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ECONOMIC COST OF ACUTE TONSILLO-PHARYNGITIS IN PEDIATRIC PATIENTS: A RETROSPECTIVE STUDY ON MEDICATION THERAPY ON MEDICAL CENTER RECORDS, IN SAKARYA, TURKEY

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To my marvelous family, especially to my precious mother…

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ABBREVIATIONS

AAP:	American Academy of Pediatrics
AE:	Adverse Event
CBA:	Cost Benefit Analysis
CDC:	Centers for Disease Control and Prevention
CEA:	Cost Effectiveness Analysis
CMA:	Cost Minimization Analysis
CUA:	Cost Utility Analysis
CPI:	Consumer Price Index (=TÜFE)
FDA:	United States Federal Food and Drug Administration
GABHS:	Group A β-Hemolytic Streptococci
HTP:	Health Transformation Program
ID:	Identification Number
IDSA:	Infectious Diseases Society of America
IMS:	Intercontinental Marketing Services
MoH:	Ministry of Health
OTC:	Over the Counter
PASW:	Predictive Analytics SoftWare
SGK:	Sosyal Güvenlik Kurumu (=SSI)
SPC:	Summary of Product Characteristics
SPSS:	Statistical Package for the Social Sciences (SPSS Inc.)
SSI:	Social Security Institution (=SGK)
RADT:	Rapid Antigen Detection Test
TL:	Turkish Lira
TÜFE:	Tüketici Fiyat Endeksi
TÜİK:	Türkiye İstatistik Kurumu
US:	United States
USA:	United States of America
WHO:	World Health Organization

ÖZET
Türkçe Başlık

Amaç: Akut tonsillofarenjit tedavisi için antibiyotik kullanılırken, maliyet önemli bir faktördür. Çalışmada esas amaç, akut tonsillofarenjitin medikal ve medikal olmayan maliyetlerini tanımlamayarak hangi antibiyotik tedavisinin düşük maliyeti olduğunu bulmaktır.

Materyal ve Metot: Bu retrospektif çalışma akut tonsillofarenjiti olan 130 pediyatrik hasta ve onların ebeveynleri ile gerçekleştirildi. Bilgiler Sakarya Üniversitesi Mediko Sosyal Merkezi'nden elde edildi. Medikal olmayan maliyet etkenlerini tanımlamak amacıyla, çocukların anne veya babaları ile telefon anketleri gerçekleştirilmiştir. Medikal maliyetler (antibiyotik tedavisinin, reçete edilen diğer ilaçların, boğaz kültürünün, diğer reçete edilmeyen ilaçların ve diğer hastane ziyaretlerinin maliyeti) ilk visit zamanı ve 2012 yılı için hesaplandı ve bu maliyetler devlet ve hasta açısından değerlendirildi. Ayrıca nominal ve reel değerlerde maliyetlerin karşılaştırılması için hesaplandı. Tüketici Fiyat Endeksi (TÜFE) ve farklı fiyat endeksleri reel değerlerin hesaplanması için kullanıldı.

Bulgular ve Tartışma: Telefon anketi 96 kişi ile tamamlanmıştır ve altı soru cevaplanmıştır. Maliyet hesaplamalarına göre, ortalama en yüksek nominal ve reel maliyet amoksisilin/klavunat kombinasyonuna aittir. Amoksisilin ise hem önceki yıllar hem de 2012 yılı için devlet ve hasta açısından ortalama en düşük reel maliyete sahiptir. Toplam medikal maliyet etkenleri içinde 2012'deki en yüksek nominal ve reel maliyet fizik muayeneye aittir. Medikal maliyetler önceki yıllardan 2012'eye azalmıştır ve bu düşüşün reel değerleri nominal değerlere göre daha fazladır. Bu çalışma, Türkiye'de çocuklarda akut tonsillofarenjitin medikal ve medikal olmayan maliyetleri ile ilgili bilgi toplayan ve değerlendiren ilk çalışmalardan biridir. Sonuçlar maliyet açısından amoksisilinin tedavisinin ilk tercih edilebilecek antibiyotik olduğunu göstermiştir ve ilaç maliyetlerindeki reel düşüş nominal değerlere göre daha fazladır. Sonuç olarak, Türk Sağlık Bakanlığı ilaç maliyetlerini değil, bütçesini direk olarak etkileyen medikal maliyetleri de son yıllarda azaltmıştır. Bunun nedeni sağlık bütçesi üzerindeki finansal baskının artmasıdırr.

Sonuç: Hastalığın ekonomik yükünü değerlendirmek açısından daha fazla farmakoekonomik çalışmalar yapılmalıdır. Böylelikle, antibiyotik kılavuzları geliştirilebilir, gereksiz ilaç kullanımı önlenebilir ve pahalı antibiyotik reçeteleri azaltılabilir.

Anahtar kelimeler: Medikal maliyet, Akut tonsillofarenjit, A grubu beta hemolitik streptokok, antibiyotik ve pediyatr

ABSTRACT

Purpose: Cost is one of the important factors when selecting an antibiotic for the treatment of acute tonsillo-pharyngitis. The main aim of the study is to describe medical and non-medical costs of acute tonsillo-pharyngitis in pediatrics and to find out the antibiotic treatment which has low cost.

Materials & Method: This retrospective study was conducted with 130 pediatric patients who had acute tonsillo-pharyngitis and their parents. Data were obtained from Mediko Social Center at Sakarya University. To describe non-medical cost parameters, telephone surveys were done with mothers or fathers of children. Medical costs (cost of antibiotic therapy, other prescribed drugs, throat cuture, other non-prescribed medicines and other hospital visits) were calculated for the time of first visit and 2012 and they were evaluated in terms of government (payer) perspective and patient perspective. In addition, nominal values and real values were calculated for comparison of costs. Consumer price index (CPI) and different price indexes were used to calculate real values.

Results and Discussion: 96 responders were completed telephone survey and six questions were answered. According to the antibiotic cost calculations, the highest nominal and real mean costs were belong to the amoxicillin/clavunate combination. Amoxicillin has the lowest real mean cost for both previous years and 2012 in terms of patient and government perspective. The highest nominal and real cost in 2012 belong to the physical examination within total medical cost parameters. The medical costs were reduced from previous years to 2012 and the real values of this decline was higher than nominal values. This study is one of the first to collect and evaluate data on the medical and nonmedical costs of acute tonsillo-pharyngitis in children, in Turkey. Results indicated that amoxicillin may be first choice for therapy in terms of cost and the real decline in drug costs are much more than nominal values. Consequently, the Turkish Ministry of Health not only reduced drug costs, but also medical costs which directly affect budget have been reduced in recent years because financial restraints on the health bugdet have increased.

Conclusion: Further pharmacoeconomic studies should be conducted for the evaluation of economic burden of disease. In this way, antibiotic guidelines can be developed, unnecessary usage of medications can be prevented and expensive antibiotic prescriptions can be reduced.

Key words: Medical cost, Acute tonsillo-pharyngitis, group A -hemolytic streptococci (GABHS), antibiotic and pediatric.

1. INTRODUCTION

Acute tonsillo-pharyngitis is generally seen in childhood and it is one of the upper respiratory system illnesses. It is one of the most frequent infection for which pediatricians, internists, and other emergency service doctors are consulted. It is indicated that, physicians can examine at least one patient with a tonsillo-pharyngitis every day and they can prescribe antibiotics for treatment[(1)]. Upper respiratory system infections make up the largest single group of acute diseases confronting the physician. This infection involves the mucous membranes and lymphatic tissues of the throat, usually including the posterior pharynx, the tonsils and the soft palate. Many children do not become ill and they can carry bacteria in their throat. However, sometimes a bacterial throat infection can occur and physicians write prescriptions for therapy[(2)].

According to Turkey Intercontinental Marketing Services (IMS) Health data, 13,068,578 prescriptions were written by physicians for similar diagnoses including acute tonsillitis, acute nasopharygitis, streptococcal pharyngitis, streptococcal tonsillitis in 2010. In addition, there were 7,010 prescriptions written specifically for streptococci in the same year.[1] Acute tonsillo-pharyngitis is a problem in Turkey according to IMS data. The prescription rate is not only important to evaluate disease in terms of pharmacoepidemiology, it is also important to evaluate economic cost of disease in terms of pharmacoeconomy.

There is an increasing concern to evaluate the economic impact of medical treatment. Therefore, a discipline has been developed and this discipline established the study of how pharmacotherapeutic methods influence resource utilization in health care known as pharmacoeconomics[(4)]. In other words, pharmacoeconomics defined as "the explanation and analysis of the costs of medical treatment to healthcare systems and society"[(5)]. Moreover,

[1] IMS provide information services for healthcare and pharmaceutical industry. Around the world it covers markets in more than 100 countries which makes it a leader in information services sector. For now, IMS tracks more than 1.3 million healthcare products, covering over 80 percent of all pharmaceutical sales worldwide. They capture information on 260+ million de-identified patients, including their diagnosis and treatment[(3)].

pharmacoeconomic reasoning starts from the point that in any real economic system, resources are rare in relation to demands and needs. This is also valid for both private and public healthcare systems. Therefore, if an individual is receiving or paying for health services, he/she should choose among available alternatives [5].

All health systems currently states concerns about the cost of medical care and pharmaceuticals in particular. Generally, health care systems focus on providing quality remedies within limited financial resources. Costs and financial restraints on the Ministry of Health (MoH) have increased in recent years and put pressure on the Turkish Health Care System day by day. Drug prescribing is an area of focus for rationalization and cost savings. Drug prescription costs became more important, because now they account for an extensive part of the total cost of health care. For instance, for developed countries it is typically between 10 % and 15 % and it is up to 30-40 % in some developing countries. Health care professionals believe that the treatment cost is equal to the drug cost itself [4], [6]. However, drug costs should not be evaluated alone. Overall costs of treatment should be considered for health care system. Cost saving may be done in other areas that emerge hidden costs such as use of other drugs, administration costs, the number of doctor visits, adverse effects and laboratory costs. In addition, non-medical costs, including time missed due to the disease, care costs, transportation costs, and etc. should also be considered. Therefore, pharmacoeconomic research identifies, measures, and compare all different costs and related consequences of pharmaceuticals and health services. There are some research methods including cost-minimization, cost-effectiveness, cost-benefit, cost-of-illness, cost-utility, cost consequences, and decision analysis [4], [5], [6]. Moreover, quality of life and other humanistic assessments were described in pharmacoeconomic research. Four common types of research methods of economic evaluation are summarized in Table 1.

Table 1 – Four Common Types of Economic Evaluation [4], [5], [6]

Research Methods of Economic Evaluation	Description of Method	Example	Cost Unit / Outcome Unit
Cost Minimization Analysis (CMA)	To calculate drug costs to evaluate the cost of a specific drug by comparing two drugs those are equivalent in dose and therapeutic effect.	Comparing two generic and therapeutic equivalents used for hypertension	Currency unit (TL or $) / Currency unit (TL or $)
Cost Effectiveness Analysis (CEA)	To measure health benefits or health outcomes across therapies according to the indication of the drug	For an asthmatic patient the cost to achieve a decrease in oral corticosteroid use	Currency unit (TL or $) / Natural unit (e.g. blood glucose level)
Cost Utility Analysis (CUA)	To determine cost in terms of utilities, generally quantity and quality of life by comparing two different drugs or procedures whose benefits may be different.	An increased duration of life of one year (without change in quality of life), or an increase in quality of life after a drug therapy or surgery	Currency unit (TL or $) / Quality adjusted life year
Cost Benefit Analysis (CBA)	To compare costs and benefits, both of which are quantified in common monetary units?	Amount willing to pay to prevent transplantation for patients with hepatitis C (willingness to pay)	Currency unit (TL or $) / Currency unit (TL or $)

Some analysis, including cost-effectiveness analysis and cost-utility analysis take economic vantage point. This point indicates perspective in pharmacoeconomic analysis and perspective affects the types of costs and benefits that will be considered relevant to the analysis. Pharmacoeconomic analysis includes five general perspectives; institutional, patient, third party, governmental and societal [7]. According to the situation and the perspective taken, cost estimates at various levels and data in various ways will be required to make pharmacoeconomic analysis. For instance, a government perspective may require information about drug costs and cost offsets and a societal perspective may need not only government, but also non-government costs and cost offsets [4], [7].

Pharmacoeconomic cost includes direct costs, indirect costs and hidden costs. Sometimes medical and non-medical costs used instead of direct and indirect costs as a terminology. Direct medical costs and direct non-medical costs are evaluated as direct costs. Hidden costs can vary from study to study, so hidden costs are flexible. Clearly, resources that are directly used in treating the patient, referred as direct costs. Medications, doctors and hospitals are example for direct

costs. The impact on the time of the patient and their friends/relatives due to treatment is evaluated as indirect cost. For instance, patient's time in undergoing treatment and lost opportunities for patient to engage in work [8].

Moreover, in line with drug group or therapeutic area, costs are often need to be listed to determine the reason of changes in costs. Cost of a drug can alter and it results from different reasons such as changes in prescription volumes, quantity per prescription or in the average cost per prescription [4]. Antibiotics cover a significant portion of total health expenditures in the world. While the cost of a prescribed single antibiotic may not be very high, newer ones are somewhat costly. The actual cost of their prescription is unknown despite the fact that they account for a large part of all pharmacy and hospital budgets. If other nonmedical costs are considered, the costs are high because great numbers of prescriptions are written around the world each day. Additionally, millions of doctor visits and prescriptions for antibiotics cause major expense for health care services. Newer antibiotics are quite costly while early antibiotics such as penicillin is not expensive. Antibiotic treatment used for infections has a cost which represents a significant part of hospital expenditure. For instance, in a comparative case-control study which was conducted in Hacettepe University Hospital, the researcher found the cost of antibiotic therapy per infected patient $1190 [9]. This cost was about 75% of the total indirect cost such as cost of prolongation of hospital stay. This finding may be due to the fact that antibiotic prices were very high in Turkey in 1997 [9], [10]. Therefore, Turkey Ministry of Health has reduced the price of antibiotics many times in recent years. Although, cost of antimicrobial treatment is an important part of health expenditure, data on this subject are limited in Turkey.

A prospective observational study was conducted in Akdeniz University Hospital to specify the daily antibiotic cost of nosocomial infections. Daily antibiotic costs were calculated per infected patient. According to the results of this study, for treatment of the nosocomial infections, piperacillin-tazobactam and amikacin were the most prescribed antibiotics, and the most expensive drug was

meropenem. Infections of urinary tract had the lowest daily antibiotic cost per infected patient among the sites of nosocomial infections. The mean daily antibiotic cost for diseases were also evaluated and pneumonia was the highest of all sites, but bloodstream infection had the highest range of daily cost[10]. This study is important to form an opinion about costs of different antibiotic options.

Cost is an important factor that affects the physicians' prescription for treatment of patients. Therefore, physicians should evaluate not only infection, but also antibiotics prices should be evaluated before prescribing an antimicrobial agent. Now, etiology of acute tonsillo-pharyngitis will be summarized so as to conseptualize the evaluation of medical costs.

1.1. Etiology of Acute Tonsillo-Pharyngitis

Sore throat is the most common symptom of acute tonsillo-pharyngitis and the cause of sore throat is usually viral. In other words, viruses are the most common cause of acute infection. Viral agents, including adenovirus, influenza virus and parainfluenza virus may cause acute pharyngitis. There are also another non-bacterial infectious agents, but, the cause is bacterial in other cases. The main bacterial cause of sore throat is *group A β-hemolytic streptococci* (GABHS). *Beta-hemolytic streptococci* cause large zones of hemolysis on blood agar and this helps to determine microbiological identification, easily. Possibly, M protein is the most important virulence factor of GABHS. This protein is required for invasive infection and it is located peripherally on the cell wall. *Group A β-hemolytic streptococci* contains a hyaluronic acid capsule, that also has an important role in initiation of infection. Large quantities of the capsule are produced by bacteria and a characteristic mucoid appearance is shown on blood agar. Therefore, they may be more virulent and a single virulent clone may cause complications that increase medical costs of the disease[11].

Pharyngitis caused by GABHS, commonly called “strep throat” since it is the most common symptom. Although the most common bacterial cause is GABHS,

only a small percentage of patients are infected by *group A streptococci*. *Group A streptococci* cause 15–30 % of cases of acute pharyngitis in pediatric patients. The cause of acute tonsillo-pharyngitis can also be other bacteria such as *Streptococci, Groups C and G*. Although these bacteria are uncommon cause of acute pharyngitis in pediatric patients, the infection caused by either of these non-GABHS streptococci have a clinical presentation similar to that of GABHS pharyngitis [(12), (13)]. Common microbial etiology of acute pharyngitis is summarized in table 2.

Table 2 – Microbial Etiology of Acute Tonsillo-Pharyngitis [(12), (13)]

Kind of the Pathogen	
Bacteria	**Viruses**
Group A β-hemolytic streptococci	Adenovirus
Streptococci, Groups C and G	Influenza virus
Arcanobacterium haemolyticum	Parainfluenza virus
Mycoplasma pneumoniae	Rhinovirus
Corynebacterium diphtheriae	Cytomegalovirus
Neisseria gonorrhoeae	Epstein-Barr

Group A β-hemolytic streptococcal pharyngitis is the common factor in acute tonsillo-pharyngitis and antimicrobial treatment is certainly needed. On the other hand, clinical features of GABHS pharyngitis overlap with other infections. Therefore, to determine cause of the pharyngitis is *group A - β hemolytic streptococci* or not, microbiological testing should be done. In other words, if the physician is not able with confidence to exclude the diagnosis of GABHS pharyngitis on epidemiological and clinical findings, a laboratory test is recommended to be done [(12), (14)].

1.2. Clinical Diagnosis of the Disease

After the evaluation of patients' epidemiological and clinical findings, the physicians have to make a diagnosis before starting a treatment with antibiotic. However, diagnosis is not easy based only on clinical findings due to the fact that the signs and symptoms of GABHS pharyngitis overlap extensively with

other infectious causes. Therefore, the physicians make assessment for both clinical and epidemiological findings. The occurrence of group A β-hemolytic streptococcal pharyngitis cannot be definitively guessed with these findings. On the other hand, they can identify people for whom the chance of GABHS pharyngitis is high or low [12], [15].

Group A β-hemolytic streptococcal pharyngitis has certain characteristic epidemiological and clinical features that are summarized in table 3.

Table 3 - Clinical and Epidemiological Findings [12], [15]

Findings Suggesting Bacterial Infections	Sudden onset (Acute)
	Sore throat
	Fever - Temperature ≥ 38 ° C
	Headache
	Pediatric patients (5 – 15 years old)
	Absence of cough
	Nausea, vomiting, and abdominal pain
	Inflammation of pharynx and tonsils
	Pharyngeal and tonsillar exudates
	Anterior cervical noes swollen or enlarged
Findings Suggesting Viral Infections	Cough
	Coryza
	Conjunctivitis
	Diarrhea

Patients either children or adult, with acute tonsillo-pharyngitis generally present with sore throat and sore throat has sudden onset. Fever is another important clinical finding and pediatric patients generally has temperature greather than 38°C. GABHS is not common among children who are under age of 3, it occurs usually between ages 5 and 15. Therefore, age is also a factor in terms of clinical decision rule for the choice of right therapy and management of disorder. Physicians describe inflammation of pharynx and tonsils with pharyngeal and swollen or enlarged anterior cervical nodes and tonsillar exudates during examination. On the other hand, none of these findings is specific for group A β –hemolytic streptococcal pharyngitis.

To diagnose GABHS pharyngitis accurately, a scoring method can be used. For example, four signs and symptoms over ten symptoms (Table 3) are used to estimate the probability of acute streptococcal pharyngitis according to the original centor score. After determining total score, the likelihood of streptococcal pharyngitis and the need for antibiotics were specified with the help of cumulative score (Figure 1) [12), (15)]. These clinical scoring systems are useful to identify patients who are at low risk of streptococcal infection and patients who have high score and high risk of infection to start antimicrobial therapy. In other words, after physicians evaluate an individual patient with presumed group A streptococcal pharyngitis according to the clinical decision rule, criteria make them flexible to start antibiotic treatment[(15)]. If a well clinical decision is performed for right diagnosis, a lower rate of antibiotic may be prescribed for pediatric patients. By this way, unnecessary antibiotic usage may be prevented and it reduces economic burden of the disorder.

Clinical decision rule was showed in Figure 1 and cases have a score of 4 or higher shows patients are at high risk of streptococcal pharyngitis, and empiric treatment is initiated. Patients who have a score of zero or 1 are at very low risk for streptococcal pharyngitis and do not need laboratory testing or antimicrobial therapy. Therefore, it is supposed that empiric treatment with antibiotics are needed due to the risk of GABHS pharyngitis (Figure 1)[(15)].

Patient with Sore Throat

Criteria	Points
Absence of cough	**1**
Fever - Temperature ≥ 38 ° C	**1**
Age 5 to 15 years	**1**
Pharyngeal and tonsillar exudates	**1**
Anterior cervical nodes swollen or enlarged	**1**
Determine Therapy According to the Cumulative Score	

Total Score	Clinical Decision
Score ≤ 0	No further testing or antibiotics prescribed
Score = 1	No further testing or antibiotics prescribed
Score = 2	Perform throat culture or rapid antigen detection tests (RADT)
Score = 3	Perform throat culture or rapid antigen detection tests (RADT) - If negative: No antibiotics indicated - If positive: Treat with antibiotics
Score ≥ 4	Consider empiric treatment with antibiotics

Figure 1 - Clinical Decision Rule for Management of Acute Tonsillo-Pharyngitis [(15)]

1.3. Laboratory Diagnosis of the Disease

The signs and symptoms of streptococcal and nonstreptococcal pharyngitis overlap too broadly for diagnosis, so it is hard to do right diagnosis on clinical findings alone. Therefore, a laboratory test is advised to be done for the determination of the presence of group A streptococci in the pharynx. To evaluate acute tonsillo-pharyngitis in laboratory, there are two broad categories; first one is throat culture and second one is rapid antigen detection test (RADT). Samples from the oral cavity gives reduced sensitivity. Thus, samples for throat

culture or rapid antigen detection test are gotten from the posterior pharynx or tonsils of the patient.

Throat culture test is still the gold standard for the diagnosis of streptococcal pharyngitis and sensivity of a single culture is 90 % – 95 %, if test result is obtained correctly. 24-48 hour turnaround time is needed for throat culture test and it requires more technical involvement although throat culture remains standard to diagnose streptococcal pharyngitis. In obtaining the result of throat culture test, a disadvantage is the delay on blood agar of swab. It may last overnight or longer. For this reason, rapid antigen detection tests have been developed and the resuçt is obtained after ten minutes. Despite the fact that these rapid tests are more expensive than culture tests, results of them are obtained faster[12), (15)].

Physicians should take into account the clinical and epidemiological findings to decide to carry out a laboratory test for microbiological identification of the disease. The 'American Heart Association', the 'American Academy of Pediatrics' (AAP) and the 'Infectious Diseases Society of America' (IDSA) recommend throat culture or rapid antigen detection test to confirm clinical diagnosis of pharyngitis [(15)]. Laboratory tests enable reduction in the unnecessary usage of antibiotics, but positive result of test can not make different acute infection from the streptococcal carriers. Testing usually is necessary for patients with acute tonsillo-pharyngitis that has clinical and epidemiological findings are not significantly different from a group A streptococcal etiology [(1), (12)].

In a research which was conducted at a managed care organization, (Cincinnati – Ohio), a cost-effectiveness analysis of treatment management strategies for pharyngitis was performed. A decision analysis model was organized to evaluate the short-term costs and cost-effectiveness. There were 7 strategies such as including neither testing for streptococcus nor treating with antibiotics; treating empirically; basing treatment on results of a throat culture; and basing treatment on results of rapid tests. As a conclusion, the culture strategy was the most effective and least expensive and if amoxicillin was prescribed orally, culture

strategy was also preferred. Hence, a throat culture from pediatric patients are generally obtained by physicians in most cases [16].

In a study which was performed at Başkent University, in Turkey, the throat culture and rapid antigen detection tests were obtained from ninety-two patients with acute tonsillo-pharyngitis. According to the results of these tests, all the patients who had the positive culture result for GABHS, had also positive rapid antigen detection test. Moreover, rapid antigen detection test lasted about ten minutes, so it was quick and reliable test to diagnose Group A streptococcal tonsillo-pharyngitis [17].

It is extremely important that physicians should perform microbiological tests to prevent unproper administration of antibiotics to large numbers of pediatric patients with tonsillo-pharyngitis. Not only does such therapy unnecessarily expose patients to the expense and hazards of antibiotic treatment, but also it contributes to the emergence of antibiotic – resistant bacteria.

On the other hand, few studies were carried out in Turkey regarding bacterial tests to reduce the rate of antibiotic administration. Generally, small number of samples were examined in these studies. In addition, hospitals in Turkey have very crowded in terms of patient number. Due to these facts, physicans think that it may take much longer to get results from the laboratory and it is too difficult to perform microbiological test for every single case. Thus, therapy with antimicrobial agents are usually started, if there is clinical or epidemiological evidence that results in a high index of suspicion[18].

1.4. Treatment of Acute-Tonsillo Pharyngitis

If there is a suspicion according to the clinical or epidemiological findings, antibiotics are prescribed for pediatric patients. An antimicrobial agent at a dose and for a duration should be initiated for patients to eradicate the organism, infected the pharynx. If the therapy is started early, complaints of the patient

resolve faster. On the other hand, for symptomatic pharyngitis, treatment is initiated if the result of microbiological test (throat culture or RADT) confirm the presence of bacteria. Patients do not continue initiated treatment unless the confirmation is obtained by results of a laboratory test. However, empiric treatment can be started to the patients who have high risk based on clinical desicion rule. Some factors such as individual economic, social and medical issues should be taken into consideration for each patient before prescription of antibiotics. These multiple factors that should be considered before initiating antibiotic treatment are summarized in Table 4 [(1), (15), (16)].

Table 4 - Factors Affecting Antibiotic Choice for Acute Tonsillo-Pharygitis [(1), (15), (16)]

Bacteriologic and clinical efficacy
Compliance issues
Patient allergies
Spectrum of activity
Dosing schedule
Potential side effects (Safety)
Taste of drug
Cost

Aim of the treatment is to prevent clinical signs and symptoms and reduce transmission to other people[(9)]. There are many antibiotics and their effectiveness for the treatment of streptococcal pharyngitis have been shown and proven. Potential antibiotic options for acute tonsillo-pharyngitis are summarized in table 5. Effective antibiotics for GABHS pharyngitis are penicillin, penicillin congeners (amoxicillin or ampicillin), clindamycin, some cephalosporins and macrolides [(15), (16)]. All trade names of antimicrobial agents including both original and generic products in Turkey are also given in Table 5.

After treatment with antibiotics about sixteen hours overall, duration of symptoms is reduced. Antibiotics have relative benefits to treat sore throat, but the absolute

benefits are modest. Treatment with antbiotics is needed to prevent occurence of complications in patients who are suffering from sore throat. The incubation period of the disease is 24 to 72 hours. Therefore, after 72 hours from initiation of therapy, patients were advised to come second visit to determine whether the clinical symptoms shorten or not [16].

Table 5 - Antibiotic Options for Acute Tonsillo-Pharyngitis [1], [12], [15]

Active Ingredient	Trade Names in Turkey	Class of Antimicrobial	Route	Dosage	Frequecy	Therapy Duration
Penicillin V	PEN-OS	Penicillin	Oral	*250 mg– children	2 or 3 times/day	10 days
Penicilin G benzathine	PENADUR L-A PENTİN-LA DEPOSİLİN BENZAPEN-LA	Penicillin	Intramuscular	*< 60 lb (27 kg): 6.0 × 10^5 units – children	Single injection	One dose
Amoxicillin	ALFOXIL AMOKSILIN AMOKSINA LARGOPEN DENTAMAX ATOKSILIN REMOXIL	Penicillin	Oral	*12.25 mg per kg or *10 mg per kg 3 – children mild GABHS *22.5 mg per kg *or* *13.3 mg per kg – children severe GABHS	2 times/day 3 times/day 2 times/day 3 times/day	10 days
Treatment for Patients with Penicillin Allergy						
Erythromycin		**Macrolide**	**Oral**	**Varies with formulation**		**10 days**
--Erytromycin ethyl succinate	ERYTHROCIN	Macrolide	Oral	*30 to 50 mg per kg per day– children	2 to 4 divided doses/day	10 days
--Erythromycin estolate	NONE	Macrolide	Oral	*20 to 40 mg per kg – children	2 to 4 divided doses/day	10 days
First-generation cephalosporins		**Cephalosporin**	**Oral**	**Varies with formulation**		**10 days**
--Cefadroxil	DURICEF CEFRADUR	Cephalosporin	Oral	*30 mg per kg– children	2 div. doses/day	10 days
--Cephalexin	MAKSIPOR SEF	Cephalosporin	Oral	*25 to 50 mg per kg – children	2 to 4 divided doses/day	10 days
FDA Approved Medications, but are not Recommended by Guidelines for Primary GABHS Therapy						
Azithromycin	ZITROMAX TREMAC AZRO AZITRO AZOMAX AZELTİN	Macrolide	Oral	*12 mg per kg – children	Once/day	5 days
Amoxicillin–clavulanate acid	AUGMENTIN AMOKSILAV AMOKLAVIN BIOMENT CROXILEX KLAMOKS KLAVUNAT KLAVUPEN	Penicllin beta-lactam inhibitor combinations	Oral	*40 mg per kg – children	2 or 3 div. doses/day	10 days

Once daily azithromycin and amoxicillin–clavulanate acid were approved by United States Federal Food and Drug Administration (FDA) to treat acute tonsillo-pharyngitis for 10 days, but these antibiotics, even when taken for once a day, are more expensive than amoxicillin. In recent days, The American Heart Association recently recommended amoxicillin and its effectiveness has been proven for the treatment of GABHS pharyngitis once daily. Additionaly, when amoxicillin is compared with twice daily or 3 to 4 times daily penicillin therapy, it has no apparent disadvantage [19].

Among antibiotics, penicillin V has proven efficacy, safety and narrow spectrum. Thus, it remains the treatment of choice for five decades and American Academy of Pediatrics, the American Heart Association, the World Health Organization (WHO), and the Infectious Diseases Society of America still recommend penicillin V therapy. In spite of recommendation, this antibiotic treatment has risk in terms of adverse events (AEs) such as anaphylaxis. Penicillin V should not be started without distinction because it also has risk of financial cost and potential to contribute emergence of resistant strains [15].

Intramuscular administration of benzathine penicillin G is another penicillin option for treatment of acute tonsillo-pharyngitis. Studies conducted between 1960s and 1970s demonstrated that oral and intramuscular administration of penicillins are equal in terms of GABHS eradication. Intramuscular penicillin is prescribed for patients who are not able to complete a ten day course of oral therapy, definitively. Additionally, when the patient feels noncompatibility with oral treatment, one dose penicillin G benzathine can be recommended. A disadvantage of intramuscular injection is the pain, but this penicillin has no compliance problems [12].

Despite the fact that there are other antimicrobial agents clinically used to treat acute tonsillo-pharyngitis, penicillin treatment is still advised by some guidelines. Oral amoxicillin, a penicillin congener, is prescribed in place of penicillin because its efficacy seems to be equal when compared.

Clinical trials were done from 1996 to 2000 and their results showed that after the usage of amoxicillin, bacterial eradication is greater than 85 percent. Amoxicillin is frequently administered to young children in place of oral penicillin V. The primer cause of the choice is the taste of antibiotic. In other words, it is accepted easily when taken orally. The serum half life of penicillin V is shorter that of amoxicillin because amoxicillin absorption is not afffected by food ingestion. Last but not least, amoxicillin is less expensive and in terms of antimicrobial activity it has a narrower spectrum than other approved once daily antimicrobial agents [(15)].

A research was carried out with 152 pediatric patients who were between 4 and 18 years old to evaluate effectiveness of tonsillo-pharyngitis treatment with amoxicillin at a dose of once daily. Patients were randomized to orally either amoxicillin or penicillin V for 10 days. For monitoring compliance, urine antimicrobial activity was used. Effect on the clinical course is evaluated as an outcome and follow-up throat cultures were done to determine eradicaton and bacteriologic treatment failure. As a result, in terms of clinical or bacteriologic responses, there were not remarkable difference between two treatment groups after 18 or 24 hours from the initiation of therapy. However, bacteriologic treatment failures were observed in 4 (5 %) of the 79 patients in the amoxicillin group and in 8 (11 %) of the 73 patients in the penicillin V group. This research showed that amoxicillin therapy for once a day is as effective as penicillin V therapy given three times a day. If additional investigations were conducted to confirm these results, once-daily amoxicillin can be accepted as an alternative antimicrobial agent for the treatment of GABHS pharyngitis [(15)].

An alternative choice to penicillin is macrolide. It is not recommended to use macrolides routinely because they increased bacterial resistance to take macrolides. Patients with type I penicillin allergy is recommended because they cannot treated with penicillin. Erytromycin is an advisable macrolide for patients who have penicillin allergy. Erytromycin stolate and ertromycin ethylsuccinate are

also recommended by current United States (U.S.) treatment guidelines. However, some patients, about 20 percent, cannot prefer this antibiotic due to its gastrointestinal side effects such as diarrhea and stomachache [(1), (14), (15)].

Oral cephalosporins can be prefered unless a patient has immediate-type hypersensivity to beta-lactam antibiotics. Actually, cephalosporin treatment should not be initiated to patients who are allergic to penicillin because cross reaction can occur. For an effective therapy to eradicate GABHS, a 10 day course of cephalosporin usage is needed. First-generation cephalosporins such as cefadroxil and cephalexin have a narrower spectrum, so they are preferable to second or third generation agents.

According to the a study, cephalosporins were found to be more effective against GABHS eradication than penicillin. Over 35 randomized trials demonstrated that the success rate of cephalosporins in treating acute tonsillo-pharyngitis was higher for all patients. When compared with penicillin therapy, other 12 studies also showed equal or better success rate about 7 days later from the start of treatment. However, evidence is insufficient to obtain clinically significant differences between penicillin and cephalosporins to treat GABHS pharyngitis. Cephalosporins are also more expensive and although penicillin is the first choice for therapy according to the guidelines, physicians broadly prescribe these expensive cephalosporins for pediatric patients. Consequently, broad-spectrum second and third generation cephalosporins will be preferable to penicillin in the future, but patients should receive alternative treatment if they do not respond the first therapy [(15), (20)].

Azithromycin is a second line treatment and patients with acute pharyngitis use it for five days. It allows once daily dosing and shorter treatment period. Currently, there is not enough evidence to advise the usage of azithromycin for routine therapy. In a multi-center study which was conducted in Harborview Medical Center, Seattle, Washington, U.S., the safety and efficacy of azithromycin was compared with that of penicillin V which was used to treat 142 patients with

streptococcal pharyngitis. Complaints of all patients with one exception in each group were reduced clinically according to the results of the study. Percentage of patients treated with penicillin were higher than percentage of patients treated with azithromycin. Azithromycin group had a higher frequency in terms of side effects including diarrhea, nausea and abdominal pain. Overall, azithromycin and penicillin V were comparable both clinically and bacteriologically [(21)]. Nevertheless, effectiveness of azithromycin to prevent acute rheumatic fever is not known and it is an expensive antibiotic. Therefore, further studies about acute tonsillo-pharyngitis should be designed and initiated for the investigation of the effectiveness of both drugs [(1), (21)].

Amoxicillin/clavulanate is an alternative antibiotic option for the treatment of acute tonsillo-pharyngitis and can be prescribed by physicians due to the fact that penicillin therapy is ineffective, occasionally. Colonization of copathogens occur in tonsillopharyngeal area and they produce beta-lactamase that cause degradation. Amoxicillin – clavulanate potassium, a combination drug, is resistant to this degradation. Some studies showed that amoxicillin–clavulanate was not superior to penicillin to cure acute infection. The number of the aerobic and anaerobic bacteris can be reduced after the use of this antimirobial agent. One disadvantage of this combination drug is its side effect. Most of the patients suffer from diarrhea, but therapy continues because it is generally mild. However, amoxicillin-clavulanate is more expensive than other antibiotics. Some studies should be conducted in the future to evaluate efficacy and determine whether its use will increase costs or not [(1), (14)].

In a research, antibiotics were identified by using the National Drug Code Directory. Some of them such as polymyxins, aminoglycosides, and antimycobacterial, antifungal, and antiviral agents were excluded. According to research, penicillin, amoxicillin (including ampicillin), erythromycin, and first-generation cephalosporins should be prescribed in the therapy of GABHS pharyngitis. All other antibiotics, including amoxicillin/clavulanate, were considered as nonrecommended considered for GABHS treatment [(22)].

1.5. Cost Analyses and Cost-Effectiveness Analyses of Acute Tonsillo-Pharyngitis

During literature search, cost analyses and cost-effectiveness analyses about acute tonsillo-pharyngitis were found and these analyses were different from each other in terms of evaluation and calculation of costs. Nevertheless, three pharmacoeconomic studies regarding medical and non medical-costs of GABHS pharyngitis have been found and they are summarized below.

In a research which was conducted at two pediatric practice sites in the Boston, US, the morbidity, medical costs, and nonmedical costs were investigated and data of school-aged children with GABHS pharyngitis was evaluated. In addition, telephone interviews were conducted with parents of eligible children and some questions were asked about disease to calculate medical and nonmedical costs. According to the results, the societal cost of group A streptococcal pharyngitis is substantial, with almost one half being attributable to nonmedical costs and the total cost of the illness among children in the country ranges from $224 to $539 million per year (2005-2006). This is the first conducted study to collect empiric data on the societal costs of tonsillo-pharyngitis in children and adolescents [(23)].

In another prospective study in Australia, the incidence, transmission, carriage, and risk factors for group A streptococcal pharyngitis were described in school-aged children and their families. Randomization was done for the selection of 202 families from 3 primary care practices and all family members were included to evaluate transmission of acute group A streptococcal pharyngitis within the household. Based on results, tonsillo-pharyngitis is still common, peak incidence occurs in school-aged children and it has higher-than-expected proportion of the potentially important role of interfamiliar transmission. Thus, the number of secondary cases may reduce within families if therapy is carried out effectively. Transmission of GABHS pharyngitis is significantly important in terms of societal burden of disease [(24)].

In another study, conducted with children in a private pediatric office, the effectiveness of once-daily amoxicillin in the treatment of GABHS pharyngitis were evaluated. Patients were randomized to receive oral amoxicillin or penicillin V for ten days. Significant difference was not found in the clinical or bacteriologic responses of the patients in the two therapy groups after patients came to the follow-up visits. Results of this study showed that once-daily amoxicillin therapy could become an alternative choice for acute tonsillo-pharyngitis if confirmed by additional studies because once-daily amoxicillin treatment is found as effective as penicillin V treatment given three times a day [(25)].

2. The Aim of the Study

This study includes pediatric patients who had received antibiotic treatment for acute tonsillo-pharyngitis and the main aim of the study is to describe medical and non-medical costs of acute tonsillo-pharyngitis in pediatrics which is based on a research which was conducted in Boston [(23)].

This study:

- considers both government perspective (payer) and societal perspective (patient perspective) to evaluate medical costs.
- tries to find out the low cost antibiotic treatment. The cost of different antibiotic treatments were compared.
- tries to determine additional medical costs and to specify non-medical costs.
- analyses the positive impact of nonmedical cost of acute tonsillo-pharyngitis on total economic burden.

3. METHODOLOGY

In this part research design and methodology of the study are presented. Data collection, study population, survey, data analysis, pharmacoeconomic evaluation methods for medical and non-medical costs and limitations of the study are defined and explained.

3.1. Data Collection

This is a retrospective study and the data of this study has been obtained from Pediatry Clinic of Mediko Social Center at Sakarya University in Sakarya, Turkey. The records of patients who received different antimicrobial agents for the treatment of acute tonsillo-pharyngitis between 2006 and 2010 were obtained for this study. These records were collected after the approval of the study by Ethics Committee of Sakarya University approved on April 14 2011. Submission to Ethics Committe was done on behalf of main investigator who is also manager of Mediko Social Center. The approval letter is presented in Appendix 1.

130 episodes of acute tonsillo-pharyngitis were identified among children who were gathered at clinic. Data collection of 130 patients were completed at the end of May 2011. After 130 patients' data were collected, a telephone survey was administered to patients' parents in order to gather data about non-medical costs associated with patients' treatments which was completed at the end of June 2011. Because of being not a computer based visit card and survey, it needed a careful working and took long time to transfer the case and survey data to electronic environment. Transfer of case and survey data to an excel list was completed at the end of August 2011.

All patients have a visit card and an identification number (ID) assigned by the medical personnel at Mediko Social Center. Visit card includes patient's visit date, demographic charasteristics and clinical characteristics of patients, family information, required laboratory tests and prescribed medications. In terms of demographic characteristics; patient's age, sex, weight, height and brief medical

history are usually asked and recorded by physicians. Education level, monthly household income and contact details are also questioned by physicians to obtain information about family.

Moreover, physicians write complaints, presenting symptoms and findings on visit card during physical and systemic examination. While collecting data for this study, instead of their real names, patients' IDs used for confidentiality purposes. Lastly, patients' cards also contain contact details of parents, so telephone numbers of survey participants were obtained from visit cards. An example of visit card is shown in appendix 2. Name and surname of the patient and telephone number of the parent were covered up with white-out in example due to patient confidentiality.

3.1.1. Mediko Social Center

Mediko Social Center was chosen for data collection because a lot of information about patient is recorded on visit cards and these cards are archived on a regular basis at the center. Due to some constraints such as limited time and cost, Sakarya University was an alternative to prefer. Ethics committee approval has also been obtained. For these reasons it was an ideal location to collect data and conduct telephone surveys.

Mediko Social Center is inside Esentepe Campus of Sakarya University. It is located on an area of 710 m^2. There are pediatry clinic, respiratory disease and smoking cessation clinic, general surgery clinic, obstetrics and gynecology clinic, cardiology clinic, dentistry clinic, diet clinic, general outpatient clinic and psychotechnic laboratory. There are also emergency service, laboratory, psychologist's meeting room, x-ray room, dark room, ultrasonography room, observation room, nurse room and counseling in the building.

Six physicians, two dentist, two psychologist, seven nurses and two technicians work at Mediko Social Center. The selected patients for this study were checked

up by three different pediatricians between 2006 and 2010. A professor pediatrician only works at pediatry clinic. Appointments are given by phone for examination on certain days of the week. Generally, university personel or university students apply for physical examination or laboratory tests. However, family of university personel or people outside the university can also apply for physician visit.

In laboratory of Mediko Social Center, 18 parameters hemogram with automatic blood count device, all biochemistry test with full automatic biochemistry autoanalyzer, hepatit and AIDS tests, blood and urine tests are carried out. All devices are calibrated and all tests were done by qualified personnel. In addition, some specific laboratory tests such as HgA1c, HPSA, prothrombine time and INR are done and hormon tests were carried out with VIDAS immuneassay otomatic hormon device. On the other hand, throat culture test for the diagnosis of GABHS pharyngitis could not be obtained from this laboratory. Therefore, throat culture tests were done in a private hospital, in Sakarya [(26)].

3.2. Study Population

The study population includes the pediatric patients diagnosed as having acute tonsillo- pharyngitis and their parents. In Mediko Social Center, Sakarya, about 3000 pediatric patients with different diagnosis were examined in pediatry clinic between 2006 and 2010. For this study, Visit cards of 130 cases from 2006 to 2010 were chosen and information on cards were transferred to an excel list. Different antibiotic groups were specified and there were 130 cases who were treated with these antibiotics for acute tonsillo-pharyngitis. Thus, all 130 cases in this period were evaluated for our study.

In addition, information regarding number of visits, laboratory tests, prescribed medicines were obtained from patient's data on visit card. Patients, between 5 and 15 years old and had suitable sypmtoms of tonsillo-pharyngitis were chosen to be consistent in terms of clinical decision rule.

Study population also includes mothers or fathers of children. To describe parameters emerge non-medical costs, parents of the patients were also included for the study and telephone surveys were done with them.

3.3. Survey Design

Survey was developed after a through examination by literature review. Necessary changes were done after review. Then, survey was presented to Ethics Committee. Time and sample size were limited, so the pilot study was not conducted. Thus, questions could not be asked to parents before obtaining Ethical Approval and if modifications for some parts of survey after pilot study are required, new submission to Ethics Committe should be done.

3.3.1. Survey

After all data of 130 patients were recorded, parents of children were called by telephone to participate in a structured telephone survey. Telephone surveys were completed with childrens' mothers or fathers who agreed to participate in the study. The telephone survey was designed to include questions in order to describe non-medical cost of acute tonsillo-pharyngitis.

The questionnaire included six questions about time missed from school or work, transportation, over the counter medications paid by the patient, transmission of the disease and other hospital visits. Acute tonsillo-pharyngitis is a medical term and the words used in communication should be understandable by survey participants. Therefore, while asking survey questions, "throat infection" term was used instead of acute tonsillo-pharyngitis.

First question of survey was about period of time that childen were not able to go to school and number of missed days. Secondly, a similar question to first one was asked to learn missed days of father or mother from work. The third

question was, to describe transportation cost and learn prefered transportation way and length of kilometers to go to visit. Fourth question was to find any used extra medication other than prescriped by physician. If used, name of medication were also asked and recorded. In the fifth question, it was asked to learn whether the throat infection was transmitted to any household members or not. Lastly, if parents and children went to another hospital due to disease was asked and name of hospital was learned. An english translation of the survey is shown in Appendix 3 and Turkish version of is shown in Appendix 4.

Due to the fact that all patients were assigned an ID number, the number for each case was noted on the questionnaire before initiation of telephone call. Before starting to ask questions, all participants were informed about content of study. There was a brief information at the top part of each survey and this information was read to each participant. They were free and they had enough time to answer questions. Responders' additional comments on questions were also noted.

The time to complete each telephone interview were also recorded. If parent could not be reached by phone once, second call was carried out. Either mother or father of the patient completed the telephone interview. After completion of all surveys, answers of questions were filled as codes to an excel sheet and answers of each case were written according to the specific case numbers of patients.

3.4. Data Analysis

Data analysis was performed by using Microsoft Office Excel 2007 and SPPS Inc PASW Statistics 18. Firstly, the retrospective data and survey results were transfered to an excel list to arrange findings, properly. Then, SPPS program was used for analyses. Descriptive analyses, including means, medians, ranges and frequencies were performed for patients' data and survey responses. Data are also experessed with tables and graphs. All costs were calculated and expressed as Turkish Liras.

3.5. Pharmacoeconomic Evaluation

3.5.1. Medical Costs

Data of episodes and surveys were used to describe medical and non-medical costs of acute tonsillo-pharyngitis in pediatrics and to find out the antibiotic treatment which has lower cost. There are six different medical costs including cost of antibiotic therapy, cost of other prescribed drugs, cost of throat culture, cost of physical examination, cost of other non-prescribed medicines and cost of other physician visit. Data analysis of these medical costs was conducted from both government and patient perspective and costs were estimated in Turkish Liras (TL). In addition, nominal values and real values were calculated for comparison of costs and consumer price index (CPI) and different price indexes were used to calculate real values.

In economics, nominal value refers to a value expressed in money terms in a given year or series of years. On the other hand, real value adjusts nominal value to remove effects of price changes over time. In addition, CPI measures changes in the price level of consumer goods and services purchased by households. The annual percentage change in a CPI is used as a measure of inflation. In Turkey, the CPI is defined by TÜİK (Türkiye İstatistik Kurumu) as “a measure of the average change over time in the prices paid by consumers for a market basket of consumer goods and services." It is shortly described as TÜFE (Tüketici Fiyatları Endeksi). TÜFE compares how much it would cost now to do exactly what consumers did in the reference-period with what it cost then. Therefore, nominal values convert to real values while evaluating economic data for different years. [27]

For this retrospective study, 2006 year was accepted as a base year and TÜFE was used to index the real value of prices of medical cost paramaters such as antibiotic prices. Therefore, all prices between 2007 and 2012 were converted to price in base year for deflating monetary magnitudes to show changes in real

values. In other words, TÜFE was used to compare how much it would cost now to do exactly what consumers did in base year with what it cost then.

3.5.1.1. Calculation of Real Values

TÜFE values of different material prices for Turkey were obtained from TUİK web site to calculate real values of different costs. TÜFE values are expressed for each month in a year. [27] The following material prices in Turkish Liras were used for calculation of stated costs;

- TÜFE values of prices of all drugs: Antibiotic cost and other non-prescribed medicines cost
- TÜFE values of prices of laboratory analysis: Cost of throat culture
- TÜFE values of physical examination prices of specialist physician: Physical examination cost and other physician visit cost.

After obtaining the above-mentioned TÜFE values, average TÜFE value of each year was calculated. Then, the average TÜFE value of 2006 is subtracted from the average TÜFE value of other years. This obtained value is divided to the average TÜFE value of 2006 and multiplied by 100. In order to find out index, the price was accepted 100 in 2006 and last obtained values are added to 100. Lastly, nominal value of the prices was divided by specified index of the year to find adjusted prices. Adjusted prices were found to express real values.

Real value calculation of an antibiotic price was summarized with an example:

- It is assumed that prices of an antibiotic are 6 TL, 4 TL and 3,5 TL for 2006, 2007 and 2008. These are nominal values.

- The average TÜFE values of drugs for 2006, 2007 and 2008 are 4,36 TL, 4,46 TL, 7,41 TL.

- Index calculation for 2007 and 2008:

  2007 Index: 100 + { [(4,46 - 4,36) / 4,36] x 100 }= 102
  2008 Index: 100 + { [(7,41 - 4,36) / 4,36] x 100 }= 170

- Real value calculation for 2007 and 2008:

  Real value of antibiotic in 2007: (4/102) x 100=3,92 TL= Adjusted price
  Real value of antibiotic in 2008: (3,5/170) x 100=2,06 TL= Adjusted price

3.5.1.2. Cost of Antibiotics

Cost of different antibiotic options were evaluated in terms of government (payer=SSI) perspective and patient perspective. Previous cost between 2006 and 2010 and 2012 cost of prescribed antibiotics were described. Previous cost refers to the cost of antibiotic at the time of first physician visit because drugs written on prescription were received after first visit. Therefore, previous cost was expressed as "cost at the time of first visit" for this study. Moreover, adjusted prices were also found and cost at the time of first visit and 2012 cost were calculated to show real values. Calculation method is explained with an example in the part of calculation of medical costs for one patient in this thesis.

For government perspective, costs were calculated from the point of Social Security Institution (SSI) and paid to public prices of antibiotics were used. Pharmacy sale price was used for patient perspective to carry out calculations. In addition, public prices and pharmacy sale prices were converted to adjusted prices for each year, so real change in price was demonstrated. All prices were obtained from RxMediaPharma 2012[2]. Due to the fact that antibiotic prices changed within the months of a year, average antibiotic prices were calculated

[2] RxMediaPharma 2012 is an interactive drug information source and used by especially pharmacists, physicians and other health care professionals from health sector. This program is designed to provide information about current drugs and pharmaceutical preparations. It is a quick, efficient and reliable computer system. It shows prices of all different forms of marketed products from 2005 to 2012.

for each year. Nominal and real values of average pharmacy sale prices between 2006 and 2012 are shown in Table 6 and 7. As seen tables, 2011 prices and 2012 prices are the same.

Table 6 – Nominal Values of Antibiotic Prices

Prescribed Antibiotics	2006	2007	2008	2009	2010	2011	2012
Alfoxil Forte Oral Suspension	3,97 TL	4,15 TL	4,35 TL	4,69 TL	4,69 TL	4,69 TL	4,69 TL
Alfoxil Tablet	5,96 TL	5,78 TL	6,06 TL	6,53 TL	6,53 TL	6,53 TL	6,53 TL
Augmentin Forte Oral Suspension	23,15 TL	22,48 TL	23,58 TL	23,48 TL	17,87 TL	13,96 TL	13,96 TL
Augmentin-Bid Film Tablet	16,58 TL	16,10 TL	16,88 TL	17,09 TL	8,18 TL	8,18 TL	8,18 TL
Erythrocin Granule for Oral Suspension	8,17 TL	7,93 TL	8,31 TL	8,97 TL	8,97 TL	8,97 TL	8,97 TL
Erythrocin Film Tablet	8,99 TL	8,74 TL	9,16 TL	9,88 TL	9,88 TL	9,88 TL	9,88 TL
Maksipor Powder for Oral Suspension	10,18 TL	9,89 TL	10,37 TL	10,89 TL	9,97 TL	9,97 TL	9,97 TL
Maksipor Film Tablet	13,86 TL	13,46 TL	14,12 TL	15,23 TL	12,67 TL	10,02 TL	10,02 TL
Sef Suspension	6,71 TL	6,52 TL	6,84 TL	7,38 TL	7,38 TL	7,38 TL	7,38 TL
Sef Film Tablet	11,39 TL	11,05 TL	11,59 TL	12,52 TL	12,52 TL	10,02 TL	10,02 TL
Zitromax Oral Suspension	7,04 TL	7,48 TL	7,84 TL	7,86 TL	6,07 TL	5,53 TL	5,53 TL
Zitromax Film Tablet	16,10 TL	16,35 TL	15,78 TL	17,03 TL	14,11 TL	8,84 TL	8,84 TL

Table 7 – Real Values of Antibiotic Prices (Adjusted Prices)

Prescribed Antibiotics	2006 BASE	2007	2008	2009	2010	2011	2012
Alfoxil Forte Oral Suspension	3,97 TL	4,07 TL	2,56 TL	2,61 TL	2,71 TL	2,20 TL	2,28 TL
Alfoxil Tablet	5,96 TL	5,67 TL	3,56 TL	3,63 TL	3,77 TL	3,07 TL	3,17 TL
Augmentin Forte Oral Suspension	23,15 TL	22,04 TL	13,87 TL	13,04 TL	10,33 TL	6,55 TL	6,78 TL
Augmentin-Bid Film Tablet	16,58 TL	15,78 TL	9,93 TL	9,49 TL	4,73 TL	3,84 TL	3,97 TL
Erythrocin Granule for Oral Suspension	8,17 TL	7,77 TL	4,89 TL	4,98 TL	5,18 TL	4,21 TL	4,35 TL
Erythrocin Film Tablet	8,99 TL	8,57 TL	5,39 TL	5,49 TL	5,71 TL	4,64 TL	4,80 TL
Maksipor Powder for Oral Suspension	10,18 TL	9,70 TL	6,10 TL	6,05 TL	5,76 TL	4,68 TL	4,84 TL
Maksipor Film Tablet	13,86 TL	13,20 TL	8,31 TL	8,46 TL	7,32 TL	4,70 TL	4,86 TL
Sef Suspension	6,71 TL	6,39 TL	4,02 TL	4,10 TL	4,27 TL	3,46 TL	3,58 TL
Sef Film Tablet	11,39 TL	10,83 TL	6,82 TL	6,96 TL	7,24 TL	4,70 TL	4,86 TL
Zitromax Oral Suspension	7,04 TL	7,33 TL	4,61 TL	4,37 TL	3,51 TL	2,60 TL	2,68 TL
Zitromax Film Tablet	16,10 TL	16,03 TL	9,28 TL	9,46 TL	8,16 TL	4,15 TL	4,29 TL

In 2003, the Turkish government launched the "Health Transformation Program" (HTP), a ten-year reform strategy intended to reduce inequalities in access to healthcare services by creating a universal health insurance fund. All drug prices have changed very rapidly since 2003 due to health transition program. Drug prices are low, not only in comparison with the other markets studied, but also in comparison with the European markets. Additionally, discounts are applied to a drug price list, which means that prices are actually even lower. Therefore, like other drugs, the prices of antibiotics in this thesis has reduced since 2006. The change in nominal prices of prescribed antibiotic options were shown in Table 6 and they are also and presented in Figure 2 and Figure 3 in this thesis. However, as seen Table 7, real decline in antibiotic prices are much more than nominal values.

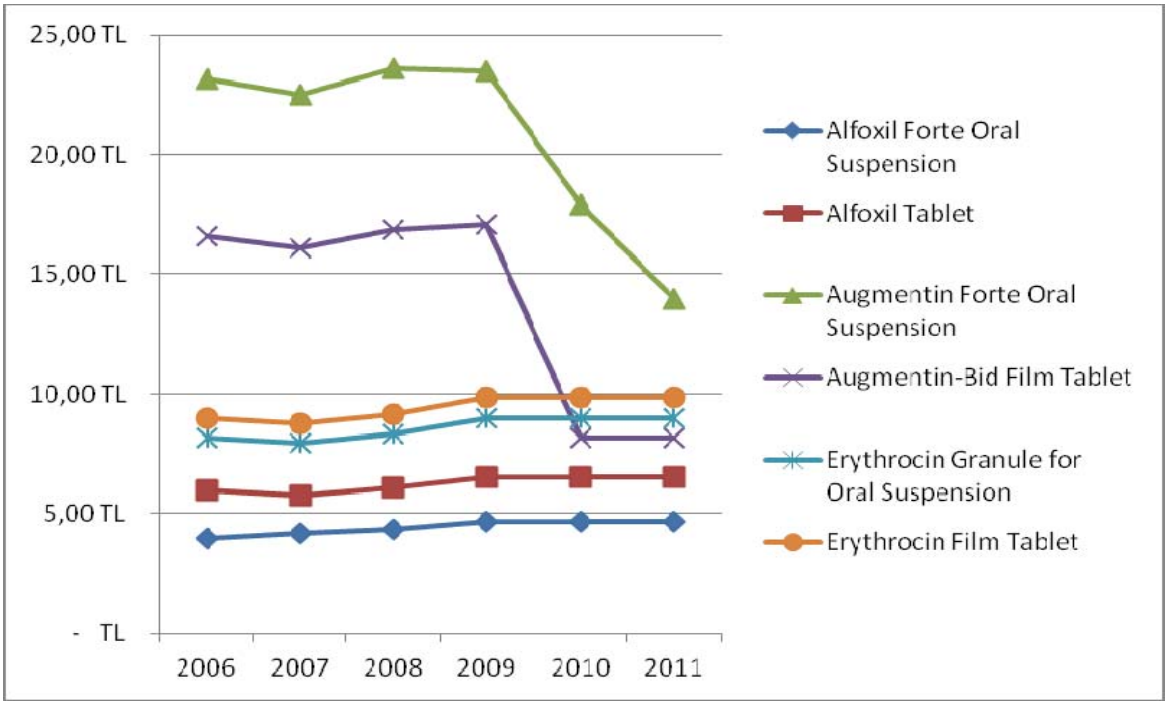

Figure 2 Change in Prices of Prescribed Antibiotic Options

(All changed prices were gathered from RxMediaPharma and the average price for each year was calculated)

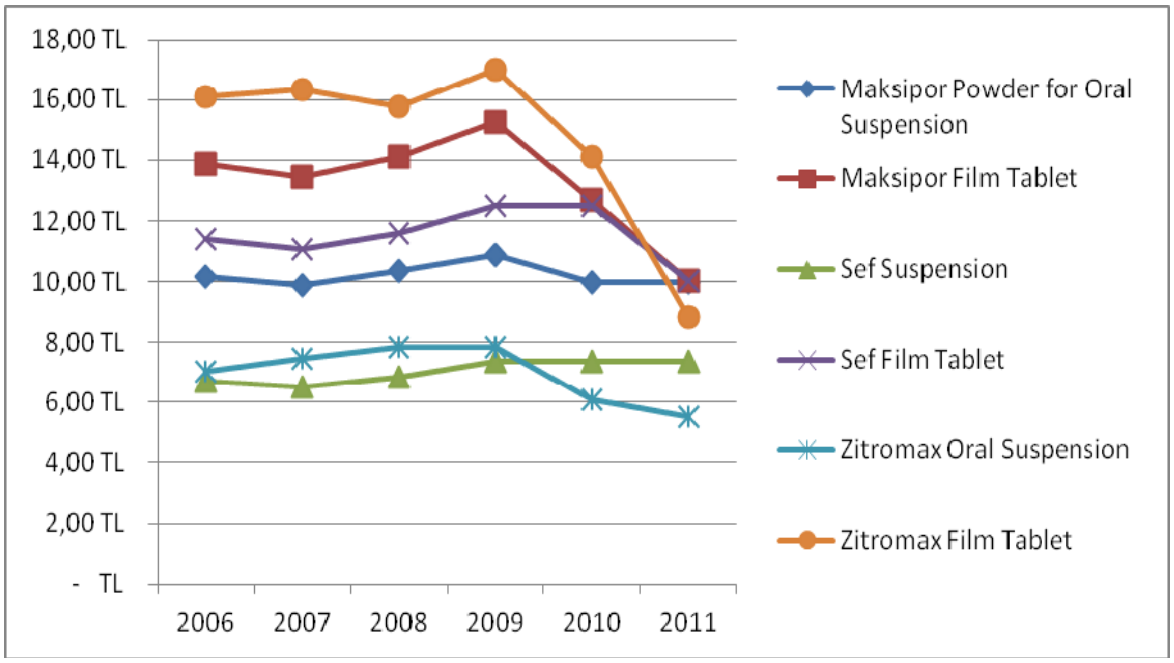

Figure 3 Change in Prices of Other Prescribed Antibiotic Options

(All changed prices were gathered from RxMediaPharma and the average price for each year was calculated)

3.5.1.3. Cost of Other Prescribed Drugs

Cost of other prescribed drugs other than antibiotics are also evaluated in terms of government perspective and patient perspective. In addition, cost at the time of first visit and 2012 cost of prescribed antibiotics were described with nominal and real values. All calculations were performed similar to the calculation method of prescribed antibiotics and showed in the part of calculation of medical costs for one patient in this thesis.

3.5.1.4. Cost of Laboratory Testing (Throat Culture)

In our study, microbiological tests were not done for most of the cases because physicians prefered empiric treatment with antibiotic for the children. Only, throat culture test was done for 33 children and thus, this study specifically does not focus on microbiological tests to evaluate its economic cost.

Patients went to a private hospital, in Sakarya for laboratory testing. The name of the hospital is Private Ada Medicine Hospital. Cost of a throat culture test was learned from this hospital. According to the received information from hospital, 2006 price of the test is 19,91 TL and the price of testing arise about 8 % every year. Therefore, nominal prices were calculated for each year (2006-2012). The nominal prices were also converted to adjusted prices after calculation of index from average TÜFE value of laboratory analysis price. Patients had to pay all amount of laboratory cost from their own pocket as this was a private hospital. Therefore, in terms of patient perspective cost was own price of each year such as 32,83 TL for 2012 and it was 0,00 TL for every year in terms of government perspective. Nominal and real prices for each year are shown in Table 8.

Table 8 – Nominal and Adjusted Prices of Throat Culture Test for Each Year

Year	2006	2007	2008	2009	2010	2011	2012
Nominal Price	19,91 TL	21,64 TL	23,52 TL	25,56 TL	27,79 TL	30,20 TL	32,83 TL
Adjusted Price	19,91 TL	23,78 TL	35,10 TL	35,51 TL	38,06 TL	40,82 TL	43,77 TL

3.5.1.5. Cost of Physical Examination

All 130 patients came to the first visit for physical examination. Some of them also came to the second or third visit. The price of one physician visit was learned from Mediko Social Center and it was the same as the price of a state hospital for each year. Cost of physical examination was evaluated in terms of government perspective (payer) and patient perspective. The same price was used for two perspectives because all patients had social security from Social Security Institution (SSI). 2012 price of examination is 15,50 TL and if patient has social security, he/she pays no money. On the other hand, if patient does not have social security, he/she has to pay the price (15,50 TL). Furthermore, real values were also calculated for each year by using average TÜFE values of physical examination prices of specialist physician. For instance, real price of examination

was 17,61 TL in 2012 whereas nominal price was 15,50 TL. Nominal and real prices for each year are shown in Table 9.

Table 9 – Nominal and Real Prices of Physical Examination for Each Year

Year	2006	2007	2008	2009	2010	2011	2012
Nominal Price	25,00 TL	25,00 TL	25,00 TL	25,00 TL	15,50 TL	15,50 TL	15,50 TL
Adjusted Price	25,00 TL	34,25 TL	31,65 TL	28,74 TL	17,03 TL	16,85 TL	17,61 TL

3.5.1.6. Cost of Other Non-prescribed Medicines

The fourth question of the telephone survey was asked to evaluate the medical cost of other non-prescribed medicines received by patients. The prices of medicines other than prescribed drugs were also obtained from the RxMediaPharma 2012 software. All calculations are performed similar to the calculation method of prescribed antibiotics and are displayed in the part of calculation of medical costs for one patient in this thesis. Nominal and real values were calculated to find out costs for the time of first visit and 2012. All costs are evaluated in terms of both government perspective and patient perspective.

3.5.1.7. Cost of Other Hospital Visit

The last question was asked to add the cost of other hospital visits for evaluation of medical costs. Some patients went to another state hospital before they came to the Mediko Social Center and some of them went to a private consulting room. The price of state hospital visit was learned from Mediko Social Center and the price of private physician visit was learned from Sakarya Medical Association by telephone call. All performed calculations for state hospital visit are similar to the calculation method of physical examination. The calculation can be found showed in the part of calculation of medical costs for one patient in this thesis. On the other hand, patients pay a visit fee for private examination depending on whether he/she has social security or not. Therefore, the costs of

private visit in 2012 and previous years (at the time of first visit) were 0,00 TL in terms of government perspective whereas it was between 90 and 100 TL in terms of patient perspective. The nominal values of both state hospital visit and private visit were also converted to real value by adjusting the price to base year, 2006. Average TÜFE value of physical examination price of specialist physician was used for calculation.

3.5.1.8. Calculation of Medical Costs for One Patient

Calculations for 130 patients were done one by one and an example was explained to show these calculations. The example is not a real patient and prices are assumed.

For instance, a nine year old, male patient came to the Mediko Social Center with his mother in 2008 and he had acute tonsillo-pharyngitis. Throat culture test was done in a private hospital. An antibiotic suspension, an analgesic and a vitamin was prescribed. His mother also stated that they had gone to another state hospital before they came to the Mediko Social Center and they bought another antibiotic. Cost calculations were shown below;

Cost of Antibiotic: The pharmacy price of antibiotic was 4 TL whereas paid to public price was 3,7 TL in 2008. In 2012, the pharmacy price of antibiotic was 3 TL whereas paid to public price was 2,8 TL. The patient received two boxes from pharmacy. The adjusted prices were calculated by index values which were 170 for 2008 and 206 for 2012.

The adjusted pharmacy sale price for 2008= (4/170)*100=2,35 TL
The adjusted paid to public price for 2008= (3,7/170)*100=2,17 TL
The adjusted pharmacy sale price for 2012= (3/206)*100=1,46 TL
The adjusted paid to public price for 2012= (2,8/206)*100=1,36 TL

Patient perspective:

Cost at the time of first visit: 4 x 2=8 TL (Nominal Price)
Cost at the time of first visit: 2,35 x 2=4,7 TL (Adjusted Price)
2012 Cost: 3 x 2 = 6 TL (Nominal Price)
2012 Cost:1,46 x 2= 2,92 TL (Adjusted Price)

Government Perspective:

Cost at the time of first visit: 3,7 x 2=7,4 TL (Nominal Price)
Cost at the time of first visit: 2,17 x 2=4,34 TL (Adjusted Price)
2012 Cost: 2,8 x 2 = 5,6 TL (Nominal Price)
2012 Cost:1,36 x 2= 2,72 TL (Adjusted Price)

Cost of other prescribed drugs (analgesic and vitamin) and other non-prescribed antibiotic were done similar to the above calculations, so they were not shown, separately.

Cost of Laboratory Testing: The nominal price of throat culture was 25 TL in 2008 whereas it was 35 TL in 2012. Cost of laboratory analysis was not paid by social security. Therefore, only prices for patient perspective was calculated and all calculated prices were equal to 0,00 TL for government perspective. The adjusted prices were calculated by index values which were 67 for 2008 and 75 for 2012.

The adjusted price for 2008= (25/67)*100=37,3 TL
The adjusted price for 2012= (35/75)*100=46,7 TL

Patient perspective:

Cost at the time of first visit: 25,00 TL (Nominal Price)
Cost at the time of first visit: 37,30 TL (Adjusted Price)

2012 Cost: 35 TL (Nominal Price)
2012 Cost: 46,7 TL(Adjusted Price)

Cost of Physical Examination: The nominal price of physical examination was 25,00 TL in 2008 whereas it was 15,50 TL in 2012. As mentioned before, the same price was used for two perspectives because all patients had social security from Social Security Institution (SSI). The adjusted prices were calculated by index values which were 79 for 2008 and 88 for 2012.

The adjusted price for 2008= (25/79)*100=31,65 TL
The adjusted price for 2012= (15,5/88)*100=17,61 TL

Patient and government perspective:

Cost at the time of first visit: 25,00 TL (Nominal Price)
Cost at the time of first visit: 31,65 TL (Adjusted Price)
2012 Cost: 15,5 TL (Nominal Price)
2012 Cost: 17,61 TL (Adjusted Price)

3.5.2. Non - Medical Costs

Telephone survey was conducted to describe non-medical costs. Non-medical cost parameters were determined by literature review. Missed time of children from school and missed time of parents from work, transportation and transmission rate of disease were described as parameters of non-medical costs. Frequencies, ranges and minimum-maximum values were used to show survey results.

In other words, cost calculation were not done and values were not found. For instance, kilometers to go to physician visit were learned, but the cost of transportation were not calculated. The cause of this is that price of one liter of petrol changes day by day in Turkey, so it is very difficult to find out correct price in 2006. Another reason is that all responders could not remember answer

of all questions for the calculation of non-meical costs. Moreover, cost of missed time of parents from work also could not be calculated because they are civil cervant and they receive their entire salaries although they do not go to work.

3.6. Limitations of the Study

- The sample size was limited because Mediko Social Center has a limited number of patients. Generally, university personnel or students go to the center for physician visit.

- All parents of 130 cases could not be reached to conduct telephone survey despite the fact that second call was done for unreachable cases.

- Subjects were not able to answer all questions with confidence because they did not have recollection of the incidence.

- Choosing the previous cases (2006-2010) brought some limitations because it was very difficult to learn actual prices in terms of medical costs. For example, prices of physicians visits were not recorded in written.

- Non-medical costs were not statistically analyzed, so actual economic cost of the disease is no defined in this study.

- Finally, some possible economic costs of our estimation is not included, such as costs incurred by sick family members, costs of adverse events and costs of complications associated with GABHS pharyngitis, all of which may have increased the total societal burden significantly.

4. RESULTS

In this chapter the results of medians, ranges, frequency, crosstabulation and other cost analyses are tabulated and summarized. This section is composed of three parts. The first part discusses the results of data on visit card. Second part is about telephone survey and lastly pharmacoeconomic costs are emphasized and illusturated in the third part.

4.1. Study Population

4.1.1. Demographic Characteristics

Frequencies are used in order to show distributions of the variables and combining variables to produce useful data for the tabulations.

130 cases have been eligible to evaluate in terms of acute tonsillo-pharyngitis. The minimum and maximum age of the pediatric patients are 5 and 12,6 years. Three age groups with equal ranges are generated for analysis. In terms of age group, 72,3 % of the children were between 5 and 8 years old and this age group is suitable for the clinical decision rule which is shown in introduction part with Figure 1. The mean age of the children evaluated in the study is 7 and 56.9 % of the children are male.

Monthly household income and education level of parents are evaluated. As seen in Table 10, the majority of the families had an household income more than 3000 TL and education level of fathers are higher than mothers. Mostly, fathers (76.9 %) are graduated from university and the rest of parents are graduated from high school. On the other hand, only 37.7 % of the mothers has university degree and 25 mothers (19.2 %) are graduated from primary school.

Demographic characteristics of study participants are tabulated in Table 10 and age and gender distributions of children are showed in Figure 4 and 5.

Table 10 - Demographic Characteristics of Study Participants

Monthly Household Income	n	Percentage (%)
1000-3000 TL	35	26,9
3000-5000 TL	48	36,9
> 5000 TL	47	36,2
TOTAL	**130**	**100**

Mother Educational Level	n	Percentage (%)
Primary School	25	19,2
Secondary School	2	1,5
High School	54	41,5
University	49	37,7
TOTAL	**130**	**100**

Father Educational Level	n	Percentage (%)
High School	30	23,1
University	100	76,9
TOTAL	**130**	**100**

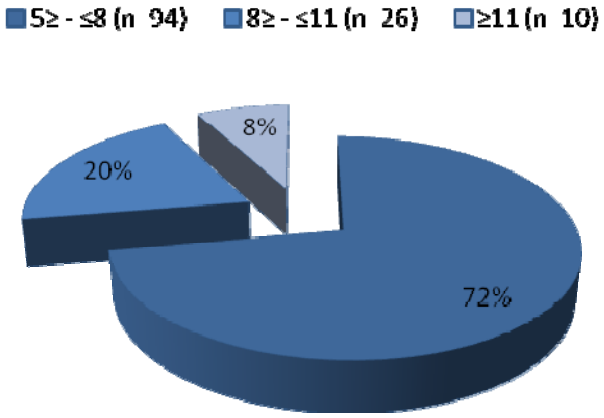

Figure 4 - Age Distribution

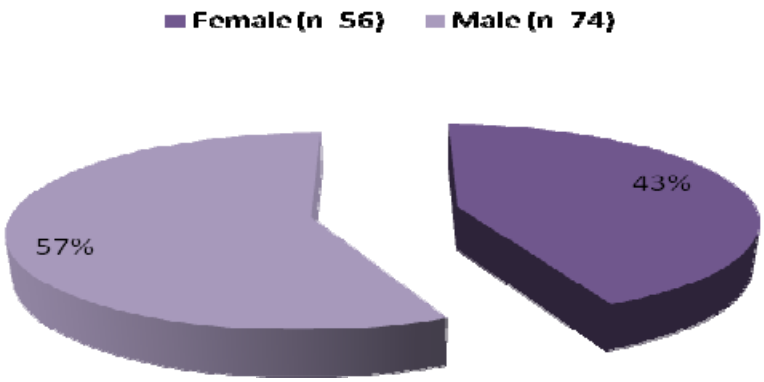

Figure 5 - Gender Distribution

4.1.2. Presenting Symptoms and Clinical Findings

When patients come to the Mediko Social Center to seek medical care, physicians ask their complaints and examine to find out symptoms and clinical findings. These sypmtoms and clinical findings are important to define diagnosis, accurately. The patient's data, analyzed for this study are suitable in terms of clinical decision rule which were mentioned in the introduction part and shown in Figure 1. For example, the age of patients are between 5 to 13, they do not have cough and all of them has fever.

All patients who visit the center, have fever (100 %). Their body temperature is greater than 38° C. They also have sore throat (33.1 %), headache (4.6 %) and abdominal pain/nausea/vomiting (4.6 %). Headache and gastrointestinal complaints are not common in all age groups. In addition to existing symptoms, all patients are examined by a physician and clinical findings are noted. They have hyperemic and hypertrophic tonsil and pharynx (99.2 %), exudates (70 %) and crypta (26.2 %) and other findings (4.6 %) such as hyperemic and hypertrophic right tympanic membrane. Hyperemic and hypertrophic tonsil and pharynx are found as clinical finding for almost all children from different age groups.

Symptoms and clinical findings of 130 cases are summarized according to the age groups in Table 11.

Table 11 - Existing Symptoms and Clinical Findings According to Age Group

Existing Symptoms (ES)								
Age group	Sore throat		Fever		Abdominal Pain / Nausea/Vomiting		Headache	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
5≥ - ≤8 (n=94)	22	16,9	94	72,3	6	4,6	4	3,1
8≥ - ≤11 (n=26)	15	11,5	26	20	0	0	2	1,5
≥11 (n=10)	6	4,6	10	7,7	0	0	0	0
Not seen ES	*87*	*66,9*	*0*	*0*	*124*	*95,4*	*124*	*95,4*
TOTAL	**130**	**100**	**130**	**100**	**130**	**100**	**130**	**100**

Clinical Findings (CF)								
Age group	Exudate		Cripta		Hyperemic and Hypertrophic Tonsil and Pharynx		Other	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
5≥ - ≤8 (n=94)	64	49,2	17	13,1	94	72,3	4	3,1
8≥ - ≤11 (n=26)	19	14,6	12	9,2	25	19,2	1	0,77
≥11 (n=10)	8	6,2	5	3.9	10	7,7	1	0,77
Not seen CF	*39*	*30*	*96*	*73,8*	*1*	0,8	*124*	95,4
TOTAL	**130**	**100**	**130**	**100**	**130**	**100**	**130**	**100**

4.2. Visits, Laboratory Test and Treatment

All patients come to the initial visit for examination. Although all children are required to come to a second visit after 72 hours from initiation of therapy, only 56 (43,1 %) of them come to the second visit. They come to the Mediko Social Center more than once due to the control visit (Table 12). Antimicrobial therapy is prescribed during the first visit. The second and third visits are control visits to evaluate symptomatic relief. All children are diagnosed with acute-tonsillo pharyngitis and no child required hospitalization.

Although Mediko Social Center has laboratory, throat culture tests are done in a laboratory of a private hospital. The results of this laboratory is reliable and throat culture is not carried out in Mediko Social Center laboratory. 33 cases

(25.4 %) were diagnosed through throat culture test, but most of the children received antibiotic treatment on the basis of symptoms and clinical findings without laboratory test. In other words, empiric treatment were initiated according to the clinical decision rule.

Generally, antibiotic, antipyretic and vitamin are prescribed for treatment. 42,3 % of children received amoxicillin for treatment of acute-tonsillo pharyngitis. The number of children (n=22) who received amoxillin/clavunate were equal to the number of children who received erythromycin. Moreover, 17 children (13.1 %) received azithromycin and as cephalosporin, cephalexin were given to 14 children (10.8 %). The trade name of prescribed active ingredient were different and patients received either suspension or tablet form of antibiotics. Physicians also prescribed some other medications for symptomatic treatment of GABHS pharyngitis. 62.3 % of cases received ibuprofen and 37.7 % received paracetamol to relief fever. As seen in Table 12, all children also used multivitamins according to the prescriptions. Trade name of other prescribed medicines were also different and syrup, tablet or drage were used. Antibiotic options were illustrated in Table 14.

Table 12 - Visits, Laboratory Tests and Treatment of Study Participants

Physician Visits	**n**	**Percentage (%)**
First Visit	130	100
TOTAL	**130**	**100**
Control Visits	**n**	**Percentage (%)**
Second Visit	56	43,1
Third Visit	2	1,5
Patients had no control visits	72	55,4
TOTAL	**130**	**100**

Laboratory Testing	**n**	**Percentage (%)**
Throat culture	33	25,4
None	97	74,6
TOTAL	**130**	**100**

Antibiotic Treatment	**n**	**Percentage (%)**
Amoxicillin	55	42,3
Amoxicillin/clavunate	22	16,9
Azithromycin	17	13,1
Cephalexin	14	10,8
Eritromycin	22	16,9
TOTAL	**130**	**100**

Other Prescribed Treatment	**n**	**Percentage (%)**
Ibuprofen	81	62,3
Paracetamol	49	37,7
Multivitamin	130	100,0
TOTAL	**130**	**100**

4.3. Survey Results

A structure telephone survey was conducted with mother or father of the patient. Out of 130 calls, 96 responders were completed the interview. Although some of parents were called twice on different days, they were not accessible and 34 parent could not respond survey questions. Six questions were asked to the participants. Mostly, mothers (51,5 %) answered questions. While conducting telephone interviews, the time to complete each survey were recorded. Minimum duration of survey is one minute and the survey takes a maximum of four

minutes. Participants were given enough time to think about questions and the mean survey duration was 2,9 minutes. 18,8 % of responders could not remember whether their child had missed any days from school due to his/her disease.

According to the results of the first and the second questions, 55,2 % of children missed school and 40,6 % of parents missed work. Normally, children with acute tonsillo-pharyngitis may return to school after 24 hours of antibiotic therapy[15]. Some patients return to school after one day from initiation of therapy. Maximum missed day for children was five days and the mean day was two. On the other hand, maximum missed day for parent was two and the mean missed day wasd 1.

Third question was about transportation and most of parents (92,7 %) came to the Mediko Social Center by their own car. Only one participant takes public transportation. Responders also specified how many kilometers they came for physician visit. 6 participants came by foot because they live in lodging buildings and these buildings are very close to the university campus. Thus, the minimum distance is 0,5. The maximum distance is 30 and the mean of distance is 9,5.

Fifth question was asked to describe transmission rate of disease within family. Although acute-tonsillo pharyngitis is a infectiouss disease, most of the family members (87,5 %) did not develop infection. Only 7 people developed disease and they were siblings of the infected children.

Fourth and last questions were prepared to evaluate medical costs. All participants were examined when they came to the Mediko Social Center and then, prescriptions were written by physicians. However, 14 children (14,6 %) visited another physician visit (state hospital or private consulting room) before they came to the Mediko Social Center and 21 children (21,9 %) received extra medications other than their prescription. Active ingredients of those extra

medications were ibuprofen, paracetamol, amylmetacresol-dichlorobenzyl alcohol (Pastil), acetylcysteine, amoxicillin/clavunate and cefuroxim. Patients generally receive ibuprofen, paracetamol alone or with antibiotic. All results of the survey were illustrated in Table 13.

Table 13 - Results of Survey

Participants	**n**	**Percentage (%)**
Mother	67	51,5
Father	29	22,3
Non-responders	34	26,2
TOTAL	**130**	**100**

	Minimum	**Maximum**	**Mean**
Survey Duration (Minute)	1,0	4,0	2,9

Time Loss	**n**	**Percentage (%)**
Child missed school	53	55,2
Child did not miss school	25	26,0
Not remember	*18*	*18,8*
TOTAL	**96**	**100**

Time Loss	**n**	**Frequency (%)**
Parent missed work	39	40,6
Parent did not miss work	43	44,8
Not remember	*14*	*14,6*
TOTAL	**96**	**100**

Transportation	**N**	**Frequency (%)**
By car	89	92,7
On foot	6 (6,3)	6,3
By public transport	1 (1,0)	
TOTAL	**96**	**100**

	Minimum	**Maximum**	**Mean**
Distance (Kilometers)	0,5	30,0	9,5

Non-prescribed medicines	**n**	**Frequency (%)**
Used	21	21,8
Not used	57	59,4
Not remember	*18*	*18,8*
TOTAL	**96**	**100**

Transmission	**n**	**Frequency (%)**
Yes (brother or sister)	7	7,3
No	84	87,5

Not remember	*5*	*5,2*
TOTAL	**96**	**100**

Another hospital visit	**n**	**Frequency (%)**
Yes	14	14,6
No	71	74
Not remember	11	11,4
TOTAL	**96**	**100**

Which hospital	**n**	**Frequency (%)**
State hospital	11	78,6
Private Consulting Room	3	21,4
TOTAL	**96**	**100**

4.4. Prescribed Antibiotic Treatments

Prescriptions of 130 cases were also recorded to evaluate and compare different antibiotic choices in terms of cost. Trade name, form, active ingredient, dosage, frequency of antibiotics were specified and these information were obtained from RxMediaPharma programme. Additionally, received number of boxes for each antibiotic were tabulated and the numbers were calculated according to the form, dosage and frequency of antibiotic. All different antibiotic choices were summarized in Table 14.

Although acute tonsillo-pharyngitis is a common disease, there are different options given by numerous practice guidelines, clinical trials, and cost analyses. Therefore, divergent antibiotics were written for 130 cases. Additionally, the active ingredient of antibiotics are different because these prescriptions were written by three different physicians. Route, dosing schedule and therapy duration of different antibiotic options are suitable in terms of treatment guidelines and Table 5 which is shown in the introduction part.

All pediatric patients received antibiotics orally and dosages were determined by physicians according to patients' age and weight. The dosages are suitable in terms of Summary of Product Characteristics (SPC) of antibiotics. There were no injection form to treat disease and suspension or tablet form were selected for pediatric patients because the usage of oral form is easier than injection form

for children. Mostly, patients used their antibiotic for ten days, but some of them were treated for fourteen days since they had different clinical findings such as hyperemic and hypertrophic right tympanic membrane. Reportedly, hyperemic and hypertrophic right tympanic membrane can show otitis media and antibiotic usage for fourteen days is necessary to treat all clinical findings of tonsillo-pharyngitis and otitis media concomitantly. Furthermore, 17 patients used azithromycin as an antibiotic were treated for five days.

According to the specified doses in prescriptions patients received enough boxes from pharmacy for therapy. Received number of boxes were different for prescribed antibiotic options due to their different form and dosing schedule. Received number of boxes from pharmacy were calculated, but all tablets or suspension of some antibiotics were not consumed at the end of treatment period due to dosage and frequency.

Table 14 - Prescribed Antibiotic Options for Treatment

Trade Name of Antibiotic	Form of Antibiotic	Active Ingredient	Dosage	Route	Frequency	Received number of boxes
Alfoxil Forte Powder For Oral Suspension	250 mg/5ml 100ml bottle/box	Amoxicillin	750 mg/day 40 mg/kg/day 60 mg/kg/day	Oral	10 days 14 days	2 3
Alfoxil Tablet	500 mg 16 tablet/box	Amoxicillin	750mg/day 60 mg/kg/day 50 mg/kg/day	Oral	10 days 14 days	1 2
Augmentin Forte Powder For Oral Suspension	400/57 mg 100ml bottle/box	Amoxicillin /clavunate	40mg/kg 12 h period	Oral	10 days	1 2
Augmentin Bid Film Tablet	500 mg/125mg 10 tablet/box	Amoxicillin /clavunate	40mg/kg/day	Oral	10 days	2 3
Erythrocin Granule For Oral Suspension	200mg/5ml 100ml bottle/box	Eritromycin	50 mg/kg/day	Oral	10 days	3 4
Erythrocin Film Tablet	500 mg 16 tablet/box	Eritromycin	50 mg/kg/day	Oral	10 days	2 3
Maksipor Powder For Oral Suspension	250 mg/5ml 100 ml bottle/box	Cephalexin	1000 mg/day	Oral	10 days	2
Maksipor Film Tablet	500 mg 16 tablet/box	Cephalexin	3 tablet/day	Oral	10 days	2
Sef Suspension	250 mg/5ml 80 ml bottle/box	Cephalexin	1000 mg/day	Oral	10 days	3
Sef Film Tablet	500 mg 16 tablet/box	Cephalexin	3 tablet/day 4 tablet/day	Oral	10 days	2 3
Zitromax Oral Suspension	200mg/5ml 15 ml bottle/box	Azithromycin	12mg/kg/day	Oral	5 days	2 3 4
Zitromax Film Tablet	500 mg 3 tablet/box	Azithromycin	1 tablet/day	Oral	5 days	2

The pediatric patients are treated with amoxicillin, commonly. A number of 55 (42,3 %) patients among 130 cases received Alfoxil® Forte Powder For Oral Suspension or Alfoxil® Tablet. 22 (16,9 %) patients used Augmentin® Forte

Powder For Oral Suspension or Augmentin Bid Film Tablet containing amoxicillin /clavunate as an active ingredient.

A macrolide, eritromycin was prefered for 22 (16,9 %) patients among 130 cases . The dose for ertromycin treatment was the same for both suspension and tablet form. Moreover, a first generation cephalosporin, cephalexin, was chosen for treatment of 14 (10,8 %) cases. The cause of choice was unknown, but Maksipor® powder for oral suspension, Sef® suspension or film tablet form of these trade names were presribed.

Lastly, a second line treatment, azithromycin, was prescribed and frequency was different from other antibiotic options. As mentioned before, azithromycin allows once daily dosing and shorter treatment period, but it is not advised for routine therapy. In our study, 17 (13,1 %) patients were treated with Zitromax® oral suspension or Zitromax® film tablet for a shorter period, 5 days.

Number of patients were different for each antibiotic. In terms of active ingredients, the least number of patients were 14 for eritromycin and the highest number of patients were 55 for amoxicillin. According to this data, number of patients (97) who used suspension were higher than number of patients (33) who used tablet form. Number of patients used different prescribed antibiotic options were shown in figure 6 and 7.

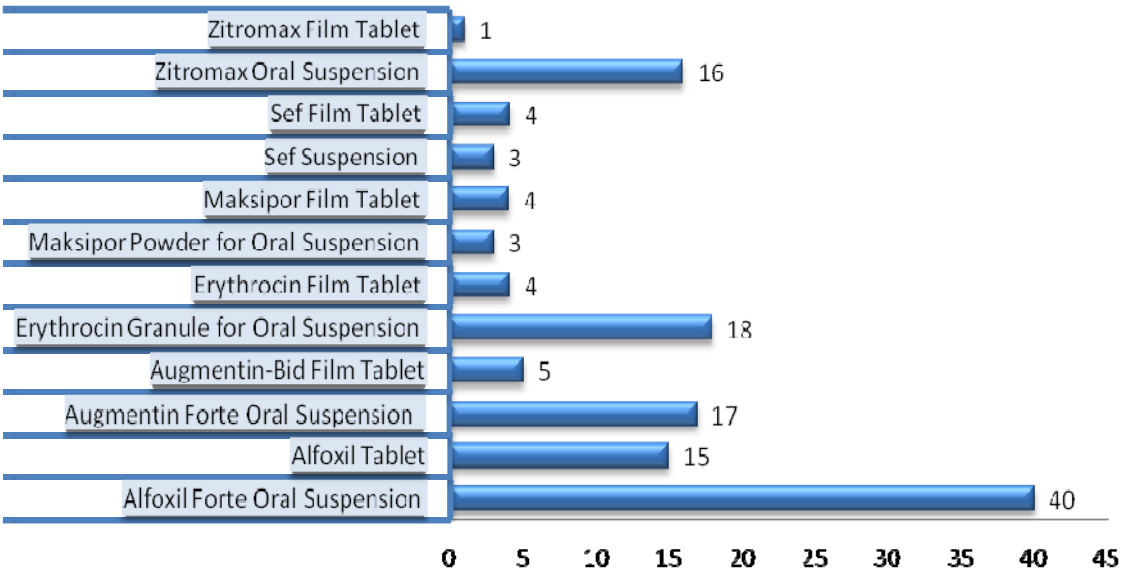

Figure 6 - Distribution of Prescribed Antibiotics

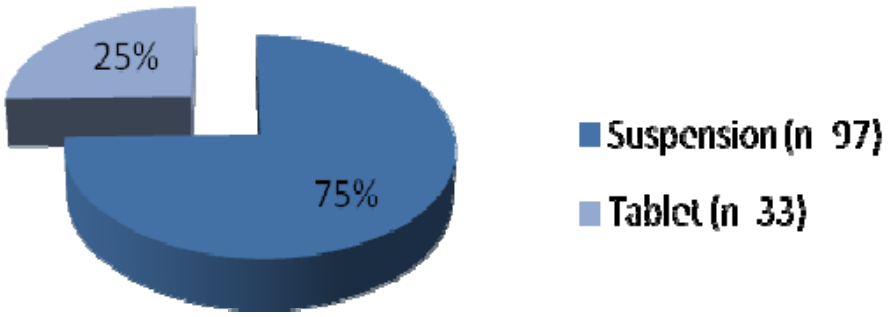

Figure 7 – Distribution of Antibiotic Forms

4.5. Medical Costs

4.5.1. Cost of Different Antibiotic Options

Minimum and maximum values of costs and median costs for each active ingredient were illustrated in Table 15 and Table 16. The tables also show nominal and real values of antibiotic costs in terms of patient and government perspestive (Payer – SSI). First of all, the cost was calculated for each case because patients were treated with different antibiotics that have different trade names. Then, cost of patients who received same active ingredient were collected to evaluate antibiotic cost. For instance, one patient receives Alfoxil Forte® Oral Suspension and another one is treated with Alfoxil® Tablet. The active ingredient of these trade names are the same, so the cost of these two cases are collected together.

The total nominal and real values of costs for patient perspective and payer perspective were demonstared in seperate tables. In addition, nominal values and real values of both cost at the time of first visit and 2012 cost were calculated for two perspective. For example, if a patient comes to the first visit on 21.12.2006 and received Alfoxil® tablet, the nominal and adjusted price of the tablet were taken at that time for calculation and the price was multiplied by received number of boxes. Then, the nominal and adjusted price of the tablet in 2012 was multiplied by received number of boxes to calculate 2012 cost. Calculation of antibiotic cost was shown in the part of calculation of medical costs for one patient in this thesis.

According to cost results shown in Table 15 and Table 16, the highest mean nominal costs (36,44 TL and 25,85 TL) were belong to the amoxicillin/clavunate, for cost at the time of first visit in terms of patient and SSI. Likewise, the real values of mean costs (32,40 TL and 21,95) were highest for amoxicillin/clavunate in terms of patient and SSI. Additionally, the highest total nominal and real costs (801,68 TL and 712,82) for cost at the time of first visit were also belong to amoxicillin/clavunate despite the fact that the number of patients used it were about half of the number of patients who used amoxicillin. On the other hand, amoxicillin treatment has the lowest mean cost

for both previous years and 2012 in terms of patient and government perspective. The minimum nominal and real costs were also belong to the amoxicillin for every year and every perspective.

Moreover, the highest mean nominal costs were 26,47 TL and 23,55 TL in 2012 and the highest total nominal costs were 582,27 TL and 518,01 TL in terms of patient and SSI perspective. These costs were belong to eritromycin treatment. The adjusted prices of eritromycin treatment was also calculated. The real values of mean costs (12,84 TL and 11,47 TL) and total costs (282,45 TL and 252,28 TL) of eritromycin were higher than costs of other actice ingredients in terms of patient and SSI perspective in 2012.

The mean nominal costs (15,71 TL and 17,81 TL) and real costs (7,85 TL and 8,65 TL) of amoxicillin/clavunate and cephalexin were also high in 2012 in terms of government perspective. The lowest nominal cost was 9,21 TL for patient and 6,95 TL for SSI if patient was treated with amoxicillin. In terms of real values, the lowest real costs were also belong to amoxicillin for patient and SSI perspective. The total nominal cost (2.519,70 TL) was highest at the time of first visit in terms of patient perspective and due to the fact that the Turkish Ministry of Health reduced the price of drugs, the total nominal cost in year of 2012 was lower than the cost at the time of first visit. Moreover, real value of total cost at the time of first visit (2.340,03 TL) was also higher than the the real value of total 2012 cost (1.033,17 TL). In general, the adjusted prices of each active ingredient were always lower for both cost at the time of first visit and 2012 in terms patient and government perspective.

Table 15 - Nominal and Real Values of Antibiotic Costs in terms of Patient Perspective

Active ingredient of antibiotic	Cost at the time of first visit – TL (2006-2010)	Cost at the time of first visit – TL (Adjusted Prices) (2006-2010)	2012 cost - TL	2012 cost – TL (Adjusted Prices)
Amoxicillin (n=55) *Mean /*	**468,98** *8,53 /*	**366,04** *6,66/*	**506,65** ↑ *9,21 /*	**245,41**↓ *4,46/*

(Minimum-Maximum)	*(6,06-14,30)*	*(3,63-11,92)*	*(6,53-14,07)*	*(3,17-6,84)*
Amoxicillin/clavunate (n=22) *Mean /* *(Minimum-Maximum)*	**801,68** *36,44 /* *(21,07-51,96)*	**712,82** *32,40/* *(22,04-49,74)*	**469,30** ↓ *21,33 /* *(13,96-27,92)*	**227,89**↓ *10,36/* *(6,78-13,56)*
Eritromycin (n=22) *Mean /* *(Minimum-Maximum)*	**542,71** *24,66 /* *(17,48-34,12)*	**480,6** *21,85/* *(10,78-31,08)*	**582,27** ↑ *26,47 /* *(19,76-35,88)*	**282,45**↓ *12,84/* *(9,60-17,40)*
Cephalexin (n=14) *Mean /* *(Minimum-Maximum)*	**372,34** *26,60 /* *(19,56-35,70)*	**344,2** *24,59/* *(19,17-34,17)*	**316,62** ↓ *22,61 /* *(19,94-30,06)*	**153,6**↓ *6,98/* *(9,68-14,58)*
Azithromycin (n=17) *Mean /* *(Minimum-Maximum)*	**333,99** *19,65 /* *(13,02-32,70)*	**326,37** *19,20/* *(14,08-32,20)*	**257,27** ↓ *15,13 /* *(11,06-22,12)*	**123,82**↓ *7,28/* *(5,36-10,72)*
TOTAL (TL)	**2.519,70**	**2.340,03**	**2.132,11** ↓	**1.033,17**↓

Table 16 - Nominal and Real Values of Antibiotic Costs in terms of Government Perspective (Payer - SSI)

Active ingredient of antibiotic	Cost at the time of first visit – TL (2006-2010)	Cost at the time of first visit – TL (Adjusted Prices) (2006-2010)	2012 cost - TL	2012 cost – TL (Adjusted Prices)
Amoxicillin (n=55) *Mean /* *(Minimum-Maximum)*	**398,22** *7,24 /* *(5,39-13,32)*	**315,39** *5,73/* *(3,03-10,60)*	**382,04** ↓ *6,95 /* *(5,46-10,92)*	**185,33**↓ *3,37/* *(2,65-3,34)*
Amoxicillin/clavunate (n=22) *Mean /* *(Minimum-Maximum)*	**568,71** *25,85 /* *(13,99-37,50)*	**483,00** *21,95/* *(12,75-31,77)*	**345,67** ↓ *15,71 /* *(10,05-20,10)*	**172,77**↓ *7,85/* *(4,88-10,59)*
Eritromycin (n=22) *Mean /* *(Minimum-Maximum)*	**482,99** *21,95 /* *(15,56-30,36)*	**427,81** *19,45* *(9,58-27,68)*	**518,01** ↑ *23,55 /* *(17,58-31,92)*	**252,28**↓ *11,47/* *(8,54-15,48)*
Cephalexin (n=14) *Mean /* *(Minimum-Maximum)*	**331,41** *23,67 /* *(17,40-31,77)*	**300,94** *21,50/* *(17,07-40,72)*	**249,34** ↓ *17,81 /* *(14,42-21,63)*	**121,07**↓ *8,65/* *(7,00-10,50)*
Azithromycin (n=17) *Mean /* *(Minimum-Maximum)*	**299,30** *17,61 /* *(11,60-30,44)*	**260,91** **15,35/** *(12,74-32,20)*	**185,16** ↓ *10,89 /* *(7,96-15,92)*	**92,45**↓ *5,44/* *(3,86-9,46)*
TOTAL (TL)	**2.080,63**	**1.862,05**	**1.680,11** ↓	**823,90**↓

As seen in Figure 8 which shows nominal and real values of antibiotic costs in terms of patient perspective, the highest difference between at the time of first visit and 2012 was for amoxicillin/clavunate. Exact numerical difference between nominal costs were 332,38 TL whereas the numerical difference between real cost

of amoxicillin/clavunate (484,93 TL) were higher than nominal cost in terms of patient perspective. The price of antibiotic containing amoxicillin/clavunate reduced about 150 % from 2006 to 2012. Therefore, the difference between its costs were higher than costs of other active ingredients. When real values were evaluated it seems real decline was much more than nominal decline.

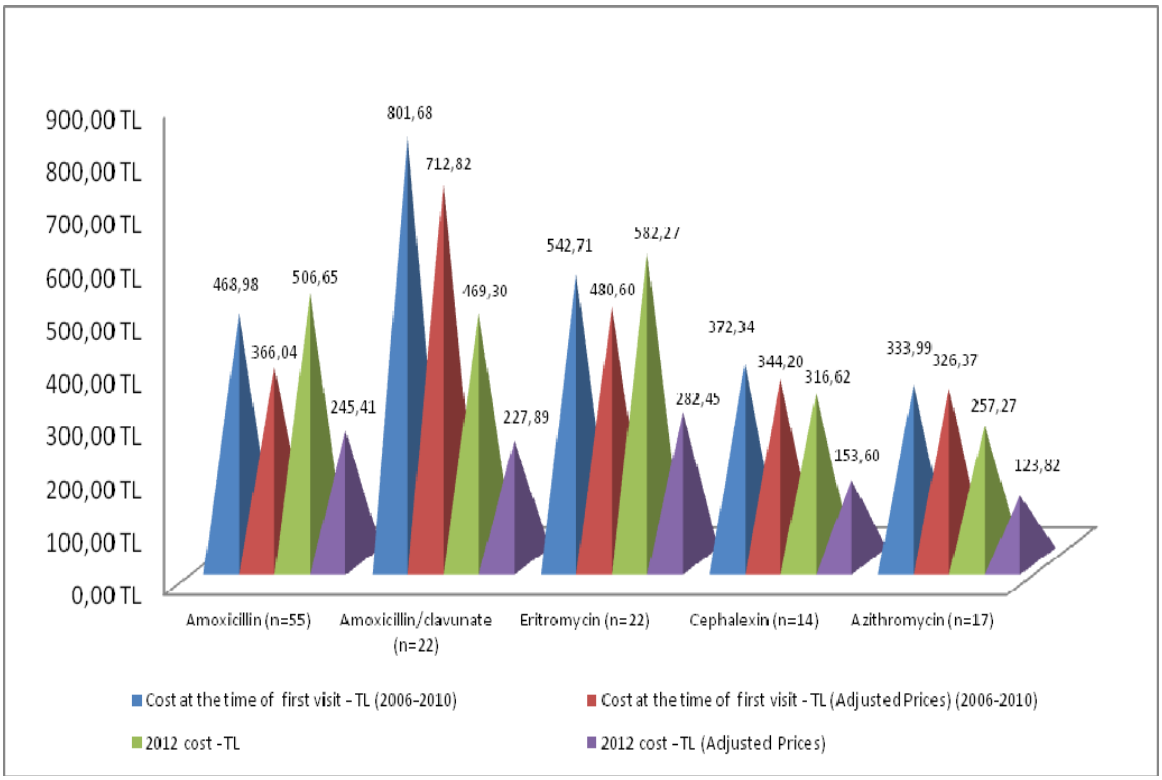

Figure 8 - Nominal and Real Values of Antibiotic Costs in terms of Patient Perspective

As seen in Figure 9 which shows nominal and real values of antibiotic costs in terms of government (payer) perspective, the highest difference between cost at the time of first visit and 2012 cost is also for amoxicillin/clavunate. Exact numerical difference between nominal cost is and 223,04 TL in terms of SSI perspective whereas between real costs is 310,23 TL. Shortly, the differences between nominal and real costs of amoxicillin/clavunate at the time of first visit and 2012 are higher than costs of other antibiotics.

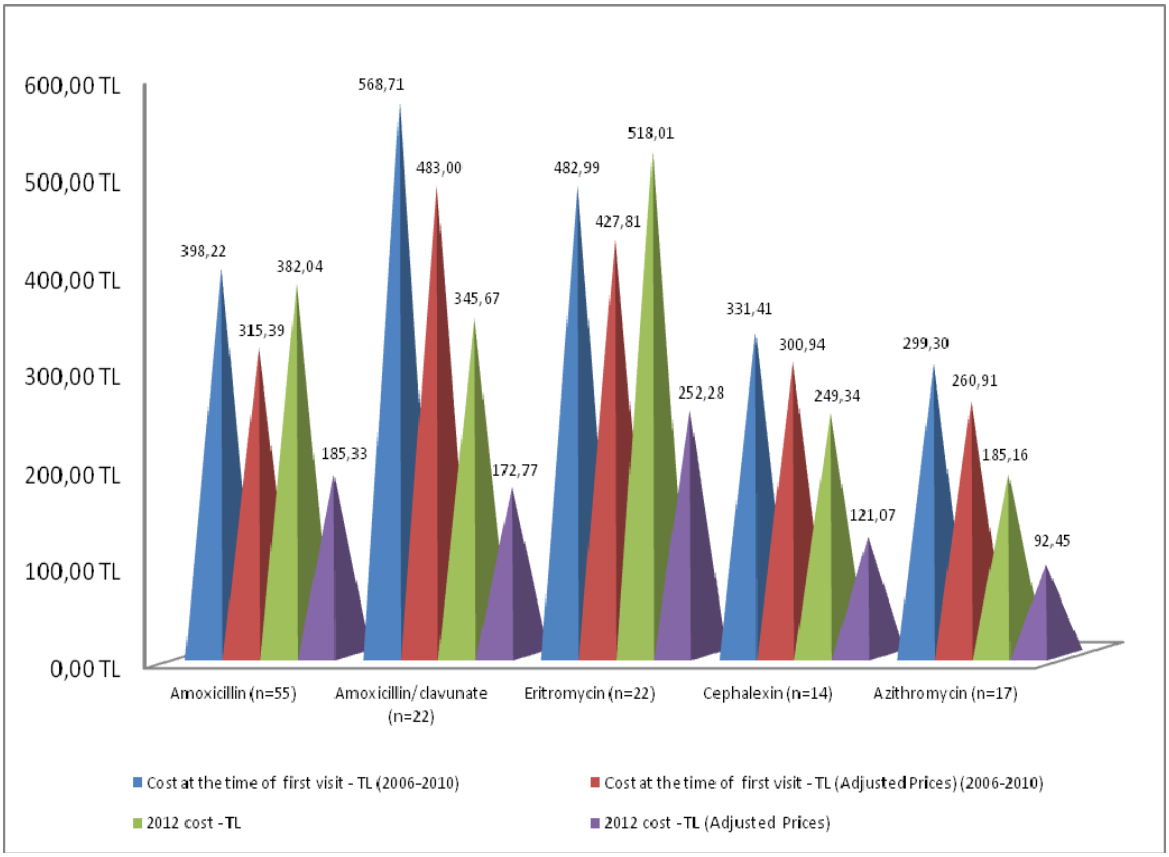

Figure 9 - Nominal and Real Values of Antibiotic Costs in terms of Government Perspective (Payer - SSI)

Generally, total nominal and real costs are reduced in 2012 when compared with costs at the time of first visit because of government health policy. However, when TÜFE values are taken into account to calculate adjusted prices, it seems the real decline is much more than nominal decline.

As seen in Figure 10, all total nominal and real costs reduce in 2012 when compared with costs at the time of first visit in terms of patient perspective. The diffeence between nominal costs is 387,59 TL, but the difference between adjusted prices is 1.196,86 TL. Therefore, real value of the difference is approximately three times the nominal value.

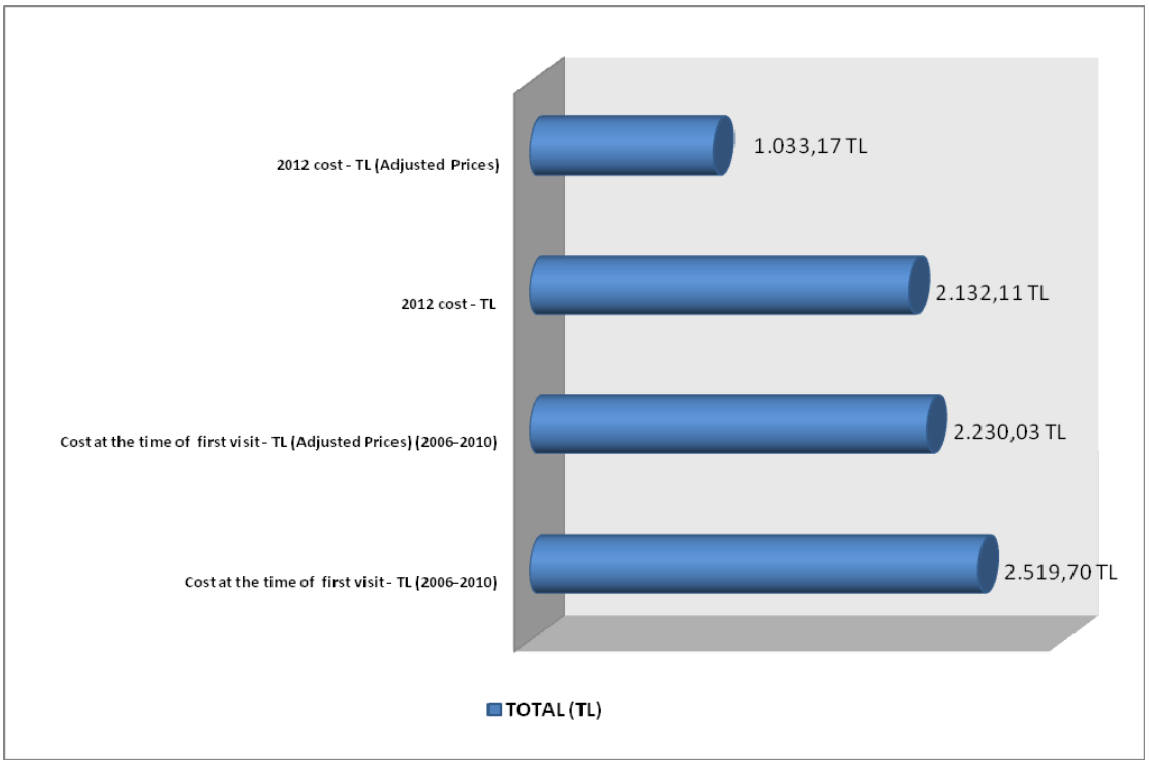

Figure 10 - Total Cost of Antibiotics in terms of Patient Perspective

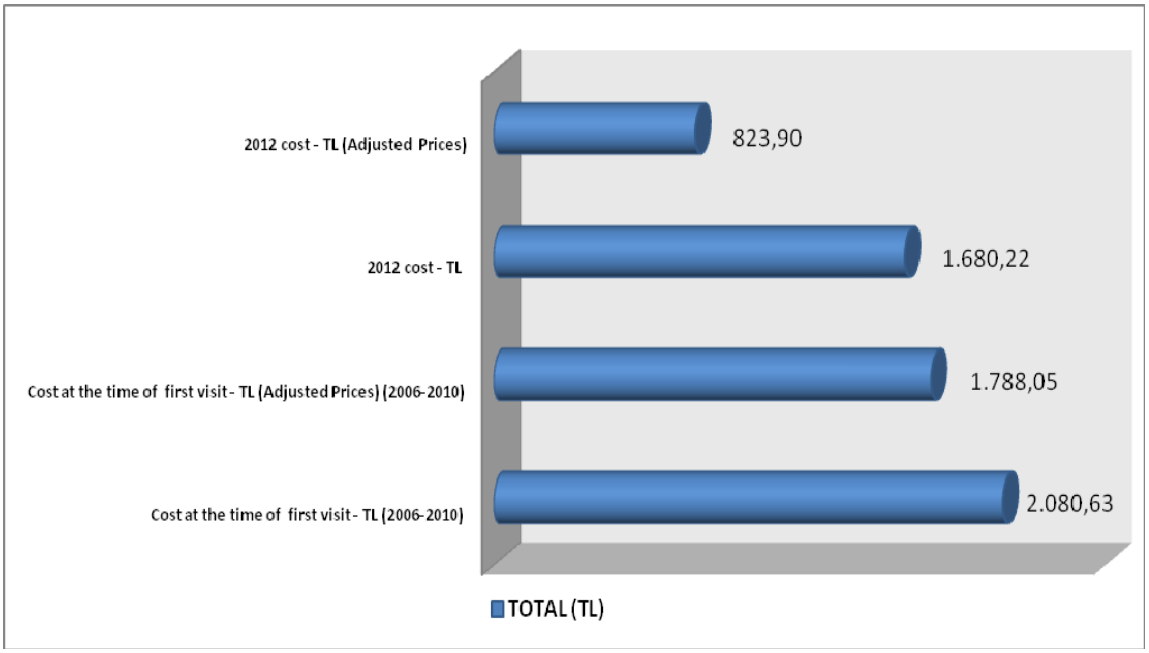

Figure 11 - Total Cost of Antibiotics in terms of Government Perspective (Payer – SSI)

Similar to Figure 10, Figure 11 shows that total cost of antibiotics reduce in 2012 when compared with costs at the time of first visit in terms of government perspective. The diffeence between nominal costs is 400,41 TL, but the difference between adjusted prices is 964,15 TL. Therefore, real value of the difference is approximately two and a half times the nominal value in terms of payer perspective. The real decline is much more than nominal decline for two perspectives. The differences between years for two perspectives are illustrated in Table 17.

Table 17 - Nominal and Real Differences Between Cost at the Time of First Visit and 2012 Cost in terms of Patient and Government Perspective

Differences Between Years	Patient Perspective	Government Perspective
Total Nominal Difference	387,59 TL	400,41 TL
Total Real Difference	1.196,86 TL	964,15 TL

If Figure 10 is compared with Figure 11 for every year to evaluate difference between two perspectives, it seems the total cost of antibiotic in terms of SSI perspective is always lower than the total cost of antibiotic in terms of patient perspective. In addition, real values of costs are always lower than nominal values. The highest difference (451,89) is belong to 2012 cost and differences between two perspectives are showed in Table 18.

Table 18 - Nominal and Real Differences Between Patient and Government Perspective For Cost at the Time of first Visit and 2012 Cost

Differences Between Perspectives	Cost at the time of first visit – TL (2006-2010)	Cost at the time of first visit – TL (Adjusted Prices) (2006-2010)	2012 cost - TL	2012 cost – TL (Adjusted Prices)
Total Difference	439,07 TL	441,98 TL	451,89 TL	209,27 TL

Finally, when real value of total costs is compared with nominal value of total costs for first visit time and 2012 in terms of two perspective, the difference in 2012 is higher than the difference in year of first visit. Furthermore, The 2012 cost in terms of patient perspective is higher than 2012 cost in terms of government perspectve. These differences are also shown is Table 19.

Table 19 - Differences Between Nominal and Real Values in terms of Patient and Government Perspective For Cost at the Time of first Visit and 2012 Cost

Differences Between Nominal and Real Vaues (Adjusted Prices)	Cost at the time of first visit – TL (2006-2010)	2012 cost - TL
Patient Perspective	286,67 TL	1,098,94 TL
Government Perspective	292,58 TL	856,32 TL

4.5.2. Other Medical Costs

In addition to the antibiotic cost; cost of other prescribed drugs, throat culture, physical examination, other non-prescribed medications and other hospital visit are calculated to evaluate medical costs. Like calculation of antibiotic cost , all other medical costs are calculated both for the time of first visit and 2012. They are described with both nominal and real values in terms of patient and SSI perspective. These medical costs are summarized in Table 20 and Table 21.

Table 20 - Nominal and Real Values of All Medical Costs in terms of Patient Perspective

Cost Parameters	Cost at the time of first visit – TL (2006-2010)	Cost at the time of first visit – TL (Adjusted Prices) (2006-2010)	2012 cost - TL	2012 cost – TL (Adjusted Prices)
Cost of Antibiotic Therapy	2.519,70	2.340,03	2.132,11 ↓	1.033,17↓
Cost of Other Prescribed Drugs	841,82	740,45	941,73 ↑	455,66↓
Cost of Throat Culture	702,61	768,78	1.083,39 ↑	1.444,41↑
Cost of Physical Examination	4.626,50	5.321,07	2.945,50 ↓	3.345,90↓
Cost of Other Non-prescribed Medicines	126,03	114,53	124,46 ↓	60,42↓
Cost of Other Hospital Visit	509,62	599,43	467,50 ↓	531,21↓
Mean Cost per Case	**71,74**	**76,03**	**59,19 ↓**	**52,85↓**
TOTAL	**9.326,28**	**9.884,29**	**7.694,19 ↓**	**6.870,77↓**

Table 21 - Nominal and Real Values of All Medical Costs in terms of Government Perspective (Payer- SSI)

Cost Parameters	Cost at the time of first visit – TL (2006-2010)	Cost at the time of first visit – TL (Adjusted Prices) (2006-2010)	2012 cost - TL	2012 cost – TL (Adjusted Prices)
Cost of Antibiotic Therapy	2.080,63	1.862,05	1.680,22 ↓	823,90↓
Cost of Other Prescribed Drugs	614,54	540,31	633,66 ↑	320,41↓
Cost of Throat Culture	0,00	0,00	0,00 -	0,00 -
Cost of Physical Examination	4.626,50	5.321,07	2.945,50 ↓	3,345,90 ↓
Cost of Other Non-prescribed Medicines	104,54	94,23	155,45 ↑	48,66↓
Cost of Other Hospital Visit	265,50	315,87	170,50 ↓	193,71↓
Mean Cost per Case	**59,17**	**62,57**	**42,96 ↓**	**36,40↓**
TOTAL	**7.691,71**	**8.133,53**	**5.584,83 ↓**	**4.732,58**

According to the tables, cost of other prescribed drugs are lower than cost of antibiotics because the price of these drugs are low and all patient just bought one box (one box of vitamin and one box of paracetamol or ibufen) to use for 3 or 4 days. Their price generally changes from 2 TL to 6 TL. Although real and nominal values of antibiotic costs are reduced within years, costs of other prescribed drugs in terms of two perpectives are increased. The patients generally have to pay from their pocket for vitamin drug even though they have social security. Therefore, vitamin prices are not directly affected by health policy and price of these drugs generally increase year after year.

Moreover, throat culture costs are calculated to evaluate laboratory work in terms of medical cost. As mentioned in methodology part, throat culture test is performed for 33 patients and patients have to pay all amount of laboratory cost from their own pocket as the test is done in a private hospital. Therefore, nominal and real values of laboratory cost in terms of Social Security Instution could not be calculated and cost in terms of patient increased due to the fact that price of the throat culture increased from 2006 to 2012. Moreover, the real raises are higher than nominal ones and the real raise in 2012 is much more than the raise in the years between 2006 and 2010.

Another medical cost is physical examination cost and the same price is used for both perspectives because all patients have social security and SSI bear the cost of physician visit. Thus, nominal and real values of total cost for each perspective are not different for the time of first visit and 2012. The nominal and real values of total costs reduced within years because government decreased price of physician visit, too. However, the tables also show that the real costs of physical examination are much more than nominal costs for the time of first visits (2006 – 2010) and 2012.

Other than prescribed medications, 21 patients receive additional drugs for the treatment of acute tonsillo-pharyngitis. Fourth question of telephone survey was asked to bring out cost of these non-prescribed drugs . The nominal and real values of cost are low because a few patient bought some extra medication other than their prescription.

Lastly, cost of other hospital visit is calculated for evaluation of medical costs. A number of 14 patients went to another physician visit due to the disease. The nominal and real value of cost in terms of SSI is lower than the cost in terms of patient because 3 patients went to the private consulting room and all amount of visit fee for private examination is paid by the patient whether he/she has social security or not. The price of private physician visit is much more than the price of state hospital visit. The percentage difference of prices between these visits is about 20 %. Therefore, real raise between years is higher than nominal raise in terms of two perspective.

Total medical costs of six parameters for 130 cases are also calculated. The nominal cost at the time of first visit is 9.326,28 TL in terms of patient perspective whereas it is 7.691,71 TL in terms of SSI perspetive. In addition, the real costs in terms of two perspectivess (9.884,29 TL and 8.133,53 TL) are higher than nominal ones for the time of first visit (2006-2010). The nominal and real mean cost per case is 71,74 TL and 76,03 in terms of patient and they are 59,17 TL and 62,57 in terms of SSI for the time of first visit. In addition, the nominal and real mean costs per case are 59,19 and 52,85 TL in terms of patient perspective in 2012. In terms of payer perspective they are 42,96 TL 36,40 TL in 2012. Consequetly, the mean medical costs are reduced from previous years to 2012 and the real values of this decline is higher than nominal values for both two perspectives.

Furthermore, the calculation of medical costs for two perspectives also show that the nominal and real values of total medical costs in terms of patient higher than the values in terms of government. The nominal value of the difference

between time of first visit and 2012 is 1.632,09 TL whereas the real value is 3.013,52 TL in terms of patient perspective. In terms of SSI perspective total medical cost also reduced in 2012 according to the time of first visit. The nominal difference between years is 2.106,88 TL the real difference is 3.400.95 TL for SSI. These total medical cost differences between years are shown in Table 22 and the real difference are higher than nominal in terms of patient and government perspective. Consequently, the Turkish Ministry of Health not only reduced drug costs, but also medical costs which directly affect budget of SSI have been reduced in recent years because financial restraints on the health bugdet have increased.

Table 22 – Nominal and Real Differences Between Cost at the Time of First Visit and 2012 Cost in terms of Patient and Government Perspective

Differences Between Years	Patient Perspective	Government Perspective
Total Nominal Difference	1.632,09 TL	2.106,88 TL
Total Real Difference	3.013,52 TL	3.400.95

The highest nominal and real cost in 2012 belongs to the physical examination within total medical cost parameters for two perspectives. The nominal percentages of physical examination cost are 38 % and 53 % for patient and SSI perspective whereas the real percetanges are 53 % and 71%. Antibiotic cost is the second highest cost and the real percentages (15 % and 17 %) for patient and SSI are close to each other. All real percentage values of medical costs in 2012 for patient perspective and SSI perspective are shown in Figure 12 and Figure 13.

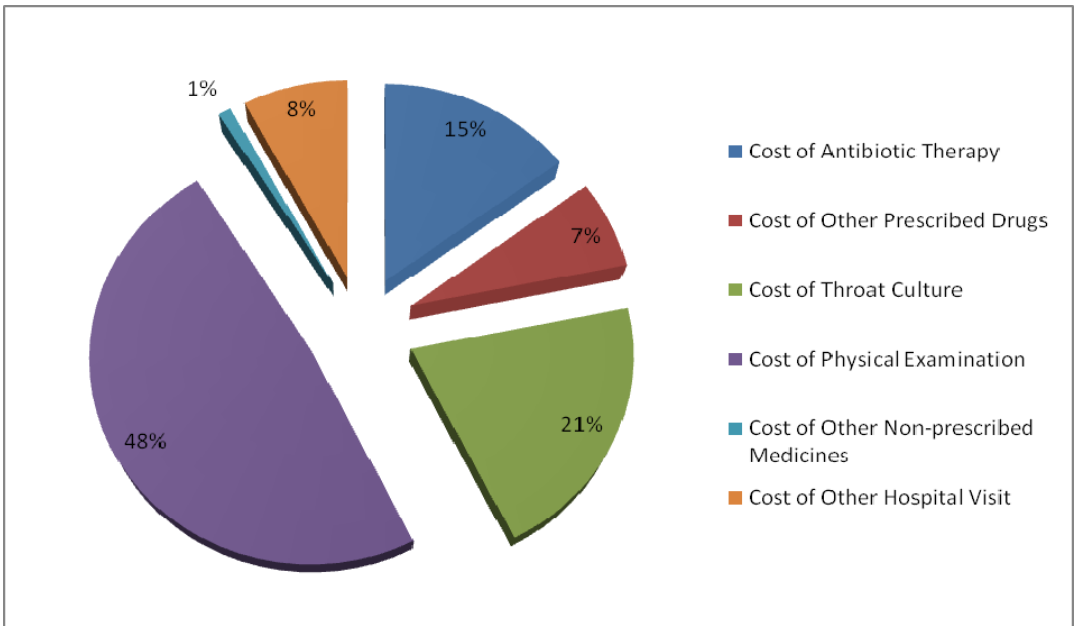

Figure 12 – Distribution of Medical Cost Parameters for Patient Perspective (Real Values – 2012)

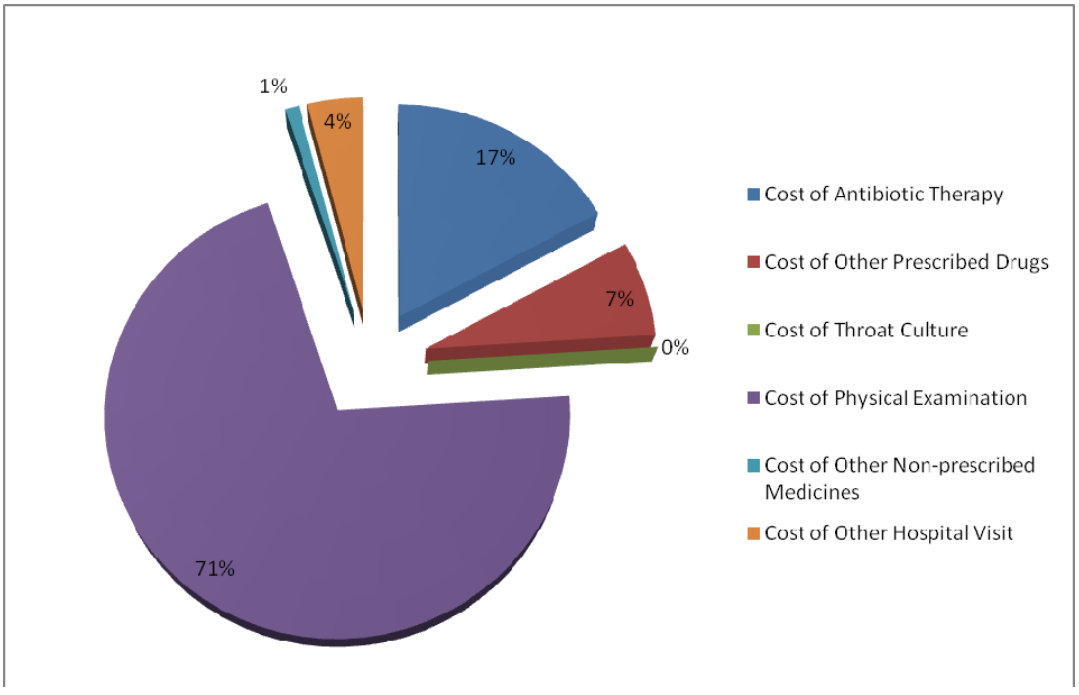

Figure 13 – Disribution of Medical Cost Parameters for Goverment Perspective (Real Values – 2012)

5. DISCUSSION

This study is the first to collect data on the medical and nonmedical costs of acute tonsillo-pharyngitis in children, in Turkey. This is also one of the first study in which medical costs of GABHS pharyngitis are evaluated in terms of patient and government perspective. Prescribed antibiotics are also described between 2006 and 2010 and cost of different antibiotic options are calculated for these years and 2012. In addition, TÜFE values are included to compare nominal values with real values. Therefore, this study specify medical costs for different years and change in nominal and real values of costs are indicated in terms of patient and government perspective.

The pharmaceutical industry is one of the few sectors in Turkey where the government has significant control over prices. All drugs have to be registered with the Ministry of Health. The rising costs associated with prescription drugs have become an important focus. The Ministry of Health determines the rates by which pharmaceutical companies can increase their prices - often lower than increases in the wholesale and consumer price indexes (CPI=TÜFE). The drug prices are not determined according to the changes in TÜFE values. Generally, the minimum price among 5 reference countries (France, Greece, Italy, Portugal and Spain) and periodic € value, determined by the Price Evaluation Commission, is used to calculate drug prices. In brief, The Ministry of Health's main policy is of purchasing the cheapest alternative among pharmaceuticals comprising of the same molecular structure and pharmaceutical policies in Turkey, especially reimbursement conditions change frequently and not always in very transparent ways. Therefore, this study also show that the real decline in drug costs are much more than nominal values when TÜFE values are included to evaluate changes from 2006 to 2012. [(28)]

Moreover, results of this study showed that amoxicillin may be first choice for therapy in terms of cost and amoxicillin was prescribed for most of the patients (n=55) in this study. Besides, The American Academy of Pediatrics (AAP), the

Centers for Disease Control and Prevention (CDC), and the Infectious Diseases Society of America (IDSA) recommend amoxicillin as the first antibiotic choice for children with sore throat due to acute tonsillo-pharyngitis[22]. It is understood that some pediatricians of Mediko Social Center prefer to prescribe amoxicillin to treat pediatric patients despite the fact that there are several antibiotic alternatives for treatment. On the other hand, the retrospective nature of the study did not allow for any intervention in the physicians' preference for antibiotic choice. If confirmed by additional studies, once-daily amoxicillin therapy may become a first regimen for the treatment of this disease in terms of cost.

IMS Health data for 2011 is obtained to overview Turkey sales of prescribed antibiotics in this thesis. According to this data, total sales of Alfoxil Forte® Powder For Oral Suspension and Alfoxil® Tablet are 2,046.704 TL where as the total sales of Augmentin Forte® Powder For Oral Suspension and Augmentin Bid® Film Tablet are 9.087.296 TL. In other words, Augmentin® is the best-selling antibiotic, in Turkey. Otherwise, we found that the amoxicillin/clavunate has the highest mean cost and total cost in terms of patient and government perspective. Thus, price of the antibitoic have been decreased year by year. Another reason of the decrease in the price of Augmentin® is that it became 20-year old product during this period and 20-year old products are not subject to external reference pricing; maintained their current prices. Of course, these specified active ingredients in this study are prescribed to treat many different infections other than acute tonsillo-pharyngitis. Nevertheless, the difference between sales data is very high and we can mention that physicians generally may not choose first antibiotic option in terms of cost.

The cost of antibiotics has declined, but some other costs such as cost of other non-prescribed medicines has arised due to increase in the price of over the counter medicines (OTC), especially vitamins. People have to pay all price of OTC drug although they have social security. The Ministry of Health do not have direct effect for the determination of the price of OTC medicines.

Decisions on inclusion/exclusion of drugs are made by the Reimbursement Commission under SSI. For instance, 120 OTC drugs were excluded from the list in 2006.[29]

Additionally, cost of laboratory work increases due to the fact that the price of throat culture is increased year after year by private hospital. If throat culture tests have been done for all 130 cases, the total medical cost for 2012 might be higher than the cost at the time of first visit. The real value of laboratory work cost are also higher than nominal value. Turkish government decided to make some new arrangements in order to decrease the costs of private hospitals in 2006 and to control the private hospitals in respect of prices within the framework of contracts . However, it is believed that there are fundamental questions about price in private hospitals.[30] As a result, total medical cost of the acute tonsillo-pharyngitis may be increasing despite the fact that Ministry of Health decreases cost of medications in terms of Social Security Institution (SSI) perspective.

Furthermore, total economic cost of acute tonsillo-pharyngitis could not be estimated because that non-medical costs of the disease were not calculated. However, economic burden of the disease increases if transportation cost is added and it varies between years due to the fact that petrol price rises day by day, in Turkey. In addition, Sakarya is not as big as Istanbul, so patients pay more for transportation if they live in a bigger city. Another non-medical cost parameter is tranmission of the disease. Secondary attacks in families also increases economic burden of the disease. Some studies about transmission rate showed that a single episode of GABHS pharyngitis within the family has broader implications in terms of extra cost of medication and time off school and work for additional family members [24].

Potential study limitations include the lack of generalizability because our sample size was limited. In addition, our response rate for survey questions was 74% and it might have affected the overall cost of illness. To calculate the true costs of antibiotic therapy, hidden costs arising from intravenous administration, labor, serum antibiotic assay, monitoring hematological and biochemical indices and

adverse effects of antibiotics must be considered. Finally, we did not include all possible economic costs in our estimate, such as costs incurred by sick family members and costs of complications associated with GABHS pharyngitis, all of which may have increased the total societal burden significantly.

6. CONCLUSION

In practice, the treatment of patients with sore throats is often driven by the wishes of the physician, in Turkey. Physicians generally make antibiotic choice and patients cannot pressure physicians to change the prescriptions. However, cost is an important factor which should determine the physician's choice of medication to treat patients in spesific stiuations. By nature of its high incidence, pharyngitis is a major health and economic issue, yet there is no agreement on how to choose right antibiotic for children with sore throats in terms of both therapy and cost. In this study, we tried to demonstrate the cost of different antimicrobial treatments for acute tonsillo-pharyngitis and show the antibiotic which has low cost. It is clear that cost of antibiotic therapy of GABHS pharyngitis is also an important factor in terms of economic burden of the disease.

In conclusion, further pharmacoeconomic studies should be conducted for the evaluation of economic cost of acute tonsillo-pharyngitis. Especially, prospective studies for long term may be conducted, so more information are obtained in terms of cost of therapy. In this way, antibiotic guidelines can be developed, unnecessary usage of medications can be prevented and expensive antibiotic prescriptions can be reduced.

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8. APPENDICES

APPENDIX 1 – ETHICS COMMITTEE APPROVAL

T.C.
SAKARYA ÜNİVERSİTESİ
Tıp Fakültesi Etik Kurulu

Sayı : B.30.2.SAÜ.0.20.05.04 . 050.01.04 /01 14/04/2011

Konu : Etik Kurul İzni Hk.

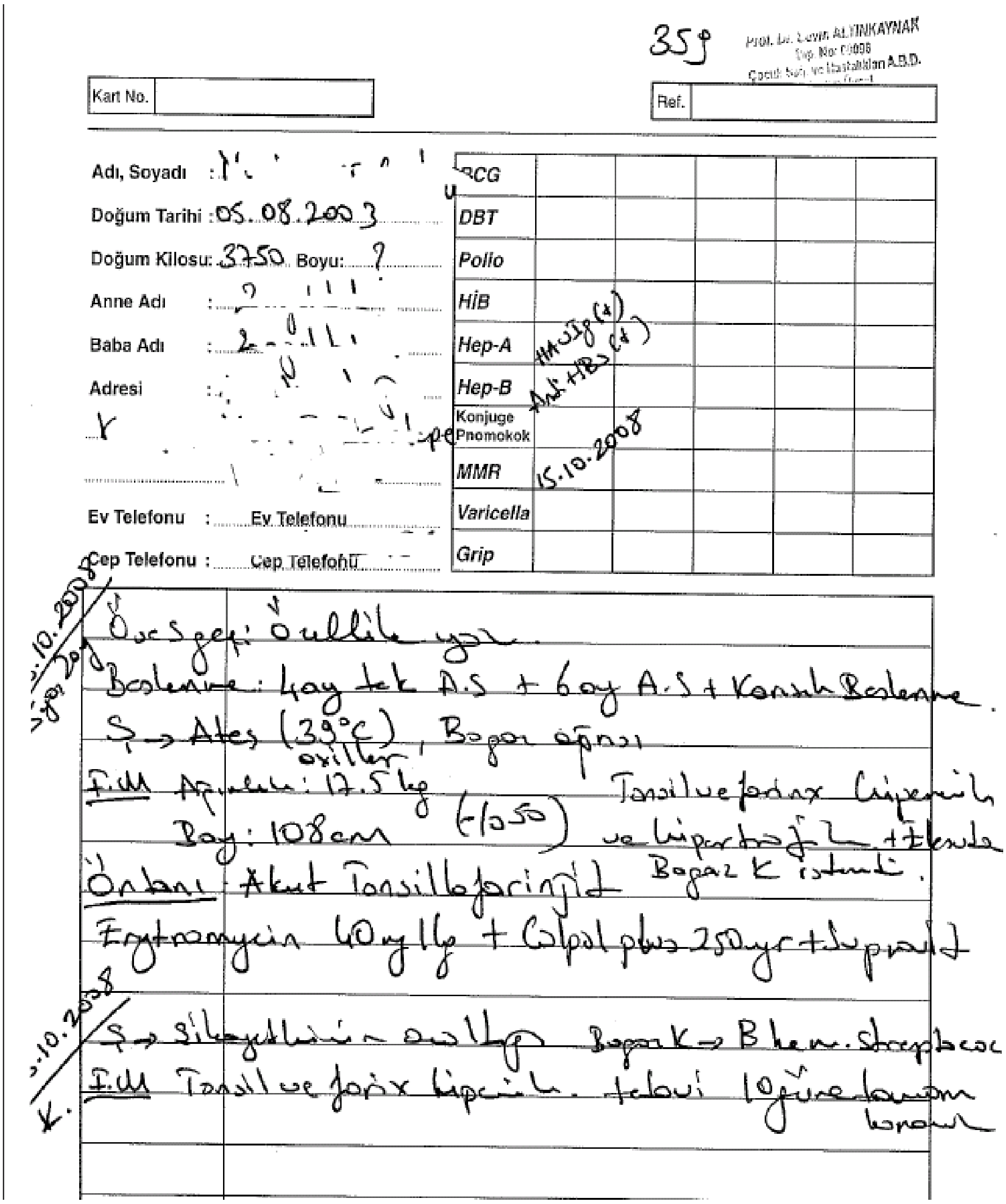
Sayın Prof. Dr. Sevin ALTINKAYNAK

Başvurunuz Etik Kurulumuzun **30/03/2011** tarihli toplantısında görüşülmüş olup, "Pediatrik hastalarda akut tonsillafranjitin ekonomik maliyeti" başlıklı çalışmanız retrospektif bir çalışma olduğu anlaşıldığından etik onay verilmesine gerek olmadığına oy birliği ile karar verilmiştir.

Bilgilerinizi rica ederim.

Doç. Dr. Hüseyin Serdi KÜÇÜKER
Başkan

APPENDIX 2 – AN EXAMPLE OF VISIT CARD


Prof. Dr. Levin ALTINKAYNAK
Çocuk Sağ. ve Hastalıkları A.B.D.

Kart No.

Ref.

Adı, Soyadı :

Doğum Tarihi : 05.08.2003

Doğum Kilosu: 3750 Boyu: ?

Anne Adı :

Baba Adı :

Adresi :

Ev Telefonu : Ev Telefonu

Cep Telefonu : Cep Telefonu

BCG					
DBT					
Polio					
HİB					
Hep-A					
Hep-B					
Konjuge Pnomokok					
MMR	15.10.2008				
Varicella					
Grip					

Boy: 108cm
Ö.tanı: Akut Tonsillofarenjit
Erytromycin

APPENDIX 3 - SURVEY (ENGLISH)

Information for families before asking survey questions: The aim of the study is to describe medical and non-medical costs of your child's throat infection which is a common disease. This questionnaire was designed to calculate non-medical costs. To perform study, all related approvals were obtained and you are free to answer survey questions. Study results might be published for scientific purposes, but your identity will always remain confidential.

Q1)Did your child miss from school due to his throat infection?

Yes ☐ If yes, please specify how many days did he miss from school?

No ☐

Q2)Did you or your husband/wife miss from work due to your child's throat infection?

Yes ☐ If yes, please specify how many days did you miss from work?

No ☐

Q3)How did you come to the physician due to your child's throat infection?

By your car: Yes ☐ No ☐

If yes, please specify how many kilometers did you come?

Public transportation (bus and etc.): Yes ☐ No ☐

On foot: Yes ☐ No ☐

Q4)Did you buy any extra medication (such as herbal tea, vitamins, minerals) other than your prescription by paying in your pocket?

Yes ☐ If yes, please specify the name of the medication?

No ☐

Q5)Did any other household member develop throat infection within that period?

Yes ☐ If yes, please specify how many other household members developed throat infection?

No ☐

Q6)Did you go another hospital within that period due to your child's throat infection?

Yes ☐ If yes, please specify the name of the hospital?

No ☐

APPENDIX 4 - SURVEY (TURKISH)

Anket Soruları Sorulmadan Önce Ailelere Yapılacak Bilgilendirme: Bu çalışmanın amacı çocuğunuz geçirdiği yaygın bir hastalık olan boğaz enfeksiyonunun tıbbi olan ve olmayan maliyetlerini hesaplamaktır. Bu anket ise tıbbi olmayan maliyetleri hesaplamak için düzenlenmiştir. Çalışmaın gerçekleştirilmesi ile ilgili tüm izinler alınmış olup soracağımız anket sorularını cevaplamak konusunda özgürsünüz. Çalışma sonuçları bilimsel amaçlarla yayımlanabilir, ancak kimliğinizin gizli kalması sağlanacaktır.

1) Çocuğunuz, geçirdiği boğaz enfeksiyonu nedeniyle okula gidemediği gün oldu mu?

   Evet ☐ Evet ise lütfen kaç gün olduğunu belirtiniz:
   Hayır ☐

2) Çocuğunuzun geçirdiği boğaz enfeksiyonu nedeniyle sizin veya eşinizin işe gidemediği gün oldu mu?

   Evet ☐ Evet ise lütfen kimin gidemediğini ve kaç gün olduğunu belirtiniz:
   Hayır ☐

3) Çocuğunuz geçirdiği bu hastalık nedeniyle doktora gelmek için ulaşımınızı nasıl sağladınız?

   Kendi arabamla: Evet ☐ Hayır ☐

   (Cevabınız evet ise lütfen doktora gelmek için kaç km yol yaptığınızı belitiniz):
   Toplu taşıma (Otobüs ve v.b): Evet ☐ Hayır ☐
   Yürüyerek: Evet ☐ Hayır ☐

4) Çocuğunuz geçirdiği bu hastalık nedeniyle reçeteniz dışında kendi cebinizden ödeyerek aldığınız bir ilaç oldu mu? (Örneğin; bitki çayı, vitamin, mineral ve vb.)

   Evet ☐ Evet ise lütfen ilacın ismini belirtiniz:
   Hayır ☐

5) Çocuğunuzun geçirdiği boğaz enfeksiyonu o dönem içerisinde ev halkından başka birine bulaştı mı?

   Evet ☐ Evet ise lütfen kaç kişiye bulaştığını belirtiniz:
   Hayır ☐

6) Çocuğunuz geçirdiği bu hastalık nedeniyle aynı dönem içinde başka bir hastaneye gittiğiniz oldu mu?

   Evet ☐ Evet ise lütfen hastane ismini belirtiniz:
   Hayır ☐

9. CURRICULUM VITAE

MERYEM ALTINKAYNAK

Adress/Telephone/E-mail	Meşrutiyet Mah. Akkirman 3. Çıkmaz Sok. No:8/4 Nişantaşı/İSTANBUL /05334636245/meryemalk@gmail.com
Place and Date of Birth	Erzurum, 01.01.1986
Education	● 2009-Present-Yeditepe University Health Graduate Studies Pharmacoeconomy and Pharmacoepidemiology ●2004-2009 Yeditepe University Faculty of Pharmacy CGPA (3.7 / 4.00) ● 2006-2009 Yeditepe University Faculty of Economics and Administrative Sciences - Double major in Business Administration CGPA (3.5 / 4.00)
Experience	• Aug 2th 2010 – Present: Abdi Ibrahim Ilac San. Tic. A.S/ Istanbul Clinical Research Associate • June 15th 2009 – July 26th 2010: Bayer Turk – Health Care /Istanbul Pharmacovigilance Associate • July 7th 2008 – August 7th 2008: Bristol Myers Squibb Company/ Istanbul Pharmacovigilance Trainee (Internship)
Foreign Languages	● English : Advanced
Certificates and Awards	● October 3rd, 7th, 2011 – Vienna School of Clinical Research Essential Skills for Clinical Research Associates (CRAs) and Monitors ● October 3rd, 7th, 2011 – Vienna School of Clinical Research Basic Clinical Research Associates and Monitors Diploma ●August 19th, 2011 – SAKDER - Regulation on Clinical Trials ●May 10th, 2011 – MK Danışmanlık - Audits and Auditing ●May 9th, 2011 - MK Danışmanlık The Biopharmaceutical Classification System and the BCS based biowaiver ●March 31st, 2011 - MK Danışmanlık -Basic Guideline to Clinical Trial Regulation ●February 25th, 2011 - Vienna School of Clinical Research ●February 24th, 25th, 2010 – MoH of Turkey General Directorate of Pharmaceuticals and Pharmacy Certificate of Completion: Pharmacovigilance Education ●August 7th 2009 – Bristol-Myers Squibb Company Turkey Certificate of Completion: Excellent performance in learning and following up the daily pharmacovigilance activities and issues during five weeks training. ●December 26th 2007 – Yeditepe University, Faculty of Pharmacy Cosmetology Project Competition: Awarded third place in marketing category. Title of Project: XLips (Lip Plumber)