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Economical access to antibiotics in an era of increasing resistance - a study from Lahore, Pakistan

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Samhällsfarmaci, React, VT 2010

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30 Högskolepoäng

Abstract:

Objective: Antibiotic resistance levels are alarmingly high, thus limiting treatment options for millions of people today. Increased resistance equals to failure of treatment and change in antibacterial regimens, and often to more expensive drugs. This study was conducted to examine the relation between antibiotic resistance and the additional economical burden on households in a low-to middle income country.

Method: Price comparison was made for 7 antibiotics used for four common infectious diseases normally treated in out-patient care. The price collection was carried out in Lahore, Pakistan a middle-to low income country. Median price for treatment with generic and innovator brand were calculated for 17 different treatment regimens.

Results: More than 38 million people, alone in Pakistan, cannot afford a whole dosage regime with amoxicillin for treatment of pneumonia. Moreover, a one-day treatment with ceftriaxone, azithromycin, cefixime for both shigella and gonorrhea are also not affordable for one fourth of Pakistan's population. A noteworthy price difference between innovator- and generic brands, for agents such as ceftriaxone, ciprofloxacin, and azithromycin were also observed.

Conclusion: At present antibiotic resistance will limit treatment for millions of people who cannot purchase antibacterial agents that are required for successful clinical outcomes. Additional economical burden on individuals caused by antibiotic resistance is worrying, and there is need for new incentives for combating antibiotic resistance.

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1 INTRODUCTION

Every year more than 11 million people die in major infectious disease many of whom derived from bacteria (WHO, 2005a). Infectious and parasitic diseases are the second leading cause of death in the world (Figure 1). The greatest burden of infectious disease is found in developing countries, where poor living conditions and unavailability of health care and treatment encourages the spread of these diseases (WHO, 2004a). Children are more prone to infectious diseases, and pneumonia, diarrhea and neonatal infections are the leading causes of death among children under the age of five (UNICEF & WHO, 2006). Infectious diseases also cause serious health problems in adults, such as decreasing productivity, infertility and death. Infections in the lower respiratory tract is the number one disease causing death in lower income countries, and accounts for 7.1 percent of all deaths in the world (Figure 1 and 2) (WHO, 2004a).

Many of these people could be cured if they received appropriate treatment such as antibiotics and basic health care services. Antibiotics have saved millions of lives over the past few decades. However, the misuse of these agents has led to a serious public health problem of today, antibiotic resistance (Laxminarayan & Malani, 2007)

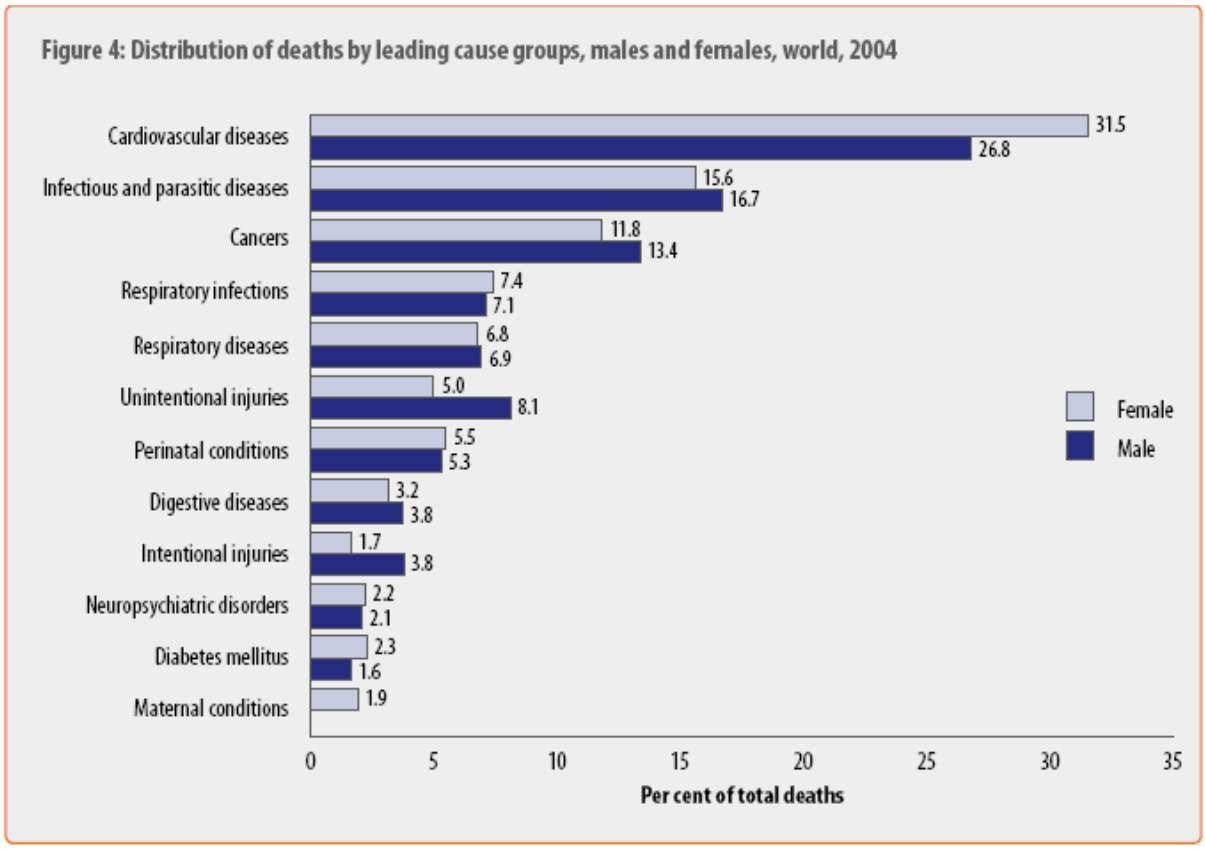

Figure 1: Figure from WHO report of global burden of disease **(**WHO, 2004).

	Disease or injury	Deaths (millions)	Per cent of total deaths
	Low-income countries[a]		
1	Lower respiratory infections	2.9	11.2
2	Ischaemic heart disease	2.5	9.4
3	Diarrhoeal diseases	1.8	6.9
4	HIV/AIDS	1.5	5.7
5	Cerebrovascular disease	1.5	5.6
6	COPD	0.9	3.6
7	Tuberculosis	0.9	3.5
8	Neonatal infections[b]	0.9	3.4
9	Malaria	0.9	3.3
10	Prematurity and low birth weight	0.8	3.2

Figure 2: Leading cause of death in low-income countries year 2004. (Low income countries = gross national income per capita, 825$ or less, in 2004) (WHO, 2004a)

1.1 ANTIBIOTIC RESISTANCE

1.1.1 Consequence of antibiotic resistance

The global problem with antibiotic resistance will continue to expand if action is not taken. Antibiotic resistance plays a crucial role for increased mortality and morbidity rates, as well as putting a considerable economical burden on patients and the society. Around 25 000 people die annually in the EU from multi-resistant bacteria, and more than 63 000 in the United States (US) (ECDC & EMEA, 2008; Laxminarayan & Malani, 2007). Mortality rates will increase, if delayed and ineffective treatments continue to be the result from antibiotic resistance (Elbasha, 2003; Roberts *et al.,* 2009). Along with this morbidity rates will also increase due to ineffective treatments. Treatment failures will consequently lead to, prolonged illness, reduced quality of life and add productivity losses to the society. Moreover, ineffective treatments that result in prolonged illness, lead to hospitalization, and need for additional laboratory tests, x-ray examinations, adding considerable economical burden on patients (Elbasha, 2003; Roberts *et al.,* 2009). Today there is little published on the economic burden that resistance contributes to in developing countries, however the economical burden for resistance is probably greater in the developing world since prevalence of resistant strains are higher in these countries (Okeke *et al.,* 2005).

Antibiotic resistance will lead us in to an era where more people will die in simple infectious disease, and surgery, transplantation will fail due to resistant bacteria's survival (ESC, 1998; WHO, 2005a). Without effective treatments and prevention of bacterial infections, we are rolling back important achievements of modern medicines such as major surgeries, organ transplantation and cancer therapy (Cars *et al.,* 2008).

1.1.2 Causes and risk factors for antibiotic resistance:

To understand antibiotic resistance, it is important to understand how antibacterial agents operate. The agents can either be bacteriostatic, inhibiting the growth of pathogen so the immune system can clear out the infection, or bactericidal, which will instead kill the pathogen. The agents can for example inhibit the cell wall synthesis, ribosome function, nuclec acid synthesis, folate metabolism and cell membrane function (Byarugaba, 2010).

However the bacteria have an ability to adapt and develop different mechanisms to survive the presence of antibacterial agents. These resistance mechanisms originates from genetic mutations and transfer genetic elements between species which can code for, (a) efflux, pumping out the agent out of the cell, (b) producing enzymes that degrade or inactivates the antibiotics, (c) receptor modification, thus inhibiting antibiotics to bind the receptor and induce its effect (Levy, 1998; Alanis, 2005). Resistance genes have been evolving with the environment long before human started to use antibiotic, and in absence of antibiotics, acquisition of antibiotic resistance mechanisms is often a disadvantage to the bacteria making it less virulent. However, some of the resistant bacteria will persist and be part of the normal microbiota. When the normal flora is exposed to antibiotics susceptible bacteria will be killed and replaced by suppressed resistant bacteria (Alanis, 2005;Elbasha, 2003). This phenomenon is referred to as selection of resistant bacteria and increases the risk for prolonged colonization with resistant bacteria, which can be further spread to other species (Levy 1998; Alanis, 2005). The undesirable effect on the microbial flora, such as eliminating sensitive bacteria that compete with the pathogenic one, can last up to two years from one course of antibiotics (Jernberg *et al.,* 2007). Patients treated with antibiotics are therefore more likely to carry bacteria with resistance genes, which can be further spread to other humans within a community, causing societal health issues (Elbasha, 2003; Levy, 1998). Moreover patients not completing a full course of antibiotics, will thus fail elimination of an infection completely, and encourage the survival and growth of resistant bacteria, making the infection more difficult to treat. In addition, suboptimal dosing, long duration of treatment and use of broad-spectrum antibiotics increases the risk for selection of resistant bacteria (Levy, 1998)

Several studies indicate that there is a relationship between use of antibiotic and development of antibiotic resistance. The relationship between antibiotic use and antibiotic resistance has been well described both on individual and societal level as well as carriage of resistant bacteria in general (Arason *et al.,* 1996; Nasrin *et al.,* 2002; Albrich, Monnet & Harbath; Taconelli *et al.,* 2007). The indiscriminate use of antibiotics in humans is at fault for rising resistance levels in pathogens such as *Streptococcus pneumonia, Neisseria gonnorhoeae* and *Staphylococcus aureus* along with other bacteria (Gorbach, 2001). In many developing countries the guidelines for antibacterial treatment are limited, and over-the-counter drug availability for antibiotics are high for self-medication, thus increasing the inappropriate use of these agents. Several studies support that antibiotics are easily purchased in pharmacies without any prescription, leading to excessive use of these agents (Llor & Cots, 2009; Plachouras *et al.,* 2010). Antibiotics are often prescribed empirically for all types of infections, both for bacterial and viral, further encouraging indiscriminate use of them (Seth, 2008). Self-diagnoses, and taking recommendations from a neighbor or handing leftover medicine to a family member or themselves, are all examples of inappropriate use of antibiotics, and further encouraging resistant strains to develop and exceed (Amabíle-Cuevas 2010; Levy, 1998). It is

estimated that about half of all antibiotic usage could be unnecessary or incorrect (wrong dose-, or bacterial drug) (WHO, 2005a; Amabíle-Cuevas 2010).

Along with use of antibiotics among humans, there is also an issue of inappropriate use of antibiotics in animals and agriculture. Bacteria carrying resistance genes, can be further transferred from animals to caretakers or through the food chain, thus contributing spread of resistance genes to the intestinal microflora of humans. Moreover these resistant genes will be spread to pathogenic bacteria and into new hosts causing emergence of resistant strains (Gorbach, 2001; Alanis, 2005). Also increased use of antibacterials in soap and disinfectants can promote the survival of resistant strains by killing susceptible bacteria, which compete with a resistant one (Levy, 1998).

Since bacteria can be transferred between humans, overcrowded areas and poor hygiene also encourages propagation of resistant bacteria (ESC, 1998). Today's globalized world includes increased international travelling, promoting a multidrug-resistant strain migrating from Spain to South Africa, the US and elsewhere, in a short period of time (WHO, 2000).

1.2 TRENDS IN ANTIBIOTIC RESISTANCE

Resistant bacteria are common in both in- and out-patient care. The development of antibiotic resistance has led to change in antibacterial therapy, thus shifted from older often more inexpensive agents to newer expensive ones, to ensure effective treatment (Foster 2010). A majority of infectious disease are cured in out-patient care, especially in developing countries. This master thesis is based on price comparison between antibacterial treatments, for four fictive patients with bacterial infections. These infectious diseases are at present common in low to middle income countries, and are often treated in non-institutional care, where medicines are purchased from out-of-pocket money (Okeke et al., 2009). The following diseases are included in this study; Pneumonia caused by S.pneumoniae, shigellosis, gonorrhea and a urinary tract infection caused by E.coli.

1.2.1 Streptococcus pneumoniae:

Pneumonia is a disease that kills over two million children each year, and is the most common cause of death among children under five. *S.pneumoniae* is one of the major pathogens causing pneumonia, which causes respiratory tract infections (UNICEF & WHO 2006). Penicillin has been the ultimate cure for pneumonia since the 1940's. However, failure of treatment with penicillin have increased, thus complicating treatment options with other β-lactams (Bartoloni & Gotuzzo, 2010).

Already in the late 1960s the first clinical case of decreased susceptibility to penicillin was documented. Resistance to tetracycline, erythromycin and chloramphenicol was also detected during the 1960s. Soon after this, in the 1970s multi resistant strains were discovered in South Africa (Jacobs *et al.,* 1978). Now days penicillin resistant in *S.pnemoniae* is widespread in the world which rises a global concern (Jacobs et al 2003; Song et al 1999). However there is an obvious geographical variation for trends of penicillin resistant strains, and the prevalence of these strains can increase remarkable over only a two years time (Jacobs et al 2003). According to a surveillance study in Asia, prevalence of penicillin resistance in some Asian countries was higher compared with countries from

Eastern Eurpoean countries (Song et al 1999). Together with this resistance to co-trimoxazole have also been reported worldwide (Bartoloni & Gotuzzo 2010; Jacobs et al 2003).

According to World Health Organization (WHO), Integrated Management of Childhood Illness (IMCI) guidelines, co-trimoxazole and amoxicillin are recommended antibiotics for treatment of pneumonia among children in developing countries (Grant *et al.,* 2009; Klugman, 2002; Schrag, Beall & Dowell, 2001). Co-trimoxazole may not be used as frequent in developed countries, but since it is an inexpensive agent it remains a choice for the management of pneumonia in developing countries (Klugman, 2002). If recommended dose of amoxicillin is not effective, a higher dose of this agent can be necessary to eradicate the infection (Grant *et al.,* 2009).

1.2.2 Shigella dysenteriae:

Shigella causes shigellosis, also known as acute bacillary dysentery. There are four species of *Shigella*, called *S.Boydii, S.sonnei, S. flexneri and S.dysentriae*. All of them can cause severe dysentery as well as high fever, abdominal cramps and rectal pain (Sur, Deen & Bhattacharya, 2004). *Shigella dysenteriae* type 1 (sd1) represents a particular threat because of the severity of disease and its epidemic potential (Niyogi 2005).

Transmission of the disease is through fecal-oral contact. It is therefore more widely spread in areas where substandard hygiene is present. Diarrhoeae is the second most common cause of death among infectious disease. Every year about 163 million people from developing countries suffer from shigellosis. Approximately 1.1 million people die annually in this disease (Niyogi 2005).

Treatment of shigellosis includes rehydration and antibiotic therapy. A shigella infection can last from two, up to ten days if treatment is not initiated. This can further lead to exacerbation of the infection, which consequently results in severe diarrhea, increased pathogen excretion and risk for disease transmission (Sack *et al.,* 2001). According to WHO, treatment should be in respect of what shigella strains circulates in the region and the local resistance patterns, since there is a considerable geographical variation in resistance strains (WHO, 2005b; Sack *et al.,* 2001).

Resistance to inexpensive commonly used antibiotics are alarmingly high for sd1. In the 1940's, all strains of shigella were susceptible to sulphonamides. Already in the late 1940´s sulphonamides were no longer effective. Increased levels of resistance made treatment with tetracycline ineffective in the late 1960s. Both Ampicillin and co-trimoxazole were considered to be appropriate treatment, until in the 1980s, when multi drug resistant strains of *S.dysenteriae* type 1 were documented (Sur, Deen & Bhattacharya, 2004; Sack et al 2001). In the earily 1980s sd1 showed susceptibility to nalidixic acid, however today WHO does not recommend treatment with nalidixic acid, due to the widespread resistance (WHO, 2005b; Sur, Deen & Bhattacharya, 2004). Recently a study including 98 *Shigella* isolates from eight countries in Asia, showed high resistance levels to co-trimoxazole followed by tetracyclines and ampicllin (Bartoloni & Gotuzzo, 2010). According to WHO guidelines, co-trimoxazole, chloramphenicol, tetracycline and ampicillin are no longer recommended treatment options due to the widespread resistance (WHO, 2005b).

WHO and other authorities do however recommend ciprofloxacin as firs-line treatment (Niyogi, 2005; Khan *et al.,* 2009; WHO, 2005b). Other agents that are considered to be effective are azithromycin, mecillinam and ceftriaxone (Niyogi, 2005). However, cases of lower susceptibility to

ciprofloxacin in sd1, and resistance to other various floroquinolones have been reported from India (Pazhani *et al.,* 2004). Indiscriminate use of ciprofloxacin can further increase resistance levels, as it has for the previous various agents used for shigellosis. Ceftriaxone which also is a recommendation from WHO, is an expensive option that has to be administered parenteral. In developing countries many people are unable to treat themselves with this agent (Sur, Deen & Bhattacharya, 2004). Emergence of resistance to ceftriaxone has also been reported due to shigella strains that produce extended –spectrum β-lactamase (ESBL), which is of major concerns (Vasilev *et al.,* 2006). Moreover, it is considered that cefixime and ceftriaxone are safer choices of medicines for children, than fluoroquinolones, that are feared to cause cartilage toxicity in children (Niyogi 2005).

1.2.3 Neisseria gonorrhoeae

Gonorrhea is a sexually transmitted disease, and if treatment is not initiated it can result in infertility, chronic pelvic pain, ectopic pregnancy and increased risk for HIV infection. The higher levels of antibiotic resistance, has led to serious public health concerns regarding the treatment to gonorrhea. Moreover, there is another problem with gonorrhea infection, that it can be asymptomatic. In developing countries where regular health controls are not affordable for a large group of people, treatment will not be initiated in time, hence leading the infection to spread in the society and resulting in reproductive consequences (Workowski , Berman & Douglas, 2008).

In 1936 when sulfonamides were first introduced, they made use for gonoccal treatment. However it did not take long until resistance emerged to sulfonamides and pencillin became the recommended treatment for coming years, until the pencillinase producing *N.gonorrhoeae* showed resistance (PPNG) (Workowski, Berman & Douglas, 2008; Tapsall, 2009). In the late 1980s pencillin resistance was widespread and was not an effective treatment for gonorrhea. Due to emergence of pencillin resistance, ceftriaxone became a effective option for gonorrhea, along with ciprofloxacin as an alternative treatment. In the 1980s tetracycline lost its effectiveness, and was not a viable treatment option anymore. Both Spectinomycin and azithromycin are antibacterial agents that can still be used for gonorrhea in some areas, however resistance has emerged because of the over use of these agents (Tapsall 2009; de Andrade *et al.,* 2010). Only a few numbers of spectinomycin resistance was documented in WHO surveillance program of the western pacific region. Therefore both azithromycin and spectinomycin could still be of choice for treatment of gonorrhea, but special care needs to be taken to monitor resistance development of these broad-spectrum antibiotics (Workowski, Berman & Douglas, 2008 ; WHO, 2008).

In the 1990s both oral regimens with fluoroquinolones (ciprofloxacin, ofloxacin) and cephalosporins (cefixime), were of recommendations (Workowski, Berman & Douglas 2008). However, resistance to quinolones increased remarkably, especially in Asia and in the pacific Islands. According to a surveilleance carried out by WHO, result suggested high prevalence of quinolone resistance in east Asia. (WHO, 2008). In the 1990's the incidence of ciprofloxacin resistant gonorrhea (CRG) increased worldwide (Plitt *et al.,* 2009). In Hong Kong the prevalence of CRG had increased from 18 to 73 percent in a period of six years (Bala, Jain & Ray, 2008). Cefixime is the most widely recommended third-generation cephalosporin. Other oral cephalosporins that also could be considered for treatment are ceftibuten, cefozopran, cefdinir and cefpodoxime(Tapsall, 2009; Tapsall, 2006). However, first clinical failure in patients treated with oral cephalosporin were reported from Japan

in 2001(Akasaka *et al.,* 2001). Today treatment with oral cefixime is of no recommendations in Japan due to a number of clinical failures (Tapsall 2009).

Today therapy with injection of ceftriaxone is recommended in many places. According to a study in Russia, ceftriaxone should be first-line treatment for gonorrhea on the basis that their study showed no failure of treatment (Kubanova *et al.,* 2008). However, reduced susceptibility towards ceftriaxone has already been detected, for examples in India (Ray *et al.,* 2005).

1.2.4 Escherichia coli

Escherichia coli is the pathogen responsible for 80 percent of all urinary tract infections (UTI) (Perfetto *et al.,* 2004). It is a common disease worldwide among out-patients. Many out-patients who can access antibiotics over-the-counter, treat themselves, which has resolved in misuse in various antibacterial agents for UTI. Subsequently emergence of resistance in various *E.coli* strains have occurred (Bericon *et al.,* 2009).

Co-trimoxazole has for a long time been first-line therapy for uncomplicated urinary tract infection (UTI) (Warren *et al.,* 1999). However, co-trimoxazole along with other first-line agents such as, ampicillin are not longer effective in various countries due to resistance. This result can be observed from Figure 3 below. Alternatively, fluoroquinoles could be of choice in areas where high rates of co-trimoxazole resistance are observed (Warren *et al.,* 1999). Originally fluoroquinolones were intended for complicated UTI, however due to overuse of these agents for non-complicated UTI, it may not be as effective for complicated UTI anymore (von Baum & Marre 2005; Warren et al 1999). Resistance in uropathogens towards fluoroquinolones among outpatients, have been observed in Spain and Slovenia. This can be explained by over-the-counter availability of these agents (Cizman et al. 2001).

In Kenya, fluoroquinolones such as ciprofloxacin is the most common agent prescribed for UTI. Resistance to this group of drugs will limit treatment options for UTI, specially in poor areas where purchase of expensive drugs is not a option (Kairuki *et al.,* 2007).

Urinary isolates in India, showed high resistance to ampicillin, followed by co-trimoxazole, fluoroquinolones such as ciprofloxacin and norfloxacin. However nitrofurantoin showed high rates of effectiveness. Therefore they considered nitrofurantoin as an empirical treatment for uncomplicated UTI (Biswas *et al.,* 2006). Cephalosporins are also used for treatment of uncomplicated UTI, however these agent are associated with more adverse effects than co-trimoxazole, for example (Miller & Tang, 2004).

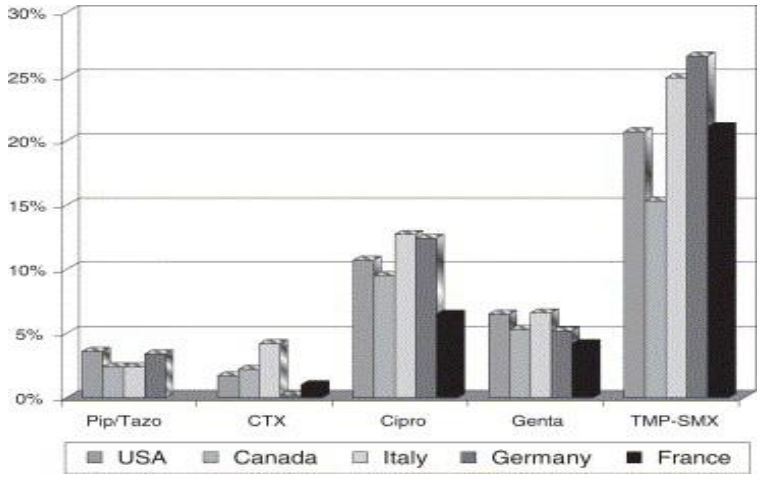

Figure3: *E.*coli isolates from 2000-2002 in USA, Canada, Italy, Germany and France, show prevalence of antibiotic resistance. (Figure constructed by von Baum & Marre with data based on Jones et al 2004). **Pip/Tazo**= piperacillin/tazobactam; **CTX**= ceftriaxone; **Cipro**= ciprofloxacin; **Genta**= gentamicin; **TMP-SMX**= trimethoprim-sulfamethoxazole (co-trimoxazole).

As previously mentioned in the section with *shigella*, concerns for strains producing extended spectrum B-lactamase remain for the future (Kairuki *et al.,* 2007). Treatment with carbapenemes are the only recommended agents left for ESBL producing strains (von Baum & Marre, 2005). Agents like cefotaxime, ceftriaxone, ceftazidime and cefepime are of great importance for treatment of severe infections, and ESBL producing pathogens will limit treatment of these agents, and therefore this is of major concerns (Kairuki *et al.,* 2007).

1.3 ACCESS TO EFFECTIVE ANTIBIOTICS

The growing problem of antibiotic resistance is limiting effective treatment for bacterial infections, thus challenging selection of appropriate and effective antibiotics at affordable prices (WHO, 2004b).

This problem is of major concern for developing countries with poor health care systems and large poor populations. Due to the increased resistance levels, old inexpensive antibiotics are no longer effective, and have to be replaced by more expensive ones, putting additional burden on individuals and health care systems. Lack of access to medicine reflects on problems in the health care system, which includes rational selection of medicines at affordable prices, along with sustainable financing and reliable supply systems (see Figure 4)(WHO, 2004b).

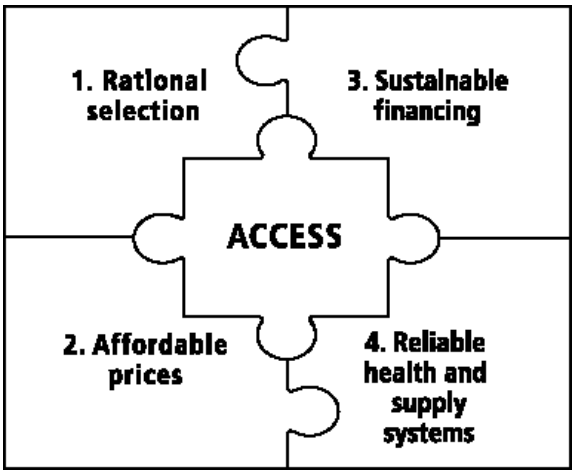

Figure 4: This picture explains the four keys for access of essential medicines. (WHO, 2004b).

1.3.1 Rational selection and use of antibiotics

Rational selection means choosing cost-effective and safe medicines based on the country's health situation. Many developing countries lack proper monitoring of local resistance levels, making it hard to design an up to date treatment guidelines. Along with this there is lack of surveillance on resistance patterns and reliable laboratories processing existing data (Okeke, 2005; Seth, 2008).

Rational use refers to the same obstacles as for rational selection, meaning only using antibiotics if necessary and avoiding use for viral infections and infections that are self-limited (Robert et al 2009; WHO, 2004b). Rational use of antibiotics would decrease the pace of resistance development and costs for health care systems and individuals (Levy 1998; Seth 2008). If appropriate treatment is not initiated, there will be a cost of wrong treatment and an additional cost for a new appropriate treatment. Susceptibility tests are considered to be cost-effective since the cost of an additional drug will not be necessary, and they will increase the likelihood for a successful treatment (Foster, 2010). A study in Thailand found that only 9 percent of 307 patients were in need of antibiotics, whereas all of the patients were administered antibiotics (Aswapokee, Vaithayapichet & Heller, 1990). In hospitals where susceptibility tests are not taken after a failure of treatment, or where resistant strains are not being monitored, the decrease of a drug's effectiveness will not be perceived until much later. During this time the infection will exacerbate, and resistance will be spread more widely in the community (Foster, 2010).

1.3.2 Affordable prices

Medicine prices play a crucial part in access to antibiotics. Since a large number of people in developing countries are economically challenged, many of them cannot afford required treatment. Ironically there is a dilemma in poor and developing nations, where antibiotics are easily obtained without prescription contributing to increased prevalence of resistance, and simultaneously there is an ongoing problem with people not accessing these agents when they are in need of them (Sosa *et al.,* 2009). One explanation is that, health expenditures like medicines have to be covered by out-of-pocket money, which includes 50-90 percent of the people in developing countries, making medicines unaffordable (WHO, 2004b). About 25-70 percent of the income is spent on health-care expenditure in developing countries, in contrast to 10 percent in developed countries (HAI, 2008).

Moreover, people purchase the amount of drug they can afford and not what they need to be cured for. Consequently this leads to untreated patients as well as it plays a crucial role for emergence of resistant strains (HAI, 2004; Sosa *et al.,* 2009).

According to the World Health Organization (WHO) one third of the population of today cannot afford the required medicine that they need (Foster2010). Resistance can increase cost with a 100-fold when first-line antibiotics fail in treatment, thus making these agent unaffordable to a large group of people (WHO 2005a). In a province of South Africa a full dosage regime for multidrug-resistant tuberculosis could cost up to US$4300 compared with US$35 for susceptible tuberculosis strains (Hensher 1999). Another example is when treatment with amoxicillin, (for pneumonia) fail. A combination with clavulanic acid can be necessary in these cases, which is far more expensive than treatment alone with amoxicillin. It should also be mentioned that, in many cases a higher dose and a longer time of antibacterial therapy can be necessary for effective treatment, thus resulting in more expensive treatments. This is only one of many examples where therapy for common infections has become much more limited and expensive (Foster 2010).

Furthermore, studies have shown that affordability is also dependent on whether the drug is an innovator brand or a cheaper generic brand. This factor, has been supported by several reports carried out from Health Action International (Cameron *et al.,* 2009; Babar et al 2007).

1.3.3 Sustainable financing and reliable health and supply system

Reliable health systems and sustainable financing are two major factors that play a crucial role for availability of drugs. Each government should be responsible to control and demand that each pharmacy keep essential medicines in stock (essential medicines according to WHO model list of 2009) so they can be available for everyone (Cameron *et al.,* 2009; WHO 2009). It is also essential that governments can assure reliable quality of medicines at affordable prices (WHO 2004b). In many developing countries there is no appropriate funding from the government to supply the required amount of drugs to the public sector, which is of great concerns (Cameron et al. 2009). Along with this there is an issue of supplying counterfeit antibiotics, which contain none, not enough or a different active substance. Thereby leading to “under-treatment”, thus promoting emergence of resistance (Newton, 2006; ESC, 1998).

In a region of Ghana it was found that ceftriaxone and ciprofloxacin were not available in hospitals or in private sectors. Both of these drugs are recommended treatment options for pelvic inflammatory disease as well as other major infectious diseases (Foster, 2010). The lack of interest in maintaining necessary medicines in stock is also a problem that plays a key role for the unavailability of drugs. This ultimately makes patients buy medicines from the private sector, where there is a distinct difference in pricing compared to the public sector, which unable poor people in affording them (Cameron *et al.,* 2009). A research carried out in Malaysia found that the retail prices of drugs in the private sector had high mark-ups. The innovator brand could be up to 16 times more expensive compared to the international reference prices (average prices offered to developing countries and are not for profit). The availability of generics was poor in the public sector. The researchers also found that dispensing doctors many times mark-up prices for cheap generics to make profit. Since

patients rely on the physicians' recommendations, they can recommend expensive agents to make profit (Babar *et al.,* 2007).

1.4 BACKGROUND OF PAKISTAN

Pakistan is considered as a lower middle income country with GNI around 980$ and a population of 174 million people (World Bank, 2008; CIA, 2009). In Pakistan there is an ongoing problem with excessive and inappropriate use of antibiotics, but in parallel access to effective antibiotics is limited to a large part of the population (HAI 2004; Zaidi et al 2009; Sohail & Sultana, 1998). Antibiotics can be purchased over-the-counter, thus contributing to inappropriate use of these agents in this country. Unfortunately there is at present no routine surveillance for antibacterial resistance monitoring resistance prevalence rates. However, resistance in *S.pneumoniae* and *Shigella* isolates are documented, even if the prevalence rate is unknown (Straus *et al.,* 1998; Sohail & Sultana, 1998). A change in susceptibility to first-line antibiotics for UTI have also been observed in a prospective study carried out in Karachi (Farooqi *et al.,* 2000).

Health insurance do not cover medicine costs in Pakistan, therefore almost all medicine purchase is out-of-pocket money. About 22.3 percent of the population lives below the poverty line (i.e earning less than 944Rs/month, 1 Swedish krona (SKR) = 11 Pakistani Rupee (PRs), 1USD = 85 PRs in May 2010) which means that treatment with essential medicines would not be affordable for a large group of people especially medicines from the private sector (UNDP, 2008; HAI, 2004; www.coinmill.com, 2010). Innovator brands are more expensive than equivalent generics. Some medicines can be up to seven times more expensive. Along with high mark-ups, there is also a problem with low availability of essential medicines in the public sector (HAI, 2004). Medicine prices are regulated by the government and the National Drug Policy promotes procurements of essential drugs according to the National Essential Drug list. However it is up to each provincial government within the country, to follow the procurements of essential medicines which have been shown to have poor adherence to (HAI 2004).

2 OBJECTIVE

The overall aim of this study was to understand how change of therapy followed by resistance development, affects treatment affordability for resource-poor populations paying for drugs directly out-of pocket.

Specific objective were to:

- Measure the prices patients pay for commonly used antibiotics
- Compare treatment cost for patients in regard to different shift in resistance
- Estimate the affordability for each created scenario in regard to treatment with innovator or generic brand

3 METHOD

3.1 DEVELOPMENT OF FICTIVE PATIENTS

Four fictive patient groups were created, all with common bacterial infections in low and middle-income countries, normally treated in non-institutional care. The four patient groups included; a child infected with *streptococcus pneumonieae,* causing acute respiratory infection; a child infected with *Shigella dysenteriae*; an adult woman with gonorrhea caused by *Neisseria gonorrhoeae*, and a patient infected with *Escherichia coli,* causing uncomplicated urinary tract infection. Each case in table 1, includes a gradually increasing resistance scenario, along with appropriate antibiotic treatment for each scenario. It should be noted that these treatment alternatives do not reflect therapy options in clinical care, they were chosen on the basis to illustrate how the cost varies for different antibiotic treatment due to different shift in resistance.

Treatment alternatives were based on scientific articles, from PubMed (www.pubmed.gov) using key words such as “antibiotic resistance”; “child *pneumonieae”; “*g*onorrhoeae* resistance”; “antimicrobial resistance in *Shigella*”; “ resistance in *E.coli*”; “treatment of *E.coli*”. Additional information was also provided from references from first found articles and given in the book “Antimicrobial Resistance in Developing Countries” (Sosa and colleagues). The treatment list for different scenarios seen in Table 1, was finalized after inputs and approvals by three experts from ReAct’s scientific network.

Table 1: Therapy options dependent on different shifts in resistance.

	Scenario 1 Baseline-treatment for non-resistant strain	**Scenario 2** Emergence of resistance to treatment in scenario 1	**Scenario 3** Increased resistance to treatment mentioned in scenario 2	**Scenario 4** Alternative treatment option when treatment in scenario 2 fails	**Scenario 5** Next possible option when treatment for scenario 1, 2, 3 and 4 fails
***S.pneumoniae*:**	**Co-trimoxazole:** 8mg/kg per day divided in two doses. 2-3 days (**Grant et al 2009).**	**Amoxicillin:** 50mg/kg divided in two doses for 3-5 days (**Grant. et al 2009).**	**Amoxicillin in higher dose**: 80-90mg/kg per (**Grant., et al 2009**).		
***Shigella*:**	**Co-trimoxazole**: 25 mg/kg Sulfamethoxazole 5 mg/kg trimethoprim for 5 days (**Bhattacharya & Sur, 2003; Ewall & Jonsson, 1984; Martin et al 2000)**	**Ciprofloxacin:** 20-30 mg/kg 2 times a day for 3 days (**Gendrel & Cohen, 2008; WHO, 2005b)**	**Azithromycin:** 12mg/kg for first day. Then 6 mg/kg for next 2-4 days **(Gendrel & Cohen, 2008) ; Basualdo & Arbo, 2003)**	**Cefixime:** 8mg/kg/day for 5 days **(Martin *et al.,* 2000; Basualdo & Arbo, 2003)**	**Ceftrioxane:** 50- 100mg/kg/day for two-five days **(WHO, 2005b)**
***N.gonorrhoeae*:**	**Amoxicillin :** 3g as one dose **(Kraus, Reynolds & Rolfs, 1988)**	**Ciprofloxacin:** 500 mg one dose **(Echols et al 1994)**	**Azithromycin:** 1 g as one dose **(Broek *et al.,* 2010).**	**Cefixime:** 400 mg as one dose **(Broek *et al.,* 2010; CDC, 2007)**	**Ceftriaxone**: 250 mg as one dose (**Broek *et al.,* 2010)**
***E.coli*:**	**Co-trimoxazole**: 400mg + 80mg, 1 tablet twice/day. Total 3 days. **(Perfetto *et al.,* 2004; Warren e al, 1999)**	**Ciprofloxacin:** 500 mg twice a day for 3 days (**Warren *et al.,* 1999; Broek *et al.,* 2010)**		**Cephalexin:** 500 mg 4 times/day for five days **(Miller & Tang, 2004)**	**Ceftriaxone:** 1 g vial injection for 5 days **(Le & Miller, 2001).**

3.2 DATA COLLECTION

3.2.1 From Pakistan

Survey area: Retail prices for antibiotics were collected from six pharmacies in the second largest city of Pakistan, Lahore with a population of more than 5 million people (figures based on 1998) (www.statpak.govpk). The survey was carried out between 15th-20th march 2010, in three public and three private pharmacies in different neighborhoods in Lahore. The selection of pharmacies were determined to capture population from different socioeconomic backgrounds, to observe if the price varied depending on what type of pharmacy (private, public, chain) the data was collected from (appendix 1).

Figure 6. Map of Pakistan. The red marked area is Lahore, where all data was collected from.(CIA,2010)

3.2.2 Data collection:

Retail prices for seven different antibiotics were collected at each pharmacy, A structured questionnaire was developed together with written instructions to guide data collection.

The questionnaire and guidelines were simplified and developed from a survey manual, which Health Action International (HAI) and WHO has used for sampling of medicine prices (HAI 2008). The price collection was carried out by Sharmeen Ziarukh, a graduate medical Dr from Karachi. Instructions for this survey were e-mailed, and further details were given over phone to clarify instructions for collecting data (Appendix III). The data collector also received a letter of endorsement explaining the objectives for this study, as well explaining confidentiality concerns, as a support if she would be questioned by pharmacists (appendix II). Contact information was also supplied in the letter for any concerns or questions (appendix II.)

The collection of medicine prices was carried out the same way at each facility to ensure reliability for collected data. First information regarding the pharmacy was reported, such as if it was a public or a private pharmacy and if it was a recognized chain pharmacy. From each facility, cost for lowest priced drug, package size, if it was innovator- or generic brand, availability of drug, was documented.

It was decided that if the pharmacist would refuse to supply any information, visit to an additional pharmacy would be included. However this was not necessary since all of the pharmacists agreed to supply the information that was needed.

3.2.3 From Databases

Prices for seven antibiotics were collected from the Management Sciences for Health (MSH) database called ”International Drug Price Indicator Guides”. Center for Pharmaceutical Management of Management Sciences for Health is a nonprofit organization and maintains the prices in this database. MSH collaborates with WHO and the medicines in the database are based on the List of

Essential Medicines (EML), suggested by WHO. The price database is supported by the UK Department for International Development (DFID) and the Medicines Transparency Alliance (MeTA). Prices in this database are provided from nonprofit drug suppliers along with commercial procurement agencies and from government- and international development agencies. The price list of medicines found in MSH will be used as a reference list to compare retail prices for medicines, purchased from Pakistan (MSH, 2009).

3.3 DATA ANALYSIS

Data from the questionnaire were entered into Microsoft Excel spreadsheet to calculate price differences and affordability. Any outstanding data was double-checked with the local data collector. Treatment costs were calculated both for a full course and for one-day supply from treatment options mentioned above in Table 1. The calculations were based on the median price values for innovator brand and equivalent generics. Median price for all antibiotics were also calculated. Affordability was measured according to HAI methodology, which states that if more than one days wage is spent on medicines, it is considered unaffordable. In this study affordability was based both on an unskilled workers minimum wage (200 Rs/day) and for those who live below the poverty-line (i.e. earning less than 31,5 RS per day)(UNDP, 2008; The cassette of Pakistan, 2008)

4. RESULTS

In Table 2 the prices and characteristics of six pharmacies are summarized. Availability of all medicines were high, in all pharmacies visited. However, the recommended strength, specified in the protocol, was not found at all pharmacies. Therefore the strength closest to the specified one was documented. The table also provides information regarding what category of costumers that visit the pharmacies. All medicines could be purchased in individual strips/capsules/vials, however a whole bottle had to be purchased for medicines in suspension. Cheapest available drug could be a generic or innovator brand.

4.1 ANTIBIOTIC RETAIL PRICES:

The cost for the same cheapest available drug varied between the pharmacies. The price for cheapest generic of the same drug varied, in contrast to innovator brand which showed no price variation between different pharmacies. Innovator brands were overall more expensive than other cheaper generics, in exception of cefixime's innovator brand, which consists of a stronger strength, making the price per mg cheaper than for generic brands of cefixime.

There was no considerable price variation between innovator brand and generics for amoxicillin. However the price was 4 fold more expensive for innovator brand than cheapest generic, for 1g vial injection with ceftriaxone. There was a 5 fold price difference for 500 mg ciprofloxacin, and 500 mg Cephalexin showed a difference of 12 fold between cheapest generic and innovator brand.

Moreover there was no obvious connection between type of pharmacy and prices. Cheapest alternative of the same drug, could be from a private or a public pharmacy. In one public pharmacy, primarily serving people who are economically challenged, only supplied expensive innovator brands. At their defense, doctors only prescribed innovator brands, and they were the only medicines they supplied to the patients. It was not clear whether they had equivalent cheaper generics.

Table 2. Medicines retail prices and dosage strength per antibiotic from six pharmacies. ***= price for innovator brand**

PHARMACY		1	2	3	4	5	6
PUBLIC/PRIVATE		Private	Private	Public	Private	Public	Public
ACCESSIBLE TO		Middle and upper class	Middle and upper class	Everyone	Everyone	Everyone	Everyone
	MEDIAN PRICE						
Amoxicillin 500 mg	**7,49**	7,40	7,5*	7,49*	7,49*	7,49*	7,50*
Amoxicillin 50mg/ml	**0,811**	0,81	0,81*	0,81*	0,85*	0,81*	0,88*
Cotrimox 400+80 mg	**1,4**	1,40	1,40	1,40	1,40	5,60	1,40
Cotrimox 40+ 8 mg /ml	**0,42**	0,42	0,42	0,42	0,60	0,42	0,42
Ceftriaxone 250 mg	**65**	141,40*	58,00	65,00	65,00	141,40*	58,00
Ceftriaxone 1 g	**200**	477,68*	200,00	200,00	200,00	477,68*	110,00
Cephalexin 500 mg	**14,42**	14,43*		1,20	12,42	14,43*	14,42*
Cephalexin 250 mg			7,375*				
Cefixime 100mg / 5 ml	**4,45**	4,07	4,83	4,00	9,53*	9,53*	4,00
Cefixime 200 mg	**27,25**	27,50	27,50	27,00	27,50		23,00
Cefixime 400 mg						51,20*	
Ciprofloxacin 500 mg	**28,05**	7,50	28,10	19,50	28,10	50,40*	28,00
Ciprofloxacin 125mg/5 ml		1,42			1,08		
Ciprofloxacin 250mg/5ml				2,67			
Ciprofloxacin 100mg/5ml							1,67
Azithromycin 500 mg	**33,167**	45,83*		25,50	18,33	45,83*	
Azithromycin 250 mg			33,17*				
Azithromycin 200mg/ 5ml	**12,9335**	14,87*		11,00	7,67	14,87*	11,00

Prices from MSH database are provided in appendix VI . The prices from MSH database can be used as price reference, to observe if the medicine prices in the pharmacies reflect the prices in MSH database. Among the seven antibiotics that were documented, co-trimoxazole was the cheapest one according to MSH database and the pharmacies (Table 3). However MSH's prices for the remaining antibiotics do not reflect retail prices found in the 6 pharmacies. Ciprofloxacin was the third most expensive antibiotic found in the pharmacies (median price), in contrast of being the second cheapest antibiotic according to MSH database.

Table 3: Medicine organized from most expensive to the cheapest (on the bottom), for median retail prices and prices provided from MSH database.

Median retail price	Median price, MSH
Ceftriaxone 1 g	Ceftriaxone 250 mg
Ceftriaxone 250 mg	Azitromycin 500mg
Azitromycin 500mg	Ceftriaxone 1 g
Ciprofloxacin 500 mg	Cephalexin 500 mg
Cefixime 200 mg	Cefixime 200 mg
Cephalexin 500 mg	Amoxicillin 500 mg
Amoxicillin 500 mg	Ciprofloxacin 500 mg
Cotrimox 400+80 mg	Cotrimox 400+80 mg

4.2 COMPARING TREATMENT COSTS AND AFFORDABILITY

In figure 7 to 10, median cost for generics and innovator brand are calculated for each created scenario. This includes cost for one-day treatment and for a full dosage regime. Cost calculations for the different scenarios from each pharmacy can be seen in appendix V.

There was a considerable cost variation for the four different diseases. Treatment with innovator brand was substantially more expensive than with generics. To measure affordability two cut off lines were made. The black cut off line represents 22.3 percent that lives below the poverty line in Pakistan, earning less than 31,5 Rs/ day. The other grey line illustrates an unskilled workers minimum wage per day (in Pakistan, 200Rs).

Gonorrhea: There is a 6 fold difference between the cheapest (amoxicillin) and the most expensive (ceftriaxone) treatment option with innovator brand (seen in figure 7). Corresponding price difference with generic only varied up to 3 times. A patient living below the poverty-line, will only afford a whole course of treatment with a cheap generic of amoxicillin and ciprofloxacin.

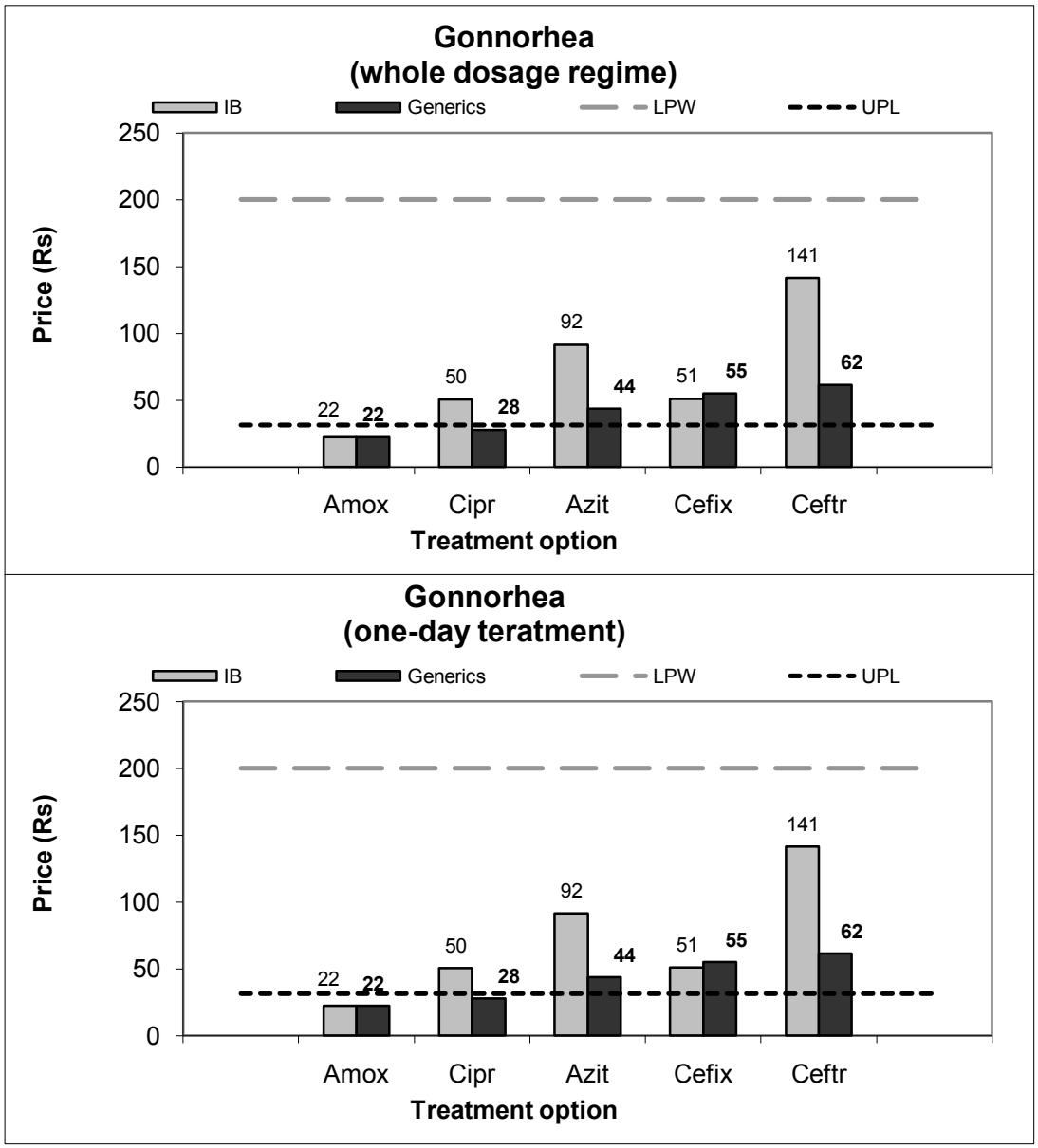

Figure 7: Cost variation with antibiotics for a whole dosage regime and cost for one day treatment, for gonnorrhea. The antibiotics in the figure reflect treatment options from table 1. **Amox=** amoxicillin; **Cipro = c**iprofloxacin**; Azit =** azitromycin**; Cefix = c**efixime **; Ceftr =** ceftriaxone. **IB =** inoovator brand**; LPW =** lowest paid worker (200/day Rs)**; UPL =** under poverty line (31,5/day). **Price=** Pakistani rupee

Shigella: An unskilled worker cannot afford one-day treatment with the innovator brand of ceftriaxone (for treatment of shigella, Figure 8). People living below the poverty line only afford a whole course of treatment with co-trimoxazole. Moreover, they can only afford one-day treatment with cheap generics of ciprofloxacin and cefixime. There is a 9 times price difference for one day treatment, with innovator brand of ciprofloxacin (the cheapest treatment of an innovator brand) and ceftriaxone (most expensive treatment of an innovator brand). The same medicines with their respective generics, show instead a 7 times price difference. A one-day treatment can be 47 times more expensive with a generic of ceftriaxone in comparison with one day treatment with co-trimoxazole. Similarly there is a 113 fold difference between one day treatment with co-trimoxazole and innovator brand of ceftriaxone. According to Figure 8, innovator brand can cost twice as much compared to cheap generics, this applies for both ceftriaxone and cefixime.

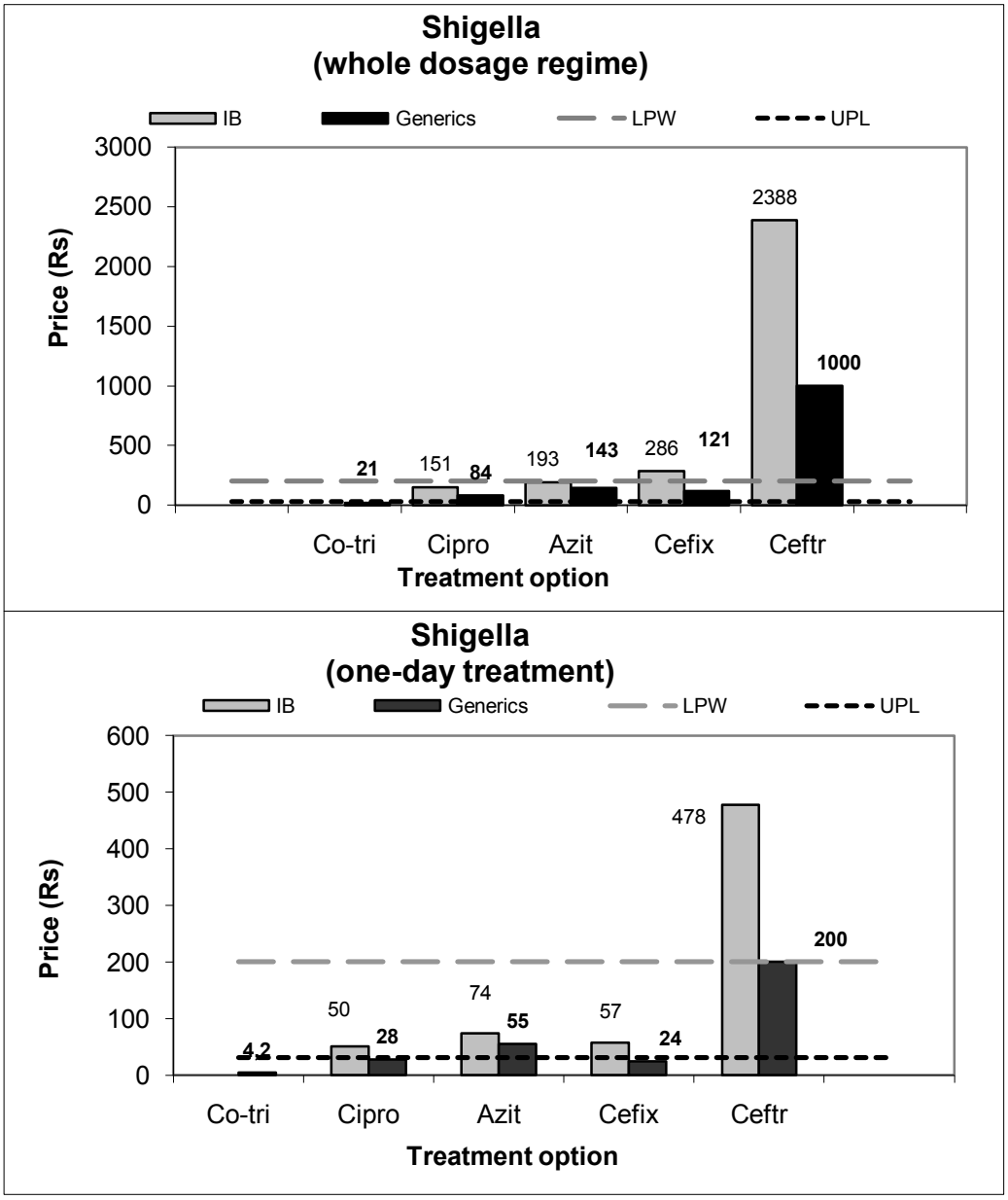

Figure 8: : Cost variation with antibiotics for a whole dosage regime and cost for one day treatment, for shigella. The antibiotics in the figure reflect treatment options from table 1. **Co-tri**= cotrimoxazole; **Cipro = c**iprofloxacin**; Azit =** azihtromycin**; Cefix = c**efixime **; Ceftr =** ceftriaxone. **IB =** innovator brand**; LPW =** lowest paid worker (200/day Rs)**; UPL =** under poverty line. **Price=** Pakistani rupee

***Pneumonia**:* According to figure 9, the majority of people in Pakistan can afford a one day treatment of both amoxicillin and co-trimoxazole. However, living under the poverty-line makes a whole dosage regime with amoxicillin unaffordable. No substantial difference is seen in cost between innovator brand and generics.

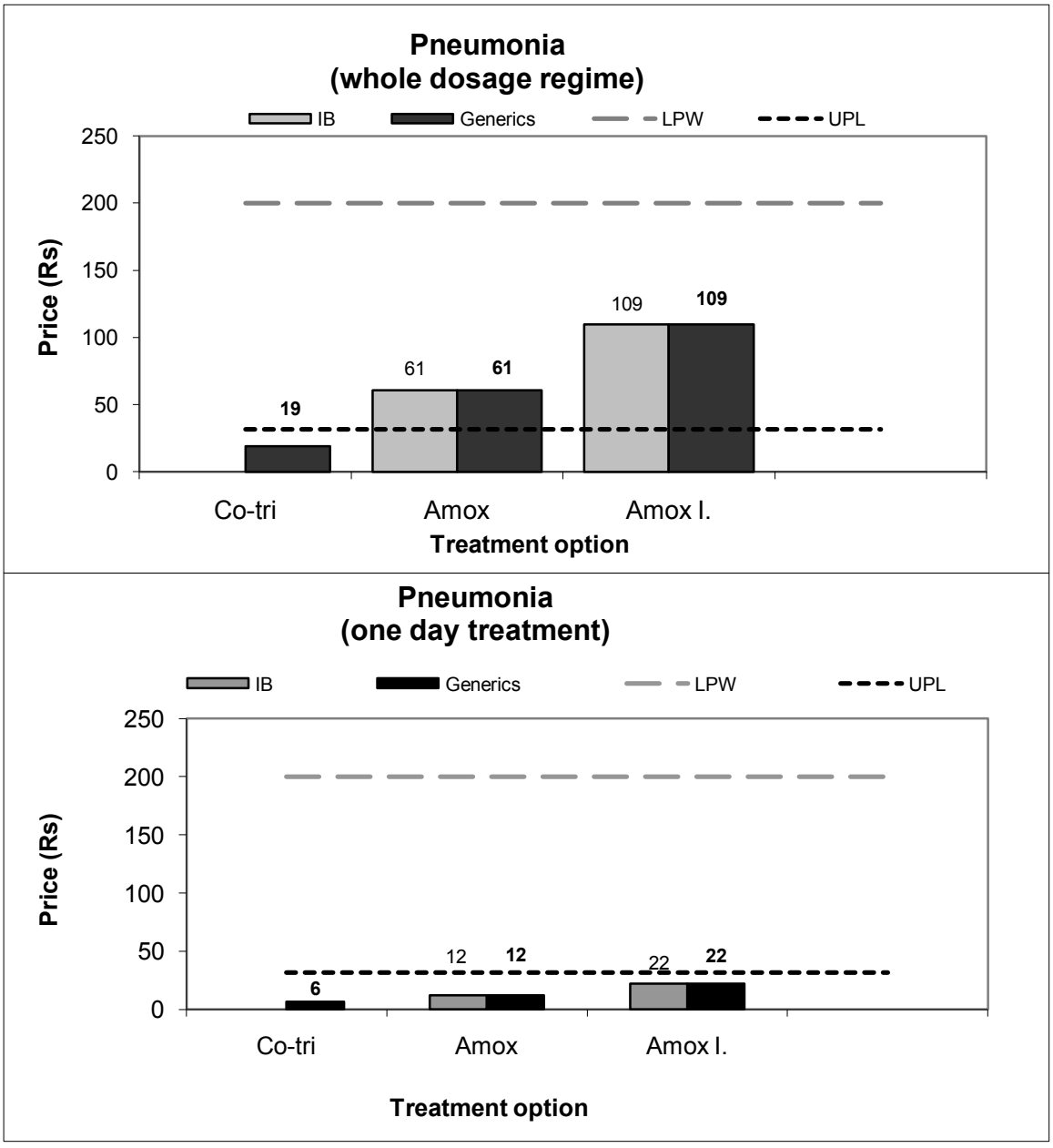

Figure 9: Cost variation with antibiotics for a whole dosage regime and cost for one day treatment, for pneumonia. The antibiotics in the figure reflect treatment options from table 1. **Co-tri** = contrimoxazole; **Amox =** amoxicillin; **Amox I** = amoxicillin increased dose. **IB =** innovator brand**; LPW =** lowest paid worker (200/day Rs)**; UPL =** under poverty line. **Price=** Pakistani rupee

UTI: From figure 9 a price difference of 66 fold can be observed, comparing the cheapest one-day treatment (co-trimoxazole) with the most expensive therapy with generic (ceftriaxone). In contrast, the difference with innovator brand of ceftriaxone and co-trimoxazole shows a difference of 160 folds. A whole course of co-trimoxazole and one-day treatment with cephalexin, is the only affordable option for those living under the poverty line. An unskilled worker could afford one-day treatment with all of the medicines, except with innovator brand of ceftriaxone.

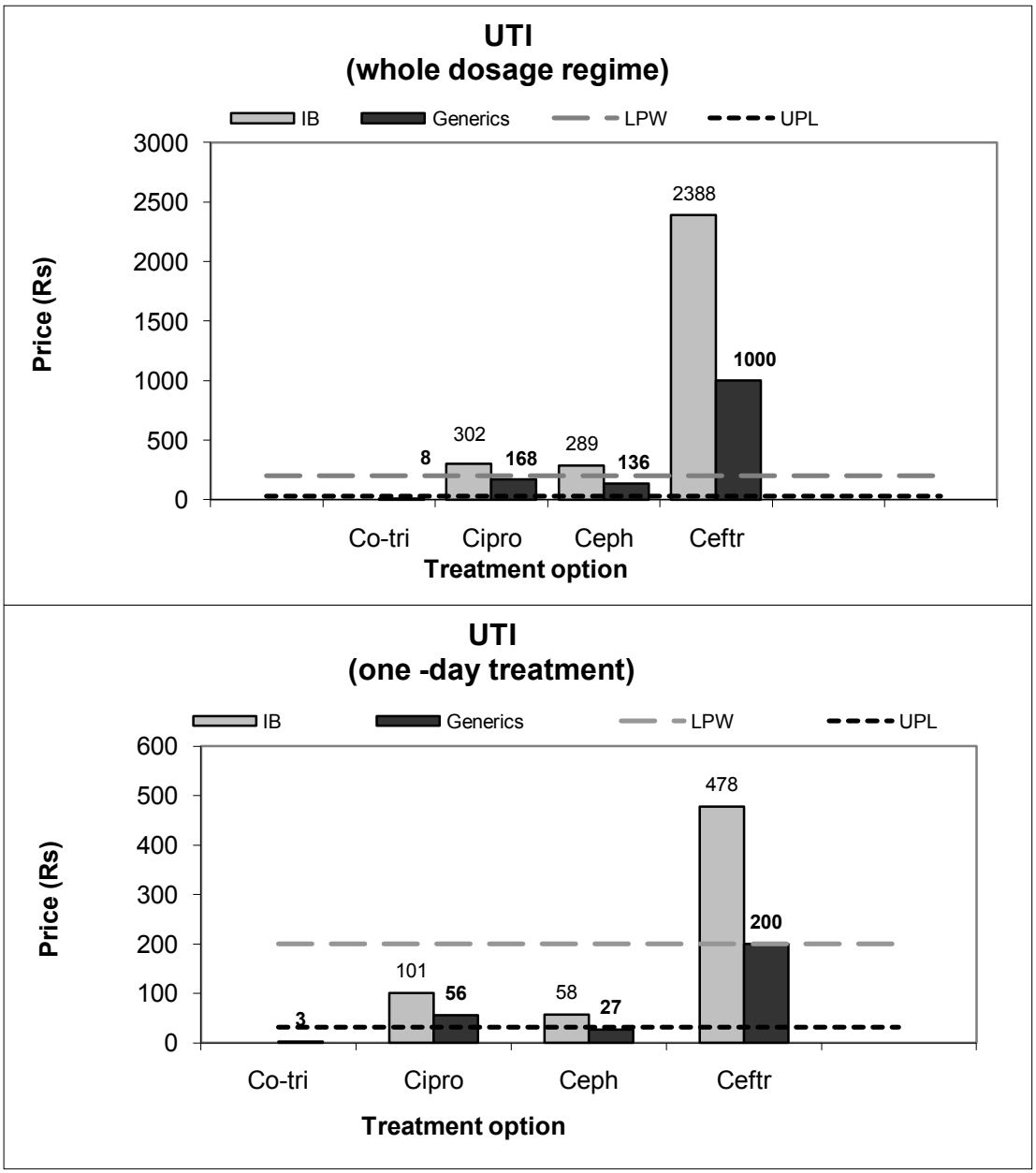

Figure 10: Cost variation with antibiotics for a whole dosage regime and cost for one day treatment, for UTI. The antibiotics in the figure reflect treatment options from table 1. **Co-tri** = co-trimoxazole; **Cipro = c**iprofloxacin**; Azit =** azithromycin**; Ceph = c**ephalexin**; Ceftr =** ceftriaxone. **IB =** innovator brand**; LPW =** lowest paid worker (200/day Rs)**; UPL =** under poverty line. **Price=** Pakistani rupee

5 DISCUSSION:

5.1 AFFORDABLE DRUGS?

Results of this study indicate that there is a noteworthy cost difference between various antibacterial treatments, making several antibiotics unaffordable to at least one fourth of the population in Pakistan (more than 38 million people). With support of various articles and studies, it can be determined that resistance is increasing, thus empirical treatments are changing, leading to more expensive treatment options. For example, this study showed that a one-day treatment for UTI can differ with 66 fold in respect of treatment option. Moreover, 22.3 percent of Pakistan's population (38 million people) will only afford a whole course of baseline-treatments (can be seen in table 1) for gonorrhea, UTI and pneumonia. Considering that prevalence of resistant strains are high for the baseline-treatments, there is a higher risk of treatment failures, thus increasing mortality, morbidity and spread of resistance. Furthermore, a person living below the poverty-line can only afford a few of the generics for one-day treatment, for all four diseases. Subsequently, the poor will only purchase the amount they afford and not what they need to eradicate the infection. This promoting the same results as mentioned for the treatment failure. An unskilled worker would afford all of the treatment options with cheap generics (represented in the diagrams), in exception of ceftriaxone. A full course treatment with ceftriaxone, for shigella and UTI, would cost a four days wage for an unskilled worker.

It should be emphasized that affordability is also dependent on whether the customer is supplied with an innovator- or a cheaper generic brand. The trend of innovator brands being much more expensive was shown in a majority of the surveyed drugs. This contributes to customers paying more than twice the price of a generic, in pharmacies where innovator brand are the only available option. This scenario was observed in one of the public pharmacies, where only price information of innovator brands were supplied, since they did not recommend equivalent generics. It is worrying to know that public pharmacies, who primarily serve the poor, recommend innovator brands which can be unaffordable for even an unskilled worker. However it can be discussed regarding what factors play at part for keeping innovator brands as the cheapest alternative in stock. One possible explanation is that, the customers demand regulates what medicines are maintained in stock. In many developing countries there is an issue with counterfeit medicines, thus making people believe that innovator brands are more reliable options. Linked to this is that, physicians often only prescribe innovator brand products, thus leading people to believe that they are the only effective medicines available. There is also a controversial aspect of this issue, where pharmaceutical companies are thought to put pressure and bribe dispensing doctors or pharmacists to promote medicines with their brands.

Amoxicillin was the only medicine where there was no noticeable price difference between generic and innovator brand. One possible explanation is that, this drug has been available on the market for decades, which makes it a rather affordable drug whether it is of innovator- or generic brand. As previously mentioned, customers demand can regulate the market, hence customer's frequent use of amoxicillin can be one factor for pushing the prices down for its innovator brand.

Moreover, from table 2 it seemed as some pharmacies had mark-ups. This was obvious in one pharmacy where the same generic brand for co-trimoxazole sold in the other pharmacies, was 4 fold

more expensive in one of them. However, the price difference could be a result of misinterpretation by the collector which will be further discussed in next section. There is also a substantial price difference between medicines dosage forms. This was noted for treatment of shigella and pneumonia, with suspensions, which were more expensive than corresponding treatment with tablets (can be seen in appendix V). Treatment with suspension requires purchase of a whole bottle, in opposed to treatment with tablets which can be purchased as single tablets, making suspension a more expensive option.

5.2 DATA VALIDITY AND METHODOLOGICAL CONSEQUENCES

5.2.1 Choice of disease and relevant treatment options:

For practical reasons only four diseases were chosen. They are considered as major infectious diseases in developing countries, with high mortality and morbidity rates along with high prevalence of resistant strains, resulting in frequent change in empirical treatment. They are along with this, common infectious disease treated in non-institutional care. For these reasons it seemed appropriate to include these specific diseases.

There were some difficulties met in the process of finding appropriate treatment for each scenario. Finding treatment in scientific articles could be contradicting, when treatment alternatives varied. Therefore the final treatment options seen in table 1 were finalized in the presence of ReAct's supervisor, along with two other doctors consultation. The antibiotics chosen for the different scenarios, mentioned in table 1, are suggestions supported with various articles, and may not necessarily reflect therapy options in today's clinical practice. The suggestions are supposed to reflect global treatment regimens, rather than specific standard treatment regimens used in Pakistan. Changes in bacteria's susceptibility, poses difficulties in selecting appropriate drug and dosage, therefore my therapy options may vary from others. All calculations made for the dosage regimens, are based on the maximum days given in table 1. Therefore treatment cost can be lower than what the result suggests, depending on susceptibility of the strain. Nevertheless, the results of this study are dependent on the selected options in table 1. Therefore the selection of therapy options will now be further discussed for each disease.

The first antibiotic regime was constructed for a child under the age of five infected with S.*pneumonieae.* The treatment options and dosage regimes were based on WHO´s recommendations for pneumonia. Co-trimoxazole was chosen as the treatment for non resistant strain, since it is an inexpensive agent, and effective on susceptible strains (Grant *et al.,* 2009). Amoxicillin is used in communities where co-trimoxazole resistance is widespread. In settings where high penicillin-resistance occurs, a higher dose of amoxicillin is of recommendation (Scott *et al.,* 2009). This disease was included for this study for its high mortality rates among children in developing countries, as well as it is a common disease treated in out-patient care (UNICEF & WHO, 2006).

Next, a child with dysentery with gradually increasing resistance was included for its high mortality rates and for the exceeding resistant strains of *Shigella*. Furthermore, this disease is widely spread in

developing countries where poor hygiene and unsafe water supplies, promotes the spread (Niyogi, 2005).

Mentioned antibiotic for base-line treatment (co-trimoxazole, seen in table 1), is becoming rare for shigella. In some developing countries treatment is already initiated with azithromycin or with a third-generation cephalosporin. Azithromycin was chosen since Basulado and Arbo found that treatment with azithromycin in children have higher levels of eradication of *Shigella,* than with cefixime (third-generation cephalosporin)(Basulado & Arbo, 2003). Co-trimoxazole was chosen on the same basis as for pneumonia. Ciprofloxacin and Ceftriaxone are recommendations from WHO that also are included in table 1 (WHO, 2005b). However ESBL producing bacteria's are emerging and therefore treatment with third-generation cephalosporin's such as cefixime and ceftriaxone are becoming limited. Both of these agents have different dosage forms, and therefore it seemed appropriate to include both of them in table 1.

The third fictive patient infected with *Neisseria gonorrhoeae,* was chosen for its high morbidity rates in developing countries and for the consequences it involves when failure of treatment occurs (Tapsall, 2009). Baseline-treatment for *N.gonorrhoaeae* was chosen with penicillin, however this is not a recommended treatment now days, due to the widespread of PPNG strains. Since my aim was to compare cost depending on different shifts in resistance, I chose to include penicillin as an option for strains that still could be susceptible. Ciprofloxacin was included since it has been and can be used for gonorrhea (Tapsall, 2006). Azithromycin is first choice of treatment in some countries where patients have severe allergic reactions to penicillin and cephalosporins, therefore this is represented as an option in table 1 (CDC, 2007). Azithromycin can also be used as a combination therapy for Chlamydia and gonorrhea, and is useful in some clinical settings (Tapsall, 2006). Third-generations cephalosporins such as cefixime and ceftriaxone are used when treatment is not successful with the other mentioned options, which is also recommended by the guidelines for doctors without borders and by Center of disease control and Prevention (CDC, 2007;Broek *et al.,* 2010). However resistance to cephalosporins are emerging and further spread of resistance will affect clinical outcomes, thus future treatment for gonorrhea will remain uncertain.

The last patient group consists of adults infected by E.coli. It was of interesting choice to this study on the basis that resistance has remarkable increased over the past few decades, hence empirical treatments options are changing. It is also one of the most common infectious disease treated among out-patients. Also, increased emergence of ESBL has limit treatment options with cephalosporins, which poses a major threat for the whole society, and the management of E.coli breakouts. Antibiotic suggestions seen in table 1 for *E.coli* are based on IDSAs recommendations. It is recommended to initiate treatment with co-trimoxazole (Warren *et al.,* 1999). Since co-trimoxazole also is an inexpensive option, it was included in table 1. However if resistant strains of *E.coli* are present in a community it can be recommended to start treatment with ciprofloxacin which is seen in table 1. Cephalosporin's were also included in the scheme since they are recommended for treatment where resistance to fluoroquinolones occur (Miller & Tang, 2004). Cephalexin was included since it can be administered orally in contrast to ceftriaxone which is given parenterally. However, cephalosporin´s are not of much use in the presence of ESBL- producing strains. Carbapenems that can be used for ESBL- bacteria, was not included since it is a very rare drug and is not used in out-patient care.

5.2.2 Additional costs:

As mentioned the findings of this study indicate that there is a substantial difference in treatment with antibiotics, making these agents unaffordable to a large group of people. However, the results from this study are only based on medicines. The economical burden on individuals and the society are greater than what has been evaluated in this study. Additional costs, such as hospitalization, laboratory results, x-ray, physical examinations, are factors pushing the economical burden of resistance to another level. Even if these cost were not calculated in this study, they should be noted. Next, cost for ceftriaxone in this study would presumable increase, considering additional cost as help with administration and syringes are not included in the calculations in this study.

The affordability which was measured according to HAI's methodology can also be further discussed, whether it is a fair method to measure affordability. An unskilled worker may have a days' wage where he or she can afford to spend more than one days wage on medicines, whereas for people living under the poverty-line, a days' wage may not feed a whole meal for a person. The affordability measured for a person living below the poverty line, would presumable show a more worrisome result than it already is, since one days salary may be difficult to spend on medicines.

5.2.3 The survey and sampling of the data:

5.2.3.1 Reliability of the prices:

According to the collector the price information was sampled without any difficulties. The collection was made the same way at all pharmacies. However, the pharmacists' level of enthusiasm of supplying price information differed. At all pharmacies, price information was received with the support of a computer, except for one. Moreover, in this pharmacy the supplier seemed distracted and told prices off his head, contributing to decreased reliability of the supplied price information, thus affecting the results. Together with this there are other factors that can have influenced the results. The collector and the pharmacist can both have misinterpreted the prices of the medicines. For example, the price for cephalexin in pharmacy 3 is considerable cheap, compared to the other pharmacies, adding suspicion that the pharmacist might have supplied wrong information.

5.2.3.2 Validity of the median price information:

HAI recommends inclusion of 30 medicine outlets in a survey for identifying affordability and availability within communities (HAI 2008). In this study only six pharmacies were included due to time limitations. The median price was calculated since there was a large price variation between the medicines, thus making the median value more accurate than the mediate value.

Since only six pharmacies were included, the cheapest available option could be either generic or innovator brand. Therefore only few figures are included for the calculation of the median price for innovator- and generic brands. In some cases the median price is based on one or two figures, leading results of being falsely too high or too low. At first it was intended to calculate the average median price for each medicine, regardless of innovator - or generic brand. However, the sampled data showed a wide range in price between innovator brand and generics, therefore it was decided to divide median price for both generic- and innovator brand.

5.3 FUTURE PERSPECTIVES

Suboptimal treatment, meaning not taking a full dose, often promotes an increased risk for development of resistance in bacteria, thus making emergence of antibiotic resistance inevitable. However, the pace of this development can be slowed down, if efforts are made to use these agents rationally. With rational use inexpensive agents will still be effective, making treatment affordable for the poor. As it is today millions of people die in infectious disease, many of whom cannot afford appropriate treatment. Access to health-care and medicines is a human right, therefore good quality of medicines should be available at affordable prices. Governments need new regulation policies for medicines, where mark-ups are controlled, and cheap generic for essential medicines are always maintained in stock at each pharmacy. Surveillance of antibiotic resistance is necessary, to use antibiotics that are effective. New rules for use of antibiotics need to be implemented, so these drugs can be preserved for the next coming generations. Supplying proper knowledge of resistance to physicians, pharmacists and the people, rational use of antibiotics may be applied, slowing down the pace of resistance, thus retaining health and economical benefits for the people. There is need for more studies focusing on the economical burden on individuals of antibiotic resistance, to further emphasize the necessity of appropriate use of these agents.

6 CONCLUSION

There is evidence of antibiotic resistance leading to changed therapy, thus often to more expensive options. This dilemma has brought additional economical burden on resource-poor populations, hence limiting treatment possibilities for millions of people. In Pakistan one fourth of the population cannot afford basic treatment regimens for common infectious diseases such as pneumonia, shigellosis, UTI and gonorrhea. It is worrisome to notice that such large part of the population cannot access adequate treatment options, for easily treated infections. Along with this, cheapest available medicine between pharmacies varies, further affecting the affordability for the poor. This problem further raises an ethical issue on how pharmaceutical companies and pharmacies do not market cheap medicine alternatives for the poor. There is need for interventions and regulations of medicine prices so they can be accessible for everyone. Even if the economic burden will not affect the people in Western society to the same extent as in developing countries, the same issues will arise regarding access to effective antibiotics if no viable options remain. Therefore this worldwide problem affects both rich and poor, proving that we in Western countries with privileges should take more action in combating antibiotic resistance, and focus our money on research and development of new antibiotics at affordable prices. Antibiotic resistance is a global problem that needs more attention and if action is not taken now, we risk losing one of the most significant achievements of modern medicine.

7 REFERENCES

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Acknowledgements:
To my supervisor, Liselotte Diaz Högberg, the data collector Sharmeen Ziarukh and ReAct.

Appendix I:

Medicine Price Data Collecting form

FORM A

Use one form for each health facility and pharmacy

Date_____

Name of town/district

_____

Name of pharmacy

_____

Type of facility

- Public
- Private

Other (please specify) _____

Independent pharmacy or chain pharmacy? (Leave it blank if you do not know)

_____

Who purchases medicine from here, as in socioeconomically differences? (as in is it for everyone, or is it located in a place where only some people have access to the pharmacy?)

_____

_____

Appendix II:

Letter of endorsement:

To whom it may concern

Ms Bina Azhar a masters student working on her thesis, at Uppsala University, Sweden will be undertaking a survey of medicine prices for antibiotics. The aim of this study is to calculate price differences for antibiotics purchased over-the-counter, reflecting different treatment alternatives for common infectious disease.

This requires sampling of price information of total _____ antibiotics (number of antibiotics) from different pharmacies or medicine outlets.

This survey is based on methods promoted by the World Health Organization and Health Action International. It is designed to identify the price differences among various antibiotics, to ensure what economical burden antibiotic resistance will or has led us to.

The pharmacies and medicine outlets will be assured complete anonymity when the results are processed and presented for this survey.

On behalf of Uppsala University, I would be grateful if you would provide full access to the information needed for this survey.

If you have any further questions, please contact the study supervisor Dr Liselotte Högberg at liselotte.hogberg@medsci.uu.se.

Signed:_____

Liselotte Diaz Högberg, MPH PhD

Researcher, Department of medical Sciences

Uppsala University, Sweden

Appendix III

Instructions for the price collection:

If possible try to find three pharmacies or medicine outlets in the public sector (government supported facilities such as hospitals), and three from the private sector. Try to select pharmacies/medicine outlets from different areas where the customer varies (different socioeconomically backgrounds). If it is hard to find medicine outlets from the public sector, then concentrate on finding private pharmacies.

If it should appear for some reason that the pharmacist does not want to supply information, then please go to one additional pharmacy.

Procedure for data collection:

1. On arrival to the medicine outlet, the data collector should introduce themselves and inform the pharmacy staff of the purpose for this survey. The data collector should also thank the staff for their cooperation and stress that the outlets identity will be kept confidential. The letter of endorsement should be shown if necessary.

2. Information regarding the facility listed in form A should be obtained. Let the staff describe their customers and uptake area in their own words.

3. Complete form B with price information:

Identify the lowest priced drug (the lowest price per pill or dose) in the medicine outlet for each listed antibiotic. Write yes or no in column H whether the lowest cost of drug is innovator brand. If the pharmacist does not know if it is innovator- or generic brand, then do write down the name found in column H or I.

It is essential to check the package price and how many tablets it contains. Bring a calculator if necessary so unit price can be calculated. Try to collect a pack size that they would recommend. The dosage regime will be written down as well, and the package size **must** cover the dosage regime.

If possible always try to collect the same pack size for each medicine. If the following pharmacy does not have the same package size as the previous one, select the closest, larger pack price. Medicines can be available as bulk packages, meaning the pharmacist repackages smaller quantities of medicine. If so, than do write this down and see that the tablets are equal to the suggested dosage regime.

Different strength of same medicine may be available. Try to search for the strength that is written in the protocol (column B). Tablets and capsules are considered as equivalent. If the dosage or strength written in column B is not available write down the closest strength in column D.

Write comments in column I, when the medicine is out of stock, if there is a discount on the price, when the strength or dosage form differs from the suggested and if medicine are handed out in bulk packages.

On behalf of React, we thank you for collecting these price information.

Best regards

Bina Azhar

Appendix IV: Form B

Generic name	**Preferred strengths and dosage forms**	**Pack size must contain at least**	**If preferred strengths or dosage form is not available, please note the closest dosage and form**	**Pack size found (number of tablets or ml)**	**Price of pack found**	**Unit price/ tab**	**Is this innovator brand? Yes /no?**	**Comments**
Amoxicillin	Tabl/caps 500 mg	15 tablets						
	Susp. 50 mg /ml	75 ml						
	Susp. 50 mg/ml	150 ml						
Sulphamethoxazole + trimethoprim (Co-trimoxazole)	Tabl/caps 400mg + 80mg	6 tablets						
	Susp 40 + 8 mg/ml	50 ml						
Ceftriaxone	Vial injection 250 mg	1 injection						
	Vial Injection 1g	5 injections						
Cephalexin	Tabl/caps 500 mg	20 tablets						
Cefixime	Susp 100mg/5ml (20mg/ml)	30 ml						
	200 mg	2 tablets						

Ciprofloxacin	Tabl/caps 500 mg	6 tablets						
	Susp. 50mg/ml	54 ml						
Azithromycin 500 mg	Tabl/caps 500 mg	1 g						
	Susp. 200mg/5ml (40mg/ml)	13 ml						

Appendix V:

Cost of treatment from each pharmacy

PHARMACY 1
Private

SCENARIO (from table 1)			Cost for one day's treatment			
	Gonorrhea	***Shigella***	*(Shigella: cost with tablets)*	***UTI***	***Pneumonia***	*(Pneumonia: cost with tablets)*
1	44,4	4,2	1,4	2,8	6,3	2,1
2	7,5	51,012	15	15	12,165	11,1
3	91,666	74,335			21,897	22,2
4	55	24,402	27,5	57,712		
5	141,4	477,68		477,68		
			Cost for whole dosage regime			
	Gonorrhea	***Shigella***	*Shigella: cost with tablets))*	***UTI***	***Pneumonia***	*(cost for tablets)*
1	44,4	21	7	8,4	18,9	6,3
2	7,5	153,036	45	45	60,825	55,5
3	91,666	193,271			109,485	111
4	55	122,01	82,5	288,56		
5	141,4	2388,4		2388,4		

PHARMACY 2
Private

SCENARIO (from table 1)			Cost for one day's treatment			
	Gonorrhea	***Shigella***	*(Shigella: cost with tablets)*	***UTI***	***Pneumonia***	*(Pneumonia: cost with tablets)*
1	45	4,2	1,4	2,8	6,3	2,1
2	28,1		56,2	56,2	12,165	11,25
3	132,668	74,335			21,897	22,5
4	55	28,998	27,5	59		
5	58	200		200		
			Cost for whole dosage regime			
	Gonorrhea	***Shigella***	*(Shigella: cost with tablets)*	***UTI***	***Pneumonia***	*(Pneumonia: cost with tablets)*
1	45	21	7	8,4	18,9	6,3
2	28,1		168,6	168,6	60,825	56,25
3	132,668	193,271			109,485	112,5

4	55	144,99	137,5	295		
5	58	1000		1000		

PHARMACY 3
Public

SCENARIO (from table 1)			**Cost for one day's treatment**			
	Gonorrhea	***Shigella***	*(Shigella: cost with tablets)*	***UTI***	***Pneumonia***	*(Pneumonia: cost with tablets)*
1	44,94	4,2	1,4	2,8	6,3	2,1
2	19,5	48,006	39	39	12,165	11,235
3	51	55			21,897	22,47
4	54	24	27	4,8		
5	65	200		200		
			Cost for whole dosage regime			
	Gonorrhea	***Shigella***	*Shigella: cost with tablets))*	***UTI***	***Pneumonia***	*(Pneumonia: cost with tablets)*
1	44,94	21	7	8,4	18,9	6,3
2	19,5	144,018	117	117	60,825	56,175
3	51	143			109,485	112,35
4	54	120	135	24		
5	65	1000		1000		

PHARMACY 4
Private

			Cost for one day's treatment			
SCENARIO (from table 1)	***Gonorrhea***	***Shigella***	*(Shigella: cost with tablets)*	***UTI***	***Pneumonia***	*(Pneumonia: cost with tablets)*
1	44,94	6	1,4	2,8	9	2,1
2	28,1	38,988	56,2	56,2	12,75	11,235
3	36,666	38,335			22,95	22,47
4	55	57,198	27,5	49,668		
5	65	200		200		
			Cost for whole dosage regime			
	Gonorrhea	***Shigella***	*(Shigella: cost with tablets)*	***UTI***	***Pneumonia***	*(Pneumonia: cost with tablets)*
1	44,94	30	7	8,4	27	6,3
2	28,1	116,964	168,6	168,6	63,75	56,175
3	36,66	99,671			114,75	112,35
4	55	285,99	137,5	248,34		
5	65	1000		1000		

PHARMACY 5

Public

Cost for one day's treatment

SCENARIO (from table 1)	*Gonorrhea*	*Shigella*	*(Shigella: cost with tablets)*	*UTI*	*Pneumonia*	*(Pneumonia: cost with tablets)*
1	44,94	4,2	5,6	11,2	6,3	8,4
2	50,4		100,8	100,8	12,165	11,235
3	91,666	74,36			21,897	22,47
4	51,2	57,198	25,6	57,712		
5	141,4	477,68		477,68		

Cost for whole dosage regime

	Gonorre	*Shigella*	*(shigella: cost with tablets)*	*UTI*	*Pneumonia*	*(Pneumonia cost with tablets)*
1	44,94	21	28	33,6	18,9	25,2
2	50,4		302,4	302,4	60,825	56,175
3	91,666	193,336			109,485	112,35
4	51,2	285,99	128	288,56		
5	141,4	2388,4		2388,4		

PHARMACY 6

Public

Cost for one day's treatment

SCENARIO (from table 1)	*Gonorrhea*	*Shigella*	*(Shigella: cost with tablets)*	*UTI*	*Pneumonia*	*(Pneumonia: cost with tablets)*
1	45	4,2	1,4	2,8	6,3	2,1
2	28	75,15	56	56	13,17	11,25
3	275 with suspension	55			23,706	22,5
4	46	24	23	57,668		
5	58	110		110		

Cost for whole dosage regime

	Gonorrhea	*Shigella*	*Shigella: cost with tablets))*	*UTI*	*Pneumonia*	*(cost for tablets)*
1	22,5	21	7	8,4	18,9	6,3
2	28	225,45	168	168	65,85	56,25
3	Azitromycin missing	143			118,53	112,5
4	46	120	69	288,34		
5	4	550		550		

Appendix VI:

Prices (in USD) from MSH database

Generic name	Dosage and form	Median price, per tablet in dollar	Highest	Lowest
Amoxicillin	Tabl/ caps 500 mg	0,0376	0,05	0,0301
	Susp. 50 mg/ml	0,0079	0,0117	0,0049
Co-trimoxazole	Tabl/caps 400mg + 80	0,0142	0,0144	0,0074
	Susp 40+ 8 mg/ ml	0,0039	0,0059	0,0025
Ceftriaxone	Vial injection 250 mg	0,7494	3,2791	0,3195
	Vial injection 1 g	0,6918	1,0584	0,3919
Cephalexin	Tabl/ Caps 500 mg	0,0713	0,0798	0,0562
Cefixime	Susp 20mg/ml	0,0423	NA	NA
	Tabl /caps 200 mg	0,1132	NA	NA
Ciprofloxacin	Tabl /caps500 mg	0,0289	0,0465	0,0081
	Susp. 50mg/ml	NA	NA	NA
Azithromycin	Tabl/Caps 500 mg	0,7191	1,9099	0,0979
	Susp 40mg/ml	0,1313	0,1692	0,0933

NA= Not availble