from the intensive to the continuation phase of treatment (Figure 1).

Figure 1: Distribution of percentage of patients by number of adverse events experienced per patient in the intensive and continuation phases of treatment

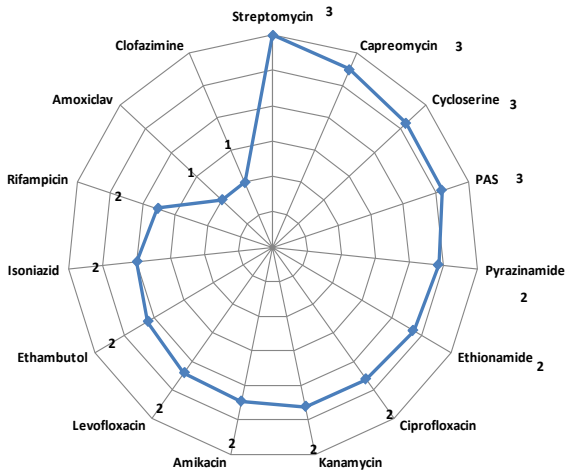


* As percentage of number of patients with HIV co-infection

SD=standard deviation; kg=kilogrammes; TB=tuberculosis; PTB=pulmonary tuberculosis; + = positive; - = negative; EPTB=extra pulmonary tuberculosis; MDR=multidrug-resistant; XDR=extensively drug-resistant; IQR=interquartile range; HIV=human immunodeficiency virus; HAART= highly active antiretroviral therapy; d4T=stavudine; AZT=zidovudine; 3TC=lamivudine; EFV=efavirenz; TDF=tenofovir disoproxil fumarate; NVP=nevirapine

The average number of adverse events experienced by patients treated using specific anti-tuberculosis medicines ranged from one to three (Figure 2). Patients using regimens that contained streptomycin, capreomycin, cycloserine, and para-amino salicylic acid (PAS) experienced the highest average number (3) of adverse events, while patients using amoxycillin/ clavulanic acid and clofazimine experienced the fewest, with an average of one adverse event per drug. The rest of the medicines were associated with a similar average number of two adverse events per patient (Figure 2).

Figure 2: Average number of adverse events experienced per patient exposed to specific anti-tuberculosis drug.



Hearing loss (decreased hearing), tinnitus, gastrointestinal tract (GIT)-related events (nausea, abdominal pains, vomiting, diarrhea and constipation) and joint pain were the predominant adverse events (Table 2). Five adverse events were more prevalent in HIV infected patients than in HIV uninfected patients (the figures in brackets show the excess frequency of occurrence in HIV infected patients as compared to HIV negative patients). These adverse events were: abdominal pains (22%); rash (16%); nausea (10%); decreased hearing (7%) and joint pain (6%). Contrarily, fever and fatigue are examples of adverse events that were reported less frequently by these patients (Figure 3).

Fourteen (93%) of the 15 reported cases of joint pain were observed in patients treated with pyrazinamide-containing regimens.

Seventy three percent of the moderate-to-severe adverse events lasted for more than three (3) months, while 60% of the mild adverse events resolved within 3 months of onset. Overall, in 53% of patients, the adverse events resolved within 3 months of onset, while 47% of patients experienced adverse events that persisted beyond 3 months. Adverse events were severe and warranted discontinuation of the suspected offending medicine in four (4) out of 26 (15%) patients. Four (4) out of the 42 (9%) patients for whom data was available recovered from their adverse reactions with sequelae.

Table 2: Frequency of adverse events in both treatment phases; intensive and continuation phases respectively

Grouped adverse events	Specific adverse events	Both phases (N=53)*	%	Intensive phase (N=53)	%	Continuation phase (N=49)†	%
Hearing loss & Tinnitus	Tinnitus	24	45%	21	40%	3	6%
	Decreased hearing	13	25%	12	23%	1	2%
	Hearing loss & Tinnitus Total	**37**	**70%**	**33**	**62%**	**4**	**8%**
GIT-related	Nausea	12	23%	8	15%	4	8%
	Abdominal pain	9	17%	8	15%	1	2%
	Vomiting	6	11%	6	11%	0	0%
	Diarrhea	5	9%	5	9%	0	0%
	Constipation	2	4%	2	4%	0	0%
	GIT Total	**34**	**64%**	**29**	**55%**	**5**	**10%**
Others	Joint pain	15	28%	13	25%	2	4%
	Headache	11	21%	10	19%	1	2%
	Fatigue	10	19%	8	15%	2	4%
	Dizziness	8	15%	7	13%	1	2%
	Rash	7	13%	7	13%	0	0%
	Neuropathy	4	8%	2	4%	2	4%
	Fever	3	6%	3	6%	0	0%
	Vision changes	3	6%	2	4%	1	2%
	Depression	2	4%	2	4%	0	0%
	Psychosis	2	4%	2	4%	0	0%
	Severe hepatitis	1	2%	1	2%	0	0%
	Decreased urine	1	2%	1	2%	0	0%
	Anemia	2	4%	2	4%	0	0%
	Loss of libido, delayed ejaculation	1	2%	0	0%	1	2%
Total of all adverse events		**141**		**122**		**19**	
Percent of all adverse events		**100%**		**87%**		**13%**	

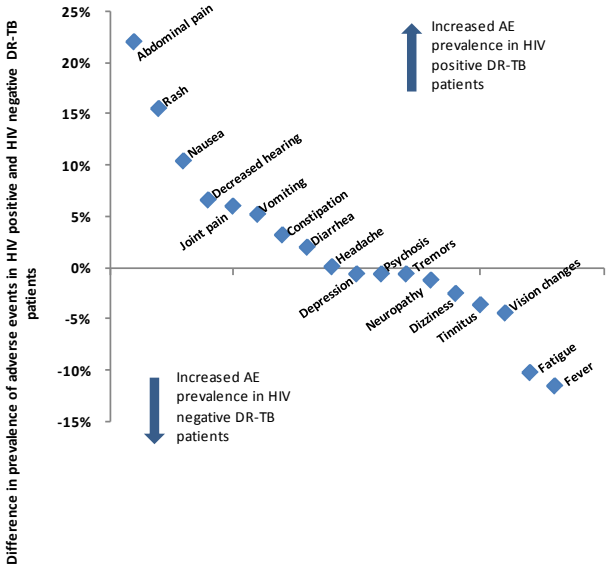
*53 of the 59 patients reported to have experienced at least one DR-TB treatment-related adverse event. All the 53 patients had either completed or were still in the intensive phase of treatment at the time of data collection. †49 of the patients had progressed into the continuation phase of treatment and were either still on continuation phase treatment or had completed treatment at the time of data collection. %= percent. Sum of column percentages may exceed 100% because a patient may experience more than one adverse event. GIT =gastrointestinal tract

Table 3: Prevalence of use and the weight-based dosing of specific anti-tuberculosis drugs in the treatment of drug-resistant tuberculosis in Namibia

Drug name	DRUG EXPOSURE		DOSING BY WEIGHT CLASS			
	Number of patients	Percent (n=59)	<33 KG	33–50 KG	51–70 KG	>70 KG (Maximum dose)
Pyrazinamide	55	93%	30–40 mg/ kg , daily	1000–1750 mg, daily	1750–2000 mg , daily	2000–2500 mg ,daily
Ethionamide	54	92%	15–20 mg/ kg daily	500 mg	750 mg	750–1000 mg
Levofloxacin	39	66%	Usual adult dose is 750 mg	750 mg	750 mg	750–1000 mg
Ethambutol	36	61%	25 mg/ kg , daily	800–1200 mg, daily	1200–1600 mg , daily	1600–2000 mg daily
Kanamycin	32	54%	15–20 mg/ kg daily	500–750 mg	1000 mg	1000 mg
Cycloserine	29	49%	15–20 mg/ kg daily	500 mg	750 mg	750–1000 mg
Amikacin	21	36%	15–20 mg/ kg daily	500–750 mg	1000 mg	1000 mg
Ciprofloxacin	19	32%	20–30 mg/ kg daily	1500 mg 1500 mg	1500 mg	
Rifampicin	13	22%	10–20 mg/ kg, daily	450–600 mg, daily	600 mg, daily	600 mg, daily
Para-aminosalicylic acid	5	8%	150 mg/ kg daily			
Capreomycin	4	7%	15–20 mg/kg	500–750 mg	1000 mg	1000 mg
Isoniazid	4	7%	4–mg/ kg daily	200–300 mg daily	300 mg daily	300 mg daily
			or 8–12 mg, 3 x wk	or 450–600 mg, 3 x wk	or 600 mg , 3 x wk	or 600 mg, 3 x wk
Streptomycin	3	5%	15–20 mg/ kg daily	500–750 mg	1000 mg	1000 mg
Clofazimine	1	2%	Efficacy and dosing in the treatment of drug-resistant TB not fully determined			
Amoxicillin/ Clavulanate	1	2%	Efficacy and dosing in the treatment of drug-resistant TB not fully determined			

Source: WHO, (2006). Guidelines for the programmatic management of drug-resistant tuberculosis: 147-8. mg=milligrammes; Kg=kilogrammes; wk = week

Figure 3: Comparison of difference in prevalence of adverse events in HIV positive and HIV negative DR-TB patients.



Discussion

Adverse events of varying severity, particularly tinnitus, hearing loss, GIT-related adverse events and joint pains were experienced by most (90%) of the patients included in this study. Most of the adverse events were reportedly experienced in the intensive phase of DR-TB treatment. Some differences in the occurrence of adverse events were observed between patients who were HIV infected and those who were HIV uninfected. Abdominal pains, rash, nausea, decreased hearing and joint pain were among the adverse events more frequently reported by HIV infected patients, whereas fever and fatigue were reported relatively less frequently, when compared with HIV uninfected patients.

The 90% prevalence of adverse events observed in the current study is higher than that reported in other studies, where it ranged from 69%-86% [4-14, 16]. It was slightly lower than the 96% reported by Tupasi and colleagues in their study of 117 patients in the Philippines [15]. The reasons for the heterogeneity in the prevalence of adverse events across the various studies is unclear, but might be related to several possible factors such as: differences in definitions of adverse events terminologies across settings, whether the adverse event was symptomatic and patient-reported (subjective) or clinician-validated (objective), whether all or only the severe and serious adverse events were studied, variations in the use of specific anti-TB agents, and/or the differences in co-morbidities and other covariates between study settings. Our study's cohort is similar to other cohorts in terms of demographics and number of anti-TB medicines used and treatment duration. In addition, treatment was according to existing guidelines [3, 17]. However, the HIV co-infection rate and the specific anti-TB agents used may differ between settings and this should be borne in mind when interpreting and comparing results of adverse events reported from different countries. Although the present study found the TB/HIV

co-infection rate to be higher than that reported in Europe and South East Asia (where HIV prevalence rates are low) [6,13,18], it is lower than that observed for Lesotho, a country in Southern Africa, which has a high prevalence of HIV infection [16].

The frequency of tinnitus (45%) in the present study was higher than the 5.1% - 24% range reported in the literature [4, 14, 15], while that of hearing loss (25%) was within the range of 6.7% - 33% reported in the literature [5, 11, 14, 15]. From the review of the literature, the reported rates of ototoxicity (tinnitus and hearing loss) ranged from 12% to 42% [6, 7, 16]. Our study found an almost double rate of ototoxicity, when compared to the 36% reported by Seung et al. [16], whose study population and HIV prevalence rates are similar to our population. It is unclear why this is so, but one possible reason could be that the majority of patients in the Seung study were still in the early stages of treatment, hence not all potential adverse events may have occurred by the time of completion of their study. The high degree of heterogeneity of ototoxicity observed in the literature could have been brought about by differences in the use of specific ototoxic anti-TB agents, as well as by the differences in the profiles of co-morbidities in the different patient population groups of the various studies.

Ototoxicity (tinnitus and decreased hearing) is predominantly associated with the use of parenteral anti-tuberculous agents (aminoglycosides and aminopeptides) [19-24]. The drug-specific rate of patient-reported tinnitus in the current study ranged from 33%- 50%, while hearing loss was 13% - 67%. These findings are above the range of 15.4% - 33% reported in studies conducted elsewhere [5, 19, 20]. The high prevalence of tinnitus and hearing loss found in our study is probably because they were symptomatic or patient-reported (subjective) and may not have been clinically validated by audiometric tests. In addition, there could have been additive effects of interaction with other concomitant and potentially ototoxic anti-TB drugs that were used in the anti-TB regimens, such as fluoroquinolones and cycloserine. Additionally, there are possibilities of interactive effects from HIV disease and the concomitant use of antiretroviral medicines, which may have contributed to this high rate of ototoxicity. This needs further investigation to uncover the possibility of these interactive effects.

The gastrointestinal tract (GIT)-related adverse events were the second most observed group of adverse events, reported by 64% of the patients. The specific GIT-related adverse events were: nausea (23%), abdominal pain (17%), vomiting (11%), diarrhea (9%), and constipation (4%). The frequency of occurrence of these specific GIT-related adverse events fall within the wide range (10.8% - 100%) which has been reported in the literature [4, 6, 7, 11, 14, 15, 16]. Since some studies have reported higher rates of specific GIT-related adverse events, it is possible that patients in our study may have selectively under-reported these adverse events during the course of their treatment.

The possibility of drug-drug interactions [10], drug-disease and disease-disease interactions should be reflected on in the present study, particularly considering that an average of five different anti-TB agents were used by each patient in the study and that over 50% of the patients had HIV co-infection, 42% of whom were on concomitant antiretroviral medication.

In our study, adverse events were severe and warranted discontinuation of the suspected offending medicine in 15% of patients. This prevalence of treatment discontinuation is lower than that reported in the literature [4, 5, 12, 14]. Generally, our findings are similar to the findings of Furin et al. (2001) that adverse events of the anti-TB medicines were bearable and did not cause discontinuation of the treatment apart from the occasional suspension of an offending agent in 11.7% of the patients [11].

Strength of the study

The data used in this study reflect real-life DR-TB treatment practices and patient experiences. The cross-sectional descriptive design enabled us to examine and describe the prevalence and profile of adverse events in the patient sample. We were able to generate a tentative hypothesis that some adverse events occur more in DR-TB patients co-infected with HIV, which is clinically important when treating this sub-group of patients.

Limitation of the study

By using retrospective data, we encountered instances of missing patient treatment records and missing data on specific variables. Furthermore, it was not possible to perform qualitative causality assessment of the adverse events using the available data, especially given the paucity of laboratory data. The adverse events recorded on the patients' side-effects monitoring form were based on patient-reported symptoms. Hence, there was a possibility of subjectivity and of selective under-reporting of adverse events by patients or the selective recording of adverse events by clinicians, which may have biased the results away from the true prevalence. Some symptoms of reported adverse events may have overlapped with symptoms of HIV/ AIDS. The small sample size and the use of data from one facility may not allow for generalization of findings beyond the studied sample.

Conclusion

This study found that adverse events, of varying severity, most commonly occur in the intensive phase of DR-TB treatment. While most patients tolerated the second-line anti-TB medicines used in Namibia's DR-TB treatment program, about 10% of patients experienced serious adverse events, with a possibility of suffering permanent disability. Some adverse events were more prevalent in DR-TB patients co-infected with HIV. The characteristics, magnitude of risk and risk factors of these serious and potentially permanent adverse events should be thoroughly examined and elucidated in subsequent prospective active surveillance pharmacovigilance or cohort studies. Therefore, clinicians, including pharmacists, should closely monitor and aggressively manage adverse events during the intensive phase of DR-TB treatment and should always consider the possibility of increased occurrence of adverse events in patients co-infected with HIV.

Authors' contributions

Evans Sagwa conceived and designed the study; collected, analyzed the data, drafted and finalized the manuscript. Brian van Wyk, Panganai Dhliwayo, Nunurai Ruswa, and Jean Paul Musasa reviewed the study protocol and manuscript. Aukje Kaija Mantel-Teeuwisse and Shanthi Pal critically reviewed the manuscript.

Acknowledgments

The authors would like to thank H.G.M Leufkens, J. Rohde, F. Mavhunga, M.Malakia, E. Moreno, A. Mengistu, C. Corbell, J. Nwokike, D. Mabirizi, A. Stergachis , R. Laing and T. Rennie for their contributions in this study. Special thanks to all the faculty members of the Pan African Thoracic Society course in methods for epidemiologic, clinical and operational research (PATS-MECOR) for their technical assistance in the interpretation of the study findings. Tuberculosis patient care and treatment is a Government and donor funded service freely provided by health facilities of the Ministry of Health and Social Services, Namibia.

Conflict of interest

None

Funding source

Funding of this study was provided by Evans Sagwa as part of his research towards the Master of Public Health degree, University of the Western Cape, South Africa.

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Research Article

Southern Med Review

The Vanuatu medical supply system – documenting opportunities and challenges to meet the Millennium Development Goals

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Citation: Brown A, Gilbert B. The Vanuatu medical supply system – documenting opportunities and challenges to meet the Millennium Development Goals. Southern Med Review (2012) 5;1: 14-21

Received: 8th Sep 2011
Accepted: 11th June 2012
Published Online: 23rd July 2012

Abstract

Objectives: Limited human resources are widely recognised as a barrier to achieve health-related Millennium Development Goals. Availability of medical supplies and suitably trained health personnel are crucial to ensuring a well-functioning medical supply system. The objective of this paper is to identify the factors which influence the availability of medical supplies within the health facilities of Vanuatu.

Methods: A qualitative triangulated strategy using semi-structured interviews, observational workplace surveys and semi-structured focus groups was developed. This research was approved by the Human Ethics Committee of the University of Canberra and was funded through a direct grant from the United Nations Population Fund Suva, Pacific sub regional office.

Results: During two weeks of data collection, 21 interviews were conducted, observational workplace surveys were completed in 19 facilities and 22 personnel participated in three focus groups across three provinces. The interviewees had a wide range of primary professional groupings and were representative of the Vanuatu health workforce. A complex array of medical supply issues are described from within the three tiered structure of the medical supply system.

Conclusion: The results of this research have further informed our understanding of the competencies required by healthcare personnel to conduct medical supply management activities effectively in Pacific Island countries. As a result of this research, a platform is provided for the government of Vanuatu to engage development partners to work toward a sustainable medical supply system.

Keywords: Essential medicines supply, medical supply, interview, pharmacy, surveys, Vanuatu

Introduction

The Pacific regional context

Limited human resources are widely recognised as an impediment to achieving the health-related Millennium Development Goals (MDGs). Many maternal and child deaths may be prevented by having ready access to essential medical supplies provided by appropriately trained health personnel (where medical supplies include medicines and medical sundries e.g. syringes and dressings) [1]. Millennium Development Goals 4, 5, 6 and 8 explicitly involve the availability of medical supplies at the primary care level - the absence of these supplies is a significant barrier [2] to meeting these goals (Table 1).

Table 1: The explicit relationship between the Millennium Development Goals (MDGs) and the medical supply system.

MDG 4. Reduce child mortality	Pneumonia, diarrhea, malaria and AIDS account for 43 per cent of all deaths in under-fives with most of these lives saved through low-cost prevention and treatment measures including antibiotics for acute respiratory infections, oral rehydration for diarrhea, and immunization [2].
MDG 5. Improve maternal health	More than 80 per cent of maternal deaths are caused by conditions such as hemorrhage, sepsis, and hypertensive diseases of pregnancy, each requiring medication and the use of medical sundries. It is estimated that meeting the unmet needs for contraception alone could cut, by almost a third, the number of maternal deaths [2].
MDG 6. Combat HIV/AIDS, malaria, and other diseases	Each disease has medication as part of the treatment protocol.
MDG 8. Develop a global partnership for development	In cooperation with pharmaceutical companies, provide access to affordable essential medicines in developing countries.

United Nations (UN).The Millennium Development Goals Report United Nations. 2010. URL: http://www.un.org/millenniumgoals/pdf/MDG_20Report_202010_20En_20r15_20-low_20res_2020100615_20-.pdf Accessed 4th February 2012.

The availability of medical supplies and suitable personnel in adequate numbers with appropriate competency is crucial to ensure a well-functioning medical supply system [3]. In many countries pharmacists perform this role; however on average across Pacific Island countries (PICs) there is less than 1 pharmacist per 10,000 population [4]. This ratio is similar to sub-Saharan African countries [3]. Some PICs have no pharmacists at all. In this environment the medical supply system is often operated by pharmacy support staff such as assistants, technicians and dispensers with a wide variance in the formal training they receive for this role [3, 4].

The majority of the population in PICs resides in rural areas which are serviced by primary healthcare facilities such as clinics and aid posts [1,4]. These facilities commonly do not employ pharmacy staff and medical supply activities are conducted by healthcare personnel such as nurses or midwives who may have little or no formal training in this medical supply role.

The International Pharmaceutical Federation (FIP) acknowledge that insufficient numbers and inadequate competency of pharmacy personnel is a contributor to continued problems in maintaining reliable medical supplies systems; an observation supported by the World Health Organisation (WHO), Australian Agency for International Development (AusAID) and other agencies active in PICs [1,5,6].

Strengthening the pharmaceutical sector has been a long-term political priority for PICs. This priority has arisen from recommendations from the meetings of Ministers and Directors of Health for PICs held since 1995 [7]. The United Nations Population Fund (UNFPA) and the University of Canberra (UC) are contributing to this process by investigating the competencies required by personnel to operate medical supply systems, and by developing appropriate and sustainable approaches to health personnel competency development. Aligned with the UNFPA mandate, reproductive health commodities (RHCs) are employed as tracer items in the investigation of country medical supply systems and the competencies required by personnel who work in them.

Vanuatu country context and the Vanuatu medical supply system

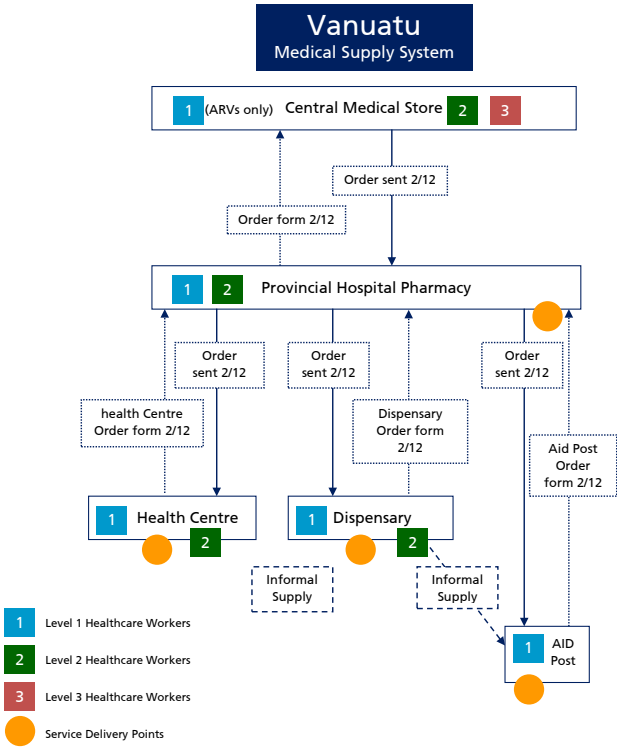
Vanuatu is a Y-shaped archipelago in the South West Pacific Ocean consisting of about eighty islands, extending approximately 1176 kilometers from north to south and covering a land area of 12,336 square kilometers. The country is divided into six provinces, namely Shefa, Sanma, Malampa, Tafea, Penama and Torba. The vast majority of the 240,000 population are Melanesians (ni-Vanuatu), with Europeans being the other major ethnic group [8].

The leading causes of morbidity include; acute respiratory infection, cutaneous abscess, malaria, asthma, diarrhoea, injuries, food poisoning, diabetes, chronic obstructive pulmonary disease and hypertension, while the leading causes of mortality include; heart disease, cancer, asthma, stroke, pneumonia, liver diseases, neonatal death, diabetes mellitus, septicaemia, and hypertension [9].

Vanuatu is geographically widespread creating challenges for medical supply distribution and communication, especially to remote areas. The Ministry of Health (MoH) is responsible for the national distribution of medical supplies to the four levels of health facilities (hospital, health centre, dispensary, and aid post) throughout Vanuatu using a national distribution system involving the Central Medical Store (CMS) in Port Vila and the Division of Pharmacy [10] (Figure 1).

The MoH is responsible for all aspects of the operation of hospitals, health centers and dispensaries, while the community, local government or faith based organisations are responsible for the provision and support of personnel for aid posts. The MoH provides training, medicines and basic medical supplies for aid posts [10].

There are currently five hospitals in Vanuatu, with a sixth hospital proposed for Torba. Two of these hospitals, Vila Central Hospital and Northern District Hospital, are major referral centres while the other three hospitals (Lenakel (Tafea), Norsup (Malampar) and Lolowai (Penama) are classified as provincial hospitals and provide referral services from local health centres and dispensaries [10]. Hospital pharmacies receive medical supplies from CMS and distribute them to dependent health centres, dispensaries and aid posts. They also provide inpatient ward services by imprest systems and outpatient dispensing services.



In 2004 there were 27 active health centres providing outpatient and inpatient services, including acute care such as care during labour and delivery, health promotion and preventive health services such as immunization. Health centres are usually staffed by a nurse practitioner who also acts as manager, a midwife and general nurse [10]. Health centres act as referral centres for dispensaries and aid posts, although urgent referrals may go directly from dispensary or aid post to hospital. In 2004 there were 74 active dispensaries, with at least one dispensary on most inhabited islands. Dispensaries provide outpatient services with a focus on basic essential health care including health promotion and preventive services [10]. Dispensaries refer complicated cases, or those requiring admission to a health centre or hospital. Dispensaries are usually staffed by a general nurse. Dispensary staff are responsible for supervising aid posts in their area. In 2004 there were about 180 aid posts, with an aid post in most villages. Aid posts are established and funded by the community in which they are based, the local or provincial government, or faith based organizations [10]. Aid posts are staffed by Village Health Volunteers (VHVs) providing first aid and community education.

Objectives

The aim of this study was to determine the factors which influence the availability of medical supplies within the health facilities of Vanuatu. A further objective was to document the medical supply activities undertaken within the various levels of the Vanuatu medical supply system.

Methods

To answer the research question a qualitative triangulated strategy using semi-structured interviews, observational workplace surveys and semi-structured focus groups was developed. This research was approved by the Human Ethics Committee of the University of Canberra (project number 10-85), and was funded through a direct grant from the United Nations Population Fund Suva, Pacific sub regional office.

The interview tool used was developed using existing World Health Organisation (WHO) medicines supply indicator survey concepts and informed by the Medication Safety Self Assessment for Australian Hospitals; applied to the context of Vanuatu [11, 12]. A separate observational workplace survey tool was developed using the same process and designed to complement the interview tool through the use of direct workplace observation. Both tools were validated in a preliminary trial involving Vanuatu pharmacy staff, with a focus on appropriate format, language and cultural considerations.To complete the triangulation of data, a semi-structured focus group format was developed using key elements of the'World Café' methodology [13].This approach to 'focus group' facilitation had previously been used by the authors (in unpublished consultancy activities),to reduce hierarchical sensitivities in mixed cadre environments,and is seen to be successful in empowering individuals to contribute as well as encouraging them to consider the opinions of others in a relaxed environment [13].

The interviews were designed to reveal the thoughts and practices of individuals while the workplace survey allowed the investigators to cross-check the interview findings with the practice situation observed in the health facilities.Site visits were undertaken in conjunction with Ministry of Health and local UNFPA counterparts to provide a vertical picture of the various levels of the medical supply system through a cluster based approach. Three provinces were visited to represent both urban and rural environments, due consideration was given to varied geography, and to be accessible by the research team over a two week data collection period.Within each province clusters of service delivery points were selected to include examples of hospitals, health centers, dispensaries and aid posts. Data was collected anonymously, then pooled and organised using the web based survey application 'Survey Monkey'. Thematic analysis was conducted using a team based consultative approach where recurring issues were prioritised and cross referenced for validity across the three data collection methods.

Results

During two weeks of data collection (18-31st July 2010) 21 interviews were conducted, observational workplace surveys were completed in 19 facilities and 22 health personnel participated in three focus groups across the three provinces. The main themes identified in this research are presented under headings of the three tiered structure of the medical supply system.

Participant and clinic demographics

The interviewees represented a wide range of primary professional groupings, with nursing being the most common (62%). This included registered nurses (RNs) and nurse practitioners. Those who classified themselves as pharmacy staff included storemen, dispensers, assistant pharmacists and intern pharmacists. Six of the 21 interviewees worked in urban locations, with the remaining 15 working in rural locations. Interviewees had worked at their current facility an average of 8 years (range 1-20yrs). The average time that interviewees had worked in their current health professional capacity was 13 years (range 1-35 years). This wide range of experiences and work histories provides a robust representative view of the issues around medical supply in Vanuatu.

Healthcare personnel retention was cited regularly as a challenge to maintain best practices around medical supply management, with staff who receive training then moving to other facilities thus losing medical supply management capacity in that facility. The healthcare personnel interviewed represented the three tiers of the medical supply system, representing service delivery to 100% of the Vanuatu population at the national level through the Central Medical Store (CMS), 68-100% at the provincial level through the three main hospitals and approximately 20% of the population through other primary care service delivery points. This provides a representative picture of the issues around medical supply in Vanuatu, in particular at the main distribution points. The 21 interviewees worked at 19 different health facilities: 1 x CMS, 3 x hospitals, 11 x health centers, 2 x dispensaries and 2 x aid posts.

Central Medical Store (CMS) – Main thematic issues

The absence of a principal pharmacist and staff to fill two other currently vacant supporting posts in CMS (at the time of the study), was placing considerable strain on existing staff, reducing their capacity to undertake regular stock management activities such as: regular stocktaking, future planning, quality assurance and yearly activity plans. The routine completion of standard operating procedures (SOPs) is also affected e.g. absence of packing slips when stock is sent to provincial hospitals. Current space in CMS was observed to be limited and is cited by staff as an impediment to efficient stock layout and movement, including inventory control activities.The recent loss of electronic order history data will impair the ability of CMS to plan for future requirements based on past ordering. Medical supplies data was previously collected using the computer based 'Mind Your Own Business' (MYOB) accounting package, but is now in the process of being replaced by the 'mSupply' computer based, medical supply management system.

The National Drugs and Therapeutics Committee was not active, removing the ability of inclusive country level decision making, which has resulted in country wide issues relating to medication selection and wastage.Default quantities ordered using the existing order forms have been observed to lead to wastage, as they are not responsive to the differing scales of service delivery points. The majority of oral medications are currently supplied in bulk containers of 1000 doses. National order forms for aid posts, dispensaries and health centres were highlighted for review by key interviewees during the survey, as they were considered to be outdated and could be better designed to encourage best practice by personnel throughout the supply chain.

Provincial hospital pharmacies – Main thematic issues

There is strong evidence of a good theoretical knowledge of medical supply management procedures amongst hospital pharmacy staff; however there is evidence that this knowledge is not routinely applied. This causes the problems with under and over supply of medical supplies. Notable examples include the absence of routine stock management activities such as unpacking and shelving of supplies received in bulk cartons. Also, many foreign medical staff travel to Vanuatu hospitals to provide clinical services for short term appointments. Interviewees gave several examples where these workers did not follow local procedures concerning medical supply or the Essential Medicines List (EML), leading to uncertainty or conflict with pharmacy staff.

Hospital pharmacies keep copies of all prescriptions dispensed and collate daily statistics around patient numbers. They also keep computerised records of stock received and distributed to dependent facilities along with hard copies of order forms received from all dependent facilities. This data was not routinely used by interviewees to inform the ordering process.

Supervisory visits are identified by pharmacy and provincial health personnel as a key activity to support pharmacy's role but the absence of a specific budget line for this purpose has limited their completion. The majority of supervisory visits occur on an ad-hoc basis when specific project funds for transport are available.

Interviewees indicated that patient counseling is considered an area with potential for greater input by pharmacy staff with the areas of dosage instructions (how much, how often, how long), relationship to food and any important expected adverse effects being identified as core areas that needed improvement. Non communicable diseases (NCDs) are seen to contribute significantly and increasingly to the burden of disease in Vanuatu; however they do not form a large part of the conditions managed by rural facilities. Most health centres and dispensaries visited had only a small number of patients receiving medication regularly for NCDs despite health statistics indicating that their prevalence is significant.

Health centres, dispensaries, aid posts - Main thematic issues

Provincial governments are responsible for the cost of the distribution of medical supplies from the provincial centre to primary health care facilities;however it was observed that this is not regularly funded by provincial governments, with individual facilities paying these costs.

Many facilities require four wheel drive vehicles to deliver medical supplies which can quickly become inaccessible after rain, which is frequent. Large rivers and the absence of roads also reduce access with many facilities only accessible via boat. Delivery of medical supplies to some villages in the interior requires personnel to walk for several days return, carrying large cartons of medical supplies. These journeys are often assisted by villagers but provide challenges to efficient and reliable supply, especially for temperature sensitive medications or large/ heavy items. These issues are amplified in the outer islands by infrequent transport and limited communication access.

Some interviewees reported attending up to nine or more work related week-long refresher workshops in provincial centres over a twelve month period. This heavy training schedule has significant consequences for service delivery; some facilities with a solo worker are closed during these training activities which can account for approximately 20% of the time they are expected to be open.All facilities visited kept an outpatient register detailing the name, diagnosis and treatment for each patient. These registers provide a detailed chronological record of the activities of the facility. The use of outpatient register was observed to be rigorous and considered important by personnel. This contrasts with other record keeping activities which were not observed to be completed, especially around medical supply management, and provides a useful model for instituting good record keeping practices.

There is evidence of good theoretical knowledge of supply management procedures amongst staff in these facilities however many of these procedures are not routinely completed or able to be applied in practice, leading to medical supply problems. Common issues include irregular making of orders and inaccurate estimates of requirements based on instinct. Records of previous orders are not routinely kept (despite procedures requiring a copy to be made and kept) hence there is no capacity for analysis of previous usage to inform ordering. Many interviewees agreed that they did not always complete required supply management activities because there was no one directly supervising them to do so. Infrequent visits from Central medical store staff or provincial hospital pharmacy staff did not provide the incentive to regularly do these activities, even though their value was recognised. A similar issue is the hesitance of personnel to make improvements to medical supply procedures even though they "...know it's not the best but it's always been done this way...". This appears to be due to personnel requiring, or feeling the need for permission to undertake changes or simply being overwhelmed by the task. Several examples were observed where personnel were unable to organise the cleaning of facilities and organisation of stock as the situation had become 'overwhelming' with no apparent starting point.

The regular order cycle for these facilities is bimonthly, with the capacity for emergency top-up orders in exceptional circumstances. A commonly observed contributor to excess stock is the reliance on emergency orders, sometimes to the exclusion of regular orders. This was especially true for those facilities within a day's drive from provincial hospitals. The issue of the lack of importance of medical supplies was brought forward by personnel. Emphasising this point is the 'word cloud' created using responses regarding the day to day responsibilities of healthcare personnel, with the most commonly reported responsibilities appearing in the largest font size [Figure 2].

Figure 2: Day to day responsibilities of healthcare personnel

A conditions checklist was completed for each of the facilities to determine if there were adequate conservation conditions and handling of medicines in the storeroom and dispensing area. Generally storerooms have adequate conservation and handling conditions, with the exception of recording of refrigerator temperatures and use of stock rotation. It was found that the dispensing areas were more problematic, with many instances of inadequate conditions. Temperature and light control, stock layout and pest control are all areas where many facilities require improvement. Unique environmental circumstances such as large amounts of volcanic dust (the island of Tanna provides the best example), are challenges that healthcare personnel face in maintaining suitable environments for medicines storage.

Discussion

Sustainable health systems strengthening

Potter and Brough provide a systematic approach to achieving sustainable health systems including medicines supply, describing the interrelationship between tools, skills, staff and infrastructure, and structures systems and roles in the wider health system [14].Our results can be categorized using the Potter and Brough model [14] (Table 2).

The documented results of our research show some interrelationship between the four categories. 'Tools' require 'Skills' which require 'Staff and Infrastructure', which in turn require 'Structures Systems and Roles'. Conversely 'Structures Systems and Roles' enable an effective use of 'Staff and Infrastructure' which enable the use of 'Skills' which in turn enable an effective use of 'Tools'. This is supported by the observations of Potter and Brough [14].

Table 2: Vanuatu medicines supply issues mapped against the Potter and Brough health system categories.

Potter and Brough health systems category	Specific Medicine supply issues revealed from the Vanuatu research
Tools	- Revision of order form required - Certain medication pack sizes may be too large.
Skills	- Inadequate stocktaking - Packing and sending procedures not followed - Medicines supply management procedures not followed Visiting medical officers not following standard treatment guidelines - Limited understanding of the use of medicine supply records for ordering practices - Potential to improve patient counselling - Limited understanding of NCD medication distribution processes - Perceived permission requirements for systems improvement - Emergency order process overused
Staff and Infrastructure	- Staff retention problems - Vacant senior pharmacy positions - Insufficient storage space - Staff feel overworked - Frequent training programs limit staff availability - Staff attitude.
Structures Systems and Roles	- Loss of national medication usage history - Absence of a full complement of national pharmacy staff - National Drugs and Therapeutics Committee inactive - Limited supervisory program - Limited budget support for transportation of medical supplies.

Brough R, Potter C. Systemic capacity building: a hierarchy of needs. Health Policy Plan 2004: 19 (5): 336-345. http://heapol.oxfordjournals.org/content/19/5/336.full.pdf+html

The results of our research provide the start of a systematic approach to strengthening the medical supply system in Vanuatu. A systematic method for improvement is support by recent WHO approaches and involves consideration of the impact of observations before improvements can be made effectively [15,16]. Part of applying this approach is to understand the implication of our findings at the three levels of the health system, and how these may affect each other.

Implications of findings

Central Medical Store (CMS)

As the national agency for medical supplies, CMS takes the leading role in forecasting, procuring, receiving, storing and distributing medical supplies for Vanuatu. CMS establishes the procedures to be followed in medical supply management for the country and any improvement in accessibility of essential medicines needs to be based upon the capacity of the facilities, staff and procedures of CMS.With this central role in mind, the absence of a principal pharmacist and senior staff means that the overseeing and leadership role required for national organisation of medical supply is missing. This is a contributing factor to all the other medical supply issues described.The absence of an active National Drugs and Therapeutics Committee impairs the ability of CMS to respond to changing prescribing patterns at a national level and reduces the possibility of multi-stakeholder engagement. The collective engagement of medical, nursing, finance and administrative staff on issues of medication selection, distribution and use may encourage greater ownership of the medical supply system, in turn providing greater support for the system across the country [18].

Provincial hospital pharmacies

These provincial hubs are the gateway for the effective supply of the primary health care facilities. The 'know do' gap between a working knowledge of the systems and procedures of the medicines supply system and the enacting of them is a significant issue disrupting effective supply to the primary health care facilities of the provinces. Of these procedures the ability to effectively and appropriately 'screen' orders submitted by primary health care facilities is the most significant. Arbitrary reductions in stock issues and a lack of understanding of what is happening on the ground at the facility level have direct implications for patients.

The lack of funds which could enable the regular transport of orders from the provincial centre to primary health care facilities and an absence of funds for regular supervisory visits are issues across PICs. With 80% of the population residing in rural areas these two issues are perhaps the greatest impediment to the effective delivery of medications to primary care facilities [1,4]. The disparity between the reported national non communicable disease burden (which is increasing) and the low amounts of medicines being used at the primary health care level is of specific concern [9]. This may be because of a significant misalignment with the process for the supply of NCD medications requiring patients to return to hospitals for ongoing supply, or the process may create such an impediment to their supply that patients discontinue treatment (NCD medication in Vanuatu may only be initially prescribed by a doctor but ongoing supply can be arranged through health centres and dispensaries by nursing staff).

Health centres, dispensaries, aid posts

A lack of stock cards and adequate storage appear to be two of the most significant resource based issues at this level of the system, while the absence of regular supervisory visits reduces the likelihood of systems being followed. This may leave some heathcare personnel feeling isolated [19]. One interviewee replied candidly that they "don't count stock regularly" even though they know they should. Another interviewee was concerned that they themselves were "too lazy" to undertake these activities regularly.

The health personnel who staff these facilities are the backbone of health service delivery. With usually only one or two staff members at each facility the workload and responsibilities around the implementation of health programs (e.g. extended program on immunisation, malaria, maternal and child health, tuberculosis, family planning) is such that medical supply management is considered one of the lowest priorities.

Appreciation of the appropriate care and respect for medical supplies is not widespread and potentially reflects a lack of understanding of its importance to the successful delivery of healthcare services.

The 'know do' gap was also evident in these facilities with participants showing a good working knowledge of many of the procedures required for medical supply management but choosing not to follow those procedures day to day. The exception in our observations was the two step 'ordering calculation' where we were unable to see any evidence of appropriate understanding or its use. This had been replaced by estimating or 'guessing' as the preferred method of determining orders.

Next Steps in the Pacific

Sustainable health systems' strengthening is difficult, especially in resource constrained environments. The WHO points to six interrelated 'building blocks' that form the foundation of a framework for sustainable health systems: service delivery, health workforce, information, medical products, vaccines and technologies, financing, and leadership and governance which could be useful to streamline this agenda[15,16].These 'building blocks' clearly identify what is essential within the health system. The blocks cannot be considered in isolation, as the six 'building blocks' are interrelated and require a systematic governmental response for sustainable whole of health systems strengthening to occur [16].

Our research findings reveal issues in each of the WHO building block areas which points to the need of a "whole of system approach" if the medical supply system of Vanuatu is to be improved.The UNFPA - UC research team is using this research to engage governments, pharmacists, doctors, nurses, pharmacy assistants and other pharmacy support workforce cadres to seek a combined solution to identified medical supply competency deficiencies in PICs.

The results of this research have further informed our understanding of the competencies required by healthcare personnel to conduct medical supply management activities effectively in PICs. It is our endeavor to further explore these competencies and to develop training approaches that will meet local requirements for competency development so that further progress toward reaching the MDGs can be maintained.

Study limitations

Both time and funding influenced the final number and location of health facilities visited as described in our methodology. The authors did not experience 'first hand' the supply issues facing more remote facilities and declare that this may be a limitation to the results revealed in this research. However, there was significant discussion of remote supply issues during the research from a wide range of interviewees and within the focus groups which partly addresses this gap.

Conclusions

It is clear from this research that the factors influencing the availability of medical supplies, within the health facilities of Vanuatu, consist of a range of interrelating issues that can be classified under: 'tools'; 'skills'; 'workers and infrastructure'; and 'structures, systems and roles'. These issues consist of both simple and complex problems involving the three levels of the medical supply chain operating within Vanuatu. Health systems sustainability theory suggests that a coordinated approach lead by the government of Vanuatu with invited development partners will be required for sustainable health systems change to occur.

Acknowledgements

The authors would also like to thank the Ministry of Health officials and health personnel from within the Republic of Vanuatu who gave of their time to participate in the site visits, focus groupsand surveys used to validate our work.

Authors' contributions

AB was responsible for the original concept and design of the manuscript. AB and BG were involved in the data collection and analysis. AB and BG were involved in the drafting, revising and final approval of the manuscript.

Conflict of interest

The authors report no conflict of interest.

Funding Source

The authors would like to acknowledge the funding provided by the United Nations Population Fund (UNFPA) Suva, Pacific sub regional office, for the data collection required in this research.

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Research Article

Southern Med Review

Perception and attitude of general practitioners regarding generic medicines in Karachi, Pakistan: A questionnaire based study

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Citation: Jamshed SQ, Ibrahim MIM, Hassali MA, Masood I, Low BY, Shafie AA, Babar ZUD. Perception and attitude of general practitioners regarding generic medicines in Karachi, Pakistan: A questionnaire based study. Southern Med Review (2012) 5; 1:22-30

Received: 10th November 2011
Accepted: 13th July 2012
Published Online: 23rd July 2012

Abstract

Objectives: In developing countries out-of-pocket payments (OOP) are as high as 80% of healthcare spending. Generic medicines can be instrumental in reducing this expenditure. The current study is aimed to explore the knowledge, perception, and attitude of general practitioners towards generic medicines in Karachi, Pakistan.

Methods: This exploratory, descriptive study was conducted on a sample of 289 randomly selected general practitioners who were dispensing at their private clinics in Karachi, Pakistan. The questionnaires were distributed and collected by hand. Data was entered to SPSS version 17. Fischer's exact test was applied to see the association between variables.

Results: A total of 206 questionnaires were included in the study. A response rate of 71.3% was achieved. Out of 206 respondents, 139 (67.5%) were male while 67 (32.5%) respondents were female. Close to three quaters of the respondents (n= 148; 71.8%) showed correct knowledge about generic medicines being a 'copy of the brand name medicines' and 'interchangeable with brand name medicines' (n= 148; 71.8%). In terms of safety, the majority of respondents (n=85; 41.26%) incorrectly understood that the generic medicines are less safe than brand name medicines. The total percentage of correct responses was seen in 53% of the respondents. More than half of the respondents agreed that locally manufactured medicines are of the same effectiveness as brand name medicines (n=114; 55.4%). Male practitioners with practice experience of 11-15 years showed positive perception towards the quality of multinational products. The Majority of respondents believed that their prescribing decision is influenced by medical representatives (n=117; 56.8%). More than three-quarters of the respondents expressed their wish to prescribe low cost medicines in their practice (n=157; 76.2%). More than one third of the respondents expressed their uneasiness to prescribe products from all local manufacturers (n=72; 35%).

Conclusion: There were gaps identified in the knowledge of respondents. Although good perception and attitude were noted among the respondents, dissemination of information regarding generic medicines may perhaps strengthen generic prescribing. There is a need to introduce 'Quality by Design' concept in local manufacturing units. This, in turn, can inculcate confidence in prescribers towards locally manufactured generic medicines.

Keywords: generic medicines, general practitioner, dispensing doctor, perception, attitude, Karachi, Pakistan

Introduction

The requirements and necessities for healthcare services are towards an upward shift. This is due to ageing population, increased life expectancies as well as new developments in treatment modalities [1]. A worldwide increase in healthcare costs poses a burden of affordability of medicines. In developing countries out-of-pocket payment is as high as 80% of healthcare spending [2]. In Pakistan the healthcare spending is less than 3% of GDP and healthcare is mostly financed by private out-of-pocket payments [3] . More than 50% of the population of Pakistan earns less than USD $ 2 per day. This huge segment of population struggles to afford both prescription and non-prescription medicines. Recently, a sharp increase in medicine prices makes the situation more vulnerable to a large segment of the population in Pakistan [4].

A large body of evidence suggested the significance of generic medicine utilization as a measure to improve affordability and healthcare budgets [5, 6]. In Pakistan the Government has highlighted the importance to market medicines by using their generic names [7].

Chronology of generic medicines in Pakistan

In 1972, Pakistan undertook the task to promote generic competition. The Pakistani Drugs Act (Generic Names) was implemented in 1972 [8]. According to the Act, the prescription by brand or patented name, and manufacturing and selling of medicines under a proprietary name was forbidden [8]. The objective of the government was to put local manufacturers in competition with multinational companies. This was expected to cause a decrease in medicine prices. However there was no significant fall in medicine prices because the competition was shifted from price to quality. Therefore, in 1976, Director General of Health issued orders for another Drug Regulating Act, which terminated the compulsive requirement of manufacturing and marketing drugs by generic names and imposed stringent manufacturing licensing requirements [8].

Justification of the Study

The pharmaceutical market of Pakistan enjoys equal division of both domestically produced generic drugs and imported branded prescription pharmaceuticals [9]. The Pakistan Pharmaceutical Manufacturers Association (PPMA) quoted total market share of domestic industry, which is 70-85% by volume and 55% by value. These figures are now shifted more in favor of domestic production [10]. As some major innovators will lose their patent in the near future, the generics-dominated domestic industry is presumably to be benefited more. The utilization of generic medicines in Pakistan is dismally low [11]. It is thus, important to explore those contemporary issues which surround underutilization of generic medicines in Pakistan.

In developing economies, apart from community pharmacies, dispensing of medicines is also done at private clinic of doctors. In the context of healthcare systems within Pakistan, healthcare services are generally received from public and private hospitals but physicians are still undertaking private practice. These general practitioners (GPs) or private practitioners are not only involved in the diagnosis of disease but they also dispense at their private clinic. They make a large share of their income by dispensing through their clinics [12]. This may be for a number of reasons; possibly monetary gains, unavailability of pharmacy services around the area, or either due to the absence of a pharmacist at community pharmacies [12]. Thus, doctors in Pakistan exercise strong influence on both prescribing and dispensing. In spite of this it is not known how doctors in Pakistan perceive and prescribe generic medicines in their practice.

Several studies have been conducted globally to explore the understanding, views and attitudes of doctors towards generic medicine prescribing [13]. Hassali et al have learned that doctors show an understanding towards generic medicine use and are therefore, inclined to prescribe generic medicines with some uncertainties related to quality, safety and efficacy [13]. There is a need to do similar research in developing countries where low cost generic medicine is the most important viable option for the majority of the population. Factors preventing and facilitating general practitioners from prescribing and dispensing generic medicines need to be explored in the context of Pakistan. Keeping in view this background and the paucity of data surrounding prescribing patterns in Pakistan, this study aims to clarify these issues.

Objectives

The objectives of this study are:

(i) To evaluate the knowledge, perception, and attitude of general practitioners regarding generic medicines

(ii) To explore the factors hindering and favoring generic drug prescribing in general practitioners

Methods

Study Population, Sampling, and Sample Size

This is a descriptive, exploratory study, which was conducted among the general practitioners who were dispensing at their private settings in Karachi. The participants were randomly selected from the list of general practitioners, Karachi branch, supplied by the Forum of General Medical Practitioners (FGMP). In this study we wanted to focus on those GPs who not only prescribe but also dispense at their private clinics. Therefore, in order to confirm the list, we contacted the pharmaceutical companies, which generally possess the practicing addresses and mobile numbers of GPs. All the GPs who participated in the study were also involved in dispensing at their private clinics. In this study the method of verifying GPs via a list of addresses and telephones was adopted by a previous study undertaken with GPs in Karachi [14]. We took a random sample by means of a Random Number Generator. Total number of GPs who were dispensing at their clinics was found to be 705. Using raosoft sample size calculator, the sample size was determined to be

249 with an 80% power and 5% significance level. The sample size was increased to 289 to account for a possible non-response rate. Therefore, 289 questionnaires were distributed by hand to general practitioners in Karachi and collected on the same day. No incentives were offered to the participants.

Data collection

The questionnaire was formed on the basis of qualitative research [15]. The questionnaire was piloted on 10 doctors. On the basis of responses obtained from the pilot tests, minor changes were made. Items which lacked clarity and comprehensiveness were deleted. In order to evaluate the internal consistency, Cronbach's alpha was computed. For the knowledge domain it was found to be 0.645. In the case of perception and attitude domains, it was found to be 0.625.

The questionnaire consisted of four parts. The first part was about sociodemographic and background characteristics of the participants. This covered age, gender, educational qualification, postgraduate qualification, number of years practicing as a GP, area of practice, average number of patients per day, and average number of medical representative visits per month.

Table 2: Knowledge of generic medicines among general practitioners

Statements	Correct Responses n (%)	Incorrect Responses n (%)
Generic medicines are copy of brand name medicines	148 (71.8)	58 (28.2)
Generic medicines are interchangeable with brand name medicines	148 (71.8)	58 (28.2)
Generic medicines are therapeutically equivalent to brand name medicines	115 (55.8)	91 (44.2)
Generic medicines must be in the same dosage form (such as tablet, capsule) as brand name medicines	156 (75.7)	50 (24.3)
Generic medicines are less safe than brand name medicines*	121(58.7)	85 (41.3)
Only those generic medicines are safe which are made by some local reputable manufacturers*	58 (28.2)	148 (71.8)
Generic medicines are available in the market of Pakistan	164 (79.6)	42 (20.4)
Generic medicines are manufactured after the patent expiry of originator/innovator	88 (42.7)	118(57.3)
Brand name medicines are of good quality than generic medicines*	59 (28.6)	147 (71.4)
Brand name medicines are required to meet higher safety standards than generic medicine*	77 (37.4)	129 (62.6)
Brand name medicines produce lesser side effects than generic medicines*	66 (32.0)	140 (68.0)
Low-priced medicines are as effective as high-priced medicines	113 (54.9)	93(45.1)

*Items are negatively coded

The third part addressed the perceptions of general practitioners about generic medicines. This included 14 statements on the views about safety, quality and efficacy of generic medicines and the reputation of local manufacturers and their low-cost brands. The fourth part evaluated the attitude of general practitioners towards generic medicine prescribing. This included 12 statements on prescribing attitude in light of the socioeconomic condition of the patient, patients' demands, influence of medical representatives, as well as quality in local manufacturers' brands. Perception and attitude domains have response categories on Likert scale: 5=strongly agree, 4=Agree, 3=neither disagree nor agree, 2=Disagree, 1=Agree.

It is important to mention that during the study no question was asked from the respondents about the bioequivalence criteria for locally manufactured generics.

Ethical consideration

Informed consent was sought from every participant. They was informed that participation is voluntary and that confidentiality would be maintained. It was further explained to them that at any point they could withdraw their participation from the study. Moreover in Pakistan, questionnaire-based studies do not need any Ministry of Health endorsement. Despite that, prior information was sent to the then Ministry of Health, Government of Pakistan for the execution of this research among GPs who were also dispensing at their clinics in Karachi.

Statistical Analysis

All the data were entered into the Statistical Package for Social Sciences (SPSS, version 17). Descriptive statistics were performed to evaluate the sociodemographic characteristics of the respondents. Fisher's exact test was applied to see the association between variables. A default Monte Carlo Simulation in SPSS software was used to reach Fisher's exact p values because the data was considerably big and, therefore, normal exact computations need more time and computer memory. A p value of less than 0.05 was considered to be statistically significant.

In the domain of knowledge only descriptive statistics were applied. In other domains, the variables were tested to see the association with age, sex, and years of practice. Fishers' exact test was applied to see the association between dependent and independent variables.

Results

A total of 209 questionnaires were returned. Three questionnaires were found to have missing values in demographics as well as other domains of attitude and perception and, therefore, discarded. Thus, a total of 206 questionnaires were included in the study. A response rate of 71.3% was achieved. Ash and associates (1997) reported that in published studies of physicians the response rate was only 54% [16] therefore the response rate of 71.3% is considered acceptable.

Out of 206 respondents, 139 (67.5%) were male while 67 (32.5%) respondents were female. The majority of respondents (n=79) were in the age range of 20-30 (38.3%) and 31-40 (n=52; 25.2%). The detailed demographic characteristics and practice information are shown in Table 1.

Table 1: Demographic characteristics of general practitioners

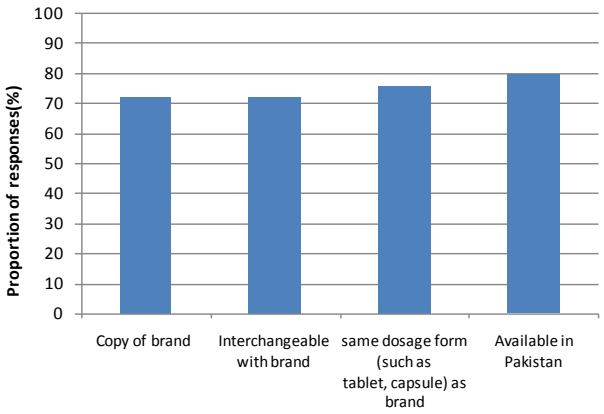
Characteristics			Frequency (%)
Age range		20-30	79 (38.3)
		31-40	52 (25.2)
		41-50	56 (27.2)
		>50	19 (9.2)
Gender		Male	139 (67.5)
		Female	67 (32.5)
Basic Medical Qualification		MBBS	196 (95.1)
		MD	10 (4.9)
Postgraduate Qualification		Yes	100 (48.5)
		No	106 (51.5)
Experience		1-5	93 (45.1)
		6-10	39 (18.9)
		11-15	26 (12.6)
		16-20	28 (13.6)
		>20	20 (9.7)
Average number of patients per day		1-30	114 (55.3)
		31-60	68 (33.0)
		61-90	20 (9.7)
		>90	4 (1.9)
Locality of Practice		Urban	147 (71.4)
		Peri-urban	59 (28.6)
Average number of medical representatives' visits per month	Multinational	1-10	196 (95.1)
		11-20	7 (3.4)
		>20	3 (1.5)
	Local	1-10	166 (80.6)
		11-20	32 (15.5)
		>20	8 (3.9)

Knowledge of Generic Medicines

When the respondents were asked about the basic information regarding generic medicines, close to three quarters of respondents (n= 148; 71.8%) answered 'yes' that generic medicines are the copy of the brand name medicines and they are interchangeable with brand name medicines. When the respondents were questioned about the manufacturing of generic medicines, more than half of the respondents (n=118; 57.28%) answered 'yes' that 'generic medicines are manufactured after patent expiry or innovator'. In terms of safety, the majority of respondents (n=85; 41.26%) answered 'no' that generic medicines are less safe than brand name medicines. In terms of quality, more than two thirds of the respondents (n=147; 71.35%) answered 'no' that 'brand name medicines are of better quality than generic medicines'. All the responses are indicated in Table 1 as correct and incorrect answers.

The total percentage of correct responses regarding knowledge of generic medicines was seen in 53% (n=110) of the respondents. The maximum number of correct responses was obtained from the statements pertaining to the basic knowledge and availability of generic medicines (Figure 1).

Figure 1: Maximum Number of Correct Responses (GM=Generic Medicine)



Perception about Generic Medicines

Table 3 represents the outcome of items in perception with respect to independent variables. When GPs were asked about the affordability of generic medicines, the majority of respondents agreed that generic medicines are more affordable than brand name medicines (n=188; 91.2%). More than half of the respondents agreed that locally manufactured medicines are of the same effectiveness as brand name medicines (n=114; 55.4%). This showed a statistically significant value with respect to age (p=0.015) and years of practice (p=0.018). Those who were in the age range of 41-50 and have been in private practice for 16-20 years showed greater significant association. Similarly, when respondents were questioned about the side effects, they disagreed that generic medicines produce more side effects than brand name medicines (n=99; 48%). This showed statistical significance with respect to age (p=0.023). Greater association was observed in respondents of more than 50 years of age. A large majority of respondents showed positive perception towards the safety of low-priced medicines (n=126; 61.2%). This indicated statistical significance with respect to age (p=0.019) with positive perception higher in the middle age range of 41-50 years.

Interestingly, in terms of quality, more than half of the respondents viewed multinational products of better quality than local company products (n=123; 59.7%) and this indicated significance with gender (p=0.034) and years of practice (p=0.021). Male general practitioners with practice experience of 11-15 years showed positive perception towards the quality of multinational products. The majority of respondents believed that their prescribing decision is influenced by medical representatives (n=117; 56.8%). This demonstrated significance with respect to age (p=0.009). This perception is mainly expressed by general practitioners of middle age group. In terms of perception regarding the reputation of local manufacturers a large majority of the doctors viewed some of the local companies as reputable generic manufacturers (n=130; 63.1%). This view showed significance with respect to age (p=0.019) and greater association was again expressed by middle age doctors of 41-50 years.

Table 3: Perception of general practitioners towards generic medicines

Statements	Agree n (%)	Neutral n (%)	Disagree n (%)	Age[a]	Gender	Exp[b]
I believe that locally manufactured medicines are more affordable than brand name medicines	188 (91.2)	9 (4.4)	9 (4.4)	0.847	0.931	0.908
I believe that locally manufactured medicines are of same effectiveness as brand name medicines	114 (55.4)	42 (20.4)	50 (24.2)	0.015*	0.758	0.018*
I view generic medicines of low quality than brand name medicines	81 (39.3)	49 (23.8)	76 (36.9)	0.142	0.702	0.604
I think generic medicines produce more side effects than brand name medicines	55 (26.7)	52 (25.2)	99 (48.0)**	0.023*	0.390	0.060
I believe low-cost medicines are as safe as high-priced medicines	126(61.1)	36 (17.5)	44 (21.3) **	0.019*	0.317	0.249
I believe that multinational products are of good quality than local company products	123 (59.7)	49 (23.8)	34 (16.5)	0.152	0.034 *	0.021*
I believe that my prescribing decision is influenced by medical representatives	117 (56.8)	43 (20.9)	46 (22.3)	0.009 *	0.534	0.282
I believe that all the local companies in Pakistan are not following Good Manufacturing Practices (GMP) guidelines as multinationals	111 (53.9)	59 (28.6)	36 (17.5)	0.303	0.001 *	0.258
I view few local companies as reputable generic medicine manufacturers	130 (63.1)	45 (21.8)	31 (15.1)	0.019 *	0.211	0.515
I believe that doctors should be educated more about prices of medicines	183 (88.8)	13 (6.3)	10 (4.9)	0.006 *	0.406	0.017 *
I believe that doctors should be given incentives to write generic names	69 (33.5)	49 (23.8)	88 (42.7)	0.012 *	0.564	0.006*
I believe that generic medicines are only meant for poor	73 (35.4)	41 (19.9)	92 (44.7)	0.613	0.161	0.695
I think that confidence should be built in the patient about the low-cost brand	149 (72.3)	40 (19.4)	17 (8.3)	0.320	0.984	0.859
I believe that it is easier to remember a brand name medicine	124 (60.2)	39 (18.9)	43 (20.9)	0.366	0.416	0.879

[a]Age range: (20-30); (31-40); (41-50); greater than 50
[b]Experience: (1-5); (6-10); (11-15); (16-20); greater than 20
* p<0.05;
**Total percentage may not add to 100 because of rounding.

Attitude towards Generic Medicines

Although more than three-quarters of the respondents expressed their wish to prescribe low cost medicines in their practice (n=157; 76.2%), approximately half of the respondents showed their hesitancy to prescribe low cost brands in some therapeutic categories (n=108; 52.4%). This showed statistical significance with respect to experience (p=0.013) and is shown in Table 4. General practitioners who have more than 10 years of practice experience expressed their doubtfulness towards the prescribing of low cost brands among some specific therapeutic classes. More than one third of the respondents expressed their discomfort to prescribe products from all local manufacturers (n=72; 35%) and this was found to be statistically significant with respect to age (p=0.038). Older general practitioners expressed greater sense of discomfort to prescribe all local manufacturers' products when compared to their younger and middle age counterparts. In the case of lack of quality check in locally manufactured products more than half of the

respondents expressed their concern towards lack of quality check in locally manufactured products (n=109; 52.9%). This was found to be in strong association with age (p=0.005) and experience (p=0.017). Highly experienced and older general practitioners expressed their concern about the quality check of locally manufactured medicines.

Table 4: Attitude of general practitioners towards generic medicines

Statements	Agree n (%)	Neutral n (%)	Disagree n (%)	Age[a]	Gender	Exp[b]
I wish to prescribe low cost medicines in my practice	157 (76.2)	20 (9.7)	29 (14.1)	0.135	0.061	0.053
I am concern about the therapeutic failures that are serious problems with some locally manufactured medicines	130 (63.1)	41 (19.9)	35 (17.0)	0.307	0.281	0.146
I am hesitant to prescribe low-cost brands in some specific therapeutic classes in my practice	108 (52.4)	44 (21.4)	54 (26.2)	0.264	0.210	0.013*
I feel that the socioeconomic condition of my patient influence the prescription	163 (79.1)	23 (11.2)	20 (9.7)	0.825	0.597	0.974
I am comfortable to prescribe products from all local manufacturers	68 (33.0)	66 (32.0)	72 (35.0)	0.038*	0.26	0.074
I feel that my personal experience with medicines influence my prescribing decisions	151 (73.3)	29 (14.1)	26 (12.6)	0.308	0.751	0.318
I feel that patient's demand of medicine influence my prescription	97 (47.1)	50 (24.3)	59 (28.6)	0.429	0.685	0.538
I feel that medical representative is a good source of information for me	158 (76.6)	24 (11.7)	24 (11.7)	0.415	0.860	0.895
I feel that pharmaceutical companies' premium offers (gifts) influence my prescribing behavior	62 (30.1)	54 (26.2)	90 (43.7)	0.021*	0.700	0.548
I feel a lack of quality check in locally manufactured products	109 (52.9)	71 (34. 5)	26 (12.6)	0.005*	0.167	0.017*
I am comfortable if the brand name medicine in prescription is changed by drug seller or pharmacist	52 (25.2)	21 (10.2)	133 (64.6)	0.126	0.882	0.210
I offer my patients generic medicines	129 (62.6)	46 (22.3)	31 (15.0) **	0.062	0.935	0.389

[a]Age range: (20-30); (31-40); (41-50); greater than 50
[b]Experience: (1-5); (6-10); (11-15); (16-20); greater than 20
* p<0.05;
**Total percentage may not add to 100 because of rounding.

Discussion

This study is the first of its kind in Pakistan to explore the understanding, perception, and attitude of general practitioners towards generic medicine utilization including factors which hinder and favor generic prescribing. The findings of the qualitative phase identified gaps in knowledge about the availability of generic medicines in Pakistan [15]. Moreover, in the qualitative phase, mixed perception and attitudes were identified towards generic medicine utilization. Some of the major implicating factors like quality, therapeutic efficacy, and distrust in local manufacturers were identified as barriers to prescribing generic medicines. Few of the contributory factors like socioeconomic condition of the patient and the influence of medical representatives were considered to be strong advocators of generic prescribing [15].

A response rate of 71.3% was achieved. The current response rate (71.3%) is counted as one of the strengths of study. In addition, Kellerman and Herold (2001) reported that non-response bias may be of less concern in physicians. This is because physicians are considered to be consistent in opinion regarding understanding, views, attitudes, training, and behavior [17].

According to the present quantitative analysis, there were gaps identified in the knowledge of generic medicines. Misunderstandings were identified about the safety, efficacy and quality of generic medicines. Nearly similar findings were reported by studies done in Australia [18], Iraq [19], and Malaysia [20]. This sparse understanding among GPs was not surprising as information gaps need to be filled initially. This could be done at undergraduate training level by making curricular innovations. We, therefore, suggest introducing a module on

Policy Awareness Interactive Discussion (PAID) as curricular innovation. This should provide basic information on health policy, pharmaceutical policy, essential drug list, innovators and generic medicines, and their availability and affordability. Later this should be followed by interactive discussion sessions among policy makers, policy analysts and future medical practitioners.

In the case of GPs, the Medical Associations and Medical Council in collaboration with the Government of Pakistan should distribute wall hangings for their private clinics. These wall hangings should be inscribed with basic facts about generic medicines. In Pakistan, only 50% of medicines are prescribed as generics [21]. Herein lies an opportunity for expansion of utilization in terms of generic prescribing. This baseline study attempts to elucidate which factors hinder and favor generic medicine prescribing.

We observed that GPs believed that locally manufactured medicines are more affordable and of the same effectiveness when compared to brand medicines. We also observed from our findings the economic condition of the patient as well as their demand influence the prescribing behavior. We tried to link those responses. This showed that GPs positive attitudes could be due to the compelling needs of patients, which make the inherent persuasive power of GPs work for prescribing. This is further confirmed by our findings which showed that the large majority of GPs reported concerns for quality check in locally manufactured medicines. This concern for quality was also supported in a recent US study [22]. A system is needed to ensure the quality of generics. The Government of Pakistan should be prompted to develop trust for local manufacturers. This could be done by conducting bioequivalence studies in some of the specific therapeutic classes and disseminate information about the similarity of both generic and brand medicines. Furthermore the government can play a positive role by means of communication messages, pamphlets and flyers about generic medicines. This could be put in line with persuasive communication theory. It is the theory that endeavors to explicate how behavior is affected by communication and attitude processes. This paradigm explains the underlying flow of doctors' behavior from communication to attitude and behavior. The aim of persuasive communication is to influence the doctor and to change the attitude. Thus, the essential intent of persuasive communication is attitude change.

In both qualitative [15] and quantitative phases doctors admitted that the persuasion of medical representatives affected their prescribing patterns and prescribing decision. Interestingly, a large body of evidence suggested that medical representatives are a good source of information and pharmaceutical industries and their representatives do have direct and indirect effect on prescribing outcomes [18, 23-29]. On the contrary, a study conducted on GPs in the UK denied any undue impact of drug representatives on their prescribing [30]. Rather than to decide on the awkward demands of industries, the prescriber must remember that generally industries run on the decades old notion of Milton Friedman (1970); that the social responsibility of any business is to amplify its gain [31]. Furthermore, previously published studies suggested that GPs consider commercial sources of drug information more powerful than non-commercial information sources[32] [33]. We propose a system where non-commercial sources of information for doctors should be promoted. Journals, product monographs, non-commercially sponsored CME programs could be useful to seek information. A 24x7 Drug Information Center (DIC) at a national level which expect to foster dissemination of unbiased information will pave the way for rational prescribing. One of the convincing findings in this study is the doctors' expectations to be educated more about the prices of medicines. This is in concordance with the previous studies done in USA and Ireland in which physicians' understanding of the cost is an important determinant in prescribing, awareness about the cost of medicines, as well as the need of interventional strategies and educational activities are prerequisites to make doctors cost-effective prescribers [34, 35]. Moreover, Howell (2007) reported that understanding drug cost is an important element of best possible prescribing [36]. We endorsed the suggestions of Cooke (2010) which highlighted the significance of a basic understanding of healthcare financing and cost-consciousness among future medical practitioners [37].

Lastly we propose to introduce 'Quality by Design' (QbD) concept for our local manufacturing units. The Government of Pakistan and the pharmaceutical industry must exercise collaborative efforts to promote this FDA proposed concept of pharmaceutical QbD. This is to introduce quality into end product by establishing cGMP compliant manufacturing plants. This will perhaps inculcate trust in prescribers towards locally manufactured generic medicines.

We identified some limitations in the study which should be taken into account.

The study was performed in only one city of Pakistan. Therefore, the current findings cannot be generalized to doctors practicing in other cities of Pakistan. Despite the study being conducted in the largest city of Pakistan, there was limited access to doctors practicing in military cantonment areas and slum areas. This, furthermore, limits the generalizability of the findings. Due to the self-report format of questionnaires, we cannot rule out the possibility of social desirability bias. If the study participants had been interviewed personally by the principal researcher along with a team of research students the study bias may have been minimized.

Conclusion

The current quantitative approach identified gaps in knowledge of generic medicines among general practitioners who are dispensing at their private clinics. Generally, good perceptions and attitudes were observed in the study. Barriers like lack of quality in generic medicines and distrust in local manufacturers were found to be implicated in generic prescribing.

Socio-economic condition of the patient and the influence of medical representatives were some of the cited measures to favor generic prescribing. Therefore, in order to have a better understanding and perception of generic medicines the doctor must be well-informed about the quality, efficacy, and safety standards of generic medicines during their academic and professional career.

Authors' contributions

SQJ, MIMI, MAH, and ZUDB were involved in conceptualizing the study. All authors contributed to paper's design and production. All authors participated in the critical revision and have approved the final version for submission.

Acknowledgements

SQJ offered her inexplicable gratitude to Mr Zubair Sulemani, Director Marketing and Business Development, Barrett Hodgson Pakistan (Pvt.) Ltd. and Mr Jamshed Ahmad, Director Marketing and Sales, PharmEvo (Pvt.) Ltd. in verifying the list of addresses of GPs. This data collection would not have been possible without their support. SQJ is also thankful to Dr Saman Nadeem, Dow University of Health Sciences, Karachi, for her uninterrupted moral and physical accompaniment in data collection.

Conflict of Interest

None

Funding Source

This work was supported by fellowship grant, Universiti Sains Malaysia, Penang, Malaysia

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Impact of regulatory requirements on medicine registration in African countries – perceptions and experiences of pharmaceutical companies in South Africa

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Citation: Narsai K, Williams A, Mantel-Teeuwisse AK. Impact of regulatory requirements on medicine registration in African countries-perceptions and experiences of Pharma companies in South Africa. Southern Med Review (2012) 5;1:31-37

Received: 21st Feb 2012
Accepted: 6th June 2012
Published Online: 23rd July 2012

Abstract

Objective: Access to medicines has long been and remains a challenge in African countries. The impact of medicines registration policies in these countries poses a challenge for pharmaceutical companies wanting to register medicines in these countries. The recent AMRHI (African Medicines Registration Harmonisation Initiative) has increased the focus on the need for harmonisation. Medicines registration regulations differ across African countries. Anecdotal evidence, based on the experience of pharmaceutical companies on progress towards harmonisation is somewhat different, i.e. that country specific requirements were a barrier to the registration of medicines. The objective of this study was therefore to determine the nature and extent of regulatory hurdles experienced by pharmaceutical companies who wish to register and supply medicines to African countries.

Methods: This cross-sectional descriptive pilot study was conducted across pharmaceutical companies, both local and multinational. These companies were based in South Africa and were also members of Pharmaceutical Industry Association of South Africa (PIASA). The pharmaceutical companies supply both the private and public sectors. An online survey was developed using Survey Monkey. Survey questions focused on the following strands: nature and level of current supply of medicines to African countries by companies, general regulatory requirements, region specific questions and country specific questions across four regional economic communities in Africa, namely; Southern African Development Community (SADC), East African Community (EAC), Economic Community of the West African States (ECOWAS) and Economic Community of Central African States (ECCAS).

Results: A total of 33 responses were received to the questionnaire of which 26 respondents were from the PIASA Regulatory working group and 7 were from the PIASA Export working group.It was noted that since most of the regulatory authorities in Africa are resource-constrained, harmonisation of medicine registration policies will contribute positively to ensuring the safety, quality and efficacy of medicines. The experience of pharmaceutical companies indicated that country specific regulatory requirements are a barrier to registering and supplying medicines to African countries. In particular, GMP inspections, GMP inspection fees and country specific labeling were cited as key problems.

Conclusion: Pharmaceutical companies operating in African markets are experiencing difficulties in complying with the technical requirements of individual African countries. Further research is required to provide a balanced perspective on the country specific regulatory requirements vs. the African Regulatory Harmonisation Initiative (AMRHI).

Keywords: medicine registration, labeling, pharmaceutical policy, Good Manufacturing Practice

Introduction

Medicines are essential to healthcare and should be available to the inhabitants of every country. Medicines regulation aims to ensure that medicines circulating in national and international markets are safe, effective and of good quality, are accompanied by complete and correct product information, and are manufactured, stored, distributed and used in accordance with good practices [1].

For many years, African medicines regulatory authorities (MRAs) have managed a broad range of responsibilities, often with limited resources [2]. Their focus has generally been on providing their population with access to a wide range of affordable essential medicines, usually multi-source generics, with less emphasis on rapid access to the latest products. As a result, African national MRAs may have experience in managing generics, but many have only limited experience in assessing, approving and registering innovator products, the vast majority of which are for global chronic diseases, such as diabetes, hypertension and cancer [2].

It is well documented that the African MRAs are under resourced and lack skills and capacity to perform their functions adequately [1, 3, 4]. Coupled with this is changing technology as well as advancements made in medicines, e.g. the increased development of biological medicines and the increased focus on healthcare in Africa. It is clear that intervention is required to ensure that the gap between African MRAs and developed country MRAs and the healthcare needs of their populations do not widen.

The African Medicines Registration Harmonisation (AMRH) Initiative is a welcome move. Investing in the AMRH initiative also provides an opportunity for African countries to strengthen their regulatory capacity, use their financial and human resources more effectively, thereby creating a more conducive environment for the attainment of the health-related Millennium Development Goals (MDGs) [5].

Very little data is available regarding pharmaceutical companies experiences in registering and supplying medicines in Africa. This study aims to shed light on the pharmaceutical companies' experiences with regards to compliance with technical requirements of medicines registration. This in turn can have an impact on the availability of medicines in African markets.

Objectives

The objective of this survey was to determine both the nature and extent of regulatory hurdles as experienced by pharmaceutical companies in seeking registration or market authorisation for medicines in African countries.

Methods

Data collection

For this cross-sectional descriptive pilot study a short survey was developed. The target groups for the survey were the Pharmaceutical Industry Association (PIASA) Export and PIASA Regulatory working groups. The Pharmaceutical Industry Association is the largest trade association in South Africa representing multinational and local companies. The group consists of individuals that have responsibility for either commercial or regulatory issues related to medicine registration in the African countries that the companies supply medicines to. Members of the Regulatory and Export working group of PIASA member companies were invited to complete the survey via email containing a hyperlink to the online survey during April 2010. Reminders were sent during April to July 2010 and the survey was closed at the end of July 2010. Separate surveys were sent to the Export and Regulatory groups of PIASA.

Only one response per company, per function, i.e. export and regulatory, was accepted to avoid duplication of responses. In instances where more than person responded from a particular company, duplicate responses were allowed only where it was appropriate to provide a more comprehensive view to a particular question. An online survey was developed using Survey Monkey. Through the experience of previous PIASA submissions to regulatory authorities and through anecdotal feedback from PIASA Export and Regulatory working groups, questions were developed to address key issues. Survey questions focused on the nature and level of current supply of medicines to African countries, availability of generics and decision-making around medicine supply and views and experiences in dealing with regulatory requirements. The questions regarding GMP requirements and country-specific requirements were posed across four regional economic communities in Africa which include: Southern African Development Community (SADC), East African Community (EAC), Economic Community of the West African States (ECOWAS) and the Economic Community of Central African States (ECCAS). The survey also included open-ended questions to allow respondents to express their views freely and in an unstructured manner.

Data Analysis

Proportions were used in descriptive analyses of dichotomous and categorical variables. Country and regional categorisation was based on the country listing per Regional Economic Communities (RECs), as per the African Medicines Registration Harmonisation Initiative (AMRHI). The four RECs were East African Community (EAC), Economic Community of Central African States (ECCAS), Economic Community of West African States (ECOWAS) and the Southern African Development Community (SADC). Some countries belong to more than one REC – refer to Table 1 for country listing for each REC, highlighting overlapping countries [5].

Table 1: Country listing of four Regional Economic Communities in Africa

SADC	ECCAS	ECOWAS	EAC
Angola	Angola	Benin	Burundi
Botswana	Burundi	Burkina Faso	Kenya
Democratic Republic of Congo	Cameroon	Cape Verde	Rwanda
Lesotho	Central African Republic	Cote d'Ivoire	Tanzania
Madagascar	Chad	Gambia	Uganda
Malawi	Congo	Ghana	
Mauritius	Democratic Republic of Congo	Guinea	
Mozambique	Equatorial Guinea	Guinea Bissau	
Namibia	Gabon	Liberia	
Seychelles	Rwanda	Mali	
South Africa	Sao Tome & Principe	Niger	
Swaziland		Nigeria	
Tanzania		Senegal	
Zambia		Sierra Leone	
Zimbabwe		Togo	

Results

A total of 33 responses were received to the questionnaire of which 26 respondents were from the PIASA Regulatory working group and 7 were from the PIASA Export working group. After exclusion of duplicate responses it was found that the 14 companies were from the regulatory group and five companies were from the export group (four of these companies were also represented in the regulatory group). Not all respondents answered all the questions and therefore the number of responses per question varies.

Current vs. future supply of medicines in Africa

Results show a high level of participation of companies in the various countries in Africa. All companies supplied medicines to the SADC region; however, the combinations and country representations differ across companies. Medicine supply by these companies covered a broad spectrum of therapeutic areas including diseases where the prevalence in Africa is high (viz. anti-infectives, HIV/AIDS) and non-communicable diseases (NCDs) viz. oncology, endocrinology and cardiovascular disease. The top therapeutic areas for all medicines supplied were as as follows: cardiovascular, endocrinology, oncology, allergy and anesthesia. The top therapeutic areas for genericmedicines were cardiovascular, allergy, anti-infectives and endocrinology. Although the current supply of medicines by companies is significant, six companies indicated that they have made a decision not to supply medicines into some African markets. Specific countries mentioned included Ghana, Nigeria, Ethiopia, Tanzania, Kenya, Uganda, Mozambique and Zimbabwe.

Reasons for companies (cited by the export group) in making decisions not to supply medicines to specific African countries were: registration costs; commercial; retention costs, GMP inspection fees and GMP inspection requirements. When asked in which markets these decisions have been made, the responses included Ghana, Uganda and Sudan. Overall, reasons related to the medicine registration process outweighed commercial or market reasons for these decisions.

All companies (five export group respondents) indicated that they had experienced instances where they were unable to supply medicines to African markets. The reasons cited for the interrupted supply were related to regulatory requirements, particularly medicines registration. One respondent cited concerns of product diversion to Western countries as the reason. The same five companies indicated that they had made decisions not to supply specific medicines to African countries. Only one company indicated that their products had been held back at customs – no additional information was provided. All five companies in the export group stated that their businesses were negatively impacted by the availability of unregistered medicines in African countries. The commercial impact of this was rated between medium and severe (medium =4; severe=1). One company mentioned Zimbabwe, Zambia, Mozambique and Malawi as the countries where the availability of unregistered medicines was a problem.

Table 2: Reasons for non-supply of medicines (n=5)

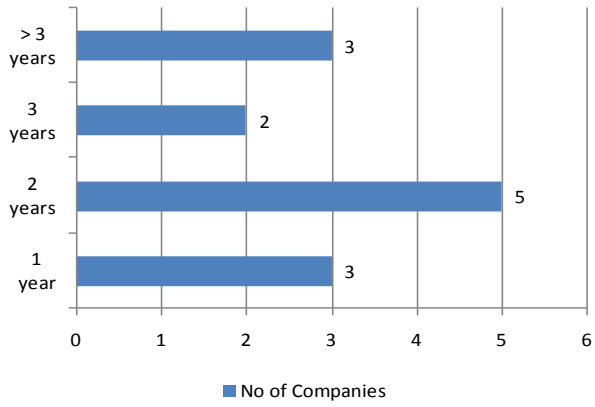
Reason	No. of Companies citing reason for not supplying medicines to specific African countries
Registration costs	4
Commercial	3
Retention costs	3
GMP Inspection fees	3
Lengthy registration	2
GMP inspection requirements	2
Unregistered medicine already available	1
Risk of counterfeit medicine	1
Generic medicine already available	1

Registration of medicines

Registration timelines experienced by companies varied in general between one and three years although time could vary between countries and three companies indicated more than three years (Fig 1). Although the results were mixed in terms of whether current African medicines registration requirements are in line with international standards, some respondents indicated that there is a level of alignment with international standards. Nine companies indicated that the registration requirements in African countries were in line with international standards (Table 3).

The majority of respondents indicated that there was a lack of recognition of international standards by African regulatory authorities with no differences across RECs. Of the total of 14 companies, 13 stated that country specific requirements, in general, were problematic to implement. The three main areas that respondents found problematic were country-specific labeling requirements, GMP inspection requirements and GMP inspection fees. Another company indicated that the regulators lacked the expertise to register biologic agents.

Figure 1: Reported timelines for medicine registration (n=14, 1 company did not provide a timeline)



GMP inspections have been cited by most companies operating in Africa as a barrier to the registration and supply of medicines. Seven companies noted that GMP inspection fees were too high, while seven companies indicated that GMP inspection requirements were a barrier to medicine registration (Table 3).Additional comments provided by the respondents included that the cost of maintaining the product was higher than the returns and sales volumes do not justify high costs nor cover registration renewal fees. A correlation was identified between commercial decisions not to supply medicines and GMP issues in specific countries (Table 4).

Table 3: Summary of survey results across the different Regional Economic Communities

Question	EAC N=11	ECCAS N=8	ECOWAS N=8	SADC N=14
No. of Products supplied to African countries (no. of responding companies)	**10**	**7**	**10**	**14**
≤10 products	3	4	3	6
11-20 products	3	3	1	4
>20 products	4	2	3	5
Alignment of registration requirements with international standards (no. of respondents)*	**11**	**8**	**8**	**15**
True	1	1	1	2
True in some cases	6	5	4	9
False in some cases	1	1	1	1
False	2	0	1	2
No information known	1	1	1	1
Lack of recognition of international standards (no. of respondents)	**10**	**7**	**7**	**15**
Yes	9	6	6	13
No	1	1	1	2
Are GMP inspection requirements a barrier to registration of medicines? (no. of respondents)*	**9**	**7**	**7**	**14**
Yes	7	6	5	8
No	0	0	0	1
No opinion	2	1	2	5
Views on GMP inspection fees (no. of respondents)*	**10**	**7**	**7**	**15**
Too high	7	5	4	7
Appropriate	1	1	1	2
Too low	0	0	0	0
Unknown	2	1	2	6
Are country specific labeling requirements problematic to implement for supply of medicine to African markets? (no. of respondents)*	**10**	**6**	**7**	**14**
Yes	10	6	7	13
No	0	0	0	1
Not applicable	0	0	0	0

*This is a subset of companies that indicated that they supply medicines in these regions (Regulatory group); data is based on no. of respondents rather than no. of companies
**This is a subset of companies that indicated that they supply medicines in these regions (Export group and Regulatory groups); data is based on no. of respondents rather than no. of companies

Table 4: Countries where companies experience problems with GMP inspections

Region	GMP issues	Commercial decision not to supply
SADC	Tanzania	Tanzania
	South Africa	
	Botswana	
	Mozambique	Mozambique
	Zimbabwe	Zimbabwe
ECOWAS	Ghana	Ghana
	Nigeria	Nigeria
	Togo	
EAC	Kenya	Kenya
		Uganda
ECCAS	None	None

Withdrawal/discontinuation of medicines (export and regulatory)

Of concern is that nine companies indicated that they have stopped supplying between one and five products. When probed for reasons for the withdrawal of the products from market, the reasons cited include registration, renewal and GMP inspection fees. One company indicated that their product had been replaced by a more innovative/convenient dosage form while another stated that opportunistic distributors and parallel importers bringing in counterfeit and cheap generics had led them to withdraw their products. The therapeutic areas, in which the products were withdrawn, included allergy, anti-infective, gastroenterology, HIV/AIDS, cardiovascular, metabolic disorders, pain management, psychiatry and gynecology. Eleven companies indicated that counterfeit medicines were a problem in some markets in Africa; specifically Kenya and Uganda. Respondents were also asked to supply reasons for the interrupted supply to determine a link, if any, to regulatory requirements. Reasons cited included delays in approval of post registration amendments to registration dossiers.

African Medicines Registration Harmonisation Initiative (AMRH)

Overall, 82% of respondents were positive about the AMRHI. While providing additional feedback some respondents stated that previous attempts at achieving harmonization had failed due to a lack of political will and commitment to implement.

Survey respondents were asked about their views on the public health impact of the current requirements for registration of medicines in African markets. There were strong views expressed regarding the delayed access to medicines and the resultant impact on health outcomes for patients. Another view was that having stringent regulatory requirements would contribute to keeping counterfeit medicines out of the market. Ethiopia was cited as an example of good management in this regard by requiring that medicines need to be on the essential drug list (EDL) before they can be registered.

Discussion

The pharmaceutical companies that participated in the survey have a strong presence in African markets. Overall, the majority of companies indicated that technical issues related to the registration and supply of medicines to these countries were problematic to implement and also a barrier to supply. Although there is some literature on the resource constraints of regulatory authorities in Africa [1, 3, 4, 5], we were unable to find data on pharmaceutical company experience in registering and supplying medicines to Africa. The question explored in this study was whether technical requirements for medicine registration was considered a barrier to registration and supply of medicines. The results showed that country specific requirements, in particular, are problematic to implement. The survey results indicated a link between pharmaceutical companies experiencing interrupted supply and regulatory requirements. The lack of alignment with international standards, impact of counterfeit medicines, GMP inspections, have impacted and will continue to impact product supply, unless changes are made to country-specific requirements as well as the recognition of international standards.

International standards contribute greatly to companies' ability to comply with regulatory requirements and from the regulator's point of view [6], it ensures not only that high standards are maintained but it also assists with functioning optimally in a resource constrained environment [7, 8, 9]. An efficient, predictable registration timeline will promote access to new medicines by encouraging more companies to register medicines in Africa. It is expected that this will positively impact the availability of medicines.

Country specific labeling requirements increase the cost of medicines to specific African countries and in some cases pharmaceutical companies either cease to supply medicines or have made decisions not to supply new medicines to these countries.

The costs, for GMP inspections, were cited as prohibitive by respondents when considering registration and supply of medicines to specific African markets. The potential impact of increased number and frequency of GMP inspections include potential delays in approval and medicine supply. Furthermore, the cost of GMP inspections could be a deciding factor in whether companies pursue registration in a country or not.

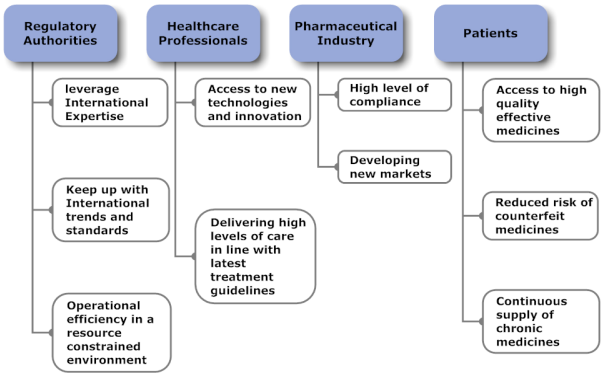
Opportunity costs in this context can be defined as the number of products that will not be registered or supplied to specific African markets therefore resulting in revenue losses for the NMRA as well as the pharmaceutical companies concerned. Perhaps more importantly, there are costs to the healthcare system as a result of the unavailability of certain medicines [10, 11].

Current regulatory requirements should be carefully scrutinized to determine whether they are value-added or non-value added with respect to the medicine registration process. In this way, the current registration processes can be streamlined, thereby shortening the overall registration timeline for medicines. There is a pressing need to address some of the regulatory burdens experienced by pharmaceutical companies in the short term, which will not only alleviate the current issues cited, but will also contribute positively to the achievement of the objectives of the AMRHI.

Medicine registration harmonisation will positively impact all stakeholder groups as illustrated in Figure 2 [5, 8, 10]. Regulatory authorities will benefit in terms of improved expertise, collaboration with other regulatory authorities and operational efficiency through sharing of information and recognition of established regulatory authority decisions. Healthcare professionals will benefit through the availability of more treatment options in order to optimise patient management. Pharmaceutical companies will benefit through the establishment of new markets and the improved ability to comply with regulatory requirements related to medicine registration. Patients will benefit through improved supply of medicines, access to high quality medicines that comply with stringent requirements of safety, quality and efficacy and reduced risk of use of counterfeit medicines.

Limitations of this study include the small sample size and that there may be bias in responses which is inherent in self reported data. The small sample size did include diverse companies, including multinational, R&D based and local generic companies. It is acknowledged that opinions may differ even between representatives from the same company. The literature states that NMRAs in Africa have to face a multitude of issues affecting medicine regulation under sometimes severely resource constrained circumstances [3, 4, 5]. Risks of over-regulation and under-enforcement are very real and can be avoided through co-operation amongst regulatory agencies that are better resourced and skilled in maintaining the highest levels of technical standards. Further research is required to understand the regulator perspectives on country specific requirements which at face value seem to be at odds with the objectives of the African Medicines Regulatory Harmonisation Project.

Figure 2: Benefits of Harmonisation [adapted from reference 5, 8 & 10]



Conclusion

It is clear from the results of this survey that pharmaceutical companies operating in Africa are experiencing difficulties in complying with the technical requirements of individual African markets. The level of complexity is increased by the consolidated manufacturing and internal supply chain arrangements within pharmaceutical companies. Managing internal and regulatory compliance requirements is resulting in companies making decisions not to supply medicines to specific African markets. There also seems to be a disconnect between the objectives of the AMRHI and the experiences of pharmaceutical companies at a country level. It is recommended that further research is undertaken in-order to investigate country specific requirements both in terms of intention and impact and also from pharmaceutical company and regulator perspectives.

Authors' Contributions

Kirti Narsai had the original idea for the paper and wrote the first draft, which was based on information requirements expressed by Eric Buch. Kirti Narsai designed the questionnaire in collaboration with Abeda Williams. Kirti Narsai also carried out the data analysis . Aukje Mantel-Teeuwisse contributed to drafting the article and reviewing the data analysis. All authors contributed to the revision of the paper and approved the final version.

Acknowledgements

The Pharmaceutical Industry Association of SA (PIASA) is a trade association of companies involved in the manufacture and/or marketing of medicines in South Africa. The membership of 18 companies includes a broad representation of foreign multinational pharmaceutical companies and local and generic companies, both large and small. We would like to thank the member companies, in particular the members of the PIASA regulatory and export working groups who participated in the survey. We would also like to say thanks to Prof Eric Buch (NEPAD Health Advisor), who requested data from the industry on harmonisation issues, which led to the development of this study.

Conflict of interest

None of the authors have any conflicts of interest that are directly relevant to the content of this study. The Department of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, employing Aukje Mantel-Teeuwisse has received unrestricted research funding from the Netherlands Organisation for Health Research and Development (ZonMW), the Dutch Health Care Insurance Board (CVZ), the Royal Dutch Pharmacists Association (KNMP), the EU Innovative Medicines Initiative (IMI), the EU 7th Framework Program (FP7), the Dutch Medicines Evaluation Board, the Dutch Ministry of Health and industry (including GlaxoSmithKline and Pfizer). Kirti Narsai is permanently employed by PIASA. Abeda Williams is permanently employed by Janssen.

Funding Source

No sources of funding were used to assist in the preparation of this study.

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Research Article

Southern Med Review

Discounts and rebates granted to public payers for medicines in European countries

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Citation: Vogler S, Zimmermann N, Habl C, Piessnegger J, Bucsics A. Discounts and rebates granted to public payers for medicines in European countries. Southern Med Review (2012) 5;1:38-46

Received: 13th May 2012
Accepted: 12th June 2012
Published Online: 23rd July 2012

Abstract

Objective: The objective of this study was to provide an overview about the existence and types of discounts and rebates granted to public payers by the pharmaceutical industry in European countries.

Methods: Data were collected via a questionnaire in 2011. Officials from public authorities for pharmaceutical pricing and reimbursement represented in the PPRI (Pharmaceutical Pricing and Reimbursement Information) network provided the information and reviewed the compilation.

Results: Information is available from 31 European countries. Discounts and rebates granted to public payers by the pharmaceutical industry were reported for 25 European countries. Such discounts exist both in the in- and out-patient sectors in 21 countries and in the in-patient sector only in four countries. Six countries reported not having any regulations or agreements regarding the discounts and rebates granted by industry. The most common discounts and rebates are price reductions and refunds linked to sales volume but types such as in-kind support, price-volume and risk-sharing agreements are also in place. A mix of various types of discounts and rebates is common. Many of these arrangements are confidential. Differences regarding types, the organizational and legal framework, validity and frequency of updates and the amount of the discounts and rebates granted exist among the surveyed countries.

Conclusions: In Europe, discounts and rebates on medicines granted by the pharmaceutical industry to public payers are common tools to contain public pharmaceutical expenditure. They appear to be used as a complimentary measure when price regulation does not achieve the desired results and in the few European countries with no or limited price regulation. The confidential character of many of these arrangements impedes transparency and may lead to a distortion of medicines prices. An analysis of the impact on these measures is recommended.

Keywords: medicines, Europe, discount, rebate, cost-containment, policy measure, payer, reimbursement, tendering

Introduction

Governments' medicines policies aim to provide to their population safe, affordable and effective medicines, with particular regard to essential medicines [1-4]. This objective is compromised by financial restraints which all European, including high-income, countries are facing [5-7]. The most commonly applied policy measures in response to the global financial crisis are price cuts, increase in co-payments, value-added tax (VAT) rates on medicines and in the distribution add-ons [8]. Such measures are usually implemented by executive order or regulation rather swiftly. During the last years, however, additional policies have been implemented in some countries: The Netherlands introduced the so-called preferential pricing policy which is a tendering system in the out-patient sector [9, 10]. In Germany rebates on medicines prices are negotiated between sickness funds and manufacturers [11, 12], and tendering-like models in the pricing and/or reimbursement process in the out-patient sector are also in place in other European countries (e.g. Denmark, Hungary, Slovakia) [13-15]. The Belgian model of such tendering by the sickness funds, the "Kiwi model", proved not successful and is no longer being

applied [16, 17]. Further examples of new approaches are risk-sharing, cost-sharing and further forms of managed entry agreements which can be described as formal arrangements between public payers and pharmaceutical companies with the aim of sharing the financial risk due to uncertainty surrounding the introduction of new technologies [18-20]. All these rather new policies have in common that they aim to manage, often on a confidential agreement level, uncertainty and that pharmaceutical companies get involved in sharing financial responsibility. Price-volume agreements, refunds by the pharmaceutical industry and further discounts and rebates granted by companies to public payers are further policy options with the same goal.

Literature is primarily available on discounts and rebates in the distribution chain, in particular regarding generic medicines [21-25]. But there is little published evidence about regulations and agreements on discounts and rebates granted by pharmaceutical companies to public payers. However, personal communications with representatives of authorities as well as of the pharmaceutical industry have suggested that discounts, rebates, refunds and similar forms are applied in some European countries.

We undertook this study to order to learn more about the existence of these measures, also in smaller countries which are often excluded from research. Another objective was to gain a better understanding of their relevance across Europe. We sought to survey and provide a mapping of discounts and rebates which pharmaceutical companies grant on reimbursable medicines to public payers in European countries. Further discounts and rebates (e.g. along the distribution chain) were not in the scope of the investigation.

Methods

The mapping exercise of manufacturer discounts and rebates in European countries was primarily undertaken via a questionnaire to public authorities for pricing and reimbursement.

Definitions and scope

The investigation addressed discounts and rebates granted by pharmaceutical companies to public payers. Discounts and rebates on all medicines in the reimbursed market (so-called reimbursable medicines, i.e. medicines covered primarily by public funds), both innovator brands and generics, were included. Both the out-patient and in-patient sectors were in the scope of the survey. Any discounts and rebates granted to wholesalers, pharmacists, other companies such as distributors and patients/consumers were excluded. Public payers, which are also called "third party payers", are, usually public, institutions which cover health or medical expenses on behalf of beneficiaries or recipients. Typically, third party payers in European countries are either National Health Services (NHS, e.g. in Italy, Portugal, Spain, UK – "Beveridge systems" funded by the state) or Social Health Insurance institutions (e.g. Austria, Belgium, France, Germany and in all Central and Eastern European countries; "Bismark systems") [26, 27].

Whereas discounts are defined as "price reductions granted to specified purchasers under specific conditions prior to purchase", rebates contain an ex-post component since they are "payments made to the purchaser after the transaction has occurred" [28]. Being mindful of additional types of discounts and rebates, we listed in the questionnaire some examples (e.g., in-kind support including "cost-free" donations, bundling procedures which offer a combination of different types of products at a reduced price). We explicitly invited the respondents to include further types which they would subsume under "discounts and rebates".

Sample group

Information was collected from the public authorities for pricing and reimbursement in European countries, in particular within the European Union (EU) zone. We aimed at achieving a high, possibly full, coverage of the 27 EU Member States, and further non-EU countries also contributed to the exercise. Respondents to the questionnaire were officials and staff of public authorities represented in the PPRI (Pharmaceutical Pricing and Reimbursement Information) network. PPRI is a networking and information-sharing initiative on pharmaceutical policies from a public health perspective which emerged from a European Commission co-funded project under the same name [29, 30]. At the time of the survey, PPRI consisted of more than 60 institutions, mainly Medicines Agencies, Ministries of Health and Social Insurance institutions, from 38 countries, including all 27 EU Member States, eight other European countries and three non-European countries, plus European and international institutions (European Commission services and agencies, OECD, WHO and World Bank)[i].

Survey instrument

We developed a draft questionnaire and piloted it with a third party payer in Austria, the Main Association of Austrian Social Security Institutions (MASSI), in February 2011. Following the pilot, we revised the questionnaire.

The finalized questionnaire consisted of a total of ten questions which explored:

- the existence of discounts and rebates to public payers,
- their types (e.g. price reductions, refunds, bundling, etc.), their design (e.g. linked to sales of a single product or the full product range of a company, based on the number of patients treated) and extent,
- the legal/contractual framework (e.g. law/regulation, agreement, tendering, individual negotiations) and the parties involved, and
- the frequency of updates.

Most questions provided several options and allowed for open-ended answers. In order that respondents had an understanding, the questionnaire started with a rationale for the survey and definitions of key terms.

[i] It is PPRI's policy not to list the names of staff and officials of institutions represented. The PPRI member institutions are listed on the website of the WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies under the section "networks": http://whocc.goeg.at/Networks/ListOfMembers.

Data collection and validation

On 25 February 2011 we sent the revised questionnaire by e-mail to the members of the PPRI network. The respondents were requested to answer the questionnaire electronically within two weeks which is the usual time for queries within the PPRI network. Furthermore, they were encouraged to forward the questionnaire to competent persons and bodies in case they were not in the position to provide answers.

We received completed questionnaires from 14 countries within the time limit. Responses from 12 additional countries arrived following reminders by e-mail or telephone. These 26 country responses came from 20 EU Member States and, additionally, from six non-EU countries. For a few missing countries, we considered information, where available, from the PPRI Pharma Profiles [31], the national PHIS Hospital Pharma Reports [32] and the PHIS Hospital Pharma Report [33].

Data were compiled at the end of March 2011, and the summary of results was shared with the PPRI network through an Intranet platform. The compilation was presented to the network members during a PPRI network meeting in Madrid in February 2012.

At the beginning of May 2012, the respondents had another opportunity to check the information from their country (as of 2011) when we sent the draft article to the PPRI network for information, approval and validation. Following the meeting and the sharing of the draft article, previously compiled information was revised and expanded; and we received responses to the questionnaire from four more countries.

The mapping comprises responses from 31 of the 33 surveyed countries (all 27 EU Member States except Poland and Romania; plus Albania, Croatia, Iceland, Norway, Switzerland, Turkey).

Confidentiality issues and approval

We are aware that the issue of discounts and rebates is a sensitive one and, at least partially, subject to confidentiality clauses in some countries.

We informed the respondents about the intention to publish the results in a scientific article during the PPRI network meeting in February 2012, and we shared the draft article for validation and approval.

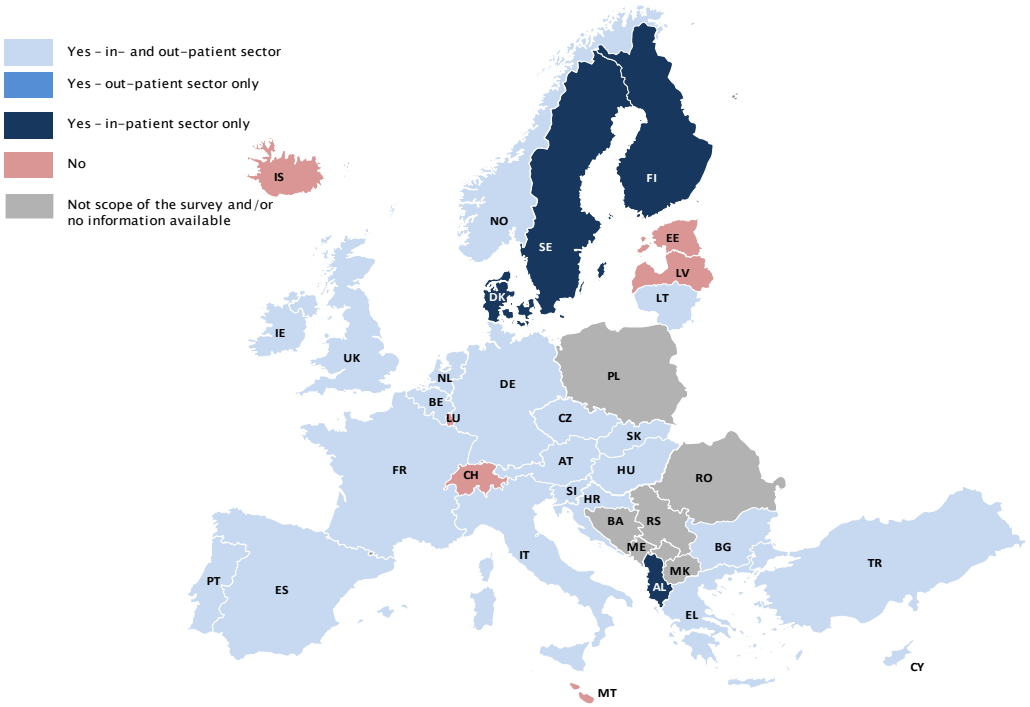
Results

The survey showed that manufacturer discounts, rebates and similar types granted to public payers do play a role in most European countries.

Mapping by countries and sectors

In 25 European countries such discounts and rebates were reported, in both the in- and out-patient sectors in 21 countries and in the in-patient sector only in four countries (Figure 1).

Figure 1: European mapping of discounts and rebates granted to public payers, 2011



Country abbreviations: AL = Albania, AT = Austria, BA = Bosnia and Herzegovina, BE = Belgium, BG = Bulgaria, CH = Switzerland, CY = Cyprus, CZ = Czech Republic, DK = Denmark, DE = Germany, EE = Estonia, EL = Greece, ES = Spain, FI = Finland, FR = France, HR = Croatia, HU = Hungary, IE = Ireland, IS = Iceland, IT = Italy, LT = Lithuania, LU = Luxemburg, LV = Latvia, ME = Montenegro, MK = Macedonia, MT = Malta, NL = Netherlands, NO = Norway, PL = Poland, PT = Portugal, RO = Romania, RS = Serbia, SE = Sweden, SI = Slovenia, SK = Slovakia, TR = Turkey, UK = United Kingdom

Discounts and rebates were common in both the out-patient and in-patient sectors. In four, particularly Northern European, countries (Albania, Denmark, Finland, and Sweden) discounts are not applied in the out-patient sector but only in the in-patient sector. Six countries (Estonia, Iceland, Latvia, Luxembourg, Malta and Switzerland) reported that no discounts from pharmaceutical companies to public payers existed.

Types of discounts and rebates

The most common form of discounts and rebates applied in European countries is price reductions. The ex-factory prices (e.g. for reimbursed medicines in Austria) or the pharmacy purchase prices (e.g. for all medicines in Cyprus) are regulated by law and price reductions are applied to this respective price type. 21 European countries reported price reductions: 16 countries both in the out-patient and in-patient sectors, three in the in-patient sector only and two in the out-patient sector (Table 1).

Refunds granted by pharmaceutical companies linked to sales volume are also common measures applied, they rank second. Eleven countries reported receiving rebates, typically in both the out-patient and in-patient sectors (seven countries; four countries in the out-patient sector only). In-kind support (e.g. buy two and get one for free) was reported by seven countries, mainly applied in the in-patient sector, and thus this type ranks third.

The questionnaire also indicated "global reductions of payments to pharmaceutical companies" and "bundling" which were reported by four countries (Austria, Germany, Hungary and Slovenia – all out-patient sector only) and four countries (Croatia, Finland, Portugal, Slovenia – mainly in-patient) respectively. The respondents could freely list additional types of discounts and rebates granted to public payers, which they used to indicate, among others, price-volume agreements and different types of risk-sharing agreements.

Table 1: Types of discounts and rebates on medicines granted to public payers in 31 European countries, 2011

Types	Countries
Reduction of prices (the controlled price type: i. e. ex-factory price or wholesale/retail prices)	Austria (oi), Bulgaria (oi), Croatia (oi), Cyprus (oi), Czech Republic (oi), Denmark (i), Finland (i), France (oi), Germany (oi), Greece (oi), Hungary (oi), Ireland (i), Italy (o[1]i), Netherlands (oi), Norway (oi), Portugal (o), Slovakia (oi), Slovenia (o), Spain (oi), Turkey (oi), United Kingdom (o[2],i)
(Global) reductions of payments to pharmaceutical companies	Austria (o), Germany (o),Hungary (o), Slovenia (o)
In-kind support	Austria (i), Croatia (oi), Cyprus (oi), Finland (i),), Netherlands (i), Portugal (i), United Kingdom (i)
Bundling (offering several products for sale as one combined product)	Croatia (oi), Finland (i), Portugal (i), Slovenia (o)
Refunds by pharmaceutical compa-nies back to public payers depending on the sales volume of medicines	Austria (oi), Belgium (oi), Croatia (oi), France (oi), Germany (o), Ireland (oi), Italy (o), Portugal (oi), Slovenia (o), Spain (oi), United Kingdom[1] (o)
Other forms:[3]	
Price-volume agreements	France (o), Germany (o), Hungary (oi), Latvia (oi), Lithuania (oi), Slovenia (o)
Risk-sharing agreements	Germany (o), Italy (o), Slovenia (o), United Kingdom[4] (i)
shared risk of potential overspending of a pre-defined target	France (oi), Croatia (oi), Hungary (oi), Italy (o), Slovenia (o)
cross product schemes[5]	Croatia (oi), Slovenia (o)
reduction of wholesale mark-ups (if pharmaceutical company provides wholesale as well)	Slovakia (oi)
all types of discounts allowed (not regulated)	Slovenia (o)
not specified	Sweden (i)

[1] Companies could choose between a price cut or payback mechanism (based on Law as July 2006).
[2] Companies could choose between price reduction, price modulation and refund.
[3] Open-ended question: information as provided by respondents whose completeness cannot be guaranteed.
[4] Dose cap schemes, single fixed price, response scheme.
[5] Pharmaceutical companies submit binding offers when they apply for inclusion in the reimbursement list. The application can be connected to a parallel proposal for reduction of a price of a medicine already included in the reimbursement list.

Coverage: All 27 European Union Member States except Poland and Romania plus Albania, Croatia, Iceland, Norway, Switzerland, Turkey. Slovenia – only information on the out-patient sector (discounts and rebates also applied in the in-patient sector).

Abbreviations: o = out-patient sector, i = in-patient sector, oi = out- and in-patient sector

As shown in Table 1, combinations of different types are applied. In the out-patient sector price reductions and refunds to public payers are common combinations and are often linked to the sales volume of a single product or the total volume of sales of all products of a specific company.

Legal and organisational framework

Discounts and rebates in the out-patient sector are often the result of individual negotiations of public payers with pharmaceutical companies which are confidential. However, framework agreements, to which all or the majority of pharmaceutical companies of a country adhere, are rarely announced. Laws and regulations stipulate the level of price reduction or refund in some countries. In a few countries a "regulation-free zone" is in place concerning discounts in the framework of the existing pharmaceutical policies (Bulgaria, Latvia). Tendering, which comprises "any formal and competitive procurement procedure through which tenders/offers are requested, received and evaluated for the procurement of goods, works or services"[28], is typically applied in the in-patient sector; only a few countries use tendering in the out-patient sector (Table 2).

Table 2: Type of contracts and agreements on discounts and rebates of public payers with pharmaceutical companies in the out-patient sector in 31 European countries, 2011

Types	Countries
Laws/regulations	Belgium, Germany, Greece, Hungary, Italy, Portugal, Spain, Turkey
Framework agreements	Austria, Ireland, United Kingdom
Individual negotiations	Austria, Belgium, Croatia, Cyprus, Czech Republic, France, Germany, Hungary, Italy, Norway, Portugal, Slovakia, Slovenia
Tendering	Denmark[1], Germany, Netherlands

[1] The tendering procedure in place in Denmark in the out-patient sector is not considered to be discount policy by country representatives.

In some countries the individual negotiations with pharmaceutical companies are led by a single public body (e.g. Main Association of the Austrian Social Security Institutions, National Health Insurance Fund in Bulgaria, Italian Medicines Agency) whereas in other countries several public stakeholders negotiate individually with companies (e.g. several sickness funds in the Czech Republic and in Germany).

Depending on the organisation of the health care sector tendering and/or individual negotiations on discounts and/or rebates in the in-patient sector are performed either by a single body (e.g. the Hospital Purchasing Agency AMGROS in Denmark, the "Central Administration of the Health System" ACSS – entity responsible for managing NHS providers funding, including hospitals, in Portugal) or by individual hospitals or procurement groups of hospitals (e.g. Austria, Germany, Finland, France, Hungary).

The frequency, duration and renewal of such agreements differ. Whereas some countries (e.g. France) conclude agreements on a yearly basis, there are others with longer validity periods such as two or three years (e.g. Austria, Croatia, Italy). Agreements can also be concluded temporarily in response to the introduction of a specific product and/or therapeutic alternative (e.g. Portugal) or to the development in pharmaceutical expenditure (e.g. Turkey).

Range of discounts and rebates in the out-patient sector

The range of discounts and rebates differs by type and country.

Discounts and rebates can be designed to be shared by all actors (pharmaceutical companies, wholesalers, pharmacies) in the pharmaceutical supply chain (e.g. in Spain). In two countries (Italy, United Kingdom), companies have the choice between price reductions (and price modulation in the UK) or payments back to public payers (Table 1).

Table 3: Range of discount and rebates in 31 European countries, 2011

Types	Range	Countries
Price reductions on specific medicines resulting from individual negotiations	0 – 50% of the respective price	Austria, Croatia, Cyprus, Czech Republic, France, Germany, Italy, Norway, Portugal, Slovakia, Slovenia
Price reductions on medicines covered by laws/regulations	3% – 32.5%	Belgium, Germany, Greece, Hungary, Italy, Portugal, Spain and Turkey
Refunds/pay back mechanisms linked to sales volume of pharmaceutical companies	1% – 8% of the sales	Austria (~1%), Belgium (6.73%), Croatia (confidential), France, Germany, Ireland (4%), Italy, Portugal, Slovenia, Spain (1.5-2%), United Kingdom

Coverage: All 27 European Union Member States except Poland and Romania plus Albania, Croatia, Iceland, Norway, Switzerland, Turkey.

Discussion

The study provided evidence that pharmaceutical companies grant different kinds of discounts and rebates on medicines to public payers. Information on discounts and rebates was reported from 25 of the 31 European countries from which information was sought. Discounts and rebates most frequently indicated are price reductions (in the out-patient and in-patient sectors), followed by refunds linked to sales volume (a measure particularly applied in the out-patient sector). Further discounts and rebates reported by some countries include in-kind support, price-volume and risk-sharing agreements. Differences exist among the countries regarding the types and extent of these measures as well as their design and place in the organizational and legal framework. Individual negotiations are the most common contractual arrangement.

The study sheds light on a very sensitive area in which scant literature exists and where there are difficulties in assessing information due to confidentiality clauses. The high response rate is therefore strength of the study.

The methodological approach chosen was a PPRI query, i.e. a survey with members of the PPRI network. There are only two parties in a country who know about such discounts and rebates: public payers and the pharmaceutical industry. We chose to address the public payers firstly because they had expressed interest in this issue under the framework of the PPRI initiative and motivated us to undertake the survey, and secondly because we could build on effective cooperation and a common understanding with them. The PPRI secretariat, which some of the authors are affiliated to, has been working for years on developing a joint language via the production and constant review of a glossary of pharmaceutical terms [28] and terminology trainings, and for this study we carefully defined the terms.

The high response rate to the questionnaire (14 responses within two weeks, and a total of 31 countries in the final compilation) confirmed the interest in the study and regarding its relevance. It clearly exceeded the average rate of nine answers to a PPRI query, thus endorsing the interest of public payers.

Despite thorough consideration of the terminology issues, misunderstandings occurred: We had to exclude a few answers (e.g. those referring to discounts and rebates granted in the distribution chain only which were not in the scope of this study). Open-ended questions included in the questionnaire helped to obtain a more complete picture but some responses were inconsistent, because, for instance, some countries listed their managed-entry arrangements such as risk-sharing agreements, while others did not. Knowing about further risk-sharing and managed entry agreements in some countries [18-20], we acknowledge that not all such agreements were reported in our study because managed-entry agreements were not the primary focus of our study. We cannot rule out the possibility that the mapping exercise might miss one or other discount and rebate being in place in a country. So, potential under-reporting is a limitation of our study.

Discounts and rebates might be used instead of statutory price regulation. Most European countries, however, have price control for medicines funded by public payers (on average around two third of pharmaceutical expenditure are covered by public payers [7, 8, 27]. The two free-pricing countries in the European Union are currently Denmark and Germany [6-8, 27], even though Germany is currently moving to some form of price control. Germany has been applying a rebate procedure: In addition to a published fixed rebate granted by the pharmaceutical industry, further rebates are negotiated between the company and the sickness funds. Each sickness fund is allowed to enter contracts with manufacturers, complementing or modifying the collective price negotiation scheme [12].

The other free-pricing country, Denmark, uses (like Germany) tendering in the out-patient sector [10, 14]. Even if Danish officials do not consider this measure to be a discount policy but as a mechanism to foster competition (tenders are made at frequent intervals of every two weeks [15, 34, 35], this policy is worth considering in the context of this study because the tendering process leads to discounted prices. Tendering in the out-patient sector is also applied in the Netherlands which is currently liberalizing its pricing system.

Discounts and rebates to public payers are also a reality in several European countries which control medicines prices. In those cases, the measures appear to be taken in order to accompany existing regulation (e.g. price control) and policy measures (initiatives to promote generics, a more rational use of medicines, etc.) since payers are under pressure to achieve savings. The need for cost-containment has been aggravated by the global financial crisis which required from the authorities to implement a bundle of sometimes rather strict, policies [8]. Arrangements on discounts and rebates have resulted in commitment of the pharmaceutical industry to contribute to savings in situations when companies would have opposed other, more "classical" or severe cost-containment measures. Discounts and rebates may also be considered as a policy option for payers in smaller markets which might not be attractive enough for the pharmaceutical industry otherwise [36, 37]. In particular with regard to prices for generic medicines, some smaller European countries have shown that they are able to achieve discounts from the pharmaceutical industry [38]. Furthermore, such discounts and rebates offer an opportunity for pharmaceutical companies to compensate for the lower purchasing power of some countries without offering incentives for arbitrage. Generally speaking, discounts and rebates are offered by the industry as part of their marketing strategy to gain market shares.

It appears at first glance that discounts and rebates offer a win-win situation for the two parties involved. It could therefore be suggested that they also benefit patients by securing the financial basis of the payers which would then be able to fund further medicines purchase. But rebates and discounts are an obstacle to transparency, as examples from other parts of the world have also shown [39, 40]: most of the discount and rebate agreements are, as the survey results confirmed, confidential, and even if stipulated by law, the individual extent negotiated remains confidential between the payers and the companies. This again impacts other policies, such as external price referencing which is in place in several European countries [27, 41].

There is concern that the discounts and rebates impede price transparency, since price comparisons are usually made with reference to official list prices, whereas the actual prices are lower [41]. In Spain one of the emergency measures in response to the global financial crisis was a discount on original products instead of a price cut because this was accepted by the industry

which shares the discount with the other actors in the distribution chain [8]: Though this discount is generally known, international price comparisons will continue to consider the non-discounted prices [42].

The example of Spain suggests the external reference pricing policy is another reason for the existence of discounts and rebates in European countries. When this pricing policy was applied, companies reacted by offering discounts and rebates [41]. The results also confirm that discounts and rebates are a common feature in the in-patient sector, as evidenced in other studies [33, 43]. Concern for limited transparency is raised again because actual hospital prices are usually not known in European countries [33]. Furthermore, unbalanced market power might be another issue in the hospital sector: While payers in the out-patient sector usually cover the whole country (in case of a National Health Service or a single payer Social Health Insurance institution) or parts of the population (e.g. sickness funds, regions), the relevant contacts for pharmaceutical companies in the in-patient sector are often individual hospitals or hospital associations. There are indications that larger hospitals receive larger discounts [44], but further components (e.g. on-patent "monopoly products" without therapeutic alternative) also play a role [33].

While we do not claim that our study provides conclusive evidence about all types of discounts, rebates and refunds granted by the pharmaceutical industry to public payers, it confirms in a systematic way that such measures do play a substantial role in European countries. For public payers it is valuable information to have an overview of the situation in other European countries and to learn about possible pitfalls of such discount and rebate agreements. Public payers must be aware that the advantages of various agreements, i.e. savings which might otherwise not have been possible and as such result in a contribution to increased accessibility of medicines, are flawed by reduced transparency, in particular by a distortion of medicines prices. With increasing use of discounts and rebates, which are often "hidden price cuts", policy makers and researchers have to be mindful of creating a situation in which the surveyed list prices may provide at best only an indication of, but do not reflect actual prices. This might be remedied by a price survey in pharmacies and dispensing points in line with the WHO/HAI price survey methodology [45-47].

Conclusions

Discounts and rebates which pharmaceutical companies grant on medicines to public payers appear to be a frequently applied policy across European countries. These mechanisms tend to be used as a complimentary measure when price regulation does not achieve the desired results especially in the European countries with no, or limited, price regulation. Discounts and rebates usually serve cost-containment purposes and/or the management of uncertainty and allow pharmaceutical companies to gain market share. Whereas these measures are likely to offer a win-win situation to the two parties involved (public payer and the pharmaceutical industry), they impact on transparency because these agreements, or at least their details, are confidential and may lead to a distortion of medicines prices. Since this study aimed to map rebates and discount mechanisms across Europe and in-depth analysis of specific regulations and agreements was not undertaken, as such further research is recommended.

Authors' contributions

All authors contributed to the paper's conception, design and production. SV wrote major parts of the article and revised the article following contributions from NZ, CH, JP and AB and feedback by PPRI network members. NZ developed the questionnaire in close cooperation with the co-authors, performed the survey, compiled the results and drafted the results section. NZ acted as key contact to the respondents of the questionnaire. All authors critically revised the article and have approved the final version for submission.

Acknowledgements

We would like to express our sincere gratitude to the members of the PPRI network (competent authorities for pharmaceutical pricing and reimbursement in the 27 EU Member States and thirteen further countries; see http://whocc.goeg.at/Networks/ListOfMembers) who participated in this mapping exercise: They responded to the questionnaire, were available for clarification and reviewed the draft article. According to the information policy agreed within the PPRI network, the names of the PPRI participants are not published. Furthermore, we thank Dr. Richard Laing, WHO Headquarters, for critically reviewing the article.

Conflict of interest

None.

Funding source

Research of the WHO Collaborating Centre (WHO CC) for Pharmaceutical Pricing and Reimbursement Policies was done under the framework of the PPRI (Pharmaceutical Pricing and Reimbursement Information) project. Funding for PPRI and WHO CC activities is provided by the Austrian Federal Ministry of Health which is legal owner of the Austrian Health Institute. This specific PPRI query was supported by a grant of the Austrian Main Association of Social Insurance Institutions (MASSI).

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Research Article

Southern Med Review

Disease related knowledge and quality of life: a descriptive study focusing on hypertensive population in Pakistan

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Citation: Saleem F, Azmil Hassali M, Akmal Shafie A, Atif M. Noman ul Haq, Aljadhey H, Disease related knowledge and quality of life: a descriptive study focusing on hypertensive population in Pakistan. Southern Med Review (2012) 5;1:47-52

Received: 10th September 2011
Accepted: 9th May 2012
Published Online: 23rd July 2012

Abstract

Objective: This study aims to evaluate the association between health related quality of life and disease state knowledge among hypertensive populations in Pakistan.

Methods: A cross sectional descriptive study was undertaken with a representative cohort of hypertension patients. Using prevalence based sampling techniques, a total of 385 hypertensive patients were selected from two public hospitals in Quetta City, Pakistan. The Hypertension Fact Questionnaire (HFQ) and the European Quality of Life scale (EQ-5D) were used for data collection. Statistical Package for the Social Sciences 16.0 was used to compute descriptive analyses of patients' demographic and disease related information. Categorical variables were described as percentages while continuous variables were expressed as mean ± standard deviation (SD). Spearman's rho correlation was used to identify any association between study variables.

Results: The mean (SD) age of the patients was 39.02 (6.59) years, with 68.8% being males (n=265). The mean (SD) duration of hypertension was 3.01 (0.93) years. Forty percent (n=154) had bachelor's degrees with 34.8% (n=134) working in the private sector. Almost forty one percent (n=140) had a monthly income of more than 15000 Pakistan rupees and 75.1% (n=289) resided in urban areas. The mean EQ-5D descriptive score (0.46±0.28) and EQ-VAS score (63.97±6.62) indicated lower health related quality of life (HRQoL) in our study participants. The mean knowledge score was 8.03 ± 0.42 while the correlation coefficient between HRQoL and knowledge was 0.208 ($p < 0.001$), indicating a weak positive association.

Conclusions: Results of this study highlight hypertension knowledge is weakly associated with HRQoL, suggesting that imparting knowledge to patients does not necessarily improve HRQoL. More attention should be given to identifying individual factors that affect HRQoL.

Keywords: Hypertension, Knowledge, Health Related Quality of Life, Correlation.

Introduction

Health Related Quality of Life (HRQoL) is defined as "a person's perceived quality of life representing satisfaction in those areas of life likely to be affected by health status" [1]. The concept of HRQoL has being used by health care professionals to describe factors other than illness affecting human health and its status [2]. These different health dimensions help healthcare professionals to understand patient perceptions of illness [2]. The development of chronic conditions with decreased life

expectancy can be disturbing for the patients [3]. The composite nature of diseases has a traumatic effect on social and economic status of patients. Although categorized as "controlled", the feeling of being ill heavily imbalances HRQoL in patients suffering from chronic illnesses. This in return, results in decreased patient satisfaction with daily life activities. HRQoL has become an important tool for the assessment of treatment outcomes from a patient perspective [4].

Within the context of chronic diseases, hypertension (HTN) in particular is counted as a major factor in decreasing life expectancy and disability-accustomed life years [5]. An estimated one billion of the world's population was diagnosed with HTN in year 2000 and this fraction is estimated to increase to 29% by the year 2025 [6]. It is also estimated that around 7.1 million people die each year due to complications of HTN [7]. This rising frequency of HTN is becoming a major public health challenge for both developed and developing countries [8]. Hypertension is apprehension significant chronic disease because of its high incidence and risk of developing associated cardiovascular disorders [9]. HTN adversely affects patients' every day activities and results in a decrease in self confidence [10], hence it is reported that hypertensive patients have reduced HRQoL scores [11-13].

In recent years, a growing demand to educate patients with chronic disorders has been reported in the literature [14-16]. Several methods have been utilized to improve patients' knowledge including; patient groups, published literature, specialist clinics, and the uptake of information technology [17]. Although the provision of disease-related information to patients has been considered good practice, it is not clear whether disease related knowledge has any impact on patients' HRQoL scores [17]. Therefore, the study aimed to examine the association between disease related knowledge and HRQoL in patients with HTN in Pakistan.

Methods

Design and settings

This study was designed as a descriptive cross sectional analysis. Patients being managed for HTN at the outpatient clinic of two tertiary care public hospitals of Quetta, Pakistan (Sandeman Provincial Hospital and Bolan Medical complex Hospital) were enrolled [18]. A prevalence based sample of 385 HTN patients was selected from May to July 2010 [19]. Patients18 years of age and above, with confirmed diagnosis of essential HTN, who had been using antihypertensive agents for the previous six months and were fluent in the national language of Pakistan (Urdu) [20] were included in the study. Patients aged below 18 and above 80 years, having co-morbidities, immigrants from other countries and pregnant women were exclusion criteria.

Ethical approval

There is no human ethical committee for non clinical studies in the institutes where the research was conducted. Therefore, permission from the respective medical superintendent was obtained in-order to conduct the study (EA/FS/1021-2).Written consent was obtained from participants prior to data collection.

Data abstraction

The Hypertension Fact Questionnaire (HFQ) and the European Quality of Life scale (EQ-5D) were used for data collection. Demographic and disease related information was also collected. All instruments were pre-tested for reliability and validity. Data from the pre-test evaluation was not included in the final analysis. Four pharmacists were trained by the principal researcher in how to administer the HFQ and EQ-5D. Group discussions were held among the pharmacists and principal researcher to ensure trustworthiness of the data collection process. The data obtained were verified and scrutinized for completeness and accuracy.

Assessment of Health related quality of life (HRQoL)

EQ-5D is a standardized instrument for use as a measure of health outcome and provides a simple descriptive profile and a single index value for health status [21]. It is composed of two portions. The EQ-5D tool consists of five domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Three levels of severity (no problems/some or moderate problems/extreme problems) are able to be selected from within a particular EQ-5D dimension. The second portion of the EQ-5D consists of a 20 cm health virtual analogue scale with two distinct end points, the best imaginable health state (score of 100) and the worst imaginable health state (score of 0) and is known as the VAS (visual analog scale) [21]. The translated Urdu version of EQ-5D was provided by Euroqol and the study was registered with Euroqol.

Assessment of knowledge about HTN

The HFQ was originally constructed in English and translated into Urdu by an independent professional translator. As the process of development and validation was completed, the final version was reviewed and approved by the researchers. The HFQ consists of 15 items which was used to assess patients' knowledge towards causes, treatment and management of HYT. The instrument was constructed after an intensive literature review [22, 23] and measured knowledge with a cut off scores of < 8 as poor, 8-12 average and 13-15 as an adequate knowledge [24]. The mean knowledge of the cohort was calculated for the final analysis.

Statistical analysis

SPSS version 16.0 (SPSS Inc., Chicago, IL) [25] was used to compute the descriptive analysis of patient demographics and disease related information. Categorical variables were measured as percentages, while continuous variables were expressed as mean ± standard deviation. The EQ-5D was scored using values derived from the United Kingdom (UK) general population survey from 1995 [26]. Spearman's rank correlation was used to explore any correlations between knowledge and HRQoL. Correlations were interpreted using the following criteria: 0–0.25 = weak correlation, 0.25–0.5 = fair correlation, 0.5–0.75 = good correlation and greater than 0.75 = excellent correlation [27].

Results

The demographic characteristics of the study patients are presented in table 1. The mean age (SD) of patients was 39.02 (6.59) years, with 68.8% of the study population being male. The mean (SD) duration of hypertension was 3.01±0.93 years. Forty percent (n=154) had bachelor's degrees and 75% (n=289) resided in urban areas. Forty one% (n=160) had a monthly income of more than 15000 Pakistan rupees.

Table 2 reports the HRQoL scores among study patients. The mean EQ-5D descriptive score was 0.46±0.28 and EQ-Vas score 63.97±6.62. A total of 29 different EQ-5D health states were described by the patients. The largest single group of participants (n=112, 29.1%) indicated no problems in the second and third domain while moderate problems in first, fourth and fifth. There was not a single patient who stated no problem in all five domains as shown in Table 3.

Table 1: Characteristics of survey respondents (n=385)

Characteristics	Frequency	Percentage
Age (39.02 ±6.59 years)		
18-27	48	12.5
28-37	186	48.3
38-47	128	33.2
>48	23	6.0
Gender		
Male	265	68.8
Female	120	31.2
Education		
Illiterate	9	2.3
Religious	62	16.1
Primary	7	1.8
Matric	51	13.2
Intermediate	51	13.2
Bachelors	154	40.0
Masters	51	13.2
Occupation		
Jobless	97	25.2
Govt. Job	78	20.3
Private Job	134	34.8
Businessman	76	19.7
Income*		
Nil	97	25.2
< Pk Rs. 5000	2	0.5
5000-10000	22	5.7
1000-15000	104	27.0
> 15000	160	41.6
Locality		
Urban	289	75.1
Rural	96	24.9
Duration of disease (3.01±0.939 years)		
< 1 year	26	6.8
1-3 years	89	23.1
3-5 years	124	32.2
> 5 years	146	37.9
> 15000	160	41.6

* 1 Pk Rs = 0.0118 US$

Table 2: HRQoL scores in hypertensive patients

Description	N	Mean EQ-5D Score	Standard Deviation	Mean EQ-VAS Score	Standard Deviation
Age					
18-27	48	0.5913	0.18401	66.81	5.652
28-37	186	0.5007	0.25706	64.68	5.862
38-47	128	0.4104	0.31491	59.87	7.160
>48	23	0.2576	0.28444	63.97	6.621
Gender					
Male	265	0.4677	0.28194	64.03	6.466
Female	120	0.4669	0.29107	63.84	6.978
Education					
Illiterate	9	0.2543	0.33554	59.44	6.521
Religious	62	0.3005	0.34637	60.63	6.744
Primary	7	0.5583	0.18048	63.57	2.992
Matric	51	0.4371	0.28744	64.59	7.245
Intermediate	51	0.5231	0.25906	65.06	5.774
Bachelors	154	0.5293	0.23171	64.84	6.130
Masters	51	0.4835	0.28105	64.59	7.119
Occupation					
Jobless	97	0.4337	0.29882	63.24	7.077
Govt. Job	78	0.4796	0.27688	64.44	7.011
Private Job	134	0.5295	0.23761	65.16	5.503
Businessman	76	0.3886	0.32602	62.36	7.080
Income					
Nil	97	0.4337	0.29882	63.24	7.077
< Pk Rs 5000	2	0.4210	0.33234	65.00	7.071
5000-10000	22	0.5628	0.19853	65.68	6.549
1000-15000	104	0.5231	0.23856	65.25	5.841
> 15000	160	0.4392	0.30643	63.34	6.735
Locality					
Urban	289	0.5113	0.25466	64.97	6.156
Rural	96	0.3356	0.32713	60.98	7.089
Duration of disease					
< 1 year	26	0.5885	0.18203	67.04	4.976
1-3 years	89	0.5158	0.25582	65.33	6.335
3-5 years	124	0.4738	0.26777	64.35	6.106
> 5 years	146	0.4110	0.31733	62.28	7.074
> 15000	160	41.6			
Total Sample	**385**	**0.4674**	**0.28444**	**63.97**	**6.621**

The mean HRQoL score was 46.74 ± 28.44 with VAS score 63.97 ± 6.621 indicting poor status of life in our study respondents

Table 3: Frequency of self-reported (EQ-5D) Health States

Health State	N	% Total	Health State	N	% Total
11112	1	0.3	21222	37	9.6
11122	21	5.5	21223	13	3.4
11123	4	1.0	21232	18	4.7
11222	39	10.1	21233	9	2.3
11223	8	2.1	22122	11	2.9
11232	2	0.5	22123	5	1.3
11233	1	0.3	22212	1	0.3
12122	12	3.1	22222	17	4.4
12222	6	1.6	22223	8	2.1
21112	6	1.6	22231	1	.3
21121	1	0.3	22232	11	2.9
21122	112	29.1	22233	18	4.7
21123	12	3.1	22322	1	0.3
21132	8	2.1	22323	1	0.3
21212	1	0.3	**Total**	**385**	**100**

Within 29 different health states, majority (n=112, 29.1%) stated moderate difficulty in the first, fourth and fifth domain respectively, where as they stated no difficulty in the second and third domain*.

Table 4 reflects the knowledge of patients about HTN. The mean knowledge score was 8.03±0.42 and median score was 8. From the cohort, 146 (37.9%) were within a poor knowledge range, 236 (61.3%) moderate and 3 patients (0.8%) demonstrating adequate knowledge about HTN. Poor knowledge was evident in responses to questions relating to onset, management (questions 3 and 5) and dietary control of HTN (questions 11, 12 and 13). Correct answers to these questions were reported as 27.8, 30.4, 13.5, 20.5 and 23.6 %, respectively.

Table 4: Responses to HTN knowledge questions

HTN knowledge item	Yes (%)	No (%)	Don't know (%)
Do you know the normal values of blood pressure?	77.9	22.1	0.0
Elevated BP is called HTN.	52.2	17.7	30.1
HTN is a condition which can progress with age.	27.8	70.1	2.1
Both men and women have equal chance of developing HTN.	20.3	79.	0.8
HTN is a treatable condition.	30.4	68.1	1.6
The older a person is, the greater their risk of having HTN.	67.3	31.2	1.6
Smoking is a risk factor for HTN.	96.4	3.4	0.3
Eating fatty food affects blood cholesterol level which is a risk factor for developing HTN.	41.0	48.6	10.4
Being overweight increases risk for HTN.	92.5	7.5	0.0
Regular physical activity will lower a person's chance of getting HTN.	42.1	56.4	1.6
Eating more salt has no effect on blood pressure.	86.5	13.5	0.0
Dietary approaches to reduce HTN do no good.	20.5	78.7	0.8
White meat is as good as red meat in HTN.	23.6	75.6	0.8
Medication alone can control HTN.	39.2	59.0	1.8
HTN can lead to other life-threatening diseases.	85.7	11.7	2.6

Knowledge was assessed by giving 1 to correct answer and 0 to the wrong answer. The "don't know "response was also taken as 0. The scale measured knowledge from maximum 15 to minimum 0. Scores < 8 were taken as poor, 8 - 12 average, and 13 - 15 adequate knowledge of hypertension. Mean knowledge was 8.03 ±0.415.
Spearman's rank correlation was used to measure the association between study variables. The correlation coefficient between HRQoL and knowledge was 0.208 (p< 0.001), indicating a weak yet significant association between quality of life and knowledge.

Discussion

Results from the present study highlight that HTN knowledge is weakly associated with HRQoL. To the best of our knowledge, and from extensive literature review, the relationship between HTN knowledge and HRQoL has not been explored. In other disease conditions such as inflammatory bowel disease (IBD), it has been reported that even though 64% of study patients were well informed about their disease, over 90% had some impairment in their reported Quality of Life (QOL) [17]. The authors reported no significant correlation between disease-related patient awareness and QOL scores (r=0.3). This is supported by the current study where despite having average knowledge, HRQoL in the study population was poor.

A number of studies have reported significant reduction in HRQoL with HTN [28-30], however there has been no attempt to associate the relationship between HTN knowledge and HRQoL. In the present study, the correlation between knowledge and HRQoL is 0.208 which is less than what was reported by Verma et al. in their study among IBD patients [17]. The current study suggests that knowledge towards disease has little or no impact on HRQoL in patients suffering with hypertension.

The reasons for this assumption are multi-factorial. It is hypothesized that an increase in disease related knowledge can decrease HRQoL. It is a logical hypothesis that as patients are informed about their conditions, the apprehension of developing further abnormalities especially in cases of chronic conditions likes HTN and diabetes affects psychological domains which disturbs the overall HRQoL. Unfortunately, after an extensive literature review, there was no data available from HTN patients supporting our hypothesis. However, Borgaonkar et al. concluded that the provision of educational booklets to IBD patients during an educational intervention decreases the HRQoL scores [31]. In a similar study of IBD patients with high anxiety levels, patients declared no benefit in terms of reduced

* [(Mobility, self-care, usual activities, pain/discomfort and anxiety/depression) Domains of HRQoL in order]

anxiety or improved HRQOL after participating in an educational program partially supporting the earlier hypothesis [32].

Within the context of developing countries like Pakistan, the HRQoL has been underused as one example of a tool borrowed from the social sciences and applied to this sort of work. Pakistan faces a severe shortage in numbers of professionals and health care facilities [33]. Furthermore, there is a huge gap in income disparity and living status between population subgroups [34]. All these factors may have a profound impact on patients HRQoL scores [17]. Besides that, lack of basic health facilities and recourses inversely affect health status and HRQoL of the population in general and specifically for patients suffering from chronic diseases like HTN.

Conclusion

The current study reported a weak yet positive association between disease-related knowledge and HRQoL scores. Adding to current knowledge, this is the first study that has been reported from Pakistan. The weak association between knowledge and quality of life is likely to be influenced by the many other factors which this study suggests. Studies focusing on in depth psychosocial profile using either an in depth qualitative exploration or multivariate analysis are recommended to get a clearer view of individualized factors affecting HRQoL.

Authors' contributions

Fahad Saleem and Noman ul Haq conducted the survey and drafted the initial manuscript. Mohamed Azmi Hassali and Asrul Akmal Shafie designed and supervised the study. Muhammad Atif and Hisham Aljadhey helped in statistical analysis, interpretation and manuscript revision. All authors read and approved the final manuscript.

Acknowledgment

The authors wish to thank the patients for participating in the study, and the hospital practice staff for their support.

Conflict of interest

The authors declare no conflict of interest.

Funding source

None

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The effect of implementing "medicines zero mark-up policy" in Beijing community health facilities

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Citation: Wei Cheng, Yunyun Fang, Dehui Fan, Jing Sun, Xuefeng Shi, Jiao Li. The effect of implementing "medicines zero mark-up policy" in Beijing community health facilities. Southern Med Review (2012)5;1:53-56

Received: 16th December 2011
Accepted: 1st June 2012
Published Online: 23rd July 2012

During the planned economy, free medical services were provided to everyone in China. Public health facilities heavily relied on government subsidies and the government set a price which was far below real costs. Medicines mark-up by public health facilities was first allowed in 1954, when the Chinese economy experienced the most difficult times [1]. Such a policy gradually evolved into a perverse incentive along with the economic reform starting from 1978, when public health facilities were encouraged to generate revenues and were allowed to issue bonuses. In turn, the income of individual staff was directly linked with revenue generation. The unchanged low level medical service fee forced providers to generate more revenue from mark-up of medicines. This contributed to unnecessary prescriptions written by doctors. Doctors preferred expensive medicines and poly-pharmacy, which contributed to increased medical cost and public out of pocket expenditure [2].

Beijing implemented the "medicines zero mark-up policy" in community health centers (CHCs) in 2007. The aims of the policy were to eradicate the afore-mentioned incentives, contain the medicines cost, and reduce the financial burden to the public [3]. Policy-makers selected 312 medicines based on the national essential medicines list. The CHCs were required to procure these medicines via government pooled tendering. Procurement and prescribing of "non zero mark-up medicines" was allowed and the CHCs were to dispense these medicines at the procurement price [4]. Government subsidized CHCs via three financial approaches: (1) in high socioeconomic districts, the government allocated fixed subsidies to CHCs and all expenditures of CHCs were secured according to defined standards. Even in areas of deficit, the government subsidy was still allocated to CHCs. No surplus was allowed to be retained by individual CHCs; (2) in the poorer districts, the government allocated income-linked subsidy, covering only staff and not other operational costs. The amount of subsidy was related to revenue generated; (3) for a few specific CHCs, the government did not bear their operational costs, but purchased services from them, i.e. compensated the mark-up loss from selling "zero mark-up medicines" based on their historical medicines sales. These CHCs were responsible for balancing expenditure against revenue and had the autonomy to retain any surplus [5, 6].

There are a number of studies which have analysed the changes of medicines cost for patients in specific facilities after implementation of this policy in Beijing [7-10]. Li's [7] regression analysis model showed that the government subsidy approach was a very important factor towards total medicines cost. We also conducted a study evaluating the effect of the "medicines zero mark-up policy" on both patients and providers. Changes in utilization of "zero mark-up medicines", medicine costs per visit, government subsidy, medicines and medical revenue of CHCs, and CHC staff salaries were measured before the introduction of the "medicines zero mark-up policy" in 2006 and then three years following implementation of the policy. Different subsidy approaches among CHCs were also compared. We divided the CHCs into 3 groups according to government subsidy approach and randomly selected 20% of the total number of CHCs adopting the same government subsidy approach in each district [11] (see Table 1.). All data were directly obtained from a health information database of the CHCs. Statistical analysis was undertaken using by SPSS® version 17.0.

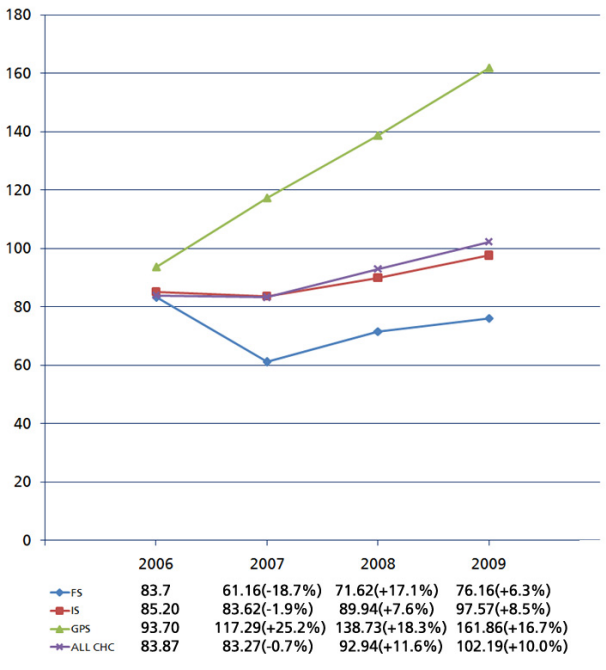
Table 1: CHC sampling scope and distribution in each district of Beijing

	Name of districts	Number of CHCs	Sample number	Fixed subsidy CHCs		Income-linked subsidy CHCs		Government purchase of services CHCs	
				Number of CHCs	Sample number	Number of CHCs	Sample number	Number of CHCs	Sample number
	Total	351	70	91	17	214	42	46	11
Fixed subsidy districts	Dongcheng	40	6	40	6	0	0	0	0
	Xuanwu	8	2	8	2	0	0	0	0
	Chongwen	5	2	5	2	0	0	0	0
	Yanqing	15	3	15	3	0	0	0	0
	Sub-total	**68**	**13**	**68**	**13**	**0**	**0**	**0**	**0**
Fixed subsidy & government purchase of services districts	Fangshan	24	4	23	4	0	0	1	0
	Sub-total	**24**	**4**	**23**	**4**	**0**	**0**	**1**	**0**
Income linked subsidy & government purchase of services districts purchase of services districts	Xicheng	7	3	0	0	6	3	1	0
	Chaoyang	42	6	0	0	34	4	8	2
	Fengtai	23	4	0	0	13	2	9	2
	Shijingshan	8	4	0	0	2	2	7	2
	Haidian	26	6	0	0	20	4	6	2
	Mentougou	11	4	0	0	9	2	2	1
	Tongzhou	30	4	0	0	19	3	11	2
	Shunyi	25	5	0	0	24	5	1	0
	Sub-total	**172**	**36**	**0**	**0**	**127**	**25**	**45**	**11**
Fixed subsidy districts	Changping	15	3	0	0	15	3	0	0
	Daxing	20	4	0	0	20	4	0	0
	Huairou	16	3	0	0	16	3	0	0
	Pinggu	18	4	0	0	18	4	0	0
	Miyun	18	3	0	0	18	3	0	0
	Sub-total	**87**	**17**	**0**	**0**	**87**	**17**	**0**	**0**

The results show that the proportion of "zero markup medicines" cost to total medicines cost per visit quickly increased in all CHCs in 2007, were maintained in 2008-9, and were achieved in 75.4%, 57.8%, and 52.6% in the fixed subsidy, income-linked subsidy and government purchase of services facilities respectively. CHCs with fixed subsidies demonstrate greater willingness to use "zero mark-up medicines".

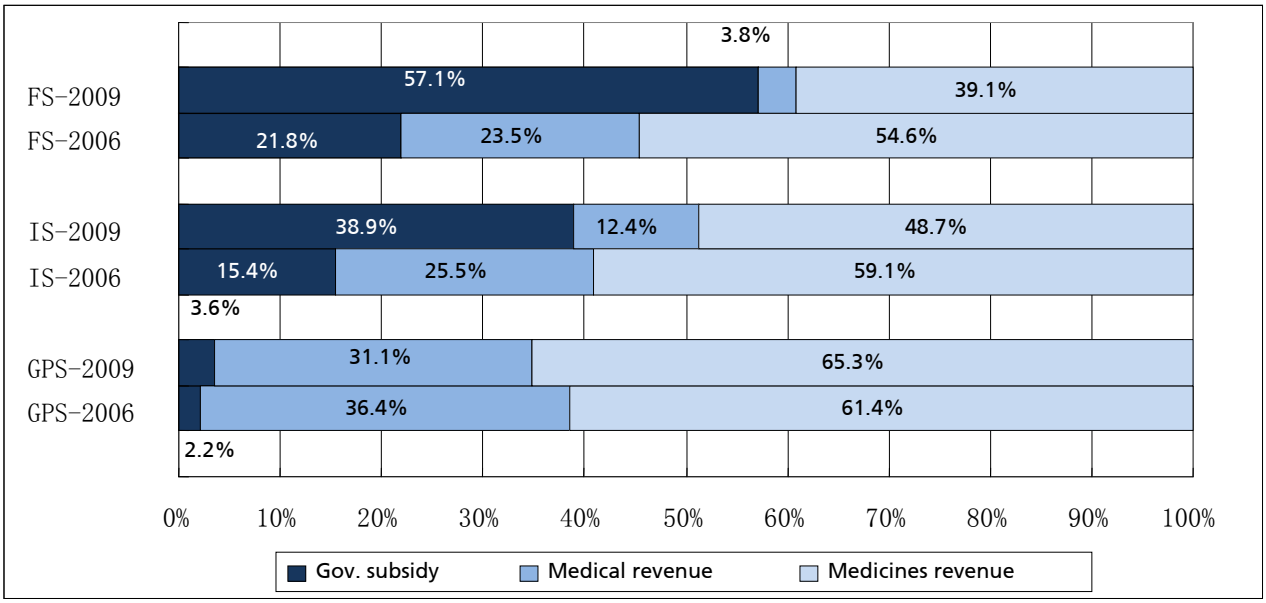
The primary data are not normally distributed and a natural logarithmic transformation was undertaken in-order to normalize the data. The following statistical tests were undertaken: (1) paired t-test for medicines cost per visit in both types of facilities in 2006 and 2007; (2) independent samples t-test for reduction of medicines cost per visit between 2006 and 2007 in both types of facilities. The results showed that there is a significant difference between the reductions in fixed and income-linked subsidy facilities (P=0.016, €=0.05, t test). The medicines cost per visit in government purchase of services facilities increased 25.2% in 2007, and kept growing during 2008-9, which is in line with the results of other studies conducted in recent years [7-10](Figure 1.).

Figure 1: Medicines cost per visit in 70 sample CHCs during 2006-9 CNY



The government purchase of services facilities generated relatively more medicines revenue and less medical revenue, while both medicines and medical revenues generated by the other two types of facility decrease (Figure 2.). The annual staff salary in all CHCs continued to rise during 2006-2009. Wang's study [9] showed the same increasing trend of CHC staff salary in Beijing in 2007-8. Facilities were government purchased services always had the lowest staff salary. Income-linked subsidy facilities consistently had the highest staff salary costs.

Figure 2: Proportion of government subsidy, medical & medicines revenue to the total income in 70 sample CHCs



Fixed subsidy facilities are more willing to adopt "zero mark-up medicines", which is probably due to the receipt of full financial support from the government and therefore they have reduced financial pressures. These CHCs have no autonomy to keep any surplus generated and so there is neither incentive for them to generate more revenue nor incentive to procure medicines outside the essential medicines list.

In the facilities where governments purchase their services budgets are not controlled by the government and so these CHCs have a strong incentive to generate revenue. These CHCs prefer "non zero mark-up medicines" in-order to generate greater medicines revenue. Income-linked subsidy facilities can potentially generate more revenue by requesting a greater level of government subsidy. Budget management may help to restrain such intentions, so these CHCs have moderate incentive to prescribe "non zero mark-up medicines". Such "incentive" and "absence of incentive" also affects other aspects of performance. Medicines costs are better contained however maintaining a level of enthusiasm for revenue generation is impacted on by fixed subsidy approaches. With the revenue generation incentive and relatively easing of control on medicines use, the government purchase of service facility would pursue the maximum of both quantity and unit price for service provided. On the one hand these CHCs try their best to attract more patients and provide more services, on the other these facilities would prescribe more medicines (either "zero mark-up medicines" or "non zero mark-up medicines") in-order to request greater government subsidy or to earn a higher level of more mark-up.

The result regarding levels of staffing salaries warrants consideration. It is assumed that with increased revenue the CHCs supported through government purchase of services should have higher salaries but this study suggests the contrary. It is possible that these CHCs did not disclose full income data so as not to affect future requests for subsidies from the government. This type of CHC is very likely to have un-official bonuses to stimulate and maintain enthusiasm for work. Salary scales in fixed subsidy facilities were significantly improved following the introduction of the "medicines zero mark-up policy" with the security of full government subsidy being in place.

The "medicines zero mark-up policy" does help in containing the rising trend in costs of medicines. The medicines cost per visit was significantly reduced one year post the policy implementation. Fixed subsidy approach was found to be more effective in reducing financial burden for patients.

There are several limitations of this study and the results need to be considered with respect to these, and further research undertaken. Data were collected from randomly sampled CHCs and factors such as facility scale and operation status were not considered. This may not fully reflect every specific aspects of the effect of policy. In responding to the inflated costs in 2008 and 2009, the study did not involve in-depth key informant interviews to explore the reasons behind this and whether it was provider driven or demand driven. The assumption is made that a more comprehensive and consistent medicines use regulation

is needed. No in-depth analysis of the contributors (changes of number of visits and quantity of medicines per prescription) to the differences in medicines and medical revenue generated by facilities was undertaken. Further, the study does not evaluate whether the quality of care provided by these facilities is affected by this policy and there is no understanding of the levels of satisfaction of the public and CHC staff. This is a rich area of future research and the current study provides a platform for doing more.

Authors' contribution

The conception and design of this evaluation study was contributed by the team led by WC. WC coordinated the process of data collection and analysis. JS contributed to the data interpretation, manuscript drafting, and critical revisions of the paper. YF and DF undertook the statistical analysis.. DF and XS contributed to data analysis and interpretation. JL significantly contributed to the data collection.

Conflict of interest statement

All authors declare that they have no conflict of interest.

Acknowledgment

We thank the Beijing Health Bureau for approving this study and supporting the field survey and data collection.

Funding source

World Health Organization (WHO)

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