Geographic variation in consumption of biopharmaceuticals among juvenile patients in Norway

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ABSTRACT

BACKGROUND: Principles of equal access to health care are indisputable goals and important foundations of the Norwegian health policy. Juvenile arthritis represents a significant cause of short- and long-term morbidity for the patients. All patients are assumed to have equal need for equal treatment interventions regardless of residence in Norway. Juveniles not having sufficient effect of traditional medical treatment are in need of more aggressive therapy. The last decades have provided major medical advances in this field, introducing biopharmaceuticals as a treatment option. Biologics, such as TNF-α inhibitors are costly and under strict regulation by the government. Therefore the consumption of such pharmaceuticals should be equal across Norway and is investigated further.

OBJECTIVE: The study assesses geographic variation in relation to consumption of biologics among juvenile patients in Norway. If a variation is found, possible explanations and significant factors will be stated. Patients from infants to 39 years of age were studied in the period between 2004 and 2007.

METHOD: Multiple regression analyses are preformed investigating the causality and relationship between the dependent variable and possible explanatory variables.

RESULTS: Significant evidence of geographic variation in the consumption of biologics is found. There are relatively large variation between the hospital trusts and number of patients receiving biologic therapy, showing a tendency of higher biologic consumption in Northern Norway. Especially Helse Finnmark has a high consumption compared to the national average.

CONCLUSION: The analyses suggest relatively large geographic variations between the hospital trusts. There is a clear tendency of larger consumption in the northern parts of Norway. Additionally the consumption of biologics increases with age and with the time period investigated.

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ACRONYMS AND ABBRIVIATIONS

ABF	Activity-based funding
AUP	Pharmacy retail price
DMARDs	Disease modifying anti-rheumatic drugs
EMEA	European Medicines Agency
HT	Hospital Trust, Helseforetak
HOD	the Ministry of Health and Care Services
IBD	Inflammatory Bowel Disease
ICD-10	International statistical classification of diseases
ILAR	International League of Associations for Rheumatology
JIA	Juvenile Idiopathic Arthritis
LIS	Drug procurement cooperation/Legemiddelinnkjøpssamarbeidet
NAKBUR	Nasjonalt Komepetansesenter for Barne- og Ungdomsrevmatologi
NSI	Norwegian Social Insurance Scheme/Folketrygden
NoMA	Norwegian Medicines Agency/Statens Legemiddelverk
NorPD	Norwegian Prescription Database
NPR	Norwegian Patient Registry
NSAIDs	Non-steroidal anti-inflammatory drugs
NSD	Norwegian Social Science Data Services
OUS	Oslo Universitetssykehus HF
RHA	Regional Health Authority, Regionalt Helseforetak
TNF-α	Tumour necrosis factor alpha

1. INTRODUCTION

The main focus in this thesis is to analyze variations in the consumption of biopharmaceuticals to juveniles with inflammatory diseases. Further it emphasises on geographic variations within the prescribing of these drugs. A key objective of the Ministry of Health and Care Services are the principles of equity for all Norwegian citizens. The central state strives to achieve equal access to health care regardless of factors like geographical location, socioeconomic status, gender and ethnicity. Important factors causing geographic differences can be linked to the population's need, the supply of specialist care, distribution of responsibility areas regarding coordination between primary and secondary care and the organization of specialist health care itself (Huseby et al 2008).

Juveniles[1] with autoimmune diseases in need of biologics are assumed to have the same utilization of the drugs in spite of residence. All patients in need of therapy and that fulfil the medical criteria are presumed to receive treatment. The consumption is based on the patients' need for treatment.

This study is designed to investigate possible equity or variations in the consumption of biopharmaceuticals to juveniles. In recent years it has been debated whether it exists a north-south gradient in the prevalence and incidence of juvenile idiopathic arthritis (JIA). The investigating of geographic variation in this field is complex. Practical problems in relation to need of large population samples, different classification criteria and diverse hospital treatments throughout the past decades hamper a comparison of the occurrence of JIA.

Recent studies suggest that there is a higher prevalence of JIA in Northern Norway (Moe and Rygg 1998). These findings are not rejected by other researcher but they claim that larger longitudinal studies are needed in order to state these differences explicitly (Flatø and Vinje 2008).Although debated, based on present research the prevalence and incidence of JIA are considered to be equal across the Norwegian population. The consumption of biologics between different hospital trusts should be matching the population needs.

[1] To simplify the term juvenile is used on all age groups from infants to the oldest age group.

The focus in this paper is based on the following research questions:

1) Is there a significant geographic variation in the consumption of biologics to juveniles between hospital trusts in Norway?

If a variation is found in research question 1:

2) What explains the geographic variation in the consumption of biologics to juveniles between hospital trusts in Norway?

1.1 Background

Pediatric autoimmune disorders are a group of heterogeneous chronic inflammatory disorders. This thesis will concentrate on juvenile patients within rheumatology, gastroenterology and dermatology receiving biopharmaceutical therapy. In pediatric medicine JIA, Crohn's disease and psoriasis represent the largest patients groups where such biologic treatment is applied. Juvenile rheumatic diseases constitute the largest share of patients.

JIA is a broad term that describes a clinically diverse group of arthritis with no apparent cause. The disease onset occurs before 16 years of age (Ravelli and Martini 2007). JIA is the most common rheumatic disease in children and one of the most common chronic illnesses in childhood. It can represent a significant cause of short and long-term morbidity as well as serious eye diseases leading to blindness. The disease can produce substantial morbidity at a young age and there is a considerable implication for provision of health care for this group (Cassidy et al 2005).

Most patients with these diseases have sufficient effect from traditional medical interventions. Still, some children with aggressive autoimmune diseases do not gain optimal effect and different treatment options are needed. The last decades have had major medical advances in treating autoimmune diseases like JIA. The advent of biological therapies has opened a new era for patients that do not have sufficient effect of conventional treatment (Cassidy et al 2005). Tumour necrosis factor alpha (TNF –α), antibodies and other biological drugs[2] are extensively used as an intervention treating these autoimmune diseases. "By definition biologics are proteins and/or derivatives thereof that modulate the immune system, down

[2] In this thesis biological drugs will also be referred to as biologics, biopharmaceuticals, TNF-α inhibitors and biological agents. TNF-α inhibitors represent the largest biological group.

regulate the inflammatory response and support tumor specific defenses" (Beoencke and Radeka p.1 2007).

Biological drugs are costly and therefore under strict regulation by the government. In 2009 TNF-α inhibitors etanercept (Enbrel), infliximab (Remicade) and adalimumab (Humira) accounted for over 1,1 billion NOK, an increase in total of 3,3 percent from the previous year. Measured in NOK the home medication Humira has an increased turnover with 29,6 percent from 2008, whilst Enbrel has a 3,4 percent decrease in the consumption. The hospital treatment Remicade is approximately constant compared with previous year. The turnover is increasing in total, but compared with the DDD (defined daily dose) the increase in NOK is less than the DDD increase. This indicates that the costs of biologics are declining due to increasing competition in the market (Apotekerforeningen 2010).

1.2 Equity and equality in the access of health care

Principles of equal access to health care are important foundations of the Norwegian health policy. The political goal of providing universal access to high quality health care services is indisputable. The "steering document" from the Ministry of Health and Care Services (HOD) to the Regional Health Authorities (RHA) defines the objective as follows: "The primary goal for the health care sector is to provide adequate and appropriate health care services for everyone in Norway, irrespectively of individual financial circumstances, social status, age, sex and ethnicity" (Helse- og omsorgsdepartementet 2009)

Many authors use equity and equality as equivalent terms. In this paper the terms will be distinguished. Although the terms are connected, equity and equality will be defined separately as the terms are not interchangeable.

Equity in health is a principle that derives from different theoretical foundations like philosophy, economics and medicine. The definition of equity can be subject to different interpretations depending on the main concern it is meant to cover. With focus on health care the main idea is that health differences are unfair. These differences are often referred to as inequalities. Inequalities that are looked upon as unfair or unjust, form what are referred to as inequities (Magnussen et al 2009).

Further, health care services are scarce resources that need to be prioritized and allocated accordingly. One challenge for most health systems is to provide both horizontal and vertical equity. Applied research on equity in the delivery of health care services often concentrates attention on the horizontal version of the principle of distribution according to need. Individuals in equal need (in terms of morbidity) are entitled to the same treatment (in terms of consumption) irrespective of income, place of residence and distance to health care, ethnicity, age and gender. This definition of equity in health; "equal treatment for equal need" will be used further in this study (Clench-Aas 2007; Doorslaer and Wagstaff 1992; Gerdtham 1997).

Norwegian medical laws such as The Patients' rights Act and The Specialist health care Act have the intention to ensure that the consumption of health services is determined by the individual's health condition, the expected treatment effect and efficiency in relation to the estimated costs (Iversen and Kopperud 2002). As stated, biologics are costly and represent a large share of the reimbursement market of pharmaceuticals. Based on the principles of equity in Norwegian health policy, one could assume that patients all over Norway receive equal treatment for equal need. Is this actually achieved in reality?

The Norwegian government has established national clinical guidelines for TNF-α inhibitors in the treatment of rheumatic diseases. This was done as an attempt to standardize the treatment of rheumatoid arthritis and to provide equal treatment for all patients independent of place of treatment or residence. Nasjonalt kompetansesenter for barne- og ungdomsrevmatologi (NAKBUR) has also developed guidelines for TNF-α inhibitors when the treatment is applied on juvenile rheumatic patients. These guidelines are recommended but not obliged for all attending pediatricians or rheumatologists with pediatric responsibility (Vinje and Nakbur 2009).

1.3 Organization and financing of health care

Universal social rights are the core of the Norwegian welfare state model. All persons who are either residents or working as employees in Norway, are compulsorily insured in the National Insurance Scheme (NIS). The welfare state is principally financed through a national progressive taxation both general and earmarked, as well as out-of-pocket payment and grants (Magnussen et al 2009).

The Norwegian health care system is organized on three levels national/state level, regional and local levels. Overall responsibility for the health care system rests on the national level, with the Ministry of Health and Care Services. It is responsible for providing national health policy, to prepare and oversee legislation and to allocate funds. The Ministry administrates most parts of the health care including public health, primary health care, secondary and tertiary health care. Nevertheless, the responsibility lies on the different levels.

From 2002, secondary and tertiary health care became a part of the national level and the central government undertook responsibility. Secondary care includes, amongst other clinical research, out-patient clinics and hospital treatment. Tertiary-level health care is highly specialized care, delivered in accordance to central government regulations.

The regional level is represented by the originally five now four regional health authorities (RHAs), the Northern Norway RHA, the South-Eastern Norway, Central Norway RHA and Western Norway RHA. 1st of June 2007 the Southern Norway RHA and the Eastern Norway RHA merged into the South- Eastern Norway RHA. Main objectives were improved exploitation of resources across the regions, better coordination in the Oslo area and more cooperation within the field of research. The Ministry made each RHA responsible for acquisition of health care from both public and private providers. The hospitals and RHAs were organized as hospital trusts. Each body is an independent, legal subject with its own provision. The last level of care is represented on the municipality level with primary health care. Primary health care, both curative and preventive services are subject to local, municipal governance. Primary care includes provision of home care services, nursing homes, preventive care, emergency care and social housing (Johnsen 2006; Magnussen et al 2009).

1.4 Financing of biopharmaceuticals

The National Social Insurance Scheme (NSI) offers reimbursement for certain medicines to patients suffering from chronic illnesses according to lists of diagnoses (ICPC-2 / ICD-10) with a set of criteria the patients have to meet. NSI financed approximately 44 percent of total drug sales in Norway in 2009. Total costs of all drugs in 2009 were 17.6 billion NOK. NSI's expenditure was 7.6 billion NOK. Within the NSI a co-payment is required from most patients. The patient's total co-payment includes cost for medicines, visits to physicians, radiology services and medical supply. If the total exceeds 1840 NOK (per 2010) in one year

the patient is entitled to an exemption card and no further payments that year. (Apotekerforeningen 2010; Johnsen 2006).

Funding of TNF-α inhibitors and other biologics has been subject to change in recent years. From the 1st of June 2006 the financial responsibility for the TNF-α inhibitors were transferred from NSI to the Regional Health Authorities (RHA). The underlying objectives of this reform and the shift in financing were to increase equity concerning the choice of TNF-α inhibitors, to ensure correct prioritization of patient treatment and to increase competition between biopharmaceuticals (Helse- og Omsorgsdepartementet 2006).

Before 1st of June 2006 the financing responsibility was split in two. Patient receiving home care treatment were covered by NSI through the "blue prescription" system. Biologics were not included in the advanced approval for reimbursement. An individual application had to be sent by a specialist for each patient eligible for biologic therapy. Patients using infusion therapy received this treatment at a hospital. The hospital treatments were debited the hospital budget through basic grants and additional reimbursement schemes (Helse- og Omsorgsdepartementet 2006).

Hagen et al 2009 evaluated these objectives finding a change in consumption as a result of the reform. After the reform a trend of increased inequality in the use of biologics between counties occurred to be broken. Still the report lacked the foundation to conclude that inequality between counties had been reduced. The probability to receive TNF-α inhibitors maintained higher in the three northern counties compared to the rest of Norway. Approximately 70 percent more patients per 100 000 inhabitants in Northern Norway RHA received TNF-α inhibitor treatment in comparison to the three remaining RHA (Hagen et al 2009).

The "steering document" of 2010 to the regional health authorities illuminates this further. "Still there are large variations in the prescribing of TNF-α inhibitors between different hospitals. National clinical guidelines are well known and have a high degree of legitimacy in the research community. Thus, this has not contributed to a larger degree of equality in the consumption between the regions" (Helse- og omsorgsdepartementet 2010). It appears to be a significant difference in the consumption of these pharmaceuticals. Following this, new analyses of the variation will be conducted in this paper.

1.5 Theory

The main objective in this thesis will then be to analyze possible geographic variations in the prescription and consumption of biologic drugs. I will specifically concentrate on analyzing the variations between hospital trusts (HT).

Equity is a phrase that can be subject to different interpretations depending on if the focus is equal opportunities or equal results. Equal opportunities concentrate on equal access to health care or equity in the point of use. Geographical location, socioeconomic status, gender and so on should not determine the access to health care services.

One overall objective of the Ministry of Health and Care Services is equality in the consumption of health care services. Through a recent study, which has revealed a significant difference in the consumption of biologics, this objective is not met in the health care today. When studying the consumption of biopharmaceuticals this objective does not seem to apply. So far no clear explanation exists for the geographic variations in the consumption of the biopharmaceuticals.

There are several different possibilities explaining the variations in the consumption of biologics. Aspects like socioeconomic status, demography, morbidity, distance to the hospital, climate, culture and the number of specialists in the region might be of significance.

The consumption of health care services will be analyzed through the microeconomic terms demand and supply. Further we will adapt these terms into a demand model for health care which form the basis of the theory in this thesis. First institutional concepts like allocation and funding of health care, the policy implications on equity and equality in the distribution of health care will be discussed in chapter three. Following that the main demand framework will be assessed. The demand for health care will be analyzed through one main demand model. The demand model describes the relation between health, socioeconomic status, need, supply and consumption of health care services. Further the services have to be allocated based on the population in need.

Other possible significant aspects of relevance to explain geographic variation will be illuminated. The aspects will be supported by reviewing scientific research conducted in the relevant fields.

1.6 Data and methodology

Data for this study is collected from the Norwegian Patient Registry (NPR) and the Norwegian Prescription Database (NorPD). NPR data provides information about the number of hospital admissions, day patient stays and out-patient consultations in specialist health care. All patients receive Infliximab with brandname Remicade during the stay.

The NorPD provides data on number of patients per municipality receiving biologic home medication in terms of subcutaneous injections. It contains data of all pharmaceuticals distributed from the pharmacy and the frequency of distribution. It presents information about the pharmaceuticals Etanercept, Efalizumab and Adalimumab with brandnames Enbrel, Raptiva and Humira. Remicade and Enbrel represent the largest groups of drugs for respectively hospital- and homemedication. The NorPD data has been aggregated to patient level and attributed gender, age and municipality of residence.

Both datasets have been aggregated to patient level attributed gender, age and municipality of residence. Further, the data was merged to form the basis of the analysis in this thesis. From the merged dataset it is possible to conduct an analysis of geographic variation in the consumption of biologics. The data was aggregated to cell level, capturing the consumption through the number of patients defined by municipality, gender, age group and time. The data collection consists of data from year 2004 to 2007. The patient group is defined as juveniles diagnosed with autoimmune diseases within rheumatology, gastroenterology and dermatology. As a common feature all patients are treated with biopharmaceuticals such as TNF-α inhibitors. The age groups stretch from infants to 39-year old patients. Age is categorized into the following age groups: 0-9 years, 10-19 years, 20-29 years and 30-39 years. When analyzing only juveniles the age groups should ideally not exceed 20-year old patients. Due to limited data material in these age groups the dataset was expanded, including younger adults.

A quantitative analysis of the dataset will be conducted. Multiple regression analysis will be performed investigating the relationship between variables. The models applied explore possible variations in the consumption of biologics through generated research questions and hypothesis.

Since this thesis does not contain individual level data it has not been reported to Norwegian Social Science Data Services (NSD). Still ethical guidelines apply when performing scientific research.

1.7 Structure of the thesis

The thesis consists of several sections each describing different theoretical and analytical aspects. The first section presents the medical pathology and indications in addition to the institutional foundation. The second part concentrates on the theoretical framework emphasizing on demand theory analyzed through a demand model. The third section describes the methodology and data applied, followed by description of the variables. The final section presents the results of the analyses, discusses possible explanations to the findings and adds it all up in the conclusion. In addition, the thesis includes an appendix.

2. DISEASE PATHOLOGY

This paper concentrates on biologic therapy within the fields of juvenile rheumatology, gastroenterology and dermatology. The frequency of patients receiving this treatment is rather low. To start with these pediatric diseases have low incidence and prevalence as well as most patients have sufficient effect of traditional interventions. Nevertheless this can be an important therapy for children who do not experience optimal effect of the conventional drugs. Biopharmaceuticals can improve the patient's situations by healing symptoms, preventing damage and disability as a result of the disease. Biologics have no curative effect, still the drugs have a disease modifying effect when applied. Further the therapy can result in remission and recovery from the disease. The children in need of this therapy are severely affected by the diseases. Without satisfactory treatment these patients might develop long-term irreversible complications in association with the activity of the disease. Further the burden of disease will not only affect the patient, but also family and possible society in the long run.

2.1 Autoimmune diseases

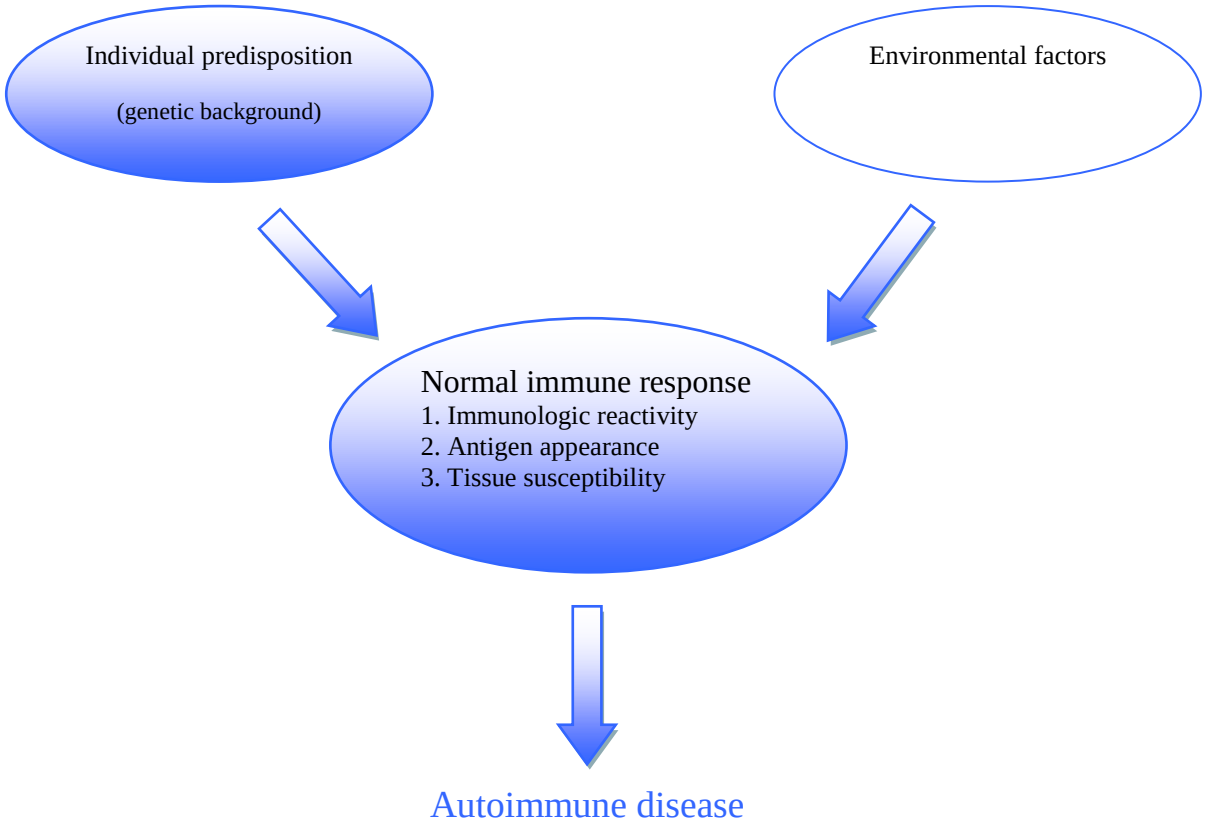
Autoimmune inflammatory diseases occur commonly in developed countries. Juvenile rheumatic diseases, inflammatory bowel disease and psoriasis are all autoimmune diseases with no apparent, known cause of origin. The treatment of these diseases is usually non-curative and is aimed at suppressing inflammatory end-organ damage.

Autoimmunity is caused by an overactive immune system. Through carrier substances the body is falsely informed about an ongoing infection in its tissue. The immune system reacts by starting a strong immune response to defend itself. Hence, the body's own tissues are attacked and continuously destroyed leading to disease. Autoimmunity and autoimmune diseases arise from an overactive immune response in the body (Cassidy et al 2005).

The development of an autoimmune disease is most probably initiated by an atypical, genetically regulated immune response to environmental antigens as described in figure 1. Infection is a potentially important exogenous factor in the introduction of autoimmunity. Both genetic and environmental factors can affect the immune response. The interaction of these factors at many levels determines the development and expression of autoimmune disorders. To simplify; autoimmunity relates to the body having a "hyperactive" immune

system treating its own body tissue as unfamiliar. This results in the body attacking the tissue, triggering inflammation and autoimmune responses.

Figure 1 Pathogenic events related to development of autoimmune diseases (Adapted from Cassidy et al 2005).



However the mechanism that triggers the immune system to cause tissue destruction is still unknown. Special therapies are needed to treat the exact responses causing autoimmunity. Biopharmaceuticals are aiming at such treatment through depressing the activity of the immune system (Cassidy et al 2005).

2.2 Juvenile rheumatic diseases

Rheumatic diseases frequently affect many different organ systems, but inflammation of the structures of the musculoskeletal system particularly joints, connective tissues, and muscles are common in most of them. Due to the effects of chronic inflammation on joints, affected children often suffer both short-term and long-term disability, impaired functional status, and poor quality of life in their adult lives. However, recent advances in treatment appear

promising and early drug therapy combined with rehabilitation can optimize the children's outcomes. Juvenile idiopathic arthritis (JIA) is the most frequent chronic rheumatic disease in children. The term JIA describes a clinically heterogeneous group of several disease subtypes of arthritis. The international League of Associations for Rheumatology (ILAR) defines JIA as "arthritis of unknown etiology that begins before the 16th birthday and persists for at least 6 weeks, when other known conditions are excluded" (Cassidy et al 2005; Ravalli and Martini 2007; Dannecker and Quartier 2009).

The classification of juvenile arthritis has been problematic for decades. Three sets of classification criteria are used to identify clinical subsets that could correspond to different chronic arthritis in childhood. Classifications developed by the American College of Rheumatology (ACR) use the term juvenile rheumatoid arthritis (JRA), those developed by the European League Against Rheumatism (EULAR) defined as juvenile chronic arthritis (JCA) and finally ILAR has provided the most recent classification. As an attempt to unite the classification criteria and set an international standard the term juvenile idiopathic arthritis (JIA)[3] was formed (Petty et al 2004; Cassidy et al 2005; Ravelli and Martini 2007). ILAR classification defines 7 subsets of JIA that represent different diseases with diverse characteristics.

[3] The classification criteria for JIA defined by ILAR will be adapted and used throughout this paper.

Table 1 ILAR classification of JIA 2001. Adapted from ILAR classification of juvenile idiopathic arthritis, second revision 2001

Category	Definition
Systemic arthritis	Arthritis in one or more joints with or preceded by fever of at least 2 weeks' duration that is documented to be daily for at least 3 days, and accompanied by one or more of the following: -Evanescent erythematous rash -Generalized lymph node enlargement -Hepatomegaly and/or splenomegaly -Serositis
Oligoathritis	Arthritis affection one to 4 joints during the first 6 months of disease. Two subcategories are recognized: -persistent oligoarthritis affecting ≤ 4 joints throughout the disease course -exstended oligoarthritis affecting > 4 joints after the 6 first months of disease
Polyarthritis *Rheumatoid Factor (RF)negative*	Arthritis affection 5 or more joints during the first 6 months of disease. A test for RF is negative
Polyarthritis *RF positive*	Arthritis affecting 5 or more joints during the first 6 months of disease; 2 or more tests for RF at least 3 months apart during the first 6 months of disease are positive.
Psoriatic Arthritis	Arthritis and psoriasis, or arthritis and at least 2 of the following: -dactylitis -nail pitting or onycholysis -psoriasis in first-degree relative
Enthesitis Related Arthritis	Arthritis and enthesitis, or arthritis or enthesitis with at least 2 of the following: -sacroiliac joint tenderness and/or inflammatory lumbosacral pain -presence of HLA-B27 antigen -onset of arthritis in a male over 6 years of age -acute anterior uveitis -history of any of these factors in first-degree relative
Undifferentiated arthritis	Arthritis that fulfills criteria in no category or in 2 or more of the above categories.

2.3 Incidence and prevalence of JIA in Norway

The measuring of incidence and prevalence of JIA has been object for discussion. Variations in estimates may be due to the different classification criteria, case ascertainment, often small population samples or to regional and time differences. This inconsistence challenges the compatibility of studies. Also, the question whether there is a north-south gradient in incidence of JIA in Europe has been raised. There is an impression that the most northern countries have a higher incidence rate compared to other European countries. Although not yet statistically verified (Berntson et al 2003).

Flatø and Vinje have analyzed international, Nordic and Norwegian studies on prevalence and incidence of JIA. Finding that an incidence (number of new cases) of JIA in Norway is varying largely from 14 to 23 cases per 100 000 population. Prevalence of the disease is 86

to148 cases per 100 000 population. An incidence peak is found in 1 to 3 year old children, with a known female predominance. Approximately 60 percent of JIA patients are females.

In Northern Norway a combined retrospective and prospective study over 15 year using EULAR criteria found an incidence rate as high as 22,6 (Moe and Rygg 1998).
Another study with inclusion of the exact Northern Norway population but over a shorter time span found an incidence of 18 per 100 000 inhabitants (Berntson et al 2003). This is an example of how incidence rates for an uncommon disease like JIA and a relatively small population at risk need to be measured over a long time period to gain accuracy. Also the method employed for patient retrieval can strongly influence the results.

Further studies and large population samples over time, with accurate diagnostic criteria are needed to detect if true geographic variations in the occurrence of JIA in Norway exist. Differences in the rate between regions and countries could generate a hypothesis regarding environmental and genetic factors that may affect the occurrence of the disease (Flatø and Vinje 2008).

2.4 Treatment therapy

Management of juvenile idiopathic arthritis is based on a combination of pharmacological interventions, physical and occupational therapy and psychosocial support. Although no drugs can cure JIA, prognosis has greatly improved due to progresses in disease management. The aim of treatment should not only focus on achieving optimal function of the joints. Also preserve the physical and psychological integrity of the child, and prevent long-term consequences related to the disease or its therapy. There has been a shift in the treatment of autoimmune diseases. It is identified that irreversible damage occurs early in the disease development. An aggressive treatment approach is therefore recognized and pharmaceutical therapy is started in an early phase, where remission of the disease will be a long-term goal.

Non-steroidal Anti-Inflammatory Drugs (NSAIDs) control pain and inflammation of the disease. This treatment is symptomatic and has been the mainstream therapy for many years and the first line of therapy. Corticosteroid for oral use or intra-articular steroid injections are used as a second line treatment in children who have not responded to conventional NSAID therapy. Injections are frequently needed at disease onset or during disease course. The medicine has a local anti-inflammatory effect in the affected joint. Injections are rapidly effective and can avoid or correct joint contractures and prevent the development of leg length

discrepancy. Although, intra-articular steroid injections are not curative, the effect can be long-lasting (Petty et al 2005; Dannecker and Cartier 2009; Vinje 2008).

Another second line treatment is so called disease-modifying anti-rheumatic drugs (DMARDs). These pharmaceuticals do not produce an immediate analgesic or anti-inflammatory effect but exert the beneficial effects weeks to months after ignition of therapy. Methotrexate is the most commonly used DMARD for treatment of JIA. The majority of JIA patients respond well to traditional treatments like NSAIDs, DMARDs and corticosteroids.

2.5 Pediatric inflammatory bowel diseases

The inflammatory bowel diseases (IBD), Crohn`s disease and ulcerative colitis, are immune-mediated disorders resulting in chronic, relapsing inflammation of the gastrointestinal tract. Symptoms can be presented as bloody diarrhea, abdominal pain vomiting and malnutrition. While no specific etiology has been defined, the complex nature of IBD supports the notion that its origin is likely multi-factorial.

Ulcerative colitis is limited to inflammation in the colon, whilst Crohn`s disease can involve any part of the gastrointestinal tract. The disease behavior in children tends to be more aggressive compared with that in patients older than 20 years at diagnosis and juveniles have a higher rate of familial occurrence. The disease management is based on long-term treatment and care. The burden of these illnesses and the economic expenses are considerable (Mcgreal and Cho 2008).

Traditional medical treatment of IBD includes sulfasalazin, 5- aminosalicylates, corticosteroids and immunosuppressive drugs. Surgical treatment might be a needed convention for some patients. The clinical course of the diseases varies widely. Diagnosed with a mild form of disease patients can reach long-term remission without permanently taking medicines. On the other side a chronic active disease with an aggressive progress need up to life-long medication. The choice of treatment therapy is individual, assessed according to the severity of the disease.

2.6 Pediatric psoriasis

Pediatric psoriasis consists broadly of groups of psoriatic patients: infantile psoriasis, a self-limited disease of infancy, psoriasis with early onset, and pediatric psoriasis with psoriatic arthritis. Psoriasis with all its subgroups has a prevalence of 2-3 percent of the Norwegian

population (Sæterdal et al 2007). About one-quarter of psoriasis cases begin before the age of 18 years. A variety of clinical psoriasis types are seen in childhood including plaque-type, guttate, erythrodermic, napkin, and nail-based psoriasis disease. Plaque psoriasis is the most common form of disease and affects about 80 percent of the patients.

The disease appears as red scaly skin plaques, with raised skin. It classically affects areas around elbows, knees and scalp. Psoriasis is not curable but with aggressive treatment the disease can go into remission and no signs of disease is shown.

Like all forms of auto-immunity, susceptibility is likely genetic, but environmental triggers are required to initiate disease activity. The most common trigger of childhood is an upper respiratory tract infection. Once disease has occurred, treatment is determined based on severity and presence of joint involvement. The therapies used for pediatric psoriasis are essentially the same as those used in adulthood. Topical therapies, including corticosteroids and calcipotriene, are the therapies of choice in the initial care of pediatric patients. Ultraviolet light, acitretin and cyclosporine can clear skin symptoms, while methotrexate and etanercept can clear both the skin and joint symptoms. Concern for psychological development for the juvenile and the aggressiveness of the disease are required when choosing psoriatic therapies (Silverberg 2009).

2.7 Biological therapy

The treatments mentioned above result in improvement for many patients. Still, there are children with insufficient medical effect that require more aggressive treatment. The advent of biologics has been of great importance for this patient group. The therapy can be given in two ways, intravenous infusion and home medication through a subcutaneous injection. Specialist health care, normally an out-patient clinic provides the intravenous infusion. Injections are managed at home by the patient or by primary care. Since the TNF-α inhibitors and other biologics are similar in their effect, both hospital and home medication can be provided to most patients.

Biologics' are protein-based drugs derived from living organisms and are designed to either inhibit or augment a specific component of the immune system (Taylor 2007). These components consist of monoclonal antibodies, soluble cytokine receptors and recombinant receptor antagonists. This includes drugs that block TNF-α such as etanercept, infliximab and

adalimumab as well as other agents such as anakinra, tocilizumab, abatacept and rituximab (Pain and McCann 2009).

The development of biologics is still a young branch of the medical and pharmaceutical field. TNF-α inhibitors and other biologics have been used in the treatment of autoimmune diseases since the last decade. Further research and a wider usage of these substances will be necessary to fully explore their full potential as well as possible long term side effects (Boehnecke and Radeke 2007). In Norway the drugs are under constant surveillance by the Norwegian Medicines Agency. Reporting of all side effects and abnormal effects are crucial for identifying potential unknown effects of the drugs.

2.7.1 Biologics in pediatric medicine

Although some biologics such as etanercept and infliximab have been established on the pharmaceutical market for a long time and are regarded as fairly "safe", special criteria apply when the therapy is applied in pediatric medicine. Some biologics which are used as treatment therapy for children are still not approved by NoMA. Hence, all patients receiving such treatment are registered in a protocol for further research and safety purposes. Rikshospitalet HT is responsible for starting new biopharmaceutical trials on children. All patients receiving new treatment therapy are obliged to register in MEDUP. So far only children receiving therapy at Rikshospitalet HT are registered. Other hospital trusts are also obliged to have their own registries (Nakbur 2010).

2.8 Cost and effect of biologics

The Norwegian Knowledge Center for the Health Services has assessed the cost-effectiveness of TNF-α inhibitors in the treatment of autoimmune diseases. For rheumatic diseases TNF-α inhibitors may be cost-effective, particularly in patients with a recent onset of the disease. The medicine seems to be more cost-effective in patients that experience a good rather than moderate response. The cost-effectiveness of TNF-α inhibitors only applies when the drug is used as a third line therapy (Aaserud et Al 2007). Regarding the IBD diseases there is uncertainty in the cost effectiveness. Biologic therapy is documented to be effective but the drugs do not seem to be cost effective as a continuous long-term use for patients with IBD diagnosis (Ringerike et al 2008). There is strong evidence that biologic therapy is efficacious in the treatment of moderate to severe psoriasis. Limited health economic studies have been

performed but one UK study indicates cost effectiveness when biologics are applied to this patient group (Sæterdal et al 2007).

The lack of large pediatric studies makes it harder to assess whether or not biologic drugs are cost effective. Calculating the long-term effect of the treatment is complicated, especially for children where data is limited. Also, it is hard to value the social cost of possible future disablement. Biological drugs are very costly and therefore it is a need for cost analyzing. Cost of health care is a continuous issue that needs constant attention. Although this is an important health economic factor, cost-effect analyses are outside the scope of this thesis and will not be discussed any further.

3. INSTITUTIONAL FOUNDATION

3.1 Clinical guidelines for juvenile patients

This study is concentrating on the somatic part of the specialist health care services. Mental health care is not a part of the analyses. Patients receiving biologic therapy for their disease are regularly in contact with specialist health care. The Norwegian government established national clinical guidelines for TNF-α inhibitors in the treatment of rheumatic diseases for adult patients. This was done as an attempt to standardize the treatment of rheumatoid arthritis and to provide equal treatment for all patients independent of place of treatment or residence.

For juveniles Nasjonalt Kompetansesenter for Barne- og Ungdomsrevmatologi (NAKBUR) has developed recommended clinical guidelines for treatment with TNF-α inhibitors and other biologics. These guidelines are instructive and recommended in clinical practice. They do not have status as a national document such as the guidelines for adults. Still, national consensus is achieved for these guidelines. The framing of the document is done in cooperation with a reference group involving specialists from all four regional health authorities.

In order to be permitted to start biologic therapy it has to be authorized by a specialist in rheumatology or a pediatrician/other specialist with knowledge of rheumatology. Further it is important that the decision makers include two or more specialized physicians at a university hospital trust. This is to ensure that the patient is an appropriate candidate for the biologic drug and that all aspects of the therapy are considered. The decision is based on the patient's history of disease, previous medical interventions and current condition (Vinje 2009). The table shows the university hospitals present in the different RHAs, showing that South-Eastern Norway RHA has the most university hospitals.

Table 2 Hospital trusts in Norway 2010:

Hospital	Municipality/County	RHA
Oslo Universitetssykehus (OUS) HT[4] includes: -Ullevål Universitetssykehus HT -Rikshospitalet-Radiumhospitalet HT -Aker Universitetssykehus HT	Oslo/Oslo	South-Eastern Norway RHA
Akershus Universitetssykehus HT	Lørenskog/Akershus	South-Eastern Norway RHA
Haukeland Universitetssykhus HT	Bergen/Hordaland	Western Norway RHA
Stavanger Universitetssykehus HT	Stavanger/Rogaland	Western Norway RHA
St. Olavs Universitetssykhus HT	Trondheim/Sør-Trøndelag	Central Norway RHA
Universitetssykehuset Nord-Norge HT	Tromsø	Northern Norway RHA

After a patient has been granted a biologic treatment, local hospital trusts with a pediatric hospital ward or outpatient clinic can perform clinical follow-ups. Nevertheless, it is advised that the patient has frequent consultations at a university hospital in addition.

3.2 Funding of Regional Health Authorities

As described in the introduction, the NSI provides reimbursement for medication to patients suffering from chronic illnesses, included in a list of diagnoses (ICPC-2 / ICD-10) fulfilling the reimbursement criteria. For each diagnosis there is a corresponding list of reimbursable medicines. The Norwegian Medicines Agency (NoMA) decides the inclusion of medicines in the reimbursement program, upon application from the pharmaceutical industry. An economic evaluation of the medicine is mandatory when applying for reimbursement. NSI financed approximately 44 percent of total drug sales in Norway in 2009. Total costs of drugs in 2009 were 17,6 billion NOK. NSI's expenditure was 7,6 billion NOK. Within the NSI a co-payment is required from most patients. Persons receiving minimum old-age pension or disability pension and children below 12 years of age do not pay a co-payment. The patient's total co-payment includes costs for medicines, visits to physicians, radiology services and medical supply. If the total sum exceeds 1840 NOK (2010) in one year the patient is entitled

[4] The merging of the health enterprises took place 1. January 2009 and will not affect the data or outcome in this study.

to an exemption card and will not have to pay further copayment that year (Apotekforeningen 2009; Johnsen 2006).

Secondary health care has been financed in various ways through the years. As of today regional health authorities are owned and granted funding by the central government. The funding consists of two parts, activity-based funding (ABF) and block grants.

From 1997 Norway implemented a prospective activity-based financing system. Funding is based on the DRG-system. The DRG weights are equal for all hospitals, irrespective of cost structure, case mix and hospital type. The background for the change in funding was to increase activity resulting in decrease in waiting lists. The share of ABF and block grants has changed frequently, varying from 30 to 60 percent. In 2005 the DRG reimbursement was 60 percent of the total cost. In 2004 and remaining years including 2010 the reimbursement share has been 40 percent. The block grants are allocated from the RHA to the health enterprises. This is based on each enterprise's need for resources and health composition of the population area the enterprise is covering (Johansen 2006; Magnussen et al 2009).

3.3 Funding of biopharmaceuticals

Funding of high cost drugs such as TNF-α inhibitors have been subject to different financing schemes since entering the pharmaceutical market. Before 2006 the financial arrangements for biopharmaceuticals were separated depending on if the medicine was distributed in a hospital or at home.

The funding of biologic home medication such as Enbrel, Humira and Raptiva were funded by NSI through the "blue prescription", with individual reimbursement after the "blue prescription" regulation § 10a. The biologics had to be prescribed in accordance with the national guidelines stated by HOD and the individual application had to be forwarded from a specialist in the medical field. Hospitals financed their own pharmaceutical consumption, including both in- and out-patient stays through the hospital budget (Helse- og Omsorgsdepartementet 2001).

According to St.prp nr.1 2005-2006 the hospitals were reimbursed 80 percent of their biopharmaceutical costs in the time period from 2002 to 1st of June 2006. The costs were covered by additional reimbursement schemes for the drug Remicade. The hospitals covered

the remaining 20 percent of the costs related to the pharmaceuticals through activity based financing (Hagen et al 2009).

Differences in the funding of the therapeutic comparable biologics Remicade, Enbrel and Humira seemed to give hospitals unfortunate incentives when choosing biologic therapy for patients. Enbrel and Humira were financed through NSI whilst Remicade was financed through the hospital budget. The requisitioners in the hospitals would not conduct cost-effectiveness evaluations and consider the costs when prescribing "blue prescription"drugs in comparison to medicines financed through the hospital budgets. Hence, the choice of biologic was affected by economic incentives in contrast to the overall socioeconomic perspective (Helse og Omsorgsdepartementet 2001).

Due to these colliding incentives the financial responsibility was transferred to the RHA from 1st of June 2006. Additionally 404.2 million NOK were granted as block grants covering the costs of Remicade, Enbrel and Humira. The financing of the pharmaceuticals were fully covered by the hospital budgets. Enbrel and Humira which are home medication were funded through the grants whilst Remicade were still partly covered by activity-based funding. From the 1st of January 2008 the funding of Raptiva was also transferred from the NSI to the RHAs. Home medications were included in the activity-based funding from 2009 as an attempt to give equal status to the biologics and reduce potential distortion effect by preferring the biologics which could give potential activity-based revenue.

The main objectives for the shift in financing were to increase equity concerning the choice of TNF-α inhibitors. The choice should not be affected by economic incentives but reflect the best medical option for the patient. This provides physicians with a better presumption for prioritizing concerning patients treated with biologics with regard to other possible treatments. Last the shift in financing attempted to increase competition between biologics. A real price competition had been nonexistent. The fact that the drugs are medically equivalent enables price competition between the producers since only one party (RHA) is financing all costs (Hagen et al 2009).

3.4 Geographic variation in distribution of specialist health care

On the basis of key statistics for specialist health care from SAMDATA there are shown relatively large variations in the consumption of specialist care in different geographical areas in Norway. To achieve equal access to specialist health care for the population certain

differences between the regions have to be accounted for. First there has to be accordance between the population's need for health care and health care supplied in the specific geographic area. Secondly, there is reason to believe that geographic differences will vary between different disease groups. Finally, the distance to specialist health care can affect the consumption of services (Huseby et al 2008).

The background for today's funding distribution of specialist health care services is the RHA's responsibility for providing certain health services to its population. The cost keys which define how the resources are allocated between the RHAs are based on conditions influencing the need for specialist health care, together with variation in the costs associated with equal supply of services across Norway. The funding is derived from a need index, capturing these costs in specialist health care services (NOU 2008:2 2008).

Based on the developed need index, NOU 2008:2 describes conditions which influence the consumption of specialist health care in a population:

- Age structure (0-5 years, 6-12 years, 13-17 years, 18-29 years, 30-39 years, 40-49 years, 50-59 years, 60-66 years, 67-79 years, 80 years and older)
- Mortality (20 years and older)
- Share of medical report
- Share of recipients of disability benefit (20-66 years)
- Share of recipients of rehabilitation benefit (20-66 years)
- Share of population without further education past primary school (20-59 years)
- Living conditions index (0-19 years)
- Living conditions index (67 years and older)
- Climate- and degree of latitude index[5] (0-66 years)
- Climate- and degree of latitude index (67 years and older)

The compositions of population, morbidity and causes that can affect health status are not equally distributed in Norway. The need for and also the supply of health care services will vary accordingly to this composition (Huseby et al 2008).

Need values are calculated for each of the four RHAs. This calculation is based on the need index and the variables expected to influence the consumption of specialist health care. Index

[5] Climate was included in the index with partial majority as there was uncertainty about the effect of this factor.

value that equals 100 is the mean need for services in the Norwegian population. Values lower or higher than 100 correspond to respectively need below or above the average need (NOU 2008:2 2008).

Table 3 Need index somatic services, NOU 2008:2, 2008

RHA	Need index -somatic specialist services
South-Eastern Norway RHA	100,6
Western Norway RHA	93,4
Central Norway RHA	101,8
Northern Norway RHA	107,6
Norway average	100,0

Sintef has analyzed the relationship between the expected consumption of specialist care and the actual consumption from 2002 to 2007. There seem to be large concurrence between the expected and actual consumption of health care in the hospital trusts. Still some trusts like Østfold and Nord-Trøndelag HT had a proportional lower consumption, while Telemark HT and Førde & Sundmøre HT had proportionally higher consumption of somatic health care. Also geographic differences were shown between disease groups. For example analysis of hospital stays and consultations show a higher share of out-patient consultations within disease groups covering joint pain, rheumatoid arthritis and cox-osteoarthritis. In addition geographic differences in number of consultations across Norway were found.

Sintef interpret the variations as a result of multiple conditions. Differences in consumptions and need of specialist health care reflect the variation in morbidity in the population, also creating difference in need for specialist care in the hospital trusts. Central factors causing geographic variation can be explained by the population's need, the supply of specialist care, distribution of responsibility areas within coordination between primary and secondary care and the organization of specialist health care itself. Other administrative and system-oriented conditions may also cause disparities (Huseby et al 2008).

3.5 Characteristics of the pharmaceutical market

The entry of biopharmaceutical has made a large impact on the pharmaceutical market. The pharmaceutical market is characterized by a high degree of market power on the supply side, mainly due to patent systems and price-inelastic demand. The market has a substantial third-

party payment where patients are covered by the NSI and has an element of asymmetric information. As a consequence of these elements the government has induced a price regulation policy on prescription drugs covered by the NSI (Brekke and Straume 2003).

The supply side of this market is comprised by the pharmaceutical producers. The patent system provides incentives to develop new drugs and investing in research, yet it provides the companies with important market power. Physicians play an important role on the demand side. Traditionally the physicians decide the patients' need for pharmaceutical treatment. The combination of low price elasticity on the demand side and high degree of market power on the supply side necessitate regulations in this market (Brekke and Straume 2003).

Biopharmaceuticals, especially TNF-α inhibitors have been object to strict regulation due to the high costs of the drugs. Since biologics entered the market a few decades ago, most biologics are still under the protection of the patent system. Once the patents expire generic producers are able to enter the market, producing biosimilars. As a result of increased competition on the supply side it is expected that the cost of biologics will fall. The Norwegian Medicines Agency has the regulatory responsibility for all pharmaceuticals. Pricing of prescription medicine is set by NoMA. Pricing is based on an international reference pricing system, comparing the pharmacy purchase price of a drug from nine European countries. The price is set, based on the average of the three counties with the lowest pharmacy purchase price. Norway will at all times achieve low pharmaceutical prices in comparison to other European countries (Statens Legemiddelverk 2010).

From 2006 the RHAs are responsible for the funding of the biologics included in this study. Therefore the Drug procurement cooperation (LIS) has a regulatory part in the pricing process. Through cooperation with the RHAs, LIS collects tenders on all available drugs in the health enterprises. This way the producer with the lowest price receives large quantum orders of pharmaceuticals. On the other side health enterprises benefit from the tenders through price reductions. There are some limitations to this cooperation. First the profit for the enterprises has to be seen in accordance to the cost of running the tenders. Secondly to gain a profit from the tendering competition, several producers have to be represented with a tender. The suppliers in the pharmaceutical market are powerful and cooperation between the suppliers can be a threat. To avoid the latter situations this kind of cooperation is constantly under surveillance and regulated by NoMA (Brekke and Straume 2003).

Hagen et al found that the introduction of tendering competition through LIS reduced prices on TNF-α inhibitors with up to 4,2 percent additional to the reference pricing system (Hagen et al 2009).

3.6 Horizontal and vertical equity

In the introduction equity in health was defined as "equal treatment for equal need". This concept is of importance when assessing geographic variations between hospital trusts. Additionally equity can be divided into two parts depending on the level of equity investigated.

Equity in health care has two components consisting of horizontal and vertical equity. Equity in the delivery of health care services often concentrates on the horizontal level. The principle of distribution according to need may be illustrated by individuals in equal need (in terms of morbidity) are treated equally (in terms of consumption), irrespective of external factors such as geographic location and socioeconomic status. People in equal need ought to be treated the same (Gerdtham 1997; Doorslaer and Wagstaff 1992).

Vertical equity exists when individuals with different levels of need consume appropriately different amounts of health care. There has been little analysis of vertical inequity in health care use. In addition to making value judgments about which variables are need variables, judgments are required about the way in which use ought to vary amongst individuals with different needs. The gathering of such data is complex and needs comprehensive methods, which still does not guarantee correct data (Gravelle, Morris and Sutton 2005).

Horizontal equity can be expressed at any stage of health care production; input, process or output. The usual expressions of production are equality of expenditure, of consumption and of access to health care.

Equality of expenditure refers to the provision of health care resources but does not consider the quality of services received. Equity referred to as expenditure is mostly used when measuring and monitoring inputs such as cost per nurse in all hospitals in a country. Equal consumption for equal need focuses on standardizing medical interventions. The consumption should be equal for all patients across a country. Adapting this to the prescribing of biologics all patients should get the same examinations and interventions for equal health conditions.

Access to health care is based on providing individuals with the opportunity to use needed health care. The latter might lead to different patterns in the consumption of health care. Individuals are free to decide whether or not to use the health care services they are provided with. Equal access for equal need is foundations in the Norwegian health care model. For example it is establish by law that equal waiting time for all patients with similar conditions must be achieved in any hospital trust (Donaldson and Gerard 2007).

Geographic equity adds on the concept of equal access to health care. To achieve equality in the prescribing of biologics, conditions like distance to health care facility and number of specialists in rheumatology have to be equally distributed. This will be discussed further when analyzing possible explanatory variables describing the variation in consumption.

4. THEORTICAL FRAMEWORK

4.1 Introduction

The focus in this thesis is to analyze if there exists a geographic variation in the consumption of biologics between hospital trusts in Norway. As described in the previous chapter supply of the health care services to patients with autoimmune diseases is regulated through several governmental bodies. Both the pharmaceutical market and health care are regulated by the central government. Also the local governments which are independent bodies are closely attached to the central government through some of their funding, like grants.

The principles of equity in distribution of health care were addressed earlier. It describes the allocation of the specialist care and how it is calculated depending on the geographic areas and the population structure. In this chapter the demand for health care is described further emphasizing on the demand theory for health care services and how the allocation should be carried out.

4.2 Need, demand and supply

Market models of demand and supply are fundamental foundations in economic theory. Health resources are scarce leaving patients and hospital trusts faced with trade-offs between resources. Knowledge of the basis of a competitive market is essential to analyze the pharmaceutical market as well as health care models (Donaldson and Gerard 2005).

The market demand curve describes the total quantity of a good demanded by all individuals in an economy at any given price. As the price rises, demand falls, due to the fact that each person demands less of the good and because some individuals exit the market. On the other side we have the supply market. The market supply curve describes the total quantity of a good that all firms in the economy are willing to produce at each price on the curve. Supply rise in accordance with the price since the firms supply more of the good and additional firms enter the market.

These curves only show the relationship between quantity, demand, supply and price. Other externalities such as demographic factors and the natural environment will not be reflected in shifts of these curves (Stiglitz and Walsh 2007). These principles of microeconomic apply as a basis in demand theory which describes the connection between need, demand and supply.

4.3 Demand theory

Health care resources have to be allocated according to the population's need. Norway is governed through a social welfare model with a public health care system based on principles of equity. As discussed earlier, the term horizontal equity meaning equal access for patients with equal need can be applied in this setting.

The social welfare model provides public goods to the Norwegian population. In order to provide health services for the whole population, the government has to apply supply side budget constraints. The funding of public goods is not unlimited and needs to be allocated between entities. A model may be derived based on microeconomic principles adapted to health care purposes.

Norway is a diverse country both geographically and population wise. The age structure and socioeconomic status of the Norwegian population can vary largely between different counties. Each municipality is provided grants, based on the population structure in the area. Even though the overall funding is governmental run each local government has responsibility to provide the public goods that are needed based on this structure.

The assessment of need of health care services on a regional level is based on the individuals need for health care. A usual assumption is that an individual's need depends on present health status, medical technology and the ability to benefit from health care services. The ability to benefit varies with factors like age and socioeconomic status. Need for health care can be a subjective matter and a person's need is unobserved. Unobserved needs for health care have to be explained by variables describing needs and supply. Proxies have to be made to best meet the need of the population (NOU 2008:2 2008). Deriving these proxies can cause challenges such as which proxies should be taken into account and how may supply side variations should be corrected for? There is no accurate answer for these challenges. This demand model can work as a guideline and foundation for making such need explorations.

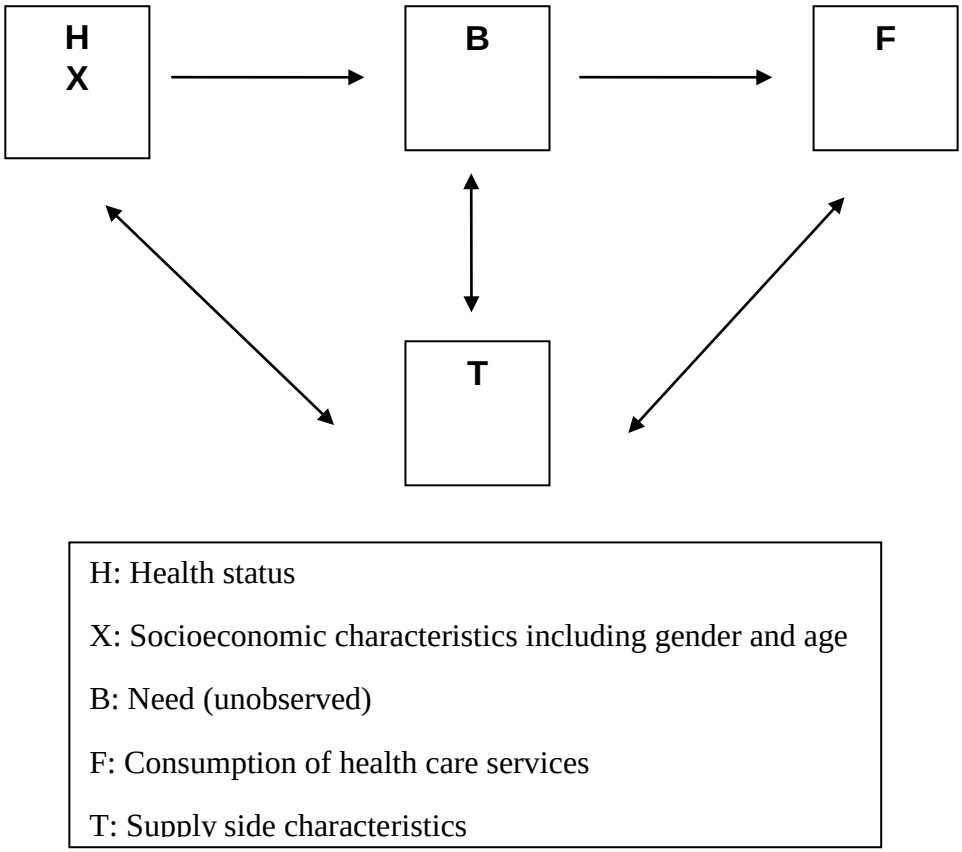


Figure 2 The relation between health, socioeconomic status, need, supply and consumption of health care services. Adapted from NOU 2008:2, 2008

The need for health care services (**B)** is an underlying factor of the consumption of such services. It may be explained by the health status (**H**) which can be a primary cause of the health care need. Need for health care arises as a consequence of injury, disease or suffering that leads to need for health care services. Age, gender and socioeconomic status (**X**) can have an effect on the need further. These factors can affect the health either as an underlying, indirect cause of a person's health state or as a direct cause where the need for health care is affected when the health status varies according to the factors mentioned.

Supply of health care (**T**) can be influenced in different ways depending on restrictions and organizational structure. As long as demand for health care is larger than the supply side, the consumption will depend on the level of supply. Hence, without any supply side restrictions need can be observed through the actual consumption of health care. The supply side on the other hand, will indirectly affect the meaning of the term need. Preventive and well-developed health care can reduce the need for health care. Thus, this can also lead to a higher need for

health care by detecting new treatable needs or demand. Further the consumption (**F**) is depending on the supply side factors. If unlimited supply of health care the consumption would be an increasing steep slope of consumption. Therefore the total consumption (**F**) depends on the level of restriction in the health care supply (**T**).

Demand for health care can be expressed as an intervening variable between need and consumption simplified in the following way:

Need = demand if no supply side restrictions and perfect information exist.

Demand = consumption/use if supply > demand

Supply side restrictions can affect both need and consumption. In situations with no supply side restrictions the need can be observed through the consumption of health care services (NOU 2008:2 2008).

Norway with its social welfare model provides health care services to the population as a whole and supply side restrictions have to apply. Budget constraints are used as such a regulatory tool. One can assume that health care workers wish to maximize the utility of patients under restricted budget constraint. The budget constraint is the limits which the health enterprises have to work within. It is a result of the revenue provided and constitutes the limitation of health care consumption. The HTs opportunity set is defined by this constraint. Normally the revenue constraint is the major limitation of the supply side. Limitations in the supply side will again affect the demand side and the possibility to meet unobserved need in the population. Other opportunity sets such as culture of a hospital and political incentives might influence the constraint (Hagen 2010).

In hospital trusts and secondary care this constraint is based on the need and demand of the population the HT is serving. As described earlier the funding of HT is based on activity-based funding and block grants with respect to key costs calculated from conditions based on the areas demographic structure. The outcomes can be measured in different ways, DRG-equivalents, number of hospital beds and outpatient consultations. Based on this structure, it is up to each hospital to find the “perfect” relationship between the population needs and the supply of health care services. Each hospital trust is then faced with a trade-off between the different services being offered.

Finally an important reflection is that the actual need for health care services might not be revealed in the consumption of the services. This is due to several factors such as the population's morbidity, socio-economic status and share of elderly. Also, there may exist subjective needs that the health care cannot observe and therefore these needs are regarded as unmet. These needs will not be described through the consumption of services and will possibly never be supplied for in the health care services.

5. DATA AND METHOD

5.1 Introduction

The first section in this chapter describes the data material that has been assessed and used in the study. It describes challenges and limitations of the data. The second part presents the method applied. The data has been analysed through a linear multiple regression analysis. Variables that are thought to have an effect on the distribution and consumption of the drugs have been included. Hypothesis are generated when describing the independent variables and tested for in the multiple regression models. The data are aggregated to cell level where patients are defined by municipality, gender and age group. The hospital trusts and years are included to perform a "fixed effects" analysis that will exploit the variation both between the municipalities and the variation of the health services within each hospital trust. Finally the operationalization and description of variables will be presented.

5.2 Data

Data for this study is collected from the Norwegian Patient Registry (NPR) and the Norwegian Prescription Database (NorPD). Data from the NPR provides information about the number of hospital admissions, day patient stays and out-patient consultations in specialist health care. All patients receive Infliximab therapy with brandname Remicade during the stay.

Out-patient- /day treatment were identified by codes:

1) Main diagnosis = infusion code (Z51.2)

2) Second diagnosis = disease diagnosis (ICD 10[6] groups K 50-52 = Noninfective enteritis, L 40-42 = Papulosquamous disorders and M 08-09 = Inflammatory polyarthropathies; juvenile arthritis and juvenile arthritis when disease is classified elsewhere. Admitted patients were identified in the opposite order where main diagnosis = disease diagnosis and second diagnosis = infusion code.

The NorPD provides data on patients receiving biologic home medication in terms of subcutan injections. It contains data of all pharmaceutical distributed from the pharmacy and the frequency of the distribution. It provides information about the pharmaceuticals Enbrel, Raptiva and Humira. Remicade and Enbrel represent the largest groups of drugs for

[6] ICD-10 Version 1, 2010.

respectively hospital- and homemedication. Both datasets containing patient numbers have been attributed gender, age and municipality of residence before aggregated to cell level.

The two datasets were merged on cell level, where a cell is defined by municipality, gender, four age groups and four years. This gives us in total 32 cells per municipality. This aggregated data file forms the basis of the analyses. From cell level it is possible to conduct analyses for investigating geographic variation in the pharmaceutical consumption

The data collection consists of data in the time period between 2004 and 2007. The patient group is defined as juveniles diagnosed with autoimmune diseases within rheumatology, gastroenterology and dermatology. As a common feature all patients are treated with biopharmaceuticals such as TNF-α inhibitors. The age groups stretch from infants to 39-year old patients. Age is categorized into following age groups: 0 to 9 years, 10 to 19 years, 20 to 29 years and 30 to 39 years.

Individual level data would be preferred when performing this kind of repeated cross sectional study with focus on patients. Individual level data denote information about individuals, either contributed by the individuals themselves in surveys or through registers. Permission from the NSD is obliged when performing studies with such individual level data. Also maintaining anonymity in the data is time consuming and outside the scope of this thesis. Therefore, analyses on aggregated level data were preformed.

NPR data only allow following a patient within the same hospital trust during one year. The dataset is based on undetectable patient id number and a patient is assigned a new id-number within every hospital trust for every year. Patients can only be followed within the same hospital trust for one year at the time. This may lead to data collection bias and overestimating of patients due to double counting. Patients that receive treatment in more than one hospital trust in the same year will not be identified. From experience we know that there are patients receiving medical consultations in more than one hospital trust during one year. One example of this is especially patients with JIA who have consultations at Rikshospitalet, OUS HT, even though they belong to another hospital trust. The Rheumatic children's ward and outpatient clinic at Rikshospitalet HT provide tertiary health care services as well as having regional and local responsibilities. In theory patients from the whole of Norway can be referred and receive treatment at this hospital. Unfortunately, the double counting cannot be dealt with since we cannot follow the patient between the hospital trusts.

Ethical guidelines apply when performing scientific research. Since the thesis does not contain sensitive individual level data, it is not subject to the requirements of the Norwegian Social Science Data Services (NSD).

There are 434 municipalities included in this dataset. We have deleted the municipalities that have been merged during the time period the data was collected. These municipalities are 1569, 1154, 1159 and 1755.

5.2.1 Justification of the data

In relation to the aggregation of the dataset certain challenges and choices of proxies need to be discussed.

Since that data set contains three different patient groups, it was debated if a variable for each specialist should be included in the analysis. To cover this field information about specialists within pediatrics, rheumatology, gastroenterology and dermatology had to be gathered. Further calculating the average distance to a HT that provides treatment for each of the different diseases. Since only the NPR dataset contains information about the number of patients in each disease group this could not be fully distinguished, making it impossible to derived new matrixes.

To compare the number of specialists there were 123 rheumatologist, 451 pediatricians, 135 dermatologists and 170 gastroenterologist in 2004 (Den Norske Legeforening 2004). Rheumatologists have the smallest share of specialists. Still there are a sufficient amount hospital trusts providing rheumatic health care services, both in- and outpatient consultations. The number of specialists and distance to hospital trust are assumed to be representative also for the remaining patient groups. This difference is disregarded as likely to affect the analyses. The number of rheumatologist and distance to a rheumatology ward or outpatient clinic are carried out as a proxy in these analyses.

Ideally when analyzing only juveniles the age group should not exceed 20-year old patients. Due to limited data material in these age groups the dataset was expanded to include young adults.

This dataset contains data from two separate databases. Such merged dataset has to be dealt with carefully when drawing conclusions from the analyses. It is important to be aware of the fact that differences in coding between hospital trusts and coding of prescription medication

may exist between the databases. Reasons for the differences can vary from cultural aspects of the hospitals and pharmacies, administrative and organizational challenges or medical differences. Therefore bias in the analyses may appear when merging two databases. Awareness of the potential problem is essential when drawing conclusions from the results.

5.3 Study design

This thesis is based on a repeated cross-sectional study also called a trend study. Since the data is collected over time from 2004 to 2007 this study is performed as a longitudinal research design. This study is a "cross-section" across the entire population and used to observe different parts or sections of the population investigated (Chambliss and Schutt 2006).

The patients investigated are not constant through the years but it is the same section of the population studied in all four years. When performing a cross-sectional study over multiple years we can examine changes over time instead of one single time point. This enables us to analyze the trend in the study and see if the consumption possibly changes over time.

The multiple regression analyses in this thesis are conducted with the Statistical Package for Social Sciences (SPSS) version 16.0.

5.4 "Fixed effect" analysis

The analyses are conducted as a "fixed effects" analysis with dummy variables for each hospital trust, altogether 24. Year coded as a dummy is also included in the model investigating the variation over time.

The "fixed effects" analysis will exploit the variation, both between the municipalities and the variation of the health services within each hospital trust. When including year in the "fixed effects" analysis it will capture if there is a significant variation over time. Including both years and hospital trust in the analysis gives a larger possibility to capture variations regarding geographic location and time.

Since the regression includes "fixed effects" the problem of heteroscedasiticity will be abolished. The "fixed effects" are additionally described in section 5.4 expressing the model in relation to the independent variables.

5.5 Multiple regression analysis

The method conducted in this paper will be multivariate regression. The model will contain one continuous dependent variable. A multiple regression analysis consists of several independent variables that are used to predict the value of the dependent variable. Since a multiple regression is based on correlation it allows us to explore the interrelationship among the set of variables.

Independent variables are included to explain the behavior of the dependent variable. Multivariate regression estimates the effect of an X-variable on Y, where the effects of other X-variables are controlled for. Multiple regression analyses investigate the causality between variables, the correlation and effect of the independent variables on the dependent variable (Eikemo, Clausen 2007 and Newbold, Carlson, Thorne 2006).

Multiple regression analyses limit the possibility to find significant results and explanations in a study if the model does not include all possible explanatory variables. The variables incorporated in the model have been extensively considered to ensure that the most likely explanatory variables are included. "Fixed effects" analysis is included to capture some of this supply side variation not already explained by the independent variables.

5.5.1 Empirical model

This empirical model for the regression analysis describes the effect the independent need, demand and supply side variables have on the dependent variable. The dependent variable Y is standardised and aggregated to cell level capturing the number of patients defined by municipality, gender, age groups and years. The following empirical model can be derived:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4 + \beta_5 D + \varepsilon$$

Footprints for cell level and county are suppressed in the model. The empirical model describes the linear relationship between Y the dependent and X_x the independent variables in the model. The coefficients can be interpreted as follows: β_1 is the change in value of Y for a unit change in X_1 while holding constant the remaining independent variables. β_0 is the regression intercept, also called the constant of regression and describes the predicted value of Y when X equals 0. The β-coefficients explain how the intercept changes for a unit change in the independent variable.

$\beta_1 X_1$ is the dummy variable gender which is defined by patients on cell level. $\beta_2 X_2$ denotes the three age groups where all patients are classified into age from 0 to 40 years based on cell data. $\beta_3 X_3$ capture the number of specialists per municipality based on the number of specialists in each county. $\beta_4 X_4$ denotes distance to the hospital from the centre of each municipality.

$\beta_5 D$ is a vector capturing the "fixed effects" included in this regression model. The "fixed effects" includes both year and hospital trusts. The vector D is created by adding the coefficient for hospital trusts denoted HT and the coefficient for years T together to form the vector denoted $\beta_5 D$ where footprints for $_{ht}$ and $_t$ is suppressed. ε is the error term for the model. It describes the residuals distance from the regression line.

5.6 Statistical assumptions for multiple regression analysis

This dataset has been aggregated containing number of patients on cell level defined by gender, age groups, years and attachment to hospital trusts. When performing a multiple linear regression analyses certain assumptions have to be fulfilled in order to trust the results obtained from the model. The assessment of these assumptions will be described in this section.

The assumption of normal distributed residuals must apply especially when handling a small dataset. This dataset contains of 434 municipalities and 5700 patient numbers. The aggregated dataset consist of 14012 cells in total. This sample size is large enough to ensure normality, generalizebility and validity of the data.

Particularly the dependent variable in this model deviates from the normal distribution curve. With skewness of 7,87 and kurtosis of 90,73 the residuals have a positively, right skewed and peaked distribution curve with many scores in the center of the curve. This is due to the cell level dataset containing value 0 when there are no patients in the municipality defined by gender, age groups and years. The dataset exists of a large enough sample size and therefore the skewness and "peakedness" in the model will not affect the result of the analysis. This is in accordance to theory of the central limit theorem. With large enough sample size the central limit theorem will ensure that even with skewed residuals the sample distribution of the coefficients will approximate a normal distribution with known mean and variance

(Eikemo, Clausen 2007). Also the dataset has been investigated in terms of outliers and extreme values that may affect the outcome of the analyses.

Correlation between and within the variables has been assessed in several ways. Tests for multicollinarity and autocorrelation have been performed. Multicollinarity is checked for through Pearson correlation (r) test and is present if two or more independent variables correlate. A correlation analysis describes the strength and the direction of the linear relationship between to variables (Eikemo and Clausen 2007). The level of which the variables are correlated is set not to exceed the value 0,7. It is hard to distinguish the effects of the variables if keeping highly correlated variables in the model. This may lead to bias in the interpretation of the model. In this analysis Pearson correlation did not exceed 0.7 in any of tests and all original variables are included in the model. Relatively high correlation 0,669 occurred between HT 24 and "Distance", but both variables were kept in three first models and adjusted for in model 4.

Absence of autocorrelation is achieved with non-collinarity between the error terms, the residuals. This can be controlled for by performing a Durbin Watson test. The three first models have a test value of 2,025 and model 4 has value 2,012. Durbin Watson test indicates no autocorrelation between the residuals when the value is 2,0. No autocorrelation is present in this model. Heteroscedasticity occurs if the variance varies with the independent variables or dependent variable. We want to ensure homoscedasticity in the model. This is accomplished when the variance of the residuals are equal across all values of the dependent variable. The heteroscedasticity is eliminated with inclusion of "fixed effects" in the model (Eikemo and Clausen 2007).

5.7 Operationalization of variables

The population's consumption of health care is based on need as well as non-needs related factors (Gravelle et al 2005). Such non-needs related factors can be affected by number of physicians, the supply of health care, travel distance to treatment center and so on. Non-needs variables that possibly will have an effect on the consumption of biologic therapy will be included in the multivariate regression model. Further the independent variables that are expected to influence the need for health care such as age and gender will be analyzed. We have derived need, demand and supply side variables based on predictions on the patients' behavior and published research. Four hypotheses stating the effect of the supply, need and demand side have also been generated.

5.7.1 Dependent variable

The dependent variable describes the consumption of biological drugs to juveniles and young adults with age between 0 to 40 years old. More precise the variable describes the total consumption of biologics through the number of patients receiving medication on cell level defined by municipality, gender, four age groups and four years per 10 000 inhabitants.

5.7.2 Independent variables

The independent variables included in the analyses express possible explanations of what affects the consumption of biologics. Each variable are described and a hypothesis is tested for each variable stated in the regression analyses.

5.7.3 Variables describing need and demand

Based on the demand model a person's need for health care is an underlying factor for the consumption of services. In addition, the health status is affecting the need and demand for services. The variables in this section constitutes the need and demand side of this model, including gender and age.

Need and demand side variables are directly attached to the patient situation. The variables also describe possible personal features that may influence the consumption of biologics across Norway.

Gender

Gender is included in the regression model as an independent variable. The variable analyzes if there are any differences in the consumption of biologic drugs in relation to gender. Gender is coded as a dummy variable that takes the value 0 for men and value 1 for women. The diseases included in this analysis, especially JIA have a female predominance. This effect is also showed for in the descriptive statistics where the dataset consist of 2565 men and 3135 women.

It is assumed that women have a higher consumption of biopharmaceuticals since they are overrepresented in disease groups presented in this thesis. Flatø and Vinje 2008 describe a female predominance in the incidence and prevalence of patients diagnosed with JIA.

Hypothesis 1: Women have a higher consumption of biologics than men.

Age groups

The independent variable age was re-coded into age groups to capture a possible geographic variation in the consumption of biologics between the groups.

Age group 0 to 9 years

The variable is coded as dummy and includes patients in the age group between 0 to 9 years of age.

Age group 10 to 19 years

The variable is coded as a dummy, including patients in the age between 10 to 19 years of age

Age group 20 to 29 years

The variable is coded as a dummy, including patients in the age between 20 to 29 years of age.

Age group 30 to 39 years

The variable is coded as a dummy, including all patients in the age between 30 to 39 years of age.

From experience, age is a reasonable stable predictor of the consumption of specialist health care. The need and hence the consumption of health care are assumed to increases with age (Nerland and Hagen 2008).

The patients in this study are rather young and the prediction of increased consumption with age is not fully satisfied. Still, patients receiving biologic treatment are increasing with age. This is due to exogenous factors such as medical indication and epidemiology of the patient groups. Biopharmaceuticals are representing a new area of medical therapy and research on the pediatric field is limited. Additionally, medical guidelines for juveniles are especially strict to ensure thorough assessment before starting a patient on the medication (Vinje and Nakbur 2009).

Hypothesis 2: The effect of age will be positive and the consumption increases with age.

5.7.4 Variables describing the supply side

In the demand model the supply side characteristics restrict the supply of health care services. The consumption of health care has to been considered in relation to the need and demand variables as well as the supply of health care services. Supply side variables describe the health care services provided that may affect the consumption of biologics in Norway.

Travel distance to specialist

This variable denotes the average travel distance from the municipality to the nearest hospital that has a rheumatologist attending. The distance includes hospitals having in- or outpatient clinics or both. Distance is measured in kilometers and is calculated from matrixes.

Studies of the consumption and access to specialist health care in Norway find a negative effect of travel distance. The consumption of specialist health care decreases with the distance to the hospital (Nerland and Hagen 2009; Hagen 2009).

Travel distance is not predicted to have a large impact on the consumption of biologics. Homemedication constitutes the largest share of the biopharmaceuticals. Regular consultations with the general physician are as important as specialist consultations, once the patient has started the intervention. As a theoretical foundation the hypothesis for negative effect in accordance to increased travel distance will be tested for.

Hypothesis 3: Patients with long travel distances to hospitals will have a negative effect on the consumption of biologic therapy.

Number of rheumatologists

The variable provides information about number of rheumatologists in relation to hospitals that provide biologic treatment. The variable is calculated from number of registered specialists in rheumatology in 2004.

As mentioned in chapter 3.1 the recommended clinical guidelines in order to receive biologic therapy involves assessment by two rheumatologists or specialists with high degree of knowledge on the field (Vinje and Nakbur 2009). The share of rheumatologists in an area will affect the supply of biologics. Predicting there will be a positive relationship between the number of specialists and consumption of biopharmaceuticals.

Hypothesis 4: There is a positive effect between the supply of rheumatologists and the consumption of biologics.

5.8 "Fixed effects" for year and HT

A possible geographic variation in consumption of biologics can be affected by other circumstances external from the variables already included. Situations and possible effects outside the scope of the variables can typically be organizational differences, population structure and different culture in the hospitals trusts. By conducting analyses on aggregated cell level and including "fixed effects" in the analyses, we eliminate much of the supply side variations in the dataset.

The analyses in this regression model are performed as "fixed effects" analyses. This is done by creating a dummy variable for each independent hospital trust. In total the variable describe 24 hospital trusts (HT) where 23 dummies were included in the model. Dummies for years were included in the "fixed effects" analyses. Year captures the time period from 2004 to 2007 where patients received biologic therapy. Year coded as a dummy will investigate the consumption over time and adjust for variation between the years.

Conducting "fixed effects" analyses will exploit the heterogeneity between the municipalities and within the catchment area of each hospital trust. The "fixed effects" dummy variables HT will then capture supply side variation and/or possible excluded need variables (Hagen 2009).

The effect of the supply side variable specialists can be captured by the variable itself but also by HT dummies. This is adjusted for in the regression analysis by performing various

analyses. The final result ended up with inclusion of three models with all variables and one model only capturing the effect of specialists and travel distance. The dummy variables for year 2007 and hospital trust 1,9 and 24 were selected as reference categories in the regression analyses, depending on the model assessed.

We do not generate any specific hypothesis regarding these "fixed effects" variables, but they will have a large impact on the results in relation to the research questions for this study. It is expected that the analysis to capture possible geographic variations between the hospital trusts.

5.9 Descriptive statistics

Table 4 Descriptive statistics of the dependent variable

Dependent	N	Min	Max	Mean	Std dev	Skewness	Kurtosis
Number of patients, cell level defined by gender, age groups, years	13785	0,00	525,32	6,6	24,47	7,87	90,73

The cell data shows large differences between the municipalities. The mean of patients receiving biologic therapy is 6,6 patients. Some municipalities have no patients whilst there are 525,32 patients per 10 000 inhabitants in one municipality. The maximum value seems so what high compared to the average number even though the numbers are standardized. The data has been checked for outliers and errors. The max value is correct belonging to municipality 1835, Træna. Also additional municipalities have high mean values, up to 500 patients per 10 000 inhabitants. One can contemplate if this is due to false coding or due to actual medical practice in the municipality. Description and result of the geographic variation will be handled in the result section. As previously commented the dependent variable has a high degree of "peakedness" and a positively skewed normality curve.

Table 5 Descriptive statistics of independent variables

Independent	N	Min	Max	Mean	Std dev	Skewness	Kurtosis
Gender	13899	0	1	0,50	0,50	0,00	-2,00
Distance	13948	0,20	858,3	127,39	139,36	2,67	8,80
Std_spes	14012	0,042	0,59	0,24	0,15	0,57	-0,21
Age group0_9	13899	0	1	0,25	0,43	1,16	-0,66
Age group10_19	13899	0	1	0,25	0,43	1,16	-0,67
Age group20_29	13899	0	1	0,25	0,43	1,16	-0,67
Age group30_39	13899	0	1	0,25	0,43	1,15	-0,67

Gender is a dummy variable which takes value 0 for men and value 1 for women. There are 2565 men and 3135 women represented in the dataset. Women constitute a larger share of the patients, respectively 53,90 percent. The distance from the municipality to the nearest hospital

varies largely between 0,20 to 858,3 kilometers; the distance is especially elevated in municipalities within the county of Finnmark. The mean distance is 127,39 kilometers.

Number of rheumatologist in the municipalities fluctuate between 0,042 to 0,59 specialists per 10 000 inhabitants. The average number of specialists is 0,24. The matrix calculating this average is based on number of specialists in 2004. According to Den Norske Legeforening, 123 rheumatologists were registered in Norway. There are great differences in the number of patients between each age group. Patients in age group 0 to 9 years of age constitute only 2,6 percent of the patients. The largest age group 30 to 39 years represents a share of 61,9 percent in a total of 5700 patients.

5.9.1 Variation in the consumption of biologics

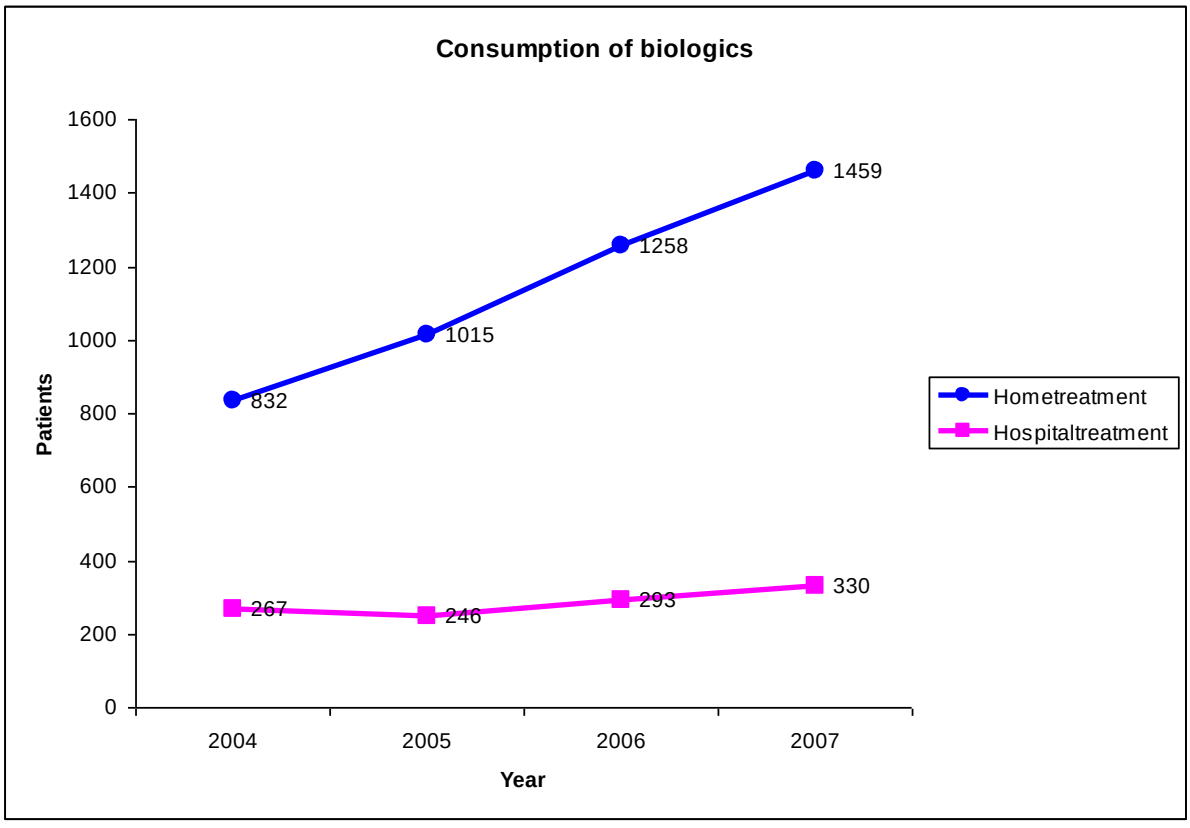


Figure 3 Consumption of biologics between 2004 and 2007

Figure 3 presents an annual increase in the consumption of biologics. The horizontal axis describes the time period and the vertical axis explains the number of patients receiving biological therapy. From 2004 to 2007 the consumption has increased with 61.5 percent in

total. Home medication account for the majority of the pharmaceuticals, respectively 80 percent of the total consumption of biologics. There is a constant consumption increase of about 20 percent per year, except 2006-2007 where the growth is close to 30 percent. The large share of home medication can be explained by the different types of biopharmaceuticals included in this paper. Respectively just one hospital medication and three home medications are analyzed.

The increase in consumption can be explained by an increasing indication of the use of these pharmaceuticals as well as new research on the field improves the knowledge of these drugs. A considerable increase in consumption is shown in all patients group besides the age group between 0 to 9 years of age where the number of patients is constant. The latter age groups account for the largest share of consumption increase.

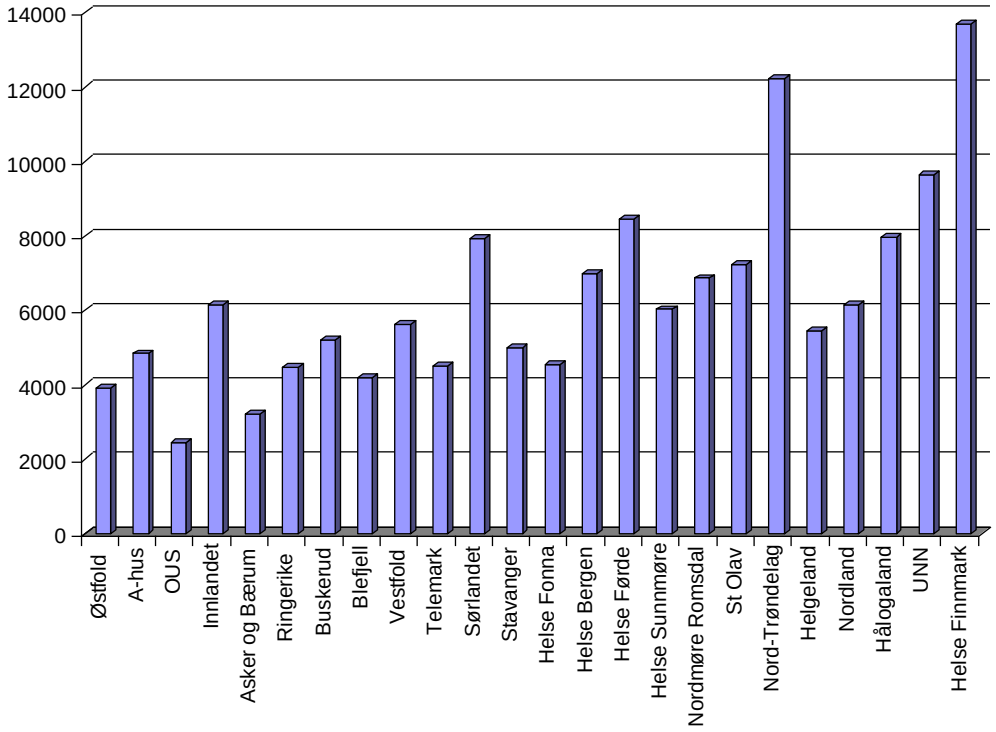


Figure 4 Consumption of biologics in HTs, based on patients population >40 years per 100 000 between 2004 to 2007.

Further figure 4 indicates large geographic variations in the consumption of biologics, measured on HT level. The figure shows the consumption based on number of patients in the municipalities belonging to a hospital trust, standardized per 100 000 inhabitants with age up to 39 years old. Helse Finnmark HT has the largest consumption of biologics. Also the consumption in Helse Nord-Trøndelag HT stands out compared with the remaining HTs. Oslo

University hospital represents the least consuming HT, also Asker and Bærum sykehus and Sykehuset Østfold have low consumption. The figure shows an overall higher consumption in the northern hospital trusts. Table 8 in the appendix shows the exact number of patients per HT.

6. RESULTS

The core objective when performing multiple linear regressions is to investigate variation in the consumption of biologics across Norway. 5700 patients are included in the time period between 2004 and 2007, capturing patients with autoimmune diseases in age group infants to 40 year of age. The study emphasizes on geographic variation in consumption of biologics which account for an increasingly large share of the reimbursed pharmaceutical costs. The analyses are based on the possible variation between the hospital trusts.

All analyses have been conducted based on the multiple regression model described in an earlier section. 4 models are included in the results, investigating different aspects of possible geographic variation in the consumption of biologics between hospital trusts.

The results, including estimates for the intercept and the independent variables, will be described and commented on based on the hypothesis stated in chapter 5.

Helse Finnmark (HT 24) has the largest consumption of biologics. Based on this an analysis excluding dummy for HT 24, year 2007 and age group 30-39 was conducted. The results from this analyze creates the foundation for further models. Sykehuset Vestfold (HT 9) is excluded in model 2, representing the national average. HT 3 Oslo had the least consumption but when excluding this HT the model showed weak significant effects, due to high standard error in the HTs. In stead Sykehuset Østfold (HT 1) represents the southern part of Norway and provides a better standard for the low consuming HTs. HT 1 is excluded from model 1.

Table 6 Regression analyses. Explanation of the variation in consumption of biologics (2004-2007).

	MODEL 1 (HT 1) Estimate β (Std error)	**MODEL 2 (HT 9)** Estimate β (Std error)	**MODEL 3 (HT 24)** Estimate β (Std error)	**MODEL 4** Estimate β (Std error)
Constant	15,149 (4,334) ***	15,533 (1,428) ***	20,912 (1,839) ***	15,466 (0,727) ***
Gender	1,362 (0,407) ***	1,362 (0,407) ***	1,362 (0,407) ***	1,362 (0,406) ***
Age group0_9	-14,943 (0,576) ***	-14,943 (0,576) ***	-14,943 (0,576) ***	-14,948 (0,574) ***
Age group10_19	-11,897 (0,575) ***	-11,897 (0,575) ***	-11,897 (0,575) ***	-11,901 (0,573) ***
Age group20_29	-10,023 (0,575) ***	-10,023 (0,575) ***	-10,023 (0,575) ***	-10,027 (0,573) ***
Std_specialists	0,454 (2,129)	0,449 (2,128)	0,443 (2,128)	1,146 (1,454)
Distance	0,004 (0,003)	0,004 (0,003)	0,004 (0,003)	0,009 (0,002) ***
Year 2004	-3,188 (0,576) ***	-3,188 (0,576) ***	-3,188 (0,576) ***	-3.193 (0,574) ***
Year 2005	-2,622 (0,576) ***	-2,622 (0,576) ***	-2,622 (0,576) ***	-2.629 (0,574) ***
Year 2006	-1,048 (0,576) *	-1,048 (0,576) *	-1,048(0,576) *	-1.053 (0,574) *
HT 1		-0,376 (1,622)	-5,752 (1,903) ***	
HT 2	0,364 (1,471)	-0,020 (1,536)	-5,397 (1,815) ***	
HT 3	-1,718 (4,335)	-2,100 (4,400)	-7,477 (4,537) *	
HT 4	-1,236 (1,217)	-1,618 (1,384)	-6,993 (1,538) ***	
HT 5	0,149 (3,203)	-0,235 (3,228)	-5,613 (3,421) *	
HT 6	-1,060 (1,764)	-1,443 (1,871)	-6,817 (1,956) ***	
HT 7	-1,598 (2,022)	-1,981 (2,107)	-7,358 (2,350) ***	
HT 8	-0,733 (1,508)	-1,116 (1,607)	-6,492 (1,832) ***	
HT 9	0,393 (1,622)		-5,367 (1,990) ***	
HT 10	0,994 (1,850)	0,610 (1,925)	-4,766 (2,127) **	
HT 11	0,944 (1,278)	0,561 (1,474)	-4,814 (1,704) ***	
HT 12	-0,591 (1,434)	-0,974 (1,576)	-6,350 (1,831) ***	
HT 13	0,062 (1,455)	-0,320 (1,593)	-5,696 (1,836) ***	
HT 14	0,812 (1,382)	0,429 (1,529)	-4,947 (1,780) ***	
HT 15	1,724 (1,331)	1,341 (1,480)	-4,034 (1,690) **	
HT 16	-0,553 (1,596)	-0,937 (1,634)	-6,314 (1,893) ***	
HT 17	3,901 (1,524) *	3,518 (1,579) **	-1,858 (1,743)	
HT 18	1,845 (1,375)	1,462 (1,483)	-3,914 (1,703) **	
HT 19	4,882 (1,372) ***	4,499 (1,495) ***	-0,877 (1,695)	
HT 20	-1,575 (1,720)	-1,958 (1,767)	-7,330 (1,457) ***	
HT 21	3,498 (1,661)	3,114 (1,696) *	-2,261 (1,768)	
HT 22	2,297 (1,425) *	1,915 (1,590)	-3,458 (1,523) ***	
HT 23	4,033 (1,611) **	3,652(1,847) **	-1,721 (1,930)	
HT 24	5,755 (1,896) ***	5,373 (1,983) ***		
R^2 (Model fit)	0,065	0,065	0,065	0,058

* = P <0,10 ** = P <0,05 *** = P <0,01

The constant is standardized and describes the number of patients consuming biological drugs per 10 000 inhabitants defined by gender, age group and time. In model 1 the number of patients receiving biologics are 15,149 patients per 10 000 inhabitants. In model 2 and 3 the number is respectively 15,533 and 20,912, depending on the reference categories chosen.

Regression model 1, 2 and 3 includes all need and demand variables as well as supply side variables and "fixed effects" for year and hospital trusts. In model 4 hospital trusts have been omitted from the analysis. This is done in an attempt to capture the effect of "Std_specialists" and "Distance" alone. The three first models consist of an equal number of independent variables. What differentiates the models is the hospital trust chosen as a reference category in each model.

Regarding the need and demand side all variables are found to have a significant effect on the consumption of biopharmaceuticals. The variable "Gender" where male is reference category has an estimate of 1,362 ($p<0,001$). This is in line with hypothesis 1 where women consume more biopharmaceuticals than men. Interpreting the estimates this indicates that there are 1,36 more female patients per 10 000 inhabitants when all other variables constant.

"Age group 0_9" ($p<0,001$), "Age group 10_19" ($p<0,001$**)** and "Age group 20-29" ($p<0,001$) have all significantly negative correlation to the consumption of biologics. In example "Age group 0_9" have 14,943 patients less per 10 000 inhabitants defined on cell level compared to the reference unit "Age group 30_39". The effect is that in the time period of analyzing the number of patients per 10 000 inhabitants are increasing with age. This is in accordance with the second hypothesis; the consumption of biologics is increasing with age.

Independent supply side variables include "Distance" and "Std_specialists". None of the variables were statistically significant in the three first models. The variable "Distance" has a p-value of 0,174 and is closer than "Std_specialists" to have a significant effect if applying a 90 % confidence interval. This has been investigated further in model 4.

The "fixed effects" variables "Year 2004", "Year 2005", "Year 2006" compared to "Year 2007" are significantly correlated. These variables capture the differences between the years included in the analyses. The negative correlation can be described as a decline in number of patients between 2007 and 2004. Put in another way, "Year 2007" is chosen as reference category, since this year constitutes the largest share of patients all previous years will be

negatively correlated when comparing. We find a clear tendency of increasing consumption in the time period.

As argued Sykehuset Østfold is excluded in Model 1. The model shows large geographic variations in the consumption of biologics between the hospital trusts. The estimates indicating number of patients compared to the reference unit HT 1 with 15,149 patients varying from -1,718 in HT 3 to 5,755 patients in HT 24 (Helse Finnmark). There are large variations in the estimates, statistically significant results are present in five HTs. Helse Finnmark HT and Helse Nord-Trøndelag have a significant effect ($p<0,01$**)** on the consumption of biologics. The northern catchment areas with Universitetssykehuset i Nord Norge and Hålogalandsykehuset also show significant geographic variation. Sykehuset Østfold treated 15,149 patients and Helse Finnmark 20,904 patients per 10 000 inhabitants given reference categories "Year 2007", "Age group 30_39" and HT 1.

Model 2 explains the variation in relation to the HT closest to the national average of biologic consumption. The national average is operationalized through the catchment area of HT 9, Sykehuset Vestfold with 15.533 patients in the model. Several HTs differ from the average after correcting for explanatory variables including the demand and supply side. Nordmøre og Romsdal (HT 17), Helse Nord-Trøndelag (HT 19), Nordlandssykehuset (HT 21), Universitetssykehuset Nord-Norge (HT 23) and Helse Finnmark have a statistically significant effect on the consumption. All these HTs are above the national average consumption, estimates varying from 3,518 (HT 17) to 5,373 (HT 24), both $p<0,001$.

Helse Finnmark has the largest variation compared to both low and average consumption. In model 3 an analysis is performed with HT 24 as reference unit. This analysis with all other variables remaining the same (cet par), shows a significant effect of all hospital trusts besides HT 17, 21 and 23. The estimates fluctuate largely between -7,477 in Oslo (HT 3) to -0,877 in Helgelandssykehuset (HT 20). The estimated for HTs can be interpreted as the change in number of patients compared to Helse Finnmark which have 20,912 patients defined by gender, age groups and years, per 10 000 inhabitants. There is a significant tendency of an overall higher consumption in the northern part of Norway. In addition northern hospital trusts HT 19, HT 21, 22, 23 have estimates close to HT 24 which indicates high biologic consumption above the national average.

In model 4 we have excluded the hospital trusts from the model, to capture the supply side effects. Model 4 is testing for hypothesis 3 where an increase in distance has a negative effect on the consumption, cet par. When excluding HTs in the analysis "Distance" becomes significant ($p<0,01$). It has a positive, although very vague effect on the consumption of biologics. This is somewhat reverse to what the research state, where long travel distance was assumed to have negative correlation with utilization. Hypothesis 3 is not supported since travel distance has a vague but positive effect on the consumption. Neither of the models shows any causality or significant effect of the variable "Std_specialist". Hypothesis 4 is rejected on a 90 % confidence interval. There are shown no significant correlation between consumption and number of specialists in any of the models included.

R square (R^2) expresses how much of the variance in the dependent variable that is explained by the independent variables in the model. The test value has a range from 0 to 1. In the three first models R square account for 6,5 percent of the variance in the consumption of biologics. In model 4 the explanatory power is smaller with a percentage of 5,8.

7. DISCUSSION

7.1 Main objectives

Principles of equal access to health care are important foundations of the Norwegian health policy. The political goal of providing universal access to high quality health care services is indisputable. The core objectives in this study have been to explore geographic variation across Norway, in relation to the consumption of biologics to juveniles. If a geographic variation is found, possible explanations and significant factors would be stated.

7.2 Main findings

Significant effects of variation in the consumption were found in all models included in the regression analyses. Model 1, 2 and 3 provide significant estimates for the independent variables "Gender", "Age group 0_9", "Age group 10_19", "Age group 20-29" and "Age group 30_39". There were found no causality between "Std_specialists" and geographic variation in any of the analyses. Model 4 finds a positive significant effect of "Distance" ($p < 0,001$). Within the "fixed effects" analysis all 24 hospital trusts are found statistically significant varying from 1 to 10 percent significance level. Model 3 has the largest effects with 19 HTs being significant and the majority with p-value < 0,001. "Year" coded as dummies are significantly correlated through the whole time period.

The northern hospital trusts with Helse Finnmark HT 24 have a much larger consumption compared with the national average and the least consuming HT, Oslo. Helse Nord-Trøndelag is the second highest consuming hospital trust after HT 24. There also is a tendency of higher biologic consumption in Northern Norway.

7.3 Discussion of results

The main conclusion in this paper emphasizes a positive answer to the research question 1 "Is there a significant geographic variation in the consumption of biologics to juveniles across Norway?". Statistically significant results are found on the supply side as well as the need and demand side in the multiple regression analyses.

There are considerable variations in the consumption between the hospital trusts. Geographic differences are present in all of the analyses. Especially Helse Finnmark stands out providing biologic treatment to more patients in relation to the other HTs. Helse Finnmark has a 35,7 to

57 percent larger consumption compared with the least consuming HT, Oslo, depending on the models analyzed. In comparison with the national average consumption Finnmark provides biologic therapy to 25,7 percent more patients after controlling for other supply and demand variables. In addition to Helse Finnmark, other northern hospital trusts have consumption above the national average. After controlling for other explanatory factors, the trend shows a larger consumption in the northern parts of Norway. The results underline the prediction of a significant geographic variation in Norway which is also found in a previous study (Hagen et al 2009). As argued initially principles of equal access to health care are important foundations of the Norwegian health policy. Equity in the providing of universal health care is an indisputable political goal. Hence, these policy implications do not appear to be applicable in this study of distribution of biologics.

Hagen et al 2009 analyzed the consumption through datasets on patient level and based on DDD (defined daily dose). They found an increasing consumption over the same time period as investigated in this study. Our results showing geographic variations are corresponding with the findings in Hagen et al 2009. Where it was found approximately 70 percent larger consumption of biologics in the Northern Norway RHA compared to the remaining RHAs. They also found no basis for a lower inequality in consumption after the change in financing of TNF-α inhibitors. Our results are somewhat less extreme but the tendency of higher consumption in Northern Norway is confirmed. There is a significantly higher probability of receiving biologic treatment in the northern parts compared to elsewhere.

In the analyses "Gender" has a positive correlation on the consumption. This indicates that female patients constitute a larger share of the consumption than male patients. In the description section the hypothesis stated that women had a larger effect on the consumption than men. The results support this premise. The differences in gender can be explained by the fact that women are predominant in relation to men regarding autoimmune diseases. This is recognized in scientific studies but the underlying reason for the gender difference is unknown (Petty et al 2007).

The variables "Std_specialists" and "Distance" are proven not to have any significant effect when dummies for HT were included in the analysis. These supply side variables may also be captured by the variation within the HT which can provide one explanation for the findings. This is in conflict with the previously stated hypothesis.

However, in model 4 where HT's are omitted from the analysis "Distance" have a vague significant effect on the consumption. Somewhat surprising is the positive effect of the variable. Prediction of negative consumption with increased distance has great support from research preformed on this field. The explanation for the deviation may lie within the geographic variation analyzed in the recent models. In all three models where HTs are included, Helse Finnmark has a significantly higher consumption compared to the other hospital trusts. Investigating the distance to hospital in HT 24 we find that the distance to the hospital varies from 0,20 to 858,3 kilometers. The majority of the patients live between 314 and 849 kilometers away. Comparing this to the national average of 127 kilometers, the significantly positive effect of distance can be recognized easier.

7.4 Possible explanations for geographic variation

Research question 2 is aiming at explaining what causes the geographic disparity across Norway. The variation in the consumption can have several possible explanations which are not mutually exclusive. Several factors will be discussed.

Hagen et al 2009 argued that the prevalence of Bechterew's disease is slightly higher in the northern part of Norway. Especially the prevalence of the Sami population belonging to catchment area Finnmark is peaked. This was used as a possible explanation for the high consumption in the north of Norway. As an attempt to investigate this explanation ICD-10 codes for Bechterew's disease were not included in this study. Therefore we cannot rely on this explanation as a possible cause of the skewed distribution of biologics. Hagen et al found no other apparent reason for the geographic differences.

Another possible yet debated explanation is the occurrence of JIA. Some studies suggest that there is a higher prevalence of JIA in the northern part of Norway. There is in general an impression of a peaked occurrence of JIA in the northern parts of the Nordic countries. No clear conclusions exist but explicit suggestions are made (Moe and Rygg 1998; Riise et al 2008).

Few population based studies have been performed on this field making it complicated to compare studies. Riise et al 2008 concludes in their study with possible geographic variation in the incidence of JIA. Although the north-south gradient are not studied they find that there the incidence differ between geographic areas. These results were in comparison with population studies in Germany and Finland. The varying results within studies may have been

influenced by differences in the classification or exclusion criteria used, varying referral bias and limited population samples studied. Still, it is argued that it might also represent time trends and geographic disparities. Equal classification criteria are needed in order to draw clear conclusions from previous studies. (Flatø and Vinje 2008). Researchers are clear on the fact that further descriptive studies in different well-defined areas must be conducted to make valid comparisons and to provide clues to etiological factors affecting the disease and its occurrence. At this time point, these studies do not provide any clear termination of a possible geographic variation in the occurrence.

So far possible explanations are ambiguously in their results. A final explanation is included in an attempt to explain geographic variations. Often the supply level of services in a hospital trust influence the number of patients treated. With increased supply of services, the hospital trust will have higher capacity to provide patient interventions. In this study Northern Norway seems to have a larger treatment capacity and supply of health care, both out- and inpatient services. Hagen et al considered the same explanation for the variation in treatment capacity, although not finding a clear answer through statistical analyses nor interviews.

The treatment capacity of a hospital trust accompanied by several other factors may affect the consumption of biopharmaceuticals. Culture of the hospital, coding of patients and medical practice such as specialists' assessment of the clinical guidelines are features that can influence the consumption. The guidelines for TNF-inhibitors for JIA are instructive and recommended in clinical practice whilst the guidelines for rheumatoid arthritis (RA) are nationally applied. These latter factors added together might provide a good base for a possible explanation for the geographic variation. As referred to earlier in this paper, Huseby et al found geographic variation in the providing of specialist health care. Arguing that one central cause for the differences was the supply level of specialist care in hospital trusts. Organizational and administrative causes were also considered to be potential reasons for this variation.

Based on this, we can assume that the hospital trusts in the Northern Norway have a higher treatment capacity then elsewhere and therefore more patients receive biological therapy. This will be in accordance with predictions where high level of supply of specialist health care within a hospital trust, have a positive effect on the consumption. The higher the supply of specialist services the higher consumption (Nerland and Hagen 2008). Further the authors find that Helse Finnmark has a higher consumption of specialist health care, but do not find the

same high consumption when describing the Northern Norway in total. Based on these studies the possible large treatment capacity in Northern Norway together with other central factors may provide the most liable explanation on the consumption disparities between hospital trusts.

7.5 Limitations

The results of this study should be interpreted with caution. The fact that the dataset consist of two different databases may bias the results. NPR data consists of data mainly for reporting of patient cases in relation to reimbursement based on activity based funding in the hospitals. The possibility of erroneous coding is present and might vary between HTs. Since it is not possible to follow the patient between hospital trusts, possible double counting of patients may occur, leading to falsely large patient numbers in the data.

Individual level data would be preferred when performing this kind of repeated cross sectional study with focus on patients. This type of data denotes information about individuals, either contributed by the individuals themselves in surveys or through registers. Permission from the NSD is obliged when performing studies with such individual level data. Also maintaining anonymity in the data is time consuming and outside the scope of this thesis. Data on aggregated level was applied in the analyses of this paper mainly due to time limitations.

To acquire a complete picture of the actual consumption of biologics between hospital trusts additional and more precise analyses are needed. If we would want to investigate juveniles with JIA explicitly, better patient level data over at longer time period, including all possible biopharmaceuticals (excluding Raptiva) would be recommended.

8. CONCLUSION

This thesis has explored possible geographic variations in the consumption of biologics to juveniles. Multiple regression analyses have been conducted investigating the causality and relationship between explanatory variables. Significant evidence of geographic variations in the consumption of biologics is found.

We find considerable effects between the hospital trusts and the number of patients receiving biologic therapy. The northern hospital trusts have a higher consumption compared to the rest of Norway. Especially Helse Finnmark has a significantly higher utilization of these drugs.

Several possible causes have been presented aiming at explaining the consumption variations. This field is complex and no apparent reason has been stated. Central factors that might describe the variation amongst others are the supply of health care services, hospital culture and the occurrence of JIA.

With the data obtained we can conclude that relatively large geographic variations are present between the hospital trusts. There is a clear tendency of larger consumption in the northern parts of Norway. Additionally, the consumption of biologics increases with age and with the time period investigated.

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APPENDIX

I) MEDUB registration of biologics. Nasjonalt Kompetansesenter for Barne- og Ungdoms Revmatisme – NAKBUR.

MEDUB registration of approved medicines for rheumatic diseases on children with non-approved indication. Registration in the database MEDUB. For 2010 the following indications and diseases apply:

Table 7 MEDUB registration of biologics 2010

Virkestoff	**Registry on non-approved indications**
Infliximab (Remicade)	All patient groups
Etanercept (Enbrel)	All patients below 4 years of age
Etanercept (Enbrel)	For treatment of subgroups of JIA, all patients have to register.
Adalimumab (Humira)	All patients below 14 years of age
Abatacept (Orencia)	All patient groups
Rituximab (Mab Thera)	All patient groups
Tocilizumab (Actemra)	All patients that are included in clinical studies

Infliximab (Remicade) for alle aldersgrupper

Etanercept (Enbrel) for aldersgrupper under 4 år

Enteracept ved undergrupper av barneleddgikt – barn som inngår i studie

Adalimumab (Humira) for aldersgrupper under 14 år

Abatacept (Orencia) for alle aldersgrupper

Rituximab (Mab Thera) for alle aldergrupper

Tocilizumab (Actemra) barn som inngår i studie

Canakinumab barn som inngår i studie.

(NAKBUR Virksomhetsplan Rikshospitalet, OUS HF January 2010).

II) Hospital trusts and number of patients

Table 8. HT number, HT name and number of patients in relation to figure 4, based on patients per 100 000 inhabitants between 2004 to 2007

HT nr	Name of Hospital Trust	Patients
1	Sykehuset Østfold HT	3894
2	Akershus Universitetssykehus HT	4833
3	Oslo Universitetssykehus HT (Rikshospitalet, Ullevål, Aker)	2456
4	Sykehuset Innlandet HT	6133
5	Sykehuset Asker og Bærum HT	3216
6	Ringerike Sykehus HT	4456
7	Sykehuset Buskerud HT	5208
8	Blefjell Sykehus HT	4199
9	Sykehuset Vestfold HT	5616
10	Sykehuset Telemark HT	4502
11	Sørlandet Sykehus HT	7925
12	Stavanger Universitetssykehus HT	5020
13	Helse Fonna HT	4532
14	Helse Bergen HT	6982
15	Helse Førde HT	8443
16	Helse Sunnmøre HT	6023
17	Helse Nordmøre og Romsdal HT	6859
18	St Olavs Hospital HT	7213
19	Helse Nord-Trøndelag HT	12218
20	Helgelandssykehuset HT	5455
21	Nordlandssykehuset HT	6149
22	Hålogalandsykehuset HT	7973
23	Universitetssykehuset i Nord-Norge HT	9641
24	Helse Finnmark HT	13692

III) Definitions and calculations of the variables

Table 9 Definition of the dependent variable

Dependent variable	Definition	Data source
Cell level Number of patients per municipality defined by gender, four age groups and four years	(patients per municipality defined by gender, age group, year / inhabitants per municipality defined by gender, age group, year) * 10 000	NPR. NorPD and SAMDATA

Table 10 Definition of the independent variables

Independent variable	Definition	Data source
Year	"Fixed effects" coded as dummy for each year 2004 to 2007.	NPR., NorPD
Gender	Dummy variable 0 = men, 1 = women	NPR, NorPD
Age group 0-9 years	(patients age 0-9/inhabitants 0-9 years defined by municipality and gender) *10 000	SSB, Statistikkbanken
Age group 10-19 years	(patients age 10-19/inhabitants 10-19 years defined by municipality and gender) * 10 000	SSB, Statistikkbanken
Age group 20-29 years	(patients age 20-29/inhabitants 20-29 years defined by municipality and gender) * 10 000	SSB, Statistikkbanken
Age group 30-39 years	(patients age 30-39 /inhabitants 30-39 years defined by municipality and gender) * 10 000	SSB, Statistikkbanken
Distance (distance rheumatologist)	Travel distance from the municipality to the nearest hospital that provides treatment with TNF-inhibitors, measured in kilometers. Calculated from matrixes.	Information on which local government that belongs to each hospital was found at Samdata
Stdspesper_10000	Number of rheumatologists in relation to hospitals that provide biologic treatment. (number of specialists/inhabitants)*10 000	Legeforeningen, list over specialists in each county of Norway, adapted from 2004.