

# International variation in drug usage

An exploratory analysis of the “causes” of variation

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## Preface

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The 2014 Pharmaceutical Price Regulation Scheme recommended that “the UK should compare itself with other countries if it is to deliver a world-class NHS”. It requested that the “industry, NHS England and the Department [of Health] work together to develop and evolve an approach to the analysis and publication of comparative information on international medicines use on a periodic basis”. Overseen by a joint Department of Health, industry and NHS England working group (the Metrics Oversight Group), the approach was to build on a report led by Professor Sir Mike Richards into the extent and causes of international variations in drug usage (the Richards report). Published in 2010, the Richards report explored levels of medicines uptake for 14 categories of drugs in 14 high-income countries during 2008/09. The update of the 2010 Richards report comprises two workstreams: a quantitative analysis of medicines usage in 2012/13 carried out by the Office of Health Economics, and a qualitative component, exploring possible causes for observed international variation in medicines uptake for a select set of conditions. This document reports on the qualitative component of the work, which was undertaken by RAND Europe.

The report was prepared as part of the project “An ‘On-call’ Facility for International Healthcare Comparisons”, funded by the Department of Health in England through its Policy Research Programme (grant no. 0510002). The project comprises a programme of work on international healthcare comparisons that provides intelligence on new developments in other countries to inform health (care) policy development in England. For more information on the project please see [www.international-comparisons.org.uk](http://www.international-comparisons.org.uk).

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## Summary

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A 2010 report into the extent and causes of international variations in drug usage (the Richards report) explored levels of medicines uptake for 14 categories of drugs in 14 high-income countries during 2008/09. There was a perception among stakeholders at that time that usage of new medicines was low in the UK when compared with other countries. The study showed that while some countries emerged as generally high or low users, there was no uniform pattern across disease areas and categories of drugs. For example, the US ranked first with regard to drug usage for all therapy areas combined, followed by Spain and France, but levels of usage were not consistently high across all disease areas. Generally lower than average levels of usage were observed for Norway and Sweden, and New Zealand had the lowest ranking in nine out of the 14 disease areas. The UK ranked eighth out of the 14 countries but usage patterns varied.

The Office for Health Economics (OHE) (the OHE report) updated the quantitative analyses of medicines uptake to 2012/13, employing the same method, and analysing the same 14 classes of medicines (plus two additional categories) and the same group of comparator countries (excluding Denmark for which up to date data were not available). This found that the US, Spain and France continued to have the highest medicines usage among all 13 countries, although the order had reversed, while Norway Sweden and New Zealand continued to rank lowest. The UK ranked ninth across all of the medicines studied, but as before usage patterns varied across drug categories and disease areas. Specifically, in 2012/13 UK usage per person was above the international average for cancer medicines launched more than ten years ago (as at March 2013) and medicines for the treatment of osteoporosis, respiratory distress syndrome, wet age-related macular degeneration and statins. But it was below the international average for 11 out of 16 categories.

It is important to recognise that there is uncertainty about the optimum level of drug usage in different disease areas and the extent to which high or low usage point to inappropriate use. The appropriate level of usage may vary because of different factors at work in different system contexts. For example, for some disease areas, high drug usage might reflect overuse as a consequence of weaknesses in disease prevention whereas low usage would point to effective and timely treatment. For other disease areas, low usage might point to failure to meet patients' needs while high usage could indicate optimal treatment.

Thus, there are a many possible reasons that might explain variation in medicines usage across countries. The 2010 Richards report noted that causes of international variations in drug usage were complex, and it highlighted a number of themes that were thought to influence the level of usage in the UK compared with other countries. These included health technology assessment processes and outcomes; service planning, organisation and direction as important enablers or barriers to usage; and clinical culture and

attitudes towards treatment. Evidence for the impact of level of spending on health was not thought to be a strong determinant as countries that spent the most on health did not always have the highest levels of usage, while those with low health expenditure could be high users of drugs.

This report builds on the analyses carried in the context of the 2010 Richards report, seeking to better understand the range of causes that may explain international variation in drug usage as observed in the 2012/13 update of the Richards report.

Specifically, we sought to provide:

- a summary overview of key features of the health systems in the 13 countries included in the 2014 update of the report
- a summary overview of the principles of drug assessment or approval processes in the 13 countries covered in the 2014 update of the report
- an exploratory analysis of the “causes” of international variation in medicines usage in five selected areas: dementia, osteoporosis, cancer, diabetes and hepatitis C.

The five areas were selected following recommendations from the Metrics Oversight Group, and confirmed on review of a draft report of the quantitative analysis presented by the OHE in summer 2014 by the Metrics Oversight Group. For each of the five disease areas we reviewed the published evidence on:

- epidemiological factors such as the disease burden (incidence or prevalence) and stage of diagnosis of the disease to understand “population need”
- international variation in drug usage to enable the placing of the quantitative findings of the OHE analysis into the wider context
- aspects of health system and service organisation that were shown to have a direct or indirect impact on drug usage, in particular reimbursement mechanisms, access to diagnosis and treatment more broadly, and other factors identified in the literature.

We drew on an iterative search of the published and grey literature using the bibliographic database PubMed, alongside Google Scholar and searches of websites of governmental and non-governmental agencies or organisations of documents on general health-related policies in the countries in question. It is important to note that it was beyond the scope of the present study to provide a comprehensive review of all possible aspects that could impact on an observed variation in drug usage across countries. A full understanding of system, service and cultural factors would require a different approach, involving working with decisionmakers and practitioners in each country to assess the specific systemic and cultural aspects that inform decisions in daily practice.

**High-income countries vary in the way they fund and organise their health systems but share some common features**

In the majority of the 13 countries reviewed in this report expenditure on health is largely from public sources, mainly taxation and mandatory health insurance. This ranged in 2012 from just under two-thirds in Switzerland to some 85 per cent in Norway and the UK. In the US, just under half of health expenditure is from public sources. The majority of countries also provide (almost) universal coverage, with residence in the given country being the most common basis for entitlement to healthcare. The US

has so far been an outlier in that entitlement to publicly funded health services was dependent on certain conditions such as age (Medicare) or income (Medicaid). The 2010 Patient Protection and Affordable Care Act (ACA) seeks gradually to expand healthcare coverage and it is projected that it will reduce the number of uninsured by half by 2022.

All systems offer a basic basket of services, including general practitioner and specialist care, and hospital inpatient and outpatient services. Among the 13 countries reviewed, access to specialist services tends to be directed by referral. Most countries have assigned a gatekeeping role to general practitioners except for France, Germany, Switzerland and the US, which have put voluntary gatekeeping arrangements in place.

All countries reviewed have introduced user charges for prescription drugs under the public system. The level of cost sharing required varies although each system applies uniform rules, with most countries offering some form of mechanism to protect the income of selected population groups.

Most countries have established national bodies that advise government or are acting on its behalf in decisions about the routine inclusion of new drugs under the publicly funded system

Decisions are typically informed by formal health technology assessments which may be carried out by the relevant institutions or commissioned externally. Public bodies with a largely advisory or guidance producing role have been established in Australia, Canada, France and the UK, whereas in all other countries reviewed, relevant organisations or agencies have a regulatory function, such as Pharmac in New Zealand, or the Federal Joint Committee in Germany. In some countries the ministry of health has remained the final decisionmaker. In the US there is no single (national) body responsible for appraising new drugs for funding but public payers have established their own systems to undertake such assessments. Cost-effectiveness is an overt criterion in informing recommendations on the inclusion of new drugs under the statutory system in Australia, Canada, New Zealand, Norway, Spain, Sweden, Switzerland and the UK. However, decisions do not depend on the cost-effectiveness as the sole criterion with countries also taking account of factors such as patient and therapeutic benefit, health need, budgetary impact and comparative effectiveness, which may play a more important role than cost-effectiveness.

There is no single, overarching “cause” explaining international variation in medicines usage in the five disease areas explored in this study

From our analyses it is not immediately obvious that any particular system characteristic such as the level of overall health expenditure, sources of system funding or coverage acts as a strong determinant of levels of medicines usage. The 2010 report *Extent and Causes of International variations in Drug Usage* suggested that health technology assessment processes and outcomes can have a significant impact on levels of usage. This observation is partly supported by observations from the disease areas reviewed in this report (dementia, osteoporosis, cancer, diabetes and hepatitis C). Policies on the inclusion of new medicines in publicly funded systems are important as they determine whether patients have routine access to a given new medicine, in particular where access is made conditional. One such condition can be the level of cost-sharing required. Thus, evidence in the field of osteoporosis suggests that patients in some European countries may face challenges in accessing osteoporosis medicines where only 50 per cent of the costs are reimbursed. At the same time, evidence in relation to drugs for dementia, osteoporosis, diabetes,

hepatitis C and, to certain degree, cancer, demonstrates that factors other than policies on the inclusion of new medicines in publicly funded systems may be equally or more important in affecting drug uptake. These include: access to (timely) diagnosis; whether or not the disease area is designated a national priority; and the clear identification of responsibilities for managing the disease and the existence of designated care pathways. Each of these factors is discussed in the following sections.

### Evidence for all five disease areas highlights the key role of ensuring access to timely diagnosis to enable appropriate treatment, including drug treatment

For example, regarding osteoporosis, available evidence highlights the role of access to bone density measurement technology (such as dual-energy X-ray absorptiometry) as a potentially greater barrier to treatment than the actual routine availability of drugs under the statutory system. While bone densitometry may in principle be available, related scans may not be (fully) reimbursed, or only reimbursed on certain conditions, which could limit access, with examples highlighted for Germany and France where access to bone densitometry is restricted and osteoporosis prescribing low. While it is difficult to relate these observations directly to variation in osteoporosis treatment uptake, evidence suggests that bone density measurement is associated with anti-osteoporotic drug prescription.

Evidence for cancer also highlights cross-country differences in access to specialists, which likely acts as an important driver for accessing timely treatment. For example, one study found the projected number of new cancer cases per number of medical oncologists substantially higher in the UK than in Austria, Germany, Italy and Sweden. Arguably, the number of specialists can only provide a proxy measure of access to specialist care and it provides little insight into the appropriateness and quality of care delivered, although the observed differences call for further investigation into the accessibility of specialist treatment in the UK.

### Evidence for all disease areas considered suggests that designating a given disease or condition a national priority is likely to lead to increases in medicines access and usage

For example, for dementia, where comprehensive plans for the detection and treatment of dementia have been put in place, these were likely to increase the number of people diagnosed with the disease and, consequently, the number of patients receiving treatment. One such example is the 2009 National Dementia Plan in England, which was associated with an increase in dementia diagnosis rate, and dementia diagnosis rates were highly correlated with prescription rates. The UK was also an example where osteoporosis had been identified as a priority, which was likely associated with a rapid increase in the prescription of osteoporosis medicines.

Making dedicated funds available was also associated with enhanced patient access to medicines as exemplified by the Cancer Drugs Fund in the UK, although questions remain about the resource implications and impact on overall outcomes of assigning specific funds to a selected disease area versus other conditions. Another example of making additional funding available comes from the US where the implementation of Medicare Part D in 2006, which enhanced drug coverage for older people, was associated with greater use of dementia medicines among Medicare beneficiaries.

The clear identification of responsibilities for managing disease and the existence of designated care pathways are important determinants of medicines usage

Studies in the fields of dementia and osteoporosis highlighted the importance of identifying clear pathways with assigned responsibilities for managing a given disease or condition. For example, for osteoporosis it was argued that the majority of patients should be managed at the primary health care level by general practitioners, with specialist referral reserved for difficult cases; a core role was also assigned to fracture liaison services, providing a system for the routine assessment and management of postmenopausal women and older men who have sustained a low trauma fracture. Evidence suggests that uncertainty about responsibilities among care providers was linked with patients falling “through the cracks”, hindering access to appropriate and timely treatment, in particular among those at increased risk of fragility fractures. Similar observations were made for dementia, with evidence suggesting that availability of memory services would increase access to timely diagnosis and thus treatment.

Each of the factors described in this report is likely to play a role in explaining international variation in medicines use, but their relative importance will vary depending on the disease area in question and the system context. It is likely that any given level of use of a given medicine in one country is determined by a set of factors the combination and the relative weight of which will be different in another country.





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# 1. Introduction

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In 2010, the Department of Health published a report led by Professor Sir Mike Richards, which presented a comparative analysis of levels of uptake of a select group of medicines in 14 high-income countries in 2008/09.<sup>(1)</sup> There was a perception among stakeholders at that time that usage of new medicines was low in the UK when compared with other countries. The report followed a commitment made in the 2009 Pharmaceutical Price Regulation Scheme (PPRS) to develop a series of measures that allow comparison of the uptake of new medicines in major European countries. The PPRS is a voluntary, non-contractual agreement negotiated between the Department of Health, acting on behalf of the UK government and Northern Ireland, and the Association of the British Pharmaceutical Industry (ABPI) on behalf of the branded pharmaceutical industry.<sup>(2, 3)</sup> Negotiated for a period of five years, the scheme seeks to control the pricing of all licensed, branded drugs sold to the NHS throughout the UK.

The commitment to comparison was renewed in the 2014 Pharmaceutical Price Regulation Scheme, which noted that “the UK should compare itself with other countries if it is to deliver a world-class NHS”.<sup>(3)</sup> It requested that the “industry, NHS England and the Department [of Health] work together to develop and evolve an approach to the analysis and publication of comparative information on international medicines use on a periodic basis”.<sup>(3)</sup> Overseen by a joint Department of Health, industry and NHS England working group (the Metrics Oversight Group), the approach was to build on the 2010 Richards report, and to comprise two workstreams: a quantitative analysis of medicine usage in 2012/13 carried out by the Office of Health Economics,<sup>(4)</sup> and a qualitative component, exploring possible causes for observed international variation in medicine uptake for a select set of conditions. This document reports on the qualitative component of the work, which was undertaken by RAND Europe.

## 1.1. International variation in drug usage: the 2010 report and 2014 update

The 2010 report *Extent and Causes of International Variations in Drug Usage* (the Richards report) explored levels of medicines uptake for 14 categories of drugs in 14 high-income countries. The range of drugs considered sought to reflect a spectrum of those used to treat acute and long-term conditions, and affecting different population groups.<sup>(1)</sup> It covered drugs for the treatment of cancer, circulatory disease (statins, thrombolytics), long-term conditions (multiple sclerosis, osteoporosis, rheumatoid arthritis biologics), mental health (second-generation dementia), infections (hepatitis C), conditions affecting children (respiratory distress syndrome, respiratory syncytial virus), and wet age-related macular degeneration (Table 1).

**Table 1 Drug categories and molecules included in the 2010 Richards report**

| Condition                            | Category   | Drug molecule   |
|--------------------------------------|--|---|
| Cardiovascular disease               | Statins  | amlodipine/atorvastatin, atorvastatin, ezetimibe, ezetimibe/simvastatin, fluvastatin, lovastatin, lovastatin/nicotinic acid, pravastatin, rosuvastatin, simvastatin   |
|                                      | Thrombolytics for the treatment of acute myocardial infarction | reteplase, streptokinase, tenecteplase  |
|                                      | Thrombolytics for the treatment of stroke                      | Alteplase   |
| Cancer                               | Drugs launched within last 5 years (baseline: 2010)            | bevacicumab, bevacizumab, bortezomib, cetuximab, dasatinib, erlotinib, lapatinib, lenalidomide, nilotinib, panitumumab, pemetrexed, sorafenib, sunitinib, temsirolimus, thalidomide, trabectedin  |
|                                      | Drugs launched 6–10 years ago (baseline: 2010)                 | alemtuzumab, bexarotene, capecitabine, ibandronic acid, imatinib, oxaliplatin, rituximab, tegafur, tegafur uracil, trastuzumab, zoledronic acid   |
|                                      | Drugs launched more than 10 years ago (baseline: 2010)         | calcium folinate + levofolinate, carboplatin, carmustine, chlorambucil, cisplatin, cyclophosphamide, docetaxel, doxorubicin, epirubicin, etoposide, fludarabine, fluorouracil, gemcitabine, hydroxycarbamide, idarubicin, ifosfamide, irinotecan, isosfamide + mesna, lanreotide, mitoxantrone, octreotide, paclitaxel, pamidronic acid, raltitrexed, temozolomide, topotecan, vincristine, vinorelbine |
|                                      | Hormonal drugs   | abarelix, anastrozole, bicalutamide, bicalutamide + goserelin, buserelin, cyproterone, exemestane, flutamide, fulvestrant, goserelin, letrozole, leuprorelin, nilutamide, tamoxifen, triptorelin  |
| Dementia                             |  | donepezil, galantamine, memantine, rivastigmine, tacrine  |
| Hepatitis C                          |  | peginterferon alfa-2a, peginterferon alfa-2b  |
| Mental health                        | Second-generation antipsychotic drugs                          | amisulpride, aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, sertindole, ziprasidone, zotepine  |
| Multiple sclerosis                   |  | glatiramer acetate, interferon beta-1a, interferon beta-1b, natalizumab   |
| Osteoporosis                         |  | alendronic acid, clodronic acid, etidronic acid, ibandronic acid, pamidronic acid, parathyroid hormone, raloxifene, strontium ranelate, teriparatide, zoledronic acid   |
| Respiratory distress syndrome        |  | beractant, calfactant, poractant alfa, surfactant (bovine lung)   |
| Respiratory syncytial virus          |  | Palivizumab   |
| Rheumatoid arthritis                 |  | abatacept, adalimumab, anakinra, etanercept, infliximab, rituximab, tocilizumab   |
| Wet age-related macular degeneration |  | anecortave, pegaptanib, ranibizumab, verteporfin  |

Source: Richards (2010) (1)

Analysing sales data for 2008/09, the 2010 Richards report documented the following key observations:

- There was no uniform pattern in drug usage across disease areas and categories of drugs among the 14 high-income countries considered.
- The US ranked first with regard to drug usage for all therapy areas combined, followed by Spain and France, but levels of usage were not consistently high across all disease areas. For example, the

US ranked high on usage of antipsychotics (rank 1), dementia drugs (rank 1), drugs for the treatment of respiratory distress syndrome (rank 1), and for rheumatoid arthritis, but only 13th (out of 14) for hormonal drugs for the treatment of cancer. France ranked highest for all cancer drugs except hormonal drugs for the treatment of cancer, but comparatively low for multiple sclerosis drugs (rank 11), antipsychotics (rank 10) and rheumatoid arthritis drugs (rank 9). Spain showed the highest usage of osteoporosis drugs of the 14 countries but had lower usage levels for statins (rank 10) and for drugs for the treatment of wet age-related macular degeneration (rank 10).

- Generally lower than average levels of usage were observed for Norway (rank 10) and Sweden (rank 13), and New Zealand had the lowest ranking in nine out of the 14 disease areas including for all categories of cancer drugs.
- The UK ranked eighth out of the 14 countries but usage patterns varied. For example, the UK ranked highly in three areas – acute myocardial infarction (rank 2), respiratory distress syndrome (rank 4) and statins (rank 2) but had a relatively low rank in seven categories. These included selected cancer drug categories, in particular cancer drugs that were launched in the 5 years preceding the review (rank 12) and those older than ten years (rank 10), dementia (rank 11), hepatitis C (rank 13), multiple sclerosis (rank 13), rheumatoid arthritis (rank 10) and second-generation antipsychotics (rank 11).

More recently, the Office for Health Economics (OHE) (2014 OHE report) updated the quantitative analyses of medicines uptake in 2008/09 as presented in the Richards report to 2012/13, employing the same method, and analysing the same classes of medicines and the same group of comparator countries (excluding Denmark for which up to date data were not available).(4) It added analyses for two sub-classes of medicines for the treatment of stroke (novel oral anti-coagulants) and hepatitis C (protease inhibitors) and for two disease areas (HIV and diabetes) to reflect uptake of newly launched medicines.

The OHE analysis found that in 2012/13 the UK ranked ninth for all of the medicines studied among 13 high income countries. Specifically, UK usage per person was above the international average for five of the 16 categories of medicines studied: cancer medicines launched more than ten years ago (as at March 2013) and medicines for the treatment of osteoporosis, respiratory distress syndrome, wet age-related macular degeneration, and statins. However, as shown in Table 2, the UK was below the international average for 11 out of 16 categories, although for three of these, UK usage was within 10 per cent of the international average (cancer medicines launched within the past five years as at March 2013), second-generation antipsychotics and thrombolytics for the treatment of acute myocardial infarction.

When compared with the average of five large European markets including the UK (EU5: France, Germany, Italy, Spain and the UK), per person usage in the UK was below the EU5 average for nine out of 16 classes of medicines and above for seven (Table 2).

**Table 2 Usage of medicines in the UK in selected disease areas in international comparison, 2012/13**

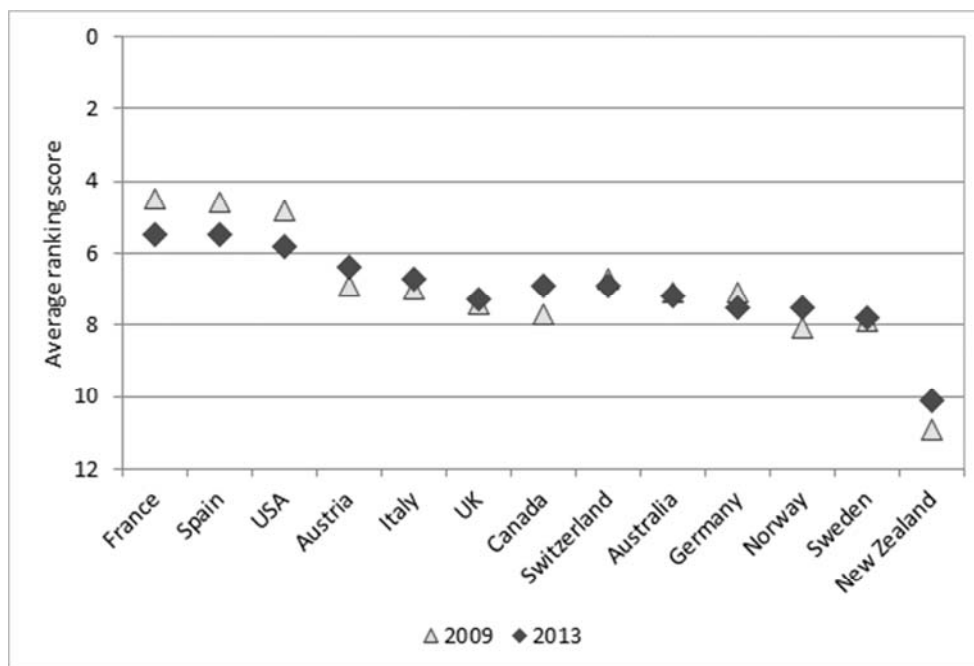
| Condition                            | Category   | UK rank 2012/13 | UK rank 2008/09 | UK usage as % of all countries average | UK usage as % of EU5 |
|--------------------------------------|--|-----------------|-----------------|--|----------------------|
| Cardiovascular disease               | Statins  | 4               | 2               | 121                                    | 130                  |
|                                      | Thrombolytics for the treatment of acute myocardial infarction                         | 8               | 2               | 98                                     | 92                   |
|                                      | Thrombolytics for the treatment of stroke  | 7               | 8               | 86                                     | 110                  |
| Cancer                               | Drugs launched within last 5 years (baseline: 2010 or 2013)                            | 7               | 10              | 92                                     | 94                   |
|                                      | Drugs launched 6–10 years ago (baseline: 2010 or 2013)                                 | 12              | 8               | 54                                     | 44                   |
|                                      | Drugs launched more than 10 years ago (baseline: 2010 or 2013)                         | 4               | 9               | 124                                    | 103                  |
|                                      | Hormonal drugs   | 9               | 5               | 73                                     | 68                   |
| Dementia                             |  | 8               | 10              | 86                                     | 83                   |
| Hepatitis C                          | Peginterferons   | 11              | 13              | 73                                     | 59                   |
| Mental health                        | Second-generation antipsychotic drugs  | 9               | 10              | 92                                     | 110                  |
| Multiple sclerosis                   |  | 12              | 12              | 35                                     | 32                   |
| Osteoporosis                         |  | 3               | 6               | 128                                    | 118                  |
| Respiratory distress syndrome        |  | 2               | 4               | 157                                    | 151                  |
| Respiratory syncytial virus          |  | 9               | 8               | 52                                     | 48                   |
| Rheumatoid arthritis                 |  | 8               | 9               | 63                                     | 93                   |
| Wet age-related macular degeneration |  | 5               | 4               | 131                                    | 137                  |
| <b>Added 2012/13</b>                 |  |                 |                 |  |                      |
| Stroke                               | Novel oral anticoagulants  | 10              |                 | 19                                     | 21                   |
| Hepatitis C                          | Protease inhibitors  | 10              |                 | 49                                     | 48                   |
| HIV                                  | HIV medicines  | 6               |                 | 95                                     | 79                   |
| Diabetes                             | Insulins   | 5               |                 | 104                                    | 102                  |
|                                      | Other antidiabetics  | 2               |                 | 156                                    | 122                  |
|                                      | Dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) agonists | 11              |                 | 33                                     | 19                   |

Source: O'Neill and Sussex (2014) (4)

Comparing usage with the earlier analysis by Richards (2010) for the period 2008/09,(1) the OHE analysis (2014) further showed that UK usage per head of population:

- had increased relative to the international average in 11 out of 16 classes of medicines
- had remained below the international average in seven out of the 11: cancer medicines less than five years old, alteplase for stroke, second-generation anti-psychotics, medicines for the treatment of dementia and for multiple sclerosis, peginterferons for hepatitis C, medicines for the treatment of respiratory syncytial virus
- exceeded the international average for cancer medicines more than 10 years old and for medicines for the treatment of osteoporosis, respiratory distress syndrome and wet age-related macular degeneration
- fell relative to the international average for cancer medicines 6–10 years old, hormonal cancer medicines, thrombolytics to treat acute myocardial infarction and TNF medicines used against rheumatoid arthritis. It also fell for statins although it remained above 100 per cent of that average.

When interpreting overall country rankings across the therapeutic groups it is important to note that average ranking scores varied only slightly among the majority of countries considered. Furthermore, when comparing countries' 2012/13 average score with that of 2008/09, the OHE analysis demonstrated that the relative positions of countries had changed only slightly but that their ranking scores had converged somewhat to become more similar, so there was less variation in average ranking scores across the sample of countries considered (Figure 1).



**Figure 1 Average ranking of ranking scores by country, 2008/09 and 2012/13**

Source: adapted from O'Neill and Sussex (2014) (4)

The 2010 Richards report and its 2014 update by the OHE are unique in that their comparative analyses covering a wide range of therapeutic areas across a broad number of countries are not available elsewhere.

Where comparative analyses are available, these typically cover a small number of disease areas, or a small number of countries (see also Chapter 2). The Organisation for Economic Co-operation and Development (OECD) in its international comparative analysis of health system indicators includes an assessment of variation in “pharmaceutical consumption” measured as defined daily doses per 1,000 population for a small number of categories.<sup>(5)</sup> In its 2013 report this comprised an assessment of consumption in five areas: antihypertensive drugs, cholesterol-lowering drugs, antidiabetics, antidepressants and antibiotics. These showed that consumption in the UK in 2011 of cholesterol-lowering drugs and antidiabetics was among the highest across OECD countries, exceeding the average of 23 OECD countries by respectively 42 per cent and 30 per cent. Consumption of antidepressants was also higher, by about 25 per cent above the OECD-23 average, while similar to the average for antihypertensive drugs.

When considering these variations it is important to recognise that there is uncertainty about the optimum level of drug usage in different disease areas and the extent to which high or low usage point to appropriate or indeed inappropriate use. The appropriate level of usage may vary because of different factors at work in different system contexts. For example, for some disease areas, high drug usage might reflect overuse as a consequence of weaknesses in disease prevention whereas low usage would point to effective and timely treatment. For other disease areas, low usage might point to failure to meet patients’ needs while high usage could indicate optimal treatment.

There are thus a number of reasons that might explain variation in medicines usage across countries. In order to explain the observed variation, Richards (2010) set out a series of hypotheses.<sup>(1)</sup> These included:

- *epidemiological factors*, namely differences in incidence or prevalence, as well as stage of diagnosis impacting on how many patients are suitable for a particular drug; usage patterns as reported by Richards (2010) (1) and by the OHE (2014) (4) were not adjusted for underlying disease prevalence
- *system factors*, such as levels of expenditure on health, pharmaceutical spending, and the nature of the pharmaceutical market
- *reimbursement factors*, including drug pricing strategies, the use of health technology assessment processes and their impact on prescribing behaviour
- *service organisation and capacity factors*, such as the extent of national prioritisation for a disease area, the role of direct access to specialists, the existence of initiatives to influence prescribing practice, capacity limitations at different stages of the patient pathway, and funding mechanisms for different modes of drug administration
- *cultural factors*, including clinical attitudes (towards risk or national guidance), the extent of research activity, the influence of different professions (for example pharmacists), patient attitudes towards treatment, and patient support organisations.

The Richards review tested these hypotheses with key stakeholder groups in the UK and it was further informed by evidence reviews. It found that causes of international variation in drug usage were complex, with no single consistent cause identified across disease areas and drug categories. The report however noted a number of themes that were thought to influence the level of usage in the UK compared with other countries:



- Health technology assessment processes and outcomes can have a significant impact on levels of usage.
- Service planning, organisation and direction setting play an important role in enabling or restricting usage.
- Clinical culture and attitudes towards treatment remain important determinants in levels of uptake.

As indicated above, the Richards review also considered factors such as the level of spending on health, but this was not thought to be a strong determinant as countries that spent the most on health, such as the US, did not always have the highest levels of usage, while those with low health expenditure could be high users of drugs; examples for the latter included Spain and the UK.

## 1.2. Our approach

In this report, we sought to build on analyses carried out to inform the 2010 Richards report,(1) principally following the same structure, and adapting to the 2014 update by the OHE where appropriate. We thus provide:

- a summary overview of key features of the health systems in the 13 countries included in the 2014 update of the report (expenditure, principles of health system finance, governance and organisation (e.g. gatekeeping), coverage, user charges)
- a summary overview of the principles of drug assessment or approval processes in the 13 countries covered in the 2014 update of the report
- an exploratory analysis of the “causes” of international variation in medicines usage in five selected areas: dementia, osteoporosis, cancer, diabetes and hepatitis C.

The five areas were selected following recommendations from the Metrics Oversight Group, and confirmed on review of a draft report of the quantitative analysis presented by the OHE in summer 2014 by the Metrics Oversight Group.

In line with the hypotheses set out in the 2010 Richards report as described above we sought to understand, for the areas under review:

- epidemiological factors such as the disease burden (incidence or prevalence) as well as stage of diagnosis of the disease to understand “population need”
- existing evidence on international variation in drug usage to enable the placing of the quantitative findings of the OHE analysis into the wider context
- aspects of health system and service organisation that were shown to have a direct or indirect impact on drug usage, in particular reimbursement mechanisms, access to diagnosis and treatment more broadly, and other factors identified in the literature.

We drew on an iterative search of the published and grey literature using the bibliographic database PubMed, alongside Google Scholar and searches of websites of governmental and non-governmental agencies or organisations of documents on general health-related policies in the countries in question. We

applied broad search terms, using different combinations of (“/” indicating “or”) “use/utilization/consumption/prevalence/burden/epidemiology”, and “international/cross-national/Europe/United States/Canada/Australia” linked to disease in question (e.g. “osteoporosis”). We used Mesh terms and free text, limiting mention of terms to abstract or title where appropriate and considering literature published from 2009 onwards. While search terms were used systematically, much of the relevant literature was identified through snowballing from forward and backward citation searching from key papers identified from the PubMed and Google Scholar searches.

It is important to note that it was beyond the scope of this study to provide a comprehensive review of all possible aspects that could impact on variation in drug usage across countries. A full understanding of system, service and cultural factors would require a different approach, involving working with decisionmakers and practitioners in each country to assess the specific systemic and cultural aspects that inform decisions in daily practice.

## 2. Overview of findings

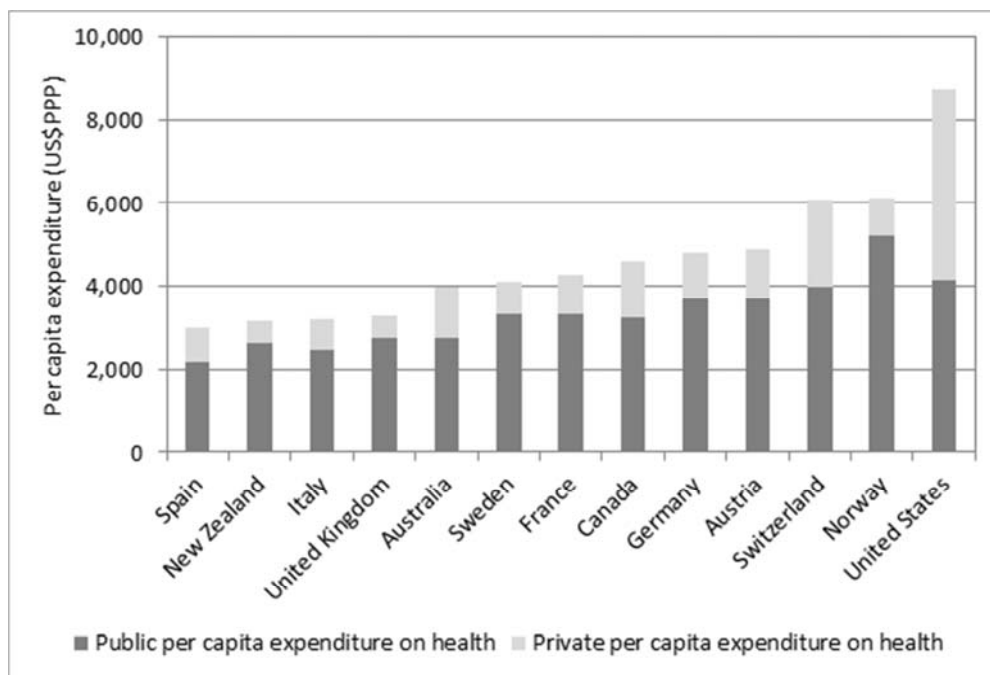
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### 2.1. Summary overview of key features of the health systems in 13 countries

Pharmaceutical policies in OECD countries vary considerably. This largely reflects individual countries' institutional, political, social and historical contexts.(6–8) We here provide a summary overview of some of the key health system features in the 13 countries included in this report in an attempt to understand the extent of differences in levels of expenditure on health generally and pharmaceuticals in particular, alongside other features of the health system such as principles of organisation and of access to health services, including pharmaceuticals. These are summarised in the Appendix. It was beyond the scope of this study to provide a comprehensive review of pharmaceutical policies in the countries considered here; these are described in detail elsewhere.(6, 8, 9) Instead we focused on selected aspects of policies on accessing pharmaceuticals under the relevant public or statutory systems that might explain observed variation in the usage of medicines across countries. As highlighted in the 2010 report, it is important to note that health systems are complex, and it is difficult to establish a direct causal relationship between a particular health system feature and the level of medicines uptake.(1)

#### *2.1.1. Principles of health system financing, organisation and access*

In the majority of the 13 countries reviewed in this report expenditure on health is largely from public sources, such as taxation and mandatory health insurance. This ranged in 2012 from just under two-thirds in Switzerland to some 85 per cent in Norway and the UK.(10) In the US, just over half of health expenditure is from private sources, with some 48 per cent of the health system funded publicly (Figure 2).

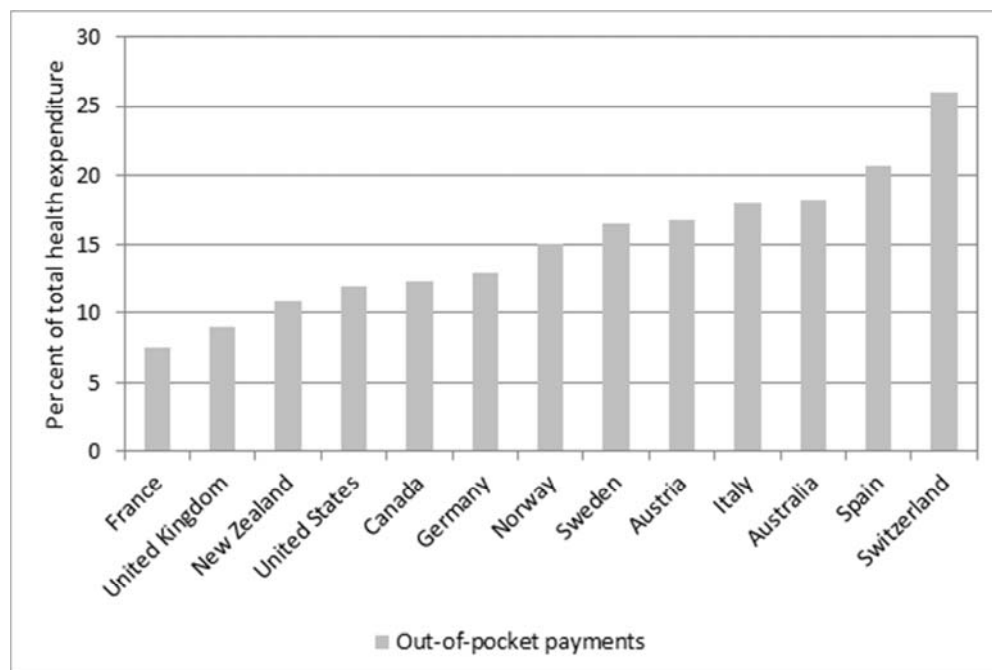


**Figure 2 Per capita expenditure on health (US\$ purchasing power parity) in 13 OECD countries, 2012**

Source: OECD (2014) (10)

Eight of the countries considered here are predominantly funded through taxation (Australia, Canada, Italy, New Zealand, Norway, Spain, Sweden, UK), accounting for between 68 per cent (in Spain) and 84 per cent (in the UK) of total health expenditure in 2012. Germany and France are mainly financed from mandatory health insurance, at respectively 68 per cent and 74 per cent of total health expenditure, with mandatory health insurance also forming an important component in the Austrian and Swiss health systems (at around 45 per cent). The US is the only country where private (or voluntary) health insurance (PHI) forms a significant part of health system financing (at 33 per cent), along with public insurance schemes such as Medicare for the elderly (at 41.5 per cent). Elsewhere, PHI accounts for around 13–15 per cent or less in France and Canada.

Out-of-pocket payments play a role in all health systems reviewed here, accounting for some one-quarter of total health expenditure in Switzerland, and about one-fifth in Spain, Italy and Australia to 7.5 per cent in France (Figure 3). However, only a small proportion of household out-of-pocket payments are through cost-sharing arrangements.



**Figure 3 Household out-of-pocket payments as percentage of total health expenditure in 13 OECD countries, 2012**

Source: OECD (2014) (10)

The majority of countries reviewed provide (almost) universal coverage, with residence in the given country being the most common basis for entitlement to healthcare. Switzerland has made the purchase of basic health insurance cover mandatory for all Swiss residents in 1996; about 80 per cent of the population hold private health insurance to cover additional services.<sup>(11)</sup> In Germany, until recently health insurance was mandatory up to a specified income threshold only; from 2009 health insurance is mandatory for all citizens.<sup>(12)</sup> The US has so far been an outlier in that it did not offer universal access to healthcare; instead entitlement to publicly funded services was dependent on certain conditions, with Medicare providing healthcare for those aged 65 years and over, Medicaid for those under a certain income threshold or the Veterans Health Administration for veterans. However, with the 2010 Patient Protection and Affordable Care Act (ACA), healthcare coverage is gradually being expanded, requiring all residents to obtain health insurance or pay a financial penalty.<sup>(13)</sup> The ACA is being phased in gradually with the most significant changes taking place in 2014. It is projected that the implementation of the ACA will reduce the number of uninsured by half by 2022 (to 25 million).

The scope of services covered under the statutory system is fairly similar among countries reviewed with all systems offering a basic basket of services, including general practitioner and specialist care, and hospital inpatient and outpatient services.<sup>(14)</sup> There is however variation in relation to services such as mental healthcare, rehabilitation, dental care and optometry. Prescription drugs are frequently covered under the publicly funded system but usually require patient co-payment (see Table 3 below).

Among the 13 countries included in this review, access to specialist services tends to require referral. Most countries have assigned a gatekeeping role to general practitioners (GPs). France, Germany, Switzerland and the US have put voluntary gatekeeping arrangements in place, with the “preferred doctor” scheme in

France including financial incentives encouraging residents to sign up with the scheme.<sup>(15)</sup> In Australia, specialists can claim a higher rebate when the patient is referred by a GP while in France and Sweden patients may access specialist care directly but they have to make a co-payment to do so.

All countries reviewed here impose cost sharing for services covered under the statutory system. While there is some variation among countries regarding cost sharing arrangements for accessing generalist or specialist care, all have introduced user charges for prescription drugs under the public system (Table 3). User charges for drugs most often take the form of co-insurance (with differentiated rates) or fixed prescription charges. Several countries also use deductibles.<sup>(16)</sup> The level of cost sharing required varies among countries although each system applies uniform rules, with most countries offering some form of mechanism to protect the income of selected population groups, for example through reduced rates (e.g. concessional beneficiaries in Australia), exemptions from charges (e.g. children and pregnant women in England, Italy, Norway and Sweden; people on low incomes in Italy and England; (some) people with chronic conditions and disabilities in England, France and Italy); annual caps on expenditure (e.g. Australia, Norway, Sweden); and complementary private health insurance covering statutory user charges (e.g. France).<sup>(14)</sup> Pharmaceuticals dispensed in the inpatient sector do not typically incur a separate co-payment.

**Table 3 Cost-sharing arrangements for prescription drugs in 13 countries**

|             | User charge required | Exemptions                  |            |                   | Maximum out-of-pocket limit   |
|-------------|----------------------|-----------------------------|------------|-------------------|---|
|             |                      | Chronically ill or disabled | Low income | Age               |   |
| Australia   | Yes                  | Yes                         | Yes        | Seniors, children | Fixed, dependent on type of patient   |
| Austria     | Yes                  |                             | Yes        | Seniors           | 2% of annual net income   |
| Canada      | Yes                  |                             | Yes        |                   | Varies by plan  |
| France      | Yes                  | Yes                         | Yes        |                   |   |
| Germany     | Yes                  | Yes                         |            | Children          | 2% of annual net household income (1% of income for chronically ill)              |
| Italy       | Yes                  | Yes                         | Yes        | Seniors, children |   |
| New Zealand | Yes                  |                             | Yes        | Children          |   |
| Norway      | Yes                  | Yes                         |            | Seniors, children | Set annually; Nkr €520 for “blue list” drugs                                      |
| Spain       | Yes                  | Yes                         |            |                   |   |
| Sweden      | Yes                  | Yes                         |            | Children          |   |
| Switzerland | Yes                  |                             |            | Children          | Set at CHF 700 for adults and CHF 350 for children (treatment costs, incl. drugs) |
| UK/England  | Yes                  | Yes                         | Yes        | Seniors, children |   |
| US          | Varies               | Varies                      | Varies     | Varies            | Varies  |

Source: adapted from Paris (2014) (16), Barnieh et al. (2014) (17), Ringard et al. (2013) (18), Thomson et al. (2013) (14)

Because of the multiple payer system, cost sharing arrangements vary widely in the US. For example, within the Medicare system, the level of reimbursement under the statutory plan depends on the type of health insurance plan taken out by the individual Medicare beneficiary, and reimbursement may be partial or in full. (19)

### *2.1.2. Principles of regulating access to pharmaceuticals*

Many, although not all, OECD countries have established national bodies separate from the ministry of health, which have either an advisory role or a regulatory function and make decisions on behalf of the ministry about the inclusion of new drugs under the publicly funded or statutory health system.(20) Decisions are typically informed by formal health technology assessments, which may be carried out by the relevant institutions or commissioned externally. Public bodies with a largely advisory or guidance producing role have been established in Australia, Canada, France and the UK. In all other countries reviewed here, relevant organisations or agencies have a regulatory function, such as Pharmac in New Zealand, or the Federal Joint Committee (G-BA) in Germany. Although some countries have established regulatory bodies separate from the ministry of health, the ministry has remained the final

decisionmaker.(21) In Austria, decisions on the inclusion (or exclusion) of medicines into the positive list (Reimbursement Codex) are made by the Federation of Social Security Institutions although decisions may be reviewed on request by the federal ministry of health.(22)

Because of the diversity of the US health system there is no single (national) body responsible for appraising new drugs for funding; however public payers such as Medicare and Medicaid, which are administered by the Centers for Medicare and Medicaid Services (CMS) and the Veterans Health Administration, have established their own systems to undertake such assessments, as have some private payers such as Kaiser Permanente, which conducts reviews to inform coverage decisions through the Interregional New Technologies Committee, among other resources.(23) The Centers for Medicare and Medicaid Services undertake or commission technology reviews to inform Medicare's national coverage determinations (NCDs).(24) In the absence of a national coverage policy an item may be covered at the discretion of Medicare contractors based on a local coverage determination (LCD). The 2010 Patient Protection and Affordable Care Act (ACA) established the non-profit Patient-centred Outcomes Research Institute (PCORI) tasked with undertaking comparative effectiveness assessments of medical treatments, including drugs.(25) The purpose of the institute is to "assist patients, clinicians, purchasers, and policymakers in making informed health decisions", but the ACA explicitly states that its work may not be construed to "permit the Institute to mandate coverage, reimbursement, or other policies for any public or private payer" or used to "deny coverage".(26)

The approach for assessment of new drugs in place in England and Wales in the form of the National Institute for Health and Care Excellence (NICE) has been considered as a yard-stick in the literature.(27) It should be noted, however, that NICE's role is limited to producing guidance, and this function is separate from pricing and reimbursement decisions, which are the responsibility of the Department of Health. While the majority of countries reviewed here employ robust criteria for pharmaceutical assessment, reimbursement or subsidy (including the use of cost-effectiveness criteria), processes employed by NICE such as the transparency of the guidance-development process, including the use of an explicit incremental cost-effectiveness ratio (alongside assessment of relative clinical effectiveness), are widely acknowledged.(28) Cost-effectiveness is an overt criterion in informing recommendations on the inclusion of new drugs under the statutory system in Australia, Canada, New Zealand, Norway, Spain, Sweden, Switzerland and the UK. At the same time, decisionmaking does not depend on the cost-effectiveness as the sole criterion with countries also taking account of factors such as patient and therapeutic benefit, health need, budgetary impact and comparative effectiveness, which may play a more important role than cost-effectiveness.(20) In countries such as Germany explicit consideration of the economic perspective has only recently become a formal requirement to inform the determination of maximum reimbursement limits for pharmaceuticals in the statutory system. From 2011 all newly licensed medicines are subject to a ("early") benefit assessment to assess the added benefit to patients and, on request, this may be followed by a cost-benefit assessment to help inform price setting.(29)

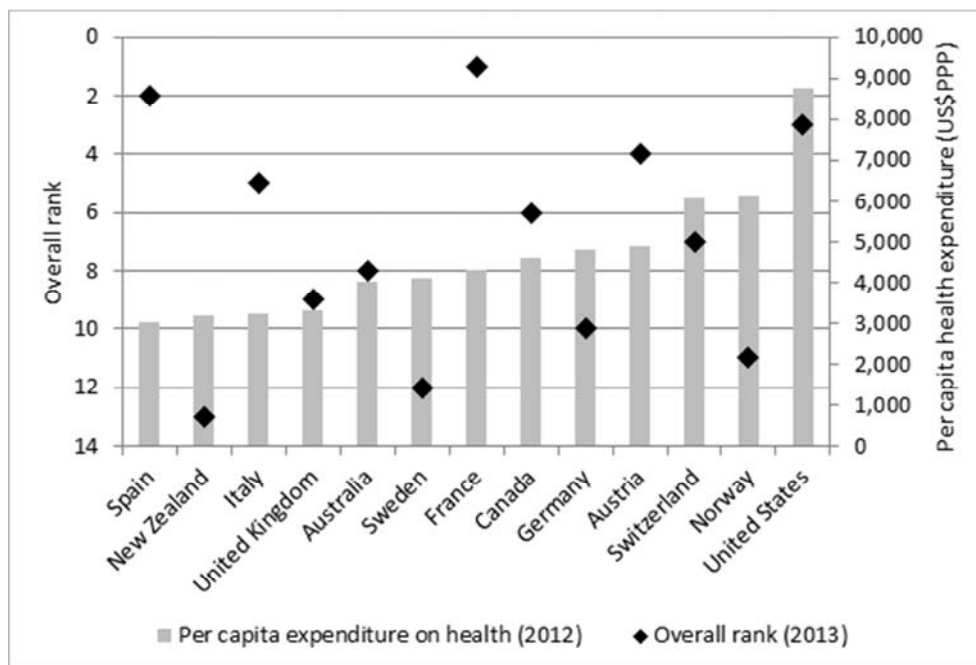
In the US, decisionmaking criteria for drug reimbursement vary by payer, but payers typically focus on therapeutic benefit although not necessarily based on a comparative assessment. For example, legislation on Medicare (Part A or B) stipulates that no payment may be made for expenses incurred for items which "are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member".(24) The determination whether or not a particular service



(including drugs) is covered by Medicare fully or with limitations takes into account whether the item or service is safe, effective and appropriate, and whether it leads to improved health outcomes.

## 2.2. “Causes” of international variation in medicines usage: an exploration of five disease areas

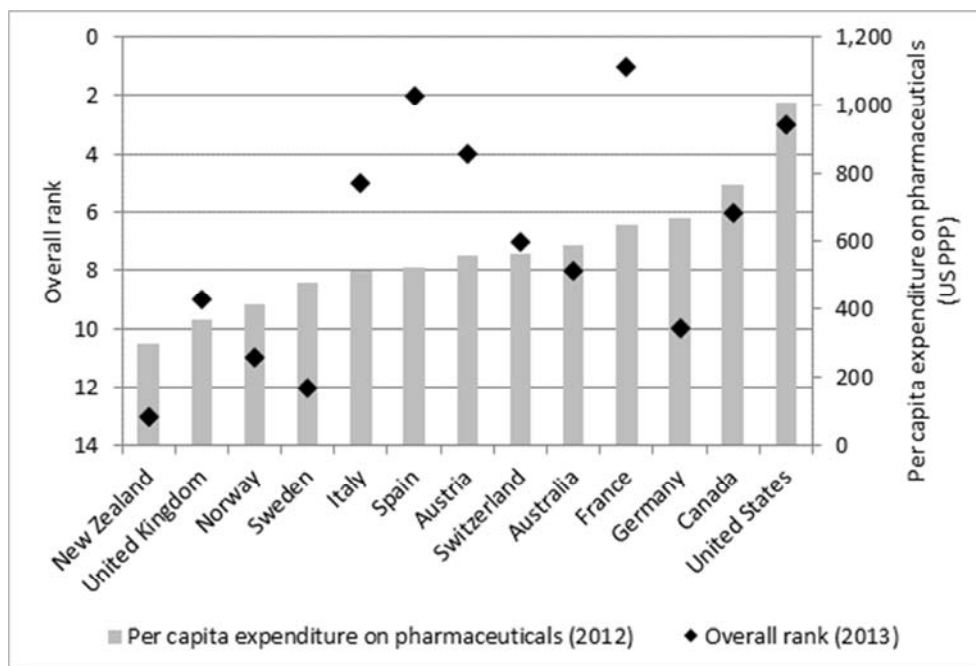
Considering general system factors as described in the preceding sections, it is not immediately obvious that any particular system characteristic such as the level of overall health expenditure, sources of system funding or coverage act as a strong determinant on levels of medicines usage. This is illustrated in Figure 4, which shows total expenditure on health per capita in 2012 (or latest available) in the 13 countries reviewed against their overall ranking of drug usage (2012/13) across the categories of drugs as described in the 2014 OHE analysis (correlation coefficient of 0.16).



**Figure 4 Total expenditure on health per capita (US\$ purchasing power parity) in 13 countries (2012 or latest available) against overall ranking of drug usage across 14 therapy areas**

Sources: OECD (2014) (10) (expenditure data); O’Neill and Sussex (2014) (4) (country rankings of drug usage)

Setting countries’ overall ranking of drug usage in 2012/13 against total expenditure on pharmaceuticals (2012 or latest available) identifies a positive correlation (correlation coefficient 0.57) (Figure 5). This indicates that countries that spend more on pharmaceuticals tend to have a higher usage, on aggregate, of the range of medicines considered in the 2014 OHE analysis but it but provides little insight on whether higher usage is appropriate.



**Figure 5 Total expenditure on pharmaceuticals per capita (US\$ purchasing power parity) in 13 countries (2012 or latest available) against overall ranking of drug usage across 14 therapy areas**

Sources: OECD (2014) (10) (expenditure data); O'Neill and Sussex (2014) (4) (country rankings of drug usage)

The 2010 report *Extent and Causes of International Variations in Drug Usage* suggested that health technology assessment processes and outcomes can have a significant impact on levels of usage.<sup>(1)</sup> As we have described above, all countries considered in this study employ some form of health technology assessment or effectiveness research to help inform recommendations or decisionmaking on the routine funding of new medicines under the public system. However, approaches vary across countries, as do the criteria that are being used to inform recommendations or decisionmaking, in particular with regard to the consideration of cost-effectiveness.

### Policies on the inclusion of new medicines in publicly funded systems

Comparative analyses of medicines use in different countries have pointed to the role of policies on the inclusion of new medicines in publicly funded systems as a potentially important determinant of variation in medicines usage.<sup>(30, 31)</sup> An early comparative study of patient access to 71 licensed pharmaceuticals in the UK and the US found that between 1999 and 2005 NICE had been slower than seven leading players in the US to issue market authorisation for a subset of 64 of these drugs.<sup>(32)</sup> The US plans were also found to be quicker in deciding whether the US would routinely fund drugs following their market approval than the UK, while the percentage of drugs covered by US plans was the same as that recommended for reimbursement and use in the NHS in the UK. Thus, while the UK was found to be slower in adopting these drugs, the end result was similar.

A more recent analysis by the European Federation of Pharmaceutical Industries and Associations (EFPIA) highlighted that for 66 new medicines with first EU marketing authorisation in the period 2008–2010, Austria, Denmark and the UK had, by mid-2011, the highest rate of availability. Availability

was measured by the number of medicines routinely available to patients in European countries and this was found to be 77 per cent in the UK (compared with for example 35 per cent in France and 38 per cent in Spain).(33) Furthermore, the average time between marketing authorisation and routine patient access (the number of days elapsing from the date of EU marketing authorisation to the day of completion of post-marketing authorisation administrative processes) was shortest in Denmark and the UK, at respectively 116 and 118 days, compared with 272 days in Sweden, 316 in France and 352 in Spain. While not directly comparable, as the analysis by EFPIA captures sales of drugs that had received market authorisation, whether or not NICE had recommended their routine use, the latter European analysis suggests that the time-to-routine access to new drugs in the UK has shortened over time. This is supported by available data on the time taken by NICE to issue appraisal guidance on new medicines.(34) Overall, available evidence suggests that processes for reimbursement recommendations or decisions on the usage of new medicines are multi-faced and complex, and their contribution to international variation in the uptake of drugs remains challenging to disentangle.

Observations from the disease areas reviewed in this report highlight that policies on the inclusion of new medicines in publicly funded systems are important as they determine whether patients have routine access to a given new medicine, in particular where access is made conditional. For example, evidence in the field of osteoporosis found that patients in some European countries may face challenges in accessing osteoporosis medicines where only 50 per cent of the costs are reimbursed; other evidence suggests that in France the reimbursement process was perceived as complex by GPs, so potentially impacting prescribing behaviour (see Chapter 3). However, at the same time, evidence for dementia, osteoporosis, hepatitis C and, to certain degree, cancer demonstrates that factors other than drug policies on the inclusion of new medicines in publicly funded systems may be equally or more important in affecting drug uptake. These include: access to (timely) diagnosis; whether or not the disease area is designated a national priority; and the clear identification of responsibilities for managing the disease and the existence of designated care pathways.

### Access to (timely) diagnosis

Evidence for all four disease areas highlights the key role of ensuring access to timely diagnosis to enable appropriate treatment, including drug treatment. For example, available evidence on osteoporosis highlights the role of access to bone density measurement technology (such as dual-energy X-ray absorptiometry) as a potentially greater barrier to treatment than the actual reimbursement of drugs.(35) While bone densitometry may in principle be available, related investigations may not be (fully) reimbursed, or only reimbursed under certain conditions, which could limit access, with examples highlighted in Germany and France. While it is difficult to relate these observations directly to variation in osteoporosis treatment uptake, evidence suggests that bone density measurement is associated with anti-osteoporotic drug prescription.(36)

Evidence for cancer also highlights cross-country differences in access to specialists, which likely acts as an important driver for accessing timely treatment. For example, one study found the projected number of new cancer cases per number of medical oncologists substantially higher in the UK than in Austria, Germany, Italy and Sweden. Arguably, the number of specialists can only provide a proxy measure of access to specialist care and it provides little insight into the appropriateness and quality of care delivered,

although the observed differences call for further investigation into the accessibility of specialist treatment in the UK.

### National prioritisation

Evidence for all disease areas considered here suggests that designating a given disease or condition a national priority is likely to lead to increases in medicines access and usage. For example, it was noted that where comprehensive plans for the detection and treatment of dementia have been put in place, these were likely to increase the number of people diagnosed with the disease and, consequently, the number of patients receiving treatment. One such example is the 2009 National Dementia Plan in England, which was shown to be associated with an increase in dementia diagnosis rate; as dementia diagnosis rates were highly correlated with prescription rates, the rate of prescriptions for dementia drugs increased by 11 per cent in 2010 and 24 per cent in 2011 compared with 2009.<sup>(37)</sup> The UK was also given as an example where osteoporosis had been identified as a priority, which was likely associated with an observed rapid increase in uptake in osteoporosis medicines.<sup>(35)</sup>

Making dedicated funds available was also found to be associated with enhanced patient access to medicines as exemplified by the Cancer Drugs Fund in the UK,<sup>(38)</sup> although questions remain about the resource implications and impact on overall outcomes of assigning specific funds to a selected disease area versus other conditions. One other example of making additional funding available comes from the US where the implementation of Medicare Part D in 2006, which enhanced drug coverage for older people, was associated with greater use of dementia medicines among Medicare beneficiaries who experienced improvements in drug coverage under Medicare Part D.<sup>(39)</sup>

### Disease management and care pathways

Studies in the fields of dementia and osteoporosis highlighted the importance of identifying clear pathways with assigned responsibilities for managing a given disease or condition. For example, for osteoporosis it was argued that the majority of patients should be managed at the primary health care level by general practitioners, with specialist referral reserved for difficult cases; a core role was also assigned to fracture liaison services, providing a system for the routine assessment and management of postmenopausal women and older men who have sustained a low trauma fracture.<sup>(35)</sup> Available evidence suggests that uncertainty about responsibilities among care providers was linked with patients falling “through the cracks”, hindering access to appropriate and timely treatment, in particular among those at increased risk for fragility fractures.<sup>(40)</sup> Similar observations were made for dementia, with evidence suggesting that availability of memory services would enhance access to timely diagnosis and thus treatment.

## 3. Dementia

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### 3.1. Background

Dementia is a neurodegenerative disease that is characterised by chronic or progressive dysfunction of brain function, resulting in cognitive decline.<sup>(41)</sup> The cognitive changes are commonly accompanied by changes in or deterioration of mood or behaviour. The most common form of dementia is Alzheimer's disease, which in Europe and North America accounts for 60–70 per cent of cases, followed by vascular dementia and dementia with Lewy bodies.<sup>(42)</sup> Dementia is one of the main causes of disability in older people and overall incidence increases with age. It is associated with a substantial economic burden, which in western Europe has been estimated to account for 1.3 per cent of GDP in 2010.<sup>(43)</sup>

There are currently no pharmacological treatments available that will cure or even alter the progressive course of dementia, albeit ongoing research investigating numerous new therapies.<sup>(42)</sup> Treatments that are available address cognitive symptoms and can help maintain function. Two classes of drugs have been approved for the management of Alzheimer's disease: acetylcholinesterase (AChE) inhibitors and the NMDA antagonist memantine.<sup>(44)</sup> In its most recent guidance from 2011, NICE recommends the AChE inhibitors donepezil, galantamine and rivastigmine for the management of mild to moderate Alzheimer's disease (under specified conditions) while memantine is recommended for managing Alzheimer's disease for people with moderate disease who cannot take AChE inhibitors or for those with severe Alzheimer's disease.<sup>(45)</sup>

The quantitative analysis of dementia medicines uptake undertaken by the OHE considered these four drugs. It found that in 2012/13 the UK ranked eighth out of 13 countries with regard to usage of dementia medicines. This presents an improvement from 2008/09, when the UK ranked tenth.<sup>(1)</sup> Comparative usage of these drugs in the UK measured as a percentage of all 13 countries increased from 64 per cent in 2008/09 to 86 per cent in 2012/13, although overall variation in usage of these drugs between countries was relatively small.

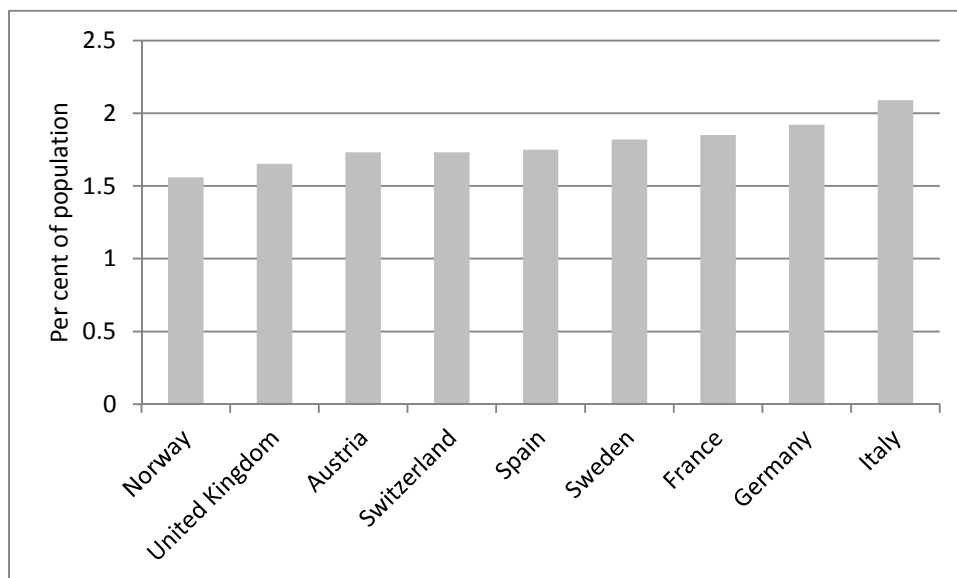
### 3.2. Explaining observed variation in dementia drug usage

#### 3.2.1. Burden of disease

One factor that could explain variation in the uptake of dementia treatments as observed in this study is difference in prevalence rates among countries. While there has been a comparatively large number of longitudinal studies of ageing in Europe,<sup>(46)</sup> it is difficult to arrive at an overview of recent country-specific prevalence data, with many studies dating back to the 1980s and 1990s.<sup>(47)</sup>

Looking first at absolute figures, current estimates suggest that in 2010 there were some 7 million people aged 60 and over living with dementia in western Europe, 3.9 million in the US and 0.3 million in Australia and New Zealand.(48) Among countries in Western Europe, numbers were estimated to be highest for Germany (1.5 million), France (1.1 million) and Italy (1.1 million). For the UK the number of people aged 65 years and older living with dementia was estimated at 773,500 in 2013 (49), while others put this figure somewhat lower at 670,000, although that figure applies to England and Wales only.(50) Variation in country-specific estimates for the number of people living with dementia has been observed in other settings, reflecting differences in underlying data sources, study design or diagnostic criteria.(47, 51, 52)

However, in order to relate differences in the uptake of treatment to disease prevalence it is necessary to consider relative figures. Prince et al. (2013) estimated the (standardised) prevalence of dementia in Western Europe in 2010 for those aged 60 years and older at 7.3 per cent, compared with 6.8 per cent in the US and 6.9 per cent in Australia and New Zealand combined.(48) The European ALCOVE project, focusing on 27 EU member states, estimated dementia prevalence in 2011 for those aged 65 years and over to be 7.23 per cent.(53) This rate is very similar to that estimated for the UK, at 7.1 per cent for those aged 65 years and older (2013) (49), although somewhat higher than that estimated by Matthews et al. (2013) for England and Wales in 2011, at 6.7 per cent (age 65 and over).(50) Recent estimates presented by Alzheimer Europe for the population aged 30 years and older in 33 European countries (2012) ranged from just over 1 per cent in Cyprus, Slovakia and Ireland to around 2 per cent in Germany and Italy.(54) These estimates are shown in Figure 6 for those countries that are included in this report.



**Figure 6 Prevalence of dementia in selected European countries, ages 30 and over, 2012**

Source: adapted from Alzheimer Europe (2014) (54)

Estimates presented in Figure 6 indicate that dementia prevalence tends to be fairly similar across countries included in this report, an observation noted for high income countries more generally.(52) However, overall prevalence data do conceal variation in disease severity in different countries, which may

be an important driver of differences in the uptake of treatment. Yet, there are few robust studies that would allow for a direct comparison of dementia severity across countries. For the UK, it has been estimated that of the total number of dementia cases, just over half have mild dementia (55.4 per cent), one-third have moderate dementia and some 12.5 per cent have severe dementia.(49)

Elsewhere, considerable variation has been reported, reflecting, to a great extent, differences in the populations studied and approaches to case ascertainment. For example, based on a clinical registry of incident dementia, one study from Catalonia, Spain, reported the frequency of mild, moderate and severe dementia to be respectively 62.4 per cent, 26.9 per cent and 10.7 per cent (2007–2009).(55) Conversely, a population-based study of community-dwelling and nursing home residents aged 65 years and older in northwestern Spain in 2009, which used active screening and subsequent diagnostic confirmation, found the distribution of dementia severity to be 30.4 per cent mild, 29.9 per cent moderate and 39.7 per cent severe.(56) Both studies used the same instrument to assess dementia severity. One other example is from Germany, where one longitudinal study of people aged 75 years who were recruited through their GP practice, found severity at baseline (2003/04) to range from 69.1 per cent mild, 17.7 per cent moderate and 13.1 per cent severe.(57) One other study, drawing on data from a population-based (older than 70 years), cluster randomised, controlled intervention trial in the primary care setting, reported 50.7 per cent to be mild, 23.9 per cent moderate and 3.4 per cent severe, although it used a different tool to assess severity.(58)

### 3.2.2. Existing studies of variation in dementia drug usage

There is only a small number of studies that directly compare the uptake of acetylcholinesterase (AChE) inhibitors or memantine across countries. Pariente et al. (2008) examined treatment in people with dementia in Belgium, France, Germany, Italy, the Netherlands, Poland, Portugal, Spain and the UK, using estimates of prevalence of dementia and of AChE inhibitor treatments based on sales and reimbursement data.(31) They found that in 2004 use of AChE inhibitors was lowest in the Netherlands, at 3 per cent of the estimated total number of people with dementia, followed by between 6 per cent and 7 per cent in Italy, the UK and Germany, and highest in Spain (17.5 per cent) and France (20.3 per cent). However, these estimates apply to the early 2000s, with more recent studies reporting increases in treatment prevalence during the 2000s, such as in Canada (59), England (37), France (60), Germany (61) or Italy (62), although comparisons are difficult because of differences in the data that are being used to assess treatment uptake.

One recent prospective observational study of patients with Alzheimer's disease in France, Germany and the UK found that at the time of enrolment into the study during 2011 the majority of patients (77.5 per cent overall) were receiving an AChE inhibitor.(63) Uptake of this drug was somewhat lower in Germany at all levels of severity compared with France and the UK, at around 73 per cent compared with 82 per cent (Table 4).

**Table 4 Use of drugs for the treatment of Alzheimer’s disease among community-dwelling patients aged 55 years and older with probably Alzheimer’s disease in the GERAS study**

|   | Alzheimer’s disease severity* |          |                             |
|---|-------------------------------|----------|-----------------------------|
|   | Mild                          | Moderate | Moderately severe or severe |
| <b><i>Patients taking acetylcholinesterase inhibitor (% total population in severity group)</i></b> |                               |          |                             |
| France  | 81.9                          | 83.8     | 74.2                        |
| Germany   | 73.7                          | 73.2     | 61.1                        |
| UK  | 82.6                          | 82.7     | 85.6                        |
| <b><i>Patients taking memantine (% total population in severity group)</i></b>                      |                               |          |                             |
| France  | 13.8                          | 26.5     | 55.9                        |
| Germany   | 19.7                          | 28.7     | 35.9                        |
| UK  | 1.0                           | 3.9      | 8.9                         |

NOTE: \*Severity classified according to Mini-Mental State examination, MMSE; mild: MMSE 21–26 points; moderate: MMSE 15–20 points; moderately severe or severe: MMSE <15 points

Source: adapted from Wimo et al. (2013) (63)

There were notable differences in the uptake of memantine, which was considerably lower in the UK than in France or Germany. Lower uptake in the UK most likely reflects the recommendations in place in England at that time, with memantine recommended for use in 2011 only.(45)

Data from Sweden indicate there was a similar uptake among patients newly diagnosed with Alzheimer’s disease and registered in the Swedish Dementia Quality Registry (SveDem) between 2007 and 2011, finding that 75.4 per cent of patients received any AChE inhibitors, 7.6 per cent used memantine and 1.3 per cent patients were treated with both.(64) Similar data were reported from a small retrospective study 241 patients in Stockholm in 2011, with 73 per cent of patients receiving treatment with AChE inhibitors, although memantine use was somewhat higher, at 11.6 per cent (dual use AChE inhibitors and memantine: 15.8 per cent).(65)

These data suggest there has been a high uptake of dementia treatments overall in the countries concerned, although it should be noted that patients included in studies were all treated in specialist centres (mostly memory clinics). Findings from an analysis of the French National Alzheimer’s databank, which records data based on specialist consultations for patients with memory disorders, suggest somewhat lower treatment rates when compared to those reported in the GERAS study described above (Table 4).(66) It found that in 76.9 per cent of cases, patients received treatment with an anti-Alzheimer’s drug: 48.3 per cent received treatment with AChE inhibitors and 14.2 per cent with memantine, while a further 14.4 per cent received dual therapy. Lower uptake rates were also reported in one population-based home care cohort study in Ontario, Canada, involving people aged 50 years or older who were assessed with the Resident Assessment Instrument – Home Care between 2003 and 2010.(59) In this study, the proportion of people with dementia receiving any dementia medication was 53.7 per cent in 2010; sole AChE inhibitor use was observed for 45.6 per cent, sole memantine use for 2 per cent, and dual use for 6.1 per cent. Among those that were treated for dementia, memantine use was 15.1 per cent.



Data from Germany suggest there has been low uptake when considering overall claims data of incident cases of dementia among people aged 65 years and older from a nationwide operating statutory health insurance fund during 2004–2006.(67) This found that 13 per cent of patients with incident dementia received AChE inhibitors within the first year after diagnosis, a figure somewhat higher than that estimated by Pariente et al. (2008) for 2004 as mentioned above, at 7 per cent.(31)

### 3.2.3. Health system and services features that may explain variation in dementia drugs usage

Pariente et al. (2008) in their assessment of uptake of AChE inhibitors in selected European countries in 2004 discussed a range of potential factors that might explain variation in dementia drug use, in particular the role of what they broadly termed “health policies”, referring to policies on the inclusion of dementia drugs under the statutory system.(31) In their study, reimbursement under the relevant national health systems ranged from 0 per cent in Italy to 100 per cent in the UK. However, a more recent comparative assessment published by Alzheimer Europe noted that in 2010 most EU members states reimbursed one or more acetylcholinesterase inhibitor, except for Bulgaria, Latvia and Malta; at that time most countries had also reimbursed memantine, while decisions were pending in Bulgaria, Italy, Latvia, Malta, Norway and Poland, as were NICE recommendations in the UK.(68) It is however important to note that it is not necessarily the reimbursement decision itself that determines access, but the indication for which treatment is being reimbursed or for which usage is recommended under the statutory system.(30)

Recommendations for the treatment of dementia with regard to acetylcholinesterase inhibitors and memantine vary across countries, and while treatments are generally recommended, access is typically dependent on meeting certain conditions, with disease severity typically considered a key criterion. Frequently (initial) prescription is restricted to specialists such as neurologists, psychiatrists or geriatrists in Australia, France, Sweden or England (45); in Australia, prescription requires prior approval (Box 1). Pariente et al. (2008) noted that where treatment initiation is restricted to specialists, differences in availability of, or access to, specialists might explain variation in usage of dementia treatment.(31)

#### **Box 1 Recommendations on the use of dementia drugs in selected countries**

##### **Australia**

The subsidy for donepezil, rivastigmine and galantamine, and of the antagonist memantine, was recommended in late 2000 as restricted benefit (requiring prior approval) for patients meeting specific requirements, such as having a specialist diagnosis of Alzheimer’s disease and a score of  $\geq 10$  in the Mini-Mental State Examination (MMSE).(71) A post-market review of all anti-dementia drugs listed on the Pharmaceutical Benefits Scheme for the treatment of Alzheimer’s disease commissioned in 2012 found that AChE inhibitors were being used in a much broader population and for longer periods of time than originally agreed as cost-effective by the Pharmaceutical Benefits Advisory Committee (PBAC).(71, 72) Based on the review’s findings the PBAC recommended a price reduction of 40 per cent and agreed to “simplify the continuing restriction to better align with current clinical use”. The aims of the changes were to “make access to these medicines clinically appropriate for prescribers and patients who respond to treatment”. (73) The revised restrictions were published in the Pharmaceutical Benefit Schedule on 1 May 2013.(74)

## France

The National Authority for Health (*Haute Autorité de Santé*, HAS) recommends cholinesterase inhibitors (donepezil, galantamine, rivastigmine) and anti-glutamate (memantine) for different stages as measured by the MMSE.(76) Combination therapy (cholinesterase inhibitor plus cholinesterase inhibitor or cholinesterase inhibitor plus anticholinesterase) is currently not recommended. The annual initial prescription is currently reserved for specialist physicians in neurology, psychiatry and specialised with further qualification in geriatrics or gerontology. The drugs are subject to special monitoring during treatment, with reassessment after six months and renewal for another six months where indicated; further evaluation is required after one year.(77)

Following re-assessment of Alzheimer's drugs, in 2007 the Transparency Commission at the HAS downgraded the added value (*amélioration du service médical rendu*, ASMR) of all compounds, from II (significant improvement) to IV (minor improvement) in efficacy and/or reduction of side-effects.(78, 79) In 2011, a further assessment sought to take account of progress in the evidence base since 2007,(80) following which the added value of the drugs was further downgraded to V ("lack of therapeutic improvement"), based on a lack of evidence that these drugs improve the benefit in the symptomatic treatment of Alzheimer's disease as per indication.(81) The medical value (*service médical rendu*) was downgraded from "important" to "low".(77) Medicines rated as low on *service médical rendu* are typically only reimbursed at 15 per cent of the cost; however, as Alzheimer's disease is classified as a long-term condition (*affection de longue durée*, ALD) Alzheimer's drugs would be fully covered under the statutory system.(82)

## Germany

Cholinesterase inhibitors (donepezil, galantamine, rivastigmine) and memantine are reimbursable under the statutory system as a therapeutic measure with single drugs up to 12 weeks (dual therapy with cholinesterase inhibitors and memantine in 24 weeks). Beyond 12 weeks (or in case of dual therapy beyond 24 weeks), further treatment is only reimbursable in case of successful treatment.(83) The reimbursement of memantine (under specific conditions) was confirmed in 2011. An initial negative assessment of the drug through the Institute for Quality and Efficiency in Health Care (IQWiG), which undertakes technology assessments on behalf of the Federal Joint Committee, was subsequently reversed in light of further analyses submitted by one manufacturer, which provided evidence of benefit for cognitive functioning among patients with Alzheimer's disease.(84)

## Sweden

The National Board of Health and Welfare recommends offering medicinal treatment with cholinesterase inhibitors (donepezil, galantamine and rivastigmine) to address cognitive impairment symptoms for persons with mild to moderate Alzheimer's disease.(85) It further recommends offering treatment with memantine for cognitive impairment in those with moderate to severe Alzheimer's disease. Treatment should be followed up at regular intervals of at least once a year to consider possible discontinuation of treatment. The National Board of Health and Welfare notes that the recommendations on treatment with cholinesterase inhibitors and memantine would be associated with an increase medication costs by a maximum of SEK 170 million (2010). The total costs for society as a whole, however, are expected to remain unchanged or to decline.

Pariente et al. (2008) further highlighted that while policies on the inclusion of dementia drugs under the statutory system, including the indication for which dementia treatment is being recommended, constituted an important determinant of observed differences, they were unlikely to (fully) explain variation across countries in dementia drug usage. Other factors to be taken into account include variation

in the diagnosis of dementia, and a number of studies have highlighted this as a particular challenge in countries such as in Germany (67) or Italy.(62) It was noted that where comprehensive plans for the detection and treatment of dementia have been put in place, these were likely to increase the number of people diagnosed with the disease and, consequently, the number of patients receiving treatment. One such example has been presented for England, which showed that the implementation of the 2009 National Dementia Plan was associated with an increase in the dementia diagnosis rate, rising by an estimated 4 per cent in 2010 and 12 per cent in 2011 compared with 2009.(37) The study, using national prescribing data and GP databases, further showed that dementia diagnosis rates were highly correlated with prescription rates, with rates of prescriptions of dementia drugs (AChE inhibitors and memantine) increasing by 11 per cent in 2010 and 24 per cent in 2011 compared with 2009. The cost of these drugs relative to total prescribing at primary care trust level increased significantly. The authors noted that increased diagnosis rates following the implementation of the national dementia plan are most likely attributable to increased awareness and initiatives addressing the quality of dementia care. For example, one survey reported an increase in the number of people by a factor of 1.5 using memory services in 2010/11 compared with 2008/09.(69) The authors were unable to link increased diagnostic rates and prescriptions directly to increased funding, while at the same time recognising that the funding that is made available is essential for meeting growing demand.(37) This latter point is also exemplified by a study in the US showing that the implementation in 2006 of Medicare Part D, which enhanced drug coverage for older people, was associated with greater use of cholinesterase inhibitors and memantine among Medicare beneficiaries who experienced improvements in drug coverage under Medicare Part D.(39)

In the Canadian context, Gill et al. (2013) reported that the availability of funding for dementia drugs was closely related to provincial elections.(70) Specifically, the authors observed that during 1999–2007 cholinesterase inhibitors were added to the provincial drug formulary in four out of ten provinces and that this association was significant, with funding announcements made between 2 and 47 days prior to elections. The authors concluded that although there was an established structure for evidence-based decisionmaking, the funding of drugs had remained a complex process that is susceptible to influence from many sources. They highlighted the importance of awareness of such influences when considering drug policies.



## 4. Osteoporosis

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### 4.1. Background

Osteoporosis is the most common clinical disorder of bone metabolism. A progressive, systemic skeletal condition, osteoporosis is characterised by low bone mass and microarchitectural deterioration of bone tissue and consequent increase in bone fragility and susceptibility to fracture. Osteoporotic fractures are a major cause of morbidity; clinical complications include disability and chronic pain. It is estimated that in developed countries around 50 per cent of women aged 50 and older will sustain an osteoporotic fracture during their lifetime.(86, 87)

Osteoporotic fractures place a high burden on populations. For the members states of the EU, the economic costs attributed to the management of osteoporotic fractures and its consequences has been estimated at €36 billion (~£28 billion) (2010), with figures for Canada placing the direct attributable healthcare costs at CAN\$1.1 billion (~£0.6 billion) (88), and the US at US\$12.2–17.9 billion per year in direct medical treatment (~£7.6–11.2 billion).(89) These figures are however likely to underestimate the “true” societal and personal costs associated with osteoporosis. This is because of uncertainty about the true burden of disease related to osteoporosis as diagnosis relies on the quantitative assessment of bone mineral density (BMD), with different techniques providing different means to predict risk depending on type of fracture and skeletal site examined.(86)

The management of osteoporosis includes interventions aimed at reducing the risk of developing osteoporosis through promoting healthy lifestyles, including physical activity and weight training as well as diets rich in calcium and Vitamin D. The treatment for those who have already been diagnosed with low BMD or fractures is aimed at preventing further bone loss to reduce the risk of initial or subsequent fracture. Approved pharmacological interventions include bisphosphonates, strontium ranelate, raloxifene, denosumab and parathyroid hormone peptides; most of these are approved for the treatment of postmenopausal osteoporosis only.(90)

The quantitative analysis of osteoporosis medicines uptake undertaken by the OHE considered the following drugs: bisphosphonates (alendronate, etidronate, ibandronate, risedronate, clodronic acid, pamidronic acid, zoledronic acid, neridronic acid and tiludronic acid), raloxifene, the parathyroid hormone teriparatide, strontium ranelate and denosumab. Of these, neridronic acid, tiludronic acid and denosumab were not previously covered in the 2010 Richards report; the 2014 update further included ipriflavone, a synthetic soy isoflavone. The OHE analysis found that in 2012/13 the UK ranked third out of 13 countries with regard to usage of osteoporosis medicines. This presents an improvement from

2008/09, when the UK ranked sixth.<sup>(1)</sup> Comparative usage of these drugs in the UK measured as a percentage of all 13 countries increased from 71 per cent in 2008/09 to 128 per cent in 2012/13. When measured as a percentage of five EU countries (France, Germany, Italy, Spain, UK), the respective figures were 41 per cent in 2008/09 and 118 per cent in 2012/13.

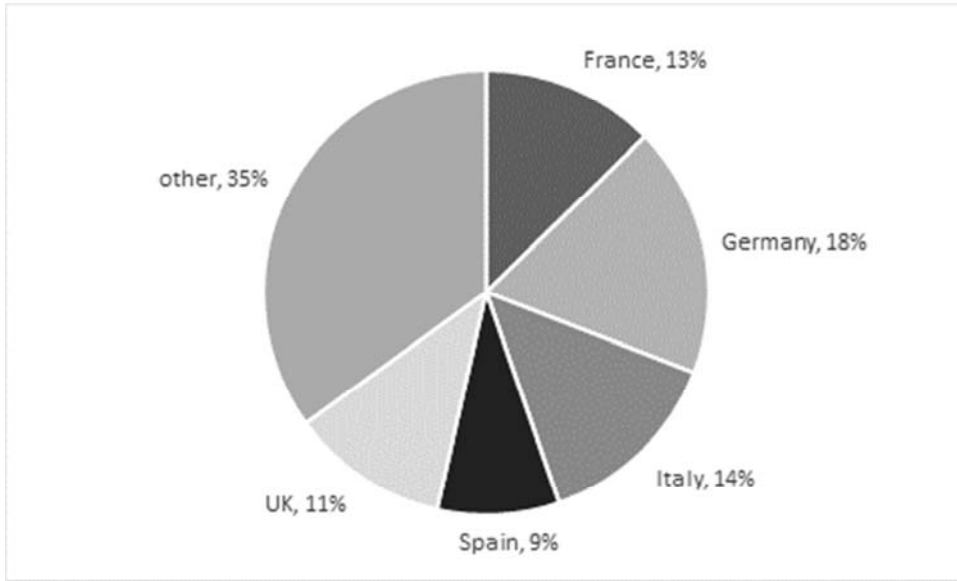
## 4.2. Explaining observed variation in osteoporosis drug usage

Recent work by a panel of experts in Europe led by Kanis and undertaken, in part, in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA) provides a systematic assessment of the epidemiology, management and health economic consequences of osteoporosis in 27 countries of the European Union.<sup>(35, 90, 91)</sup> Published analyses used a combination of literature review, economic modelling, stakeholder survey and detailed country case studies, focusing on data from 2010 onwards. They also included an analysis of sales data estimating uptake of osteoporosis treatments from 2001 to 2011. The following sections mostly draw on this work, with evidence for countries other than EU member states covered in this report added where appropriate and relevant.

### 4.2.1. Burden of disease

The diagnostic criterion for osteoporosis is based on the measurement of BMD, with low bone mass and osteoporosis defined relative to the average level in young healthy women.<sup>(92)</sup> As bone loss occurs with advancing age, osteoporosis is most common among people aged 50 years and older, where the incidence of fragility fractures increases progressively.<sup>(90)</sup> Accordingly, considering populations aged 50 and over as at risk means that among EU countries, in 2010 Germany had the highest number of people at risk, at 33 million, followed by Italy, France, the UK, Spain and Poland.<sup>(90)</sup>

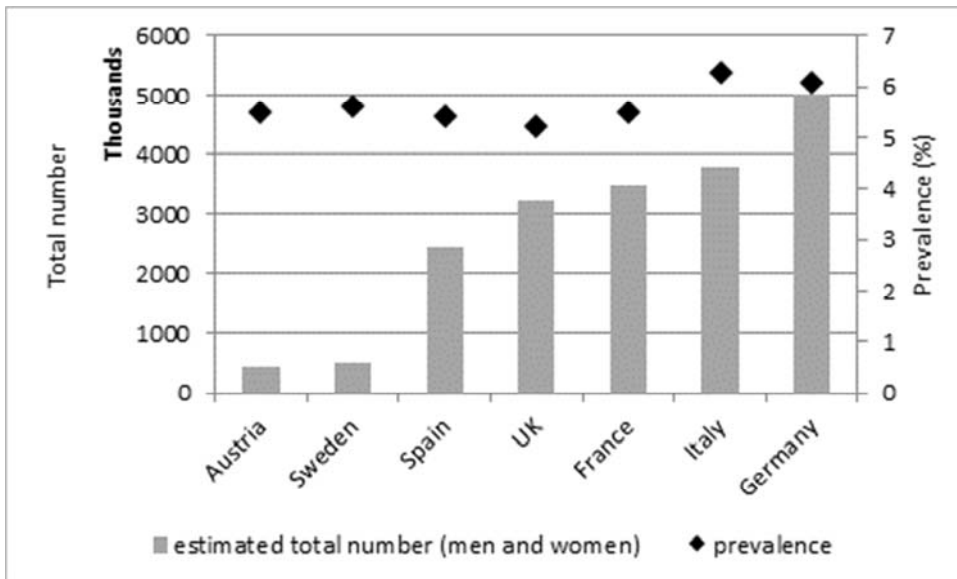
Given the diagnostic criterion for osteoporosis, precise estimates of the prevalence of osteoporosis would require country-specific data on the distribution of femoral neck BMD, but such data are not available for most countries. In order to assess prevalence, Hernlund et al. (2013) used data from Sweden, which applied reference ranges for bone mass by age to estimate the prevalence of osteoporosis. Assuming that the distribution of mean femoral neck BMD and the rate of bone loss are similar across countries at age 50, the Swedish data formed the basis for prevalence estimates for EU member states. This found that in 2010 the estimated total number of men and women with osteoporosis in the then 27 EU countries was 27.6 million, largely women (22 million). This is illustrated in Figure 7, which shows that in 2010 the five countries with the highest populations (France, Germany, Italy, Spain and the UK) accounted for about two-thirds of all female osteoporosis cases in the EU-27 (proportions were similar for men, data not shown).



**Figure 7 Prevalence distribution of osteoporosis among women in the EU and the five countries with the highest populations in 2010**

Source: adapted from Hernlund et al. (2013) (90)

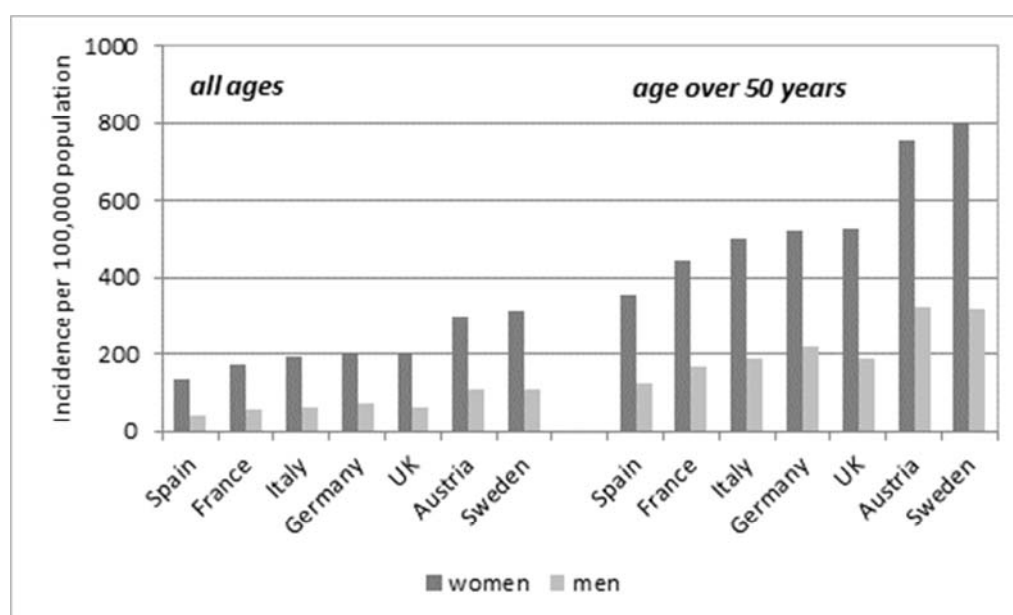
Figure 8 disaggregates these figures further, providing prevalence figures for the subset of EU members states covered in the 2014 OHE report. It combines prevalence figures for men and women, although it is important to recognise that the burden among women is among four times that in men. Prevalence rates among women over 50 ranged from 21.9 per cent in the UK to 22.6 per cent in Germany and Spain. Among men over 50, prevalence rates ranged from 6.1 per cent in Italy to 6.9 per cent in Sweden.



**Figure 8 Estimated number of people (men and women) with osteoporosis and prevalence in the population aged over 50 years in seven EU countries, 2010**

Source: adapted from Hernlund et al. (2013) (90)

The diagnosis of the disease relies on the quantitative assessment of bone mineral density as a major determinant of bone strength, but the clinical significance of the disease lies in the fractures as a consequence of increased bone frailty.(92) Hernlund et al. (2013) noted that information on the incidence of fragility fractures varies between European countries, and where data are available, these most commonly refer to hip fractures. Drawing on available literature and datasets, Hernlund et al. calculated standardised hip fracture rates for 27 EU countries, observing a three-fold variation in annual incidence rates among women, ranging from a low of 110/100,000 population in Romania and 130/100,000 in Poland to a high of 314/100,000 in Sweden and 333/100,000 in Denmark. For men, incidence rates were typically half those seen for women. This is further illustrated in Figure 9, which presents standardised hip fracture rates for men and women in seven EU countries covered in the 2014 OHE report.



**Figure 9 Standardised hip fracture rates for men and women (per 100,000 per year) in seven EU countries, 2010**

Source: adapted from Hernlund et al. (2013) (90)

The reasons for variation in hip fracture rates across countries are not well understood, although there is some suggestion that higher levels of wealth measured as gross domestic product (GDP) is associated with higher hip fracture rates.

Overall, in 2010, hip fractures accounted for approximately one-fifth of all fractures in European countries, followed by vertebral (16 per cent) and forearm fractures (15 per cent), with the remaining 50 per cent considered to be causally related to osteoporosis located in areas such as femur, pelvis, rib and sternum, among others. Translating overall incidence figures into absolute numbers, Hernlund et al. (2013) found that Germany had the highest absolute burden for all fracture types in both men and women (around 725,000 incident fractures in 2010), which in part reflects its large population size but also the comparatively high fracture incidence.(90) This was followed by the UK, at some 536,000 incident fractures, Italy (465,000), France (377,000) and Spain (205,000).



#### 4.2.2. Existing studies of variation in osteoporosis drug usage

The aforementioned assessment of the epidemiology, management and health economic consequences of osteoporosis in 27 countries of the European Union also included an analysis of trends in the uptake of osteoporosis treatments, using international sales data (volume and value) for the period 2001–2011.(90) Osteoporosis drugs considered included alendronate, denosumab, etidronate, ibandronate, parathyroid hormone (PTH) 1–84, raloxifene, risedronate, strontium ranelate, teriparatide and zoledronic acid. It further provided an estimate for “population coverage” calculated as the number and proportion of the population aged over 50 years that was treated, expressed in relation to the estimated number of patients considered eligible for treatment.

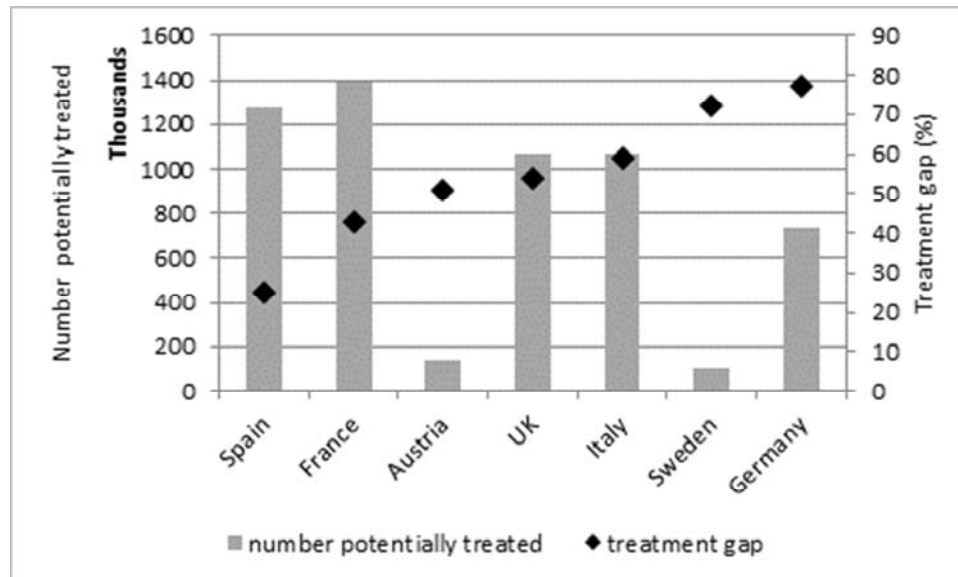
Taken all osteoporosis treatments considered in the analysis together, it found a steady increase in population coverage in all 27 EU countries from 2001, with an indication of reaching a plateau in the late 2000s in a number of countries, including France, Sweden and the UK, while coverage appeared to decline in Austria from 2007 and in Spain from 2009. However, among the seven EU countries captured in the present study, Spain showed consistently the highest coverage rate, with, in 2011, an estimated 8 per cent of the population 50 years or older that was treated, followed by the UK (just under 6 per cent), and Italy and Austria (around 5 per cent). Coverage was lower in Sweden, at 3.5 per cent and consistently lowest in Germany, at around 2.5 per cent.

Disaggregating osteoporosis treatment usage by individual drugs, the analysis found considerable variation between countries. Alendronate was the most commonly used treatment, with a steady increase in uptake until approximately 2008, after which uptake tended to reach a plateau in many countries. In 2010, the UK was among the countries with the highest uptake rates, at 1,140 defined daily doses (DDDs) per 100 persons aged 50 years or older (only surpassed by Hungary at 1,580 DDD/100 and Ireland at 1,170 DDD/100; EU27 average: around 700 DDD/100). This compared with between 650 DDD/100 in Sweden and 800 DDD/100 in Spain to around 500 DDD/100 in France (following a peak in 2006) and just over 400 DDD/100 in Germany. The UK also had the steepest increase in uptake of alendronate during the 2000s, accelerating from 2005 in particular. Conversely, when considering denosumab, the latest drug to be introduced for the treatment of osteoporosis from 2010, Germany was among the countries with the highest uptake initially, although data are difficult to interpret.

Overall the analyses by Hernlund et al. (2013) suggested a decline in the population coverage with osteoporosis treatments over the past two years, with considerable variation in actual uptake levels between countries. Similar observations were made for Norway, which also recorded a decline in the use of osteoporosis drugs from the mid-2000s, in particular bisphosphonates(93), as did Australia.(94)

To better understand treatment uptake, Kanis et al. (2013) estimated a “treatment gap”, which refers to the proportion of men and women at high risk of fracture that receive therapy for osteoporosis in the 27 EU countries.(35) This found considerable variation among countries, with the treatment gap for women varying from 25 per cent in Spain to 77 per cent in Germany (the gap was larger for countries that had joined the EU after 2004) (Figure 10). Importantly, the authors noted that large treatment gaps were identified in countries with populations at both high and low risk of fracture. Hernlund et al. (2013) highlighted that all EU countries included in their analysis had higher estimates for women who should be treated than those actually receiving treatment. This was not necessarily the case for men, with data for

countries such as the UK indicating that the volume of osteoporosis drugs that are being sold would be sufficient to cover treatment for more patients than the number identified to be at risk of fracture (a “negative” treatment gap).



**Figure 10 Percentage of women eligible for treatment and treatment gap in seven EU countries, 2010**

Source: adapted from Kanis et al. (2013) (90)

#### 4.2.3. Health system and services features that may explain variation in osteoporosis drugs usage

Kanis et al. (2013) considered a range of factors acting at system and service levels that can potentially explain observed variation in osteoporosis drug usage across EU countries. One area considered was the inclusion of drugs in the publicly funded system and data were collected using a survey among EU members of the International Osteoporosis Foundation (IOF), which was carried out at the end of 2012.(35) This found that most treatments were included in most countries, with full reimbursement provided in six out of the seven EU countries considered in the present study (Table 5). In Spain, only 50 per cent of the treatment is being reimbursed and this was considered an important barrier for patients to access treatment. In France, the reimbursement mechanism for osteoporosis was seen as complex by GPs (40), which was associated with a loss of interest in managing the disease.

**Table 5 Availability of osteoporosis treatments in seven European countries, 2012**

|         | Bisphosphonates | SERMs | Strontium ranelate | PTH analogues | Denosumab | Reimbursement            | Reported impediment to treatment |
|---------|-----------------|-------|--------------------|---------------|-----------|--------------------------|----------------------------------|
| Austria | Yes             | Yes   | Yes                | Yes           | Yes       | 100%                     | No                               |
| France  | Yes             | Yes   | Yes                | Yes           | -         | 65%                      | Yes (professional)               |
| Germany | Yes             | Yes   | Yes                | Yes           | Yes       | 100%                     | No                               |
| Italy   | Yes*            | Yes   | Yes                | Yes           | Yes       | 100%                     | Yes (professional)               |
| Spain   | Yes             | Yes   | Yes                | Yes           | Yes       | 50%; 100% for pensioners | Yes (patient)                    |
| Sweden  | Yes *           | Yes   | Yes                | Yes           | Yes       | 100%                     | No                               |
| UK      | Yes             | Yes   | Yes                | Yes           | Yes       | 100%                     | No                               |

Notes: Bisphosphonates – alendronate, ibandronate, risedronate, zoledronic acid; PTH – parathyroid hormone derivatives (PTH, teriparatide); SERMs – selective oestrogen receptor modulators; \*not all bisphosphonates available

Source: adapted from Kanis et al. (2013) (35) and Hernlund et al. (2013) (90)

However, overall differences in the levels of reimbursement of treatment do not seem to be sufficient to explain observed variation in the uptake of osteoporosis drugs. Kanis et al. (2013) highlighted the role of access to diagnosis, in particular the assessment of bone mass with dual-energy X-ray absorptiometry (DXA) as a potentially greater barrier to treatment than the actual reimbursement of drugs,(35) an observation also put forward by Conklin et al. (2011) in an earlier review of the quality of care for osteoporosis in four countries (England, France, Germany and Spain).(40) Thus, in 2012, the number of DXA units per million population ranged from a low of 8.2 in the UK and 8.4 in Spain to 28.7 in Austria and 29.1 in France. However, availability of DXA units does not necessarily translate into (appropriate) use, with for example data from the 2012 IOF survey showing that in Italy the average waiting time for DXA was at 83 days more than twice the average wait in the EU27, despite the comparatively high number for DXA units across the country (18.6/million population).(35) Kanis et al. (2013) attributed this to the observation that in Italy many DXA units are located in research centres or the private sector and are therefore not accessible to the majority of the population. Conversely, in the UK, the average waiting time for a DXA assessment was 11 days despite the comparatively lower number of DXA units, reflecting that GPs have access to scans. In some other countries, although DXA is in principle available, DXA scans are not (fully) reimbursed, or only reimbursed on certain conditions, which could limit access. For example, in Germany reimbursement of DXA scans is only granted for those who had experienced a fracture, and in France reimbursement is dependent on meeting specific clinical risk factors. It is difficult to relate these data directly to variation in osteoporosis treatment uptake, although evidence suggests that bone mass assessment is associated with anti-osteoporotic drug prescription.(36)

According to Hernlund et al. (2013), there has been a steady increase in the uptake of osteoporosis drugs in the UK during the 2000s, with only the last period (2010/11) showing some plateauing of this increase.(90) This last point seems to contradict the observed increase in osteoporosis drug usage in the UK between 2008/09 and 2012/13 when compared with other countries, as observed in the 2014 OHE

analysis of drug usage described earlier.(4) However, Hernlund et al. (2013) also noted that key European comparator countries experienced declines in osteoporosis drugs uptake from the late 2000s, in particular France and Spain. Therefore, the relative improvement seen in the UK might simply be due to a simultaneous decline in comparator countries, which was also observed for Norway and Australia, as noted above. At the same time, the analysis by Hernlund et al. (2013) did not consider most recent developments in the UK and elsewhere, including the likely impact on drug usage following the inclusion of osteoporosis in the national Quality and Outcomes Framework from 2012, which provides GP practices in the UK with a financial incentive to diagnose and treat osteoporosis in their patients. It builds on an earlier scheme introduced in 2006/07, which incentivised GPs to provide “enhanced services” including the diagnosis and treatment of osteoporosis.(40) In addition, the UK operates a system of clinical audits that seeks to improve patient care and outcomes through a systematic review of care in line with explicit criteria and the implementation of change, such as through the National Hip Fracture Database.(95)

Kanis et al. (2013) highlighted that making osteoporosis a priority will prompt the development of a national action plan, and it may provide clear support for education and awareness programmes. Among EU member states considered in the present study, only a small number had identified osteoporosis as a national priority and developed a subsequent action plan, including the UK and Italy (Table 6).

**Table 6 Osteoporosis or musculoskeletal disease as a national priority in seven EU countries**

|         | National health priority (date) | Government support | Scope  | Action plan |
|---------|---------------------------------|--------------------|--|-------------|
| Austria | No                              |                    |  |             |
| France  | Yes (2004)                      | Yes                | Nutrition, exercise, falls prevention          | No          |
| Germany | No                              |                    |  |             |
| Italy   | Yes (2005)                      | Yes                | Nutrition, falls prevention                    | Uncertain   |
| Spain   | No                              |                    |  |             |
| Sweden  | Yes (2012)                      | Yes                | Not yet defined                                | No          |
| UK      | Yes (2009)                      | Yes                | Nutrition, exercise, fracture liaison services | Indirect    |

Source: adapted from Kanis et al. (2013) (35)

## 5. Cancer

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### 5.1. Background

Cancer is the uncontrolled growth and spread of cells. The growths often invade surrounding tissue and can metastasize to other sites. Cancer is a generic term for a large group of diseases that can affect any part of the body and there are over 200 different types of cancer. Cancers figure among the leading causes of death worldwide, accounting for 8.2 million deaths in 2012.(96)

Cancer has been associated with a substantial societal burden. Estimates for Europe have placed the economic burden associated with cancer at €126 billion in 2009 (~£100 billion), with healthcare accounting for 40 per cent.(97) Productivity losses because of premature death were estimated at €42.6 billion (~£33 billion), with one other study placing these costs at €75 billion (~£60 billion).(98) Both studies estimated the costs to be highest for lung cancer (accounting for 15–23 per cent of total costs), followed by breast cancer (9–12 per cent) and colorectal cancer (8–10 per cent).

Cancer control includes a wide range of measures, with treatment typically involving a selection of one or more interventions, such as surgery, radiotherapy or chemotherapy. The goal is to cure the disease or considerably prolong life while improving the patient's quality of life. With increased understanding of the underlying disease processes there have been considerable advances in cancer treatments, resulting in increased treatment options.(99) Reflecting these developments, there is now a wide range of drugs that are used in chemotherapy, hormone therapies and, more recently, biological therapies.

The quantitative analysis of cancer medicines uptake undertaken by the OHE considered 135 different cancer drugs, distinguishing drugs that were licensed in the past five years (n=31) from those that were licensed six to ten years ago,(20) and those licensed more than ten years ago,(60) as well as cancer hormone drugs.(24, 4) The 2014 OHE analysis showed that there was no consistent pattern in cancer drug usage in 2012/13 in the UK relative to comparator countries across the four categories:

- Cancer drugs that were licensed in the past five years (as at March 2013): the UK ranked seventh; comparative usage as a percentage of all 13 countries was 92 per cent (EU5: 94 per cent).
- Cancer drugs that were licensed six to ten years ago: the UK ranked twelfth; comparative usage as a percentage of all 13 countries was 54 per cent (EU5: 44 per cent).
- Cancer drugs that were licensed more than ten years ago: the UK ranked fourth; comparative usage as a percentage of all 13 countries was 124 per cent (EU5: 103 per cent).
- Cancer hormone drugs: UK ranked ninth; comparative usage as a percentage of all 13 countries was 73 per cent (EU5: 68 per cent).

Thus with the exception of cancer drugs that were licensed more than ten years ago, usage in the UK was below the international average, although the relative levels varied across categories. It is difficult to directly compare trends over time given that cancer drugs approved in the past five years as considered in the 2010 Richards report would now fall into the category of drugs that were licensed six to ten years ago; furthermore, the OHE analysis captured a wider range of drugs in each of the four categories.

It was not possible, in the context of the present report, to review evidence on variation in usage of the large and diverse number of cancer drugs considered in the quantitative analysis undertaken by the OHE (2014). Instead, the following provides a summary overview of studies that have examined variation in access to and usage of cancer drugs more generally, along with analyses that have considered the role of health system and service organisation factors in explaining observed variation in cancer treatment in the countries considered in the OHE study.

## 5.2. Explaining observed variation in cancer drug usage

The quality of cancer care has become the focus of a number of international comparative efforts, including the EURO CARE collaborative research project on cancer survival in Europe, which commenced in 1989 (100), and more recently the International Cancer Benchmarking Partnership (ICBP), which was initiated in 2009 by the Department of Health in England and comprises a research collaboration between 12 jurisdictions in six countries: Australia (New South Wales, Victoria), Canada (Alberta, British Columbia, Manitoba, Ontario), Denmark, Norway, Sweden and the UK (England, Northern Ireland, Wales) (101), and the OECD, as part of its Health Care Quality Indicator Project.(102) Much of the existing comparative work focuses on cancer care pathways with little direct comparison of cancer drug usage. Where cancer drug are addressed, analyses tend to focus on principles of availability rather than empirical evidence of actual access to and uptake of drugs. Moreover, the majority of these latter studies date the mid- and late 2000s and are therefore do not reflect the current situation.

### 5.2.1. Burden of disease

Cancer is one of the few diseases where individual survival data are often captured routinely in a readily accessible format. This has led to their widespread use for assessing differences between populations and over time. The GLOBOCAN series of the International Agency for Research on Cancer provides estimates of the worldwide incidence and mortality from major cancers (103), with EUCAN, which is part of the European Cancer Observatory (ECO), providing estimates for countries in Europe specifically.(104, 105) The most recent GLOBOCAN series reported that there were 14.1 million new cases and 8.2 million cancer deaths in 2012.(96) The most commonly diagnosed cancers were lung (1.82 million), breast (1.67 million) and colorectal (1.36 million) cancer.

Table 7 disaggregates these data for selected high-income regions in North America (Canada and US), the European Union (28 member states), western Europe (which includes Austria France, Germany and Switzerland), northern Europe (includes Norway, Sweden and the UK) and southern Europe (includes Italy and Spain).

**Table 7 Summary indicators of cancer burden in selected high-income regions, 2012**

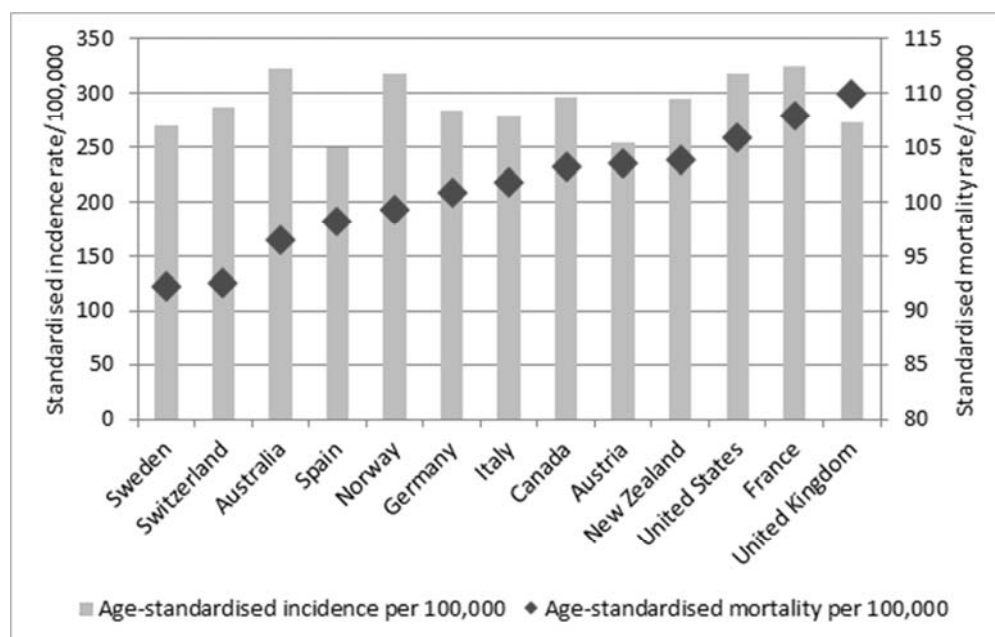
|  | North America                                       | EU-28   | Western Europe                                      | Northern Europe  | Southern Europe                                     | Australia and New Zealand                                    |
|--|---|---|---|--|---|--|
| <b>New cancer cases</b>                                    |   |   |   |  |   |  |
| Age-standardised rate (per 100,000)                        | 315.6   | 273.5   | 298.7   | 277.4  | 253.6   | 318.5  |
| Risk of getting cancer before age 75 (%)                   | 30.9  | 27.3  | 29.6  | 27.5   | 25.3  | 30.7   |
| <b>Cancer deaths</b>                                       |   |   |   |  |   |  |
| Age-standardised rate (per 100,000)                        | 105.5   | 109.4   | 105.0   | 108.0  | 105.2   | 97.6   |
| Risk of dying from cancer before age 75 (%)                | 11.2  | 11.5  | 11.0  | 11.2   | 10.9  | 9.9  |
| 5-year prevalent cases, adults (per 100,000)               | 1888.2  | 1690.4  | 2018.6  | 1658.6   | 1585.3  | 1901.8   |
| 5 most frequent cancers (defined by total number of cases) | Prostate<br>Breast<br>Lung<br>Colorectal<br>Bladder | Breast<br>Prostate<br>Colorectal<br>Lung<br>Bladder | Prostate<br>Breast<br>Colorectal<br>Lung<br>Bladder | Prostate<br>Breast<br>Colorectal<br>Lung<br>Melanoma of skin | Colorectal<br>Breast<br>Lung<br>Prostate<br>Bladder | Prostate<br>Colorectal<br>Breast<br>Melanoma of skin<br>Lung |

Source: adapted from GLOBOCAN (2014) (103)

Note: Estimates of worldwide age-standardised incidence and mortality as provided by GLOBOCAN use the World standard population (96), while EUCAN uses the European standard population.(104) The World standard population presents a younger population compared to the European standard population; EUCAN estimates for individual European countries or regions (such as those reported by Ferlie et al. (2013) (106)) are therefore higher than those provided by GLOBOCAN.

Disaggregating data further by individual country, GLOBOCAN data highlight some variation in the incidence and the mortality (Figure 11) from cancer among the 13 countries considered by the 2014 OHE analysis.

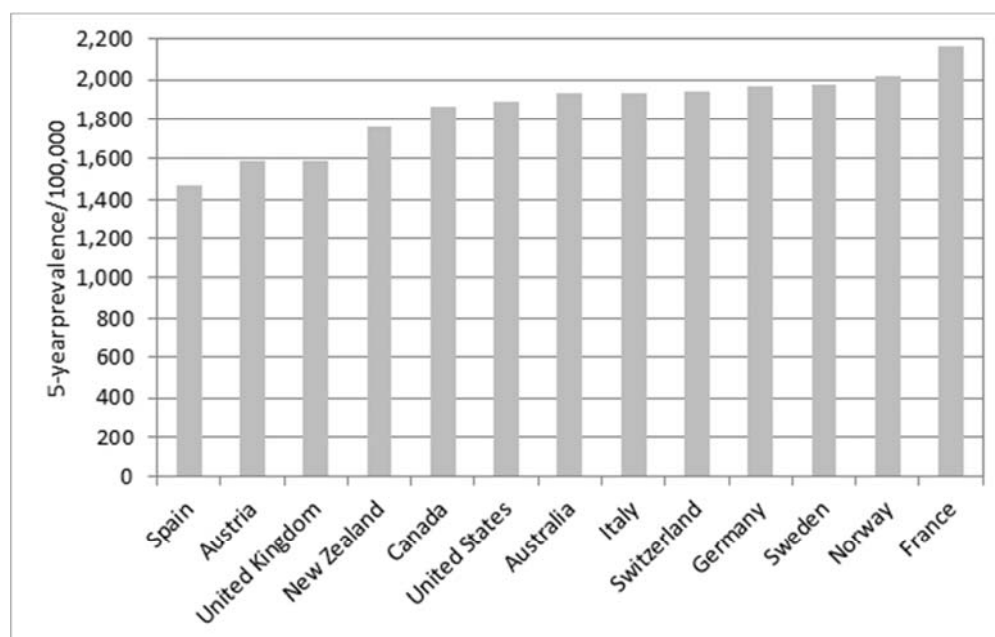
**Figure 11 Age-standardised incidence and mortality rate for all cancers (excl. non-melanoma skin cancer) per 100,000 population, both sexes combined, in 13 countries, 2012**



Source: adapted from GLOBOCAN (2014) (103)

As a consequence, five-year prevalence also varies across countries (Figure 12). Variation in the prevalence of cancer between countries highlights differences in need, and while observed differences in the prevalence influence cancer drug usage in different countries, the extent of this variation does not appear to be sufficiently large to fully explain observed differences in cancer drug usage.

**Figure 12 Five-year prevalence all cancers (excl. non-melanoma skin cancer) per 100,000 population, both sexes combined, in 13 countries, 2012**



Source: adapted from GLOBOCAN (2014) (103)

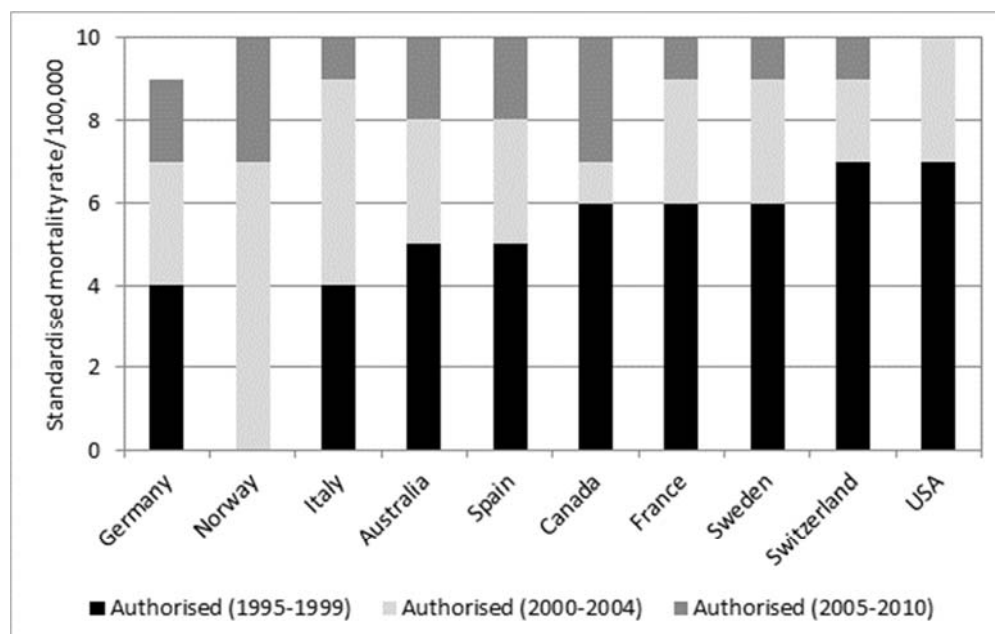


### 5.2.2. Existing studies of variation in cancer drug usage

As indicated above, there are few international comparative studies of cancer drug uptake. Wilking et al. published a series of analyses in the mid- to late 2000s that sought to provide a comparison of patient access to cancer drugs in Europe using sales data.(107–109) They reported wide variation across countries on a number of indicators such as sales or the time period by which new cancer medications became available to patients. For example, their 2005 report considered 56 cancer drugs in 19 countries and rated Austria, Spain and Switzerland to be the leading countries to adopt the newest cancer drug therapies that were made available between 1999 and 2004. Conversely, Norway and the UK were identified as “below-average adopters” of new drugs for the treatment of a range of cancers, including breast cancer, colorectal cancer, lung cancer and non-Hodgkin’s lymphoma. The work suggested there was a link between access to new cancer medicines and survival from cancer, although these suggestions were challenged on methodological grounds.(110)

More recent data are presented by the OECD, although these focus most on licensing and financing arrangements.(102) The OECD collected data on the authorisation and clinical use of ten innovative cancer drugs that had been authorised between 1995 and 2010, with data reproduced for a subsample of countries included in the present report in Figure 13. Data suggest that the US tended to authorise the reviewed drugs earlier than the comparator countries, followed by Switzerland, Sweden and France.

**Figure 13 Authorisation of ten innovative cancer drugs in ten countries between 1995 and 2010**



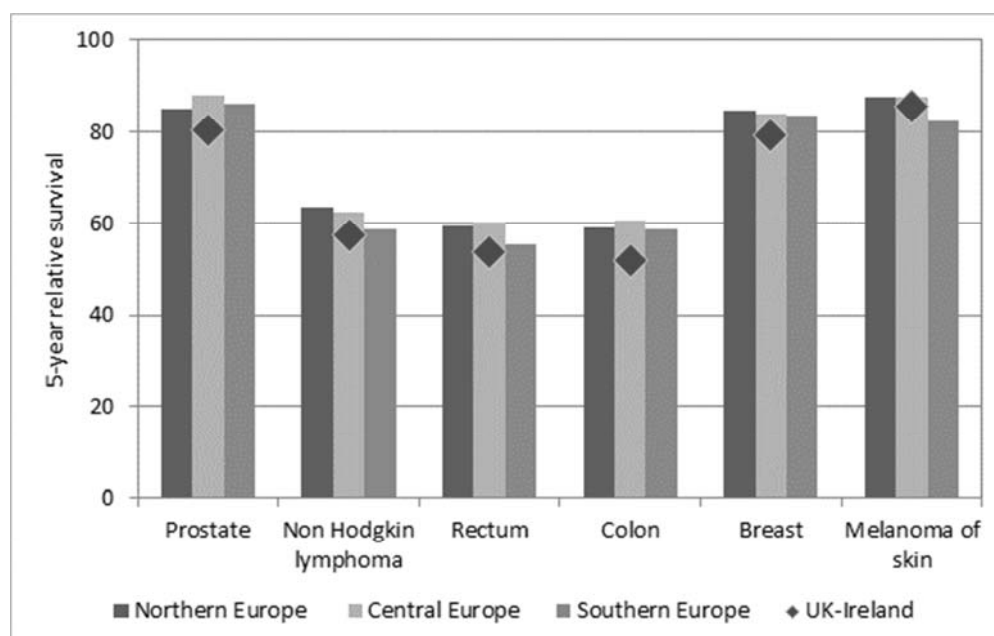
Notes: Innovative drugs considered were Herceptin (trastuzumab), Avastin (bevacizumab), Aromasin (exemestane), Femara (letrozole), Arimidex (anastrozole), Evista (raloxifene), Erbitux (cetuximab), Eloxatin (oxaliplatin), Camptosar (irinotecan) and Xeloda (capecitabine)

Source: adapted from OECD (2013) (102)

Other countries tended to be slower in their authorisation processes, confirming the earlier observations by Wilking and colleagues (109) that access to innovative cancer medicines and, by implication, uptake varies between countries, although empirical data on uptake were not presented.

The impacts of variation in access to innovative medicines on cancer outcomes at population level are difficult to ascertain. Analyses that have drawn on cancer registry data undertaken by the EUROCARE consortium and International Cancer Benchmarking Partnership provide indirect evidence on the effects of variation in access to timely treatment, including pharmacological treatment, on cancer survival. For example, reporting data on 45 cancer types in 25 European countries and the four countries of the UK (capturing about 50 per cent of the population in the EU plus Iceland, Norway and Switzerland), the EUROCARE-5 project found consistent variation internationally in survival rates. In particular, despite improvements over the period 1999–2007, five-year relative survival in the UK remained below the European average for cancer sites such as prostate, rectum, colon and breast as well as melanoma of the skin (Figure 14).(111) Disaggregating survival by age, de Angelis et al. (2014) further showed that the survival gap for breast cancer in the UK was concentrated mainly among older women aged 75 years and over, whereas survival at ages 44–64 was comparable to other European regions, while still slightly lower.

**Figure 14 Five-year relative survival, selected cancer sites, in four regions in Europe, 2000–07**



Notes: Northern Europe – Denmark, Finland, Norway, Iceland, Sweden; Central Europe – Austria, Belgium, France, Germany, Netherlands, Switzerland; Southern Europe – Croatia, Italy, Malta, Portugal, Slovenia, Spain; UK-Ireland – Northern Ireland, England, Scotland, Wales, Ireland

Source: adapted from de Angelis (2014) (112)

Recent analyses from the International Cancer Benchmarking Partnership examined the impact of differences in stage at diagnosis on survival for a small number of cancer sites, including lung cancer (113), breast cancer (114), colorectal cancer (115) and ovarian cancer.(116) For example, Walters et al. (2013) reported that in 2004–2007 age-standardised one-year survival from non-small cell lung cancer was lowest in the UK, at 30 per cent and highest in Sweden, at 46 per cent. Lower survival in the UK (and in Denmark) was attributed, in part, to a more adverse stage distribution while survival within each stage of disease was also generally low in the UK and high in Sweden.(113) The authors noted that low stage-specific survival could point to poorer levels of stage-specific treatment, citing evidence of lower

provision of chemotherapy and radiotherapy for the UK than for Australia, Canada and Sweden, and pointing to a need for wider access to optimal treatment.

In a related study, the authors identified a similar pattern for breast cancer survival in 2000–2007, although overall survival rates were substantially higher.<sup>(114)</sup> Age-standardised three-year net survival was lower in the UK and Denmark, at 87–89 per cent, compared with 91–94 per cent in Australia, Canada, Norway or Sweden. Similar to lung cancer, women in the UK had low survival for more advanced disease stages compared with other countries while stage distribution was comparatively favourable. As with lung cancer, this points to possible shortcomings in access to or the effectiveness of stage-specific treatment, including access to drug therapy. Similar observations were made for colorectal cancer<sup>(115)</sup> and, to a lesser extent, ovarian cancer.<sup>(116)</sup>

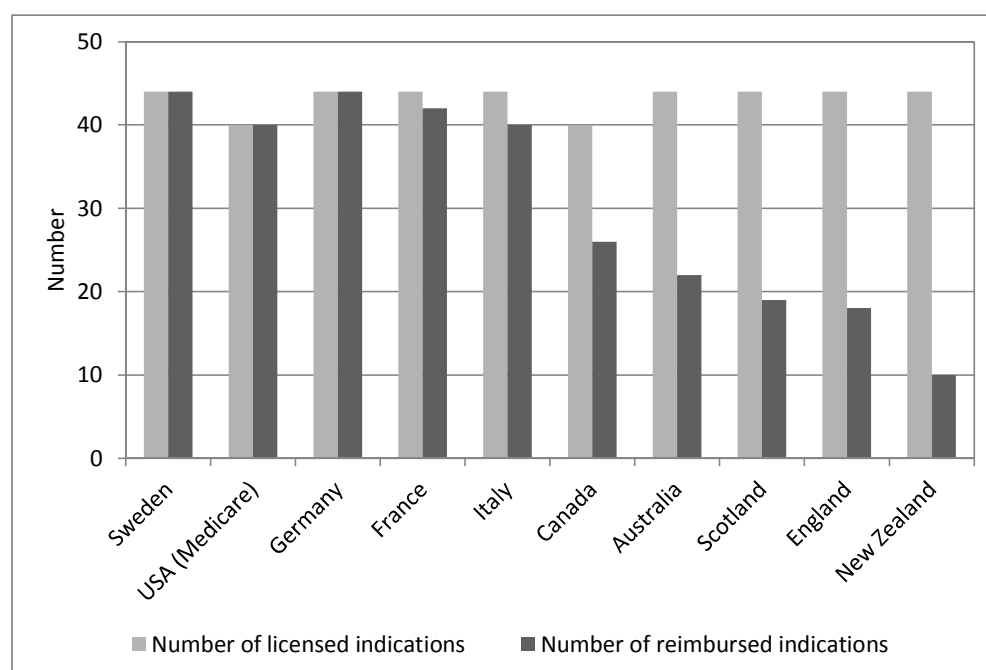
However it is important to note that the above analyses examined survival among people diagnosed with cancer during 2004–2007 and it is conceivable that cancer treatment, including timely access to cancer medicines, have improved as actions have been taken in the UK to enhance timely diagnosis (see below).<sup>(117)</sup>

### 5.2.3. Health system and services features that may explain variation in cancer drugs usage

While there is little robust empirical evidence on the uptake of cancer drugs across countries, recognition of the high costs associated with cancer treatment, and in particular new innovative medicines, have prompted comparative assessments of system approaches to the organisation and funding of cancer care more broadly.<sup>(118–120)</sup>

Cheema et al. (2012) reported one of the few comparative studies that focused on the inclusion of cancer drugs under the publicly funded system in 13 countries: Australia, Canada (Ontario), England, Finland, France, Italy, Germany, Japan, New Zealand, the Netherlands, Scotland, Sweden and the US (Medicare Parts B and D).<sup>(121)</sup> Using a combination of document review and a survey of health authorities involved in decisions about the inclusion of drugs under the publicly funded system, they analysed licensed indications for ten cancer drugs (bevacizumab, bortezomib, cetuximab, erlotinib, imatinib, pemetrexed, rituximab, sorafenib, sunitinib and trastuzumab). By early 2010, a total of 48 indications had been approved, although the number of approved indications varied, from 44 in Europe (approved) by the European Medicines Agency, Australia and New Zealand, to 40 in the US and in Canada, and 36 in Japan. Considering decisions about the inclusion under the publicly funded system of licensed medications of those approved in the relevant region of country, Finland, France, Germany, Sweden and the US had included the highest percentage of indications (90–100 per cent) while Canada (54 per cent), Australia (46 per cent), Scotland (40 per cent), England (38 per cent) and New Zealand (25 per cent) had included the least. This is further illustrated for ten countries included in the present study (Figure 15).

**Figure 15 Number of licensed indications of ten cancer drugs and number of indications approved for inclusion under the publicly funded system in ten countries, 2010**



Source: adapted from Cheema et al. (2012) (121)

Finland, Sweden and the US (Medicare) also reimbursed off-label indications; for example Sweden had included bortezomib and trastuzumab in the National Reimbursement System for use at the discretion of treating medical oncologists. Also, off-label indications for intravenous cancer drugs were reimbursed by hospitals if included in the hospital's practice-based guidelines led by medical oncologists.

Among the five countries with the fewest number of indications included (Australia, Canada, England, New Zealand and Scotland), a reason for not recommending the given indication for inclusion in the publicly funded system by the relevant agency was most often that the drug was deemed not cost-effective, while in New Zealand the main reason was the high cost of a given drug. Some indications that were initially not recommended for inclusion (nine in Australia, five in Canada, and three in England, New Zealand and Scotland) were subsequently approved through risk-sharing agreements or special pricing arrangements.

One other study, comparing the US and Australia and focusing on cancer drugs approved between 2000 and 2009, found that only a third of cancer drugs that were available in the US were funded under the statutory system in Australia.(122) However, the authors observed that out-of-pocket payments for US Medicare patients were considerably higher and they highlighted that the approach used in Australia had contributed to lower prices and so enhanced affordability for payers and patients for the drugs considered.

The debate about differences in the availability of cancer medicines across countries and the cost of cancer treatment have prompted considerable public debate in a number of countries, including the UK, with Sullivan et al. (2011) pointing to "a lack of evidence-based sociopolitical debate, and a declining degree of fairness for all patients with cancer".(123) A number of countries have put in place separate funding mechanisms to ensure access to innovative drugs, such as Australia, Germany and France.(102) In England, the government introduced a Cancer Drugs Fund (CDF) in 2010 as a means to address a

perceived disparity in patients' access to cancer drugs compared with other countries.(38) The CDF provides £200 million annually to fund cancer drugs. Initially introduced for a period of three years, the CDF is to be continued beyond 2014 and with an additional budget of £160 million over two years.(124) A recent study by Chamberlain et al. (2014) found that the introduction of the CDF was associated with increased prescribing for three of the five drugs on which NICE had had issued negative guidance or for which recommendations had been mixed (positive and negative recommendations for different indications).(38) This was the case for sorafenib, for which the prescribing volume increased by 29 per cent post CDF introduction, while the prescribing volume for bevacizumab increased by a factor of three. Prescribing also increased substantially for two drugs awaiting NICE appraisal before the introduction of the CDF (lapatinib, panitumumab) (subsequently not recommended). Prescribing volumes for drugs that were recommended by NICE were not affected by the CDF. The authors highlighted that while the CDF did provide access to drugs that were deemed not cost-effective by NICE it did not necessarily accelerate access to new cost-effective drugs (although it did so in Wales). They further noted that their observations will have important implications for resource allocation in the NHS vis-à-vis other disease areas, and they highlighted the need for a better understanding of (other) mechanisms to make appropriate therapies available within the NHS.

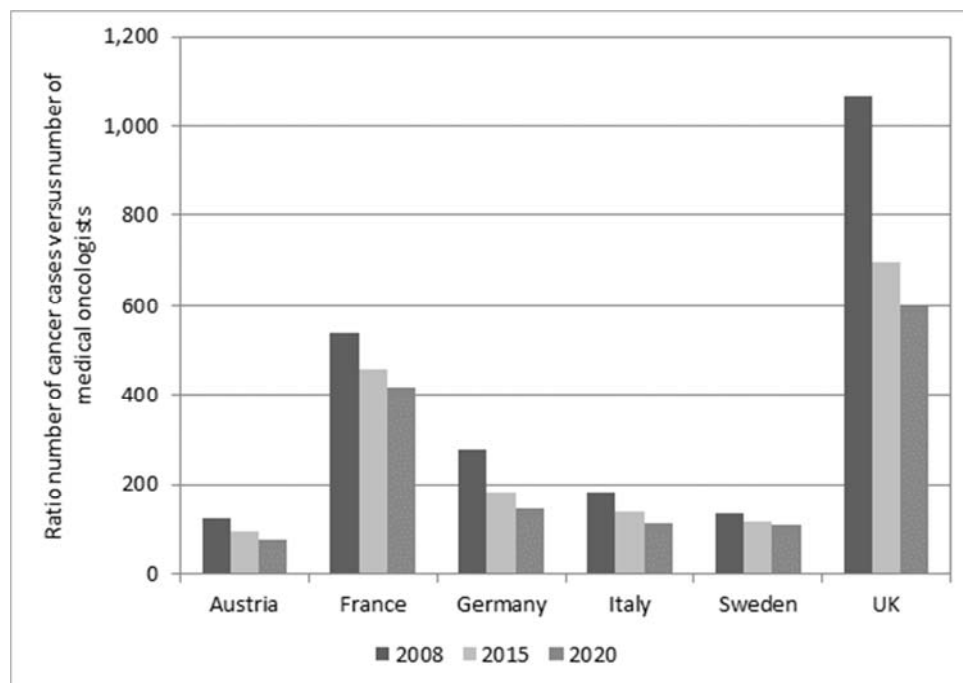
We highlighted above that while there is little direct empirical evidence of factors that impact cancer drug usage across countries, a number of studies have focused on system and service factors and their role in determining cancer outcomes. Among these, some argued that higher spending on health was associated with improved outcomes for cancer patients, for example when comparing cancer incidence and mortality between western and eastern European countries.(125) Philipson et al. (2012) associated higher health spending, in particular higher cancer care costs, in the US with greater survival gains for cancer patients than those in European countries.(126) However, the study's findings were challenged because of its reliance on the Surveillance, Epidemiology, and End Results (SEER) database, which covered only 14 per cent of the population at the time of the study (127), reflecting concerns voiced elsewhere in the usage of SEER data for international comparison of cancer survival.(128)

More recently, Uyl-de Groot et al. (2014), examining the relation between cancer mortality and costs in countries of the European Union, were unable to find evidence of a significant correlation between the number of deaths per 100,000 population and per-capita expenditure on cancer (Pearson correlation coefficient: -0.31; not significant).(129) Instead, they highlighted the complexity of cancer care in determining outcomes, with others pointing to issues around access to timely specialist care and, by implication, appropriate (drug) treatment specifically. For example, Brown et al. (2014) examined the role of health system factors for cancer outcomes in six countries: Denmark, Norway, Sweden, the UK (England, Wales and Northern Ireland), Canada (British Columbia, Manitoba, Ontario) and Australia (New South Wales, Victoria).(130) They focused specifically on the role of primary care in the light of other work that pointed to a potentially adverse impact of primary care gatekeeping on cancer outcomes by delaying timely diagnosis.(131) Using a narrative review, their analysis did not identify specific or consistent relationships between features such as regulation, financing, the degree of comprehensiveness of primary care services, the level of cost sharing and the type of primary care providers within healthcare systems with differences between countries. Factors that were identified to be of potential importance in relation to untimely cancer diagnosis and poorer cancer outcomes included centralisation of services, free

movement of patients between primary care providers, access to secondary care, and the existence of patient list systems, although the authors were not able to provide empirical evidence for a causal correlation between healthcare system characteristics and cancer outcomes.

De Azambuja et al. (2014) provided some further insight into variation in access to specialist care by examining the availability of medical oncologists in a range of countries in Europe and relating this to the incidence of cancer.(132) This found considerable variation across countries, with the actual (2008) and projected (2015, 2020) number of new cancer cases per number of medical oncologists substantially higher in the UK than in Austria, Sweden, Italy and Germany (Figure 16). Arguably, the number of specialists can only provide a proxy measure of access to specialist care and it provides little insight into appropriateness and quality of care delivered, although the observed differences call for further investigation into the accessibility of specialist treatment in the UK.

**Figure 16 Ratio of the number of new cancer cases and of the number of medical oncologists in six countries, 2008, 2015 and 2020**



Source: adapted from de Azambuja et al. (2014) (132)

## 6. Diabetes mellitus

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### 6.1. Background

Diabetes occurs as a consequence of the human body unable to produce sufficient amounts of the hormone insulin, which regulates blood glucose, or to use insulin effectively.(133) People with diabetes are unable to absorb glucose appropriately and as a result glucose remains circulating through the body. This can lead to long-term damage and disabling and potentially fatal health complications. In high-income countries, diabetes is a leading cause of cardiovascular disease, blindness, kidney failure and lower-limb amputation.

The most common form of diabetes is type 2, which typically occurs in adults, although it is increasingly seen in young people, including children.(134) Diabetes type 1, which is caused by an autoimmune reaction, typically occurs in children or young people and the prevalence of type 1 diabetes is also increasing, although at a lower level than type 2. Overall, the number of people with diabetes has doubled during the past 20 years, making it one of the most important public health challenges globally. Diabetes is associated with a high economic burden, with the global expenditure on diabetes estimated at US\$376 billion (~£230 billion) in 2010, and this expenditure has been projected to rise to US\$490 billion (~£305 billion) in 2030.(135) More recent estimates by the International Diabetes Federation placed global expenditure on diabetes in 2013 at US\$548 billion (~£340 billion), and this is projected to increase to US\$627 in 2035 (~£390 billion).(133) In 2013, expenditure in the US accounted for more than one-third of the global expenditure (at US\$299 billion, approximately £185 billion), followed by the European region, at US\$147 billion (~£91 billion). Among high-income countries, diabetes-associated expenditure per person with diabetes ranged from US\$3,295 (£2,048) in Spain, US\$3,501 (£2,175) in Italy and US\$3,994 (£2,483) in the UK to US\$9,800 (£6,091) in the US, US\$9,873 (£6,137) in Switzerland and US\$10,369 in Norway (£6,445).

Aspects of the pathophysiology and causal pathways for type 1 and type 2 diabetes remain inadequately understood, challenging the effective treatment of type 2 diabetes in particular.(136) It is clear that those with diabetes type 1 will not survive without a regular supply of insulin, while type 2 diabetes is largely preventable and complications can be prevented or delayed through a combination of lifestyle changes, oral medications or insulin therapy, depending on the status of the condition.(137) There are different types of pharmaceutical treatments which, alongside insulin, aim to normalise blood glucose levels. These include metformin, sulphonylureas, alpha glucosidase inhibitor (acarbose), glitazones, glinides (nateglinide and repaglinide), gliptins (dipeptidyl peptidase-4 or DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) agonists.(138)

The quantitative analysis of medicines uptake undertaken by the OHE considered three types of medicines for the treatment of diabetes: insulins, other antidiabetics and DPP-4 inhibitors and GLP-1 agonists, with the latter two combined to represent newer, innovative diabetic medicines.(4) The 2014 OHE analysis found that in 2012/13 the UK ranked:

- fifth out of 13 countries with regard to usage of insulins (UK usage as a percentage of EU5 average: 102 per cent; all countries: 104 per cent)
- second out of 13 countries with regard to usage of other antidiabetics (UK usage as a percentage of EU5 average: 122 per cent; all countries: 156 per cent)
- eleventh out of 13 countries with regard to usage of DPP-4 inhibitors and GLP-1 agonists (UK usage as a percentage of EU5 average: 19 per cent; all countries: 33 per cent).

As diabetes medicines were not covered in the 2010 Richards report (1) it is not possible to assess the extent to which these patterns have changed over the past five years.

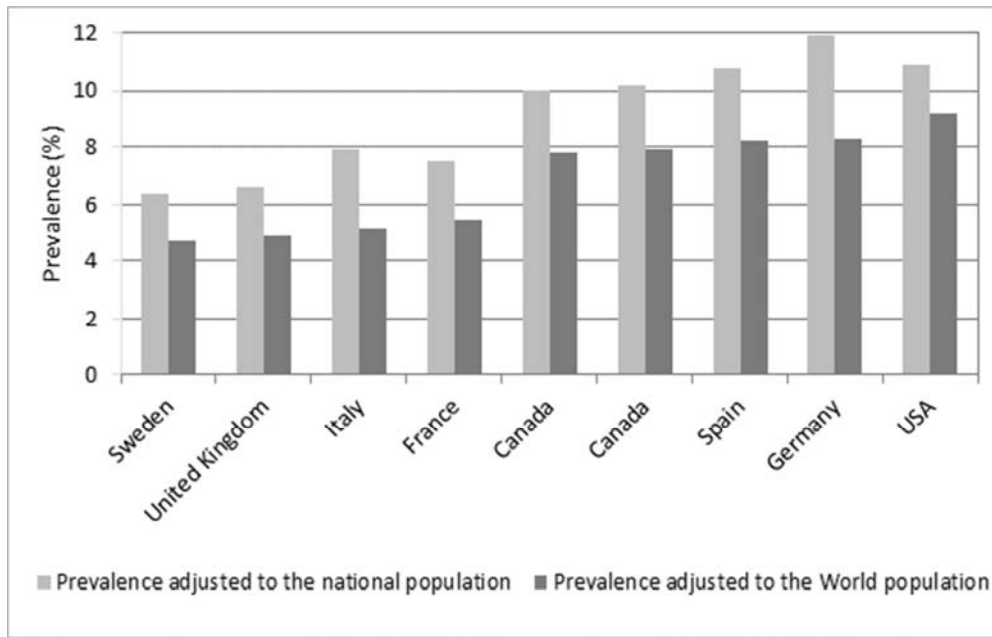
## 6.2. Explaining observed variation in diabetes drug usage

### 6.2.1. Burden of disease

The most recent estimates by the International Diabetes Federation suggest that in 2013 there were 382 million people living with diabetes globally.(133) This figure is similar to that previously forecasted for 2030, suggesting that the burden of diabetes has consistently been underestimated during the past two decades.(134) It is being estimated that by 2035 the number of people with diabetes will have risen to almost 600 million.(133) In the absence of comparable national diabetes registration systems it is difficult to come to a precise understanding of the country-specific diabetes burden.(139) The estimates provided by the International Diabetes Federation are based on a comprehensive review of the published literature reporting age-specific diabetes prevalence, alongside data compiled from national health surveys undertaken in individual countries; these then served as a basis to produce estimates for age-specific prevalence for adults aged 20–79 for each country using logistic regression and applied to population estimates for the given year under study.(140) Figure 17 presents these data for 10 of the 13 high-income countries covered in the 2014 OHE report.



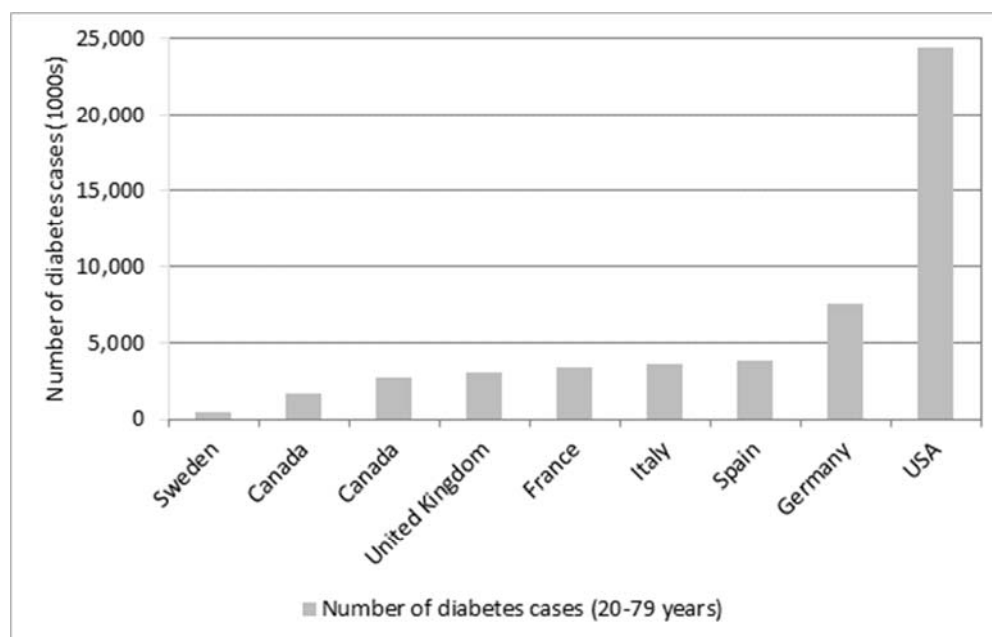
**Figure 17 Estimated prevalence of diabetes in ten high-income countries, 2013**



Source: adapted from Guariguata et al. (2014) (140)

Considering estimated prevalence adjusted to the World population, in 2013, diabetes prevalence was highest in Spain (8.2 per cent), Germany (8.3 per cent) and the US (9.2 per cent) and lowest in Sweden (4.7 per cent) and the UK (4.9 per cent). Prevalence figures as estimated by Guariguata et al. (2014) are somewhat higher than those described by Kanavos et al. (2012) in a study that sought to assess the diabetes burden and expenditure in five EU countries (France, Germany, Italy, Spain and the UK).(139) However, the study by Kanavos et al. (2012) drew on estimates derived from surveys undertaken in the latter half of the 2000s. Applying prevalence estimates provided by Guariguata et al. (2014) to the population aged 20–79 years, the number of people with diabetes ranged from 439,000 in Sweden to 24 million in the US, mainly reflecting the large difference in population size (Figure 18).(140)

**Figure 18 Estimated number of people with diabetes (20–79 years) in ten high-income countries, 2013**

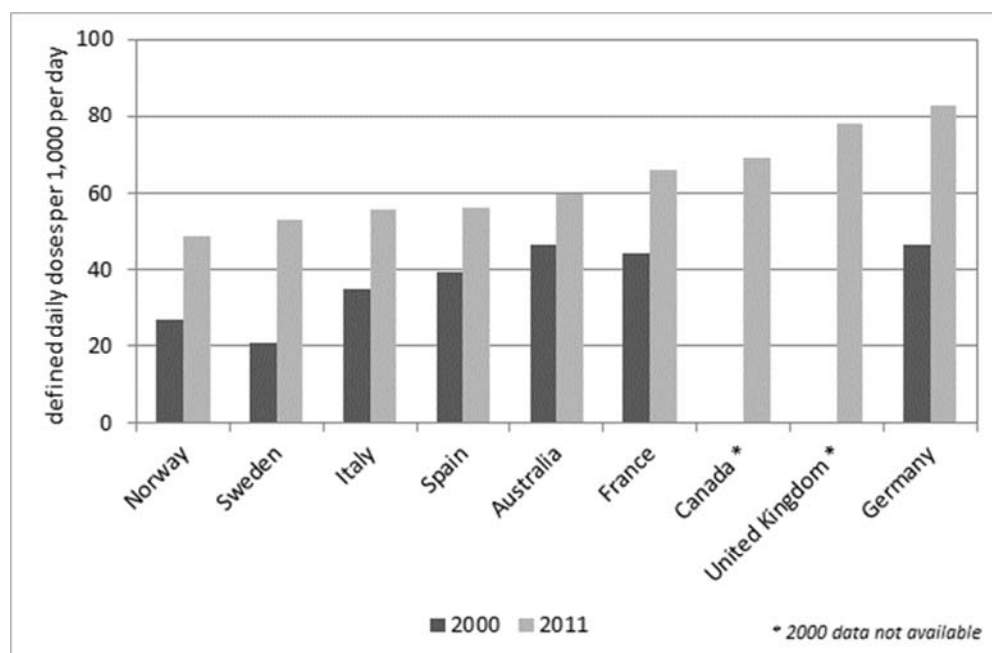


Source: adapted from Guariguata et al. (2014) (140)

The prevalence of diabetes is projected to increase in most high-income countries, with the proportional change in the number of people with diabetes between 2013 and 2035 estimated to range from 7.3 per cent in Germany to between 37 per cent (Spain) and 40 per cent (Australia).<sup>(140)</sup> The observed variation in the diabetes burden across countries considered in this report is likely to partly explain observed variation in diabetes drug usage.

### 6.2.2. Existing studies of variation in diabetes drug usage

We noted in the introduction to this report that the OECD, in its international comparative analysis of health system indicators, assesses variation in “pharmaceutical consumption” measured as defined daily doses per 1,000 population for a small number of categories.<sup>(5)</sup> In its 2013 report this included an assessment of the consumption of medicines for the treatment of diabetes. This found that in 2011 consumption in the UK was among the highest across OECD countries, only surpassed by Germany, and exceeding the average of 23 OECD countries by 30 per cent (Figure 19). The OECD attributed observed differences in patterns of diabetes medicines consumption to differences in the underlying disease prevalence, alongside differences in clinical guidelines and prescription behaviours, among other factors. However, the analysis by the OECD did not disaggregate data for different types of diabetes medicines and it is therefore unclear to what extent usage of newer diabetes medicines including DPP-4 inhibitors and GLP-1 agonists varies across countries.

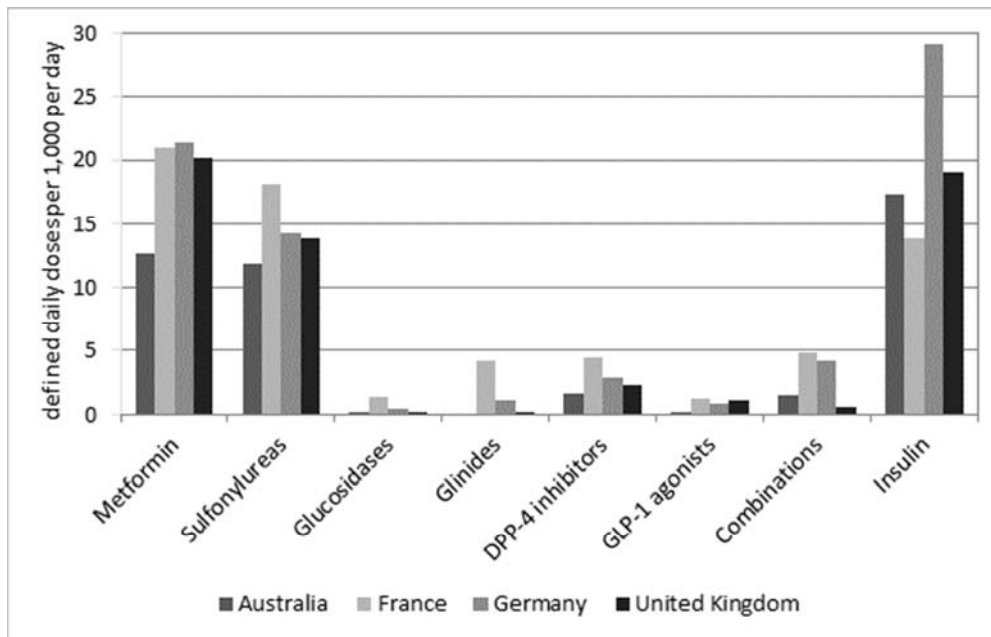
**Figure 19 Diabetes medicines consumption in nine high-income countries, 2000 and 2011 (or nearest year)**

Source: adapted from OECD (2013) (5)

Such an analysis was undertaken by Pichetti et al. (2013) who assessed the use of diabetes medicines by type of molecule in four countries: Australia, France, Germany and the UK.(141) The study considered insulin, metformin, sulphonylureas, glucosidases, glinides, glitazones, DPP-4 inhibitors and GLP-1 agonists. Using pharmaceutical sales data, the study found that in 2011 Germany had the highest use of diabetes medicines, at 74.5 defined daily doses (DDD) per 1,000 population and day, followed by France (69.3 DDD per 1,000 and day) and the UK (60.1), while for Australia usage was found to be considerably lower (46.6). These usage patterns differ slightly from those reported by the OECD described above, most likely reflecting differences in data sources.

When disaggregating usage of diabetes medicines by type of molecule, Pichetti et al. (2013) observed that the proportion of oral drugs as a proportion of all diabetes medicines was highest in France, accounting for some 78 per cent, compared with between 60 per cent in Germany and 67 per cent in the UK. At the same time, France showed the lowest proportion of the use of insulin, at 20 per cent, compared with 32 per cent in the UK, 37 per cent in Australia and 39 per cent in Germany. Metformin was the most commonly used oral anti-diabetic, with consumption patterns fairly similar across the three European countries, while lower in Australia (Figure 20), followed by sulphonylureas. Usage of other oral anti-diabetics was considerably lower across countries, although France had comparatively higher levels of use of glinides, a drug used only a little in the other three countries, and DPP-4 agonists. In 2011, the latter accounted for just over 8 per cent diabetes medicines sales in France compared with about 6 per cent in Germany and the UK and 4 per cent in Australia.

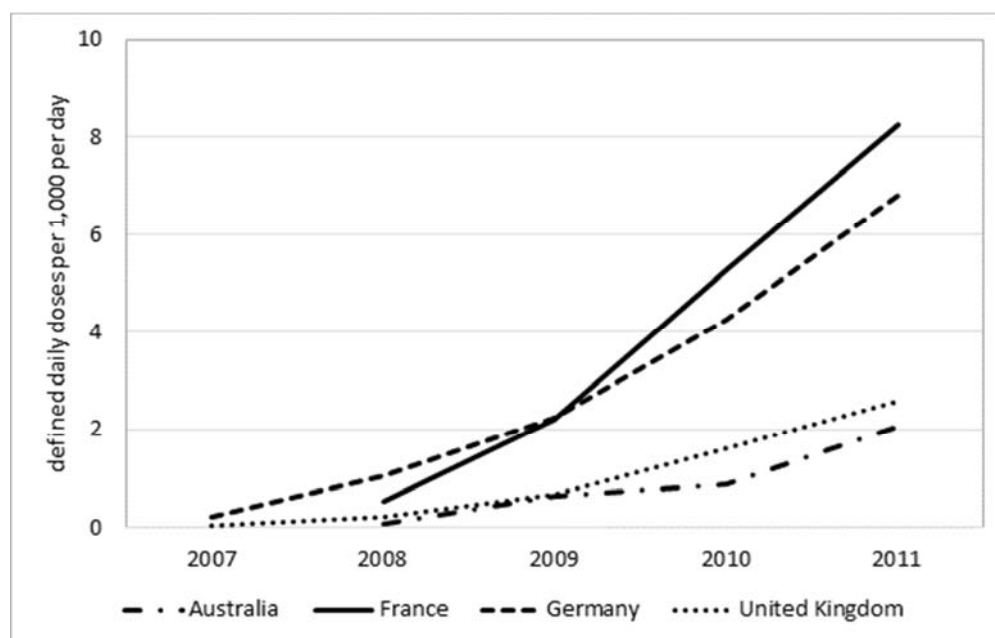
**Figure 20 Oral diabetes medicines consumption in Australia, France, Germany and the UK, 2011**



Source: adapted from Pichetti et al. (2013) (141)

Pichetti et al. (2013) noted that there was a tendency in France to use more expensive recent molecules, compared with the other three countries.(141) However, when combining usage of DPP-4 agonists as monotherapy with combination therapy containing DPP-4 agonists, Germany was on par with France, with this group accounting for some 15 per cent of new oral anti-diabetics prescriptions while in Australia and the UK this was only half that level. The authors further noted that the uptake of these new medications was more rapid in France and Germany than it was in the UK or Australia (Figure 21). When interpreting variation in medicines usage across countries it is however important to reiterate that usage data were not adjusted for the underlying prevalence of diabetes. It is therefore difficult to make an assessment as to appropriateness of usage observed in different countries.

**Figure 21 Usage of DPP-4 agonists (monotherapy and in combination) in Australia, France, Germany and the UK, 2007–2011**



Source: adapted from Pichetti et al. (2013) (141)

### 6.2.3. Health system and services features that may explain variation in diabetes drugs usage

Pichetti et al. (2013) in their analysis of the usage of different types of diabetes medicines in Australia, France, Germany and the UK identified decisions on the inclusion of a given medicine under the publicly funded system as the main factor explaining observed variations.(141) Specifically they highlighted the role of economic evaluation in the issuing of recommendations on whether a medicine should be made routinely available, with economic considerations, they argued, more systematically applied in Australia and the UK than in France or Germany. While in both France and Germany it has recently been made possible to more explicitly consider economic aspects in recommendations for the funding of new medicines, this had so far not been applied to diabetes medicines. The authors further highlighted the role

of economic evaluation in determining “rules of priority” as applied in Australia, referring to the practice that specific medicines can only be prescribed following prior authorisation, with prescribing recommendations in the UK (and, more recently, France) prioritising diabetes treatment according to their efficiency.

It is difficult to assess the impacts of different usage levels of diabetes medicines on outcomes among people with diabetes from this analysis. Clearly, the successful management of diabetes requires access to high-quality medication, but also to devices that permit the control of blood glucose levels, alongside support structures that enable people with diabetes to self-manage their condition (and timely access to specialists in case of complications). Taken together these factors all influence diabetes outcomes, as highlighted in a 2013 report by the European chapter of the International Diabetes Federation.(137) It documented the findings of a series of surveys targeting national health institutions, healthcare professionals and people with diabetes in 47 countries in Europe in 2013 to understand access to medicines and medical devices for diabetes care. Complemented by interviews with member associations of the International Diabetes Federation and other stakeholders, including the pharmaceutical industry, and desk research, the study covered 12 categories of diabetes supplies, including medicines (human insulin and insulin analogues, metformin, DPP-4 inhibitors and other oral or injectable medicines). The study did not directly compare usage of different types of diabetes medicines across countries but analysed factors around the availability of these medicines and the extent to which people with diabetes in individual countries can access them. Table 8 summarises these for a subset of countries covered in the present report.

**Table 8 Availability and accessibility of anti-diabetes medicines in seven European countries, 2013**

|         | <b>National guideline for diabetes care</b> | <b>Specific prescription criteria for anti-diabetes medicines</b>   | <b>Financial coverage of anti-diabetes medicines</b>   |
|---------|---|---|--|
| Austria | Yes   | <p>Prescription criteria are related to the reimbursement classification: depending on the “box” into which medicines have been classified, these may be prescribed without additional criteria, for specific indications only, or require ex-ante approval from health insurance funds:</p> <ul style="list-style-type: none"> <li>• Some newer oral and injectable medications require authorisation prior to prescription and can be prescribed only to people who are failing to achieve good glycaemic control with other therapies.</li> <li>• Some long-acting insulin analogues can be prescribed only to certain people with diabetes (for example, people with type 2 diabetes with nocturnal hypoglycaemia).</li> </ul> <p>The “box” system applied to medicines is perceived by some to delay access to new medications as it involves lengthy procedures until the medicine is effectively available to people and tight prescription criteria apply for a prolonged period.</p> | Insulin and anti-diabetes medications are free of charge (prescription charges apply).   |
| France  | Yes   | <p>The French National Authority for Health recommends that newer medications should be used mainly as second- or third-line treatment.</p> <p>Most people are treated with insulin, and especially people with type 1 diabetes are using insulin analogues</p>   | Under the Long-Term Illness (ALD) Scheme, medicines and medical devices for diabetes are fully covered by the mandatory health insurance system and people are |

|             | <b>National guideline for diabetes care</b> | <b>Specific prescription criteria for anti-diabetes medicines</b>  | <b>Financial coverage of anti-diabetes medicines</b>   |
|-------------|---|--|--|
|             |   | and insulin pens.<br><br>Metformin is the first-line oral medication and is the most widely prescribed.  | exempt from dispensing fees.<br><br>To become eligible the prescriber must apply (on the patient's behalf) to the person's health insurance fund. It is estimated that about one-third of people with diabetes are not enrolled in the ALD scheme. |
| Germany     | Yes   | <p>Prescription criteria are directly related to reimbursement and prices, with health insurance funds deciding on the criteria and prices according to which products they cover for each category of patient.</p> <ul style="list-style-type: none"> <li>• In recent years, health funds have tended to apply further criteria, especially on newer medicines and technologies.</li> <li>• Evaluations are not carried out in the same way across health funds and the likelihood of having a request for reimbursement rejected varies.</li> </ul> <p>Metformin appears to be the most widely prescribed oral medication, and is used mainly by people with type 2 diabetes. DPP-4 was only recently (2013) approved for the routine use under the statutory system for a period of initially 2 years (and pending successful price negotiation between the health insurers and industry).(142)</p> | Insulin and anti-diabetes medications are free of charge (prescription charges apply).   |
| Norway      | Yes   | Newer medications are subject to specific prescription criteria.   | Insulin and anti-diabetes medications are fully or partially reimbursed  |
| Sweden      | Yes (implementation varies by region)       | Not reported.  | <p>Insulin: free of charge</p> <p>Anti-diabetes medication: free or partially reimbursed (with upper limits set on annual expenditure)</p>   |
| Switzerland | Yes   | <p>Certain medications, in particular newer medicines, can be prescribed only by a specialist or only as a second- or a third-line treatment. This includes DPP4-inhibitors.</p> <p>GPs may prescribe some new oral medication, but their uptake varies across diabetes centres.</p> <p>The use of oral medication for people with diabetes other than type 2 diabetes is limited. Metformin is the principal first line of pharmaceutical treatment for type 2 diabetes.</p>  | Insulin and anti-diabetes medicines: free but user charges apply (up to a ceiling of CHF 700 per year).  |
| UK          | Yes   | <p>Guidelines in place recommend the use of newer medications, including insulin analogues and DPP4-inhibitors, mainly as second- or third-line treatment.</p> <p>Metformin and sulphonylureas appear to be the most widely used oral medications for people with type 2 diabetes. It is estimated that about 30% of people with type 2 diabetes will be moved by their healthcare team to insulin therapy.</p>  | Insulin and anti-diabetes medicines: people with diabetes on insulin or oral medications are exempt from the prescription fee but they must apply for an exemption certificate to benefit from this.   |

Source: adapted from International Diabetes Federation Europe (2013) (137)

These findings highlight that while principally there appears to be good access to diabetes medicines in the countries studied, there may be pockets of patient groups for whom access will be more difficult. However, again as highlighted above, it is difficult, on the basis of available data, to establish a direct link to diabetes outcomes.



## 7. Hepatitis C

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### 7.1. Background

Hepatitis C is a leading cause of complications from chronic liver disease, including liver cirrhosis, liver failure, liver cancer and death.<sup>(143)</sup> Some 75–85 per cent of acute disease cases progress to become chronic, because of the protracted course of the infection and because disease complications may only appear decades after contracting the hepatitis C virus (HCV). As a consequence, the infection is often diagnosed in a late stage where treatment options are limited.<sup>(144)</sup>

Current treatments that can successfully clear HCV in most patients and that are recommended by NICE are interferon- $\alpha$ -based therapies.<sup>(145)</sup> The primary goal of antiviral treatment of chronic HCV infection is the attainment of a sustained viral response, defined as undetectable serum HCV-RNA levels six months after cessation of treatment. In recent years there has been what has been referred to as a “revolution” in the treatment of HCV infection, with newer, interferon-free combinations of drugs expected to cure more than 90 per cent of infections.<sup>(146)</sup> These newer treatments include viral protease inhibitors such as telaprevir or boceprevir, which NICE has recently recommended for the possible treatment of genotype 1 chronic hepatitis C.<sup>(147, 148)</sup>

The quantitative analysis of HCV medicines uptake undertaken by the OHE considered peginterferon alfa-2a and peginterferon alfa-2b, with boceprevir and telaprevir added. The OHE analysis found that in 2012/13 the UK ranked eleventh out of 13 countries with regard to usage of HCV medicines. This presents a small improvement from 2008/09, when the UK ranked thirteenth.<sup>(1)</sup> Comparative usage of these drugs in the UK measured as a percentage of all 13 countries increased from 56 per cent in 2008/09 to 73 per cent in 2012/13. When measured as a percentage of five EU countries (France, Germany, Italy, Spain, UK), the respective figures were 43 per cent in 2008/09 and 59 per cent in 2012/13.

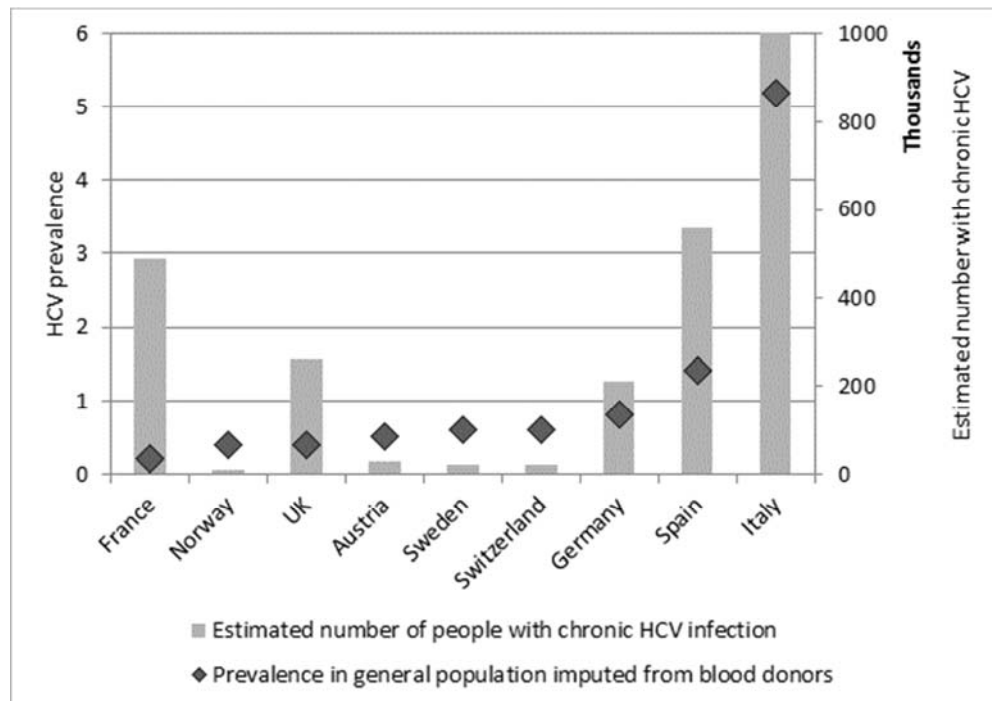
### 7.2. Explaining observed variation in hepatitis C drug usage

#### 7.2.1. Burden of disease

Global estimates place the proportion of people infected with hepatitis C at 2–3 per cent of the world’s population, which equates to some 120–170 million people.<sup>(149)</sup> For the WHO European region it has been estimated that some 15 million are living with hepatitis C.<sup>(150)</sup> Of these, an estimated 2 million are current drug injectors. Hope et al. (2014) provided estimates for the number of people living with chronic HCV infection.<sup>(149)</sup> Figure 22 illustrates estimates for countries included in the 2014 OHE report. This shows considerable differences in both the number of people affected as well as prevalence rates in the

general population, with Italy showing the highest burden overall, while prevalence rates were also somewhat elevated in Spain and Germany.

**Figure 22 Prevalence and estimated number of people with chronic HCV infection, selected European countries, 2008**



Source: adapted from Hope et al. (2014) (149)

The most recent estimates for the UK suggest that around 215,000 individuals are chronically infected with HCV, with prevalence rates of between 0.4 per cent (~160,00) of the adult population in England and 0.7 per cent in Scotland.(151) Most of HCV infections in the UK are of genotype 1 and genotype 3 (~90 per cent). However, more than half of people with chronic hepatitis C are unaware of their infection. HCV predominantly affects marginalised populations, with people who inject drugs showing the highest observed prevalence (measured as having tested positive for antibodies to HCV) of just under 50 per cent in England in 2012, although with substantial variation across regions.(152) Hospital admissions and deaths attributable to HCV-related end-stage renal disease and liver cancer continue to rise, with admissions rising from 612 in 1998 to 2,268 in 2011; deaths rose from 98 in 1996 to 381 in 2011.(151) HCV-related mortality is expected to peak in the coming decade in many western countries.(153)

### 7.2.2. Existing studies of variation in hepatitis C drug usage

In England, using national data on pharmacy purchasing and prescribing, Public Health England (2013) estimated that about 27,500 patients with HCV could have been treated with peginterferon as part of the NICE recommended combination therapy between 2006 and 2011, just under 20 per cent of the total chronically infected population.(151) The number of people receiving antiviral treatment steadily

increased between 2006 and 2010, although the rate of increase slowed over time and there was a small decline of 6 per cent fewer patients treated in 2011 than in 2010.

The WHO's 2013 global policy report on the prevention and control of viral hepatitis in WHO member states presented data reported by member states on the range of policies they had implemented to address viral hepatitis.(150) Thirty-four member states reported that publicly funded HCV treatment was available. Out of 12 countries that provided further information, 86 per cent said that they had included ribavirin on their essential medicines list (or the drug was subsidised by government), 80 per cent said so for peginterferon, 68 per cent for interferon alpha, and 39 per cent each for telaprevir and boceprevir.

### 7.2.3. Health system and services features that may explain variation in hepatitis C drugs usage

The 2013 WHO report provided structured assessments of countries' national strategies on viral hepatitis. These are summarised further for the subset of countries included in the 2014 OHE report in Table 9. This seems to suggest that the UK is among those countries with the most comprehensive policies as it relates to the prevention and control of HCV infection, although it is difficult to assess the extent to which policies are being implemented in practice. All countries appear to fund the same range of antivirals for the treatment of HCV infection and it is not immediately obvious from data shown in Table 9 why countries differ in relation to HCV drug usage.

**Table 9 National strategies and programmes related to the prevention and control of hepatitis C infection in eight European countries, 2012**

|         | <b>Written national strategy or plan on the prevention and control of viral hepatitis</b> | <b>Routine surveillance for HCV</b> | <b>Awareness raising</b> | <b>National policy on preventing HCV among people who inject drugs</b> | <b>National policy relating to screening and referral to care for HCV</b> | <b>Funding</b>  |
|---------|---|-------------------------------------|--------------------------|--|---|---|
| Austria | Yes   | Yes                                 | -                        | Yes  | -   | Interferon alpha<br>ribavirin   |
| France  | Yes<br>(plus designated government unit/department responsible for viral hepatitis)       | Yes                                 | (Yes)                    | Yes  | Yes   | Interferon alpha<br>pegylated interferon<br>ribavirin<br>boceprevir<br>telaprevir |
| Germany | -   | Yes                                 | -                        | -  | -   | Interferon alpha<br>pegylated interferon<br>ribavirin<br>boceprevir<br>telaprevir |
| Italy   | (Programme targeted to specific populations)  | Acute HCV                           | (Yes)                    | Yes  | -   | Interferon alpha<br>pegylated interferon<br>ribavirin<br>boceprevir<br>telaprevir |
| Spain   | (Programme targeted to  | Acute HCV                           | -                        | Yes  | Yes   | Interferon alpha<br>Pegylated interferon  |

|             | <b>Written national strategy or plan on the prevention and control of viral hepatitis</b> | <b>Routine surveillance for HCV</b> | <b>Awareness raising</b> | <b>National policy on preventing HCV among people who inject drugs</b> | <b>National policy relating to screening and referral to care for HCV</b> | <b>Funding</b>  |
|-------------|---|-------------------------------------|--------------------------|--|---|---|
|             | specific populations)   |                                     |                          |  |   | Ribavirin<br>boceprevir<br>telaprevir   |
| Sweden      | (Designated government unit or department responsible for viral hepatitis)                | Yes                                 | Yes                      | Yes  | Yes   | Interferon alpha<br>pegylated interferon<br>ribavirin<br>boceprevir<br>telaprevir |
|             | (Programme targeted to specific populations)  |                                     |                          |  |   |   |
| Switzerland | (Programme targeted to specific populations)  | Yes                                 | -                        | Yes  | -   | Pegylated interferon<br>ribavirin<br>boceprevir<br>telaprevir                     |
| UK          | Yes   | Yes                                 | Yes                      | Yes  | Yes   | Interferon alpha<br>pegylated interferon<br>ribavirin<br>boceprevir<br>telaprevir |

Source: adapted from WHO (2013) (150)

Other evidence suggests that HCV detection rates in the UK are lower than elsewhere, however, that evidence dates to the late 2000s and it is unclear whether it still applies today. Lettmeier et al. (2008) examined the market uptake of peginterferons for the treatment of hepatitis C in 21 European countries during 2000–2005.(154) They estimated the number of those ever treated to range between a high of 16 per 100 prevalent cases in France to less than 1 per cent of cases in countries such as Greece, Poland and Romania. The UK was among the countries with a relatively low number of patients treated, at around 3.5 per cent (the average rate across 21 countries). Lettmeier et al. (2008) highlighted the role of under-detection of prevalent cases, citing evidence that in France, which had operated an active screening policy for hepatitis C, about 40 per cent of cases remain undetected, whereas in Spain, for example, this figure was estimated at 80 per cent. High uptake of treatment in France has been attributed to a government-led campaign and investment in hepatitis C services, with detection rates doubling since 1994 and awareness levels rising from 24 per cent to 56 per cent during the same period, a figure that was four times higher than in the UK.

Low rates of treatment have a substantial impact on the future burden of disease associated with HCV. For example, assuming current treatment levels of approximately 3 per cent per year, Public Health England estimated that the number of cases of end-stage renal disease and liver cancer will rise from 1,170 (95% credible interval (CrI) 1,060–1,300) in 2014 to 1,680 in 2033 (95% CrI 1,460–2,000). It further estimated that the number of cases of end-stage renal disease and liver cancer could be substantially

reduced by increasing the number of those receiving treatment. For example, it was estimated that 190 (95% CrI 170–240) additional cases per year could be averted if treatment was increased by 100 per cent over the next ten years.

A 2010 international survey of 697 physicians providing HCV treatment from 29 countries HCV identified a number of barriers to treatment, and the perception of barriers was strongly associated with physician knowledge, experience and region of origin, with the fewest barriers reported by physicians in Nordic countries.<sup>(155)</sup> Among physicians in European countries 71–83 per cent believed that government or payers recognised treatment guidelines, while only over half of respondents felt that healthcare providers have adequate knowledge of HCV guidelines. Globally, less than one-quarter of physicians felt that the general public was aware of HCV and know that it is a curable disease. Only 35 per cent of physicians included in the survey believed that patients have adequate access to HCV treatment providers, with the lowest percentage in the US (17 per cent) and the highest in Nordic countries (62 per cent).



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## Appendix A

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Tables A.1–A.4 summarise the main characteristics of pharmaceutical policies in 14 countries along with some general information about their health systems, drawing on a range of sources as indicated, as well as the Health Systems and Policy Monitor by the European Observatory on Health Systems and Policies<sup>a</sup>, Paris and Belloni (2013)<sup>b</sup> and Sorensen et al. (2008).<sup>c</sup>

Table A.1 describes key features of the health systems of Australia, Austria, Canada, Denmark, France, Germany and Italy; Table A.2 presents similar information for New Zealand, Norway, Spain, Sweden, Switzerland, UK (England) and the US.

Tables A.3 and A.4 summarise general principles of decisionmaking on new drugs under the statutory system; the use of positive and/or negative lists; policies on co-payments for pharmaceuticals; time between licensing and reimbursement decisions or, where relevant, guidance providing recommendations on usage; and the role of cost-effectiveness criteria in decisionmaking. Table A.3 offers these details for Australia, Austria, Canada, Denmark, Finland, France, Germany and Italy; Table A.4 presents an overview of policies in place in New Zealand, Norway, Spain, Sweden, Switzerland, UK (England) and the US.

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<sup>a</sup> European Observatory on Health Systems and Policies. The Health Systems and Policy Monitor. URL: <http://www.hspm.org/mainpage.aspx> (accessed September 2014).

<sup>b</sup> Paris V, Belloni A. Value in pharmaceutical pricing. OECD Health Working Papers, No. 63. Paris: OECD Publishing, 2013.

<sup>c</sup> Sorenson C, Drummond M, Kanavos P. Ensuring value for money in health care: The role of health technology assessment in the European Union. Copenhagen: World Health Organization on behalf of the European Observatory on Health Systems and Policies, 2008.

**Table A.1 Key health system features: Australia, Austria, Canada, Denmark, France, Germany and Italy**

|  | <i>Australia</i> | <i>Austria</i> | <i>Canada</i> | <i>Denmark</i> | <i>France</i> | <i>Germany</i>   | <i>Italy</i> |
|--|------------------|----------------|---------------|----------------|---------------|--|--------------|
| <b>Health care financing (2012 or nearest year)</b>  |                  |                |               |                |               |  |              |
| <i>(% total health expenditure)</i>  |                  |                |               |                |               |  |              |
| <i>Taxation</i>  | 68.4             | 32.6           | 68.7          | 85.8           | 3.8           | 8.8  | 77.7         |
| <i>Social security schemes</i>   | 0.0              | 44.6           | 1.3           | 0.0            | 73.6          | 68.3   | 0.3          |
| <i>Private health insurance</i>  | 8.3              | 4.8            | 12.3          | 1.7            | 13.3          | 9.3  | 1.0          |
| <i>Out-of-pocket payments</i>  | 18.3             | 16.7           | 15.0          | 12.4           | 7.5           | 12.9   | 18.0         |
| <i>Other</i>   | 5.1              |                | 2.7           | 2.8            | 0.9           | 0.7  | 3.0          |
| <i>Total expenditure on health (% GDP)</i>   | 9.1              | 11.1           | 10.9          | 11.0           | 11.6          | 11.3   | 9.2          |
| <i>Public expenditure on health (% total health expenditure)</i>   | 68.4             | 75.9           | 70.1          | 85.8           | 77.4          | 76.7   | 77.3         |
| <b>Pharmaceutical expenditure (2012 or nearest year)</b>   |                  |                |               |                |               |  |              |
| <i>Total expenditure on pharmaceuticals (% total health expenditure)</i>                                       | 15.6             | 12.2           | 18.0          | 6.5            | 15.8          | 14.4   | 16.9         |
| <i>Per capita expenditure on pharmaceuticals and other medical non-durables (US\$ purchasing power parity)</i> | 588              | 561            | 771           | 295            | 651           | 668  | 514          |
| <b>Coverage by the statutory system</b>  |                  |                |               |                |               |  |              |
| <i>Coverage</i>  | Automatic        | Automatic      | Automatic     | Automatic      | Automatic     | Mandatory (from 2009)  | Automatic    |
| <i>% population covered under statutory system (2012 or nearest year)</i>                                      | 100.0            | 99.9           | 100.0         | 100.0          | 99.9          | Statutory health insurance: ~87%<br>private health insurance: ~11% | 100.0        |

Table A.1 Key health system features: Australia, Austria, Canada, Denmark, France, Germany and Italy (continued)

|   | <i>Australia</i>   | <i>Austria (22)</i>   | <i>Canada</i>  | <i>Denmark</i>   | <i>France</i>  | <i>Germany</i>  | <i>Italy</i>   |
|---|--|---|--|--|--|---|--|
| <b>Scope of services covered by the statutory system (14)</b><br><i>(Austria: (22))</i> | Free or subsidised access to most medical services; inpatient and outpatient hospital care; physician services; some allied health services for the chronically ill; prescription drugs; specified optometric and dental surgery services; mental health services; rehabilitation. | Ambulatory general and specialist care; hospital care; dentistry; physiotherapy, occupational and speech therapy; psychotherapy; home nursing care; rehabilitation; travel and transportation; sickness benefits; therapeutic aids; illness prevention. | All medically necessary physician, diagnostic and hospital services. There is no nationally defined statutory benefits package; most coverage decisions are made by provincial or territorial governments with varying levels of additional benefits, such as outpatient prescription drug coverage, dental care, home health care, physiotherapy, independent living aids and ambulance services. | All primary, specialist and hospital services; preventive services; mental health services; dentistry for those under 18 years and long-term care. Subsidies apply to outpatient prescription drugs, adult dental care, physiotherapy, home care and optometry services. | Hospital care, ambulatory care; prescription drugs, devices and transport; certain preventive services for defined groups; partial coverage of mental health and long-term care, minimum coverage of outpatient eye and dental care. | Preventive services, inpatient and outpatient hospital care; physician services; mental health care; dental care; prescription drugs; medical aids; rehabilitation; palliative care; sick leave compensation. | Primary and specialist (ambulatory and hospital) services; prescription drugs; dental treatment for some groups; preventive medicine; home care. |
| <b>Cost sharing arrangements</b>  |  |   |  |  |  |   |  |
| GP or specialist  | Yes  | Yes   | No   | No   | Yes  | Yes   | Yes (specialists only)   |
| Inpatient   | No   | Yes   | No   | No   | Yes  | Yes   | No   |
| Pharmaceuticals   | Yes  | Yes   | Yes  | Yes  | Yes  | Yes   | Yes  |
| Dental  | Yes  | Yes   | Yes  | Yes  | Yes  | Yes   | Yes  |
| <b>Access to specialists</b>  | GPs have a gate-keeping role in so far as recognised. Specialists can claim a higher rebate when the patient is referred by a GP. Patients   | GPs have no gatekeeping role, although they are usually the first entry point for patients. Referral is required for radiological   | GPs have a gatekeeping role. Patients can choose, and have direct access to, a specialist, but GP referral is most   | Vast majority (98%) of patients require a referral. Possibility for others to opt out and receive care without referral but with co-payment.   | Voluntary gatekeeping is in place through a preferred doctor scheme ( <i>médecin traitant</i> ) in the ambulatory care   | GPs have no formal gatekeeping role. Since 2007, health insurance funds are required to offer GP-centred care plans (GP contracts), in  | Patients require a referral, except for some selected services and emergencies. GPs have a gatekeeping role and incentives to                    |

|  |   |  |   |  |   |  |
|--|---|--|---|--|---|--|
| can choose their preferred specialist. | examination or laboratory diagnosis. A fee is required to access the services of just over half of physicians (the “non-contracted”). | common because many provinces pay lower fees for non-referred consultations. | Access to a hospital requires a referral for all. | sector with higher co-payments for patients accessing care outside this coordinated care pathway.(156) | which members agree to always seek care through their family physician first. About 20% of the population have joined such plans (2010).(157) | prescribe and refer only as appropriate. |
|--|---|--|---|--|---|--|

Table A.2 Key health system features: New Zealand, Norway, Spain, Sweden, Switzerland, UK (England) and US

|  | <i>New Zealand</i> | <i>Norway</i> | <i>Spain</i>           | <i>Sweden</i> | <i>Switzerland</i> | <i>UK (England)</i> | <i>US</i>  |
|--|--------------------|---------------|------------------------|---------------|--------------------|---------------------|--|
| <b>Health care financing (2012 or nearest year)</b>  |                    |               |                        |               |                    |                     |  |
| <i>(% total health expenditure)</i>  |                    |               |                        |               |                    |                     |  |
| <i>Taxation</i>  | 74.9               | 74.2          | 68.3                   | 81.3          | 20.3               | 84.0                | 6.1  |
| <i>Social security schemes</i>   | 7.8                | 10.4          | 4.7                    | -             | 45.5               | -                   | 41.5   |
| <i>Private health insurance</i>  | 4.8                | 0.0 (2003)    | 5.6                    | 0.3           | 7.2                | 2.7                 | 33.4   |
| <i>Out-of-pocket payments</i>  | 10.9               | 15.0          | 20.7                   | 16.5          | 26.0               | 9.0                 | 12.0   |
| <i>Other</i>   | 1.6                | 0.8 (2002)    | 0.8                    | 1.9           | 1.0                | 3.8                 | 7.1  |
| <i>Total expenditure on health (% GDP)</i>   | 10.0               | 9.3           | 9.4                    | 9.6           | 11.4               | 9.3                 | 16.9   |
| <i>Public expenditure on health (% total health expenditure)</i>   | 82.7               | 85.0          | 73.0                   | 81.3          | 65.8               | 84.0                | 47.6   |
| <b>Pharmaceutical expenditure (2012 or nearest year)</b>   |                    |               |                        |               |                    |                     |  |
| <i>Total expenditure on pharmaceuticals (% total health expenditure)</i>                                       | 9.4                | 7.0           | 17.8                   | 12.3          | 9.2                | 12.3                | 12.0   |
| <i>Per capita expenditure on pharmaceuticals and other medical non-durables (US\$ purchasing power parity)</i> | 297                | 414           | 523                    | 478           | 562                | 367                 | 1,010  |
| <b>Coverage by the statutory system</b>  |                    |               |                        |               |                    |                     |  |
| <i>Coverage</i>  | Automatic          | Automatic     | Social insurance-based | Automatic     | Mandatory          | Automatic           | Automatic or means-tested for population subgroups |
| <i>% population covered under statutory system (2012 or nearest year)</i>                                      | 100.0              | 100.0         | 99.0                   | 100.0         | 100.0              | 100.0               | 32.6   |

**Table A.2 Key health system features: New Zealand, Norway, Spain, Sweden, Switzerland, UK (England) and US (continued)**

|   | <i>New Zealand</i>  | <i>Norway</i>   | <i>Spain</i>   | <i>Sweden</i>   | <i>Switzerland</i>  | <i>UK (England)</i>   | <i>US</i>  |
|---|---|---|--|---|---|---|--|
| <b>Scope of services covered under the statutory system</b> | Public health preventive and promotional services; inpatient and outpatient hospital care; primary care services; inpatient and outpatient prescription drugs; mental health care; dental care for school children; long-term care and disability support services. | Primary care, inpatient and outpatient care, dental care; preventive medicine, palliative care; prescription drugs; psychologist and psychiatrist care. | Primary health care, including general health and paediatric care, outpatient and inpatient surgery and care, emergency and acute care, long-term disease management, some dental care, transportation, mental health care, rehabilitation and prescription drugs. The basket of services on offer varies by region. | Public health and preventive services; inpatient and outpatient hospital care; primary health care; inpatient and outpatient prescription drugs; emergency care; mental health care; dental care for children and young people; rehabilitation services; disability support services; patient transport support services; home care; nursing home care. | Primary and specialist (hospital) services and pharmaceuticals subject to co-payment; emergency care; physiotherapy; home care; some preventive measures; mental health care; optometry for children. | The National Health Service (NHS) covers preventive services (screening, immunisation, vaccination); inpatient and outpatient (ambulatory) hospital (specialist) care; physician (general practitioner) services; inpatient and outpatient drugs; some eye, dental and long-term care; mental health care; learning disabilities; palliative care and rehabilitation. | Services covered vary by public system (e.g. Medicare, Medicaid, Veterans Affairs) typically include inpatient and outpatient hospital care and physician services. Many also include preventive services, dental care, physical therapy and prescription drug coverage. |
| <b>Cost sharing arrangements</b>                            |   |   |  |   |   |   |  |
| GP or specialist  | Yes   | Yes   | No   | Yes   | Yes   | No  | Variable   |
| Inpatient   | Yes   | Yes   | No   | Yes   | Yes   | No  | Variable   |
| Pharmaceuticals   | Yes   | Yes   | Yes  | Yes   | Yes   | Yes   | Variable   |
| Dental  | Yes   | Yes   | Yes  | Yes   | Yes   | Yes   | Variable   |
| <b>Access to specialists</b>                                | Patients require a referral. GPs have a gatekeeping role.   | Patients require a referral. GPs have a gatekeeping role.   | Patients require a referral. GPs have a gatekeeping role.  | Primary care has no formal gatekeeping function although some counties operate a gatekeeping system. Patients may choose to access specialists directly and without   | GPs have no formal gatekeeping function. Patients have free access (without referral) to specialists unless enrolled in a gatekeeping managed care plan.  | Patients require a referral. GPs have a gatekeeping role.   | Varies with insurance. Primary care doctors have no formal gatekeeping function, except within some managed care plans. Direct payment of a full (uninsured) or  |

| <b>New Zealand</b> | <b>Norway</b> | <b>Spain</b> | <b>Sweden</b>  | <b>Switzerland</b> | <b>UK (England)</b> | <b>US</b>   |
|--------------------|---------------|--------------|--|--------------------|---------------------|---|
|                    |               |              | referral but will then<br>have to make a co-<br>payment. |                    |                     | partial (insured) fee<br>is generally required<br>to access physicians. |

**Table A.3 Decisionmaking on the funding of new drugs under the statutory system: Australia, Austria, Canada, Denmark, France, Germany and Italy**

|  | <i>Australia</i>   | <i>Austria</i>  | <i>Canada</i>  | <i>Denmark</i>   | <i>France</i>  | <i>Germany</i>   | <i>Italy</i>  |
|--|--|---|--|--|--|--|---|
| <i>Primary body responsible for assessing new (outpatient) drugs for funding or subsidy under the statutory system</i> | Pharmaceutical Benefits Advisory Committee (PBAC)  | Federation of Austrian Social Security Institutions (HBV)   | Canadian Drug Expert Committee (CDEC) and the Canadian Agency for Drugs and Technologies in Health (CADTH) Common Drug Review (CDR)  | Danish Medicines Agency (DKMA)   | Transparency Commission (CT, part of the High Authority for Health, HAS)   | Federal Joint Committee (G-BA)   | Technical Scientific Committee (CTS), which is part of AIFA (Italian Medicines Agency)  |
| <i>Summary of process</i>  | <p>PBAC requires a value for money case for each new drug, which is then subject to assessment by HTA organisations contracted by PBAC. The Minister for Health is responsible for reimbursement decisions, though the decision may be referred to the Cabinet depending on expected budget impact.</p> <p>Decisions on drugs for use in public hospitals are made by states with some having established advisory committees and working groups to assess requests.</p> | <p>The HBV is responsible for devising a positive list of reimbursable medicines (Reimbursement Codex). It is advised by the Pharmaceutical Evaluation Board (HEK) at the HBV. The Pharmaceutical Evaluation Board also makes recommendations to the Independent Medicines Commission at the federal ministry of health, which reviews on request the decisions of the HBV.</p> | <p>CDEC is part of CADTH's Common Drug Review (CDR) process and makes recommendations to each of the participating federal and provincial or territorial publicly funded drug plans regarding the listings on their formularies. It also makes recommendations on the identification, evaluation and promotion of optimal drug prescribing and use in Canada. Hospitals determine their formularies through their Pharmaceutical and Therapeutics Committee.</p> | <p>DKMA decides on information received by the Reimbursement Committee (within DKMA). The Danish Centre for Health Technology Assessment (DACEHTA) is responsible for assessments of new drugs (especially new cancer drugs).</p> <p>The Coordinating Council on the introduction of hospital medicines (KRIS) and the regional Pharmaceutical and Therapeutic Committee determine hospitals' formulary lists.</p> | <p>CT is responsible for assessing drugs for reimbursement and produces technical advice for the Ministry of Health on new drugs. CT advice is on the level of actual clinical benefit and of improvement of clinical benefit; HAS may also make recommendations after assessing specific pharmaceuticals.</p> <p>Hospital pharmaceuticals are approved by the Ministry of Health.</p> | <p>Licensed prescription drugs are automatically covered (except drugs for trivial diseases, inefficient drugs and lifestyle drugs). G-BA receives advice from the Institute for Quality and Efficiency in Health Care (IQWiG), which assesses the effectiveness of drugs and issues prescribing recommendations.</p> <p>Individual hospital commissions decide on the hospital formulary.</p> | <p>The Inter-ministerial Committee for Economic Planning (CIPE) provides the CTS with eligibility criteria for the reimbursement of a new drug; the same criteria apply to inpatient drugs.</p> |



**Table A.3 Decisionmaking on the funding of new drugs under the statutory system: Australia, Austria, Canada, Denmark, France, Germany and Italy (continued)**

|  | <i>Australia</i>   | <i>Austria</i>   | <i>Canada</i>   | <i>Denmark</i>  | <i>France</i>   | <i>Germany</i>  | <i>Italy</i>  |
|--|--|--|---|---|---|---|---|
| <i>Principal role of the assessing body: advisory or regulatory*</i>                     | <u>Advisory</u> : PBAC makes recommendations to the Government           | <u>Regulatory</u> : Decisions by the HBV on the inclusion or exclusion of medicines into the positive list may be subject to review by the Independent Medicines Commission on request | <u>Advisory</u> : CDEC makes formulary listing recommendations for Canada's publicly funded plans | <u>Regulatory</u>   | <u>Advisory</u> : Transparency Commission reports to the Ministry of Health   | <u>Regulatory</u>   | <u>Regulatory</u>   |
| <i>Positive and/or negative list</i>   | Positive list: Pharmaceutical Benefits Scheme (PBS)                      | Positive list: Reimbursement Codex   | Individual payers positive lists  | Positive list   | Positive list (separate lists of innovative drugs allowing for special funding arrangements)  | Every licensed drug is covered under SHI except for lifestyle drugs and others ("negative" list)  | Positive and negative lists   |
| <i>Arrangements for co-payment for pharmaceuticals: ambulatory or out-patient sector</i> | General beneficiaries: AUD 36.10<br>Concessional beneficiaries: AUD 5.90 | Prescription fee per pack of €5.15 must be paid, with an annual cap of 2% of yearly net income. Exemptions exist for those on incomes below a certain threshold.                       | A variety of income-related deductibles and co-payments offered by provinces or territories.      | Prescribed medicines are reimbursed according to 4 reimbursement rates based on patient's annual pharmaceutical expenditure: 0%, 50%, 75%, 85% of the retail price. | Highly effective drugs have a 0% coinsurance rate; all other drugs carry coinsurance rates of 40–100% based on therapeutic value. Nonreimbursable co-payment of €0.50 per prescription drug, up to €50 per year per person. | i) children <18 years: exempt<br>ii) adults: 10% of the cost subject to a charge of €5–10 per prescription, unless the price is at least 30% below the reference price. | Regions can choose to introduce co-payments or not. Since 1993, patients have paid for the total cost per prescription up to a ceiling of €36.15. |

Note: \*Advisory bodies are defined as bodies that make reimbursement recommendations to a national or regional government, ministerial or self-governing body. Regulatory bodies are accountable to health ministries and responsible for listing drugs for reimbursement or subsidy under the statutory system (Sorenson et al., 2008).

**Table A.3 Decisionmaking on the funding of new drugs under the statutory system: Australia, Austria, Canada, Denmark, France, Germany and Italy (continued)**

|  | <i>Australia</i>   | <i>Austria</i>   | <i>Canada</i>   | <i>Denmark</i>  | <i>France</i>  | <i>Germany</i>  | <i>Italy</i>  |
|--|--|--|---|---|--|---|---|
| <i>Is cost-effectiveness, an overt criterion for recommendations on whether to include a drug under the public system?</i> | <p><u>Yes</u></p> <p>Requires a “value for money” case for each new drug.</p> <p>In addition, PBAC takes into account: the importance of the clinical area; the availability of alternative treatments; the likely effect of listing on the health system and other therapeutic activities; and the investment of the sponsor in primary research</p> <p>No formal cost-effectiveness threshold.</p> | <p><u>No</u></p> <p>Pharmaceutical Evaluation Board examines the therapeutic uses of medication. It carries out evaluations based on pharmacological, medical or therapeutic and economic factors.</p> <p>Medicines included in the positive list must have a therapeutic effect which is observed in patients in Austria and internationally, be in line with current scientific opinion, and be of benefit to patients as part of their treatment.</p> | <p><u>Yes</u></p> <p>However, processes and rules for formulary listing differ among provinces and territories. Except for Québec, all Canadian jurisdictions consider CEDAC’s recommendations for their decisions.</p> <p>Economic considerations range from simple budget impact analysis to more elaborate cost-effectiveness studies provided by the manufacturer.</p> <p>No formal cost-effectiveness threshold.</p> | <p><u>No</u></p> <p>A health economic analysis may be enclosed by the pharmaceutical companies to demonstrate to the Reimbursement Committee the cost-effectiveness of a new drug, but this is not mandatory.</p> | <p><u>No</u></p> <p>Decisionmaking is based on criteria focusing on medical benefit or therapeutic value.</p> <p>Moves have been made to include economic evaluation into CT assessments.</p> <p>In 2008 a HAS Commission for Economic Evaluation and Public Health (CEESP) was established to oversee the integration of cost-effectiveness into public decisionmaking and in clinical practice.</p> <p>No formal cost-effectiveness threshold.</p> | <p><u>No</u></p> <p>Federal Joint Committee’s decision is based on medical need and efficiency.</p> <p>The 2007 health reform mandated IQWiG to extend its assessments to also evaluate the cost-effectiveness of drugs. It applies a newly developed “efficiency frontier” approach to all its economic evaluations; it does not include a formal cost-effectiveness threshold.</p> <p>From 2011 all newly licensed medicines are subject to a (“early”) benefit assessment to assess the added benefit to patients and, on request, this may be followed by a cost-benefit assessment to help inform price setting.</p> | <p><u>No</u></p> <p>Decisions are largely based on clinical effectiveness and disease relevance rather than cost-effectiveness.</p> |

**Table A.4 Decisionmaking on the funding of new drugs under the statutory system: New Zealand, Norway, Spain, Sweden, Switzerland, UK (England) and US**

|  | <i>New Zealand</i>   | <i>Norway</i>   | <i>Spain</i>   | <i>Sweden</i>   | <i>Switzerland</i>  | <i>UK (England)</i>   | <i>US</i>   |
|--|--|---|--|---|---|---|---|
| <i>Primary body responsible for assessing new (outpatient) drugs for funding or subsidy under the statutory system</i> | Pharmac Board  | Norwegian Medicines Agency (NoMA)   | Dirección General de Farmacia y Productos Sanitarios (DGF) at the Ministry of Health   | Pharmaceutical Benefits Board (LFN), as part of the Dental and Pharmaceutical Benefits Agency (TLV)   | Federal Office of Public Health (BAG)   | National Institute for Health and Care Excellence (NICE) is responsible for the provision of guidance to the NHS on the usage of particular technologies; Department of Health is responsible for pricing and reimbursement decisions   | Within public system: Centers for Medicare and Medicaid Services (CMS); Veterans Health Administration (National Formulary)   |
| <i>Summary of process</i>  | Pharmac's decisions are informed by the Pharmacology and Therapeutics Committee (PTAC), which takes PHARMAC's nine decision criteria into account. Decisions are usually made by the PHARMAC Board, or by the Chief Executive acting for the Board.<br><br>Hospital Pharmaceuticals Assessment Committee informs Pharmac on inpatient drugs. | NoMA evaluates the pharmaco-economy of new drugs; in cases of considerable budgetary impact of a new drug, the Ministry of Health or Parliament has the final decision. In hospitals the decision rests with specialists. | The Director General of the DGF signs off the decision to fund or reject the public funding of a new drug. The same procedure applies for inpatient pharmaceuticals. | TLV/LFN receives economic evaluations submitted by the pharmaceutical companies and decides on the inclusion or exclusion of drugs under the statutory system, as well as retail price (decision applies to both outpatient and inpatient drugs). | BAG decisions are informed by recommendations from the federal drug commission (EAK). A drug may be included in the positive list ( <i>Spezialitätenliste</i> , "specialty list") if it is licensed by Swissmedic, and meets the criteria of effectiveness ( <i>Wirksamkeit</i> ), appropriateness ( <i>Zweckmäßigkeit</i> ) and economic viability ( <i>Wirtschaftlichkeit</i> ) (WZW).<br><br>Since 2009, SL-listed drugs are subject to a review every 3 years | NICE aims to assess all important new drugs (subject to its exclusion criteria); where NICE recommends usage of a product commissioners (NHS England and clinical commissioning groups) are obliged to fund the drug within the terms of the relevant NICE guidance. Where NICE does not recommend a drug, this does not prevent its use (there is no "delisting"), but funding would be subject to agreement by the relevant | Coverage decisions about licensed prescription drugs are taken by the individual public and private payers. CMS reviews or commissions reviews to inform Medicare's national coverage determinations (NCDs); it can take in advice by the Medicare Evidence Development and Coverage Advisory Committee (MEDCAC). In the absence of a NCD an item may be covered at the discretion of Medicare contractors based on a local |

|  | <b>New Zealand</b>                      | <b>Norway</b>     | <b>Spain</b>      | <b>Sweden</b>                                | <b>Switzerland</b>                                 | <b>UK (England)</b>   | <b>US</b>   |
|--|---|-------------------|-------------------|--|--|---|---|
|  |   |                   |                   |  | to confirm whether they should remain listed.(158) | commissioner, and would generally be exceptional.   | coverage determination (LCD).                         |
| <i>Principal role of the assessing body: advisory or regulatory*</i> | <u>Regulatory</u>                       | <u>Regulatory</u> | <u>Regulatory</u> | <u>Regulatory</u>                            | <u>Regulatory</u>                                  | <u>Regulatory</u> : Department of Health<br><u>Advisory</u> : NICE  | <u>(Regulatory)*</u><br>*public system                |
| <i>Positive and/or negative list</i>                                 | Positive list (Pharmaceutical Schedule) | Positive list     | Negative lists    | Positive list (National Drug Benefit Scheme) | Positive list                                      | Negative and "grey" list (covering drugs for specific conditions only); these are not related to medicines assessed by NICE | Positive and negative lists, depending on health plan |

Note: \*Advisory bodies are defined as bodies that make reimbursement recommendations to a national or regional government, ministerial or self-governing body. Regulatory bodies are accountable to health ministries and responsible for listing drugs for reimbursement or subsidy under the statutory system (Sorenson et al., 2008).

**Table A.4 Decisionmaking on the funding of new drugs under the statutory system: New Zealand, Norway, Spain, Sweden, Switzerland, UK (England) and US (continued)**

|  | <i>New Zealand</i>  | <i>Norway</i>  | <i>Spain</i>  | <i>Sweden</i>  | <i>Switzerland</i>   | <i>UK</i>   | <i>US</i>   |
|--|---|--|---|--|--|---|---|
| <i>Arrangements for co-payment for pharmaceuticals: ambulatory or out-patient sector</i> | If prescribed by a primary health organisation practitioner the maximum co-payment is NZD 5 on up to 20 items per family per year, after which items are free. There are no charges for children under 6 years. | Drugs listed on the “blue list” are subject to co-payments of up to Nkr 520 (€70) per prescription. Patients must pay full price for non-essential drugs on the “white list”. Children under 16 years and patients with certain diseases are exempt. | Patients pay a 40% co-payment.<br><br>Specific groups such as AIDS or chronic disease patients are subject to a 10% co-payment capped at €2.64 per prescription.<br><br>Pensioners and those with special permission are exempted from co-payment.<br><br>Non-reimbursable drugs: full costs. | Patient pays full price up to SEK 1,100 annually, after which the subsidy gradually increases to 100%. | Insured persons pay a fixed annual amount (franchise) of CHF 300 plus a deductible of 10%. This applies to treatment costs generally, incl. drugs. The deductible increases to 20% for drugs where the price exceeds the average of all drugs with the same preparation by at least 20%. This applies to branded drugs and generics.<br><br>The sum of the franchise and the deductible is limited by a fixed maximum per year (CHF 700 for adults, CHF 350 for children). | Charges for prescriptions items as follows: GBP 8.05 for each item, GBP 29.10 for a 3-month prepayment certificate (PPC) and GBP 104 for a 12-month PPC. No charges for certain groups of medications; certain groups of individuals are exempt from prescription charges (e.g. over 60 years of age, under 16 years of age). | <b><u>Medicare Part B (Medical Insurance):</u></b><br>20% of Medicare-approved amount when obtained through the doctor’s office or pharmacy. Drugs dispensed in hospital outpatient require co-payment of up to 100% if not covered under Part B.<br><br><b><u>Medicare Part D (prescription drug coverage):</u></b><br>Depending on drug plan (requiring premiums of ~USD 39.40 per month), and yearly deductible, of no more than USD 310 (2014). Medicare drug plans have different “tiers” of coinsurance or co-payments, with different costs for different types of drugs. Coverage gap: must pay 72% (generic) or 47.5% (brand) of drug costs out of pocket once USD 2,850 (2014) limit has been |

| <i>New Zealand</i> | <i>Norway</i> | <i>Spain</i> | <i>Sweden</i> | <i>Switzerland</i> | <i>UK</i> | <i>US</i>   |
|--------------------|---------------|--------------|---------------|--------------------|-----------|---|
|                    |               |              |               |                    |           | <p>reached on covered drugs.(19)</p> <p><b>Medicaid:</b> Maximum allowable co-payment (2013) USD 3.90; for some groups 20% of costs.(159)</p> <p><b>VA:</b> USD 8 for each 30-day supply of medication for non-service-connected conditions; veterans in priority groups 2–6 are limited to USD 960 annual cap. Drugs for service-connected conditions are free.(160)</p> |

**Table A.4 Decisionmaking on the funding of new drugs under the statutory system: New Zealand, Norway, Spain, Sweden, Switzerland, UK (England) and US (continued)**

|  | <i>New Zealand</i>  | <i>Norway</i>                        | <i>Spain</i>  | <i>Sweden</i>   | <i>Switzerland</i>   | <i>UK</i>   | <i>US</i> |
|--|---|--------------------------------------|---|---|--|---|-----------|
| <i>Is cost-effectiveness, an overt criterion for recommendations on whether to include a drug under the public system?</i> | <u>Yes</u><br>An additional 8 criteria are taken into consideration by Pharmac when deciding on a new drug, including clinical risks and benefits, health needs the population and government priorities. | <u>Yes</u><br>No explicit threshold. | <u>Yes</u><br>Criteria considered include price in relation to therapeutic value, cost-effectiveness and budget impact. | <u>Yes</u><br>Criteria considered in decisionmaking include the therapeutic benefit, the patient benefit, cost-effectiveness, the availability of therapeutic alternatives, and equity.<br>No formal threshold. | <u>Yes</u><br>(as defined by the principle of “value-for-money”).<br>A new drug has to be effective, appropriate and value for money in order to be included in the positive list.<br>Effectiveness is the most important criterion. | <u>(No)</u><br>Pricing and reimbursement decisions for branded medicines are made by the Department of Health under the rules of the relevant pricing system (the Pharmaceutical Price Regulation Scheme 2014 or a statutory alternative scheme).<br>Cost-effectiveness is not a criterion in these decisions.<br>NICE provides guidance to the NHS on the usage of medicines (note that this is completely separate from the pricing and reimbursement decision). In NICE’s technology appraisals, cost and the cost-effectiveness ratio are key criteria; others include strength of available evidence, health impact, acceptability, clinical and government policy priorities, and | <u>No</u> |

| <i>New Zealand</i> | <i>Norway</i> | <i>Spain</i> | <i>Sweden</i> | <i>Switzerland</i> | <i>UK</i> | <i>US</i>   |
|--------------------|---------------|--------------|---------------|--------------------|-----------|---|
|                    |               |              |               |                    |           | <p>health need.</p> <p>No fixed threshold;</p> <p>application of range of £20,000/QALY to £30,000/QALY (up to £50,00/QALY for products that met a specific set of criteria relating to usage at end of life); NICE usually recommends the usage of clinically effective products in indications with incremental cost-effectiveness ratios below £20,000/QALY; NICE may recommend products at higher thresholds but additional justification is required.</p> |