ACCESS TO INNOVATIVE TREATMENTS IN MULTIPLE SCLEROSIS IN EUROPE

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CONTENT

Introduction

MS is an inflammatory and neurodegenerative immuno-mediated disorder of the central nervous system, characterized by inflammation, demyelination and primary or secondary axonal degeneration. Clinical manifestations are signs of neurological dysfunctions, e.g. visual and sensory disturbances, limb weakness, gait problems and bladder and bowel symptoms, followed by recovery or by an increasing disability because of irreversible functional disability over time. There are less specific symptoms such as fatigue which interfere both with patients' quality of life and productivity, regardless of the degree of disability and disease status.

Until the mid-nineties, no therapy was available and treatment was essentially limited to symptomatic relief. When the first disease modifying MS drugs (interferon-beta and glatiramer acetate) were introduced, their price – compared to their benefit apparent in clinical trials – appeared high and prompted an intense debate whether investment in these treatments represented an efficient use of public resources. The major benefit of treatment, both from a medical and economic point of view, comes from delaying progression to functional disability, and is thus difficult to show in the short or even medium term.

As a consequence, the expected value of these new treatments had to be modelled. Early modelling studies of biologics show different results for a number of reasons, the most important being the underlying data, the country of study and the perspective adopted. All models incorporate a number of assumptions, but the paucity of data is more pronounced in some countries and some studies. More importantly, however, reimbursement or health technology assessment agencies in few countries take a societal perspective. In this perspective, all costs regardless of who incurs them – the health care system, the patient, society as a whole – are taken into consideration. In the case of MS, as for other chronic progressive diseases, it appears difficult to argue that costs outside the health care system should not be considered in the decision making process. Production losses due to temporary and permanent loss of work capacity and the dependency on informal help are a major, if not the largest, part of total costs of the disease.

Due of the uncertainty regarding the effectiveness of the treatments and their cost, most countries had protracted reimbursement discussions. However, all countries allowed treatment for patients with relapsing-remitting disease on the health care budget with relatively few restrictions. The reasons were likely the absence of any treatment other than symptomatic interventions, a clearly defined population with a relatively low prevalence (0.05-0.1%) and hence a somewhat limited budget impact. In chronic progressive diseases it is often important to treat as early as possible to maximize the effect on the disease process. MS is no exception and in recent years, treatment after a first clinically isolated symptom has been shown to delay the definite diagnosis of MS. Disease-modifying agents should thus ideally be used as early as possible in the course of the disease, to avoid the development of permanent functional limitations associated with dependence for daily activities and frequently loss of work capacity. This will increase the number of patients on treatment.

A number of economic studies have been performed in Europe but no comparative data on how different countries across Europe use the disease modifying drugs exist.

In this report on access to treatment in 30 European countries (27 EU member states plus Iceland, Norway and Switzerland) as well as Turkey, we will address

1) The burden of the disease in terms of epidemiology and the effect on quality of life
2) The cost of the disease in Europe, using a predictive cost model and updated epidemiological and economic data
3) The uptake over time of biologic treatment and the number of patients treated, using available sales data from IMS, adjusted where necessary and possible
4) The conditions and hurdles that affect usage and differences between countries and current knowledge on the value of these treatments, with a focus on parameters that have an economic effect.

with the objective to provide material for discussion of how to fully utilize the opportunities created by medical research and innovation.

Chapter 1 - Burden of Multiple Sclerosis

We are grateful for general advice to Jan Hillert, MD PhD (Karolinska University Hospital, Stockholm Sweden).

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1 Burden of Multiple Sclerosis

1.1 Summary

In this chapter we define the burden of Multiple Sclerosis (MS) as the burden for people living with the disease resulting from reduced health (reduced quality of life) and for Society from the number of people affected (prevalence). The economic burden will be discussed in the next chapter.

The literature gives conflicting data on the prevalence of MS, with numbers varying from 10/100,000 to 216/100,000 population. Behind this large variation are differences in both the definition of the disease and the populations to which prevalent cases are related to. This represents a difficulty when estimating and comparing the proportion of the patient population on treatment with innovative treatments in different countries. We therefore propose a standardized way of estimating prevalence, using data from countries where prevalence by age groups is available. With this method, we estimate the prevalence in the European population >19 to be 118/100,000 (0.12%), with a total number of patients>19 in Europe (defined as EU27 plus Iceland, Norway and Switzerland) of 470,000. Applied to the total population, prevalence would be estimated a 93/100,000 (0.09%). Our purpose is to arrive at a prevalence rate that can be used to estimate the total burden of the disease Europe and to analyze the uptake of new drugs and the share of patients treated.

The burden on patients - expressed as utility, a preference-based quality of life index anchored between 0=death and 1=full health - is one of the heaviest (with low utilities) among chronic progressive diseases. The average utility has been estimated at around 0.5-0.55, but most importantly, in decreases from values close to normal to values below 0.1 as the disease progresses to severe health states with severe impairment. It is thus very important to have good estimates of the prevalence of patients with severe disease where the burden is largest.

On average, a population of MS patients looses around 0.25-0.3 QALYs per year at all age, compared to the normal population. From the available data we can estimate that the total burden of MS in Europe in terms of QALYs lost per year is 135-140,000. Of these, 65,000 QALYs are lost for mild disease (55% of patients), 41,000 for moderate disease (25% of patients) and 30,000 for severe disease (20% of patients).

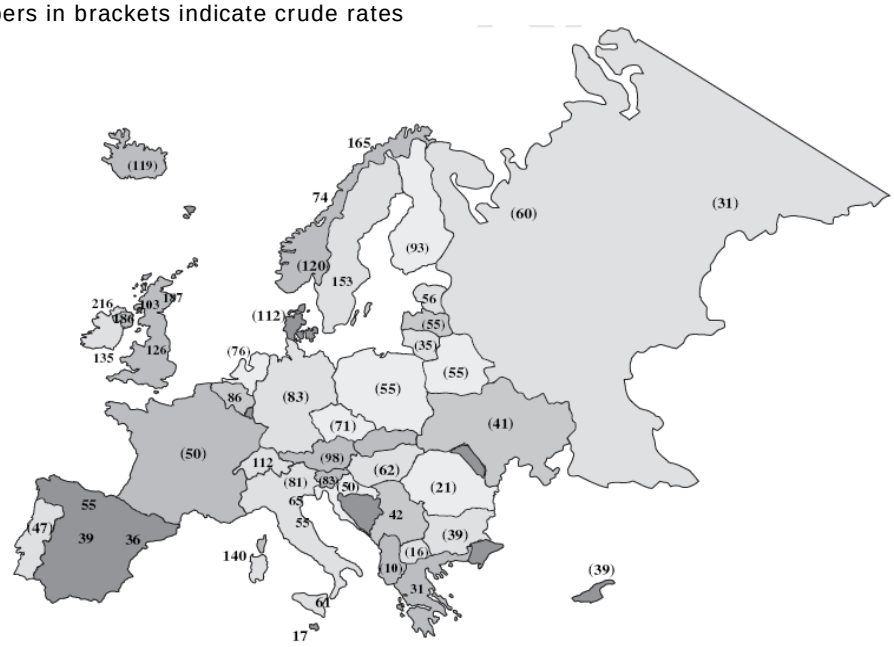
1.2 Prevalence of MS

1.2.1 Literature review

The prevalence of MS has generally been estimated at 0.05-0.1% of the adult population, with an average of 83/100,000 over the past three decades, but ranges from 10/100,000 to 216/100,000 has been reported in published studies [1]. Similarly, incidence ranged from 0.5/100,000 to 12/100,000 of the adult population, with a mean estimated at 4.3/100,000 [1]. An in-depth review of almost 200 published studies was performed in 2002 and updated in 2006, highlighting the differences [1, 2], as shown in Figure 1-1, but no attempt was made to adjust or extrapolate the numbers to different countries. Nevertheless, we base most of our comments on this review by Pugliatti and colleagues.

Figure 1-1 Reported prevalence rates [1]

Numbers in brackets indicate crude rates



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Although rates may indeed be different between different populations and countries, this large range is likely due to the quality and methodology of the studies performed, age groups included, reporting of crude or adjusted rates, as well as the timing of the study. Indeed, one could expect that diagnosis has been improved particularly in the last decade, with the availability of effective treatments.

It is thus difficult to directly derive an estimate of the number of prevalent patients in the different European countries. However, this is a prerequisite to estimating the total cost of MS in Europe, analyzing the uptake of the biologics and evaluating the proportion of patients on treatment. We therefore first discuss the issues related to the published literature and the difficulty to draw conclusions on the prevalence rates in the different countries, and then propose an approach to estimating European prevalence.

1.2.1.1 Diagnostic criteria and timing

MS is and inflammatory and neurodegenerative immuno-mediated disorder of the central nervous system, characterized by inflammation, demyelination and primary or secondary axonal degeneration [3]. Clinical manifestations are signs of neurological dysfunctions, e.g. visual and sensory disturbances, limb weakness, gait problems and bladder and bowel symptoms, followed by recovery or by an increasing disability because of irreversible functional disability over time [4]. There are less specific symptoms such as fatigue which interfere both with patients' quality of life (QoL) and productivity, regardless of the degree of disability and disease status [5].

The majority of epidemiological studies used the Poser criteria to define MS [6]. However, these criteria define patients as clinical definite MS or clinically probable MS, which thus may lead to differences in studies. More recently, magnetic resonance imaging (MRI) has been incorporated into diagnostic criteria [7], and the new criteria are currently used more often, e.g. in clinical trials. Compared to the Poster criteria, prevalence rates appear higher when using McDonald criteria [8].

As a consequence, it may be expected that reported prevalence is increasing over time, but it is difficult to establish a time trend in available studies. Nevertheless, three studies from Norway reported increasing rates with time: 74/100,000 in 1993, 121/100,000 in 1995 and 165/100,000 in 2001. Similarly, two studies in northern Italy reported 69/100,000 in 1993 and 81/100,000 in 1999. In western Poland rates increased from 45/100,000 in 1981 to 55/100,000 in 1995. A study in a French region (Lorraine) found that age-adjusted prevalence increased between 1990-2002 [9]

It is clearly impossible to verify whether this trend is due to better diagnosis or simply a consequence of the study methodology, and this is not our objective. Rather we want to highlight possible causes for the wide range of prevalence rates reported.

1.2.1.2 Incidence

Figure 1-2 Reported (crude) incidence rates [1]

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When comparing incidence to prevalence, the variation in reported prevalence does not seem to be supported. The incidence rate reported for Poland is 2.2/100,000 and for France 4.3/100,000, yet prevalence rates are reported as 50 and 55/100,000, respectively. Spain and Rumania have similar prevalence estimates (36-55/100,000 and 41/100,000, respectively) – yet incidence is reported as 3.8/100,000 in Spain and 0.2/100,000 in Romania. Population survival rates are higher in France and Spain compared to Poland and Rumania and these numbers appear thus questionable.

Differences are also reported in countries that are apparently more similar. In the Nordic area, Norway reports an incidence of 8.7/100,000, Sweden of 5.2/100,000 and Finland 5.1/100,000 - yet, prevalence is reported as 120/100,000, 153/100,000 and 93/100,000, respectively. Germany and France report similar incidence rates (4.2/100,000 and 4.3/100,000, respectively) – yet prevalence is estimated at 83/100,000 and higher in Germany and 50/100,000 in France.

Again, it is not the objective of this report to evaluate or criticize epidemiological data in detail, but we conclude that incidence and prevalence data reported do not seem to match.

1.2.1.3 Samples and Reporting

Published studies have included different populations or have been performed in different geographic areas within countries, and some findings were surprising. For instance rates within Italy vary from 61/100,000 to 140/100,000. Rates in the United Kingdom range from 103/100,000 to 186/100,000. Only four studies included a nationwide sample: Austria (1999), Denmark (1996), France (1986) and Iceland (1999). Other studies included between less than 1% of the country's population up to 30%, with most however limited to less than 10%. The influence of this on the findings is difficult to judge. But while it is generally accepted that there are differences between and within countries, we would argue that the magnitude of the differences reported appears unlikely to be true.

Studies may also have included samples with a different age structure. In particular, prevalence in the population above 65 years appears difficult to establish and published rates vary between 0/100,000 and 313/100,000. Furthermore prevalence for this particular age group is often stated as approximate only, and some studies may simply not have included it.

It is striking to observe that rates for the group between 65 and 75 years in the Nordic area are very high, and in the Mediterranean area very low: Spain reports 8/100,000 while Scandinavian countries report rates around 200/100,000. Differences in the same magnitude are reported for the population over 75 years.

We argue that this is likely due to differences in diagnosis over time, where more focus has been put on MS diagnosis in Northern Europe for a long time, resulting in patients diagnosed 3 decades or more age arriving in these older age groups today. One could indeed expect that over the next 2 decades these differences might disappear, as the new treatments enhance the focus on diagnosis across European countries.

Finally, many studies report data without adjusting to population age and gender distribution, and overall figures may thus not be fully accurate.

1.2.1.4 North-South Gradient

It is commonly accepted that prevalence is higher in Northern Europe than in Southern Europe, although it is difficult to understand where the separation line should be. Do countries like Austria, Germany and Switzerland belong to the North? If so, how should then France be classified, Northern or Mediterranean? If the former belong to the North, how different are then prevalence rates from the "true" Northern countries, Scandinavian countries and the United Kingdom? And why would Finland have rates similar to Germany rather than to Sweden and Norway? Also, purely in terms of latitude, the Baltic States would be classified as Northern, yet their rates are similar to the Mediterranean area or even lower…

Considering this, we find it difficult to classify countries into North-South groups. Rather, as Pugliatti and colleagues, we would argue again that this apparent geographic trend is predominantly due to better diagnoses earlier in some countries and better accuracy of epidemiological survey methodology. Nevertheless, a certain heterogeneity appears to exist between different population groups, e.g. very high rates in Scotland, Northern Norway, or Sardinia.

1.2.2 Estimation of Prevalence

1.2.2.1 Approach

The issues discussed above may not be problematic when considering one country at a time, or when simply reviewing existing literature. However, in this report, we build the estimate of the cost of MS in all European countries on three types of data: the mean cost per patient based on available cost analyses adjusted for economic factors, total sales of biologic drugs in each country, and prevalence. The latter is a crucial input, as it is used to estimate the proportion of patients treated in each country to calculate the mean drug cost per prevalent patient, and to extrapolate the mean cost per patient to total national and European costs.

In a previous economic paper [10] we based our cost estimates on the prevalence rates for each country as summarized by Pugliatti and colleagues. However, in view of the issues discussed above, we now argue that prevalence might be more similar across Europe, and that the considerable differences observed could be to some extent a consequence of

- the timing of the study (due to changes in diagnostic criteria and focus on rapid correct diagnosis)
- the region of observation (urban, rural; economic situation of the area)
- the study methods (design, sample, age adjustment)
- the age structure of a country (proportion of patients over 65)
- medical tradition and access to specialists for diagnosis.

We therefore propose to use a more general calculation to estimate diagnosed prevalence in the adult population, using the following approach:

1. Part of the variation in prevalence is due to the age structure, i.e. prevalence will be higher in countries with a larger population of elderly Consequently, we used prevalence rates for 5 different age-groups throughout our calculations (**20-34, 35-49, 50-64, 65-74, 74+**) and applied population numbers to age specific prevalence rates . These age groups allow a more refined estimate and also differential cost analysis particularly in terms of workforce participation and mean salary. The cut-off at age 20 is justified by the way population data are generally reported.

Table 1-1 Published data by age and country [1]

Country	Previous year	0–17 year	18–34 year	35–49 year	50–64 year	65–74 year	75+ years
Belgium (Flanders)	1991	1	61	161	157	86*	32*
Denmark	1996	5	51	195	236	228	112
Estonia (south)	1989	1	47	141	71	17	8
Greece (Evros)	1999	5	59	85	41	5	5*
Ireland (Co. Wexford and Donegal)	2001	4	84	346	358	224	94
Italy (Ferrara, north)	1993	6	63	125	104	38	13
Italy (L'Aquila, central)	1996	10	86	103	51	7*	7*
Italy (Sardinia, insular)	1997	7	147	312	163	82*	61*
Italy (Sicily, insular)	1995	5	65	137	77	25	0
Malta	1999	0	26	36	28	0	0
Norway (Nord-Trøndelag Co.)	2000	0	102	282	349	194	122
Norway (Oslo)	1995	2	65	200	255	177	90
Poland	1981	1	73	75	68	16*	16*
Spain (Mostoles, central)	1998	6	43	88	37	8*	8*
Spain (Teruel, east)	1996	2	51	78	33	6*	6*
Spain (Valladolid, north)	1997	22	91	78	57	5*	5*
Sweden (Västerbotten Co.)	1997	4	103	295	267	223	87
Switzerland (Canton of Berne)	1986	5*	55*	120–230*	220*	115–220*	40*
UK (East Scotland)	1996	4	91	383	358	176	89
UK (Leeds Health Auth.)	1996	–	15–70*	150–250*	200–250*	150*	60*
UK (North Cambridgeshire)	1993	–	10–75*	200–300*	250–300*	170*	75*
UK (northern Ireland)	1996	4	81	343	377	313	60
UK (South-east Scotland)	1995	7	97	356	363	261	103

*Approx.
**Only Poser Committee *et al.* definite MS.

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2. Also in view of the cost estimates, it is important to take into account disease severity. A large number of studies have shown the steep increase in costs between mild and severe disease [11]. Most often studies have reported costs for mild, moderate and severe disease, using the EDSS (Expanded Disability Status Scale [12]) to define groups. Definitions have varied somewhat, but we used the definition published in a recent series of observational studies [11]: **EDSS <4, 4-6.5, >6.5**. A number of epidemiological studies have reported detailed data on the severity distribution [1], and we estimated the mean proportions to be **55%, 25% 20%**, respectively, for the groups defined above.

Table 1-2 Published data by disease severity [1]

Country	Year	EDSS 0–3.5 (%)	EDSS 4.0–6.5 (%)	EDSS 7.0–9.5 (%)
Austria	1999	69	26	5
Belgium (Flanders)	1990s	54	23	23
Germany	2004	46*	39*	15*
Hungary (Csongrad Co.)	1999	58	22	20
Italy (Ferrara, north)	1993	62	13	25
Italy (Sardinia, insular)	1997	65	20	15
Italy (Sicily, insular)	1995	61	16	23
Norway (Nord-Trøndelag Co.)	2000	56	28	16
Spain (Mostoles, central)	1998	80	15	5
Spain (Teruel, east)	1996	60	22	18
Spain (Valladolid, north)	1997	58	29	13
Sweden	1998	36*	27*	37*
The Netherlands (Groningen)	1990s	43	18	39
UK (northern Ireland)	1996	32.5	47.5	20

*Approx.
**Only Poser Committee *et al.* definite MS.

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3. For cost estimates, prevalence is required by gender, as health care consumption, but most importantly workforce participation and income differs between men and women. Similar to overall numbers, the women to men ratio in published studies varies greatly as well, from 1.1 to 3.4 [1], which we would argue to be due to sample selection. On average the proportion of men reported is however around 30-35% and we hence use a **women to men ration of 2** (67% women, 33% men) for our calculations.

Table 1-3 Published data by gender [1]

Country	Previous year	Women (95% CIs)	Men (95% CIs)	Women:men ratio
Albania	1988	11(–)*	10(–)*	1.1
Austria	1999	–	–	2.5**
Belgium (Flanders)	1991	101 (80–115)	74 (59–89)	1.4
Bulgaria (Svoge and Trojan)	1995	52 (28–87)	26 (10–54)	2.0
Croatia	1969–1991	–	–	1.8
Cyprus	1988	39 (24–59)	37 (23–57)	1.1
Czech Republic	1970–1978 (mean)	–	–	1.5
Denmark	1996	155 (145–165)	89 (84–95)	1.8
Estonia (south)	1989	63 (53–75)	37 (29–47)	2.0
Finland (Uusimaa)	1993	123 (114–132)***	60 (54–67)***	2.3
Germany (South Lower Saxony)	1986	–	–	2.9
Greece (Evros)	1999	–	–	2.8
Hungary (Csongrad Co.)	1999	182 (–)	66 (–)	2.7
Iceland	1999	157 (136–181)	72 (59–88)	2.2
Ireland (Co. Donegal)	2001	282 (243–327)	85 (64–111)	3.4
Ireland (Co. Wexford)	2001	154 (122–191)	88 (64–117)	1.7
Italy (Ferrara, north)	1993	91 (78–106)	46 (36–58)	2.1
Italy (L'Aquila, central)	1996	68 (57–83)	37 (28–48)	2.1
Italy (Padua, north)	1999	111 (99–123)	50 (41–58)	2.3
Italy (Sardinia, insular)	1997	205 (188–224)	83 (72–95)	2.5
Italy (Sicily, insular)	1995	62 (51–75)****	55 (44–68)****	1.2
Malta	1999	20 (14–27)	13 (8–19)	1.5
Norway (Nord-Trøndelag Co.)	2000	205 (171–243)	123 (97–153)	1.7
Norway (Oslo)	1995	–	–	2.1**
Norway (Troms and Finnmark)	1993	89 (73–108)	58 (46–73)	1.4
Republic of Macedonia	1990s	–	–	1.7
Romania (Mures Co.)	1986	–	–	1.3
Spain (Mostoles, central)	1998	54 (40–70)	33 (23–47)	1.6
Spain (Teruel, east)	1996	41 (26–55)	24 (12–35)	1.7
Spain (Valladolid, north)	1997	74 (52–102)	41 (24–65)	2.0
Sweden (Västerbotten Co.)	1997	202 (179–228)	105 (89–125)	1.9
Switzerland (Canton of Berne)	1994	137 (127–148)	62 (56–69)	1.8
The Netherlands (Groningen)	1992	–	–	1.7
UK (E Scotland)	1996	262 (241–285)	100 (86–115)	2.8
UK (Leeds Health Auth.)	1996	141 (–)	52 (–)	2.8
UK (N Cambridgeshire)	1993	–	–	2.2
UK (northern Ireland)	1996	230 (–)	104 (–)	2.3
UK (South-east Scotland)	1995	257 (242–272)	112 (102–122)	2.5
Ukraine (Vinnytsya)	2001	–	–	2.1
Yugoslavia (Belgrade)	1996	54 (49–59)**	28 (24–32)**	1.9

*Rose *et al.* definite and probable MS.
**Only Poser Committee *et al.* definite MS.
***Age-adjusted data.
****Onset-adjusted prevalence rate.

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4. Costs are further influenced by the age distribution within these three EDSS groups, particularly the proportion of patients above 65 for which indirect costs are excluded. We used patient data from a French epidemiological cohort in Lyon prior to the use of disease modifying drugs [13, 14] as well as data from the Stockholm MS registry [14] to estimate the mean age in the three EDSS groups. Both these cohorts represent a large proportion of patients in their defined area and can thus be considered population based. In the mild group, the mean age was 37 years, in the moderate group 45 years and in the severe group 48 years.

5. Finally, **countries were grouped into 5 clusters**, based on similarity in geographical situation, ethnic groups and published findings by age. This also allowed accounting for the differences in prevalence due to medical tradition (earlier and more accurate ascertainment of diagnosis). Even if true prevalence was higher than found in some of these studies, it is only those patients actually diagnosed that are candidates for receiving the new disease modifying treatments.

1.2.2.2 Calculations

The table below shows the country groupings and age-specific prevalence rates used in our calculations. These rates were then applied to the age structure of the individual countries and the number of prevalent patients per age group and in total estimated.

Table 1-4– Prevalence rates used for the calculations

Group	*Countries*	*Prevalence >19 (per 100,000) by Age Groups **				
		20-34	**35-49**	**50-64**	**65-74**	**74+**
1	**Denmark, Finland, Germany, Iceland, Ireland, Norway, Sweden, United Kingdom**	75	200	240	200	90
2	**Austria, Belgium, Luxembourg, Netherlands, Switzerland**	70	160	155	100	40
3	**Czech Republic, France, Hungary, Italy, Portugal, Slovenia, Spain**	65	125	110	70	20
4	**Cyprus, Estonia, Greece, Latvia, Lithuania, Malta, Poland, Slovakia**	65	125	75	35	10
5	**Bulgaria, Romania, Turkey**	45	90	40	10	5

*Expected number of currently diagnosed patients >19 per 100,000

The results were then compared to the published studies and also other sources of data. In particular, the MS International Federation has published an “Atlas” of MS across the world that contains prevalence and incidence data (www.atlasofms.org). Upon closer examination, most of the numbers in the MS Atlas come as expected from the published studies and are hence already taken into account in our estimates. A few countries without own studies used the highest available prevalence rates for their estimates. We have chosen to ignore the differences between these numbers and our results, as for the purpose of this report we are interested in diagnosed patients, not in potentially underlying prevalence. A detailed comparison of the differences can be found at the end of this chapter.

Figure 1-3 – Age structures in the different countries (>19)

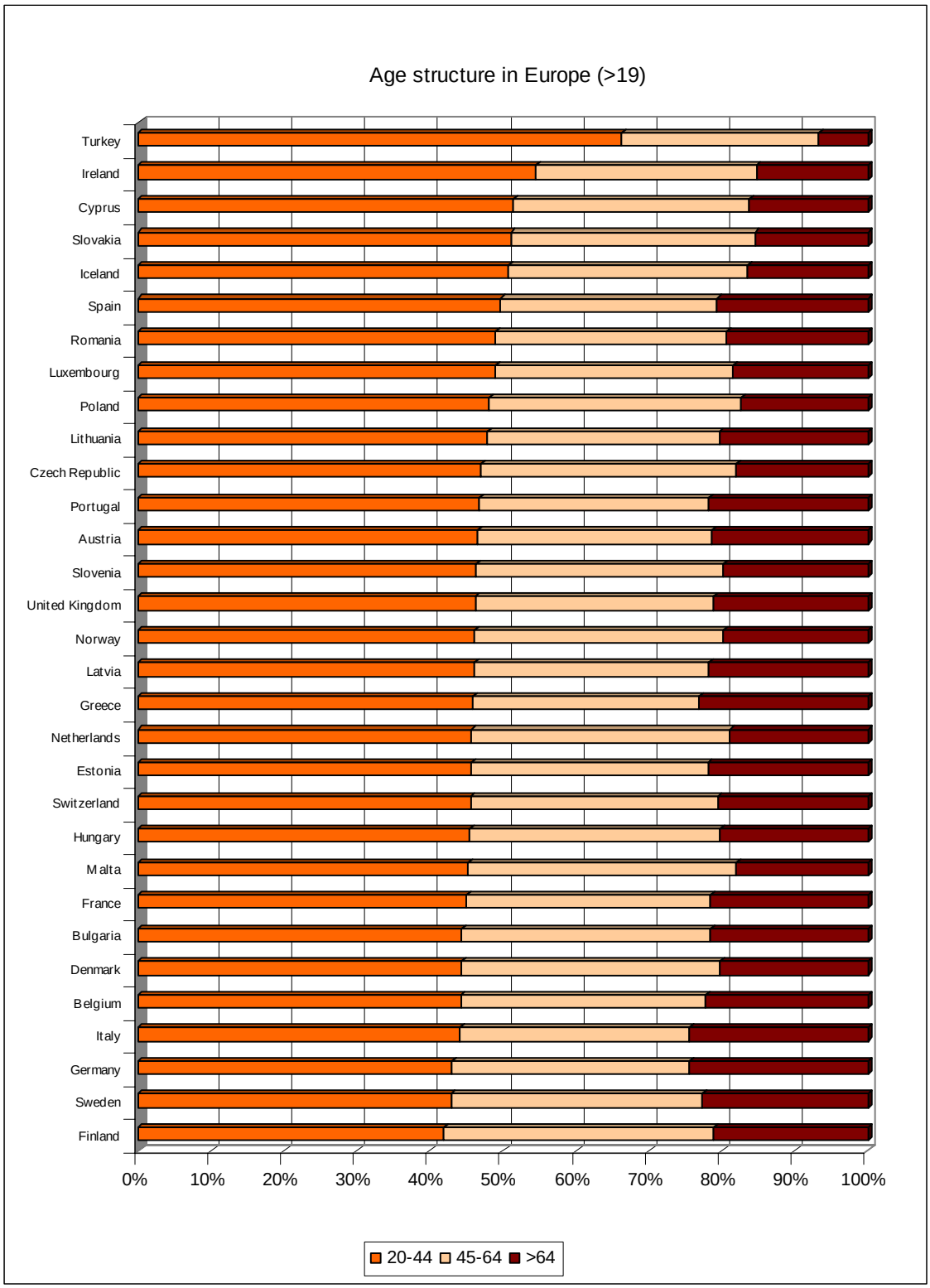


Table 1-5 – Prevalence rates and estimated number of patients (>19)

Country	Population >19 (000')	Patients >19	Prevalence >19 per 100,000	Prevalence per 100,000 population
Austria	6,485	7,685	119	93
Belgium	8,113	9,516	117	90
Bulgaria	6,158	2,930	48	38
Cyprus	576	453	79	59
Czech Republic	8,126	8,113	100	79
Denmark	4,104	6,997	170	129
Estonia	1,038	795	77	59
Finland	4,039	6,924	171	131
France	47,375	47,626	101	75
Germany	66,032	113,120	171	137
Greece	8,960	6,668	74	60
Hungary	7,904	7,928	100	79
Iceland	212	342	161	114
Ireland	3,099	4,896	158	115
Italy	47,717	47,608	100	81
Latvia	1,786	1,374	77	60
Lithuania	2,576	2,027	79	60
Luxembourg	358	425	119	90
Malta	309	235	76	58
Netherlands	12,380	14,872	120	91
Norway	3,451	5,741	166	123
Poland	29,207	22,469	77	59
Portugal	8,355	8,381	100	79
Romania	16,610	8,159	49	38
Slovakia	4,105	3,211	78	60
Slovenia	1,604	1,622	101	81
Spain	35,424	35,214	99	80
Sweden	6,916	11,590	168	128
Switzerland	5,852	6,971	119	93
United Kingdom	45,871	76,851	168	127
Turkey	44,823	24,940	56	34

The average prevalence in the population over 19 years for Europe 27+3 (excluding Turkey) was estimated at 0.13%. Applied to the total population, the prevalence rate would be 0.093%. Although our estimates focus on actually diagnosed cases, we believe that after the developments in the MS field (several new drugs, better diagnostic tools, earlier diagnosis) these rates appear acceptable.

Figure 1-4 – Estimated Prevalence >19 (cases per 100,000 population)

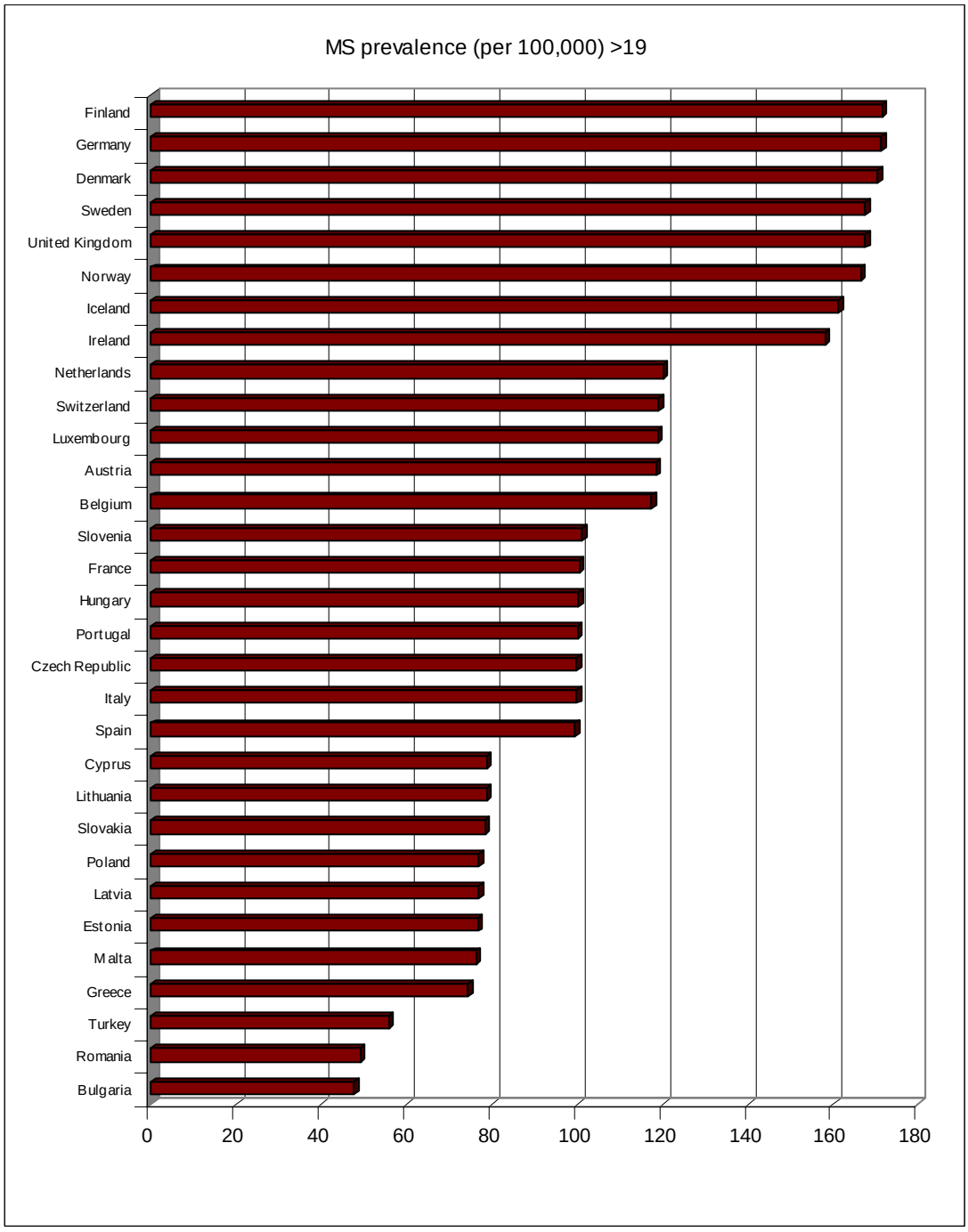
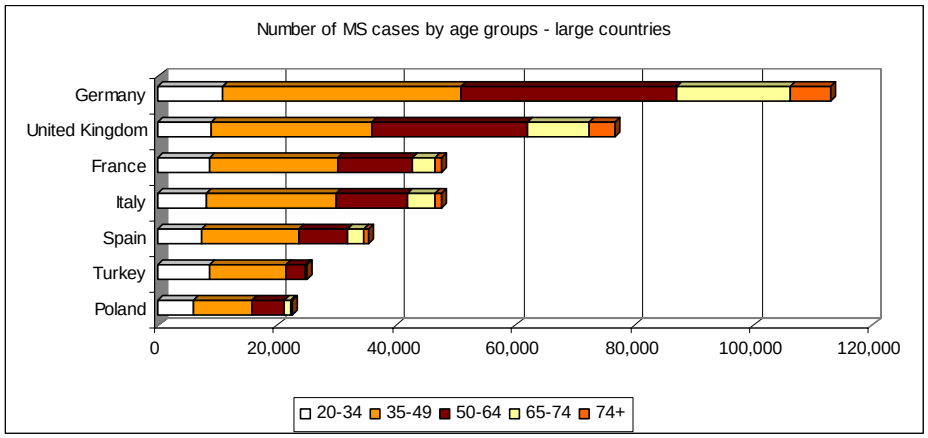


Figure 1-5 – Estimated number of patients



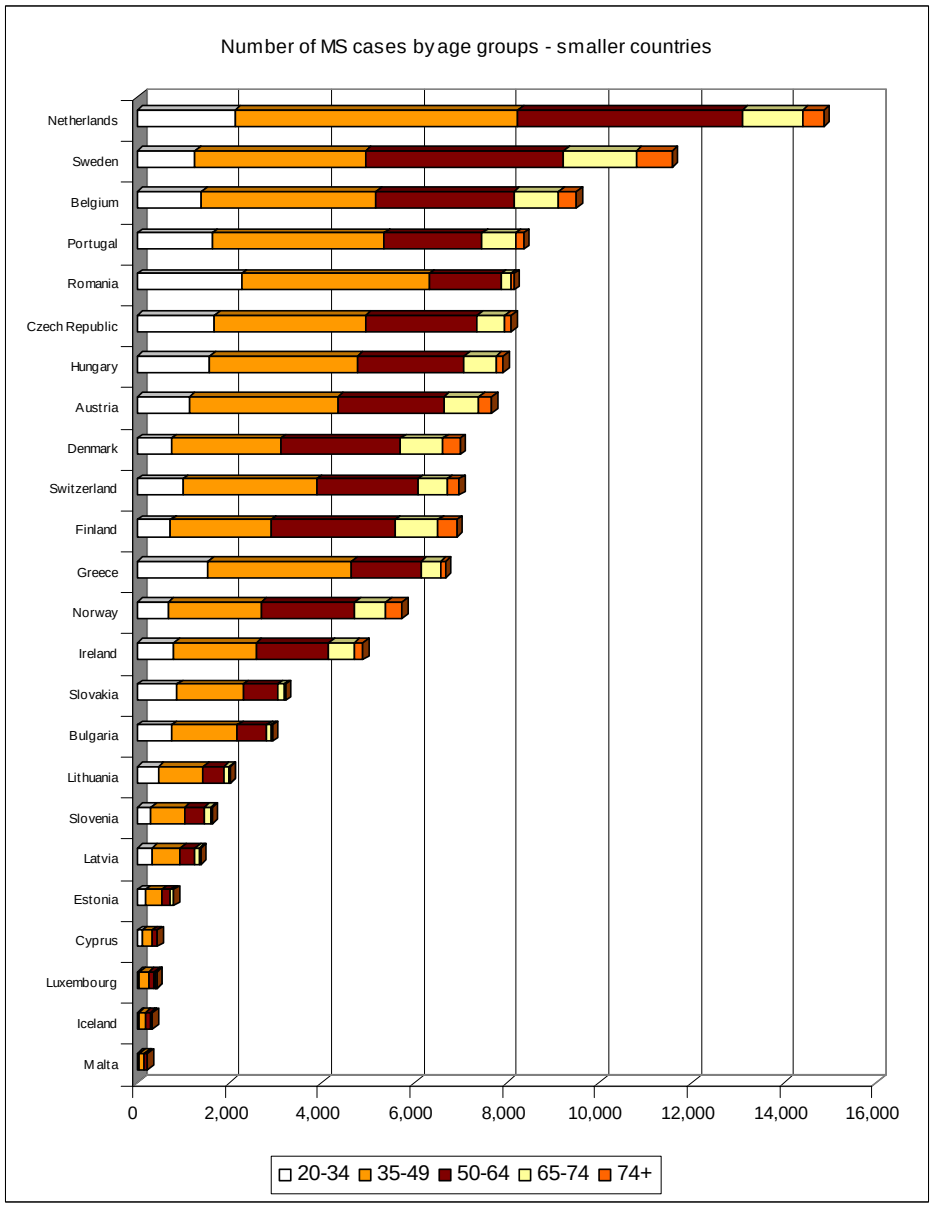
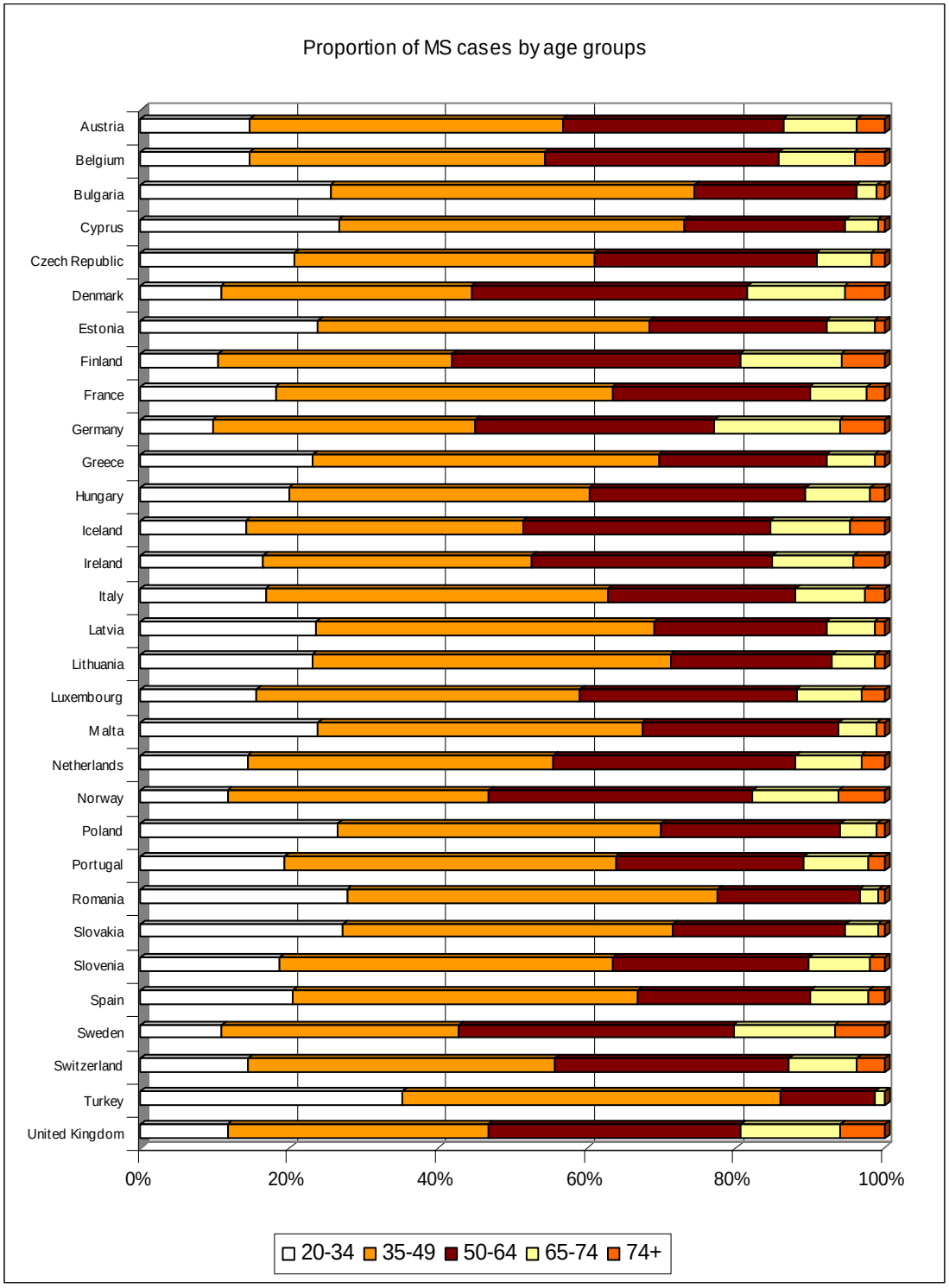


Figure 1-6- Estimated proportions of patients in different age groups



Using our model, the total number of diagnosed patients was estimated at 470,000 in Europe (EU27+3), of which 410,000 in Western Europe (old EU15+3) and 60,000 in Central/Eastern Europe (new EU markets).

Table 1-6 - Total Estimated Number of Patients

	Number of patients by age groups					*Total*
	20-34	35-49	50-64	65-74	74+	
EU 27+3	71,500	188,000	139,500	53,000	19,000	**471,000**
W.Europe (EU15+3)	57,000	162,000	125,000	49,500	18,500	**412,000**
E.Europe (new EU)	14,500	26,000	14,500	3,200	800	**59,000**
Turkey	8,800	12,700	3,200	300	0	**25,000**

1.2.3 Comparison to Published Data

As discussed above, our estimates differ somewhat from published data, because

- we used similar rates across groups of countries to compensate for study and population differences
- we applied age specific rates to country populations to overcome the different reporting of crude and adjusted rates
- we used somewhat higher rates than reported in some countries with the rationale that in the last one or two decades prevalence has increased due to better and earlier diagnosis
- we largely ignored incidence rates as these often did not correspond to expected prevalence.

The comparison to the MS Atlas published by the International MS Society (MSIF) shows that most estimates were based on published rates or on the higher range of available prevalence rates in countries with no studies. Also prevalence rates and the number of patients do not always correspond. In a number of countries, our estimates are thus lower than the Atlas but close to published rates.

A special comment has to be made regarding Portugal. Published rates for Portugal are low, but similar to published rates for Spain. The number of patients indicated in the MS Atlas for Portugal is according to published rates, but much higher than published rates for Spain. When calculating the number of patients treated using actual IMS sales data and the published prevalence, we found that the vast majority of patients would be on treatment (i.e. a higher % than in any other European country). This appeared not reasonable and we hence adjusted the prevalence to the rates used for Spain.

Table 1-7 – Comparison of Estimates to Published Data

Country	Cases per 100,000 population				Total cases	
	Literature [1]	MS Atlas	Our estimates (population)	Our estimates (population >19 years)	MS Atlas (total cases)	Our estimates (cases >19)
Austria	98	100	93	119	8,000	7,685
Belgium	88	88	90	117	9,093	9,516
Bulgaria	39	44	38	48	4,000	2,930
Cyprus	39	110	59	79	800	453
Czech Republic	71	130	79	100	13,000	8,113
Denmark	122	122	129	170	7,500	6,997
Estonia	51	100	59	77	1,500	795
Finland	93,107,188	100	131	171	6,000	6,924
France	50	80	75	101	80,000	47,626
Germany	83,127	149	137	171	122,000	113,120
Greece	39	78	60	74	9,000	6,668
Hungary	62	176	79	100	20,000	7,928
Iceland	119	110	114	161	320	342
Ireland	121,185	100	115	158	10,000	4,896
Italy	53,58,69,81,144	90	81	100	54,000	47,608
Latvia	55	50	60	77	2,500	1,374
Lithuania	17	65	60	79	4,629	2,027
Luxembourg	73,120,164	101	90	119	450	425
Malta	17		58	76		235
Netherlands	76	100	91	120	16,000	14,872
Norway	73,120,164	125	123	166	6,000	5,741
Poland	45,55	120	59	77	50,000	22,469
Portugal	47	50	79	1000	5,000	8,381
Romania	21	31	38	49	8,000	8,159
Slovakia		18	60	78	8,400	3,211
Slovenia	83	151	81	101	3,000	1,622
Spain	32,43,58	59	80	99	40,000	35,214
Sweden	154	100	128	168	13,000	11,590
Switzerland	110	110	93	119	9,000	6,971
Turkey		34	34	56	25,000	24,940
United Kingdom	97,107,168, 184,187	110	127	168	85,000	76,851

1.3 Health Burden

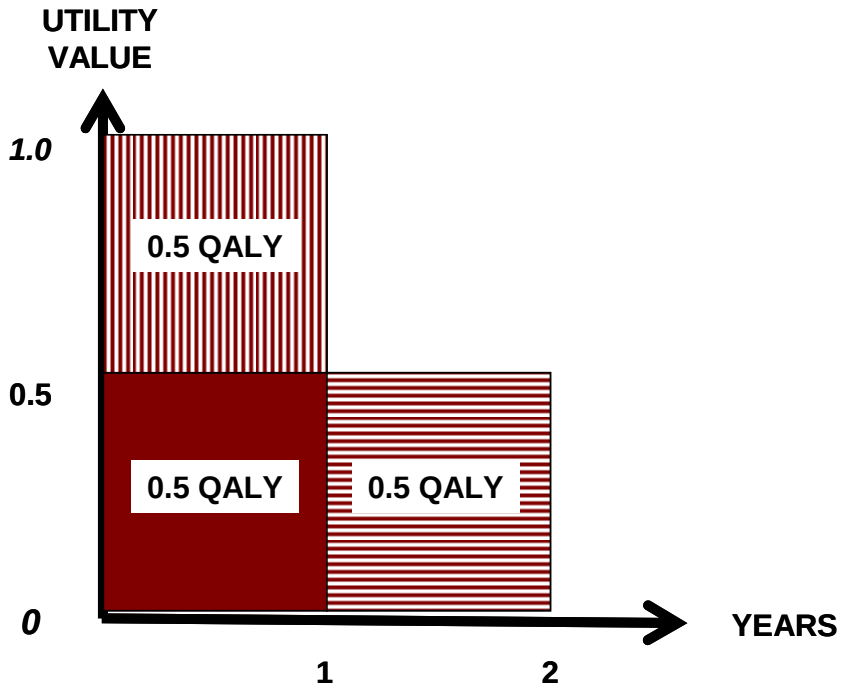
"Health burden" is defined here as the impact on patients' health related quality of life and their ability to perform daily activities.

On a macro-level, where one of the key requirements is comparability across diseases, the health burden is generally measured by disability-adjusted life-years (DALY), a two-dimensional measure integrating mortality and disability (morbidity) developed by the World Health Organization (WHO)[15]. In simple terms, one DALY can be thought of as one year without disability lost. The measure does thus not include health related quality of life, but is based on disability.

In health economic studies, the quality-adjusted life-year (QALY) is preferred. As the DALY, it is a two-dimensional measure, combining life-years with a weight (called utility) between 0 (representing death) and 1 (representing full health) that represents the population's preference for given health states [16]. The major differences of the QALY to the DALY are that utility does incorporate health related quality of life and that 0 and 1 are clearly anchored with reference values established with the general population.

As shown below, the weighting of life-years with their quality allows comparing the effect of treatments that predominantly improve health related quality of life (e.g. in MS) to treatments that predominantly affect survival (e.g. in cancer). Living 2 years with a utility of 0.5 results in 1 QALY - which is the same as living 1 year in full health (utility 1.0).

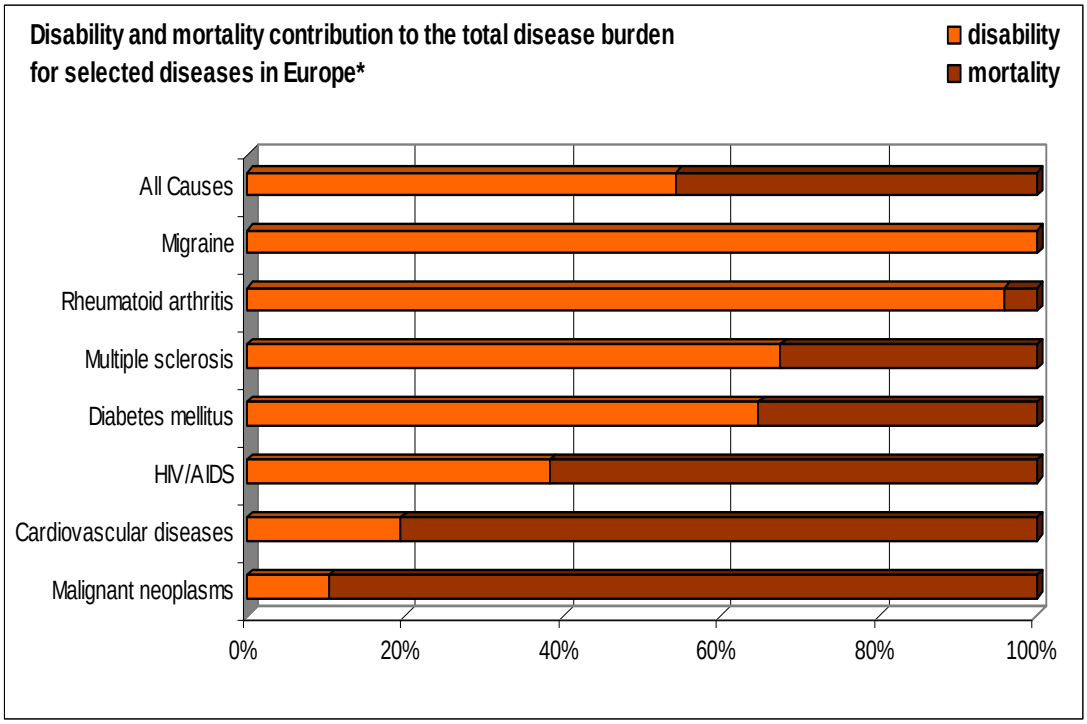
Figure 1-7 The concept of the quality adjusted life year



1.3.1 DALYs in MS

The loss of DALYs is thus composed of two inputs, mortality (years of life lost) and disability (years of disability), and to compare across diseases, it is interesting to investigate which part contributes most to the measure. For the total burden of disease in Europe, the split between years of life lost and years of disability is approximately 50%-50% as shown in the figure below [15]. However the distribution between disability and mortality to the disease burden varies greatly depending on the type of disease. The entire burden of migraine comes from disability, and for RA the burden due to premature mortality is limited. For MS, the impact on mortality has been highlighted in recent years, in particular with data from the Danish population-based MS registry [17]. The most recent DALY estimates by WHO attribute around one third of the health burden of MS to premature mortality, despite the severe disability that most patients experience. One reason for this is that the onset of MS is very early.

Figure 1-8 – The share of morbidity and mortality in the disease burden of MS



**WHO sub-region EUR A (Andorra, Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, Norway, Netherlands, Portugal, San Marino, Slovenia, Spain, Sweden. Switzerland, United Kingdom)*

1.3.2 QALYs in MS

QALYs have been widely used and accepted for economic evaluation in MS. As the disease manifests itself with a number of different symptoms – sensory disturbances, limb weakness, gait problems, neurogenic bladder and bowel symptoms - and irreversible functional disability and premature mortality, a measure that combines the impact on quality of life and life expectancy appears the most appropriate tool to evaluate of the burden of the disease and the health gain with treatment.

Compared to many other chronic diseases, mean utility in MS is low, as shown in Fig 1-9 below. More importantly, though, a considerable number of studies have shown that it decreases rapidly right from the onset of the disease [14,18-26]. Indeed, it is most astonishing how similar utilities related to disability are across European countries when measured with the same instrument (the EQ-5D [19]) in studies using the same methodology [20] (Fig 1-10). In MS, mean utility is thus strongly influenced by the disease severity of the sample, and small samples may produce biased results. This can be observed in a study that used interview techniques to assess utilities and thus necessarily enrolled a small sample only [21].

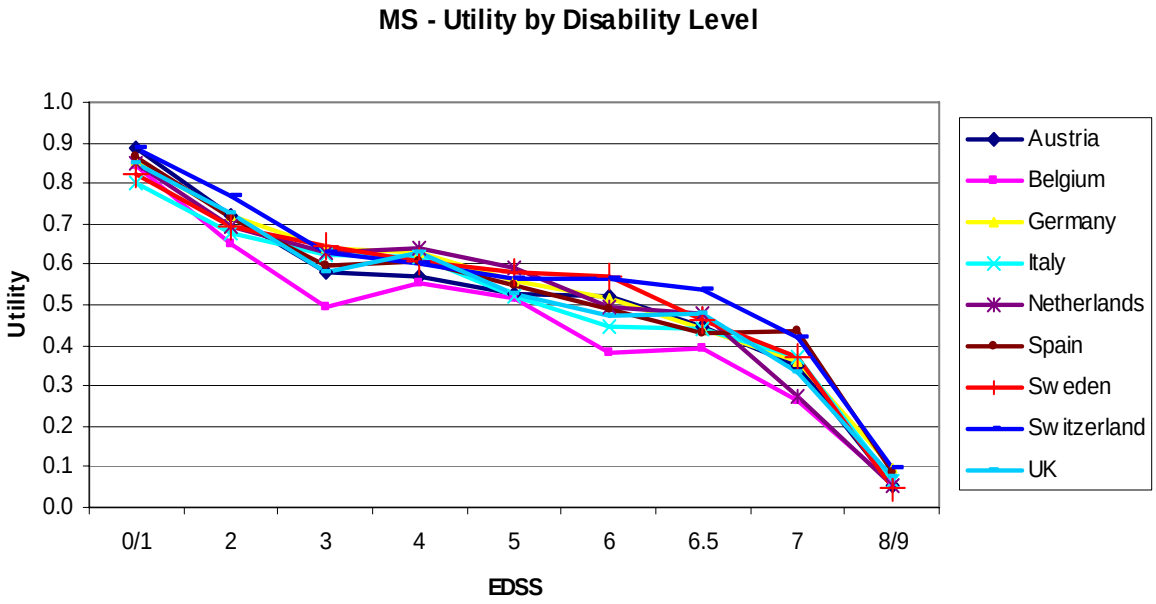
Utility is closely correlated with disability, expressed on a scale between 0 and 9 with the Expanded Disability Status Scale (EDSS) [12]. Although the EDSS focuses strongly on ambulation and may not capture the mental disability to its full extent, it has been shown to be highly correlated not only with utility, but also costs. It is hence not surprising that the QALY is the measure of choice to assess the effect of treatment.

Figure 1-9 – Utilities in different chronic diseases.

Disease	*Mean utility*	*Sample size*
Other rheumatoid arthritis	0.43	120
Rheumatoid arthritis	0.50	1487
Multiple sclerosis	**0.56**	**13186**
Angina pectoris	0.57	284
Acute myocardial infarction	0.61	251
Atrial fibrillation and flutter	0.61	189
Chronic ischaemic heart disease	0.64	789
Gastro-oesophageal reflux disease	0.67	216
Crohn's disease (regional enteritis)	0.69	73
Essential (primary) hyptertension	0.69	82
Malignant neoplasm of prostate	0.72	83
Non-insulin-dependent diabetes	0.76	159
Ulcerative colitis	0.79	61

Source: adapted from Curry et al, Value in Health 2005

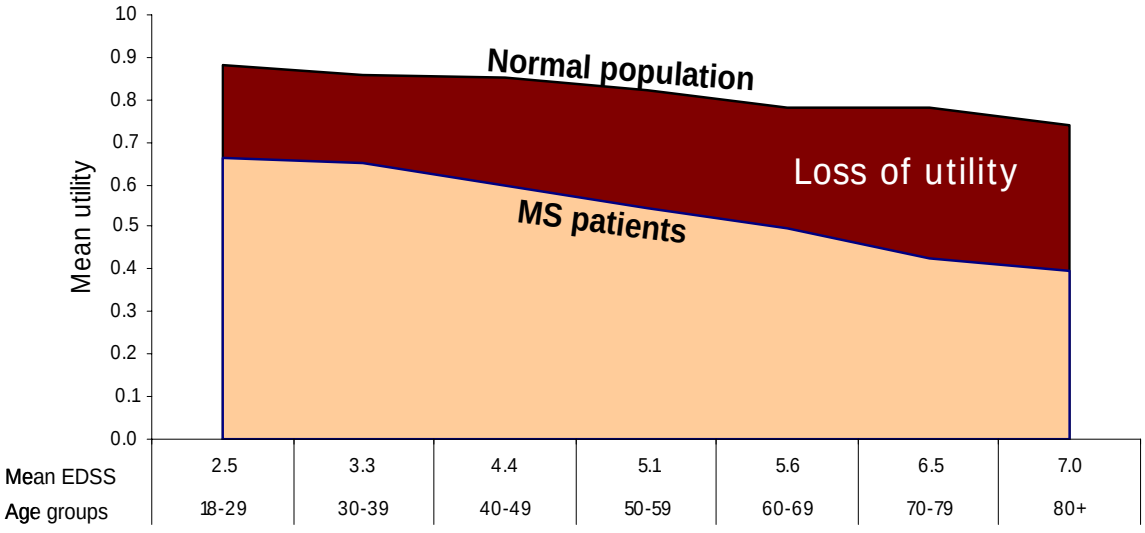
Figure 1-10 – Utility related to disease severity [20]



Source: Adapted from [20]
Utility was measured in all studies using the EQ-5D [19].

When mean utilities of patients with MS are compared to those of an age-matched sample of the general population, as illustrated in Fig 1-11 for Germany, the loss of QALYs can be estimated at around 0.3 QALYs per year, or expressed differently, a 30% loss of quality of life (adapted from [22])

Figure 1-11 Utility loss in MS compared to the normal population



Note: Example: German women

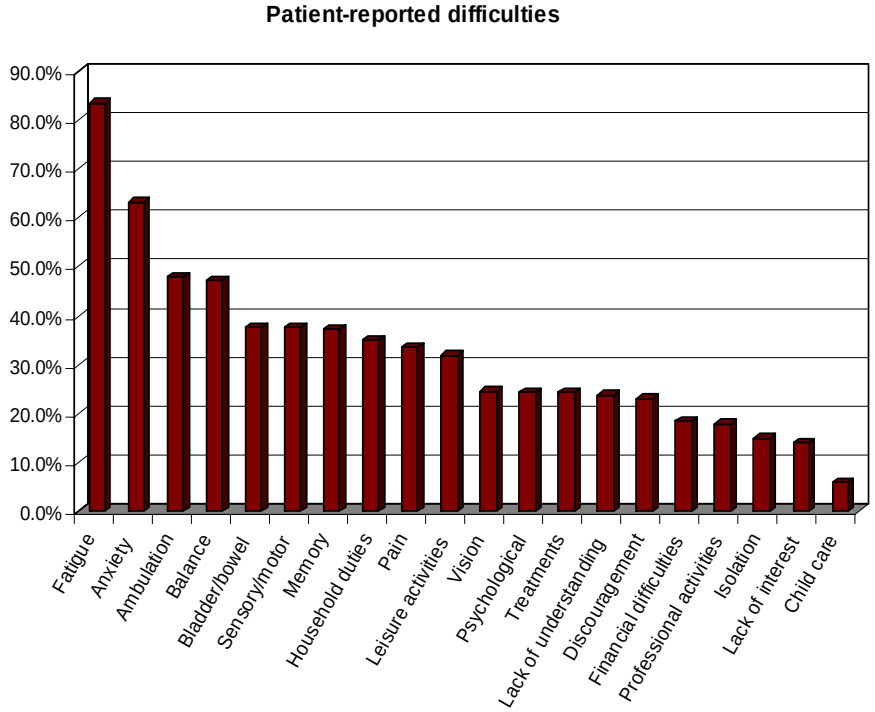
From these available data, it is possible to estimate the total burden of MS in Europe in terms of QALYs lost. Using a simplified estimate based on the average loss of 0.3 QALYs per year above and the total number of patients, we can estimate the total burden as approximately 140,000 QALYs lost every year, the majority (88%) in Western Europe.

Using estimates of mild, moderate and severe disease prevalence, and average age in these groups from the Stockholm MS registry, the total loss of QALYs for mild disease is 65,000 QALYs, for moderate disease 41,000 QALYs and for severe disease 30,000 QALYs, leading to a total loss of 136,000 QALYs per year.

1.3.3 Disease Symptoms

As discussed above, EDSS may not capture all the difficulties patients with MS experience. In a recent survey in France [14] participants were asked to indicate the symptoms, activities of daily living and other issues that were most affected by the disease or posed the greatest problems for them. Of the 1355 participants, 1349 answered the question. Fatigue represented a problem for almost all patients (84%), followed by anxiety regarding the evolution of the disease (63%), and ambulation, balance, bowel/bladder symptoms and sensory/motor disturbances for 40-50% of patients. (Data on file, personal communication G.Kobelt and Ligue Française pour la Sclérose en Plaque).

Figure 1-12 – Rating of disease symptoms

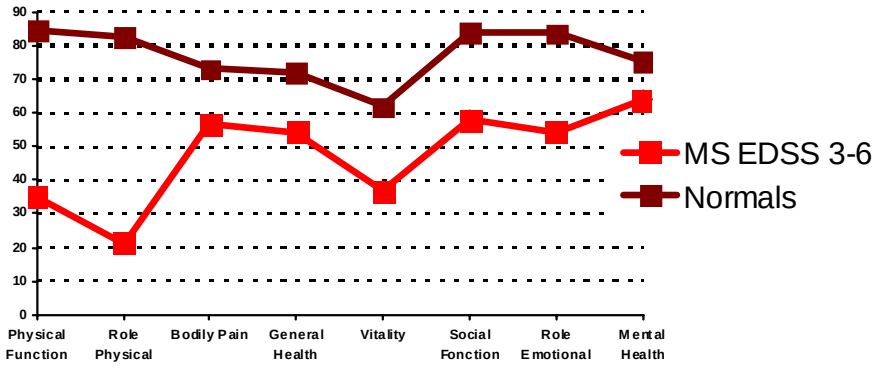


Source: data on file, adapted from [38]

1.3.4 Health Related Quality of Life

Nevertheless, physical disability remains the major impact on patients' health-related quality of life (HRQoL). An early study in Canada evaluated the effect of the disease on HRQoL [23]. The study used a generic QoL questionnaire, the SF36 [24] and compared scores of MS patients to those of an age and gender matched normal population. We illustrate the results below for the patient group with moderate disease (EDSS 3.0-6.0). As can be seen in Figure 1-13, the largest decrement in HRQoL occurs indeed in the two physical domains of "Physical Function" and "Physical Role Fulfillment".

Figure 1-13 – Impact on HRQoL measured with the SF-36



1.4 Conclusions

This chapter summarizes the literature on prevalence of MS and the impact the disease has on patients. The data on the health burden are among the best documented, with a series of large surveys across Western Europe. The data on prevalence are more difficult to interpret and we have therefore proposed an approach to estimating prevalence from existing detailed data sets. The results yields the prevalence for patients that are diagnosed rather than the estimated potential number of patients, as this is more relevant when estimating the proportion of patients that receive treatment.

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Chapter 2 - Cost of Multiple Sclerosis

CONTENTS

TABLES

FIGURES

2 Cost of Multiple Sclerosis in Europe

2.1 Summary

In this chapter, we estimate the total cost of Multiple Sclerosis (MS) in Europe, based on the cost per patient and on the prevalence of diagnosed patients.

Multiple sclerosis (MS) is one of the diseases with the most extensive research on costs and quality of life. In Europe, a number of large studies have been performed, many studies on certain of the economic aspects exist, and review papers have been published. The most recent literature on the cost of MS includes a series of comprehensive cost analyses covering ten countries including around 15,000 patients, by the same research group. Since these analyses all use the same methodology and are consistent in their approach, they are a good basis for a European-wide analysis of the cost of MS.

We used and refined a previously developed cost-model to estimate total costs of MS in Europe. Since costs increase with increasing disease severity, the earlier model had stratified costs into three severity groups using a functional scale (EDSS). In our current analysis we use instead age-groups as the main parameters, to account for a different prevalence at different ages, different disease severity levels over time as well as different costs due in particular to differences in work force participation and income. Within these age groups, costs were then re-stratified according to the severity distribution in the study series.

The age groups in the model are the same as in the calculation of prevalence in the previous chapter, except for the fact that all patients above 65 are combined into one group. Costs were estimated as proportional costs for the different types of resources (health care, non-medical costs, production losses and informal care). We used economic indicators to impute costs for countries without published data for all cost categories except for the disease modifying treatments. There are considerable differences in the use of these drugs across Europe, and imputation is therefore less feasible. The cost of the biologic drugs was thus directly extracted from international sales data.

The average cost per patient with MS in Europe was estimated at €36,000, with as expected a clear difference between Western Europe (€39,000) and Central/Eastern Europe (€11,600). The total cost of the disease was estimated at €15 billion, of which slightly over €14 billion occur in the old EU countries with 410,000 MS patients and €650 million in the new EU countries in Central and Eastern Europe with 60,000 diagnosed patients.

The majority of costs are outside the health care system: Health care costs are estimated at a mere 32% of total costs, of which biologics represent around one third. Non medical costs are estimated at 10%, informal care at 22% and production losses at 36% of all costs. .

These estimates are somewhat higher than what was previously found. The annual cost per patient is however similar, considering overall cost increases over time. The overall cost is higher, due to refined and higher prevalence and cost estimates.

2.2 The economic burden of Multiple Sclerosis

Information about the cost of a disease provides important general information to policy makers, but can not be used directly for decisions about resource allocation to individual treatments. Cost-of illness studies do, however, constitute important data that can serve as a basis for cost-effectiveness analyses of health interventions. Presenting an overall picture of costs will also facilitate the interpretation of ad-hoc studies that only focus on specific cost items or situations (e.g. payer versus social perspective).

The economic burden of a disease is a complement to information about the health burden. Multiple sclerosis (MS) is one of the diseases with the most extensive research on costs and quality of life. In Europe, a number of comprehensive studies have been performed, many studies on certain of the economic aspects exist, and review papers have been published [1-3]. We will therefore not provide a further in-depth review of these studies but only summarize study findings and issues related to their interpretation briefly.

The considerable cost, both to the health care system and to society, of MS as a chronic progressive and disabling disease has been recognized for a long time. Estimating the precise costs incurred due to a disease is difficult and cost-of-illness estimates are thus often surrounded with a certain degree of uncertainty. A number of factors influence the results, such as the country where the study has been performed, the study objectives, the samples included, prevalence estimates, and not the least the methodology used [2]. Major methodological issues in cost of illness studies pertain to how costs due to the disease can be separated from other unrelated costs patients may incur, what perspective is adopted for the analysis, a societal perspective (all costs regardless of who pays) or a payer perspective (only costs carried by the health and care and social systems). The largest differences will occur due to the perspective, but even within the studies using the same perspective large differences may arise due to the method of calculation, in particular the way production losses are valued; the human capital approach uses the wage rate as a proxy for an individual's productivity for the entire duration, while the friction cost method assumes that any person on sick-leave or early retirement will be replaced within 4 months and no loss will occur.

Table 2-1 – Cost differences due to perspective and calculation methods

	Perspectives ***Germany*** ***Annual cost per patient (N=2973; € 2005)[4]***		*Calculation Method* ***Netherlands Societal perspective Annual cost per patient (N=1549; € 2005) [5]***	
	Public payers	Societal	Human Capital Method	Friction Cost Method
	Mean	Mean	Mean	Mean
Health care costs [1]	14949	17165	8371	8371
Non-medical costs [2]	634	5922	7576	7576
Production losses [3]	3404	16911	***611***	***13476***
Total annual cost	**18 987**	**39 998**	**16 558**	**29423**

1) Inpatient and outpatient care; 2)Investments, services, transport, informal care;
3) Production losses, patients <65

Another important difference can result from the data collection methodology. The source of information can be from medical charts, national statistics or patient questionnaires. Medical charts will yield the most limited information, as only health care costs will be captured, and even these often not comprehensively. National statistics will allow including in addition productivity losses to payers (invalidity pensions, sick leave compensation). However, both will miss entirely patient-borne costs, and particularly in MS, these costs are substantial (see direct non-medical costs in table 2-1), due to investments that are needed to help performing daily activities as well as informal care from family. The table below illustrates differences in costs when using administrative data bases or patient questionnaires.

Table 2-2 Cost differences due to data collection methods

	Total estimated cost in the country	
	Top-down study € (1999)	Bottom-up study € (1999)
Germany	775 million * [6]	1520 million [7]
Sweden	250 million ** [8]	430 million *** [9]

* *adjusted from 1997 to 1999*
** *adjusted from 1994 to 1999*
*** *adjusted for national disease modifying drug usage*

2.2.1 Findings in early studies

A comprehensive review of studies was performed in 2005 within a project of the cost of disorders of the brain [1]. The majority of studies included were performed in the latter part of the 1990s, when the interest in basic information on costs of MS was rising with the introduction of the disease modifying treatments (DMTs). Most of the studies thus did not include the cost of the new treatments. The studies differed as expected considerably in terms of objectives and methodology, and it proved impossible to compare the results directly. Nevertheless, a common picture emerged:

- Costs outside the health care system (productivity losses, informal care and services) represent an important part of total costs.
- Prior to the use of DMTs, inpatient care and rehabilitation dominated direct medical costs.
- Costs increase with increasing disease severity (measured with a functional scale, the EDSS)[1], and thus logically also with age and disease duration.

[1] *EDSS (Expanded Disability Status Scale) measures predominantly functional impairment, with a focus on ambulation. The scale progresses from 0 (normal) in half point steps to 9.5 (10 = death), and levels are well described e.g. with the need for 1 cane, 2 canes, wheel chair or bedridden. Disease onset in most patients is with relapsing-remitting disease (RRMS) where EDSS increases initially during disease exacerbations and then returns to the previous levels. With time recovery is incomplete and disease progression is more gradual (defined as secondary progressive disease, SPMS). Conversion from RRMS to SPMS generally occurs around EDSS 3-5.*

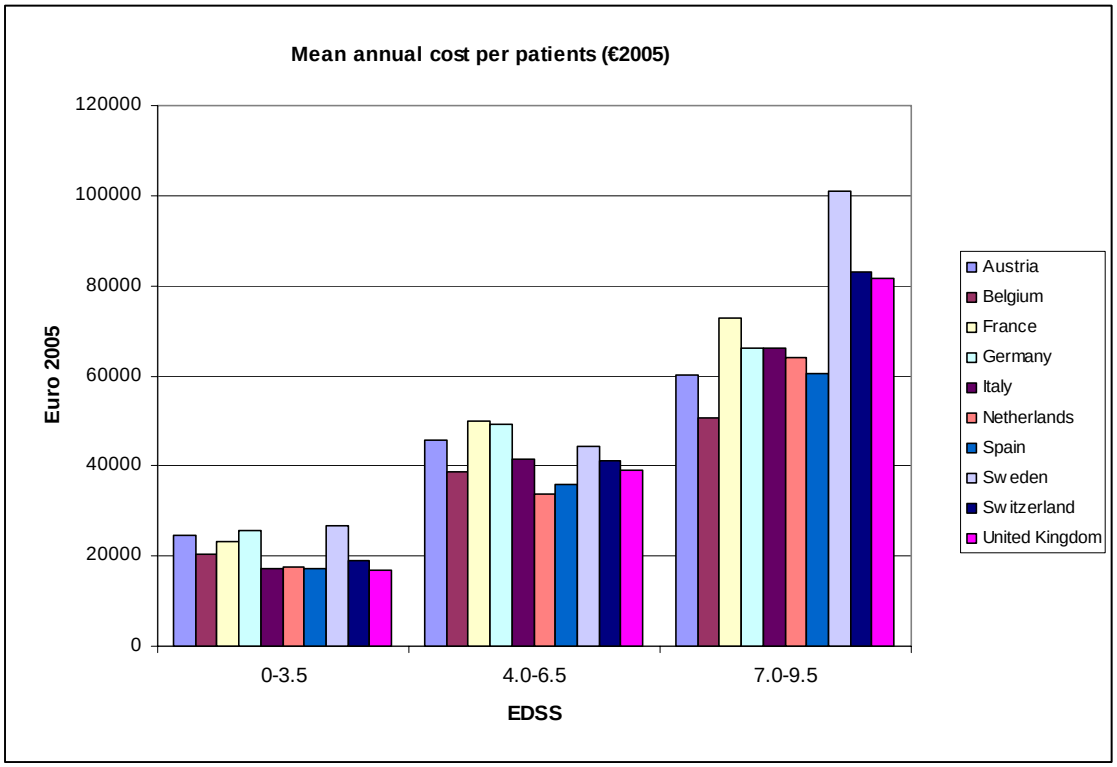
- Patients with secondary progressive disease (SPMS) have higher costs than patients with relapsing disease (RRMS), not because of a difference in the disease, but because patients with SPMS are at higher EDSS levels.
- Around 30-40% of patients will have to leave the workforce early, on average at an age around 45.
- Men have higher costs then women, due to higher production losses (a consequence of higher salaries and longer working hours).
- Drug costs were very limited (%) prior to the introduction of the DMD.

2.2.2 Findings in recent studies

In 2005 a large survey of the cost of MS was performed in 9 western European countries[10] and subsequently in one more country (France) [11], using identical methodology. This series of studies provides a detailed overview of costs in Western Europe.

On average, costs for patients with mild disease (EDSS 0-3) were around €22,000 per year, for patients with moderate disease (EDSS 4-6.5) around €45,000 per year and for patients with severe disease (EDSS 7-9.5) around €75,000 per year (adjusted to 2008 €). Health care and social services costs represented on average 45%, with one third due to DMTs. Production losses averaged 36% and informal care 18%.

Figure 2-1 Mean annual costs per patient by level of disease severity [12, 13]



Adapted from Kobelt et al [11,13]

Table 2-3 Description of samples in the European Survey of Cost of MS

	Austria	Belgium	France	Germany	Italy	Nether-lands	Spain	Sweden	Switzer-land	United Kingdom
Recruitment [1]	NMSS	Clinics	NMSS	Clinics	NMSS	Clinics	NMSS	NMSS	NMSS	NMSS
Response rate	35%	38%	42%	38%	31%	52%	32%	75%	45%	19%
Sample size (No)	1019	799	1355	2793	921	1549	1848	1339	1101	2048
Proportion women	70%	68%	75%	72%	66%	69%	64%	73%	64%	75%
Proportion living alone	28%	19%	20%	21%	13%	16%	10%	28%	23%	14%
Mean age	50	48	49	45	46	47	45	53	53	52
Proportion aged 65+	13%	12%	19%[2]	18%	9%	8%	6%	16%	21%	19%
Proportion employed and working [3]	29%	34%	31%	35%	41%	32%	26%	24%	31%	25%
Proportion on early retirement due to MS	**45%**	**33%**	**28%**	**34%**	**33%**	**42%**	**34%**	**36%**	**34%**	**44%**
Mean age at diagnosis	35	35	37	35	34	37	33	39	36	39
Mean age at first symptoms	32	32	33	32	30	31	30	32	33	32
Mean EDSS	**4.4**	**4.2**	**4.4**	**3.8**	**4.6**	**3.9**	**4.5**	**5.1**	**4.5**	**5.1**

** adapted from Kobelt et al [13]*

1) NMSS = National MS Societies (patient associations), Clinics = Neurology clinics 2) aged 60+, the official retirement age in France 3) excluding patients on long-term sick leave

Costs in this study series are influenced by the overall disease severity in the sample (mean EDSS level, see table above), but in general the mean cost per patient represented costs for a patient at the median EDSS level. However, the use of health care resources and services is not only influenced by disease activity (relapses) and severity (function), but also by the organization and availability of care and the ease of access. Despite the relative similarity of the samples, there was substantial variation both in frequency and quantity of health care consumption such as inpatient admissions and length of stay, medical consultations, physiotherapy and the use of DMTs [10, 13]. The proportions of patients using services such as home help or investing into modifications to the house or the car were more comparable across the countries, but availability and/or cost nonetheless influenced consumption. Thus, there were considerable differences in the intensity of the usage of services, or the extent to which informal care was needed, as different countries provide different levels of service. Nevertheless, the average cost of a relapse was very similar across all countries at around €3000 per relapse. The cost of relapses were primarily due to hospitalization, informal care and sick-leave.[10]

Unfortunately, there are few studies in countries in Eastern Europe. The only study available for inclusion in our estimates was a prospective follow-up of a small cohort from Poland, also published in 2005 [14]. The study followed 148 patients prospectively and divided costs by disease severity. Costs were reported for 5 months, but for better understanding it is assumed here that they can be annualized. Costs were estimated at €6000 at EDSS <4, €8400 at EDSS 4-6, and at €10,100 at EDSS >6.5. Indirect costs represented in all three groups around 65% of total costs.

2.3 Modelling the Cost of MS

Functional disability (EDSS) was thus identified as the major cost-driver, with obviously a strong correlation with age and disease duration. EDSS is also an efficacy measure in all clinical trials and systematically included in epidemiological data bases or registries, which makes it an ideal measure to include in economic studies, both cost of illness studies and cost-effectiveness analyses estimating the effect of slowing disease progression.

Costs in health economic studies are divided into direct and indirect costs:

- Direct costs are costs directly linked to the treatment, detection, prevention or care of an illness. They are further separated into medical cost, i.e. costs that occur in the health care sector, and non-medical costs that occur in other sectors, such as social services, community or to the patients themselves.
- Indirect costs are production losses that result as a consequence of an illness, premature death or treatment of an illness.

These definitions are used in most studies, but there is some discussion as to whether informal care should be considered a direct or an indirect cost. Informal care costs can be estimated in three different ways: production losses for those carers who work, replacement cost using as proxy the cost of professional carers, or loss of leisure time for all carers. Data on informal care are rather scarce in the data at our disposal, and we therefore present informal care as a separate item in this report. Other non-medical costs such transportation, social services, etc are integrated into direct costs.

2.3.1 Model design

We developed a model, based on earlier work [15] that allows estimating the cost of MS in Europe despite of the fact that data are not available for all countries. The model uses data on the cost per patient from published studies and comparative economic indexes to estimate costs for countries for cost data are missing or incomplete in the following way:

- Health care costs (direct medical costs) were imputed using the healthcare spending per capita and the comparative price levels in health care;
- Non-medical costs were calculated differently depending on the type
    - Cost of goods (devices and investments) were imputed as direct medical costs, using health care expenditure levels and comparative price levels in health care;
    - using national price levels;
    - Cost for services were adjusted by the cost of labour in health care;
    - Informal care, estimated as the cost of leisure time estimated from disposable income after tax, was imputed using the comparative index of cost of labour;
    - Production losses were imputed using the comparative index of cost of labour and level of work participation in each country by age group and sex.

The costs per patient estimated are then combined with the country-specific prevalence to obtain the total cost of MS per country included the report.

The model can thus be likened to a prevalence-based cost of illness study that estimates total annual costs for a prevalent patient population, based on the mean annual cost per patient. These latter costs can be estimated using either aggregated resource consumption from available statistics, or by collecting actual resource consumption in a representative sample of patients.

For the model, costs were divided into medical costs, drugs, non-medical costs, informal care and production losses (indirect costs). Non-medical costs were further separated into services (formal help in home, transportation) and products (aids/devices/adaptations/other) to enable imputations using the appropriate economic indicators. In a first step, available annual costs per patients for each of these categories were extracted from the studies selected for the model. In a second step these costs were inflated to the same base year (2008) using country specific consumer price indexes (CPI). Finally, costs were adjusted into a common currency (Euro), using 2008 average exchange rates.

The prevalence of MS was estimated in five age groups, 20-34 years, 35-49 years, 50-64 years, 65-74 years and >74 years (see chapter 1) and costs were thus calculated for this same age distribution. This allows a more precise calculation of in particular production losses, as salary levels tend to be different between the three first age groups and not estimated for patients above retirement age. The two oldest groups were therefore combined into one group for cost calculations. Although retirement age varies slightly between the countries, we used 65 as the generally accepted retirement age.

2.3.2 Model data

2.3.2.1 Costs

In view of the rare occurrence where a large multinational study with consistent methodology is available [10, 11]., we based our cost estimates on this set of patient data from Austria, Belgium, France, Germany, Italy, Netherlands, Spain, Sweden, Switzerland and the UK, complemented with the additional study from Poland. No other relevant recent studies were identified in a comprehensive literature research (PubMed, Health Economic Evaluations Database (HEED). The table below shows costs by country, stratified by disease severity (EDSS <4, 4-6.5, and >6.5), in the European study [4, 5, 11, 16-22]. Costs were adjusted to 2008 using the CPI of the specific country and converted to € 2008.

Table 2-4 Studies included in the model calculations

Country	Author	Year of cost data	Age (mean)	n	EDSS	Total annual cost of MS (€ 2008)
Austria	Kobelt [16]	2005	50	1019	<4	€ 18,181
					4-6.5	€ 28,089
					>6.5	€ 46,132
Belgium	Kobelt [22]	2005	48	799	<4	€ 25,966
					4-6.5	€ 48,203
					>6.5	€ 63,317
France	Kobelt [11]	2006	49	1355	<4	€ 24,818
					4-6.5	€ 53,573
					>6.5	€ 78,102
Germany	Kobelt [4]	2005	45	2793	<4	€ 20,633
					4-6.5	€ 39,287
					>6.5	€ 51,375
Italy	Kobelt [21]	2005	46	921	<4	€ 26,754
					4-6.5	€ 51,259
					>6.5	€ 68,983
Netherlands	Kobelt [5]	2005	47	1549	<4	€ 17,736
					4-6.5	€ 42,920
					>6.5	€ 68,385
Poland	Orlewska [14]	2005	43	148	<4	€ 8,508
					4-6	€ 12,118
					>6	€ 14,340
Spain	Kobelt [18]	2005	45	1848	<4	€ 17,180
					4-6.5	€ 35,825
					>6.5	€ 60,419
Sweden	Kobelt [20]	2005	53	1339	<4	€ 27,570
					4-6.5	€ 45,769
					>6.5	€ 104,492
Switzerland	Kobelt [19]	2005	53	1101	<4	€ 18,948
					4-6.5	€ 41,169
					>6.5	€ 82,807
UK	Kobelt [17]	2005	51	2048	<4	€ 20,158
					4-6.5	€ 42,106
					>6.5	€ 83,298

As anonymous patient level data were available to us for this survey, it was possible to perform some re-analysis for the purpose of our model. The previous model had stratified the data by disease severity. In the current model, we used age groups instead as the main parameter, as mentioned above. Within each of these age groups, costs were then again stratified by the three EDSS groups. At all levels, costs were separated into the categories mentioned above: medical costs, drugs, non-medical costs, informal care and indirect costs. The cost of biologics was added separately, using actual sales data from IMS.

2.3.2.2 Economic comparative data

Data on health care expenditure, price levels, labour costs as well as population statistics were obtained from WHO [23] and Eurostat [24] and are presented in table below. Information not available in Eurostat, e.g. some data for the non-EU countries, was taken from national statistics databases for the specific countries [25, 26].

Table 2-5 Price levels in health care an health expenditure per capita [23, 24]

	Comparative price level index EU27 – Health 2007	*Health expenditure per capita 2005 (PPP €)*	*Comparative health exenditures per capita index EU27*
EU27	100	1,755	100
Austria	107	2,417	137
Belgium	110	2,132	120
Bulgaria	29	642	36
Cyprus	102	902	51
Czech Republic	47	1,255	71
Denmark	152	1,940	110
Estonia	53	663	37
Finland	127	1,511	85
France	107	2,426	137
Germany	103	2,403	136
Greece	81	2,178	123
Hungary	54	1,074	61
Iceland	170	2,061	116
Ireland	131	2,072	117
Italy	123	1,491	84
Latvia	44	686	39
Lithuania	46	665	38
Luxembourg	123	3,504	198
Malta	58	1,450	82
Netherlands	101	2,400	136
Norway	159	2,530	143
Poland	44	758	43
Portugal	87	1,403	79
Romania	37	464	26
Slovakia	51	828	47
Slovenia	71	1,427	81
Spain	84	1,737	98
Sweden	123	2,056	116
Switzerland	138	2,798	158
United Kingdom	117	1,780	101
Turkey	58	452	26

Table 2-6 Labour costs and employment rate by age [24]

	Monthly labour cost EU27 - All branches		Monthly labour cost EU27 - Health and social work		% employed (20-44 yrs)		% employed (45-64 yrs)	
	€ 2006	Comparative levels (EU27=100)	€ 2006	Comparative levels (EU27=100)	women	men	women	men
EU27	3,117	100	2,723	100	68%	83%	54%	71%
Austria	3,827	123	3,373	124	76%	89%	55%	72%
Belgium	4,047	130	2,960	109	70%	81%	48%	67%
Bulgaria	243	8	255	9	70%	78%	56%	67%
Cyprus	2,091	67	2,546	67[E]	76%	88%	56%	84%
Czech Republic	1,028	33	982	36	66%	86%	58%	75%
Denmark	4,481	144	3,423	126	81%	89%	67%	77%
Estonia	840	27	782	29	71%	85%	74%	75%
Finland	3,685	118	2,725	100	75%	84%	70%	69%
France	4,382	141	:	141[E]	71%	82%	58%	66%
Germany	3,868	124	3,333	122	73%	83%	61%	74%
Greece	:	71[A]	:	71[E]	59%	83%	42%	76%
Hungary	947	30	841	31	60%	77%	50%	60%
Iceland	5,032	161	:	161[E]	81%	91%	82%	93%
Ireland	:	128[D]	:	128[E]	70%	86%	54%	78%
Italy	:	104[B]	:	104[E]	57%	81%	41%	69%
Latvia	532	17	534	20	73%	83%	68%	75%
Lithuania	646	21	586	22	72%	78%	66%	74%
Luxembourg	4,625	148	4,850	178	69%	85%	49%	68%
Malta	1,445	46	1,592	58	53%	88%	19%	68%
Netherlands	:	133[C]	:	133[E]	80%	91%	59%	77%
Norway	:	152[D]	:	152	81%	86%	73%	81%
Poland	889	29	697	26	64%	77%	44%	60%
Portugal	1,618	52	1,872	69	72%	83%	58%	74%
Romania	414	13	457	17	63%	74%	50%	67%
Slovakia	775	25	621	23	64%	79%	51%	70%
Slovenia	1,673	54	1,922	71	78%	85%	53%	67%
Spain	2,203	71	2,439	90	66%	84%	45%	75%
Sweden	4,518	145	3,765	138	78%	85%	75%	80%
Switzerland	:	138[D]	:	138[E]	77%	91%	70%	85%
United Kingdom		137	4,258	156	72%	86%	63%	77%
Turkey	624 [26]	20	:	20[E]	27%	81%	20%	59%

[A]Based on data from 2003, [B]Based on data from 2002, [C]Based on data from 2005, [D]Extrapolation from 2006 OECD data, [E]Based on data for all branches

2.3.3 Results

We estimate that there are currently **470,000 patients** with a diagnosis of MS in the EU27 + 3 (Iceland, Norway, Switzerland), with a total cost to society estimated at **€ 15 billion**.

The cost in Western Europe was estimated at slightly over € 14 billion for 411,000 patients with a diagnosis.

Table 2-7 estimated annual cost of MS by country, total

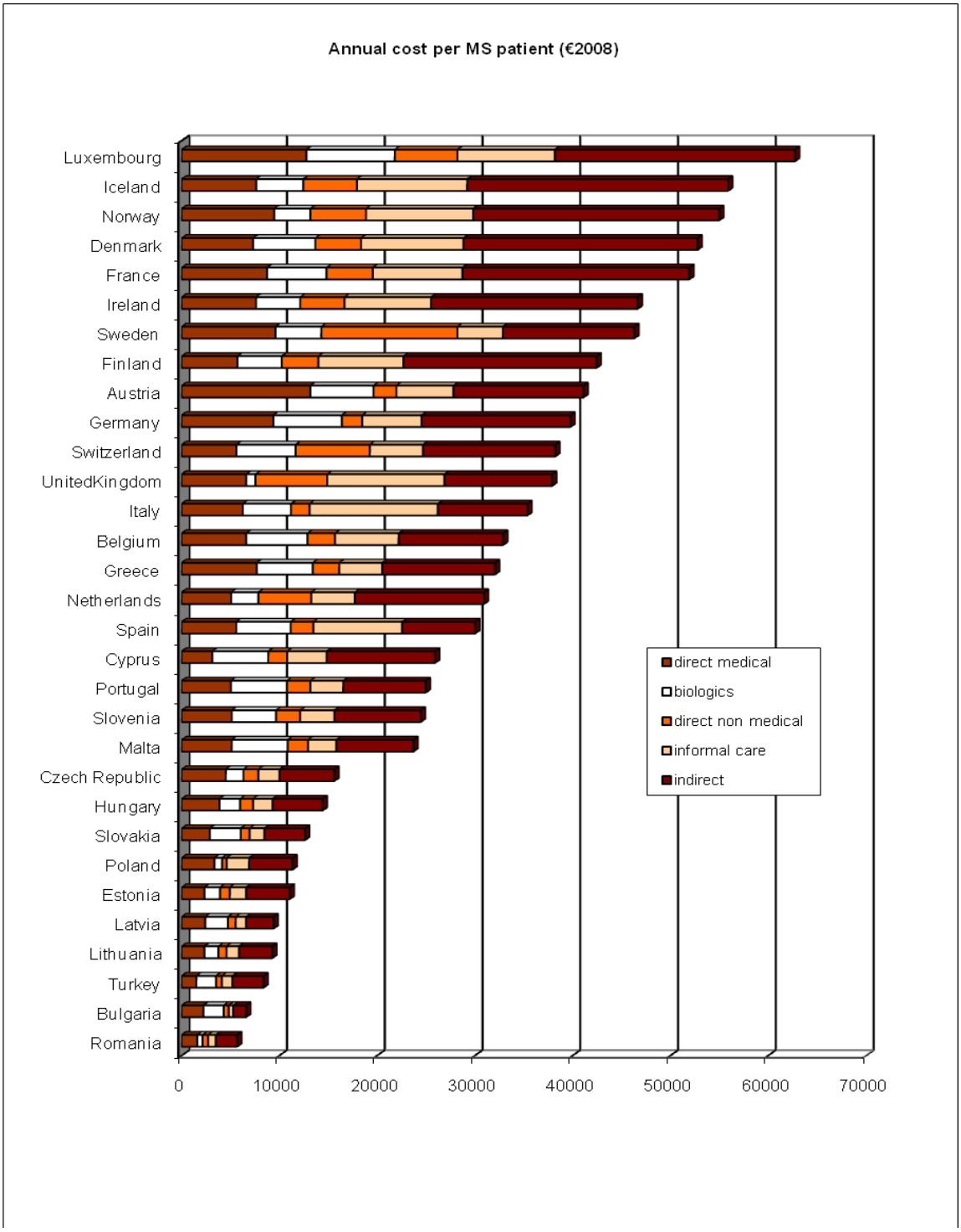
Country	*Total cost of MS (million € 2008)*	*Total cases (>19)*
Austria	281.7	7,685
Belgium	277.0	9,516
Bulgaria	18.6	2,930
Cyprus	11.3	453
Czech Republic	117.3	8,113
Denmark	324.5	6,997
Estonia	8.3	795
Finland	257.1	6,924
France	2,294.8	47,626
Germany	3,761.7	113,120
Greece	200.2	6,668
Hungary	104.6	7,928
Iceland	17.2	342
Ireland	204.7	4,896
Italy	1,491.9	47,608
Latvia	12.0	1,374
Lithuania	17.7	2,027
Luxembourg	24.3	425
Malta	5.3	235
Netherlands	417.7	14,872
Norway	278.1	5,741
Poland	244.4	22,469
Portugal	190.6	8,381
Romania	45.0	8,159
Slovakia	38.8	3,211
Slovenia	36.4	1,622
Spain	950.5	35,214
Sweden	437.4	11,590
Switzerland	237.0	6,971
United Kingdom	2,407.9	76,851
Turkey	206.7	24,940
Total EU27 + 3	14,920	470,745
Total Western Europe	14,070	412,116
Total Eastern Europe	643	58,628
Total Turkey	207	24,940

Mean annual total costs per patient were estimated at € 35,900 in the EU27+3, with a range from € 5,700 (Rumania) to €62,700 (Luxembourg).
The mean cost per patient in Western Europe was estimated € 39,300 and in the new EU member states in Central/Eastern Europe at € 11,600.

Table 2-8 Mean estimated annual cost per patient (€ 2008)

Country	*Mean annual total cost per patient (€ 2008)*					
	Total	**Direct medical (excl.biol)**	**Biologics**	**Direct non-medical**	**Informal Care**	**Indirect**
	Mean, €	*Mean, €*	*Mean, €*	*Mean, €*	*Mean, €*	*Mean, €*
Austria	41,102	13171	6452	2352	5823	13303
Belgium	32,883	6609	6272	2818	6517	10667
Bulgaria	6,590	2238	2070	510	467	1306
Cyprus	25,904	3147	5723	1935	4034	11066
Czech Republic	15,610	4517	1808	1533	2148	5603
Denmark	52,761	7309	6372	4674	10466	23940
Estonia	11,053	2344	1582	998	1679	4450
Finland	42,431	5720	4522	3753	8706	19730
France	51,926	8741	6090	4724	9166	23204
Germany	39,767	9388	7006	2082	6071	15220
Greece	32,051	7695	5723	2715	4400	11518
Hungary	14,410	3877	2115	1324	1995	5099
Iceland	55,881	7630	4819	5491	11278	26663
Ireland	46,636	7625	4511	4536	8849	21114
Italy	35,357	6268	4923	1908	13104	9153
Latvia	9,399	2423	2320	793	1061	2802
Lithuania	9,268	2343	1435	819	1278	3394
Luxembourg	62,722	12773	9038	6411	9957	24542
Malta	23,700	5131	5723	2083	2893	7871
Netherlands	30,919	5068	2781	5407	4464	13199
Norway	54,981	9480	3700	5686	10957	25158
Poland	11,340	3361	794	446	2313	4426
Portugal	24,965	5041	5725	2407	3366	8425
Romania	5,677	1603	538	577	777	2183
Slovakia	12,622	2892	3162	908	1504	4156
Slovenia	24,444	5136	4523	2472	3492	8821
Spain	30,011	5592	5572	2313	9082	7452
Sweden	46,289	9612	4684	13929	4644	13420
Switzerland	38,215	5610	6049	7593	5436	13527
United Kingdom	37,878	6617	938	7339	11985	10999
Turkey	8,374	1517	2011	590	1087	3170
Average EU27 + 3	35877	7114	4474	3704	7795	12735
Western Europe	39326	7665	4905	4111	8640	13943
Eastern Europe	11632	3243	1443	847	1856	4245

Figure 2-2 – Mean annual cost per patient with MS (€ 2008)



We also present costs by age groups, excluding however the cost of biologics. As the use of biologics is taken from actual IMS sales data rather than from the literature, differential use by age is not available. While one may expect that usage is lower in the older age groups, as disease has converted to secondary progressive and advanced to higher EDSS levels, we have preferred not to make any assumption.

Figure 2-3 Costs by age groups (excluding biologics)

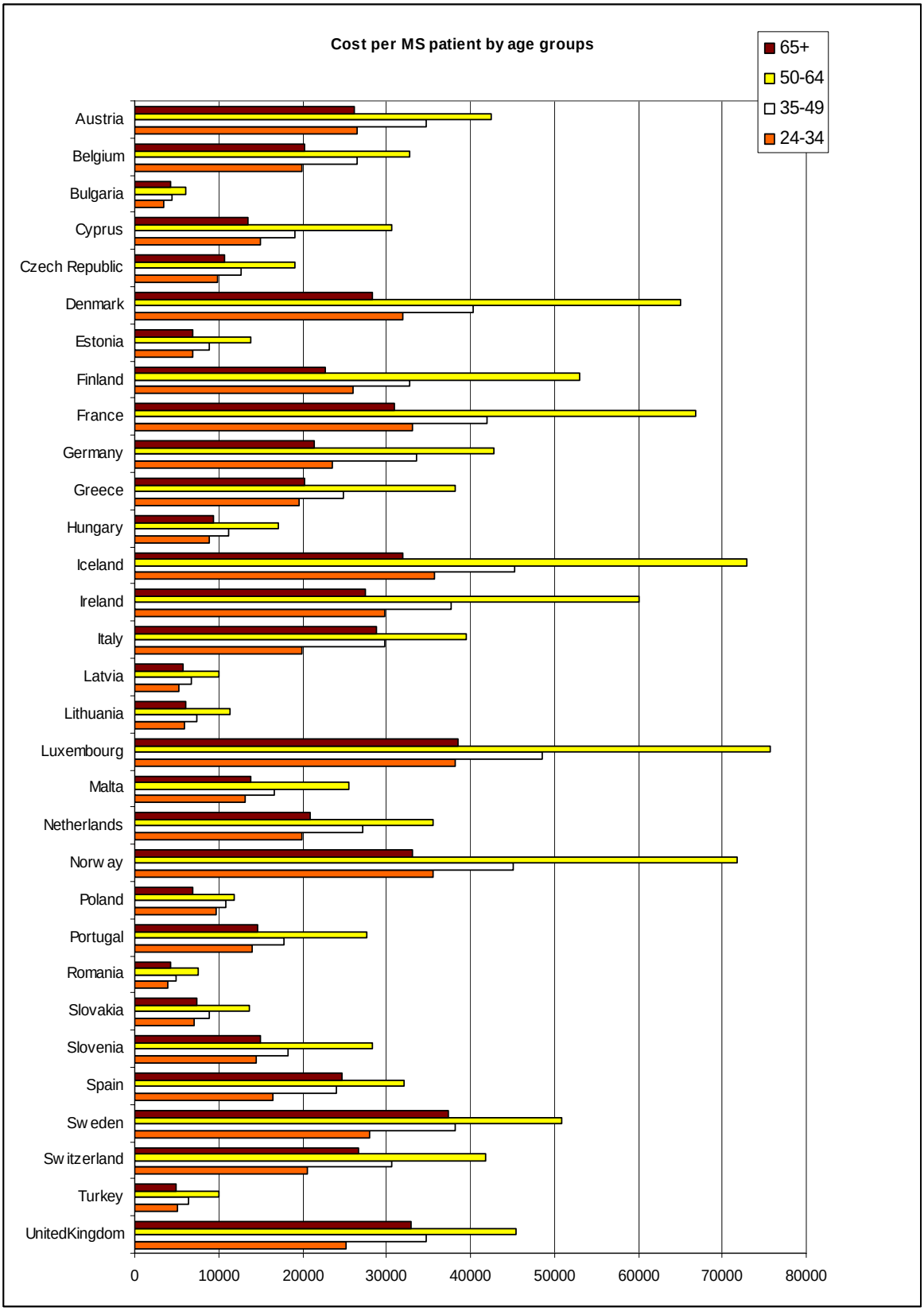


Figure 2-4 Structure of Costs (EU27 + 3)

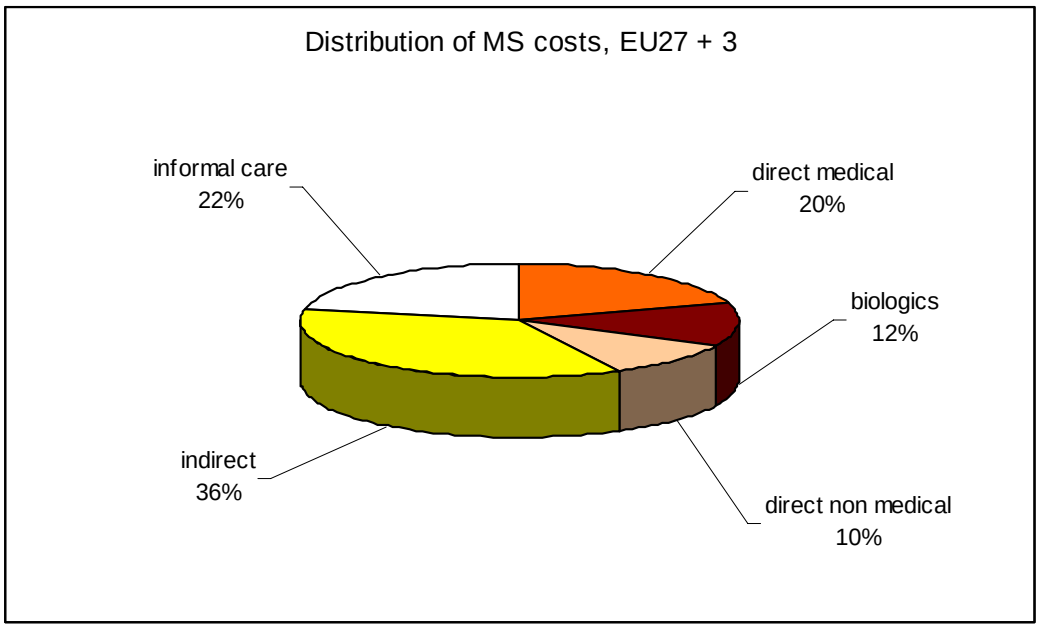
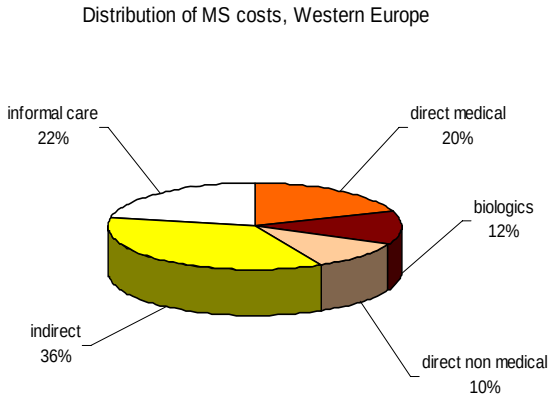
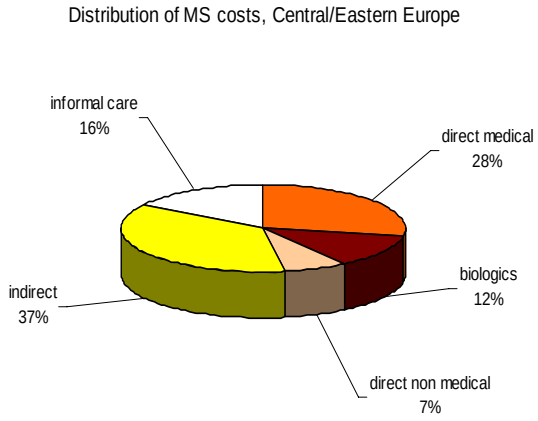


Figure 2-5 Structure of Costs (Western and Central/Eastern Europe)





As in previous studies, we found that costs outside the health care sector dominate costs: production losses, informal care, non-medical costs that are often only partially reimbursed represent over two thirds of all costs. In Central and Eastern Europe medical costs represent a larger proportion of costs, as income levels are lower. Biologics are estimated at around 12% of total costs across Europe.

It is however possible that drug costs are slightly underestimated, as these costs were estimated as ex-factory costs, without additional margins. As these drugs are mostly hospital products, actual sales prices by country are not available. However, margins are likely very small. Nevertheless, it is possible that the cost of biologics per patient is somewhat underestimated in chapter 2.)

2.4 Conclusion

In this chapter, we have refined previously published estimates of the cost of MS by using a different calculation of the number of prevalent and diagnosed patients, as well as new information on the costs per patient and type of resource by age and gender. Also, usage of DMTs is no longer based on estimates, but on actual sales data (IMS Health) from the different countries.

In the most recent estimation [15], mean annual costs per patient were estimated at €31,000, with a range between €10,000 to € 54,000. Our current estimates of the mean cost per patient are slightly higher at €36,000 (+16%), due essentially to the time factor and increasing use of biologic treatments. However, it is interesting to note that the range is considerably larger (€ 5,700 to € 62,700). The explanation is most likely the use of different age groups and actual sales data for biologic treatments rather than imputations.

Total costs in Europe amounted in our study amount to € 15 billion, of which slightly over €14 billion occur in the old EU countries (Western Europe) with 410,000 patients and €650 million in the new EU countries in Central and Eastern Europe with 60,000 patients.

Biologics represent on average 12% of total costs in all parts of Europe. However, it has to be borne in mind that for the new EU countries very limited data is available on actual costs, and that the majority of costs (except biologics) were thus imputed from Western Europe with adjustments for economic factors. It is nevertheless surprising that the proportion represented by biologics is the same, as their cost was taken from actual IMS sales data.

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Chapter 3 - Uptake of Biologic Treatments

We gratefully acknowledge the contribution of Leif Wixström for statistical support and to Per Troen, IMS Health, London, for help with interpretation of IMS data.

CONTENT

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3 Uptake of Biologic Treatments

3.1 Summary

This chapter provides a description of current access to biologic disease-modifying treatments (DMTs). In the absence of readily available information on the number of patients treated in any country in Europe, we use international sales data on volume (units, mg and I.U.) and value (in €) form IMS, as well as estimated prevalence in each country to derive the number of patients treated.

IMS data are incomplete in some countries, and this has been verified with IMS staff. However, in most cases it has not been possible to identify comparable data that could be incorporated into the IMS data set, and limited adjustments were therefore made.

The drugs included in the report are Avonex (interferon-β-1a), Betaferon (interferon-β-1b), Copaxone (glatiramer acetate), Rebif 22/44 (interferon-β-1a), Tysabri (natalizumab). The first 4 were introduced in the second half of the 1990', while Tysabri was introduced only in mid 2006 and limited data are hence available. Although IMS data are available since launch of these products, we present only the last 5 years for which better data in terms quantities (units) were available.

Results are presented as sales (€2008) per prevalent patient (using prevalence estimates presented in chapter 1), the estimated proportion of treated patients, and the total number of patients estimated to be on treatment in each country.

Compared to indications such as Rheumatoid Arthritis, access to biologics for MS patients is more even.

- *In Western Europe, around 45% of patients are on treatment, with a range between 40% and 50%, which indicates that a majority of patients with relapsing-remitting disease are treated. An exception to this is the United Kingdom where NICE recommendation and a risk sharing scheme have resulted in low access .*
- *Usage in Central/Eastern Europe is as expected lower, mainly due to lower overall income levels, and between only 5% and 25% of patients are on treatment. An exception to this is Slovenia where usage is at the lower end of Western Europe. The difference between the old and new EU countries is not as large as could be expected today, as a consequence of lower prices established in these countries prior to their joining the EU.*

It is however also very interesting to note that the usage pattern across countries is somewhat different from what was observed for Rheumatoid Arthritis. While Germany had rather limited uptake of RA drugs, it is among the countries with the best access for MS drugs. Similarly, Austria had very limited uptake of RA drugs, but is only behind Luxembourg for MS drugs. Norway where the use of RA drugs was found to be by far the highest has below average use of MS drugs. Ireland had good access to RA drugs but low access to MS drugs. Access to biologics in RA was considerably better for RA than for MS in the United Kingdom, even if it was overall low. These differences cannot be explained from our data, but it is possible that they are related to initial restrictive reimbursement or medical assessment of the treatments. Also, the data for MS the United Kingdom have to be considered with caution, as it is possible that not all sales are captured in our data.

3.2 Methods

In order to discuss what factors determine access to new therapies, a description of the current access is required. Ideally, this would be information on the number of patients actually treated in each country and for what indication, as well as what proportion of patients this represents. Unfortunately, such data are not readily available, and one might think that such primary information would improve the discussion regarding access. Currently, the necessary information has to be derived indirectly.

We use overall sales data from IMS (units, volume and value) and average annual dose per patient and drug to estimate the number of patients treated in each country. These data are then combined with our prevalence estimates (chapter 1) to estimate the proportion of patients treated and the mean cost per prevalent patient. This cost, in turn, is used as an input into the cost model (chapter 2) to estimate the total cost of the disease in Europe.

3.2.1 Data

IMS data are currently the only source of comparative data at an international level, despite a number of shortcomings. It is likely that in no country are 100% of sales captured, but it is difficult to define the magnitude of underestimation. For some countries it is known that part or all of hospital sales are omitted and certain wholesalers or other channels of distribution not included. Similarly, it is possible that sales are overestimated in some countries as a consequence of the sample of pharmacies and hospitals that provide data. We have thus refrained from an overall adjustment to the data. Individual country issues and adjustments have been discussed with IMS.

For the uptake curves, no adjustments were made, as it is not possible to adjust over several curves. Rather, countries with questionable data have been excluded from the figures. An exeption to this is the United Kingdom (see below). Corrections have however been made in all countries where relevant to the calculation of the proportion of diagnosed patients on treatment at the end of 2008, and for the mean cost of biologics per patients used in chapter 2.

The following adjustments were made:

- In Portugal, only hospital sales are available, but as biologics are essentially used within the hospital setting, we felt that this was not a large issue. Also, Portuguese data were only available for the past 2 years.
- In a number of countries, hospital sales are not fully captured by IMS, and we have proceeded as follows:
    - In Greece, sales per patient reported represented around 10% of those in countries like Hungary or 5% of countries like Portugal. We have hence imputed the sales from Portugal.
    - Sales reported for Luxembourg and Ireland on the contrary were comparatively high, but we had no basis to make adjustments. It is possible that sales in Luxembourg concern some of the neighbouring countries, but this is difficult to assess..
    - The Baltic States are thought to be incomplete, but as they were also relatively high and no other data were available, we made no changes.
- No data at all were available for Cyprus, Iceland and Malta. For Cyprus and Malta, we imputed sales from Portugal, and for Iceland we imputed average data

from the Nordic area, considering the similarity of the GDP per capita and health care spending per capita.

- Finally, in the United Kingdom, IMS data also only capture hospital sales. While this may not be a major problem in countries like Portugal (see above), dispensing in the UK does take place in primary care as well, including home delivery to patients. We have therefore added the data from the NHS primary care prescription statistics 2007 for England (http://www.ic.nhs.uk/statistics-and-data-collections/primary-care/prescriptions/prescription-cost-analysis-2007), adjusted to the United Kingdom and extrapolated for the year 2008 using growth rate in the hospital prescriptions data from IMS. Nevertheless, our numbers have to be considered with caution, as it is possible that not all sales are captured within the two data-sets used.

Table 3-1 – Adjustments made to IMS dataset

Country	*Reason or data source*	*Adjustment*
Cyprus	No data	Imputation of Portuguese data
Estonia	Incomplete hospital sales	None
Greece	No hospital sales	Imputation of Portuguese data
Iceland	No data	Imputation of average sales in Denmark, Sweden, Finland
Ireland	Incomplete hospital sales	None
Luxembourg	Incomplete hospital sales	None
Latvia	Limited data	None
Lithuania	Limited data	None
Malta	No data	Imputation of Portuguese data
Portugal	Only hospital data for 2007/8	None
United Kingdom	Hospital sales only	Complemented with NHS primary care prescription data

Another difficulty may arise from parallel trade. Although drugs launched in the last two decades have generally a rather narrow price band across Europe, traditional price control mechanisms, adaptation to distribution channels and currency fluctuations may have led to some price differences. As the price of biologic treatments is comparably high, even small differences make parallel trade worthwhile.

Theoretically, IMS corrects for parallel trade, but is obviously depending for this on reporting. It is thus difficult to say how accurate the corrections are. However, in a previous report on Rheumatoid Arthritis we have approached the issue by verifying the data from Norway where parallel export was known to exist. Data from Farmastat (that collects sales from wholesalers who are legally obliged to exclude parallel export) were found to be very similar to those reported by IMS.

We therefore accepted that IMS data are a solid source in most countries for international comparison purposes, with the exception of the data for the United Kingdom.

3.2.2 Treatments

3.2.2.1 *Use*

Four of the five currently available biologic treatments for MS were initially introduced in Europe between 1995 and 2002 (see table below). One treatment was introduced recently, but due to a severe (but rare) adverse effect has been indicated only for patients with "breakthrough disease" (patients with relapses despite biologic treatment) or patient intolerant to standard biologics.

All five drugs have been licensed for relapsing-remitting or relapsing progressive disease. Betaferon has also been approved in secondary progressive MS as well, but the data is weak as only one clinical trial has shown an effect in secondary progressive MS. None of the drugs is licensed in primary progressive MS.

More recently, Avonex and Betaferon have been approved for use in patients with a first clinically isolated symptom (CIS) indicative of MS, with the objective to delay the onset of clinically definite MS. There is an ongoing discussion whether CIS should be defined as MS as well, which would mean that our prevalence figures may be slightly underestimated.

Table 3-2 Year of first introduction in Europe (EMEA approval)

	RRMS	SPMS	CIS
Avonex	1999	-	2005
Betaferon	1995	1999	2006
Rebif	1998	-	-
Copaxone	2001	-	-
Tysabri	2006	-	-

3.2.2.2 *Prices*

Most MS drugs were introduced prior to the expansion of the EU to include Central and Eastern European countries, and we can thus observe that a certain level of price discrimination has taken place. Indeed, prices are considerably lower in most Central and Eastern countries compared to the old EU markets. The annual ex-factory cost per patient ranges from €6500 in Estonia to €15,000 in Germany. End-user prices may show a different relationship, as wholesale and retail margins differ among countries. However, biologics in many countries doe not follow standard distribution channels, but this information is not available in standard data sets such as IMS.

Table 3-3 Average weighted price / year in old and new EU countries

Countries	*Average annual cost (ex-factory price) 2008*
Western Europe *Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom*	**€ 11,950**
Central and Eastern Europe *Bulgaria, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Slovakia, Slovenia*	**€ 9,830**

Today, clinicians have thus a considerable number of well-used treatments at their disposal that have a similar price within most countries and a similar effectiveness, but differ somewhat in their adverse effect profile (flu-like symptoms, neutralising anti-bodies, injection site reactions). The latest drug introduced (Tysabri) has shown the strongest clinical efficacy, but due to its rare but severe side-effect (PML) can only be used when other drugs fail. Also, Tysabri requires infusion rather than self-injection. The choice of which drug to use first, and in what sequence further drugs should be used, is thus rarely influenced by the price but remains with the clinician and patient. Clinicians are likely to give a high level of importance to the side-effect profile, while patients may be willing to accept a higher risk. Finally, the amount and type of services provided by the manufacturers may also play a role in the treatment selection.

3.3 Results

We first present estimated sales per product in 2008 and estimated market shares in the 4th quarter 2008 using sales per prevalent patient. For completeness, we also present estimated total sales per 100,000 population by individual country. Finally, uptake curves over time in the different markets are presented.

3.3.1 Sales and Market Share

Table 3-4 Estimated sales in € 2008 (ex factory prices) based on IMS data

	Estimated sales € 2008 millions	*Estimated Market Share 2008 (sales)*
Avonex	974,000	24%
Betaferon	823,000	20%
Copaxone	772,000	19%
Rebif	1,115,000	27%
Tysabri	427,000	10%

Figure 3-1 Estimated market shares (using sales in € per prevalent patient)

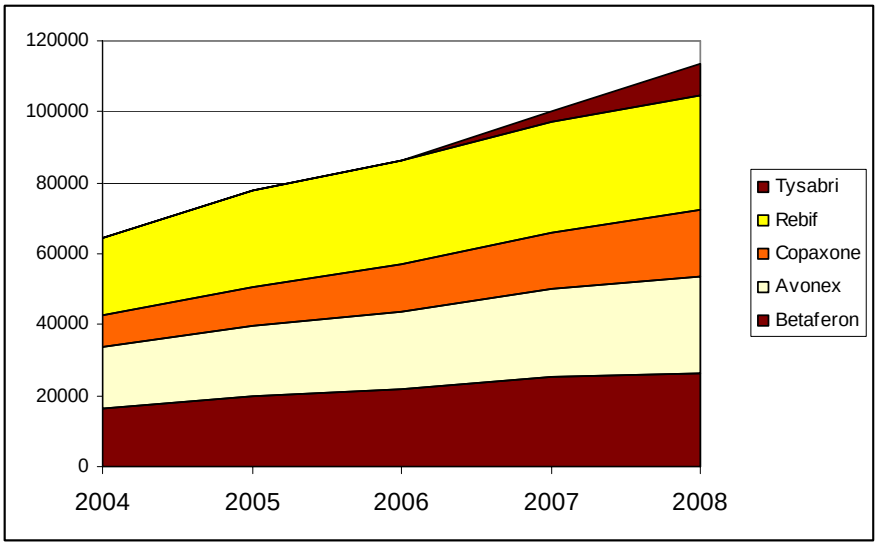
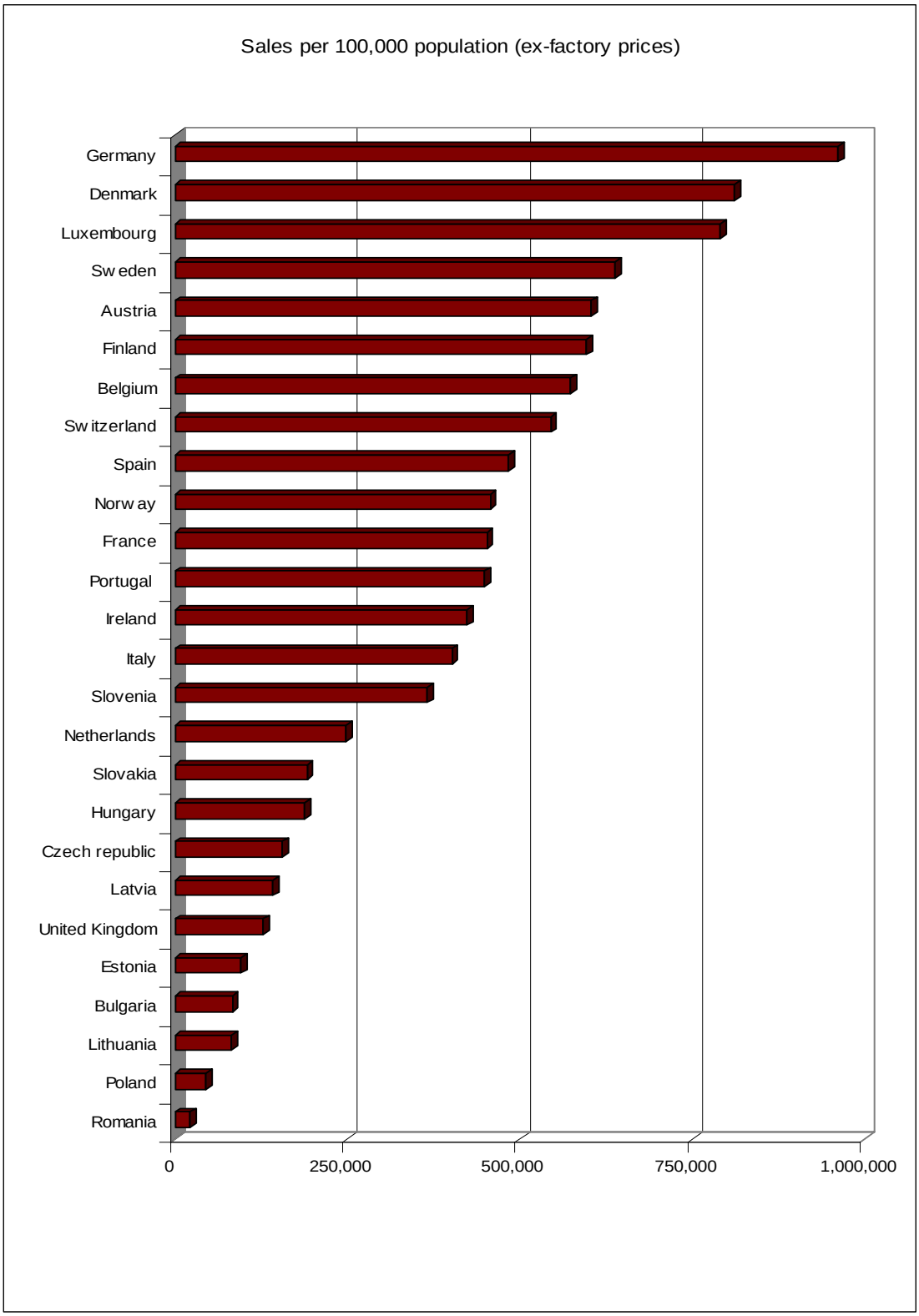


Figure 3-2 Estimated sales (2008 €) per country (per 100,000 population)



3.3.2 Uptake of Treatments

Uptake curves are based on three main inputs: drug quantities sold (units, mg or I.U.), total sales and prevalent patients. Results are presented as

- total number of patients estimated on treatment
- sales per prevalent patient
- proportion of patients on treatment
- sales per 100,000 population

The number of patients on treatment was calculated, using the absolute number of units sold of each drug and the dosage in the label and verified against mg or I.U.
Sales per prevalent patients were calculated from the absolute sales in Euro applied to the prevalence numbers estimated in chapter 1 of this report. If prevalence is found to be different, the numbers will change.
The proportion of patients on treatment was estimated using the above results compared to the annual treatment cost in each country.
Finally, sales per 100,000 population was estimated using absolute sales in each country compared to the population. This elilminates any uncertainty inherent in our prevalence calculations.

For this calculation, we have assumed full treatment years. The actual number of patients who have access to biologics is therefore probably somewhat higher, as patients may be off treatment for some months (e.g. between treatment switches), or even be treated intermittently.

We illustrate below these calculations for the five big markets. Subsequently, we will concentrate on the absolute number of patients and the proportion of prevalent patients on treatment. E13 represents the average for the old EU12 countries plus Norway and Switzerland, but excluding Portugal (for which only 2008 data were available): Austria, Belgium, Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Spain, Sweden, Switzerland, United Kingdom.

The average cost per patient estimated here has been adjusted for estimated total cost of biologics (including estimated infusion costs for Tysabri) into our cost model in chapter 2. (However, it is important to remember that these costs were estimated as ex-factory costs, without additional margins. As these drugs are mostly hospital products, actual sales prices by country are not available. But margins are likely very small. Nevertheless, it is possible that the cost of biologics per patient is somewhat underestimated in chapter 2.)

3.3.2.1 *The 5 Large Markets (illustration of calculations)*

Figure 3-3 Estimated total number of patients treated (5 large markets)

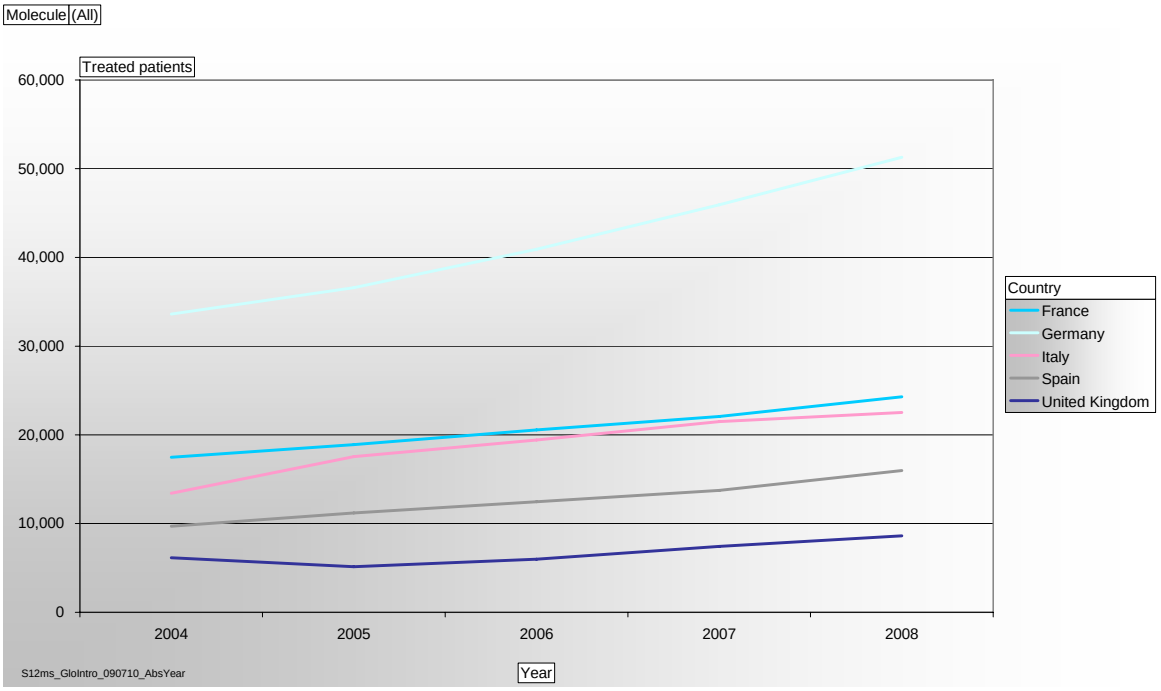
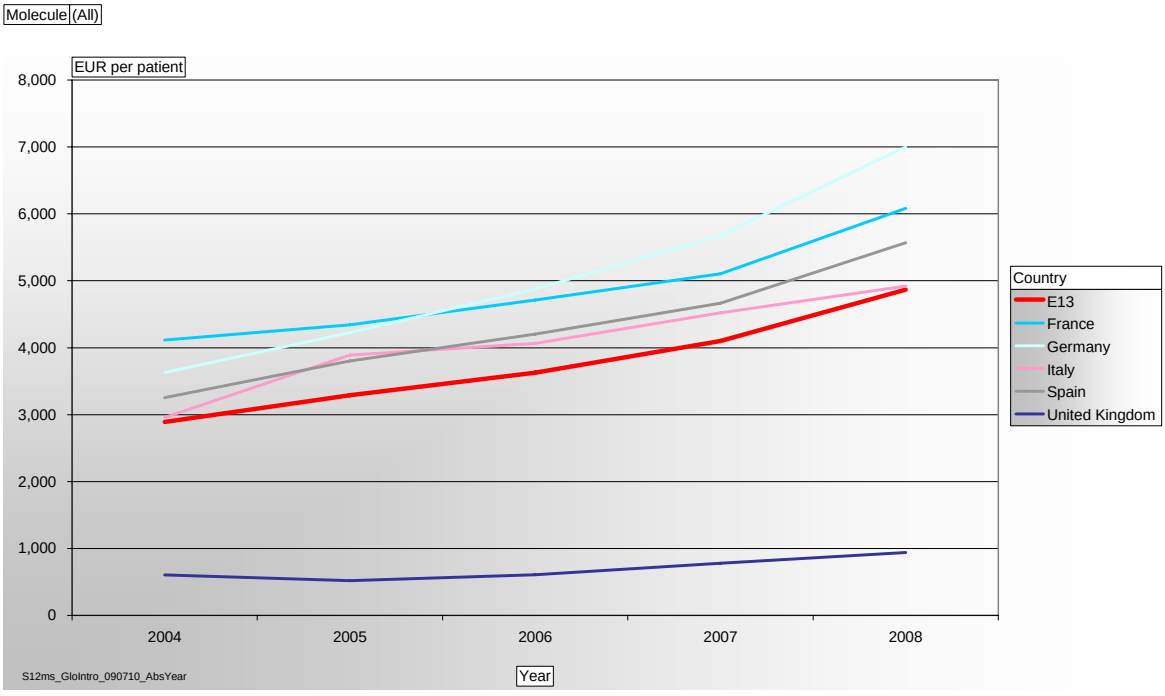
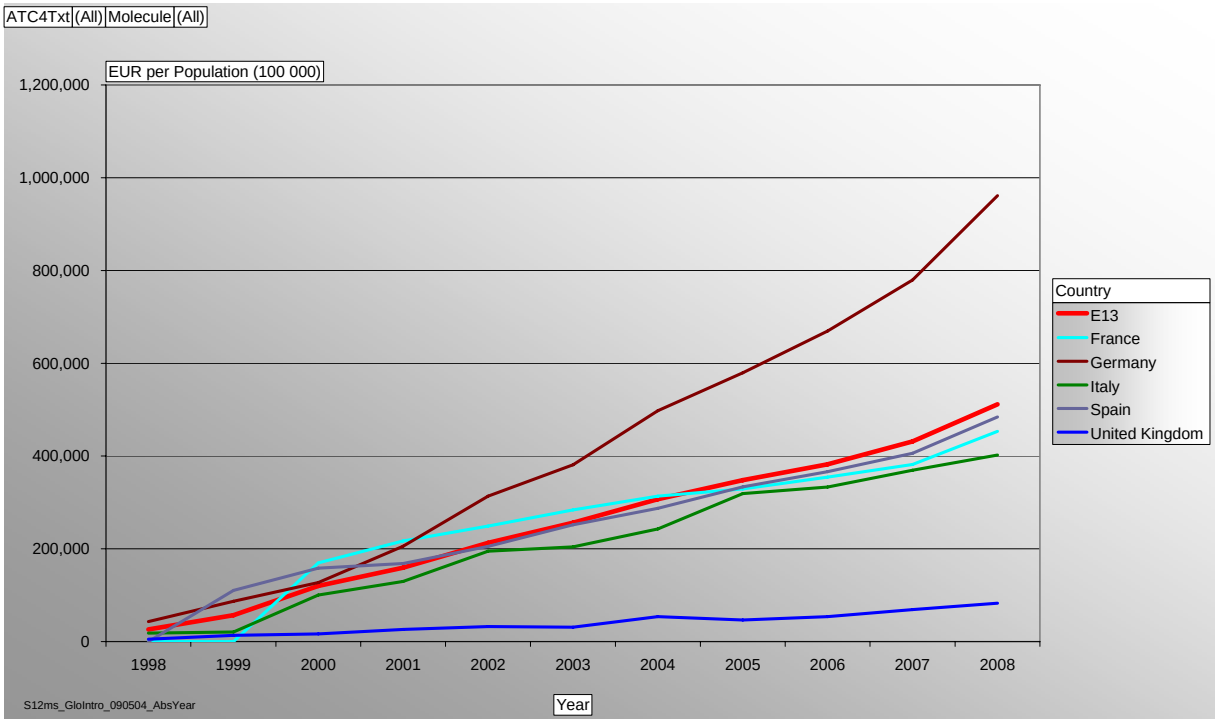


Figure 3-4 Estimated annual sales (€ 2008) per prevalent patient (5 large markets)



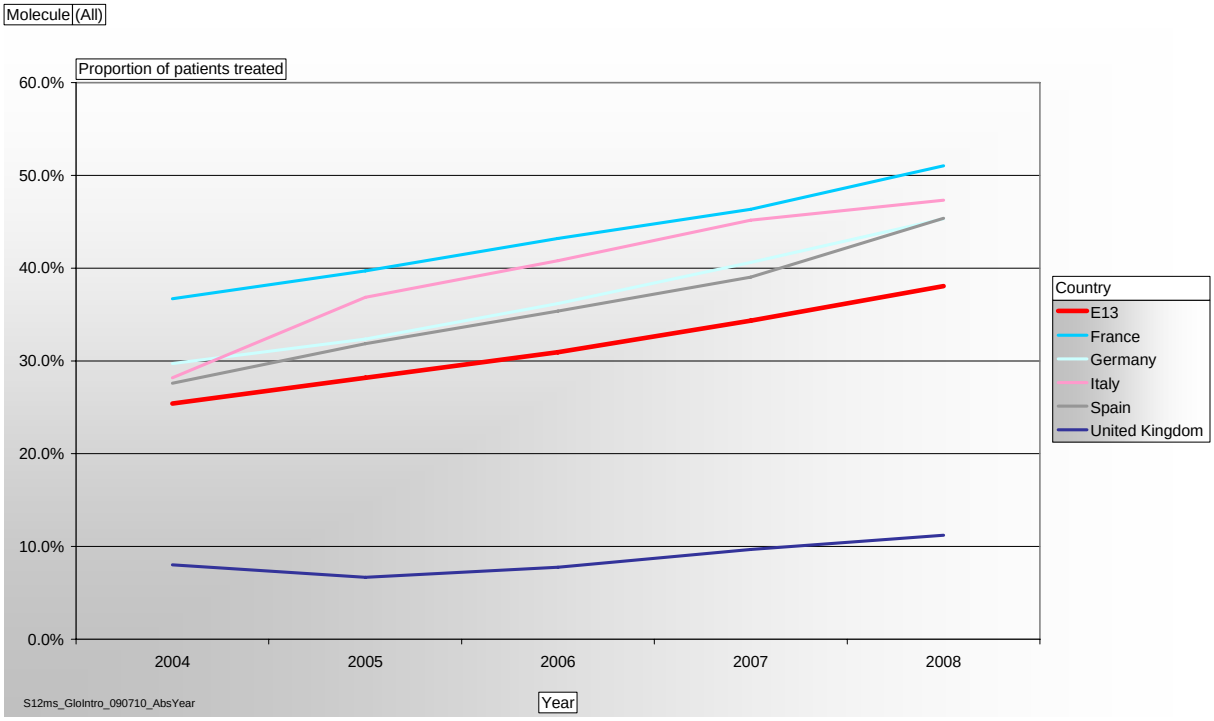
E13 = Western European markets

Figure 3-5 – Estimated annual sales per 100,000 population



E13 = Western European markets
Only IMS data for the United Kingdom (hospital sales)

Figure 3-6 Estimated proportion of patients on treatment*



** assumes 12 month treatment for all patients*
E13 = Western European markets

The 4 types of analyses can be interpreted as follows:

- The absolute number of patients does not provide any direct comparison, as populations and prevalence differ between countries. Rather, they provide interesting information for the individual countries. Nevertheless, some interpretation is possible: France, Italy and the United Kingdom have similar populations around 60 million, yet the number of patients treated in France and Italy is much larger than in the United Kingdom. Spain with a population of around 45 million has as expected around 25% less patients on treatment. Germany with a population of around 85 million would be expected to have around 40% more patients than e.g. France, but has twice as many. This is explained by almost twice the prevalence estimated for Germany compared to France, Italy and Spain. We can thus conclude that access is similar in France, Germany, Italy and Spain, but vastly inferior in the United Kingdom. Indeed, with a similar (or even higher) prevalence than Germany, similar access as Germany in the United Kingdom would mean that 33-40,000 patients should be on treatment rather than slightly less an estimated 8500-9000.

- The curves of estimated sales per prevalent patient add the price dimension and corrects for prevalence. The interpretation leads to similar conclusions as above. Ex-factory prices (unweighted averages of all products) in France and Spain are about 20% and in Italy about 30% lower than in Germany. Taking this into account, we can again see that these 4 markets have similar usage: Italy spends around 30% less than Germany per prevalent patient, Spain around 20% less and France around 15% less. Thus, access appears best in France. Spending in the United Kingdom is as above substantially lower, but here the results are heavily influenced by the recent devaluation of the British Pound versus the Euro. Indeed, the current average price is only around 55% of the German price in Euro. Adjusting for this would however still mean that the UK should spend around €3500-4000 per patient rather than around €1000.

- The same results emerge from the calculations of the sales per 100,000 population. Note however that for this calculation, IMS data have not been adjusted.

- The curves of estimated proportions of prevalent patients on treatment corroborate the interpretation of the previous curves. Germany, France, Italy and Spain are very comparable, at between 40% and 50% of prevalent patients, with France having the best access among the four. A further interpretation that can be added is that in the 4 markets, the vast majority of patients with relapsing-remitting disease (estimated at around 50-60% of patients) are on treatment. The United Kingdom falls way behind with only around 11-12% of patients on treatment.

In the following, we will show uptake of the different treatments in these 5 markets as an illustration.

3.3.2.2 *Uptake of individual treatments*

Figure 3-7 – Uptake of Avonex (5 large markets)

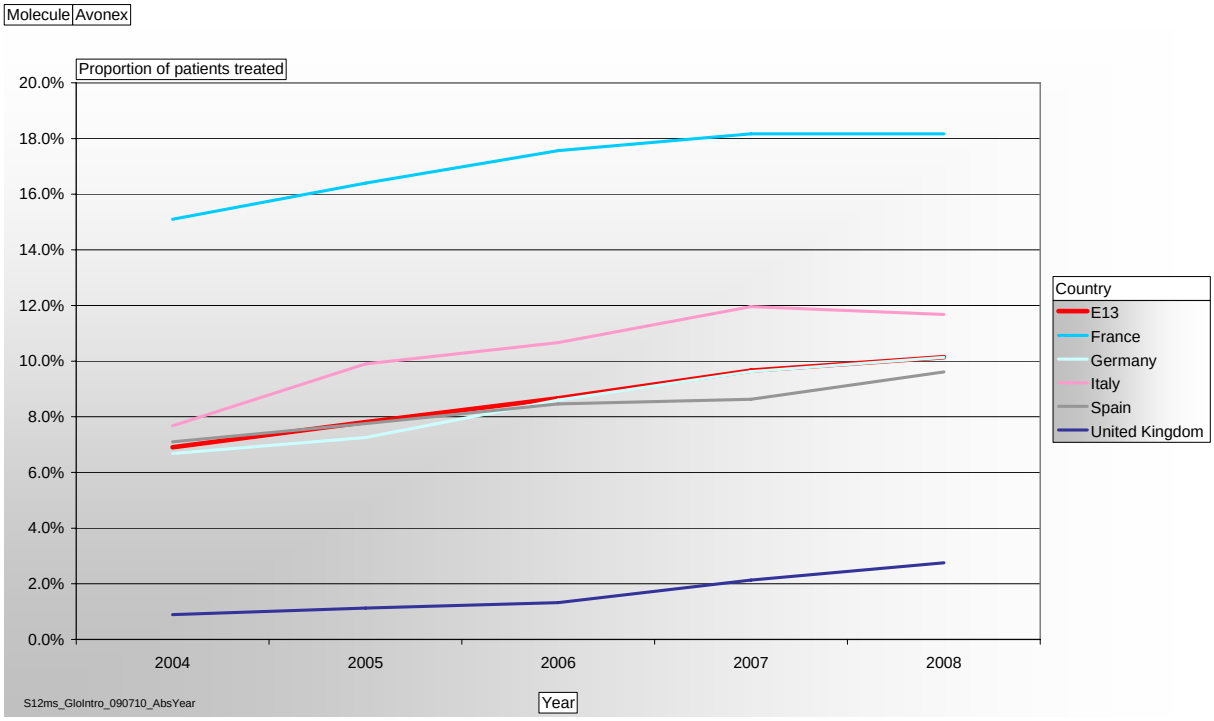


Figure 3-8 – Uptake of Betaferon (5 large markets)

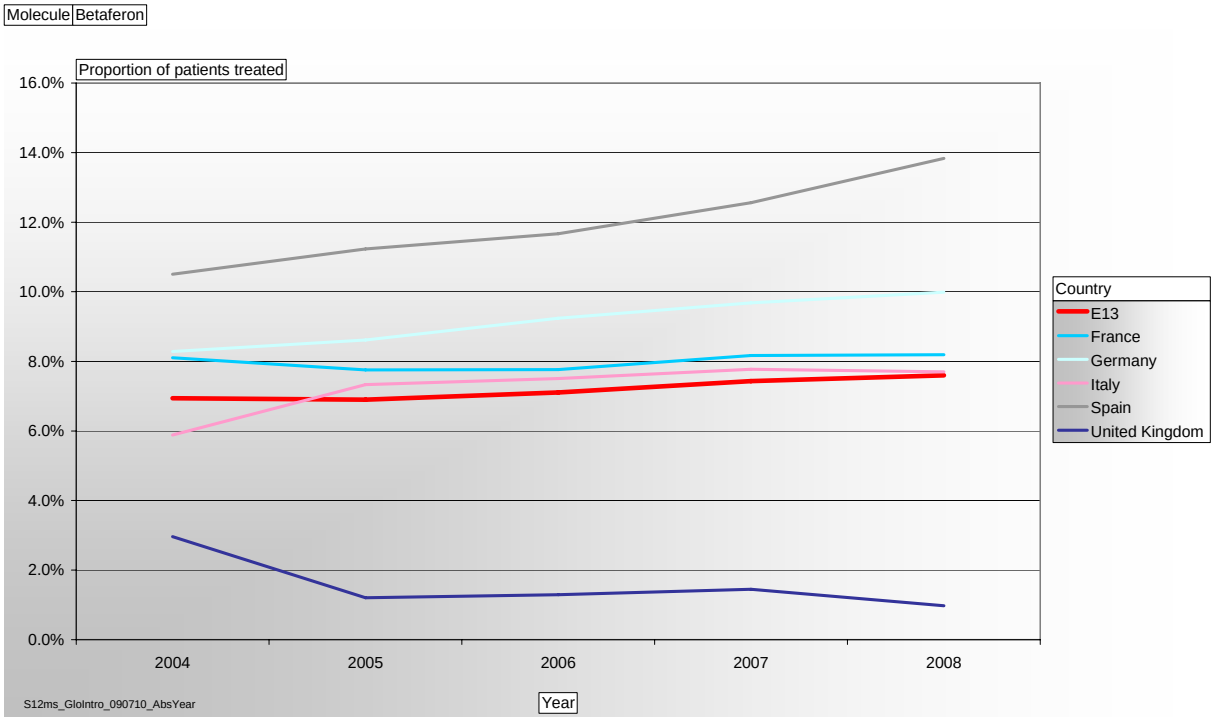


Figure 3-9 – Uptake of Copaxone (5 large markets)

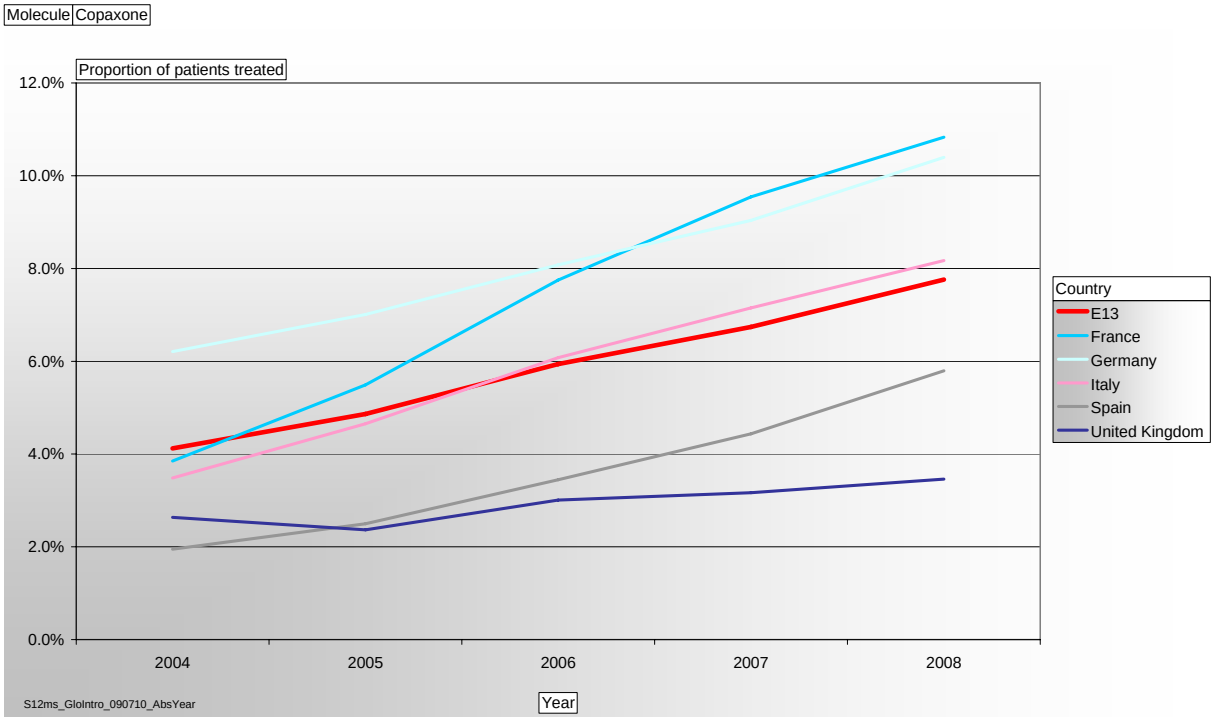
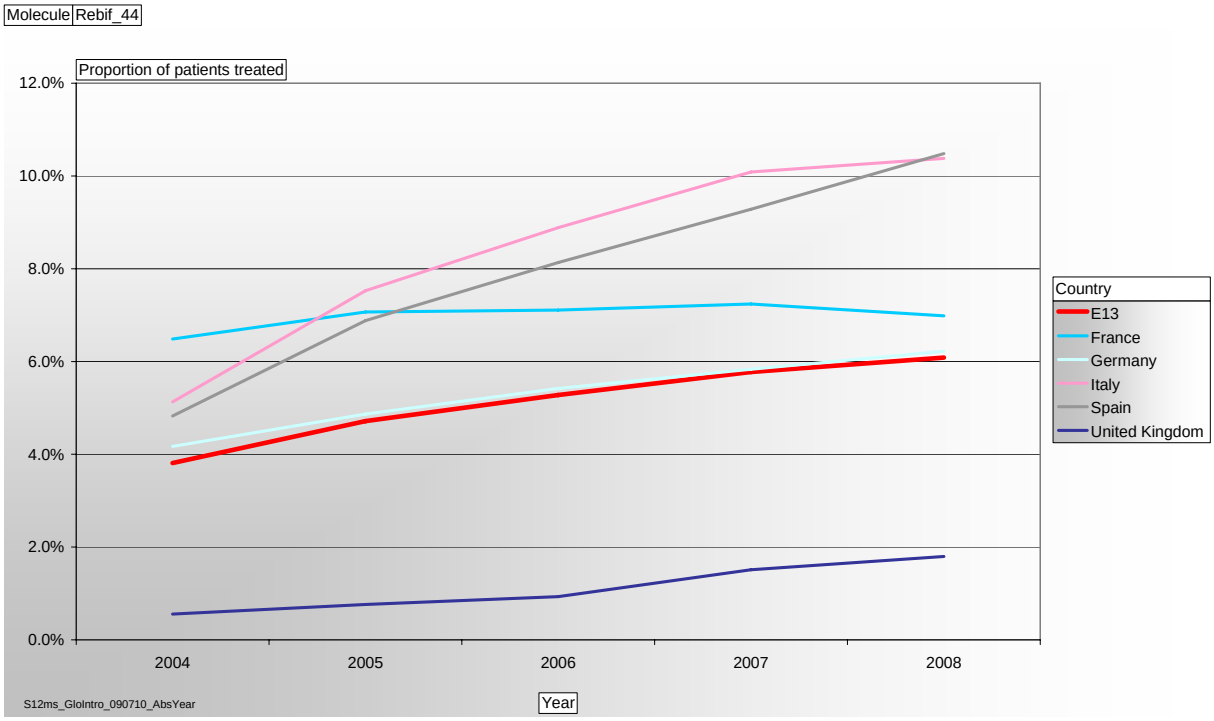
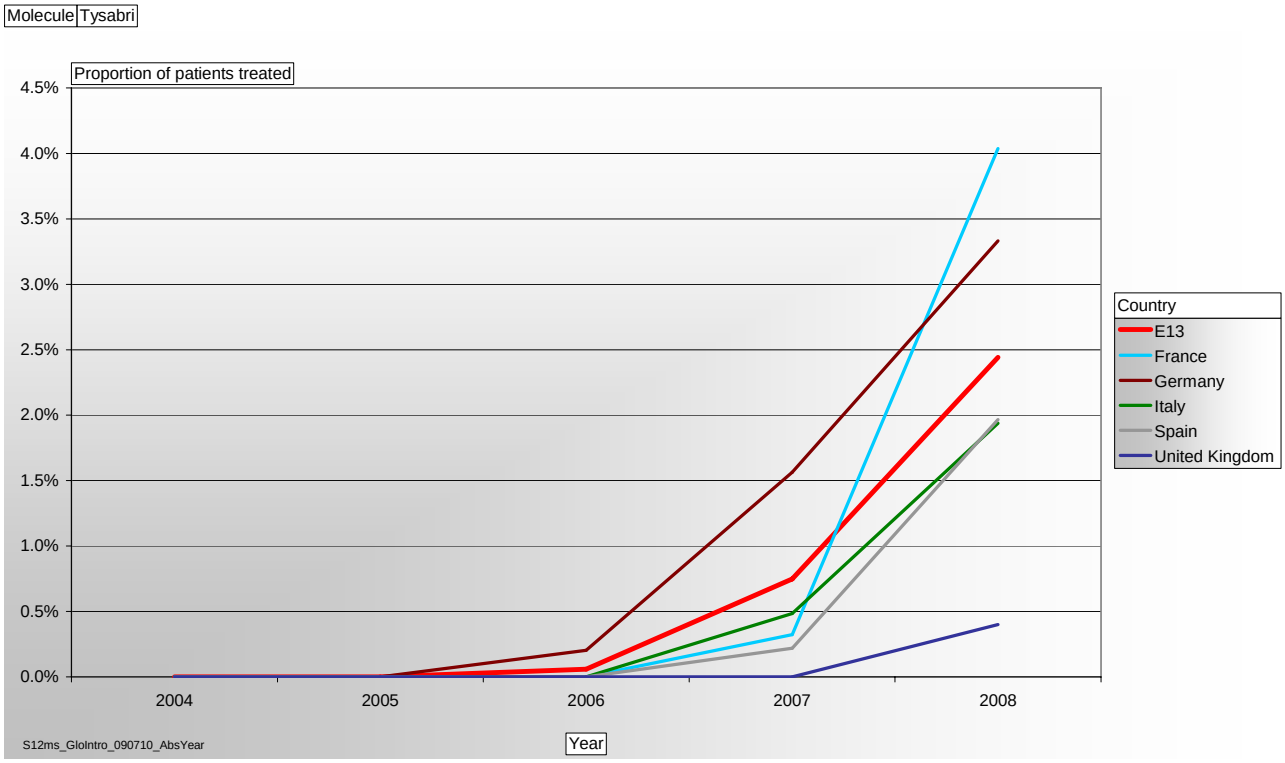


Figure 3-10 – Uptake of Rebif44 (5 large markets)



Note: Although separate data for both Rebif22 and Rebif44 were used for all the calculations, we only show detailed data for Rebif44. EU13 usage for the two dosages combined reaches 10%, with Italy using most of Rebif22.

Figure 3-11 – Uptake of Tysabri (5 large markets)



From these details we can see that

- France uses predominantly Avonex and Copaxone, with Tysabri increasing very rapidly immediately after reimbursement. This confirms what has been seen in other areas with effective and innovative drugs, i.e. that France has very few restrictions to usage for this type of treatment.
- Spain has a preference for Betaferon and Rebif, while the other three treatments are at or somewhat below the EU13 average.
- Italy has a clear preference for Rebif, followed by Avonex, with the other three treatments being used at around the EU13 average.
- Germany is at or above the EU13 average for all 5 treatments, but appears to use Copaxone to a large extent.
- The United Kingdom appears to have some preference for Copaxone and Avonex.

In the following, for the smaller markets, we will only present the total number of patients estimated to be on treatment in the different countries and the proportion of prevalent patients on treatment. This eliminates the direct influence of price differences on the up-take curve – although the influence of price on uptake is obviously still underlying the results. This will be analyzed further in the next chapter.

3.3.2.3 *Nordic Area, Ireland*

These markets have a similar prevalence of MS and can thus be compared.

Figure 3-12 Estimated proportion of patients on treatment (Nordic Area)

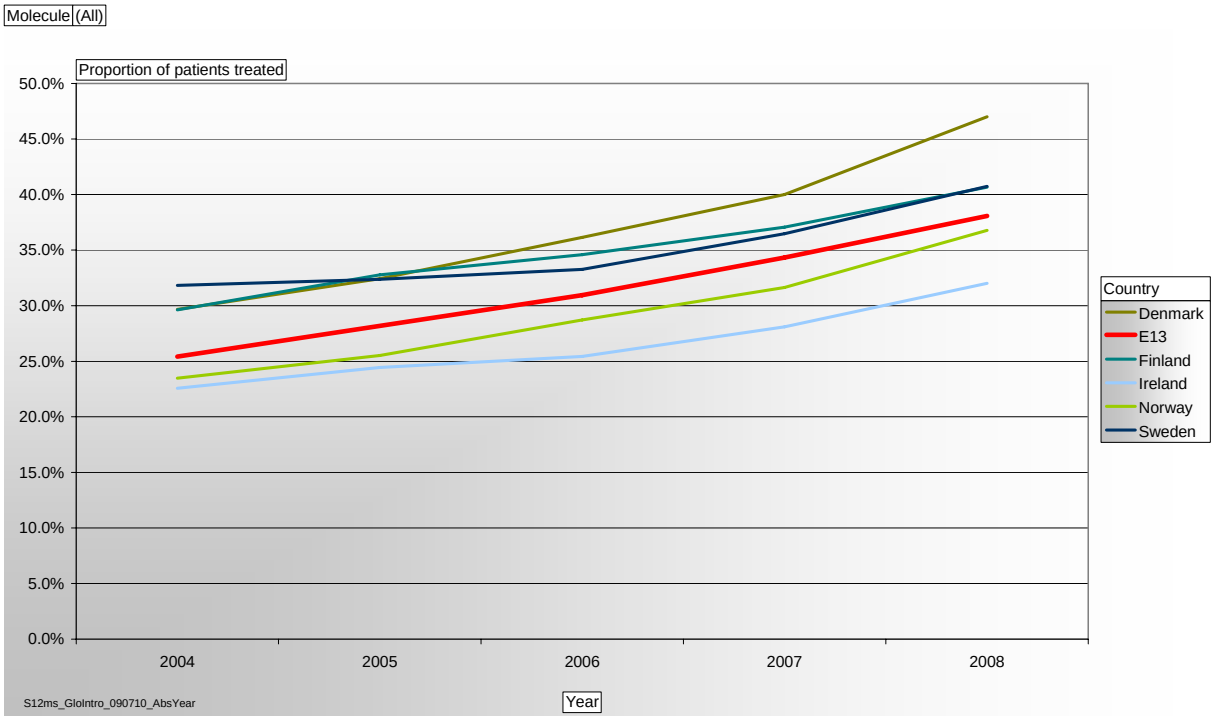
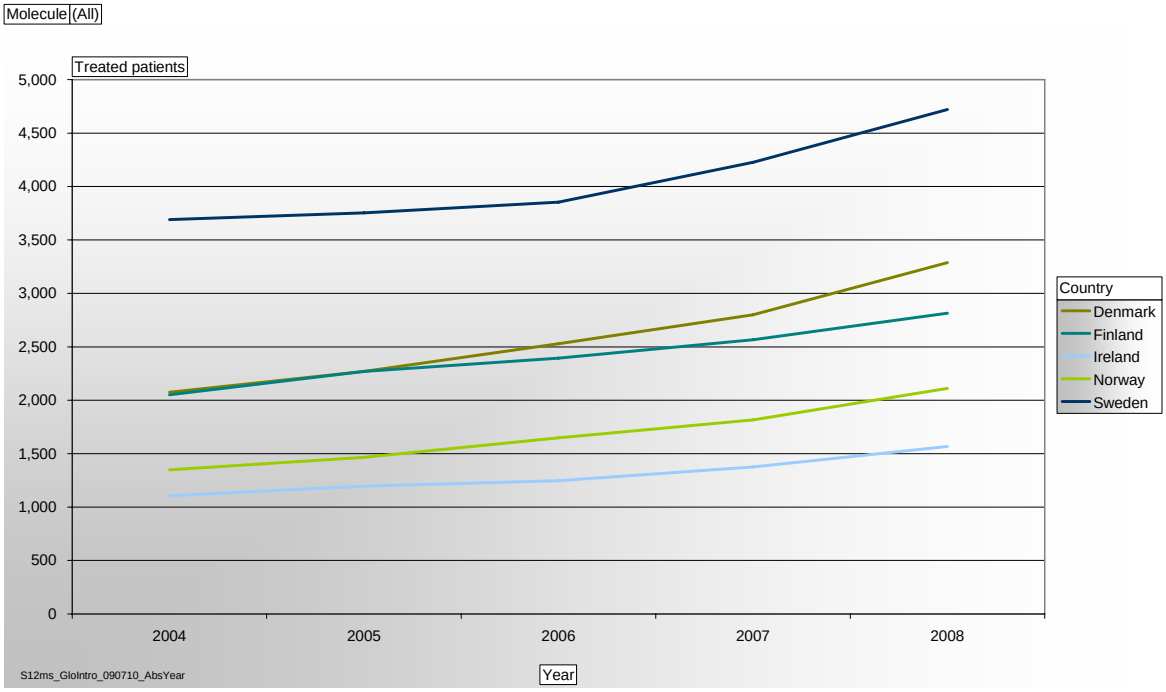


Figure 3-13 Estimated total number of patients treated (Nordic Area)



3.3.2.4 *Small Western European Countries*

Again, these markets have a similar prevalence of MS and can thus be compared.

Figure 3-14 Estimated proportion of patients on treatment (small W.European markets)

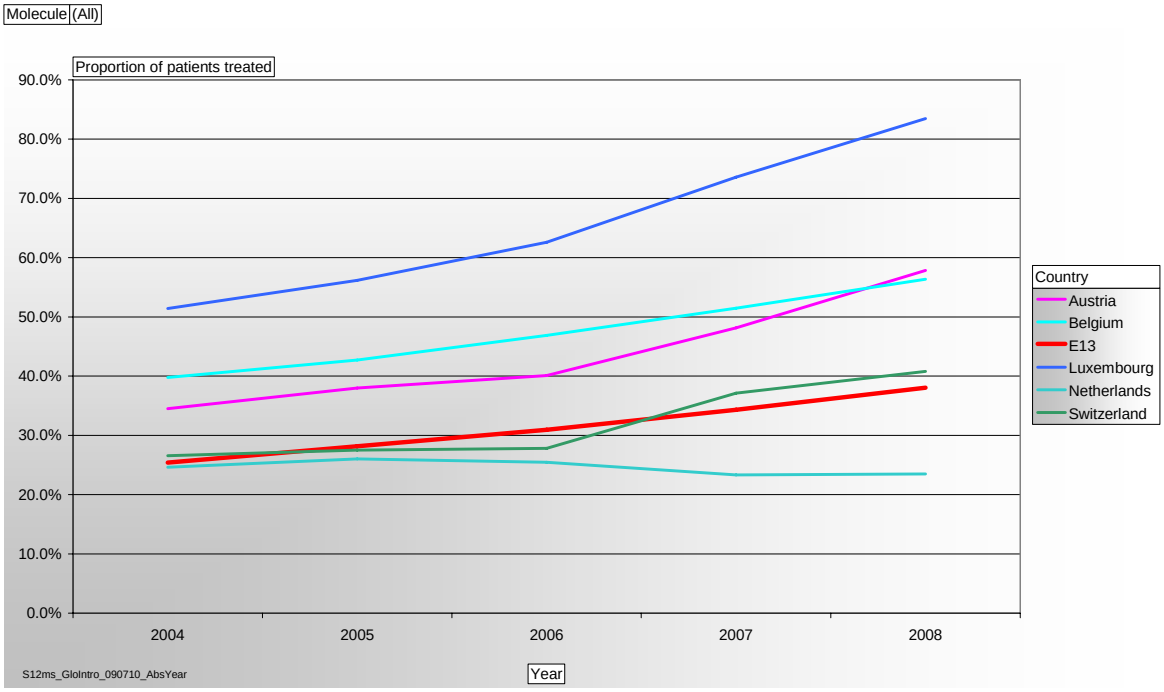
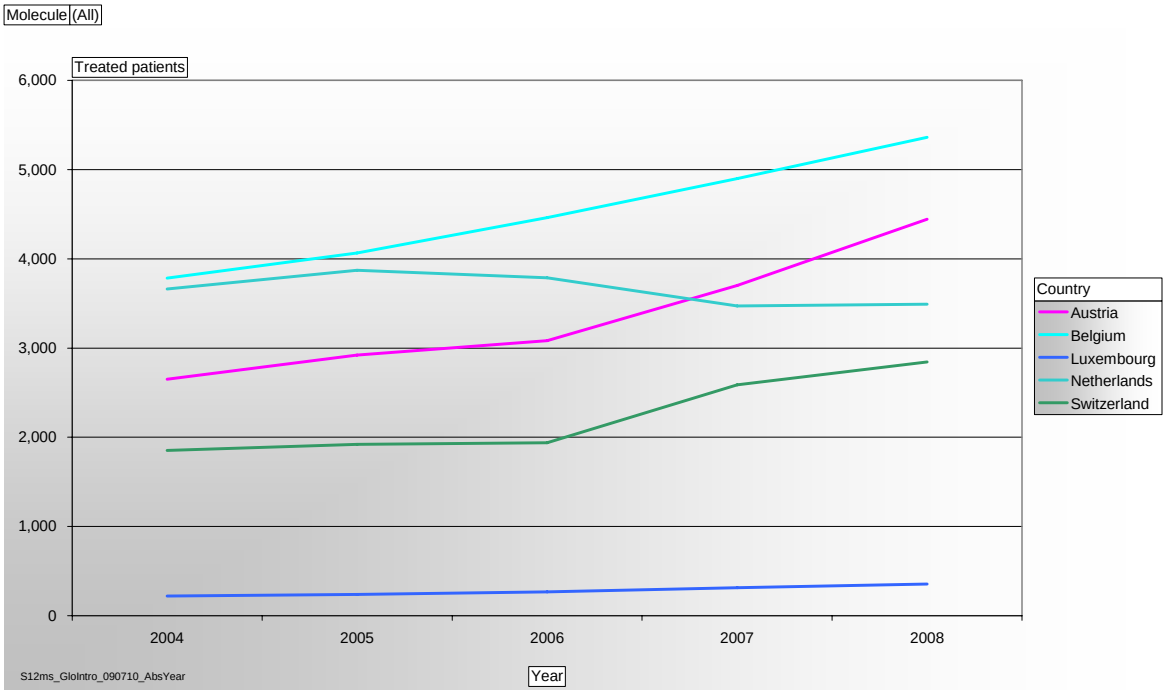


Figure 3-15 - Estimated number of patients on treatment (small W.European markets)



3.3.2.5 *New EU member states*

The Baltic States have been excluded due to incomplete data.

Figure 3-16 Estimated proportion of patients on treatment (selected new EU countries)

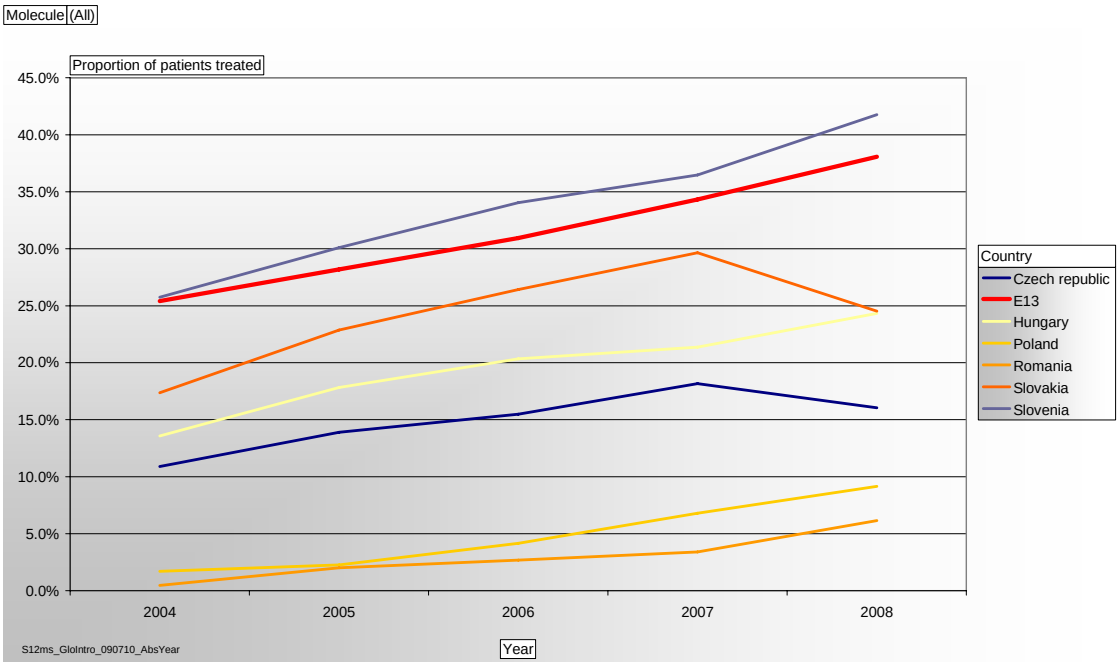
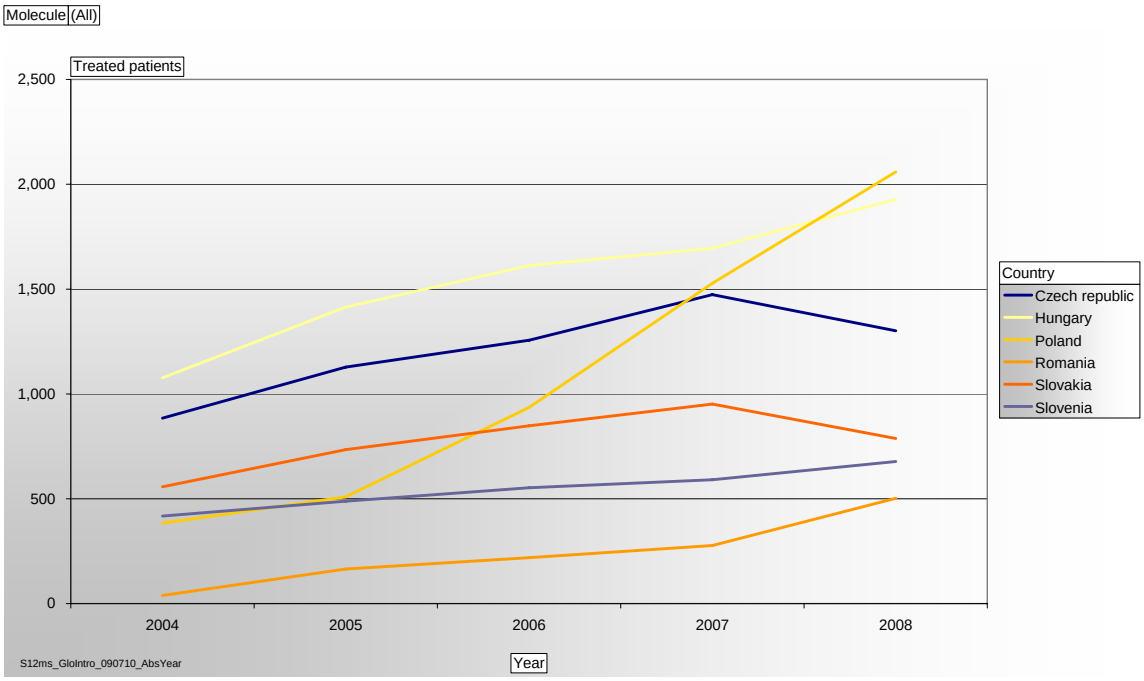
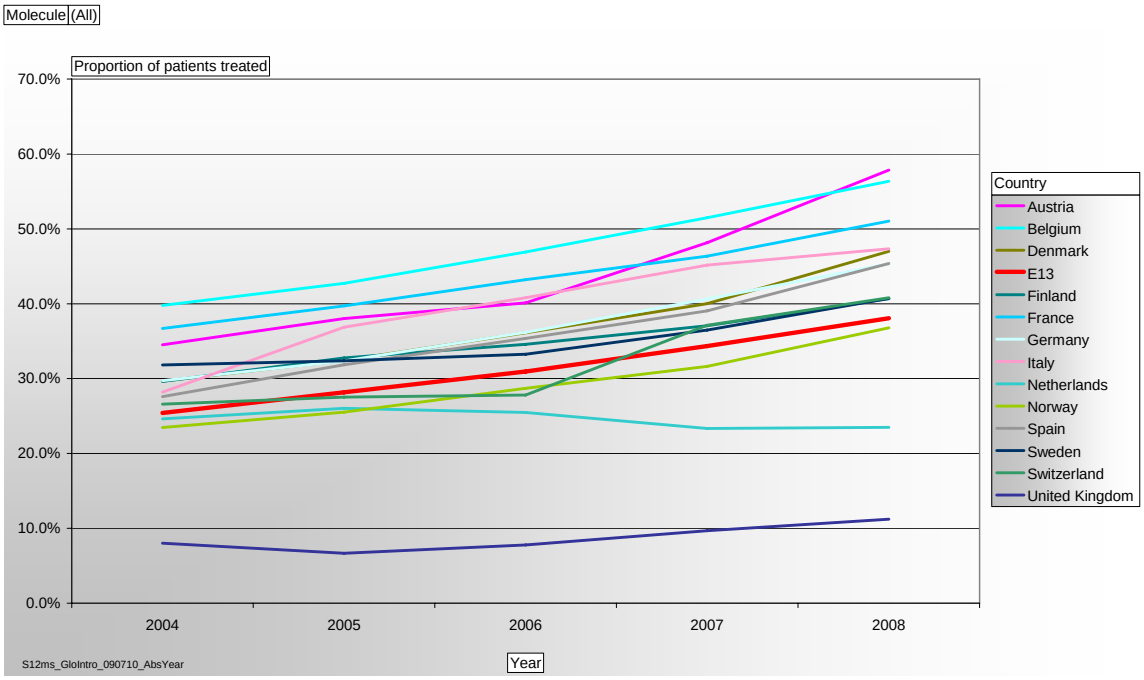


Figure 3-17 Estimated number of patients on treatment (selected new EU countries)



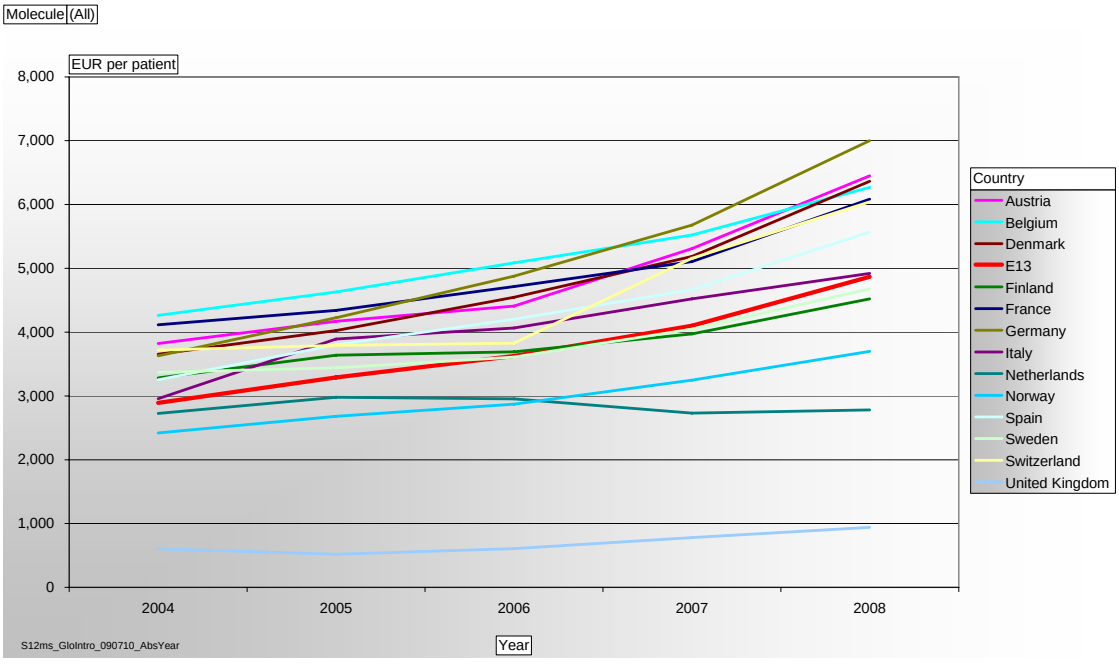
3.3.2.6 *Comparison of E13 countries*

Figure 3-18 Proportion of patients on treatment in E13 countries



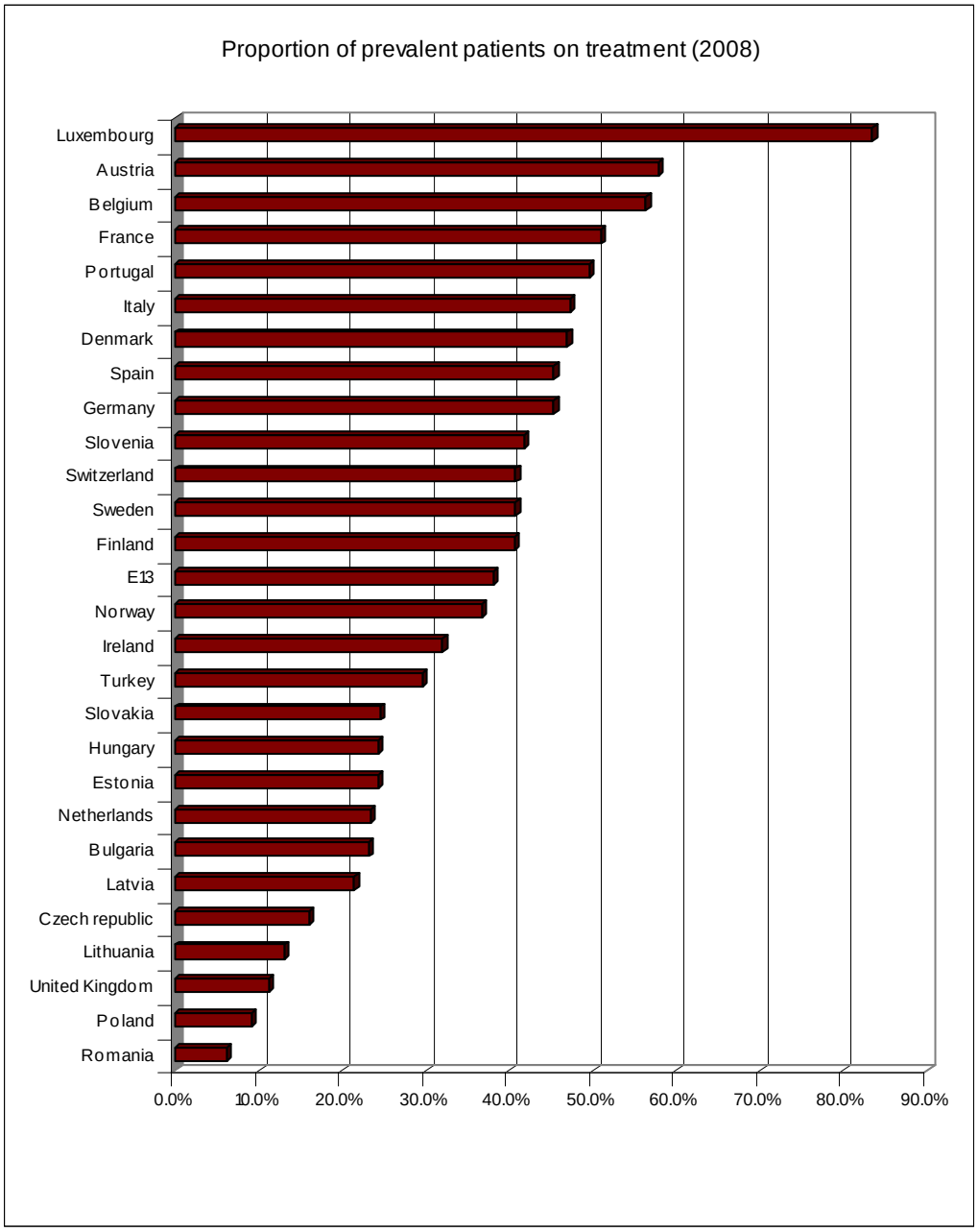
Usage in most of the EU13 countries lies between 40-50% of patients on treatment, above the EU13 average. Norway is slightly below average and the Netherlands appear the most conservative (with the obviously exception of the United Kingdom). The Dutch data confirm what was earlier found in a European study on the cost of MS (Kobelt et al, JNNP 2006;77:918-26; see also chapter 2).

Figure 3-19 – Sales per patient (€ 2008), E13



3.3.2.7 *Proportion of patients treated across Europe*

Figure 3-20 Estimated proportion of patients on treatment end of 2008



For these calculations, we have used our own prevalence estimates. When changing prevalence according to published studies (essentially in the Central and Eastern European states, with only small adjustments in Western Europe), overall results and ranking of countries do not change. Front runners remain Luxembourg, Austria, Belgium, France and the lowest usage is in Rumania, Poland, the United Kingdom and Latvia.

3.4 Conclusion

In order to compare access to biologic DMTs in Europe in the absence of actual data on the number of patients on treatment, the following information is required:

- prevalence data
- sales data
- drug prices.

Neither of these datasets was readily available, and we have based our estimates on the following methods:

- Prevalence has been re-estimated using age adjustments and country clusters, to overcome the fact that prevalence studies are old, diagnostic criteria have changed and data are often inconsistent.
- Sales data were available both as volume (units) and value (Euro) from IMS, and with a number of adjustments, these data have been used.
- We have also derived the manufacturing price from the IMS data set; end-user prices were not used, as biologics are distributed through special channels in many countries and wholesale and pharmacy margins can not be applied.

Drug uptake presents the expected influence of the economic wealth of European countries, despite price discrimination resulting in lower prices in Eastern Europe. Within the old EU country group, usage appears relatively similar (with the exception of the United Kingdom). In our estimates, 40-50% of patients are on treatment, but this number has to be seen in the light of our prevalence estimates.

Chapter 4 - Determinants of Access

CONTENT

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FIGURES

4 Determinants of access to treatment in MS

4.1 Summary

An important determinant for access and reason for restrictions in the use of the biologic treatments has been their cost and impact on health care budgets. This chapter discusses the importance of economic factors in the reimbursement and prescription of biological treatments for MS patients, as well as other factors that influence usage and lead to different use among countries

The largest differences in access to innovative drugs are the consequence of a price fixed globally for the drugs and differences in wealth among countries in Europe. Thus, we observe difference in affordability, access and usage between Western Europe and the new EU member states. Health technology assessment studies and economic evaluations also have to be seen in front of this background. A treatment at an annual cost between €10-15,000 will lead to different cost-effectiveness results in countries where the average total annual cost of the disease for a patient ranges from less than € 6,000 to over € 60,000 per year. Lower cost off-sets and thus higher cost-effectiveness ratios in countries with lower income and health care spending are not the only factors. The threshold value, i.e. what a country can spend on innovation is also lower in these countries.

In multiple sclerosis (MS), the difference between old and new EU member states is somewhat attenuated, as prices for MS treatments were in part established prior to the EU enlargement and consequently are lower in many of the new member states than in Western Europe. Despite of that, the proportion of patients on treatment is less than half of that in Western Europe.

When the biologic disease modifying MS treatments (DMTs) were first introduced, their high price led to considerable debate. The benefit of treatment being long term and thus difficult to establish in clinical trials, questions regarding the effectiveness of these treatments were raised. Early economic evaluations ranged from less than € 10,000 to over € 1 million per quality-adjusted life-year (QALY) gained, depending on perspective, time horizon, clinical trial and study concept. But while most countries had protracted reimbursement discussions, all countries allowed treatment for patients with relapsing-remitting disease on the health care budget.

Beyond the economic factors, access to treatment is defined by medical practice, but also the ease of access to care and availability of care. For instance, some countries have lengthy referral processes to specialists that can lead to late diagnosis and treatment. Other factors that influence usage are, among others, prior approval requirements, limitations in prescribers of biologics and institutional or practice budget limitations or caps. Our data suggest however that these hurdles have largely disappeared and differences among countries with similar economic conditions are small.

Proof of the cost-effectiveness of DMTs in clinical practice is still not available, as the major benefit comes from slowing disease progression. Modelling remains the only possibility to estimate the value for money of the investment. However, modelling can include clinical practice data from registries and long-term follow-ups from clinical trial, and some information is emerging.

4.2 Introduction

When disease modifying MS drugs (DMTs) were first introduced, their price – compared to their apparent benefit in clinical trials – appeared high and prompted an intense debate whether investment in these treatments represented an efficient use of public resources.

Initially hospital drugs, they are used to a large extent in an outpatient setting. In countries with a public reimbursement for drugs, this means that inclusion in the reimbursement system is a very important criterion for funding of, and access to, the treatments. The reimbursement systems for drugs and the criteria for reimbursement have seen a rapid change in many countries during the last two decades, with costs and value for money becoming more important factors for reimbursement. Cost-effectiveness has emerged as an additional criterion to fulfil before a new drug reaches the market, alongside clinical safety, efficacy, effectiveness and quality that are requirements for marketing approval by the EMEA and national Medicine Agencies.

Although reimbursement decisions were made after protracted negotiations in most countries, the treatments were approved without many restrictions for relapsing-remitting MS. There are likely two main reasons for this: The absence of any treatment other than symptomatic interventions, a clearly defined population with a relatively low prevalence (0.05-0.1%) and hence a limited budget impact of treatment.

Under these circumstances, the treatments gained good access and we estimate that currently between 40-50% of patients in Western European countries are under treatment: The estimated number of treated patients 165-170,000 of a diagnosed prevalence of 410,000 patients. In Central and Eastern Europe the uptake is between 5-25% (with the exception of Slovenia where more patients are on treatment), and affordability remains an issue despite lower prices.

Thus, with the exception of the case of the United Kingdom, differences in uptake of MS drugs are essentially related to the different income per capita (GDP) in the different parts of Europe. Drugs are competing in a global market, and in particular in the EU with free movements of goods, they are priced within a more or less narrow price band to avoid parallel trade. This de facto makes it difficult for countries with a lower GDP to afford innovative treatments and creates large differences in access.

4.3 Affordability

For this analysis, we first established relative prices and relative expenditure per capita, using Germany as an index of 100 in both cases. Comparing the two provides an index on how well biologics at the given price can be taken up within the health care budget. A higher index indicates more difficulties to afford.

From these calculations, we can as expected see clearly that Western Europe can better incorporate these treatments into health care expenditures, by a factor of two to three. Germany at an index of 100 has one of the highest indexes in the old EU countries, as a consequence of a relatively high price.

Compared to e.g. Rheumatoid Arthritis (RA), the difference between old and new EU countries is smaller in MS, as a consequence of lower prices in Eastern Europe

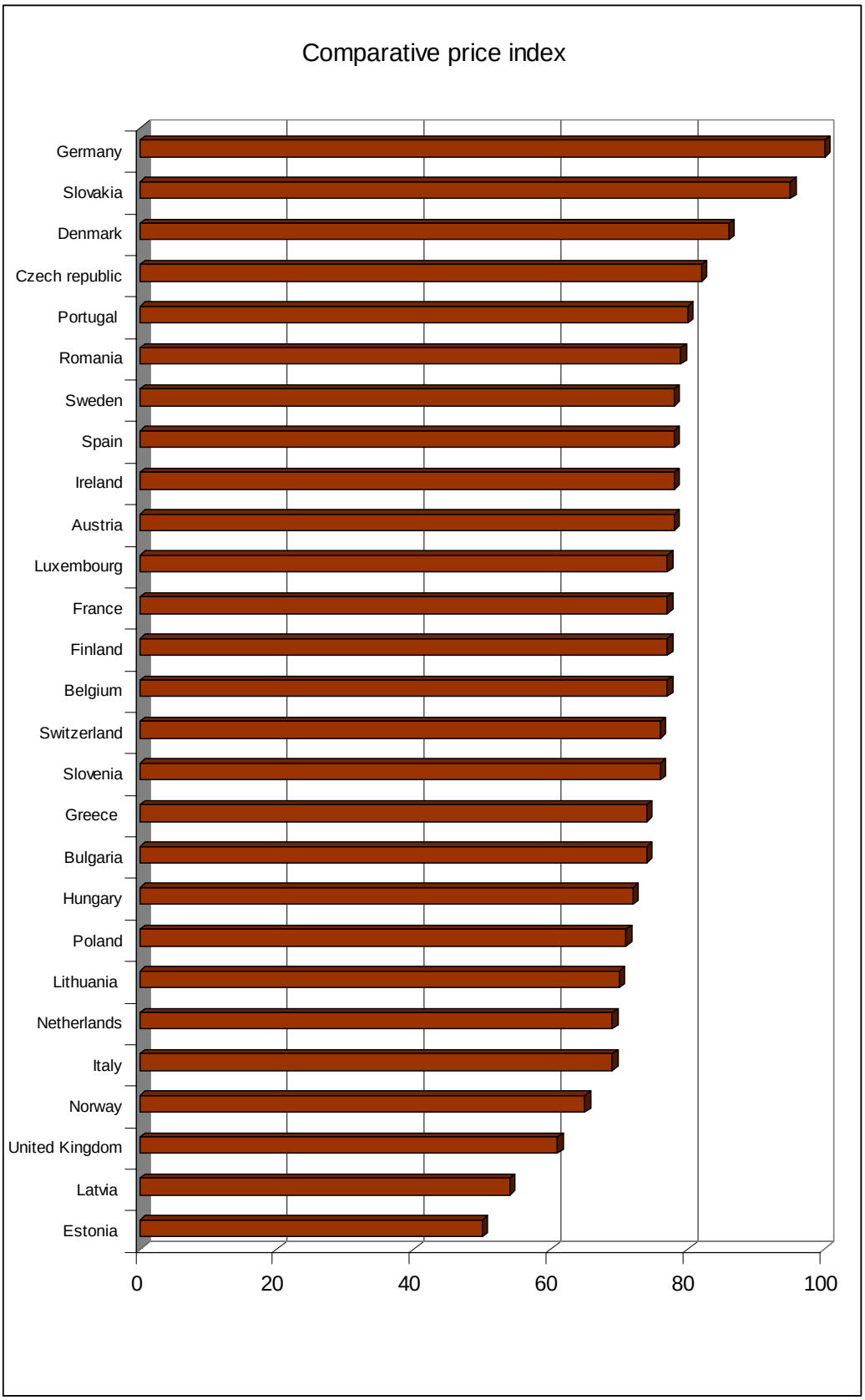
for MS drugs. Indeed, in many of these countries MS drugs were priced prior to their joining the EU, which allowed some adaptation to the economic environment, which was not the case for RA drugs. As MS prevalence is lower and the budget impact of new treatments hence more limited, MS patients have better access to innovative treatments in Central and Eastern Europe than RA patients.

Table 4-1 Comparison of prices, health expenditures and ability to afford

Country	Price index [1] Germany = 100	Relative health expenditure/capita [2,3] Germany=100	Affordability index [4] Germany=100
Austria	72	107	67
Belgium	72	103	70
Bulgaria	58	28	206
Czech republic	73	45	163
Denmark	88	100	88
Estonia	42	31	136
Finland	72	79	91
France	77	102	75
Germany	100	100	100
Greece	85	74	115
Hungary	56	45	126
Ireland	91	91	100
Italy	67	78	87
Latvia	70	30	233
Lithuania	71	25	284
Luxembourg	70	180	39
Netherlands	77	94	82
Norway	65	134	49
Poland	56	27	208
Portugal	75	63	119
Romania	57	19	298
Slovakia	83	39	214
Slovenia	70	64	110
Spain	79	73	109
Sweden	74	95	78
Switzerland	96	128	75
Turkey	44	29	152
United Kingdom	54	82	66

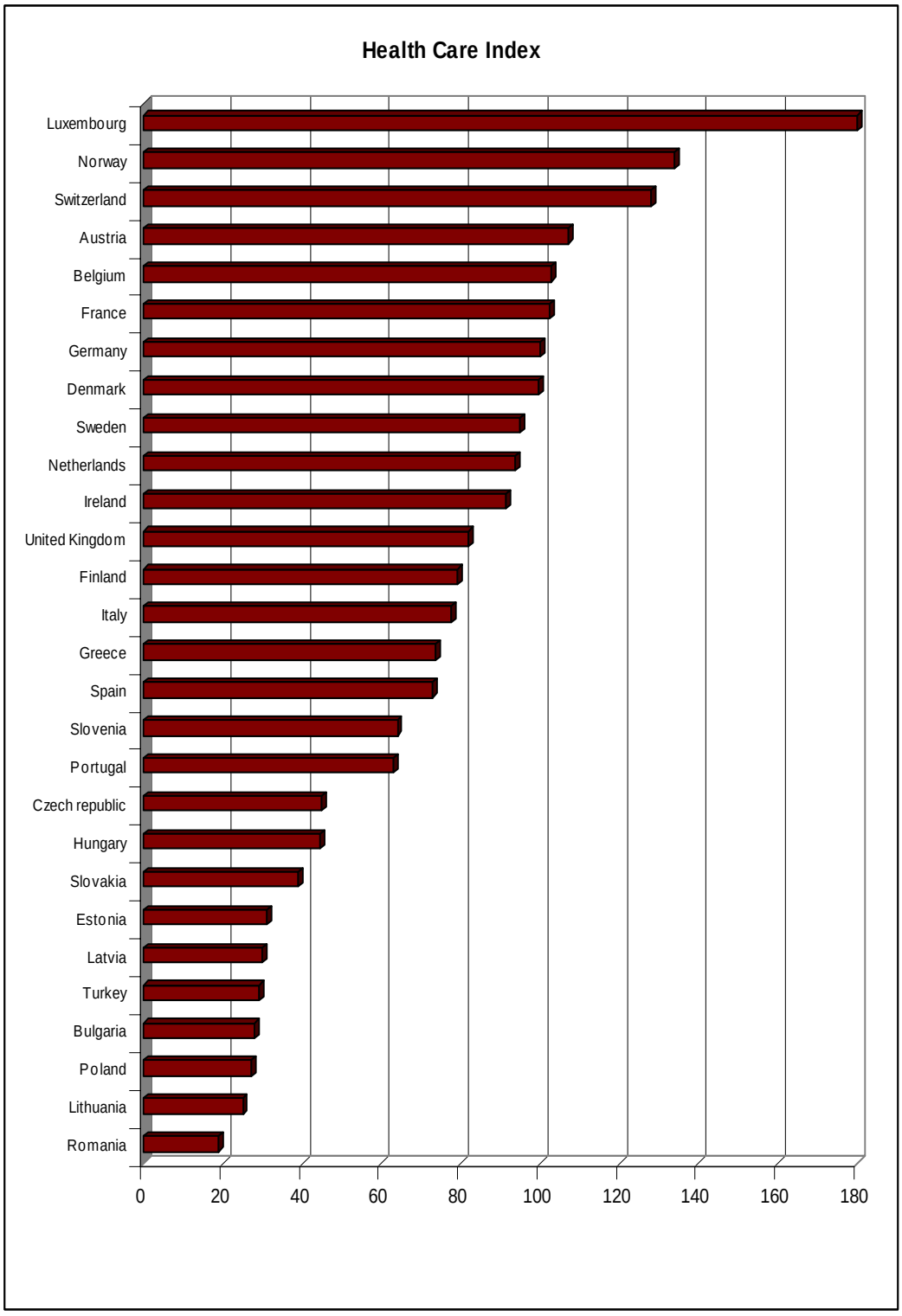
1) *Price index based on weighted average of the 5 products. Germany = 100*
2) *Source: OECD Health Data 2008*
3) *Source: WHO statistical information system, 2006 adjusted*
4) *Calculated comparing the index of health care expenditures to the price index. Higher indexes indicate lower affordability.*

Figure 4-1 Price comparison across countries (Germany=100)*



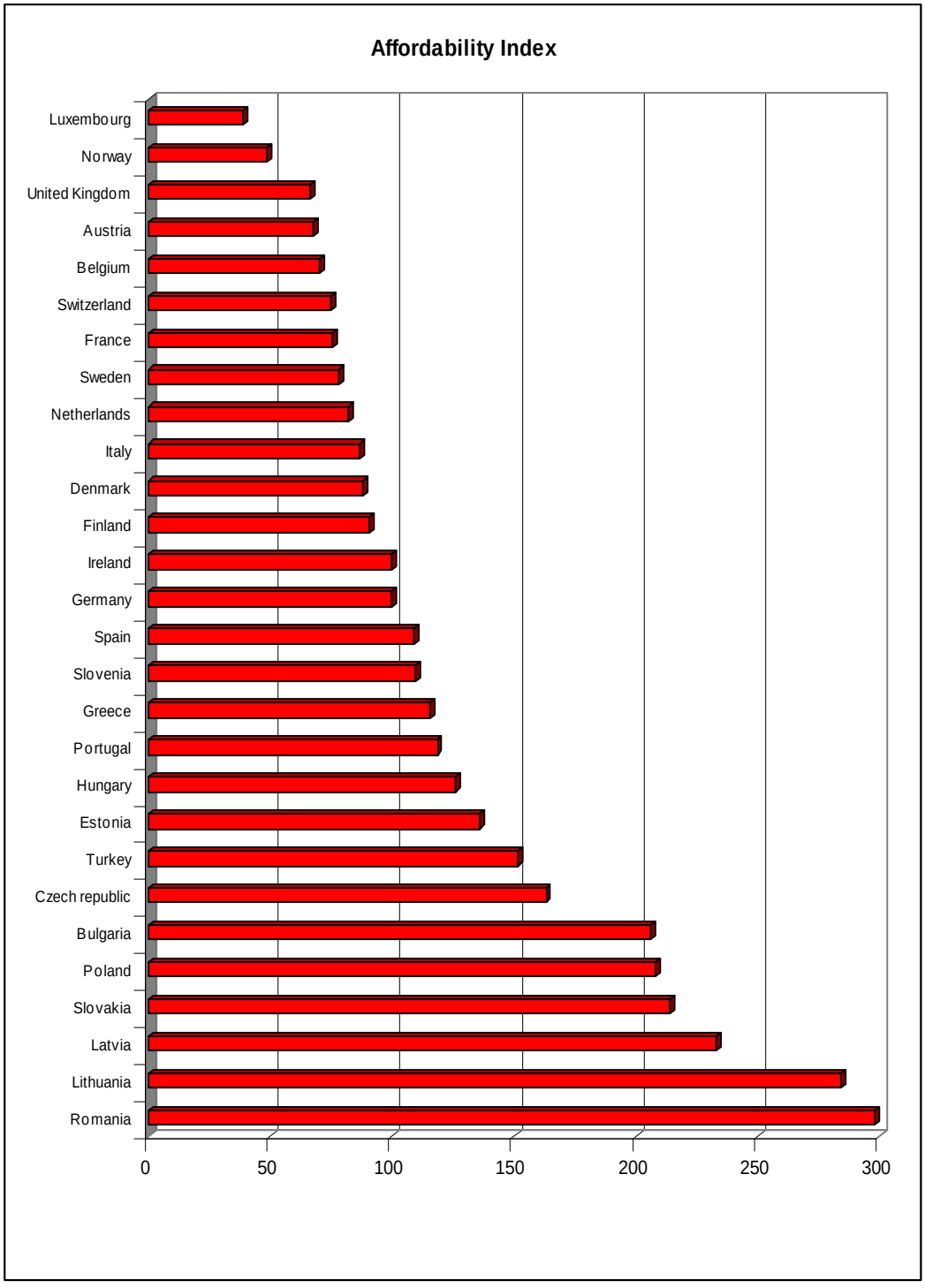
**Weighted manufacturer prices*

Figure 4-2 – Comparison of health expenditure/capita (Germany=100)



Source: OECD Health Data 2009, WHO Health Statistics

Figure 4-3 – Affordability Index (Germany = 100)



Comparison of health expenditures per capita (index) to the price of biologics (index). Low indexes indicate good affordability, high indexes indicate difficulties to afford.

4.4 Price

The cost of MS treatments does not appear to have a major influence on usage, with the obvious exception of the differences in countries' economic conditions between Western and Central/Eastern Europe.

Within Western European countries, the price band is very narrow as expected. In the majority of countries the ex-factory price is around 70-80% of the German price, and most treat an estimated 40-50% of patients. Considering the uncertainty in the prevalence, we would consider this similar. Germany and Denmark, despite a higher price, treat at a similar level as other countries. Below average treatment occurs in Norway, the Netherlands, Ireland, and the United Kingdom. Norway has been shown to treat conservatively and our estimates confirm numbers published in 2007 (28%) [1]. Similarly, conservative treatment compared to other Western European countries has been shown for the Netherlands [2]. Both these countries have a lower affordability index (see Figure 4-3) and thus better possibilities to pay. Ireland is well within the mid-range of prices and an affordability index similar to Germany, but only treats around 30% of patients. The Neurological Alliance of Ireland reported a severe lack of neurologists who treat MS patients in Ireland (http://www.nai.ie/Ease/servlet/DynamicPageBuild?siteID=1842&categoryID=101). The low usage in the United Kingdom is likely a direct consequence of restrictive NICE guidance that will be discussed below, despite a historically lower price.

Some of the recent currency shifts versus the Euro have "disturbed" the price band in Western Europe. During 2008, the Norwegian Krona and in particular the British Pound have depreciated against the Euro and biologics in these countries have therefore comparatively low prices in Euro, despite being countries with traditionally high pharmaceutical prices. During 2009, this has also been the case for the Swedish Krona, but this does not affect our data that include the time up to end of 2008. The effect of these currency changes will be an increase in parallel export, particularly into Germany. However, the influence on usage is likely limited, as in fact a minor part of the difference reaches the end-user.

Price has a strong influence overall in Central and Eastern Europe, but lower prices (between 10 and 50%) have made the differences to Western Europe less large than in other medical fields such as e.g. Rheumatoid Arthritis. However, price does not explain the variation among these countries. Slovakia has a price rather close to Germany, yet is one of the countries that treats the highest proportion of patients. Contrary to this, the Czech Republic, with a lower price than Slovakia, treats fewer patients. Price does however explain low usage in Romania, where the price is the same as in most Western European countries, affordability about three times less (index 300) than Germany. A similar picture emerges for Poland.

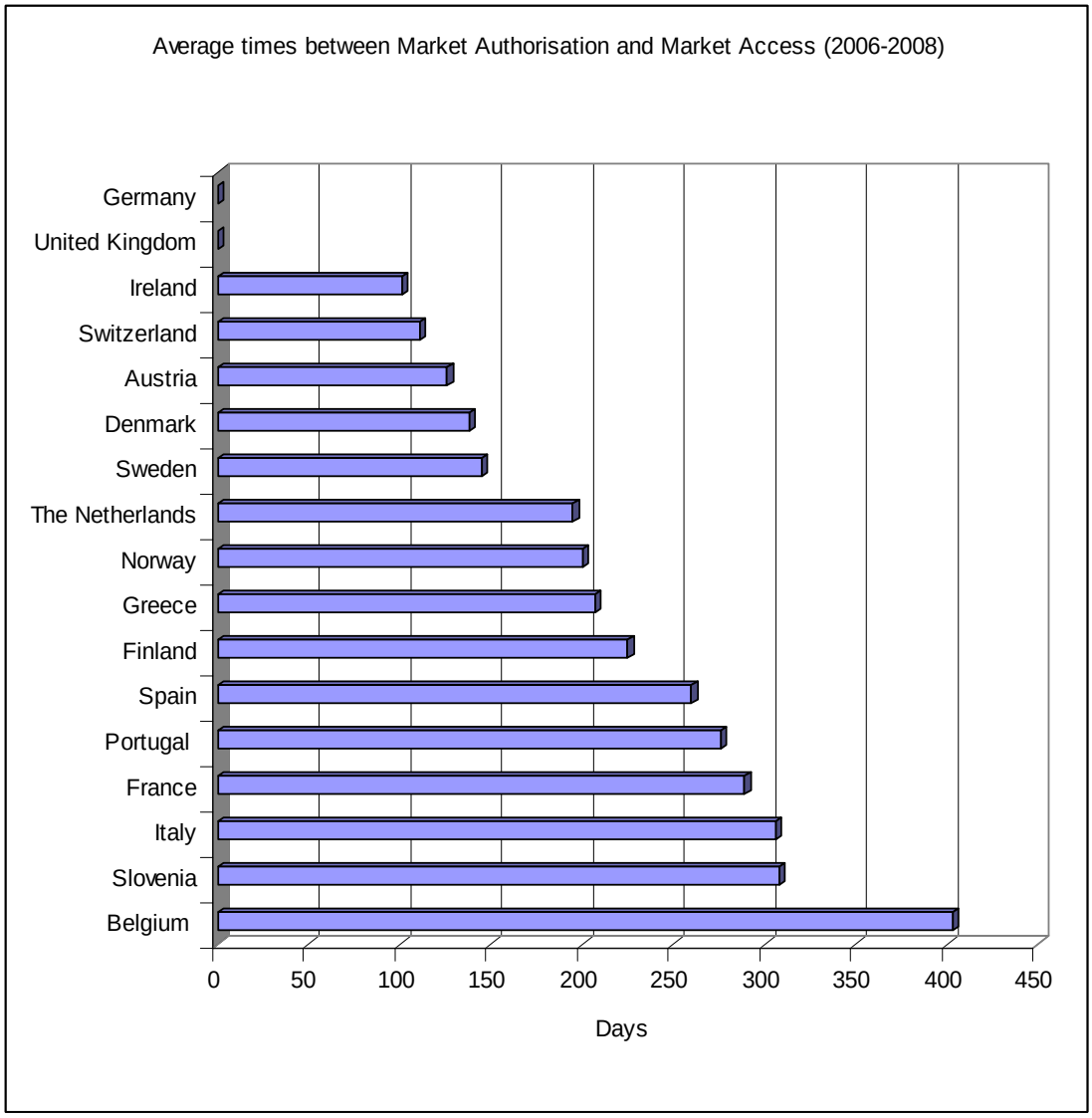
4.5 The reimbursement process

Most countries have formal mechanisms for making national reimbursement decisions, with the exception of Germany and the United Kingdom where no specific decisions have to be made before a drug can be prescribed under the reimbursement system.

The reimbursement process can take more or less time, depending on the country and also on the technology in question. As an indication, we show below preliminary results of the 2009 "Patients W.A.I.T. Indicator" produced by IMS Health based on

EFPIA's database on first marketing authorisation in the period 2006-2008. Compared to the 2008 indicator, little has changed. The delay from EMEA authorisation to completion of the reimbursement process in 15 European countries (excluding Germany and the United Kingdom) varies from 101 to 403 days, compared to 98 to 412 days in the previous report.

Figure 4-4 – Patients W.A.I.T. Indicator



Source: IMS Health, data on file

A delay in reimbursement is, however, not always associated with low usage, but only with a delay. This can be illustrated with the example of Italy and particularly France that both take on average almost a year to complete the reimbursement process. But once reimbursed, uptake of treatments is very fast, as shown below. We can also observe that usage is immediate after licensing in Germany. In the Nordic area, reimbursement decisions are rapid and uptake steady.

Figure 4-5 – Uptake after reimbursement decisions (5 large markets)

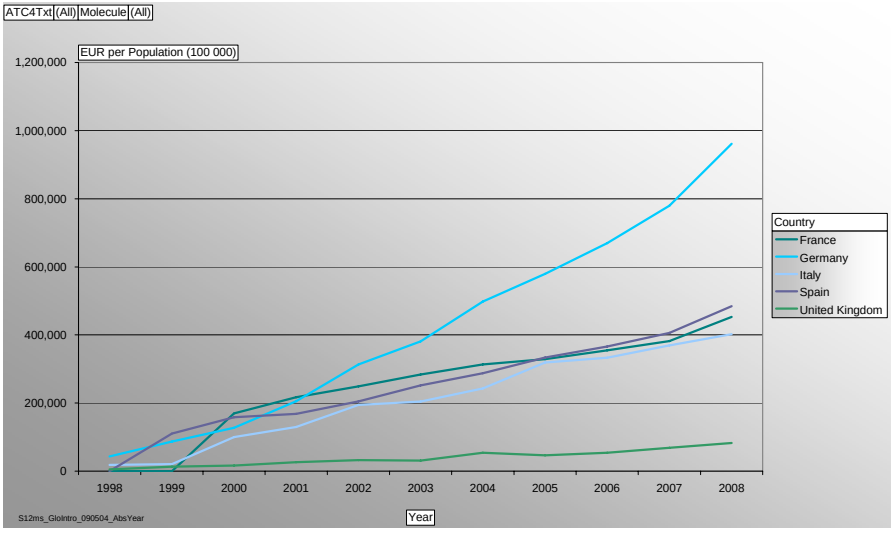
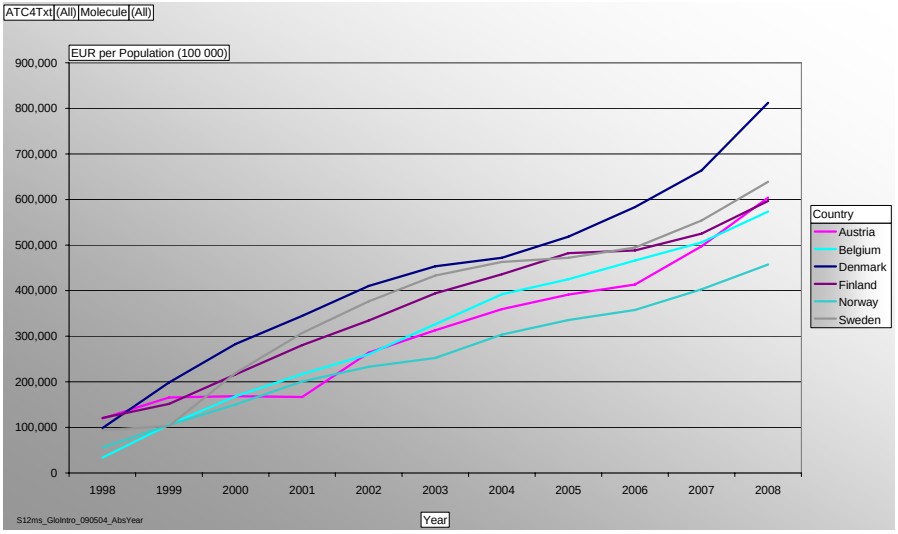


Figure 4-6 – Uptake after reimbursement decisions (Nordic area)



4.5.1 Economic evaluation in the reimbursement process

In Belgium, Finland, the Netherlands, Norway, Portugal and Sweden there is a formalized decision-making process where economic evaluation and the issue of cost-effectiveness play an important role. In France, Italy and Spain, cost-effectiveness information is used as additional information for pricing and reimbursement decisions, although not as formally as in the countries above. For Denmark and Switzerland the role of economic evaluation and cost-effectiveness is not a formalized part of the decision-making process. The UK has no formal restriction for pricing and reimbursement of drugs, but the government still controls the pricing and can, for example, require price cuts and paybacks from companies. A number of Eastern European countries have also recently introduced economic evaluation into their reimbursement process (e.g. Hungary, Poland, Czech Republic, and Lithuania) [3].

Within these processes it is sometimes possible to define the eligible patient populations more restrictively than in the market access authorisation by the EMEA, (although actual control mechanisms are lacking in most countries). The most obvious example of such a process is the United Kingdom. Although no formal reimbursement negotiations are required and treatments can be used on the NHS both in England/Wales and Scotland immediately after EMEA approval, uptake of innovative expensive treatments is limited until NICE and SMC have evaluated them. In MS, the evaluation by NICE has been particularly lengthy and restrictive. After an initial negative opinion based on an unfavourable cost effectiveness ratio, a risk sharing scheme was put in place in 2002. Within this scheme 7000 patients were to receive treatment and the cost-effectiveness in clinical practice compared to the economic model that NICE had produced. The model had predicted an incremental cost-effectiveness ratio of £36,000 [4], and in the case this was not shown in clinical practice, the cost of treatment was to be adjusted by the manufacturers. According to the Department of Health (DoH, (Feb 2009, www.mtrust.org.uk/information/opendoor/articles/0902_02.jsp), between 2002 and 2005, 5000 patients received treatment and are followed under this scheme, and while this database may prove a valuable source of clinical data, there appears still to be no formal economic evaluation available.

However, this situation does explain the low usage of DMTs shown in our data for the United Kingdom. The DoH estimates that between 2002 and 2005, the scheme enrolled 80% of all patients, and that since 2002, 10,000 patients had had access. This is slightly higher than our estimates of around 8500 patients on treatment in 2008, and may have several explanations: We calculated the number of patients as full-year treatment, and a number of patients may have started or stopped during the year. Also, discontinuation rates for DMTs are known to be high due to adverse events (flu-like symptoms, neutralizing anti-bodies) and the need to inject, and a proportion of these 10,000 patients may no longer be on treatment. Finally, it is possible that IMS does indeed not capture all data.

In other countries, if restriction existed, they were less formal. Initially, the number of prescribers was limited and certain administrative hurdles such as prior approval were put in place in certain countries. But mostly the initial hurdles were financial, particularly at the hospital budget level, and this is likely still the case in the new EU countries. Restrictions for usage only for a limited group of clinically defined patients - as they exist e.g. in the field of Rheumatoid Arthritis where clinical guidelines pursue partially the objective to ensure access for patients with the highest medical need without creating issues for funding – do not seem to exist and clinical guidelines in MS deal essentially with patient management.

4.6 Treatment guidelines

Market authorisation and reimbursement of drugs does not ensure their utilisation. For most diseases there are a number of reimbursed drugs to choose between, and treatment recommendations/guidelines form important guidance for physicians in many countries. Such information may be provided at international, national or local levels. A number of clinical guidelines do exist in MS, but will not be reviewed here in detail, as they do not appear to include restrictions to usage. A list of available guidelines can be found at http://www.rhn.org.uk/institute/cat.asp?catid=937.

An example of clinical treatment recommendations are the guidelines of the Association of British Neurologists in 2007 that recommend treatment of patients with a clinical isolated syndrome (CIS) and patients with both relapsing-remitting

MS and secondary progressive MS with at least one super-imposed relapse per year (www.abn.org.uk). From our data it would appear that there is a large gap between these guidelines and actual clinical practice. The European Federation of Neurological Societies (EFNS) has issued guidelines regarding the measurement of neutralizing-antibodies interferon-beta and actions to be taken, as well as guidelines on the treatment of relapses (www.efns.org).

4.7 Patient Eligibility

The clinical trials of the different biologics had enrolled a certain type of patients with active relapsing disease, defined somewhat loosely by the number of relapses in the past 1 or 2 year (generally at least 2 in the past 2 years). This defined automatically in most countries the type of patients who were eligible for treatment and few countries imposed further restrictions.

Mostly, however, usage was self-limiting due to the high cost as well as the difficulty to assess the medium and long term benefit. While all clinical trials have shown a significant reduction of relapses (~30%, except Tysabri 60%), the consequence of this on the long term course of the disease was unclear. An early registry study in Norway had shown that the frequency and intensity of relapses early in the disease predicted a bad prognosis [5], while other data were more ambiguous regarding a relationship between relapses and disease progression [6]. This latter data set also provided evidence that once patients reached an EDSS of 4, progression to EDSS 6 and 7 was strikingly similar between patients with primary progressive disease or relapsing remitting disease [7]. A similar conclusion was reached from data in the natural history cohort in Ontario (Canada) [8]. In chronic progressive diseases, early intervention is key and MS is no exception to this. In the early phase of relapsing-remitting MS, the reduction in the number and the severity of relapses should delay progression to EDSS 4.

DMTs are only licensed for use in patients with confirmed relapsing-remitting MS, or a clinically isolated event (CIS) indicative of MS. However, the precise point of conversion to secondary progressive MS is difficult to establish. In the Ontario natural history cohort, patients converted between EDSS 1 and 6, with a mean/median of 3 [9]. Also, most patients are thought to still have super-imposed relapses, and it is thus not desirable to discontinue treatment too early – particularly as there is no other treatment to go to. The ABN guidelines mentioned above are an expression of this. This also explains why many patients with secondary progressive disease are currently under treatment, has also been shown in an economic analysis using data from the Swedish MS registry [10]. A number of countries, among them Australia and the United Kingdom, have however limited use/reimbursement to patients below EDSS 7 (which corresponds to being in a wheel chair for a large part of the time). Countries likely also differ in how early treatment is instituted, i.e. whether patients with a CIS will receive treatment prior to the confirmation of the diagnosis.

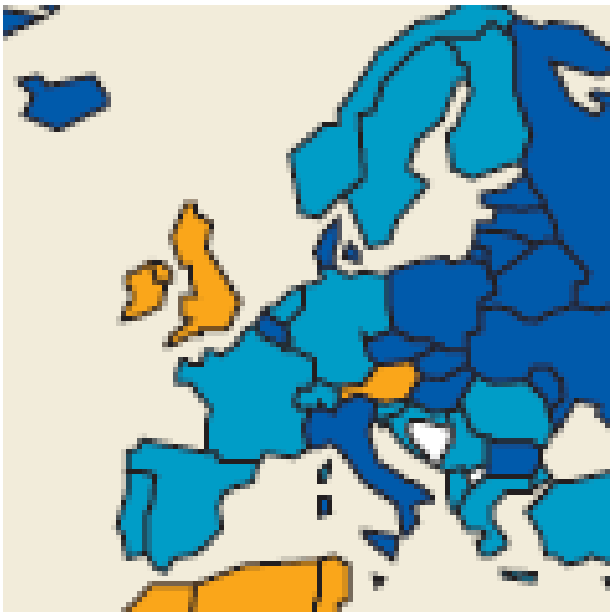
In the absence of any other treatment for MS, most of the financial and non-financial hurdles disappeared over the last decade. As mentioned earlier, the United Kingdom remains an exception within Western Europe where currently between 40-50% of patients qualify. Although this range still appears quite large, we would describe uptake as relatively similar across countries, compared to other fields. Part of the variation in our estimates may also be due to the available data (IMS) or to our prevalence estimates. Comparing the 4 large markets of France, Germany, Italy and Spain we can observe a very similar uptake (see chapter 3).

Differences between countries may emerge in the future, as new drugs are introduced. Tysabri, due its adverse event profile, has been limited by the EMEA to patients with breakthrough disease (relapsing despite DMT treatment) or patients that cannot tolerate any of the 4 standard DMTs. This limits the number of eligible patients, but still leaves considerable freedom to interpretation of what breakthrough disease or intolerance to standard treatment is. It is likely that countries will interpret these restrictions more or less stringently and usage will differ considerable. The limited market, and the need for MRI testing prior to use and very stringent monitoring during use has led to a high price, around €24,000 compared to the range of €6,000 to €15,000 for the standard DMTs. The fact that Tysabri was introduced very recently also means that the price band can be expected to be very narrow, and that affordability issues will play a greater role. Most likely thus, the overall access to DMTs will diverge across Europe. Even within the 5 large Western European markets, we can already observe differences (see chapter 3, Figure 3-11): France has a very rapid uptake after reimbursement despite a doubling of the price compared to standard DMTs, as expected from the limited price-consciousness in health care provision. Germany has increased usage more slowly, although the price difference to the highest priced DMT (Rebif44) is only around 40%.

4.8 Provision

An initial barrier to usage of the DMTs was the availability of specialized MS centres and in many countries the manufacturers of DMTs support provision with specialised MS nurses. It appeared also that in some countries neurologists specializing in MS were lacking. According to the WHO Neurology Atlas 2004 (http://www.who.int/mental_health/neurology/epidemiology/en/index.html) the number of neurologists is the highest in Europe, but there is also variation: Austria, Ireland and the United Kingdom reported less than 1 neurologist per 100,000 population (yellow), while Denmark, Belgium, Denmark, Italy, the Baltic States, Bulgaria, the Czech Republic, Slovakia, Poland Reported more than 5 per 100,000 population (dark blue). All other countries lie in between.

Figure 4-7 Density of Neurologists

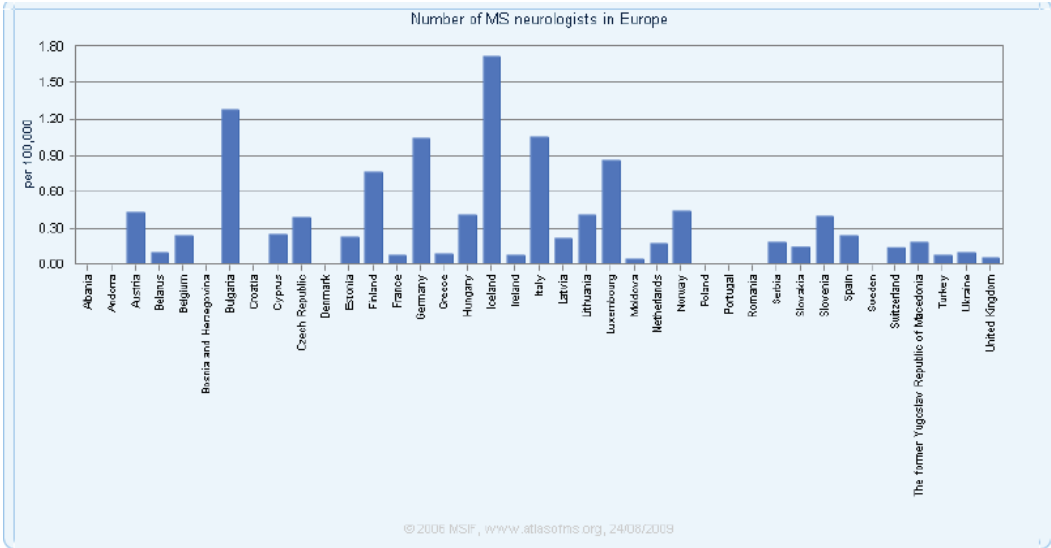


Yellow: 0.11-1 / 100,000
Light blue: 1.01-5 / 100,000
Dark blue: >5

Source: WHO Neurology Atlas 2004

These numbers do, however, not indicate how many neurologists specialize in MS, but research into whether there are currently enough centres and personnel is not part of this report. The MS ATLAS of the Federation of MS Societies (MSIF) provides some data as shown below, but the information is sketchy and originates from a simple questionnaire to national MS societies, without means for verification.

Figure 4-8 Estimated number of MS Neurologists per 100,000 population



Source: MSIF Atlas (www.atlasofms.org)

4.9 Health technology assessments

Health technology assessment (HTA) reports published by national or regional HTA agencies often form part of the evidence for treatment recommendations/ guidelines and are by themselves important influences for treatment choices. The European Network for Health Technology Assessment initiative (EuNetHTA, http://www.eunethta.net) defines HTA as a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner, with the aim to inform the formulation of safe, effective, health policies that are patient focused and seek to achieve best value. Economic evaluations are thus an integral part of HTA and reports include a review of previously published economic evaluations for the treatments in questions and may also include a new economic evaluation.

Assessment by HTA agencies support decision-making in healthcare at all levels and are intended for those who make choices regarding healthcare options, including professional caregivers, healthcare administrators, planners and health policy-makers. They can thus be expected to have a strong influence on the uptake of treatments. In some cases there is a direct link between the assessment by the HTA agency and funding for the technology appraised, for example in England/Wales with the National Institute of Clinical Excellence (NICE) or Scotland with the Scottish Medicines Consortium (SMC). In England and Wales there is a direct link between the issuance of a positive guidance on a new drug therapy by

NICE and the budget allocated to this new drug therapy by the National Health Service (NHS). Despite of the fact that economic evaluations cannot be transferred from one country to another, guidance documents issued by NICE appear to have an impact on decision-makers beyond the borders of the UK.

4.9.1 Overview of HTA studies

HTA agencies in most countries have performed technology assessments in the late 90' and a complete review would be beyond the purpose of this report. Not all reports included explicit cost-effectiveness analysis, and a number of them is only available in English as summaries. We therefore mention only a few of the reports here.

- The NHS HTA Programme in England and Wales published a first report in 1998[11] assessing the cost-effectiveness of interferon-β-1a versus standard care (best supportive care) in the treatment of relapse-remitting MS to approximately £810,000 per QALY gained based on available clinical follow-up data. A modelling of possible yet unconfirmed effects of progression over 5 and 10 years resulted in cost-utility ratios of approximately £330,000 and £230,000 respectively.
- In 2001, a NICE-commissioned HTA was conducted assessing cost-effectiveness of glatiramer acetate and the different interferon-β drugs available in the UK to no treatment (best supportive care) in the treatment of relapse-remitting and secondary progressive MS in concordance with the indication for respective drug[12]. Resulting cost-effectiveness ratios varied between £39,000-£106,000 over a 20-year time horizon. Based of the results neither interferon-β nor glatiramer acetate were recommended in the treatment of MS in England and Wales[13]. However, as a consequence of considerable opposition from patients and professional organisations and the uncertainty of long-term outcomes of these drugs, a risk-sharing scheme was set up for these drugs in the UK starting in 2002 (see 4.5.1.).
- In 2007, an evaluation of a model submitted to NICE assessing the cost-effectiveness of natalizumab in the treatment of highly active relapse-remitting MS concluded that the modelling approach was pragmatic given the available data. The cost per QALY gained of natalizumab versus interferon-β-1a, glatiramer acetate and standard care respectively were assessed to £43,000, £44,000 and £56,000 respectively in the model submitted by the manufacturer[14]. Based on the results natalizumab was subsequently recommended by NICE as an option for the treatment of rapidly evolving severe relapsing–remitting multiple sclerosis[15].
- The Swedish assessment was just a brief document, an "early assessment of new medical technologies" published in 1999 discussed the clinical effect of interferon-β, the lack of other effective drugs, the healthcare costs of treating MS patients with interferon-β, and the need for the establishment of guidelines with treatment indications without stating a clear treatment recommendation [16].
- The German HTA published in 2008 consisted of a literature review with the purpose of assessing the clinical effectiveness and the cost-effectiveness of natalizumab and different β-interferons. The health economic evidence identified for interferon-β was heterogeneous, ranging from cost-saving to cost-effectiveness ratios of over €1.5 million, as a result of widely differing model assumptions. No cost-effectiveness analyses for natalizumab were identified. It was concluded that long term economic effects are uncertain[17].
- The Norwegian report assessed the cost-effectiveness of natalizumab and concluded that it was less costly and more effective than best supportive care or a 2nd line treatment with another DMTs in the societal perspective [18].

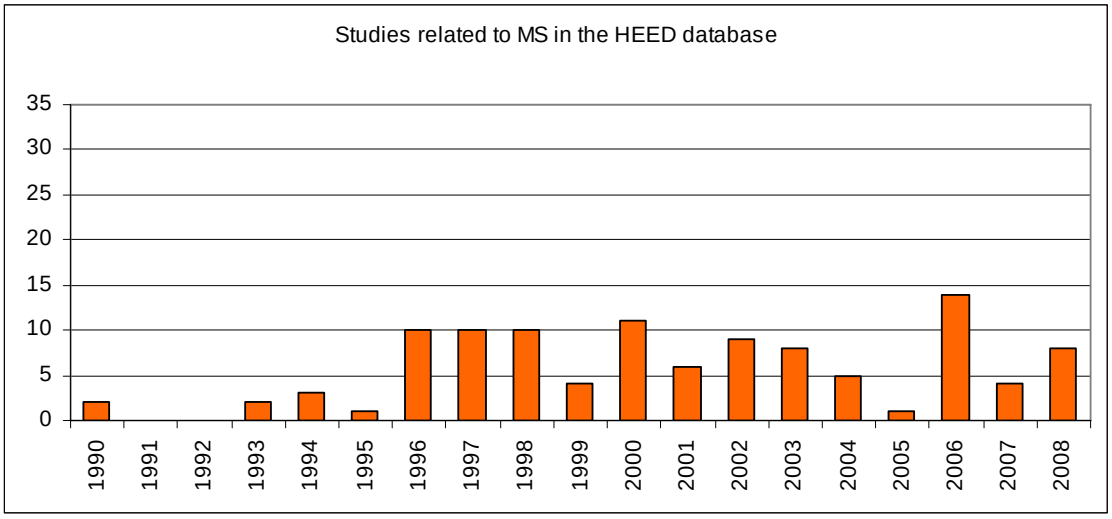
4.10 Health economic studies in MS

A large number of economic evaluations have been published, by the manufacturers of DMTs, academic groups and HTA agencies (see above). A small number of studies has looked at the cost per relapse avoided, an outcome that is partial only and does not give the full value of treatment in view of the long disease duration. The vast majority of studies have therefore evaluated the effect on progression in the long term. This has always implied modelling using both clinical trials and epidemiological and natural history data.

Health economic models should represent best available knowledge, and are hence only as good as the underlying data. Regardless of the modelling technique, they should give the same results when using the same data. It is rare, however, that all required data are available, and assumptions regarding a number of parameters are always necessary. Different assumptions will lead to different results. And, by their nature, they can be subject to different opinions, interpretations and critiques. It can be difficult even for specialists to fully understand all details of published models, essentially because of the limited space available for thorough explanations. The large differences in cost-effectiveness ratios published have to be seen in this light and over time modelling studies in MS have been well accepted as a decision support.

The Health Economic Evaluation Database (HEED) has been developed as a joint initiative between the Office of Health Economics and the International Federation of Pharmaceutical Manufacturers' Associations. It contains information on cost-effectiveness studies and economic evaluations of medicines and other treatments and medical interventions. A search in the database focusing on MS studies gives an overview of the availability of health economic studies in MS. The figure below presents the number of studies in HEED related to MS published in 1990-2008. In total, 108 MS studies were identified in the database. Few studies were from before the mid-1990s introduction of the first biological treatments in MS. Thereafter the number of studies published per year has been fairly constant.

Figure 5-1 Studies on costs, patient outcomes and cost-effectiveness in HEED related to MS between 1990 and 2008



4.10.1 Overview of Economic Evaluations

Published studies cost-effectiveness analyses have shown quite different results and it is not always easy for the non-specialist to see where these differences originate. It is therefore important not to compare studies, but take each study in its own right for the information it provides, evaluate the methodology and underlying data used. A number of parameters influence the results, such as:

- the country of study - underlying cost structures and possibly patient management differ;
- the year of the study - penetration of innovative drugs may differ;
- the perspective of the analysis - the societal perspective includes all costs both within and outside the health care sector and is thus relevant for MS, compared to the payer perspective that limits itself to health care costs;
- the outcome measure used – an intermediary measure such as relapses avoided that likely underestimates the effect of treatment, or the effect of treatment on progression
- the time horizon of the analysis – an effect on progression will affect costs and outcome over the very long time, and longer time horizons are thus better able to capture the effect of treatment.

Figure 4-9 Published health technology assessments and cost-utility analyses of MS treatments

Country	HTA	Perspective	Interventions compared	Data source (clinical effect)	Patients included	Time-horizon	Result (cost/QALY)	Currency and year	Ref
			interferon-β						
Italy		Healthcare provider/ Societal	interferon-β-1b from diagnosis of clinically isolated syndrome/ interferon-β-1b at diagnosis of clinically definite MS	Clinical trial with extrapolation	CIS/CDMS	25 years	Healthcare provider: €2,600 Societal: Dominating (less costly – more effective	€ 2006	23
Sweden		Societal/ healthcare provider	interferon-β-1b/best supportive care	Clinical trials and longitudinal data (Canada)	RRMS / SPMS diagnosis to severe disability	10 years	Societal: €7,800 Healthcare provider: €49,800	SEK 1999	24

Sweden		Societal/ healthcare provider	interferon-β-1b/best supportive care	Clinical trial and longitudinal data (Canada)	SPMS	10 years	Societal: SEK257,000 Healthcare provider: SEK447,000	SEK 1999	[25]
Sweden		Societal/ healthcare provider	interferon-β-1b/best supportive care	Clinical trial with extrapolation	SPMS	10 years	Societal: SEK342,000 Healthcare provider: SEK542,000	SEK 1998	[27]
UK		Societal/ healthcare provider	interferon-β-1b/best supportive care	Clinical trial	RRMS	10/20 years	Societal: £14,600 (10 years)/ £3,000 (20 years) Healthcare provider: £30,500 (10 years)/ £13,700 (20 years)	£ 1999	[28]
UK		Healthcare provider	interferon-β-1b /best supportive care	Clinical trial	RRMS and SPMS	Lifetime	£51,600	£ 1998	[26]
UK	**X**	Healthcare provider	interferon-β-1b/best supportive care	Clinical trial with/without extrapolation	RRMS	5 years/10 years	5 years: £328,300/ £809,900 (with/without effect on progression) 10 years £228,300 (with effect on progression)	£ 1997	[29, 30]
UK		Healthcare provider/ societal	interferon-β-1a/best supportive care	Clinical trial with extrapolation	RRMS	2-20 years	Healthcare provider: £27,000-£37,900 Societal: Dominating (less costly – more effective)	£ 1995	[31]
UK		Healthcare provider	interferon-β-1b/best supportive care	Clinical trial	SPMS	2.5 years	Healthcare provider: £1,024,700/QALY	£ 1995	[32]
			glatiramer acetate						
Spain		Societal	glatiramer acetate/interferon-β	Clinical trials	RRMS	Lifetime (53 years)	Glatiramer acetate dominates (less costly, more effective)	€ 2001	[20]
UK		Healthcare provider	glatiramer acetate/best supportive care	Clinical trial	RRMS	8 years	£22,600-£64,600	£ 2000	[21]

			interferon-β and glatiramer acetate						
UK	**X**	Healthcare provider	interferon-β-1a/ interferon-β-1b/glatiramer acetate/best supportive care	Clinical trials with extrapolation	RRMS and SPMS	20 years	interferon-β-1a: £48,100-£106,200 interferon-β-1b: £38,800-52,500 glatiramer acetate: £97,700 (all compared to no treatment)	£ 2001	[12, 22]
			Natalizumab						
Norway	**X**	Societal/ healthcare provider	natalizumab/other DMTs/best supportive care	Clinical trial/ registry (Stockholm) and longitudinal data (Canada)	RRMS	20 years	Society: Natalizumab dominating (less costly, more effective) over both comparators Healthcare provider: NOK 432,100 versus other DMTs /NOK 121,700 versus best supportive care	NOK 2002	[18]
Sweden		Societal/ healthcare provider	natalizumab/other DMTs	Clinical trial/ registry (Stockholm) and longitudinal data (Canada)	RRMS	20 years	Societal: Dominating (less costly, more effective) Healthcare provider: €38,200	€ 2005	[10]
UK		Societal/ healthcare provider	natalizumab/other DMTs (interferon-β, glatiramer acetate)/best supportive care	Clinical trial/ meta analysis of clinical trials) and longitudinal data (Canada)	Highly active RRMS	30 years	Societal: £2,000-£8,200 Healthcare provider: £18,700-£25,500	€ 2006	[19]

RRMS=relapsing-remitting MS, SPMS=secondary progressive MS, CIS=clinically isolated syndrome, CDMS=clinically definite MS

4.11 Effectiveness in Clinical Practice (Registries)

As discussed above, data on long term effectiveness of DMTs in clinical practice are still scarce. Most of the available information comes from open extension studies to the pivotal randomized clinical trials and thus without an appropriate control group [33]. This makes it difficult to use the information in cost-effectiveness studies, and modelling to combine different datasets continues to be required.

In the pivotal clinical trials, relapses were reduced on average by 30% for the standard DMTs (Avonex, Copaxone, Betaferon, Rebif) and by 60% by the latest drug (Tysabri) [34-38]. The effect of treatment on progression has also been estimated from these trials, albeit with different methods in the different trials and it is thus not easy to quantify. Trials showed either a trend toward improvement or a statistically significant reduction in disability progression [33].

A recent review of the extension studies to these trials suggests that long-term follow-up of patients originally enrolled in randomized clinical trials consistently show that delayed or discontinued treatment provides less benefit than continuous therapy [33]. The longest follow-up of a trial with the highest ascertainment (328 of 372 patients, 88%) was with Betaferon for 16 years [39]. Results showed that patients remaining on long-term treatment had a slower progression to EDSS 6.0 compared with those who had been treated for a short period only. In the group with drug-exposure of <80% of the time over the 16 years, 46.9% of patients reached EDSS 6.0. In the group with ≥80% exposure, this number was 35.7%. Safety was excellent, with a lower mortality after 16 years in patients in the active group during the trial. Long-term extension studies with the other three treatments lasted 8-10 years, and two studies suggest a potential impact on disease progression with early and intensive treatment of around 1 EDSS point [40-42].

When the DMTs were first introduced, their usage was from the start followed-up in existing registries (e.g. Denmark, France, Norway, Sweden), or new registries were established (Germany, Italy, Spain, United Kingdom). For an overview of the largest registries, see [43]. However, data on long-term effectiveness and in particular on cost-effectiveness in clinical practice are only starting to emerge.

A recent modelling study in Sweden included a comparison of the natural history cohort in Ontario (Canada) and patients treated with with standard DMTs in clinical practice and followed in the Swedish MS registry [10]. The results indicated that standard treatment was both more effective and less expensive than no treatment, with the caveat, however, that there may be differences in the patient material as MS appears to have changed over time.

Table 4-2 Cost-effectiveness (€ 2005) of using standard DMTs in the Stockholm MS registry compared to no treatment (natural history)[10]

	Total cost (€)	Incremental cost (€)	Total effect (QALY)	Incremental effect	Incremental cost/QALY (€)
No treatment (natural history)	623 570		8.39		
Disease-modifying treatments (Stockholm MS registry)	613 680	- 9890	8.99	0.60	Dominant (less cost and more effect)

Adapted from [10]

Another modelling study estimated the long-term cost of MS under different hypotheses [44] in France. Resource consumption and utility by disease severity (EDSS) were taken from a large cost of illness survey in France. Disease progression for patients not on DMT treatment was estimated from the EDMUS registry in Lyon, France, and compared to disease progression for patients on treatment in the Stockholm MS registry. This comparison clearly has to be considered with caution, as the data come from two different datasets, different years and different countries. While on the one hand it is not possible to affirm that patients in EDMUS would not have the same treatment benefit as patients in Stockholm, the contrary can also not be assumed.

The analysis showed clearly that the full treatment gain can only be shown in the long-term, which explains why real-life data are still scarce. Over a 20-year time horizon, the incremental cost of treatment of patients with relapsing-remitting MS at the start (all patients on treatment) compared to no treatment was estimated at €4250, for a QALY gain of 0.28. If only 55% of patients are treated, the incremental cost was estimated at €2250 for a QALY gain of 0.15. In both cases, the incremental cost per QALY is around €15,000. In a 10-year time-frame, Incremental costs are €27,250 for a QALY gain of 0.12, and one has to conclude that treatment is not cost-effective.

These results were estimated in the societal perspective, where all costs – including informal care and production losses – are included. Indeed, in a disabling disease such as MS that strikes young adult, excluding costs outside the health care sector that represents more than half of all costs do not appear logical. However, many reimbursement authorities or HTA agencies (e.g. NICE, SMC) only consider health care and social service costs, which partly explains high cost-effectiveness ratios.

Table 4-3 The long term cost of MS with and without DMT treatment [44]

Table 4A Costs and quality-adjusted life-years (QALYs) over 20 years (€2007, discounted 3%)

	All costs included		Productivity losses excluded		QALY	Incremental QALY
	Cost	Incremental cost	Cost	Incremental cost		
Societal perspective						
Untreated	428,750		173,700		8.96	
Partially treated (55%)	431,200	2250	184,500	10,800	9.11	0.15
Fully treated	433,200	2000	193,250	11,000	9.24	0.13
Payer perspective						
Untreated	158,500		114,750		8.96	
Partially treated (55%)	169,200	10,700	128,200	13,400	9.11	0.15
Fully treated	177,900	8700	139,200	11,000	9.24	0.13

Table 4B Costs and quality-adjusted life-years (QALYs) over 10 years (€2007, discounted 3%)

	All costs included		Produtivity losses excluded		QALY	Incremental QALY
	Cost	Incremental cost	Cost	Incremental cost		
Societal perspective						
Untreated	199,000		70,500		5.55	
Partially treated (55%)	210,250	11,250	86,000	15,500	5.62	0.07
Fully treated	219,500	9250	99,000	13,000	5.67	0.05
Payer perspective						
Untreated	65,000		47,250		5.55	
Partially treated (55%)	80,000	15,000	63,250	16,000	5.62	0.07
Fully treated	92,250	12,250	76,500	13,250	5.67	0.05

Source: Kobelt et al, Multiple Sclerosis 2009. Reprinted with permission.

4.12 Conclusion

The major difference in uptake of biologic DMTs for MS in Europe is due to macro-economic conditions. Indeed, despite lower prices in most the EU member states, usage in Central and Eastern Europe is less than half that of Western Europe.

Within these new member states, a large part of the difference is also due to differences in wealth, with access in e.g. Slovenia almost at the level of Western Europe, but Romania with extremely limited access.

Within Western Europe, differences are neither explained by price nor by economic conditions. Four countries appear to treat a lower than average number of patients: Ireland, Netherlands, Norway and the United Kingdom. In Ireland, a severe lack of MS neurologist may affect usage; the Netherlands and Norway have been shown previously to use DMTs conservatively; the extremely low usage in the United Kingdom is a consequence of a restrictive NICE guidance.

However, overall uptake is good with as many as 40-50% of patients on treatment in Western Europe, compared to e.g. Rheumatoid Arthritis. This may appear surprising in light of the fact that the effectiveness of biologics in RA has been quite well documented and can be seen even in the short term, which is less the case for DMTs in MS. A number of conclusions can be drawn from this:

- The absence of any other treatments makes a higher uncertainty about both the effectiveness and the cost-effectiveness acceptable.
- In view of the limited number of MS patients, reimbursement decisions are based more on budget impact analysis than on cost-effectiveness analysis.
- Safety of the treatments has been shown.
- Emerging data on the effect of early treatment on disease progression are convincing.

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