The causes of international variation in drug usage: an exploration of the evidence

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(based on work undertaken at RAND Europe & funded by the UK Department of Health)
Background

- Perception among stakeholders that the usage of new medicines was low in the UK compared to other high income countries
- Comparative analysis of levels of uptake of selected medicines in 14 high-income countries
  - No uniform pattern across disease areas and categories of drugs
  - US ranked first for all therapy areas combined, followed by Spain and France
  - General lower than average levels of usage in Norway, Sweden and New Zealand
  - UK ranked 8th out of 14 countries but usage pattern were not consistent across disease areas
Background

- 2014 update of quantitative analysis of Richards report
  - Same method, analysis of same class of medicines (with some additions) and same countries (except Denmark)
  - UK ranked 9th (out of 13) for all studied medicines
  - Higher than international average for 5 of 16 categories of medicines: selected cancer medicines, and medicines for the treatment of osteoporosis, respiratory distress syndrome, wet age-related macular degeneration, statins
  - Below international average for remaining 11 categories
  - Compared to average of 5 large European markets (France, Germany, Italy, Spain, UK), per person usage in UK was below the EU5 average for 9 of the 16 medicine categories
Comparing per person medicines usage in the UK 2008/9 and 2012/13

- Increased relative to the international average in 11 out of 16 classes of medicines
- Remained below the international average for 7 of these 11 medicines/therapeutic areas
  - cancer medicines < 5 years old, alteplase for stroke, second-generation anti-psychotics, dementia, multiple sclerosis, pegylated interferons for hepatitis C, respiratory syncytial virus
- Exceeded the international average for 4 medicines/therapeutic areas
  - cancer medicines >10 years old, osteoporosis, respiratory distress syndrome and wet age-related macular degeneration
- Fell relative to the international average for 5 medicines/therapeutic areas
  - cancer medicines 6–10 years old, hormonal cancer medicines, thrombolytics for acute myocardial infarction, TNF medicines for rheumatoid arthritis, statins

Source: O’Neill & Sussex, 2014
Average ranking of ranking scores by country, 2008/9 and 2012/13

Source: Nolte & Corbett, 2014
What explains international variation in drug usage?

- What is the optimum level of drug usage in different disease areas?
- To what extent does high or low usage indicate appropriate or indeed inappropriate use?
- The appropriate level of usage may vary because of different factors at work in different system contexts
  - high drug usage in some areas might reflect overuse because of weaknesses in disease prevention whereas low usage would point to effective and timely treatment
  - low usage in other areas might point to failure to meet patients’ needs while high usage could indicate optimal treatment

Source: Nolte & Corbett, 2014
Richards review 2010

Explaining differences in usage

2.24 Importantly, this study set out not only to quantify the extent of any variation, but also to comment on its possible causes. At the beginning of the project, a series of hypotheses were developed by the steering group, which might explain variations in usage. The hypotheses are summarised in Box 3.

Box 3 (continued)

Cultural factors will explain levels of drug usage, including:
- clinical attitudes towards risk;
- the extent of research activity;
- clinical attitudes towards national guidance and direction;
- the influence of different professions, for example pharmacists;
- patient attitudes towards treatment; and
- the existence of well-developed charities and patient support organisations.

Epidemiological factors will explain levels of drug usage, including:
- differences in incidence and/or prevalence; and
- stage of diagnosis impacting upon how many patients are suitable for a particular drug.

Box 3: Summary of hypotheses used in seeking to explain the causes of international variations

A variety of hypotheses were tested with experts:

System factors will explain levels of drug usage, including:
- levels of expenditure on health;
- the proportion of overall health budget spent on medicines;
- the extent of restrictions on prescribing;
- the nature of pharmaceutical marketing activity within a sector; and
- the impact of investment in primary and secondary prevention.

Reimbursement factors will explain levels of drug usage, including:
- the relative price of a drug in a particular country;
- the existence of health technology assessment processes; and
- health technology assessment outcomes which have a strong effect on prescribing behaviour.

Service organisation and capacity factors will explain levels of drug usage, including:
- the extent of national prioritisation for a disease area;
- the impact 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.

2.25 These hypotheses were tested against the findings with a range of UK experts:

- Patient representatives were asked for their observations, including views on the impact of patient preference on levels of drug usage.
- Clinicians were asked for their observations, including whether they were aware of different clinical practices in different countries.
- Pharmacists and public health doctors were asked for feedback from their professional networks.
- Academics were asked to provide any examples of studies looking at differences in clinical practice and to provide a review of health system factors.
- Manufacturers were asked to provide observations on the reasons for variations in sales.

2.26 These experts were asked to provide feedback in a variety of formats, including:
- workshops for clinicians, pharmacists and public health specialists;
- structured interviews with patients and patient representative groups; and
- written submissions to the project.
What explains differences in international variation in drug usage?

- 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

**Richards Review 2010**

- Causes of international variation in drug usage are complex
- Three core areas of importance for drug usage levels in the UK
  - Health technology assessment processes and outcomes
  - Service planning, organisation and direction setting enabling or restricting usage
  - Clinical culture and attitudes towards treatment determining levels of uptake

Source: Nolte & Corbett, 2014
An exploratory analysis of the ‘causes’ of international variation in drug usage

- Builds on 2010 Richards Review
- Provides
  - a summary overview of key features of 13 health systems included in the 2014 quantitative update of the report
  - a summary overview of the principles of drug assessment or approval processes in these 13 countries
  - an exploratory analysis of the “causes” of international variation in medicines usage in five selected areas
    - Dementia
    - Osteoporosis
    - Cancer
    - Diabetes
    - Hepatitis C
What we did

• 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 into the wider context
  – aspects of health system and service organisation that were shown to have a direct or indirect impact on drug usage, e.g.
    – reimbursement mechanisms
    – access to diagnosis and treatment more broadly
    – other factors identified in the literature
  – Iterative search of the published and grey literature using PubMed & Google Scholar; searches of websites of governmental and non-governmental agencies or organisations for documents on general health-related policies in each country

Source: Nolte & Corbett, 2014
High-income countries vary in the way they fund and organise their health systems

Per capita expenditure on health (US$ purchasing power parity) in 13 OECD countries, 2012 (data source: OECD 2014)
Out-of-pocket payments play a role in all reviewed countries

Household out-of-pocket payments as percentage of total health expenditure in 13 OECD countries, 2012 *(data source: OECD 2014)*

Source: Nolte & Corbett, 2014
Prescription drugs usually require patient co-payment (2014)

<table>
<thead>
<tr>
<th>Country</th>
<th>User charge required</th>
<th>Exemptions</th>
<th>Maximum out-of-pocket limit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Chronically ill or disabled</td>
<td>Low income</td>
</tr>
<tr>
<td>Australia</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Austria</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Canada</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>France</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Germany</td>
<td>Yes</td>
<td>Yes</td>
<td>Low income</td>
</tr>
<tr>
<td>Italy</td>
<td>Yes</td>
<td>Yes</td>
<td>Low income</td>
</tr>
<tr>
<td>New Zealand</td>
<td>Yes</td>
<td>Yes</td>
<td>Low income</td>
</tr>
<tr>
<td>Norway</td>
<td>Yes</td>
<td>Yes</td>
<td>Low income</td>
</tr>
<tr>
<td>Spain</td>
<td>Yes</td>
<td>Yes</td>
<td>Low income</td>
</tr>
<tr>
<td>Sweden</td>
<td>Yes</td>
<td>Yes</td>
<td>Low income</td>
</tr>
<tr>
<td>Switzerland</td>
<td>Yes</td>
<td>Yes</td>
<td>Low income</td>
</tr>
<tr>
<td>UK/England</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>US</td>
<td>Varies</td>
<td>Varies</td>
<td>Varies</td>
</tr>
</tbody>
</table>

Source: Nolte & Corbett, 2014
Most countries have national bodies advising on inclusion of new drugs under public funding

- 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 reviewed countries, relevant organisations or agencies have a regulatory function (Pharmac in New Zealand; Federal Joint Committee in Germany)
- Some countries have established regulatory bodies separate from the ministry of health, although the ministry has remained the final decisionmaker
- In the US, public payers have established their own systems for appraising new drugs for public funding
  - Patient-centred Outcomes Research Institute (PCORI) tasked with undertaking comparative effectiveness assessments of medical treatments, including drugs, to ‘assist’ decision-making but not mandate

Source: Nolte & Corbett, 2014
There is no single, overarching ‘cause’ explaining international variation in drugs usage

Total expenditure on health per capita (US$ PPP) in 13 countries (c. 2012) against overall ranking of drug usage across 14 therapy areas

Correlation coefficient: 0.16

Source: Nolte & Corbett, 2014
There is no single, overarching ‘cause’ explaining international variation in drugs usage

Total expenditure on pharmaceuticals per capita (US$ PPP) in 13 countries (c. 2012) against overall ranking of drug usage across 14 therapy areas

Source: Nolte & Corbett, 2014
What is the role of policies on the inclusion of new medicines in publicly funded systems?

• Overall processes are multi-faced and complex, and their contribution to international variation in the uptake of drugs remains challenging to disentangle

• Policies determine whether patients have routine access to a given new medicine, in particular where access is made conditional
  – Osteoporosis: patients in some European countries may face challenges in accessing osteoporosis medicines where only 50% of the costs are reimbursed

Source: Nolte & Corbett, 2014
## Availability of osteoporosis treatments in 7 European countries, 2012

<table>
<thead>
<tr>
<th>Country</th>
<th>Bisphosphonates</th>
<th>SERMs</th>
<th>Strontium Ranelate</th>
<th>PTH Analogues</th>
<th>Denosumab</th>
<th>Reimbursement</th>
<th>Reported impediment to treatment</th>
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</thead>
<tbody>
<tr>
<td>Austria</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>100%</td>
<td>No</td>
</tr>
<tr>
<td>France</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>-</td>
<td>65%</td>
<td>Yes (professional)</td>
</tr>
<tr>
<td>Germany</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>100%</td>
<td>No</td>
</tr>
<tr>
<td>Italy</td>
<td>Yes*</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>100%</td>
<td>Yes (professional)</td>
</tr>
<tr>
<td>Spain</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>50%</td>
<td>Yes (patient)</td>
</tr>
<tr>
<td>Sweden</td>
<td>Yes*</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>100%</td>
<td>No</td>
</tr>
<tr>
<td>UK</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>100%</td>
<td>No</td>
</tr>
</tbody>
</table>

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

Adapted from Kanis et al. (2013), Hernlund et al. (2013)
What is the role of policies on the inclusion of new medicines in publicly funded systems?

- Overall processes are multi-faced and complex, and their contribution to international variation in the uptake of drugs remains challenging to disentangle.
- They determine whether patients have routine access to a given new medicine, in particular where access is made conditional:
  - Osteoporosis: patients in some European countries may face challenges in accessing osteoporosis medicines where only 50% of the costs are reimbursed.
  - Evidence for dementia, osteoporosis, hepatitis C and, to certain degree, cancer finds that factors other than policies on the inclusion of new medicines in publicly funded systems may be equally or more important in affecting uptake:
    - access to (timely) diagnosis
    - whether or not the disease area is designated a national priority;
    - the clear identification of responsibilities for managing the disease and the existence of designated care pathways.

Source: Nolte & Corbett, 2014
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

Osteoporosis

- Access to bone density measurement technology (such as dual-energy X-ray absorptiometry) is a potentially greater barrier to treatment than the actual reimbursement of drugs
- Bone densitometry may in principle be available, related investigations may not be (fully) reimbursed, or only reimbursed under certain conditions, which could limit access (e.g. Germany and France)
- Some evidence that bone density measurement is associated with anti-osteoporotic drug prescription

Source: Nolte & Corbett, 2014
Ratio of the number of new cancer cases and of the number of medical oncologists in 6 countries

Adapted from Azambuja et al. (2014)

Source: Nolte & Corbett, 2014
National prioritisisation

- Designating a given condition a national priority is likely to lead to increases in medicines access and usage

**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 of those receiving treatment
- 2009 National Dementia Plan in England was shown to be associated with an increase in dementia diagnosis rate
  - 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

**Osteoporosis**

- UK also identified osteoporosis as a priority, which was likely associated with an observed rapid increase in uptake in osteoporosis medicines

Source: Nolte & Corbett, 2014
Osteoporosis or musculoskeletal disease as a national priority in 7 EU countries

<table>
<thead>
<tr>
<th></th>
<th>National health priority (date)</th>
<th>Government support</th>
<th>Scope</th>
<th>Action plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>Yes (2004)</td>
<td>Yes</td>
<td>Nutrition, exercise, falls prevention</td>
<td>No</td>
</tr>
<tr>
<td>Germany</td>
<td>No</td>
<td></td>
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<tr>
<td>Italy</td>
<td>Yes (2005)</td>
<td>Yes</td>
<td>Nutrition, falls prevention</td>
<td>Uncertain</td>
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<td>Spain</td>
<td>No</td>
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<tr>
<td>Sweden</td>
<td>Yes (2012)</td>
<td>Yes</td>
<td>Not yet defined</td>
<td>No</td>
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<tr>
<td>UK</td>
<td>Yes (2009)</td>
<td>Yes</td>
<td>Nutrition, exercise, fracture liaison services</td>
<td>Indirect</td>
</tr>
</tbody>
</table>

Adapted from Kanis et al. (2013)
“In the last five years about 80,000 people received drugs through the Fund... [but there is no data] to assess the impact of the Fund on patient outcomes, such as extending patients’ lives, or to demonstrate whether this is a good use of taxpayers’ money.”

“The cost of the Fund grew from £175 million in 2012/13 to £416 million in 2014/15, an increase of 138% in two years.”

“There is agreement that the Fund is not sustainable in its current form and NHS England and the National Institute for Health and Care Excellence (NICE) are currently consulting on proposals to reform the Fund from April 2016.”
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

Osteoporosis

– Suggestion that patients should principally be managed at the primary health care level by general practitioners, with specialist referral reserved for difficult cases

– Core role for 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 finds 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

Source: Nolte & Corbett, 2014
Summary and conclusion

• There is considerable variation in the usage of medicines for different therapeutic areas across high-income countries.

• France, Spain and the US tend to have higher than average levels of usage for all therapy areas combined while usage levels tend to be lower in Norway, Sweden and in particular New Zealand.

• The ‘causes’ of this variation are multi-faced and complex, and high or low levels of uptake may not mean that usage is (in)appropriate.

• Policies that determine the inclusion of new medicines in the publicly funded basket of services affect medicines uptake in different settings.

• Equally or more important factors include: access to (timely) diagnosis, whether the disease area is a designated national priority, and identified care pathways and responsibilities.

• 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.

Source: Nolte & Corbett, 2014