

Original Research Article**EVALUATION OF ANTIBIOTICS USE BASED ON VARIOUS PARAMETERS USED FOR SELECTION OF ANTIBIOTICS IN NISHTER HOSPITAL MULTAN PAKISTAN****Qasim Shahzad, Muqet Wahid**

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ABSTRACT

This study was ignited with the aim to evaluate rational use of antibiotics in Pakistan. The research was conducted to assess the antibiotic prescribing pattern of the physicians in renowned hospitals in Pakistan. This study is descriptive in nature. The population took under study was from the different wards of Nishter Hospital Multan. The 150 respondents were the patients admitted in different wards of the hospital. The aided questionnaire survey method was used to fetch the data and analyzed by the help of SPSS 17. The results shows that more than 50% patients receive the antibiotics empirically, Less than 40 % are to be witnessed to be receiving antibiotics prophylactically and only the limited numbers of patients are able to have received antibiotics specifically. As most of the antibiotics are used empirically this is supposed to be the major reason for the development of resistance.

Keywords: Antibiotics, prescription, pharmaceutical care, antibiotic resistance**Corresponding author:** Qasim Shahzad, Bahauddin Zakariya University Multan Pakistan. E.: qasim.shahzad71@yahoo.com; T.: +923317076006**INTRODUCTION****Limitations of study**

This research is limited to one city as per the problem of permission to collect data and geographical limitations.

Practical implications

The conducted study is helpful in way to address the problem of irrational antibiotic usage in Pakistan and will help the practitioners to improve the way of the prescription of antibiotics for the patients.

Originality/ value

The review of literature revealed that there is a lack of this kind of studies in the Pakistani setting. This attempted to describe how the antibiotics are prescribed irrationally and how this prescribing practice contributes to the global scenario of the development of the resistance of antimicrobials towards the antibiotics.

Purpose

The purpose of this study was to evaluate the type and the dosage regimens of the antibiotics administered prophylactically, empirically and specifically and to check the rationality of prescribing pattern in Nishter Hospital Multan.

1. To check whether the patient is renally or hepatically impaired if so, then the dose is adjusted or not.
2. To check the interacting drugs within the prescription of inpatients

3. To check whether the microbiological tests are done.
4. To check the dose of antibiotic prescribed to check whether it is appropriate, overdose and underdose.

Antibiotics are biochemical materials which will constrain the expansion of, and even terminate, damaging microbes. They derived from completely different microbes or alternative alive organisms, and are manufactured in large amount by using the process of fermentation. Though the mechanism by which antibiotic act weren't unconcealed till the 20th century, the antibiotics were first used by Chinese over 2500 years past. Presently, antibiotics designate a huge business that is going to enhance every annum. **1-2**

Choice of an antimicrobial agent

Best and sensible choice of antibacterial agents for the treatment of bacterial diseases calls for clinical assessment and elaborate knowledge of pharmacological and microbiological factors.

In general antibiotics have three uses:

- Empirical therapy
- Definitive therapy
- Prophylactic or Preventive therapy.

When to start with empirical, or initial, therapy, the broad spectrum antibiotics should be used that is effective against wide range of pathogens because the exact pathogen involved has not yet been outlined. Antibiotics may be used in combination or alone during the empirical therapy.

Nevertheless, when the causative agent is distinguished, definitive antimicrobial therapy should be started with a more specific antibiotics that have narrow spectrum and low-toxicity. Failure to identify the bacteria so that definitive therapy with the narrow-spectrum agent can be instituted and failure to use the narrow spectrum antibiotics when an organism has been identified are two common ways in which antibiotics are misused **3**.

Pre-surgical antimicrobial prophylaxis.

Antibiotics are used prophylactically before preparing for surgery to reduce the incidence of post-surgical infections at the site of surgery. Sufferers going through operations affiliated with high rates of infections, those involving prosthetic material implantation, and also including those where the outcomes of infection are severe should be given antibiotics before surgery. The pre-surgical antibiotic(s) must encompass the expected microorganisms and be made available at the desired site when the first cut for the surgical procedure is made, and satisfactory concentrations in the serum must be kept throughout the surgical procedure. For most of surgical procedures, a single dose of cephalosporin antibiotics given over a period of an hour earlier the first cut is made is sufficient for large number of cases. The duration of administration of prophylactic antibiotics should not exceed greater than 24 hours for most of cases **4**.

Antibiotic use and resistance

Antibiotics, over tuned the therapy of diseases caused by microorganisms when initially landed into practice. They are categorized as lifesaving drugs, and are among the most important drugs in each hospital formulary and are made available to all when needed. Approach to antibiotics is an important problem and it involves the factors, both at the patient level and health system level. Additionally, the resistance to antibiotics menaces to wear away this valuable drug source. Antibiotics must be practiced with a great attention as the resistance to antibiotics is related to its consumption **5**.

Antibiotic use

Antibiotic consumption is determined on the part of healthcare provider and the patient side. Most of the patients use antibiotics without consulting their physicians. A large number of people either use self-medication or purchase antibiotics directly from the pharmacy stores without diagnosing their disease states in poor countries⁶⁻⁷. Even when healthcare and drugs from the state-supported sector is free, deficiency of confidence in caregivers can forbid patients from seeking aid. The discussion between doctor and the patient is a complex co-ordination, and a variety of things will force the physician's and their patients in their choices to consume antibiotics. These factors will include the wealth status, limited time for consultation, available data, opinions of doctors about particular antibiotics and patient load⁸⁻¹².

The phrase 'microbiological drug resistance' specifies the microorganisms that will remain alive at the high level of antibiotics, which could be lethal to microorganisms in normal circumstances. The resistant strains of microbes are different from wild types because they have gained resistance either by gene transfer or through mutation in their genetic makeup. The microbes either inherit the resistance genes from their parents or acquired it from the environment¹⁴⁻¹⁶. The recent development of resistance in microbes towards the antibiotics, in clinics and in society had severe consequences, and due to this the golden period of antibiotics may have come to an end. At present most of the nosocomial infections in United States are unaffected to most of the antibiotics, which were later used to cure these infections¹⁷⁻¹⁸.

Antibiotic use in Pakistan:

In Pakistan, average amount of drugs in each prescription are about four, and in these antibiotics drugs are about seventy six percent. Nearly seventy five percent of antibiotics drugs are given by injection. As well as, in the THQ hospitals the antibiotics are prescribed to seventy eight percent of patients, and out of them seventy four percent receive antibiotics drugs via injections. The antibiotic prescription relative frequency in case of children of age 1-15 was as high as 84%¹⁹.

METHODOLOGY

This study is descriptive in nature. The study is carried out in the five inpatient wards of Nishtar Hospital (pediatric, medicine, urology, surgery and oncology) between the 6th June 2013 and 6th July 2013. The sample population belongs to this, Data was collected by seeing the inpatient prescription charts from which we gather the demographic data of the patient, family history, diagnosis of patient, results of microbiology if done, antibiotic prescribed, dose and dosage interval, laboratory test reports to know about the renal and hepatic functions, drug interaction. A total of 150 patients were analyzed in different departments. The results are analyzed by using the SPSS program. The sampling was carried out on the base of stratified simple random technique. The descriptive from the sample is given in table 1.

Data analysis

This research is descriptive in nature so it will be defining the results based on descriptive tests. The frequencies and percentages are widely used in tests.

RESULTS AND DISCUSSION

The case notes of 150 patients admitted to the different departments of Nishtar hospital were surveyed during a one month period. Out of the 150 patients 127 (84.7) are males and 23 (15.3) are females.

Table no 1: Total no. of wards and patients visited in them

Wards	Frequency	Percent	Valid Percent	Cumulative Percent
pediatric	18	12.0	12.0	12.0
medicine	50	33.3	33.3	45.3
urology	24	16.0	16.0	61.3
surgery	52	34.7	34.7	96.0
oncology	6	4.0	4.0	100.0
Total	150	100.0	100.0	

Table 2: gender of patients

Sex	Frequency	Percent	Valid Percent	Cumulative Percent
Male	127	84.7	84.7	84.7
female	23	15.3	15.3	100.0
Total	150	100.0	100.0	

Table 3: Age groups of patients

Age				
Age group	Frequency	Percent	Valid Percent	Cumulative Percent
0-10	17	11.3	11.3	11.3
11-20	29	19.3	19.3	30.7
21-30	31	20.7	20.7	51.3
31-40	25	16.7	16.7	68.0
41-50	15	10.0	10.0	78.0
51-60	14	9.3	9.3	87.3
61-70	12	8.0	8.0	95.3
71-80	6	4.0	4.0	99.3
>80	1	.7	.7	100.0
Total	150	100.0	100.0	

Age of patients:

Renal and hepatic functions are poorly developed in the newborns, and become deteriorated in old peoples making them particularly vulnerable to the toxic effects of antibiotics because most of antibiotics are eliminated by hepatic or renal route. In our study we make different age groups which are shown in the given table 3.

Body mass index:

It is a "statistical measurement" which measures a person's weight and height. It is a useful tool to estimate a healthy body weight based upon how tall a person is. It is calculated by different formulas given below:

In SI units:

$$BMI = \frac{\text{weight in kilograms } \left(\frac{kg}{m^2}\right)}{\text{Height in meters}^2}$$

In US/UK units:

$$BMI = \frac{(\text{weight in pounds} * 703) (\text{lbs/inches}^2)}{\text{height in inches}^2}$$

It is an important tool to identify the obesity problem in the population.

It provides the simple numeric value of person's fatness and thickness which allows the health professionals to discuss over either the patient is overweight or underweight and by this they can adjust the dose. In our study we made following categories of BMI and we have calculated BMI by using the US/UK units.

Classification of various classes of BMI

The result of our study is given in the following table.

Table 4: BMI of patients

BMI				
BMI categorical	Frequency	Percent	Valid Percent	Cumulative Percent
<18.5	34	22.7	22.7	22.7
18.5-25	96	64.0	64.0	86.7
25-29.5	16	10.7	10.7	97.3
>30	4	2.7	2.7	100.0
Total	150	100.0	100.0	

Occupation of patient:

Occupation helps to predict the socio-economic status of the patient. It is also crucial to assess either the practice is done on the basis of pharmaco-economics or not. Most of the patients come to Nishter Hospital Multan belong to the profession of labor class or having poor socioeconomic background. As the Hospital belong to Government so most of drugs are provided free off cost to patients. This aspect is important related to private hospitals where the caregivers are more concerned with the money. The data on the occupation of patients collected by us is given in the following table.

Table 5: occupation of patients

Occupation				
categories	Frequency	Percent	Valid Percent	Cumulative Percent
labor	36	24.0	24.0	24.0
farmer	21	14.0	14.0	38.0
store keeper	9	6.0	6.0	44.0
govt servant	6	4.0	4.0	48.0
private job	13	8.7	8.7	56.7
pvt business	6	4.0	4.0	60.7
student	47	31.3	31.3	92.0
house wife	12	8.0	8.0	100.0
Total	150	100.0	100.0	

Income of patient:

The data about the income of patient is also collected to know about the socioeconomic status of patients. The data collected related to the income of patients is given below.

Table 6: income of patients

Income				
Income categories	Frequency	Percent	Valid Percent	Cumulative Percent
<5000	95	63.3	63.3	63.3
5000-10000	21	14.0	14.0	77.3
11000-15000	9	6.0	6.0	83.3
16000-20000	6	4.0	4.0	87.3
21000-25000	13	8.7	8.7	96.0
>25000	6	4.0	4.0	100.0
Total	150	100.0	100.0	

Microbiological testing of specimen obtained:

Antimicrobial therapy should be given to hospitalized patients in the presence of supporting microbiological data. Bacterial cultures and gram stains of samples obtained from the infection site is important in determining the causative agent of infection and in such a way helps in the selection and application of most appropriate drug therapy. In this way chances of microbes to become resistant to the available antibiotics are likely to be reduced. Following are the result of our study regarding this aspect.

Table 7: Results of microbiological tests.

Microbiology				
	Frequency	Percent	Valid Percent	Cumulative Percent
DONE	11	7.3	7.3	7.3
NOT DONE	139	92.7	92.7	100.0
Total	150	100.0	100.0	

Diagnosis of patient:

When patient see the doctor for the first time, it is not always possible to diagnose the disease at that time. On the basis of the clinical presentations and the patient profile, the physicians diagnose the disease provisionally. The final diagnosis is made on the basis of the laboratory findings and the current clinical presentations. However the therapy of disease cannot be linger on till the final diagnosis is made, because it may worsen the condition.

For the precise diagnosis, the role of patient and his family members is vital. Everything which the patient feel related to his disease must be told to the physicians. Some silly matter for the patient may be a vital point for a diagnosis and treatment. Following is data of our study related to this aspect.

Table 8: final diagnosis of patients

Final diagnosis				
Diagnosis of patients	Frequency	Percent	Valid Percent	Cumulative Percent
Gastro enteritis	8	5.3	5.3	5.3
enteric fever	7	4.7	4.7	10.0
anemic heart failure	2	1.3	1.3	11.3
pneumonia	12	8.0	8.0	19.3
viral encephalitis	1	.7	.7	20.0
CLD	9	6.0	6.0	26.0
CV accident	7	4.7	4.7	30.7
meningitis	6	4.0	4.0	34.7
appendicitis	6	4.0	4.0	38.7
perforation of duodenum	4	2.7	2.7	41.3
gall bladder perforation	2	1.3	1.3	42.7
renal stones	10	6.7	6.7	49.3
enlarged prostate	6	4.0	4.0	53.3
spinal injury	6	4.0	4.0	57.3
head injury	24	16.0	16.0	73.3
Sub arachnoid hemorrhage	2	1.3	1.3	74.7
acute lymphoblastic leukemia	2	1.3	1.3	76.0

osteosarcoma	1	.7	.7	76.7
breast cancer	1	.7	.7	77.3
non-Hodgkin's lymphoma	1	.7	.7	78.0
pain epigastric	3	2.0	2.0	80.0
intestinal obstruction	6	4.0	4.0	84.0
Tb	2	1.3	1.3	85.3
RTI	1	.7	.7	86.0
Fire arm injury	1	.7	.7	86.7
bladder cancer	1	.7	.7	87.3
carcinoma of colon	1	.7	.7	88.0
pesticide intake	3	2.0	2.0	90.0
stricture urethra	5	3.3	3.3	93.3
hydrocele	1	.7	.7	94.0
CRF	3	2.0	2.0	96.0
diabetic foot	1	.7	.7	96.7
undescended testis	1	.7	.7	97.3
pain in penis	1	.7	.7	98.0
pneumo+CLD+CRF	1	.7	.7	98.7
CLD+CRF	1	.7	.7	99.3
enlarged prostate and renal stones	1	.7	.7	100.0
Total	150	100.0	100.0	

Class of antibiotics prescribed:

Antibiotics are categorized on the basis of chemical nature and the mechanism by which they act. Some of the antibiotics act by inhibiting the synthesis of the cell wall of bacteria, these include the antibiotics containing the beta-lactam ring in their structure (e.g. penicillin) and other agents which act by inhibiting the cell wall synthesis which don't contain beta-lactam ring include vancomycin, carbapenems and bacitracin. Other agents act directly on the plasma membranes of the microbes causing the increase in plasma membrane permeability, which causes the cellular components to leak out of the cell. Some antibiotics act on the bacterial ribosomes and cause the inhibition of protein synthesis. Another class of antibiotics acts on the enzyme DNA gyrase [1]. We considered the class of antibiotics prescribed to know whether it is clinically indicated in that specific disease and to check the appropriateness of antibiotic use for therapeutic indication. Following is data of our study related to this aspect.

Appropriateness of antibiotics prescribed:

Appropriateness of antibiotics prescribed may slow the rate at which the resistance becomes widespread throughout the community. Following are the results of our study related to this aspect.

Table 9: frequency of class of antibiotics prescribed

Class				
	Frequency	Percent	Valid Percent	Cumulative Percent
3 Gen .cephalosporins	61	40.7	40.7	40.7
quinolones	28	18.7	18.7	59.3
macrolides	3	2.0	2.0	61.3
beta lactamase inhibitor	24	16.0	16.0	77.3
carbapenems	2	1.3	1.3	78.7
3 rd gneneration+4th generation cepalosporins	1	.7	.7	79.3
3 rd Gen.cephalosporins+glycopeptide	2	1.3	1.3	80.7
3 rd Gen cephalosporins+aminoglycoside+glyc opeptide	2	1.3	1.3	82.0
3 rd Gen cephalosporins+glycopeptide	1	.7	.7	82.7
4 th Gen. cephalosporins+quinolones	10	6.7	6.7	89.3
quinolones+4th Gen. cephalosporins+aminoglycoside	1	.7	.7	90.0
macrolides+beta lactam inhibitor	7	4.7	4.7	94.7
penicillin+1st Gen. cephalosporins+aminoglycoside	1	.7	.7	95.3
penicillin+4th Gen. cephalosporins+glycopeptide	1	.7	.7	96.0
3 rd Gen. Cephalosporins+aminoglycoside	1	.7	.7	96.7
3 rd Gen. cephalosporins+beta lactam inhibitor	1	.7	.7	97.3
1 st Gen. cephalosporins+aminoglycoside	1	.7	.7	98.0
penicillin+aminoglycoside	1	.7	.7	98.7
1 st Gen. cephalosporins+macrolides	1	.7	.7	99.3
3 rd Gen. cephalosporins+macrolides	1	.7	.7	100.0
Total	150	100.0	100.0	

Dose of antibiotics prescribed:

The dose of antibiotics differ based on various factors that include age, body weight, liver function status , kidney function status and the infection intensity. It is important to select the antibiotic according to the disease state and it is given in optimum dose. If antibiotics are given in inappropriate amount it may result in emergence of resistance. For the antibiotics with a narrow therapeutic index, excessive doses must be

avoided and their concentrations must be monitored in the plasma. Following are the results of our study related to this.

Table 10: appropriateness of antibiotics prescribed

Appropriateness of antibiotic prescribed				
	Frequency	Percent	Valid Percent	Cumulative Percent
Rational	141	94.0	94.0	94.0
Irrational	9	6.0	6.0	100.0
Total	150	100.0	100.0	

Table 11: Dose of antibiotics prescribed

Dose				
	Frequency	Percent	Valid Percent	Cumulative Percent
Appropriate	120	80.0	80.0	80.0
over dose	30	20.0	20.0	100.0
Total	150	100.0	100.0	

Table 12: Justification for antibiotic use

Justification of antibiotic use				
	Frequency	Percent	Valid Percent	Cumulative Percent
Empiric	89	59.3	59.3	59.3
prophylactic	53	35.3	35.3	94.7
specific use	8	5.3	5.3	100.0
Total	150	100.0	100.0	

Justification of antibiotics use:

As we have said earlier that there are three parameters of antibiotic use

- empiric
- prophylactic
- specific use (definitive)

So we also considered in our study these three parameters to justify whether the antibiotics are prescribed empirically, prophylactically or specifically. The results of our study related to this aspect are given in the following table.

DISCUSSION:

The major consideration for the proper use of antibiotics, which is the major concern at present, is to select the agent with optimal activity at the proper dose and dose interval and for proper duration.

The secondary, but still important concern is to minimize the development of resistance and provide the health facilities at a reasonable cost. There are considerable evidence that the anti-microbial agents are often abused and used excessively which lead to the emergence of resistant microbes.

The study was conducted on the 150 patients out of which 127 (84.7%) are males and 27 (15.3%) are females as given in table 2. The patients are divided in different age groups the data of the patients with different age groups is shown in the table 3. The age is important in predicting the dose and dosage interval because in new born the renal and hepatic functions are under developed and are deteriorated in old peoples. So in them the dose should be adjusted according to their renal and hepatic functions.

Another parameter used for the adjustment of dose is also checked and that is the body mass index (BMI) of the patients, by this we evaluate either the patient is overweight, underweight or have an optimal weight. The dose of certain drugs has to be adjusted in the overweight and underweight patients. There are about 34 (22.7%) patients are with the BMI of <18.5, 96 (64.0%) patients are with BMI range from 18.5-25, 16(10.7%) patients are with the between the 25-29.5 and only 4 (2.7%) patients have the BMI >30.

The income data collected on the 150 patients shows that 95 (63.3%) patients have monthly income <5000, 21 (14.0%) patients have monthly income in range of 5000-10000, 9(6.0%) patients have monthly income in range of 11000-15000, 13(8.7%) have monthly income between 16000-20000 and only 6(4.0%) have the monthly income above 25000. So the physicians must select the effective and the economic antibiotics to reduce the economic burden and to encourage the patients to complete the course of antibiotics for the specified time period which if remain incomplete due to the economic burden may lead to emergence of resistant microbes.

The most widely used antibiotic in Nishter Hospital Multan is 3rd generation cephalosporins. About 61(40.7%) patients receive 3rd generation cephalosporins 28(18.7%) patients receive quinolones and 24(16%) patients receive beta-lactamase inhibitor and the rest of patients have prescribed different other antibiotics.

Microbiology testing is necessary before the institution of the antibiotic therapy, but in the life threatening cases where the institution of antibiotics become necessary the specimen must be collected before the institution of antibiotics and after the determination of the infecting microorganism's definitive therapy must instituted as soon as possible to minimize the emergence of resistance. The studies shows that in 11 (7.3%) patients microbiology is done while in 139(92.7%) patients microbiological testing is not done which is the main reason for the irrational antibiotic use and lead to the emergence of resistance.

Appropriateness of antibiotics prescribed is also checked, whether the antibiotic prescribed is according to the clinical condition or not. About 141 patients receive the antibiotics according to their clinical condition and 9 receive the antibiotics not according to the clinical conditions.

The dose of antibiotic administered must also be considered a means of irrational practice. Study shows that in 120 (80.0%) patients dose administered is optimal and in 30(20.0%) patients higher doses of antibiotics are administered which may lead to the development of resistance. So to minimize this incidence physicians must administer the antibiotics in optimal doses according to clinical condition.

Study on the justification of antibiotic use indicates that 89(59.3%) patients receive the empiric therapy, 53(65.3%) patients receive antibiotics prophylactically and 8(5.3%) patients receive antibiotics after the

recognition of infecting microorganism. As most of the antibiotics are empirically used so chances of the microbes to become resistant to available antibiotics are increased.

CONCLUSION

Antibiotic resistance is a major health problem worldwide. Resistance to antibiotics is related to its wrong selection and use. No new class of antibiotics has been introduced over the last two decades'. So due to wrong prescribing practices we sooner going to evade the valuable miracle drugs and era of antibiotics came to an end. To save the antibiotics and to allow them to serve us the only way is use them wisely and appropriately.

REFERENCES

1. Crueger, W. *Biotechnology: A Textbook of Industrial Microbiology*. Sunderland: Sinauer Associates, Inc., 1989.
2. Kirk Othmer Encyclopedia of Chemical Technology. New York: John Wiley & Sons, 1992.
3. Morell, Virginia. "Antibiotic Resistance: Road of No Return." *Science* 278 (October 24, 1997): 575-576.
4. Stinson, Stephen. "Drug Firms Restock Antibacterial Arsenal." *Chemical & Engineering News* (September 23, 1996): 75-100.
5. Katzung, Bertram G. *Basic and Clinical Pharmacology*, 10th edition. Section VIII, Chapter no 51: Clinical use of antimicrobial agents – Harry W Lampiris, MD, & Daniel S. Maddix, PharmD, New York: McGraw, Hill Medical, 2007, p. 867
6. Goodman & Gilman's manual of pharmacology and therapeutics- 11th Ed. (2006): ,section VIII Chemotherapy of microbial diseases, General Principles of antimicrobial therapy - Henry F. Chambers, p. 714
7. Bratzler DW, Houck PM. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. *Clin Infect Dis*. 2004;38(12):1706-1715.
8. Levy SB, Marshall B, Schluenderberg S, Rowse D, Davis J. High frequency of antimicrobial resistance in human faecal flora. *Antimicrob Agents Chemother* 1988;32:1801_6.
9. Barlow, R. and F. Diop (1995). "Increasing the utilization of cost-effective health services through changes in demand." *Health Policy Plan* 10(3): 284-95.
10. Bojalil, R. and J. J. Calva (1994). "Antibiotic misuse in diarrhea. A household survey in a Mexican community." *J Clin Epidemiol* 47(2): 147-56.
11. Delgado, E., S. C. Sorensen, et al. (1994). "Health seeking behaviour and self-treatment for common childhood symptoms in rural Guatemala." *Ann Soc Belg Med Trop* 74(2): 161-8.
12. Larsson, M., G. Kronvall, et al. (2000). "Antibiotic medication and bacterial resistance to antibiotics: a survey of children in a Vietnamese community." *Trop Med Int Health* 5(10): 711-21.
13. Gilson, L., N. Palmer, et al. (2005). "Trust and health worker performance: exploring a conceptual framework using South African evidence." *SocSci Med* 61(7): 1418-29.
14. Haak, H. and A. P. Hardon (1988). "Indigenised pharmaceuticals in developing countries: widely used, widely neglected." *Lancet* 2(8611): 620-1.
15. Sterky, G., G. Tomson, et al. (1991). "Drug use and the role of patients and prescribers." *J Clin Epidemiol* 44 Suppl 2: 67S-72S.

16. Butler, C. C., S. Rollnick, et al. (1998). "Understanding the culture of prescribing: qualitative study of general practitioners' and patients' perceptions of antibiotics for sore throats." *BMJ* **317**(7159): 637-42.
17. Rowe, A. K., D. de Savigny, et al. (2005). "How can we achieve and maintain high quality performance of health workers in low-resource settings?" *Lancet* **366**(9490): 1026-35.
18. Brugha, R. and A. Zwi (1998). "Improving the quality of private sector delivery of public health services: challenges and strategies." *Health Policy Plan* **13**(2): 107-20.
19. Radyowijati, A. and H. Haak (2003). "Improving antibiotic use in low-income countries: an overview of evidence on determinants." *SocSci Med* **57**(4): 733-44.
20. EFSA (2008). "Scientific Opinion of the Panel on Biological Hazards on a request from European Food Safety Authority on food borne antimicrobial resistance as a biological hazard." *The EFSA Journal*(765): 1-87.