ACCESS TO MEDICINES: COMMON PROBLEMS, COMMON SOLUTIONS?

Peter Stephens

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Toegang tot geneesmiddelen: gewone problemen, maar ook gewone oplossingen?

(met een samenvatting in het Nederlands)

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door

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CHAPTER 1

GENERAL INTRODUCTION

BACKGROUND

Medicines protect, maintain and restore people's health [1]. Medicines are critical to health systems strengthening. Without medicines, health care workers are limited in what they can do. Without medicines, confidence in the local health system declines [2].

At least one third of the world's population has no regular access to medicines [3]. Even in the developed world achieving equitable access to good quality care has been difficult to achieve [4]. Two main challenges have been highlighted - first how to increase access to existing medicines and second how to promote the development of new medicines [2]. These challenges are of particular relevance to low and middle income countries but they are faced by all countries of all income levels to a greater or lesser extent. A review of global disparities in cancer care commented that, "Inequality is inherent in all healthcare systems. Only its magnitude, form and victims change with national resources, socio-political systems, governance and biomedical advances" [5]. Differences between countries can be wide, but this is also true of differences between particular populations within countries [4].

Despite the work of civil society, healthcare professionals, policy makers and commentators, and the dramatic increase in new global funding mechanisms such as the Global Fund for Aids, TB and Malaria (GFATM), the challenge of access to medicines remains. Even though the Millennium Development Goals (MDGs) are seen as the most widely supported and comprehensive development goals the world has ever established, and even though most activities targeted those focussing on maternal and child health and communicable disease, many are said to see the MDGs as "unfinished business". We are now being urged to help prevent a post 2015 "slow down" [6].

Investigations into access to healthcare have been categorised as taking one or more of three different perspectives. Health seeking studies follow patients through the disease and treatment pathway, from diagnosis, through treatment and into secondary prevention. Such studies attempt to understand why patients seek access to healthcare services and investigate the interactions between patient and healthcare professional. Health service studies focus on supply – on the availability, affordability, accessibility, adequacy and acceptability of the treatments received. Livelihood approaches take a patient perspective, emphasising the difficulties that people face in utilising their knowledge, networks and physical or financial resources [4].

In recent times investigators have been encouraged to combine these perspectives and take a systems approach. Social and cultural conventions influence equity [2]. The health sector is seen within the wider context of political and market forces that drive funding, choices and innovation [7]. These wider contexts allow significant changes in the environment to be taken into account. Already mentioned are the dramatic increases in funding for AIDS, TB and malaria. Also significant however are the drive to data transparency, the ongoing development of market shaping strategies and burgeoning economic growth. As regards the latter it is said for example by the World Bank that East Africa will reach Middle Income status in the next 10 years if current trends continue [8]. Others point to the rise of the middle class in low and middle income countries. The number of people in Sub-Saharan

Africa, for example, that earn between $10 and $100 per day will rise from just 2 million in 2009 to more than 107 million in 2030 [9].

OBJECTIVE

Despite the dramatic increase in interest in, and focus on, the access to medicines agenda over the last 40 years [2], controversies remain. Some are ever-present and others have emerged more recently as priorities have changed or as understanding has improved.

This thesis investigates four cross-cutting controversies further, notably aspects of pharmaceutical R&D, equity, generics policies and scale up. It looks to understand both the specific context but also to draw conclusions that have global or regional significance. It approaches these four cross-cutting controversies in the belief that some solutions can only be found through global action and that lessons learnt in one country can be applicable to others, as long as the differences in context are understood.

The background to these four cross-cutting controversies and the reasons for the choice of perspective is outlined in the following section.

OUTLINE

Pharmaceutical research and development (R&D)

Pharmaceutical R&D is said to have delivered impressive new medicines, but it is also said to be in need of reorientation, primarily due to its lack of focus on diseases of poverty [10]. At the same time it is argued that pharmaceutical R&D is now a global endeavour, characterised by global markets and global research networks [10]. Recent studies now claim that from this perspective pharmaceutical R&D has in fact responded to both public health and market needs. Investigators find a positive correlation between the burden of disease and the number and type of new chemical entities launched at both regional and country income level [11, 12].

Productivity in pharmaceutical R&D is also claimed to be in decline. Some argue that the current model is unsustainable, others that as a result of mergers and acquisitions of pharmaceutical companies, the capacity for R&D is being progressively "dismantled" [13]. Concern has led to initiatives aimed at reducing regulatory burdens or providing new market incentives. But recent analyses suggest a different picture. Some suggest that the number of launches of new molecular entities is increasing again [11]. More than this, others have argued that we may be using the wrong measure – what matters is not numbers of new molecular entities but the value of those medicines in the market. Taking this view it is argued pharmaceutical R&D has recovered. Productivity they argue, defined as R&D spend compared to peak sales, has doubled between 2008 and 2013 [14].

Chapter 2 of this thesis describes two studies. The first looks at the productivity and focus of pharmaceutical R&D. It looks at total activity in Phases I-III of development and through onto approval, not simply the number of new molecular entities launched. Molecules are linked to indications and to originator in order that comparisons between

burden of disease and between public and private sector activity can be compared. The second study concentrates on the development of vaccines, regarded as perhaps one of the most cost-effective solutions to prevent both communicable and non-communicable disease in poor countries. It looks to explain why the success of vaccine R&D appears to have declined and the implications that this has on future development.

Equity

Equity is defined as "the absence of avoidable or remediable differences among groups of people, whether those groups are defined socially, economically, demographically, or geographically" [15]. Information to investigate equity is not always available [3]. In 2005, for example, it was stated that "[t]here are not enough data to conclude that [obstacles to care] lead to lower use of medicines among women, but based on available evidence this seems likely" [16]. Likewise in 2013 it was stated that across Europe at least "It is unknown if inequity in access to medicines exists in the elderly" and that research was needed [17].

Chapter 3 of this thesis describes three studies. The first investigates prescribing rates for men and women in three diseases across 15 lower and middle income countries. Actual prescribing rates are compared to those that might be expected if prescribing were to reflect the burden of disease. The second and third studies look to describe the impact of age on access to treatment. The two studies take contrasting viewpoints. The first examines the over-use of antipsychotics in the elderly with dementia. In this case the prescribing of antipsychotics may indicate the denial of more appropriate treatment. The second examines the use of high and low cost antifungal medicines in the treatment or prophylaxis of life-threatening illness. It complements those studies where differences between the rates of treatment between old and young may have been confounded by patient choice. In the case of differences in the use of high and low cost antifungals by age, patient choice is not a factor – the decision both to offer and accept treatment has been made.

Generic policies

A pro-generic policy is seen as a key component of policies to counter high prices, this in turn being one of the six critical policies recommended by the task force charged with examining access to medicines as part of the MDGs [2]. Whilst many countries have implemented pro-generic policies, we know comparatively little about the private sector pharmaceutical market in low and middle income countries (LMICs) as compared to the public sector, and even less about the market dynamics between originator/brand name and generic versions of the same medicine [18].

Chapter 4 of this thesis describes two studies. The first describes patterns of generic use in the private sector across 19 low and middle income countries, also attempting to understand the market drivers of those changes seen. The second study looks to understand choice, using prescribing data to investigate the impact of patient and doctor factors on the use of higher cost formulations in Brazil.

Scale up

Scaling up pilot studies is prone to failure. In international health five challenges have been identified – budgeting, absorptive capacity at macroeconomic, health system and community levels, planning and implementation ability, equity and quality [19, 20]. To provide focus, commentators will often argue for ring-fenced funding [20]. To provide scale we are urged to work with the private sector. Even high priority disease programmes it is said will fail to meet targets without making use of the private sector [21]. Private sector strategies in the developing world include market based initiatives (for example social marketing, vouchers or franchising), administrative measures (including tighter regulations and training) and consumer empowerment (such as the establishment of institutional infrastructure through which consumers can seek redress) [21, 22].

Social marketing is the application of commercial marketing techniques to health problems. It uses a combination of mass advertising and branding to distribute free or subsidised products. It looks to work with the private sector to maximise the impact of public sector or donor funds. Social marketing has been applied to the distribution of reproductive health commodities, bed nets, hand washing and water purification [21]. Recent studies have looked to counter the claims made in the 2000s that the feasibility and impact, particularly in relation to equity, of social marketing was unproven [22, 23]. Claims that social marketing programmes increase the size of the commercial market, however, are not always supported by the evidence. In 1998 a social marketing programme for oral contraceptives, for example, was said to have created 60 commercial users for every 100 women served by the programme [24]. In 2009 however a social marketing programme in Kenya distributing both free and subsidised condoms was found to have reduced the share of both the subsidised and full priced condom segments [25].

Chapter 5 of this thesis describes two studies. The first describes the impact, and potentially perverse effects, of the introduction of ring-fenced funding to the use of cancer medicines in England. The second focuses on the impact of social marketing on the private markets in a selection of countries in francophone Africa. In these markets the percentage of women using modern methods of contraception is particularly low with a median value of less than 20%. With a target of 75% of demand being met with modern contraceptives being proposed [26], and donor funds not necessarily being inexhaustible [19], the question of whether or not social marketing programmes "spill over" into or "crowd out" the commercial sector is important for the future development of private sector initiatives in the developing world.

PERSPECTIVE

Most governments the world over declare that citizens should be able to access good quality healthcare [4]. Even in the developed world however, the demand for healthcare outstrips the resources allocated to fund it [11]. This is as true of medicines as it is of healthcare delivery. All countries, regardless of income level, struggle to define the appropriate package of care and deliver it to all citizens in an equitable manner.

It is nevertheless clear that access to medicines in the developing world faces challenges that are not faced by policy makers in the developed world, or at least not to the same extent – for example human resource shortages or basic infrastructure. Nevertheless as was indicated in the recent Priority Medicines for Europe and the World, the health needs of Europe and much of the rest of the world are converging [11]. Others have gone further arguing that the North-South divide is no longer applicable and that post 2015 MDGs can, and must be, universally relevant [27]. This so-called "commonality of interests" is driven by the increasing burden of non-communicable diseases (NCDs). In almost all countries development of health systems that can meet the challenge of NCDs is a priority [28]. Even in Africa, the burden of NCDs is rising and NCDs are projected to exceed communicable, maternal, perinatal and nutritional disease as the most common causes of death by 2030 [29].

At the same time we are urged to assess not only the volume but also the equity and quality of the care delivered. As others have pointed out, however, data in the developing world is not always accessible. Even though the MDGs have been universally supported, for example, progress cannot always be measured [27]. Many countries, at least in the past, have little usable mortality data and weak surveillance systems [29]. We are now being urged to develop integrated monitoring and evaluation systems with integrated patient level data to improve the responsiveness of health systems in the developing world to the challenge of NCDs [28]. In such circumstances where information systems are weak but policies are needed, the developed world can provide lessons, often perhaps of what not to do or at least of what it may pay to be aware. The developed world is for example relatively information rich. In addition, in those with comprehensive social insurance systems, healthcare delivery is more equitable, at least between people of different socio-economic classes [30]. Whilst therefore developed countries do not offer a controlled environment, they do offer opportunities to understand both future information needs and the ability to isolate some of the impacts of certain policy approaches.

METHODS

This thesis is founded on analysis of quantitative data. Four different data types are used, alone or in combination – national level sales databases, large scale survey data of doctor consultations and of households, longitudinal patient data and a descriptive database detailing developments in pharmaceutical R&D.

The author worked with pharmacy system suppliers, the UK Department of Health, the National Information Governance Board, Caldicott Guardians at hospital Trust level and the National Ethics Service in the UK to establish the longitudinal patient database. The papers relating to the use of antifungals and antipsychotics in the elderly are the first to be published from that database.

In contrast, the large scale survey data of doctor consultations have long been collected by IMS Health, and several studies have used the projected data to describe the impact of policies. No studies have, however, previously used the sample data. The sample data is richer, particularly

for low and middle income countries where out of pocket payments are recorded, and being richer also allow for multi-level analysis as described in the paper on low cost generics in Brazil. The use of quantitative analysis to understand the patient-doctor interactions in relation to the prescribing of generics in low and middle income countries adds to previously published work, the vast majority of which has been primarily qualitative in nature.

During the course of the thesis, the author carried out one qualitative study, its aim being to highlight the range of factors that affected, and led to variations in, the use of medicines used to treat eight different conditions and which had been recommended by the National Institute of Health and Clinical Excellence in England. With the encouragement of the Metrics Oversight Group, a joint UK Department of Health, Pharmaceutical Industry and National Health Service group, the author interviewed 27 practising clinicians (24 specialists, three GPs), four healthcare commissioners or Department of Health policy consultants, eight patient organisations or patients, eight nurse specialists or cancer network pharmacists and eight industry representatives. 24 of the interviewees were recommended by the Department of Health, 8 by industry. The remainder were found via literature search. Each interviewee was provided with an opportunity to comment on the author's summary of the discussion. The report was reviewed by the Department of Health, industry and the National Institute of Health and Clinical Excellence prior to its release. The report was published in the so-called "grey literature" and does not therefore form part of this thesis [31].

CONTINUITY

The thesis complements prior work carried out by the PhD programme at the WHO Collaborating Centre for Pharmaceutical Policy and Regulation within the Utrecht Institute for Pharmaceutical Sciences. Several prior theses also stress the need to better understand global and regional trends in access so as to drive policy on an international basis [32, 33]. Like others, this thesis continues to emphasise the need to better understand the drivers and implications of private sector behaviour so as to improve access to medicines [33, 34]. And like other theses, it reflects the analytical opportunities created by the advent of new electronic data capture systems and the drive for transparency and accountability amongst governments and donors alike [34].

CONCLUSION

This thesis looks to examine particular aspects of access to medicines that not only have relevance now but also in the future. Each study is placed within its own context, whether that be national, regional or country income level but in the Discussion, a broader perspective is taken. This thesis attempts to draw links across the studies, attempting to highlight cross-cutting themes that will nevertheless be of particular relevance to those working in the developing world.

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CHAPTER 2

PHARMACEUTICAL RESEARCH & DEVELOPMENT: PRODUCTIVITY AND ORIENTATION

CHAPTER 2.1

RESEARCH AND DEVELOPMENT

The World Medicines Situation 2011.
Geneva, World Health Organisation, 2011.

Stephens P, Leufkens HG.

SUMMARY

- Pharmaceutical research and development (R&D) has been critical to the reduction and control of disease but it faces unprecedented challenges. Many have questioned the sustainability of pharmaceutical R&D in the face of burgeoning clinical trial costs and a consistently high failure rate across all development phases.
- The mismatch between investments and the likely return from neglected diseases research is a key reason why commercial R&D has been unable to plug all pharmaceutical gaps or to invest in proportion to disease burden.
- The industry makes a growing contribution to neglected disease research, even if this remains a relatively small proportion of total research activity. Academic institutions appear to largely follow the same pattern as industry.
- Many initiatives have been launched to streamline the research, development and regulatory processes. These will help reduce the costs of innovation. Countries need, however, to strike the appropriate balance between developing new innovative capacity and making more of existing tools, including measures to improve public health through improved diagnosis and prevention. The choice will be different from country to country and depend on economic and technological circumstances.
- The need for cost efficiencies has driven a substantial number of clinical trials away from Europe and the USA and into other locations. This movement adds to an increasingly complex regulatory future where a variety of initiatives are emerging that will bring products to market faster, but in a way that requires greater regulatory oversight post-launch. Resources will be needed in all countries to adequately fund such scrutiny.

BACKGROUND/INTRODUCTION

Since the large-scale introduction of antibiotics in the 1940s, pharmaceutical innovation has continued to contribute to significant improvements in the treatment and prevention of disease. However, in the minds of some commentators at least, that innovation has both failed to address the needs of the developing world and is now unsustainable given the rising costs of R&D.

In 1986, the Commission on Health Research for Development published a report indicating that only 5% of the global R&D budget (then estimated to be in the region of US$ 30 billion) was spent on diseases that predominantly affect people in low-income countries, and it led the call for a change in emphasis [1]. In 2004, the Priority Medicines for Europe and the World Project reported that concerns had been expressed "…both at the international level and in Europe, at the lack of research to fill pharmaceutical gaps", these being identified as "diseases of public health importance for which pharmaceutical treatments do not exist (lack of basic scientific knowledge or market failure) or are inadequate (lack of efficacy or safety concerns or because the delivery mechanism or formulation is not appropriate for the target patient group)" [2].

In 2006, the Global Health Diagnostics Forum concluded that the current diagnostic tools "are largely inadequate for meeting health needs in developing countries" and that commercial partners have "shown limited willingness to engage in the development of new diagnostics for the developing world"[3]. In the same year, the Commission on Intellectual Property Rights, Innovation and Public Health reached a similar conclusion, claiming that "…current government policies and company strategies including incentive and funding mechanisms, both in developed and developing countries, have not generated sufficient biomedical innovation relevant to the needs of most developing countries…" and that "This tragic failure by all governments to address poverty and sickness in developing countries has become a worldwide subject of great concern" [4].

At the same time as industry and the public sector have been encouraged to increase their focus on diseases affecting lower-income countries, the average costs and complexity of developing pharmaceuticals successfully have escalated to an apparent all-time high. Estimates said to be appropriate to the industry's situation give a range of out-of-pocket expenditure of between US$403-873 million per New Molecular Entity (NME) launch, which when capitalized gives figures of US$ 802-1778 million [5].

These estimates are acknowledged to be much higher than those presented by the TB Alliance (US$115-240 million) [4]. It is, however, clear that estimates vary dramatically according to the scope of the costs included in the various estimates (for example, drug target discovery or technology licences), the therapeutic area and thus the state of the science and probability of success, geographical focus and regulatory requirements. Individual companies also appear to operate with dramatically different costs. While this means that averages can be difficult to interpret, a review of 60 years of pharmaceutical innovation calculates that the costs of new molecular entities (NMEs) "…have been growing exponentially at an annual rate of 13.4% since the 1950s" [6].

Along with these rising costs it appears that the number of products in development has declined, or at best, in some clinical areas, remained relatively constant [7]. This is echoed

by the relatively stable number of U.S. Food and Drug Administration-approved NMEs and biological licence applications since at least 2005 [8]. Overall, analysis suggests that new drug output from pharmaceutical companies over the last 60 years has "essentially been constant, and remains so despite the attempts to increase it" [6].

In 2004, Rawlins raised the question of whether the current medicine development process is still sustainable given the rocketing costs and the decline of pharmaceutical innovations in many clinical areas [9]. This concern is as relevant today as it was then, if not more so. Paul et al. argue that given the relative probability of success of any molecule entering clinical development, the number of molecules entering clinical development every year must be 9 (or 11 if all small molecules) to yield a single NME launch per year. It is claimed that most large companies aim for 2-5 launches per year and therefore 18-45 Phase I starts would be required annually [5]. Analysis of the top 50 companies in terms of the numbers of products in development at January 2009, as shown in IMS Health's R&D Focus database [7], reveals that only 10 achieved more than 9 Phase I starts, and only 3 companies more than 18 in the whole of 2009 (see Table 1).

The unprecedented challenge to the industry's business model together with the failure of market-based incentives to develop sufficient medicines for the developing world has led to a wide range of different initiatives. Some are focused on the innovation process, such as the Innovative Medicines Initiative in Europe [10] or the Critical Path Initiative in the USA [11], and at the same time a significant discussion has started on the role of regulatory systems in bringing medicinal products to the patient in a timely, and, from a benefit-risk perspective, responsible fashion [12]. Others, such as the Intergovernmental Working Group on Public Health, Innovation and Intellectual Property have begun a programme to ensure greater clarity of R&D needs within tropical diseases and childhood illnesses, greater innovative capacity within the developing world and sustainable financing of such R&D efforts [13, 14]. Still more, such as the initiatives and organizations established by the Bill and Melinda Gates Foundation, have provided new finance and resources to drive R&D in diseases that primarily affect the developing world.

This chapter looks at both the success and failure rates of pharmaceutical R&D, reviews the latest information on diagnostics and examines the focus of both public and private

Table 1: Phase 1 starts for the whole of 2009 for those companies with the most compounds in development in January 2009

Number of Phase 1 starts in 2009	Number of companies
≤9	40
≤18	7
≤27	1
≤36	2
≤45	0

Source: IMS Health [7]

sector efforts in pharmaceutical R&D. The final section looks at these issues from the perspective of policy-makers and the challenges that they face.

SITUATION ANALYSIS

2.1

Pharmaceutical R&D: success rates

In order to explain current pharmaceutical gaps it is helpful to examine how individual molecules are developed into successful medicinal products. Although the classical phased model of drug development now no longer consistently reflects the true pharmaceutical R&D process, the model can nevertheless provide useful insight into the susceptibility of drug development to failure.

Overall failure rates in pharmaceutical R&D are high. The most common reasons given for failure are lack of efficacy (25%), clinical safety concerns (12%) and toxicological findings in pre-clinical evaluation (20%) [10]. Strategic reasons also play their part. In an analysis of Phase II failures from 2008-2010 for new medicines and major indications of existing medicines, strategic reasons were given as the reason for failure in 29% (25/87) of cases, although the figure for Phase III and submission failures between 2007-2010 was just 7% (6/83) with lack of efficacy being cited as the primary reason for failure (66%) [15,16]. Some have argued, however, that the high rates of failure due to lack of efficacy may be due to commercial incentives that "could encourage poor decisions to pursue the development of compounds that only generate weak evidence of effectiveness at Phase II and have an even higher risk than typical of failure at Phase III" [17].

A study of success and failure in pharmaceutical R&D since 1990 concluded that "... during the Nineties, the attrition rate of pharmaceutical R&D projects …increased, especially in [Phases] II and III. In [Phase] II, the probability of success has dropped from almost ½ to less than ⅓ while projects that started phase III in year 2000 have a probability of success that is almost one half [that of] projects that entered phase III ten years before." The same study also found that over this time period, projects that targeted lethal diseases, pathologies causing complications and organ damage or pathologies with a multifactorial or unknown aetiology generally had lower success rates [18].

In the analysis that follows, data held within IMS' R&D Focus database were used to study the success or otherwise of R&D activities by both the public and private sectors. A total of 6666 compounds, including drug delivery systems, listed as being in active development in January 2000 were followed through to April 2009, a period of just over nine years. Compounds that were described as being suspended or discontinued were classified as failures as were compounds for which no activity had been recorded at any time in the three years prior to April 2009. Only 5440 compounds were able to be linked to the August 2009 database, with 1226 not found. A further 253 compounds were excluded on the basis that they had been redesignated as a "Technology" and for an additional 1450 compounds the actual phase of failure could not be determined. Marketed drugs being further investigated were placed in a separate category.

Only 11% of compounds in pre-clinical development in January 2000 progressed beyond that phase. For compounds in Phase II, only 34% progressed to Phase III or beyond and for those in Phase III, 52% progressed further (Table 2). The proportion of compounds that failed is shown in Table 3. Ninety-five percent of all those molecules in the pre-clinical phase had failed by August 2009 and the rate of failure was still 55% for Phase III. The progression rates in Phases I and II seen in this study are very similar to those derived from the 13 companies belonging to the Pharmaceutical Benchmarking Forum [5] whereas those for pre-clinical and for Phase III are lower. Other sources thus appear to paint an even bleaker picture but if another analysis is to be believed, failure rates in R&D may actually be getting still higher - at least in Phase II [15].

One area that continues to show higher success rates, however, is further investigation of marketed drugs. In this analysis an additional 828 launched molecules were found to be being further investigated. The attrition rate for these was just 2% (including those products that were withdrawn from the market).

Biological compounds have been said to have a greater chance of success than traditional small molecules (Table 4). More recent data confirm this impression. In this study of 4275

Table 2: Progression rates by phase*

2000 stage	Number proceeding to next phase or later by April 2009	%
Pre-clinical (n=1768)	201	11%
Clinicals† and Phase I (n=367)	183	50%
Phase II (n=421)	144	34%
Phase III (n=214)	112	52%
Pre-registration and Registered (n=144)	102	71%

Source: IMS Health [7]
* Calculated as the percentage of molecules in a given phase in January 2000 progressing to at least the next phase of development by April 2009
†Clinicals is a term used to mean in clinical development but of unknown phase

Table 3: Percentage of compounds failing by phase

Phase (number of molecules at this stage in January 2000)	Number of compounds that had failed by August 2009	% failed
Pre-clinical (n=2518)	2380	95%
Clinicals (n=20)	16	80%
Phase I (n=573)	446	78%
Phase II (n=768)	594	77%
Phase III (n=298)	164	55%
Pre-registration (n=129)	59	46%
Registered (n=53)	18	34%

Source: IMS Health [7]

Table 4: Comparison of progression and success rates of biotech and conventional pharmaceuticals [22]

Transition rates	Biotech†	Pharmaceuticals‡
Phase I-II	83.7%	71.0%
Phase II-III	56.3%	44.2%
Phase III-Approval	64.2%	68.5%
Overall success	30.2%	21.5%

† 522 compounds in clinical development between 1990-2003
‡ 534 compounds in clinical development between 1983-1994

drugs in development between 2003-2010, biologics were "almost twice as likely as new molecular entities (NMEs) to get approved for a lead indication (26% and 14% respectively)" [19]. Biologics constituted 31% of total NMEs launched in the USA between 1998 and 2003, and 32% in the period 2004 to 2008. In 2010, biologics constituted 25% (6/21) of the U.S. FDA's Center for Drug Evaluation and Research approvals, these figures excluding the six additional biologics approved by the Center for Biologics Evaluation and Research [21].

Pharmaceutical R&D: in relation to disease burden

In an ideal world, spending and investment in pharmaceutical R&D would be driven by medical need, and there would be a direct correlation between the burden of diseases and conditions and R&D spending on medical products for those diseases and conditions. The reality is, however, far from this notional ideal. In 2002, the Global Forum for Health Research reported that only 10% of R&D spending is directed at the health problems that are responsible for 90% of the global disease burden. A disparity between medical need and the makeup of pharmaceutical R&D investment in terms of the type of compounds in development suggests one of, or a mix of, three things - adequate treatments are already available; current understanding of the disease or science does not allow new medicines to be developed; or that there is no commercial or other incentive to work on new medicines for that disease.

Using information from the IMS Health's R&D Focus database it is possible to compare the number of Disability Adjusted Life Years (DALYs) lost to a given disease with the number of compounds in development for that disease. In this particular analysis, the number of DALYs lost has been broken down by country income category (high, middle and low), it being assumed that diseases that affect high-income countries are more likely to be attractive targets for R&D investments than are those that only affect low-income countries.

According to IMS Health, in April 2009 there were 6491 compounds in active development (excluding those defined as drug delivery systems or reformulations). The IMS database holds information on the medical indications for which the compounds are being developed, with many compounds being investigated for more than one indication. The database sometimes uses terms that cannot be easily linked to the International Classification of Diseases (ICD), for example "pain" or "inflammation". However in 8487 instances, it was possible to link the indication listed in the database to an ICD code,

which in turn allows links to be made to WHO's published DALY rates [23]. In order to compare the distribution of DALYs lost and that of compounds' indications, both sets of information were converted to percentages. The conversion was carried out within each ICD level. Hence, the percentage contribution of non-communicable conditions to disease burden was calculated using the total number of DALYs as the denominator, whereas the percentage contribution of endocrine disorders was calculated using the total number of DALYs attributable to non-communicable conditions only as the denominator.

The results of the analysis indicate that the vast majority of products currently being investigated are for non-communicable diseases and conditions. Non-communicable conditions constitute 85% of all medical conditions being investigated.

Among the non-communicable diseases, malignant neoplasms and neuropsychiatric disorders have the greatest impact in terms of DALYs lost across all country income categories. R&D activity also focuses in these areas (Table 5) although the focus on malignant neoplasms is almost twice the burden of the disease (7-17% of lost DALYs versus 35% of all indications cited). More information on the types of work being done in malignant neoplasms and neuropsychiatric disorders is described below:

- **Malignant neoplasms:** Only 75% of all the compounds in development for the treatment of malignant neoplasm could be linked to a lower level within the ICD

Table 5: Non-communicable disease indication distribution in active R&D programmes

	DALYs			No. conditions being investigated [7]
Non-communicable conditions	**High income %**	**Middle income %**	**Low income %**	**All phases %**
Malignant neoplasm	17%	12%	7%	35%
Other neoplasms	0%	0%	0%	5%
Diabetes mellitus	3%	3%	2%	4%
Endocrine disorders	2%	1%	1%	7%
Neuropsychiatric disorders	30%	27%	27%	16%
Sense organ disorders	9%	12%	13%	3%
Cardiovascular diseases	17%	21%	21%	8%
Respiratory diseases	7%	8%	8%	5%
Digestive diseases	5%	5%	7%	4%
Diseases of the genitourinary system	1%	2%	2%	2%
Skin diseases	0%	1%	1%	3%
Musculoskeletal diseases	5%	5%	3%	7%
Congenital abnormalities	2%	2%	6%	1%
Oral diseases	1%	1%	1%	0%

DALY: Disability Adjusted Life Year

classification. Within this subset, however, it appears that little work is being carried out on compounds for mouth and oropharynx cancers or cancers of the cervix and uterus, despite their rather significant contribution to DALYs lost. In contrast skin cancer represents a relatively small proportion of the disease burden (2-4%) but takes a relatively high proportion of indications cited (9%).

- **Neuropsychiatric disorders:** IMS data suggest that development activity is focused on Alzheimer and other dementias, schizophrenia, Parkinson disease and multiple sclerosis. Only schizophrenia has a significant impact in lower income countries. In contrast unipolar depressive disorders contribute a third of all DALYs lost to neuropsychiatric disorders across all income categories (32-36%) but there is currently little activity in this area (8%), probably a reflection of the state of current science and the availability of existing medicines.

Within the group of infectious and parasitic diseases, the most striking disparity between need and investment is in diarrhoeal diseases. There appears to be very little current development activity in this area (see Table 6). Part of the apparent mismatch may be a consequence of early work on diarrhoeal diseases being categorized as bacterial infection, and so not being classified appropriately. The relatively high focus on HIV and hepatitis C is

Table 6: Infectious and parasitic disease indication distribution in active R&D programmes

	DALYs			No. conditions being investigated [7]
Infectious and parasitic diseases	**High income %**	**Middle income %**	**Low income %**	**All phases %**
Tuberculosis	7%	20%	9%	3%
STDs excluding HIV	8%	4%	3%	1%
HIV/AIDS	23%	26%	18%	17%
Diarrhoeal diseases	16%	23%	25%	1%
Childhood-cluster diseases	2%	4%	11%	3%
Meningitis	4%	4%	4%	1%
Hepatitis B	3%	1%	1%	3%
Hepatitis C	6%	1%	0%	10%
Malaria	0%	2%	14%	3%
Tropical-cluster diseases	1%	2%	4%	1%
Leprosy	0%	0%	0%	0%
Dengue	0%	0%	0%	1%
Japanese encephalitis	0%	0%	0%	0%
Trachoma	0%	1%	0%	0%
Intestinal nematode infections	1%	2%	1%	0%
Other infectious diseases	38%	13%	13%	56%

DALY: Disability Adjusted Life Year

almost certainly influenced by the burden of these diseases in high income countries. That malaria and TB also feature relatively highly should also not be a surprise given the recent not-for-profit sector's work on these conditions.

Pharmaceutical R&D: in relation to "pharmaceutical gaps"

WHO's Priority Medicines for Europe and the World Project identified pharmaceutical diseases and conditions for which drug therapies are still lacking or are inadequate (and which it has defined as "pharmaceutical gaps") [2]. Although these gaps affect all citizens of the world, in drawing up its list of priority areas for health research, the Priority Medicines Project placed emphasis on those research needs that were also relevant for countries in economic transition. In all, 16 areas were identified, some rather more specific than others. In the case of cancer, for example, the requirement is for greater R&D investment overall (i.e. across all cancer types) whereas in the case of depression, the perceived need is for treatments for young people in particular.

In Table 7 below, R&D activity as of August 2009 is summarized in volumetric terms for a number of these pharmaceutical gaps - those that can be defined using the ICD system. Treatments for depression in young people cannot, for example, be distinguished in this way. In all of the cases investigated some R&D activity was detected but its quality and likely success are unknown. Public-private partnerships are involved in about half of the compounds in development for neglected disease and a quarter of those for malaria and TB.

The level of antibacterial R&D activity using different sources has been the subject of a detailed review, conducted jointly by the European Centre for Disease Prevention and Control (ECDC) and the European Medicines Agency. The authors of the review confined their analysis to products at later stages of development (Phase II or later). The findings published in a Joint Technical Report [24] revealed that of 66 new active agents in development as of March 2008, only 27 were considered to have either a new target or a new mechanism of action, so potentially offering a benefit over existing antibiotics. Of these 27, 15 could be systemically administered and of these 15, 8 were active against Gram-negative bacteria, and 7 against Gram-positive bacteria. Of the 8 active against Gram-negative bacteria, only 4 had activity based on actual data, and of these, none acted via new mechanisms of action. The authors concluded that "…the lack of systemically administered agents with activity against Gram-negative bacteria displaying new mechanisms of action found in this study is particularly worrisome, and more so when the high attrition rates for agents in early stages of clinical development is taken into consideration. In fact it is unclear if any of these identified agents will ever reach the market, and if they do, they may be indicated for use in a very limited range of infections….Therefore, a European and global strategy to address this serious problem is urgently needed, and measures that spur new antibacterial drug development need to be put in place."

A similar conclusion was reached in a paper commissioned by the European Union. In their final report the authors also suggest a series of push, pull and hybrid finance mechanisms to stimulate innovation in antibiotic development [25]. More recently, a WHO Expert Group critically reviewed about 45 such models as part of a wider effort to

Table 7: R&D activity in areas identified as needing research, as of August 2009 [7]

TREATMENT						
	Phase					
	Discovery	Preclinical	Phase 1	Phase II	Phase III	Pre-registration & Registration
Smoking cessation	1	4				
Alcoholic liver disease	1	4		1		
COPD	12	28	26	37	3	3
Osteoarthritis	5	7	4	11	2	1
Alzheimer's	44	99	40	42	8	
ND - Trypanosomiasis	5	1	1			
ND - Chagas	6		1			
ND - Leishmaniasis	4	3	1		1	
Malaria (excluding FDC)	11	8	2	4	2	
TB	13	10	2	3		1
HIV - FDC		1	2	2		
HIV - Other	46	51	23	35	9	
Stroke (neuroprotectant)	3	11	6	2	3	
Stroke (other)	5	23	8	9	6	
Anti-diabetics	71	111	92	74	22	8
Anti-diabetics (long acting)		5		4		1
CV - FDC		6	2	3	11	4
Influenza	9	26	1	3	2	
Antibacterial	49	154	34	27	10	5
Antibacterial (MRSA)	2	45	12	13	2	4
Antibacterial (New*)	6	19	4	4		2

*New defined as any record of the following terms: DNA topoisomerase inhibitor; DNA gyrase inhibitor; dihydrofolate reductase inhibitor and monoclonal antibody.

VACCINE						
	Phase					
	Discovery	Preclinical	Phase 1	Phase II	Phase III	Pre-registration & Registration
Smoking cessation				3		
ND - Trypanosomiasis		1				
ND - Chagas	1					
ND - Leishmaniasis		3	1			
Malaria	4	9	6	3		
TB	3	8	2	3		
HIV	9	22	12	16	1	
Influenza	10	38	22	8	5	11

COPD - Chronic Obstructive Pulmonary Disease, ND - Neglected Disease, FDC - Fixed Dose Combination, TB – Tuberculosis, HIV - Human Immunodeficiency Virus, CV – Cardiovascular, MRSA - Methicillin Resistant Staphylococcus Aureus

evaluate options for R&D financing of Type II and III disease research. (Type I diseases are those that have similar prevalence within both developed and developing countries, such as heart disease, asthma, diabetes or cancer. Type II diseases are those that have a greater prevalence in developing countries, e.g., AIDS or TB, and Type III are those that only afflict the very poor, such as river blindness, malaria, or Chagas disease) [26]. A new indirect tax, voluntary business and consumer contributions and/or new donor funds emerged as being the best hope of providing sustainable and substantial funds for research in the future [14].

In addition to identifying priority areas for new drug development, the 2004 Priority Medicines for Europe and the World Project also highlighted the urgent need for better diagnostic tools, especially for TB, Alzheimer disease, osteoarthritis and chronic obstructive pulmonary disease (COPD). As shown in Table 8, the potential benefits of improved diagnostic tools in the developing world are immense. Their potential in the developed world is no less significant.

Promising developments in the field of diagnostic R&D include the use of rapid diagnostic tests (RDTs) to identify targeted pathogens; this would greatly improve the use of antibiotics as well as reduce the cost and time needed to conduct clinical trials [29]. Genomics-based molecular diagnostics that can be linked to therapeutic products have also been deemed to be critical to targeted drug developments of the future.

Analysts report that up to August 2009 there had been 28 drug-diagnostic co-development projects - 17 are in the oncology area and the remainder covering cardiovascular, central nervous system, autoimmune disease, infectious diseases, HIV and growth factors [28].

Despite these promising developments, in lower and middle income countries at least, the gap between the need for new diagnostic tools and delivery remains large. The workshop held by the Academy of Medical Sciences at the end of 2008 concluded that "…efforts to address the burden of infectious diseases in LMIC [low and middle income countries] have largely focused on new therapeutic interventions, whilst the importance of diagnostics has often been neglected. As a result current diagnostic methodologies are often inappropriate to local needs and contexts of LMIC…Importantly, there has been a focus on developing RDTs [Rapid Diagnostic Tests] for infectious diseases at the expense of tests for non-communicable diseases and this imbalance will need to be addressed in the coming years" [29].

Driving pharmaceutical R&D: the changing roles of the public and not-for-profit sectors

Several groups and organizations, among them the European Union, philanthropic foundations such as the Bill and Melinda Gates Foundation, the National Institutes for Health in the USA and other organizations have established mechanisms to support public sector research into diseases where there is little or no commercial incentive.

The IMS R&D Focus database contains information about which organizations are responsible for the development of which compound. These data have been used to analyse the level of academic and/or not-for-profit involvement in pharmaceutical R&D; the results are shown in Tables 9 and 10. Compounds in active development that are the responsibility

Table 8: The potential of diagnostic tool R&D in infectious diseases [27]

Infectious disease area	Clinical decision points	Potential DALYs or lives lost per year
ALRI	Identification of children <5 years with bacterial ALRI among those presenting with ALRI for antibiotic treatment or in severe cases for hospitalization	A new diagnostic test for bacterial ALRI with at least 95% sensitivity and 85% specificity accompanied by greater treatment access and minimal laboratory infrastructure requirements could save >405,000 adjusted lives. A new diagnostic for severe ALRI would also bring significant benefit provided access to effective hospital care is increased globally.
HIV/AIDS	Identification of HIV infection in infants aged <12 months	A test with 90% sensitivity, 90% specificity and minimal laboratory infrastructure requirements could save ~180,000 DALYs if 5% of the targeted population had access to ART, and ~2.5 million DALYs could be saved if 100% of the population had access to ART.
Diarrhoeal diseases	The detection of *G. lamblia, C. parvum* and enteroaggregative *E. coli* to reduce diarrhoea-related stunting in children	A test with 90% sensitivity, 90% specificity and minimal laboratory infrastructure requirements for each of the pathogens G. *lamblia*, C. *parvum* and enteroaggregative E. *coli* could reduce the prevalence of stunting by 12.5% and save 2.8 million DALYS. The result assumes that the cost of treatment is US$6 and the positive externalities associated with treatment are equal to 0.25 DALYs.
Malaria	Diagnosis in febrile children aged <5 years in sub-Saharan Africa	A test with 95% sensitivity, 95% specificity and minimal laboratory infrastructure requirements could save ~1.8 million adjusted lives and prevent 996 million unnecessary treatments a year. A new test with no infrastructure requirements and 90% sensitivity and specificity would save ~2.2 million adjusted lives and prevent ~447 million unnecessary treatments per year.
TB	Diagnosis of active infections in symptomatic individuals with or without concomitant HIV infection	A rapid diagnostic requiring no laboratory infrastructure, with at least 85% sensitivity for smear-positive and smear-negative cases could save ~400,000 lives annually.
Sexually transmitted infections	Syphilis screening of antenatal women	A new diagnostic test that is at least 86% sensitive, 72% specific, requires minimal laboratory infrastructure and has either a 100% rate of return for test results or a 100% treatment rate could save >138,000 adjusted lives and avert >148,000 still births. A similar test requiring no laboratory infrastructure could save >201,000 adjusted lives and avert 215,000 still births.
Sexually transmitted infections	Gonorrhoea and Chlamydia screening and diagnosis in female CSWs	A new diagnostic with 86% sensitivity and 90% specificity for both gonorrhoea and chlamydia that requires minimal laboratory infrastructure could save ~3 million DALYs, avert >12 million incidents of gonorrhoea and chlamydia infections, and prevent >161,000 HIV infections among female CSWs in sub-Saharan Africa, China, and south-east Asia. A test that requires no laboratory infrastructure could save ~4 million DALYs, avert >16.5 million incidents of gonorrhoea and chlamydia infections, and prevent 212,000 HIV infections.

AIDS – Acquired Immunodeficiency Syndrome, ALRI – Acute Lower Respiratory Infection, ARI – Acute Respiratory Infection, C. parvum – Cryptosporidium parvum, ART – Antiretroviral Therapy, CSW – Commercial Sex Worker, DALYs – Disability Adjusted Life Years, E. coli – Escherichia coli, G. lamblia – Giardia lamblia, HIV – Human Immunodeficiency Virus, TB – Tuberculosis.
Source: Urdea M et al. [27]

of academic organizations alone are flagged as such in the database and scrutiny of the other compounds allowed the identification of those involving academic or not-for-profit organizations as a patentee, licensor or developer. Spin-off companies established by universities are classified as for-profit organizations.

According to IMS Health, a total of 6491 molecules were in active development in August 2009. Academic or not-for-profit organizations alone were responsible for 608 compounds. Joint ventures between academic or not-for-profit organizations and industry were responsible for an additional 358 compounds. An analysis of drugs approved by the FDA between 1998 and 2007 (as opposed to an analysis of drugs in development) confirms this impression. In this analysis the authors concluded that the university sector could be attributed with 24% of the total output [30]. We see a similar picture, but in reverse in relation to research into neglected disease. In the latest G-Finder Survey covering 2009, the proportion made up by private pharmaceutical company funding of total funding for neglected disease R&D had increased by 12% over 2007, now constituting 13% of total funding [31].

Analysis of the IMS database shows that there is no apparent difference between the overall patterns seen in R&D activity as described earlier and that attributed to academic or not-for-profit organizations within the database. Tables 9 and 10 serve to illustrate this below. There is a similar preponderance towards non-communicable conditions and within these conditions, malignant neoplasms and neuropsychiatric conditions predominate.

The similarity between the academic community and industry is not surprising. Since the 1980s in the USA, universities were permitted to take out patents based on inventions arising from publicly funded research and as the Commission on Intellectual Property Rights, Innovation and Public Health concluded in 2006, "The great majority of health research funded by the public sector, takes place in developed countries, and its priorities principally reflect their own disease burden, resource position and social and economic circumstances" [2]. If, however, the public sector has moved towards collaboration with the private sector, there has also been a movement in the other direction. The challenges to the industry's current R&D business model have driven contacts between industry and academia with even now further moves towards "open innovation" being mooted [32,33], this being where new product ideas from outside the organization are welcomed and where intellectual property is permitted to be used by others.

The location of pharmaceutical development

The percentage of R&D revenues being spent by PhMRA member companies outside of the USA has remained relatively constant since 1980 [34]. There have, however, been dramatic changes in the location of clinical research.

The European Medicines Agency found that around a quarter of all patients recruited for pivotal trials filed between 2005 and 2008 were enrolled in Latin America, Asia, the Commonwealth of Independent States and Africa [35]. In a global ranking of overall country effectiveness for clinical trials, based on an analysis of patient pool, cost efficiency,

regulatory conditions, relevant experience, infrastructure and environment, the UK and the Czech Republic rank sixth, with the USA, China, India, Russia and Brazil all featuring higher in the league table [36].

The increasing involvement of lower and middle income countries in pharmaceutical R&D has not necessarily led to a greater focus in these countries on the diseases that

Table 9: High-level distribution of indications being investigated, by academic or not-for-profit involvement, as of August 2009 (n=966 molecules, 1454 indications)

	% All†	% Academic‡	% Any academic in JV	% Any academic involvement (alone or JV)
Communicable maternal, perinatal, and nutritional conditions	15%	17%	15%	16%
Non-communicable conditions	85%	83%	84%	83%

†% All = commercial alone, academic alone, academic + commercial
‡Academic includes Not for Profit
JV – Joint Venture
Source: IMS Health

Table 10: Non-communicable conditions, by academic or not-for-profit involvement, as of August 2009 (n=966 molecules, 1454 indications)

Non-communicable conditions	% All†	% Academic‡	% Any academic in JV	% Any academic involvement (alone or JV)
Malignant neoplasm	35%	45%	55%	50%
Other neoplasms	5%	5%	5%	5%
Diabetes mellitus	4%	3%	3%	3%
Endocrine disorders	7%	5%	5%	5%
Neuropsychiatric disorders	16%	15%	11%	13%
Sense organ disorders	3%	3%	2%	2%
Cardiovascular diseases	8%	7%	5%	6%
Respiratory diseases	5%	3%	1%	3%
Digestive diseases	4%	2%	3%	2%
Diseases of the genitourinary system	2%	1%	1%	1%
Skin diseases	3%	2%	2%	2%
Musculoskeletal diseases	7%	7%	5%	6%
Congenital abnormalities	1%	1%	1%	1%
Oral diseases	0%	0%	0%	0%

†% All = commercial alone, academic alone, academic +commercial
‡Academic includes Not for Profit
JV – Joint Venture
Source: IMS Health

predominantly affect them. One study found that in the five years between 1997/1998 and 2003/2004, for example, while overall investment in pharmaceutical R&D surged in India, "it has become less targeted towards the health needs of the developing world." The authors of the study proposed that the incentives provided by local patents in their own markets were more than outweighed by the "push towards global products created by growing numbers of research relationships with multinational firms" [37].

The quality (good clinical practice, methodology and ethics) of trials should, of course, be independent of wherever the study is conducted. It is clear that the trend of changing locations of clinical development will continue to pose challenging questions for national policy makers.

FUTURE CHALLENGES AND ISSUES

Civil society has questioned the pricing and marketing practices of industry and its focus on blockbuster markets, often for valid reasons. Industry has responded, not perhaps sufficiently in the eyes of some, with an increasing number of compounds for neglected diseases, and particular initiatives, such as patent pools and technology transfers [26, 38]. Public sector funders have also responded, for example, by allocating an increasing amount of funds to tropical diseases [4].

In spite of these measures it remains true that R&D in both the public and private sectors has failed to generate sufficient innovations to meet the pharmaceutical demands of the developing world. The challenge faced by the industry's R&D business model, described above, in terms of productivity demands that new initiatives be developed. With productivity stable or declining, escalating costs are making commercial and public sector developments increasingly unaffordable for many more diseases affecting both low and middle income countries.

In 2006, the Commission on Intellectual Property Rights, Innovation and Public Health concluded that… "In the longer term, the development of innovative capacity for health research in developing countries will be the most important determinant of their ability to address their own need for appropriate health-care technologies." This led to a "global strategy and plan of action." The plan has eight elements:

- an assessment of health needs in developing countries and identification of R&D priorities;
- promotion of R&D on diseases which substantially or overwhelmingly affect people in developing countries, and also diseases which affect rich and poor countries with large numbers of vulnerable populations in both;
- exploration and implementation, where appropriate, of possible incentive schemes for R&D;
- improvement of R&D capacity in developing countries;
- improvement, promotion and acceleration of technology transfer;
- improvement of access to all health commodities by effectively overcoming barriers to access;
- sustainable financing for R&D in developing countries; and
- develop mechanisms to monitor and evaluate the implementation of the strategy and plan of action, including reporting systems.

As this, and other initiatives to streamline and accelerate the drug development process, take hold, care needs to be taken to exploit the opportunities in ways that are appropriate to the economic and social circumstances and technological capabilities of each country [4]. Only relatively few low income countries have the capability of developing a genuinely innovative capacity [4, 39]. Other countries may find it more appropriate to focus on other areas, such as public health and the incremental development of existing technologies to resource-poor settings. This latter point may be particularly relevant to the application of medicines used to treat the so-called Type 1 diseases, diseases that occur commonly in both rich and poor countries. Much is talked about neglected diseases and Type III disease, diseases that are overwhelmingly or exclusively incident in the developing countries, but there remain considerable hurdles in applying technologies designed for the developed world, particularly in the area of Type 1 disease.

As innovative capacity grows, care also needs to be taken to ensure that the attractions of developed world markets do not swamp the needs of the developing world. This is clearly a difficult area but we may be able to take some comfort from both recently announced technology transfer agreements [40] and the recent proposals as to how universities in the developed world can ensure minimum levels of research into global health issues [41]. The agreement between GlaxoSmithKline and the State-owned Oswaldo Cruz Foundation in Brazil gives access to one of the most complex vaccine technologies in the world and at a discounted price. The not-for-profit venture between Merck and the Wellcome Trust in India is built on a business model that once a vaccine has been developed to proof of concept stage, an Indian biotechnology firm will take over its further development, on the understanding that the vaccine will be sold at an affordable price. In the USA, six universities, the National Institutes for Health and the U.S. Centers for Disease Control have recently announced a "plan to facilitate access to university innovations with a clause ensuring global access to low-cost products by manufacturers for treatment of infectious diseases." To ensure that careers in global health research are attractive there is also a call that neglected disease research should be included in a set of new metrics for faculty appointments.

The fact that lower and middle income countries are taking an increasingly large share of clinical trials also needs to be taken into account. It is important that policy makers ensure that such trials are, and can be seen to be, carried out according to the appropriate scientific and ethical standards. Some anecdotal reports relating to the conduct of some clinical trials make uncomfortable reading [42, 43]. It is clear that if low and middle income countries are to derive long-term benefit from the globalization of R&D, sufficient resources will need to be put in place by both the countries themselves and the regulators in the developed world. Several initiatives are already under way. They include the European and Developing Countries Clinical Trials Partnership, the Supporting Strategic Initiatives for Developing Capacity in Ethical Review, the Developing Country Vaccine Regulatory Network and the guidance issued by the European Medicines Agency for the acceptance of clinical trials conducted in third countries [35, 44, 45]. Hopefully countries in the developing world can build on these.

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CHAPTER 2.2

VACCINE R&D: PAST PERFORMANCE IS NO GUIDE TO THE FUTURE

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ABSTRACT

Vaccines offer the most cost-effective solution to prevent both communicable and non-communicable disease in poor countries. Published studies suggest that vaccine research is seeing declining success. This study updates the latest analyses on success rates in vaccine research, and examines the potential causes of decline and their ongoing impact. Success rates are shown to decline, the observed probability of market entry being just 1.8%, almost a fourfold decline over 5 years, but in the context of a very different product portfolio from that seen in earlier studies. DNA vaccines see high Phase I failures as expected, and therapeutic vaccines have lower success rates than prophylactic vaccines. The changing scientific challenge, lack of investment and lack of co-operation are highlighted as potential causes of the decline. Many issues have now been resolved, but co-operation between academia, regulators and industry remains a significant challenge, requiring links across new disciplines and technologies.

INTRODUCTION

New drug output from pharmaceutical companies over the last 60 years has been constant despite costs rising exponentially at an annual rate of 13.4% [1]. Vaccine output appears, however, to have declined. The market entry probability of vaccines in preclinical development in 1983 was calculated at 0.22 [2], that of prophylactic vaccines in 1995 at 0.11 [3] and that of both prophylactic and therapeutic vaccines in preclinical development in 1998 at 0.07 [4]. This apparent decline warrants further investigation. Vaccines have been described as the "greatest contribution modern medicine has made to humanity" [5], and vaccines remain an important, perhaps essential, component in the strategies to defeat HIV, malaria, neglected disease and cancer [6-9]. This paper calculates the market entry probability of vaccines in development in more recent times, looks at potential reasons for the ongoing decline and discusses their likely impact on current and future vaccine development success.

METHOD

The study tracked the progress of vaccines in active development in IMS Health's R&D Focus database. This database has been used in several prior studies of development phase transition rates, but not previously for studies of vaccine research and development [10]. The main sources of information for R&D Focus are company press releases, company interviews and websites, and scientific conferences. R&D Focus lists the product name, the "latest news" about the product, whether or not the product has been discontinued or is still in active development and its mode of action. Indications are denoted by European Pharmaceutical Market Research Association Anatomical Therapy Classification (EphMRA ATC) [11] and, for this study, were also derived from the author's examination of the latest news. The latest phase of development is recorded in R&D Focus but for some records, this is shown as "discontinued" or "suspended". In these cases, the latest phase as recorded in the latest news was used. Projects for which no news is heard for more than 36 months are deemed to be discontinued in the database.

Progress was tracked from January 2003 to November 2013, a study period of just under 11 years, similar to the latest reported average development time for vaccines (10.71 years) [4]. Projects linked to the EphMRA ATC for vaccines in active development in January 2003 were extracted. Of the 435 projects identified 79 were excluded, 42 because the product had already been launched, 15 because the project related to the development of an adjuvant or drug delivery technology only, and 12 because later extracts indicated that the entries were duplicates or had been inaccurately linked to the vaccine code. Text searches were used to track the remaining 356 projects through to November 2013. Text searches were carried out using the product name and information in the latest news as declared in January 2003. 4 could not be tracked with any certainty and were excluded. A total of 352 projects thus remained. Of these, 199 were classified as prophylactic vaccines, a further 20 as both prophylactic and therapeutic vaccines, and the remainder as therapeutic vaccines, based on the information given in the latest news. These numbers and proportions are similar to those described in other databases [4, 12].

Observed and maximum success rates were calculated and compared to previous studies. For the purposes of comparison, success rates were defined as per the method used in these other studies. Market entry probability was thus defined either as the proportion of projects reaching the registration phase or as the proportion of projects actually launched. Maximum success rate assumes that all of projects still in active development as of November 2013 (regardless of current phase) reach the market. Transition rates, or in other words the probability of a project in active development in January 2003 progressing to at least the next development phase, are also shown.

To examine the current state and trends in vaccine research, a similar process was followed with data being extracted on projects in active development from the databases constructed as at January 2005, 2007, 2009, 2011 and 2013.

RESULTS

67% of the projects in development as of January 2003 targeted infectious disease, 24% targeted cancer. Of the 352 projects, 21 (6%) were still in active development but had not yet reached registration. Infectious diseases could be further broken down into 71 different target diseases or infectious agents, HIV being the largest with 35. Cancer could be broken down to 28 different tumours or combinations of tumour targets. Prostate cancer and melanoma vaccines were the largest categories. Prophylactic vaccines constituted 56% of all projects, and therapeutic vaccines 40%, with the remainder being described as having potential in both areas.

This distribution of disease targets is very different from earlier studies. In 1998, anthrax, hepatitis B, HIV, influenza, malaria and Japanese Encephalitis Virus infection constituted 49% of projects in active development [4]. In this study, this group of diseases made up just 22% of those projects in active development, in part because of a very different number of vaccines in development for influenza. Changes in the relative proportions of vaccines targeted at different diseases continued post 2003. Cancer vaccines continue to grow whilst infectious diseases, notably bacterial infections, hepatitis and HIV decline (Figure 1).

Success and transition rates are also very different (Figure 2), and are seen to decline over time, even if the maximum success rate seen in this study is used as the basis of comparison. The maximum market entry rate of vaccines in preclinical development is just one quarter of those at the same stage in 1998 (0.018).

Success rates differ by type of vaccine (prophylactic or therapeutic), by disease target (infection versus cancer) and by technology (DNA or other) (Figure 3). Success rates for therapeutic vaccines, for those directed at cancer and those delivering DNA were substantially lower.

The lower Phase I success rates for DNA vaccines are expected. Many Phase I DNA vaccine trials are used to distinguish plasmid components that have a greater effect on vaccine immunogenicity and are not intended to progress through to Phase II [13]. Nevertheless that low success rate of DNA vaccines in later phases is still disappointing. As a relatively new technology at this time, it was seen as one that could revolutionise the prevention and treatment of infectious disease. DNA vaccines were recognised to be relatively safe as

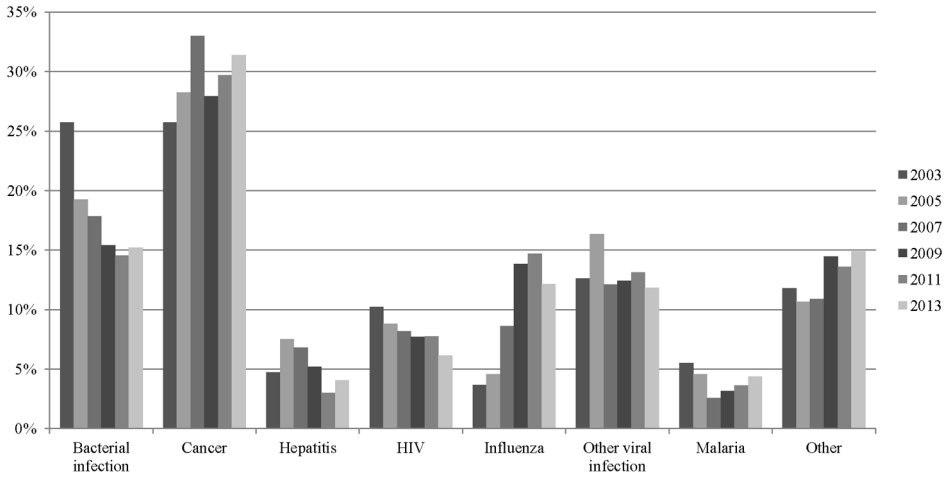


Figure 1: *Changes in the percentage of projects in active development by disease over time*

they contain no pathogenic organism, capable of being designed to counter several disease variants simultaneously as well as offering advantages in terms of ease of administration and stability which make them particularly suitable for resource poor settings [14].

DISCUSSION

This study describes a continuing decline in the overall market entry probability of vaccines, even when DNA vaccines are excluded. The decline affects both therapeutic and prophylactic vaccines, the former constituting more than a third of all projects in active development but delivering just two actual vaccines to market.

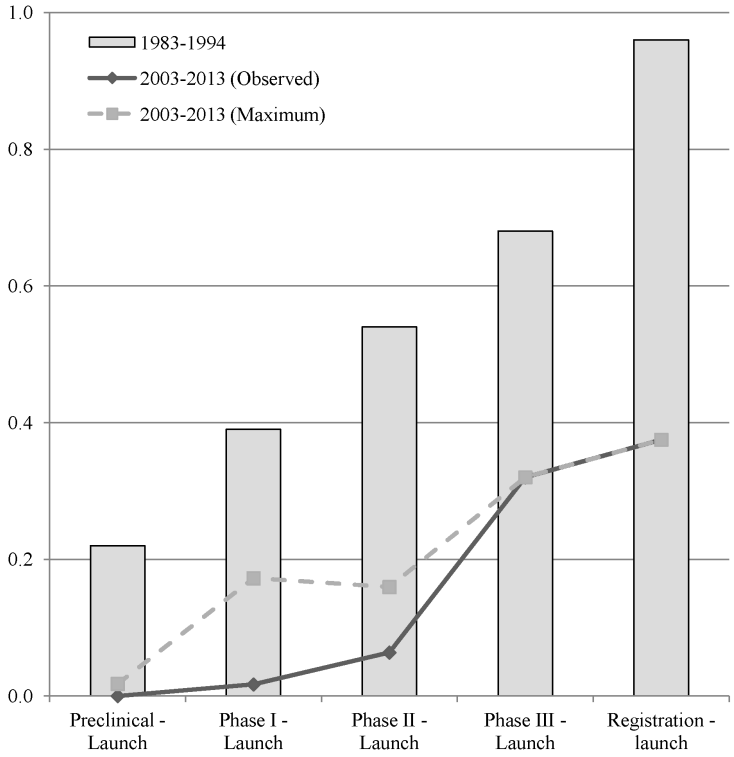
The decline described is not compensated by an increase in the number of projects in active development. In 1998 the number of vaccines in preclinical development was just over 100, and in 2003 was over 160 [12]. At the same time market entry success declined almost fourfold.

In 2005 it was suggested that the aggregate cost per successfully developed vaccine was at least $200-500m [15]. This study assumed that the probability of success was 0.22. This current study found a probability of success of just 0.01 and would so seem to demand that these cost estimates are revised.

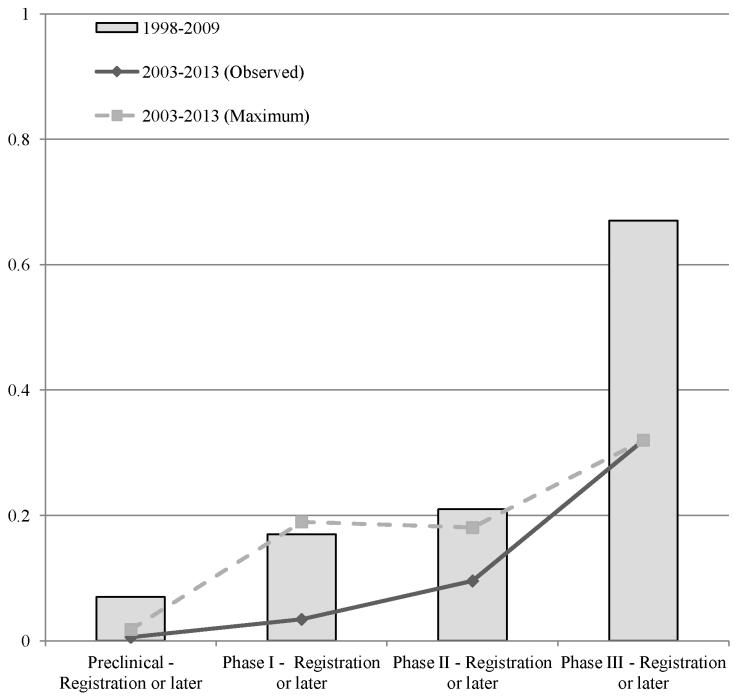
Some of the reasons for the decline in market entry probability are clear – scientific challenge, the availability of investment and lack of co-operation between and within academia and industry. A key question is whether these same obstacles remain today.

In 2003 vaccine research and development was moving into areas that even now are proving to be resistant to scientific endeavour. Cancer vaccines and new technologies such as the delivery of DNA were taking a substantial share of total development projects. This direction of change has continued into more recent times with cancer vaccines increasing as a proportion of total projects in development (Figure 1). In 2011, however, a review of

(A)


1.0
0.8
0.6
0.4
0.2
0.0
1983-1994
2003-2013 (Observed)
2003-2013 (Maximum)
Preclinical - Launch
Phase I - Launch
Phase II - Launch
Phase III - Launch
Registration - launch

(B)


1
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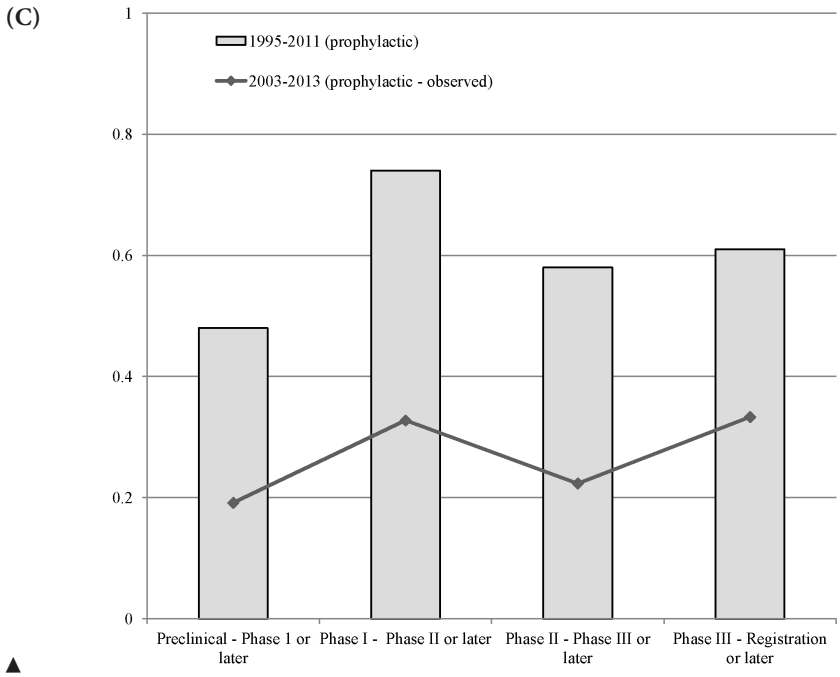
1998-2009
2003-2013 (Observed)
2003-2013 (Maximum)
Preclinical - Registration or later
Phase I - Registration or later
Phase II - Registration or later
Phase III - Registration or later



▲

◄ ***Figure 2:*** *Success and transition rates between projects in active development as of January 2003 (lines) compared to the results of earlier studies (bars). (A) Comparison with projects in active development as of 1983 (B) Comparison with projects in active development in 1998 (C) Comparison of transition rates with prophylactic vaccines in active development as of 1995. Maximum success rate assumes that all 2003 projects still in active development as of November 2013 reach the relevant success criteria.*

cancer vaccines concluded that "it is at least doubtful that any reliable anti-cancer vaccine strategy will emerge in the near future" [16]. DNA vaccines as late as 2010 were found to be safe but to be limited by the relatively modest immune response elicited [13]. And in 2007 the International AIDS Vaccine Initiative set out the reasons why the development of HIV vaccines was unusually difficult – rapid and varied mutation of the virus, no convenient animal model to use in testing preclinical concepts and the unacceptable risk of using live-attenuated or killed whole virus vaccines in humans for fear of causing infection [17]. Such scientific challenges are not necessarily permanent, however, and neither may they be any greater than those that have been overcome before [17]. Indeed recent advances in DNA and cancer vaccine research have been described that promise much [18, 19]. Moreover some argue that such obstacles are relative, not absolute, and dependent largely on the amount of investment in vaccine research and development [20].

Lack of investment and relevant expertise has in addition been postulated to be one of the reasons behind the relatively small increase in the number of vaccines in Phase III clinical trials as compared to the larger increases in all other phases between 1995 and 2008 [12]. In part this will have been due to the constriction in the number of large

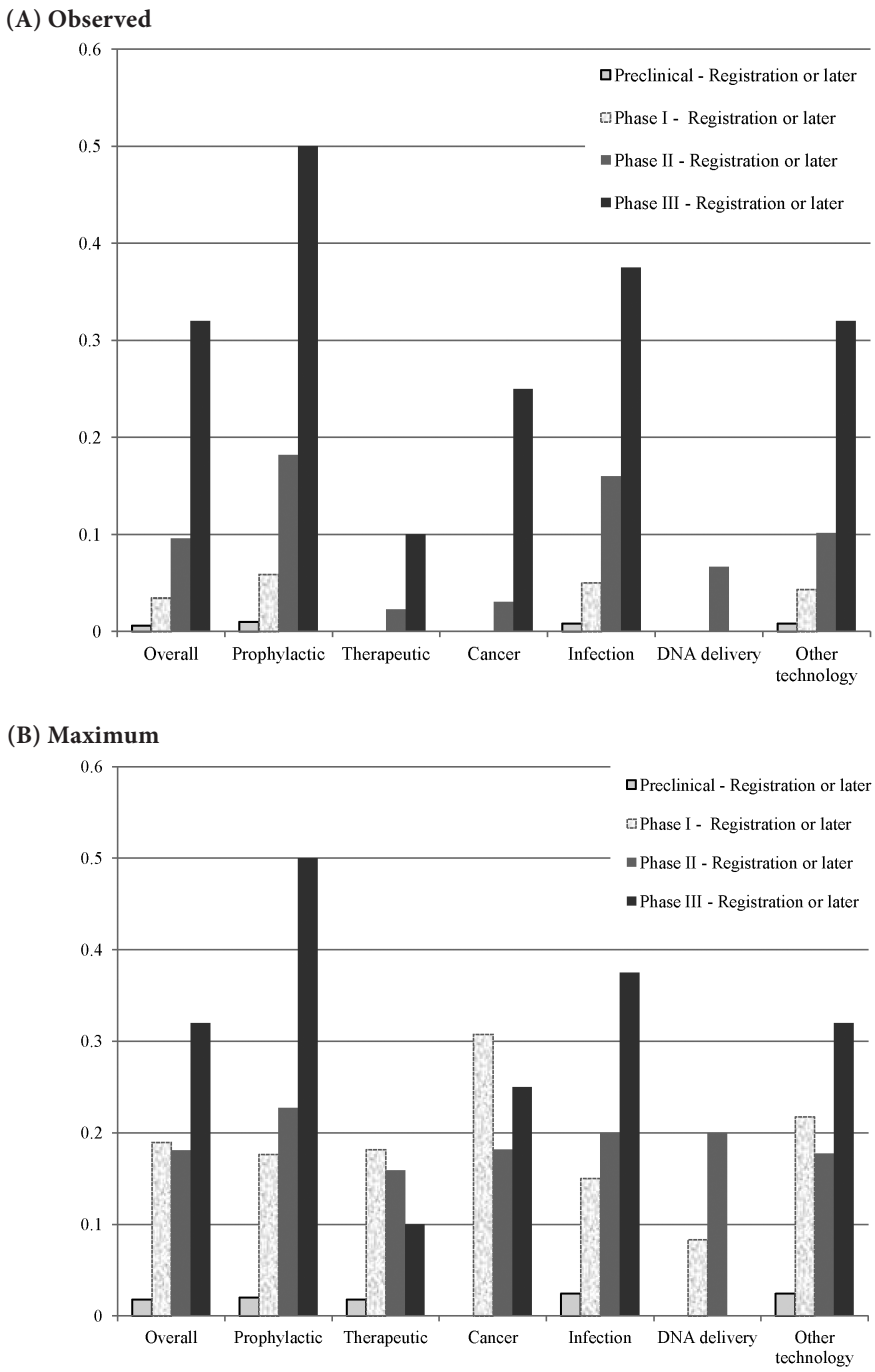


Figure 3: *Success rates by type of vaccine, disease target and technology. (A) shows the observed success rate. (B) shows the maximum possible success rate if it is assumed that all projects still in active development as of November 2013 are successful.*

pharmaceutical companies investing or being involved in vaccine research [17]. One driver of pharmaceutical companies declining interest appears to have been the regulatory burden, described as "lengthy, cumbersome and expensive", making vaccine development "a dangerous and risky financial "gamble"" [21]. There is however renewed commercial interest in vaccine development, in part due to the entry into this area of the Bill and Melinda Gates Foundation in 1994, these being augmented by the donations from Warren Buffet [22]. There is also an increasing awareness amongst regulators as regards the opportunity costs of risk aversion in regulation [23]. Whatever the reason though, the ratio of Phase II to Phase III vaccine projects in active development now seems to be on an upward trend (Figure 4).

Lack of co-operation between and within academia and industry was highlighted as a major factor in the lack of progress seen in HIV vaccine research over this period [17, 24]. The need for co-operation across multidisciplinary fields has also been cited as a critical component of success in cancer vaccines [25]. A wide variety of initiatives are already in place, not just in the vaccine field [24] but across the research and development pathway in general [26, 27]. Some commentators however still have concerns. They feel that vaccine development has not kept pace with breakthroughs in basic science and technological development, and that such programmes are constrained by the milestone-based, short-term nature of research funding [21, 28].

In conclusion it is clear that whilst this most recent analysis shows a continuing decline in vaccine market entry success rates, it should not be assumed that this trend cannot be reversed. Vaccine research changed in focus at this time and thus the scientific challenges it faced also changed. Levels of investment at least for HIV vaccines have almost tripled [20] and analysis has suggested that industry interest in research has increased [12, 22]. Co-operation between and within academia, regulators and industry remains important, however, and whilst initiatives have been put in place, this perhaps remains the biggest challenge facing vaccine research as it requires links to be made across new disciplines and technologies.

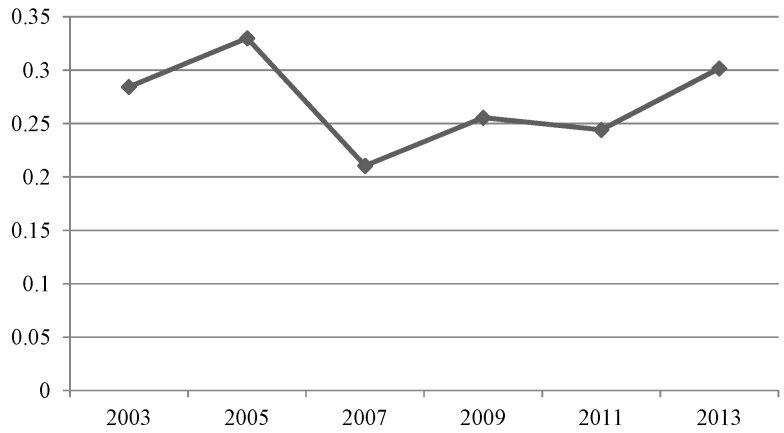


Figure 4: *Ratio of Phase III to Phase II vaccine projects in active development by year*

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CHAPTER 3

ACCESS TO MEDICINES: THE EFFECTS OF GENDER, AGE AND DEPRIVATION

CHAPTER 3.1

DOES ACCESS TO MEDICINES DIFFER BY GENDER? EVIDENCE FROM 15 LOW AND MIDDLE INCOME COUNTRIES

Health Policy. 2013 Apr;110(1):60-6.

Stephens P, Ross-Degnan D, Wagner AK

ABSTRACT

Objective

To examine gender differences in access to prescribed medicines in 15 lower and middle income countries.

Methods

The proportion of consultations with at least one prescription for women in three age groups (<15, 15-59, 60+ years) with acute respiratory infections (ARI), depression and diabetes in routine audits was compared to the expected proportion calculated from WHO Global Burden of Disease estimates. Newer oral hypoglycaemic medication prescribing was also analysed. Differences reported by country, age group, and condition.

Findings

487,841 consultations examined between January 2007 and September 2010 in low (n=1), lower middle (6), and upper middle income (8) countries. No country favoured one gender exclusively, but gender differences were common. Taking the 15 countries together, only diabetes treatment revealed a significant difference, with women being treated less often than expected (p=0.02). No consistent differences found across countries grouped by World Bank income category, WHO region or Global Gender Gap Index. Overall, women had equal access to newer oral hypoglycaemics.

Conclusion

Gender differences in access to prescribed medicines for three common conditions are common, but favour neither gender consistently. This challenges prevailing hypotheses of systematic disparities in access to care for women. Evidence about gender disparities should influence policy design.

INTRODUCTION

Gender has been defined as the "socially constructed roles, behaviours, activities and attributes that a given society considers appropriate for men and women" [1]. Gender equity is a concern in many social and economic domains, including health. Indicators measuring mortality rates, household allocation of resources for medical care, and allocation of food and education all point to the presence of gender inequity in many parts of the world, with South Asian countries often highlighted as showing strong evidence of bias against women [2-4].

In relation to the provision of health care, gender equity is generally taken to mean meeting the health needs of men and women in an equitable way, including equitable access to health services given need [5]. Gender differences in health have been well documented. For example, the World Bank recently reported skewed sex ratios at birth that favour males, excess female mortality in infancy and early childhood, high maternal mortality, and excess female mortality due to HIV/AIDS [6]. However, information on the effect of gender on access to medicines is sparse. In 2005, Baghdadi speculated that "[t]here are not enough data to conclude that [obstacles to care] lead to lower use of medicines among women, but based on available evidence this seems likely"[1].

A recent gender-stratified assessment of the management of chronic conditions in seven countries reinforces this view. It indicated less effective management of blood glucose, blood pressure, and hypercholesterolemia among women with diabetes in four low and middle income countries [7]. Another recent prospective study of the use of medications for secondary prevention for cardiovascular disease in urban and rural communities in 16 low, middle and high income countries concluded that fewer women than men took medicines in all settings [8]. The aim of the present study was to determine whether these gender differences are typical in low and middle income countries (LMICs), across different diseases and in settings with high levels of out of pocket payments.

MATERIALS AND METHODS

Data source and environment

We used data collected routinely by IMS Health [9] (IMS) on consultations by contracted general practitioners and specialists in 15 LMICs (Table 1, Supplementary Information). In each country, IMS designs a sampling frame to represent the national distribution of prescribers, recruiting doctors across a range of regions and specialties. We used data collected between January 2007 and September 2010, with a mean of 12 quarters of data per country (range 4-15). Data were aggregated across this time period to create a large sample of physicians, consultations and prescriptions.

Eligible consultations were those during which at least one medicine was prescribed. In the study countries, physicians agreed to record data on every consultation within a pre-determined week per quarter or semester. Physicians recorded the patient's sex, age, diagnoses, and medications prescribed as free text. IMS codes diagnoses according to the ICD-10 classification [10] and classifies prescribed medications according to the European Pharmaceutical Market Research Association (EphMRA) Anatomical Therapeutic Classification (ATC) system [11].

Consultations in the LMICs studied tend to be paid from different sources and physicians frequently provide care in both the public and private sectors. In our sample of prescribers and consultations (Table 1 Supplementary Information), the median percentage of doctors who had recorded a private consultation for at least one of the three conditions studied was 77% (interquartile range 69%-83%, data available for 10 of 15 countries). The median percentage of consultations for the three conditions studied (depression, diabetes, or acute respiratory infection) paid for out of pocket or through private insurance was 67% (interquartile range 25%-81%). Data from the WHO National Health Accounts (Table 2 Supplementary Information) also indicate that private payment for medicines predominates in the study countries, with private pharmaceutical expenditure constituting a median of 74% (interquartile range 61%-90%) of the total pharmaceutical expenditure [12].

Study conditions

Based on ICD-10 codes used in the World Health Organisation (WHO) burden of disease report [13], we selected consultations from the IMS database for patients diagnosed as having depression, diabetes, or acute respiratory infection, three conditions commonly treated in outpatient settings in all countries.

Diabetes represents a significant and growing health burden, particularly in South Asian countries [14] where gender differences are thought to be more prevalent than elsewhere [3-5]. Significant and potentially avoidable differences in mortality rates between men and women with diabetes have also been reported in at least one country [15]. Nevertheless, there is a severe shortage of gender-specific data on the global diabetes epidemic in lower and middle income countries [16].

Like diabetes, depression represents a significant cause of morbidity and is forecast to become the foremost cause of disability in under-developed countries by the year 2020 [17].

We included consultation data for acute respiratory infections as an example of a common acute condition. Gender differences in access to outpatient treatment have been demonstrated in nine middle income countries (including five of the study countries) [3].

Country, consultation and patient categorisations

We used World Bank income categories available as of July 2008, the approximate midpoint of the data collection period, to classify countries. We report on one low income country (Pakistan), six lower middle income countries (Colombia, Indonesia, Peru, Philippines, Thailand and Tunisia) and eight upper middle income countries (Argentina, Brazil, Lebanon, Mexico, Poland, South Africa, Turkey and Venezuela). We also classified countries according to WHO region and according to the 2010 Global Gender Gap Index rank (GGGI) [18]. Country GGGI ranks were divided into quartiles and countries allocated to the appropriate quartile (Table 2, Supplementary Information).

Consultations for diabetes and depression were included if the physician had recorded both a relevant diagnosis and prescribing of a drug from a relevant ATC category (A10, drugs used to treat diabetes or N6, psycho-analeptics, excluding anti-obesity preparations,

respectively). Consultations for acute respiratory infections were included on the basis of the relevant diagnosis only; drug type was not used to filter the treated consultations due to the very wide range of classes of drugs that were being used in this condition. Consultations meeting these criteria are termed "eligible consultations." We divided eligible consultations into three patient age categories corresponding to those used in the WHO Global Burden of Disease (GBOD) estimates (0-14, 15-59, 60+).

Outcome measures

Gender differences in eligible consultations

We compared the expected numbers of eligible consultations for women with the observed numbers in each country, condition, and age group.

To calculate expected numbers of eligible consultations, we used the 2004 gender, age, and diagnosis-specific GBOD estimates [19] for each country. These are expressed as Disability Adjusted Life Years (DALYs). The estimates take into account the numbers of men and women in each country. The total burdens reported of each of the study diseases for men and women were converted to percentages. These percentages were used to calculate the expected proportions of eligible consultations for men and women in each country, diagnosis, and age group. Table 3 in the Supplementary Information illustrates the method used.

Using the IMS data, we then calculated the observed numbers of eligible consultations for women and men by diagnosis and age group. Finally, the gender-specific proportions of observed eligible consultations were compared to the expected proportions based on GBOD, as calculated above.

Only the results for women are shown, since a higher than expected proportion of consultations for women indicates a corresponding lower proportion of consultations for men, and vice-versa.

Type of medicines prescribed for diabetes

In addition to overall access to medicines, women and men may differ in their degree of access to newer, generally more expensive, medicines. To explore this potential difference, we examined the types of medications prescribed for diabetes, which were grouped into four categories – insulins, newer oral agents (dipeptidyl peptidase-4 inhibitors, glinides, glitazones, and glucagon-like peptide-1 analogues), traditional oral agents (alpha-glucosidase inhibitors, biguanides, sulphonylureas), and other. We calculated the expected numbers of eligible consultations with prescriptions for newer antidiabetic medications for women, based on the observed proportion of all eligible consultations for diabetes during which newer medicines were prescribed.

Statistical analysis

We depict graphically the direction and magnitude of differences between observed and expected numbers of eligible consultations for women. We used the Sign Test to test for consistency in direction of these differences at a condition and country group level [20]. We

used the Chi-square one sample test to compare observed and expected outcomes at country, condition and age group levels, with cells containing fewer than 100 observations excluded.

RESULTS

Across 15 countries and three target conditions, we analyzed 487,841 consultations with a total of 855,476 medications prescribed by at least 8,234 physicians per semester. Table 4 (Supplementary Information) shows the numbers of doctors recording one or more eligible consultations for each condition, the number of eligible consultations by country for each condition and the numbers of drug items prescribed.

Gender differences by country

Figure 1A-C presents the difference between the observed versus expected proportions of eligible consultations for women by age group and country for each of the three conditions.

In the group of 15 countries as a whole, the proportion of eligible consultations for women with diabetes was significantly (p=0.02) lower than expected; this difference was driven primarily by differences in the oldest age group (60+). There were no consistent differences between observed and expected proportions for depression (p=0.36) or acute respiratory infections (p=0.88). In the latter case, however, in the youngest age group in 10 out of 15 countries, boys received a disproportionate share of prescriptions and in the 15-59 year age group, women received more prescriptions than expected.

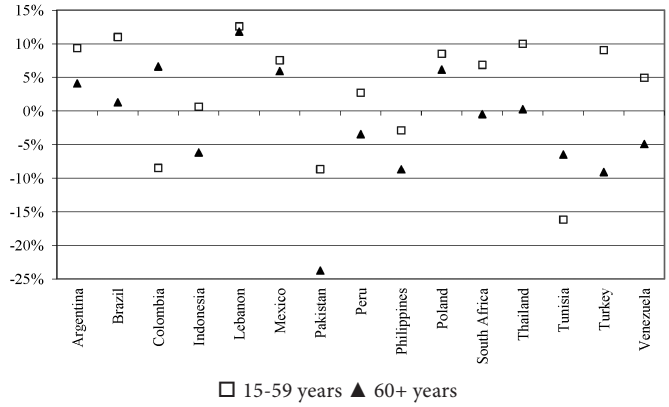
At country level, we also see the direction of gender difference change with age for other conditions. For example, women 15-59 years old in Colombia with diabetes had a disproportionate share of eligible consultations, while those over 60 years had a lower than expected share. Likewise in Pakistan, women over 60 years are treated less frequently than expected for diabetes, while women age 15-59 were treated more frequently than expected.

Figure 2 summarizes the distribution of differences between the observed and expected number of eligible consultations (expressed as a percentage of the expected number) by gender across all conditions and age groups combined. No country favours men or women exclusively, but no country is without any gender difference. Overall, observed proportions of eligible consultations were significantly lower than expected for women in 48 tests of difference, significantly higher in 33 tests and not different from expected in 27. Nine countries have greater numbers of these significant differences in proportions that favour men, while two countries have a greater number favouring women and four countries have an equal number of significant differences for each gender. South Africa, Turkey and Pakistan show the greatest difference in favour of men, while Argentina and Poland the greatest difference in favour of women.

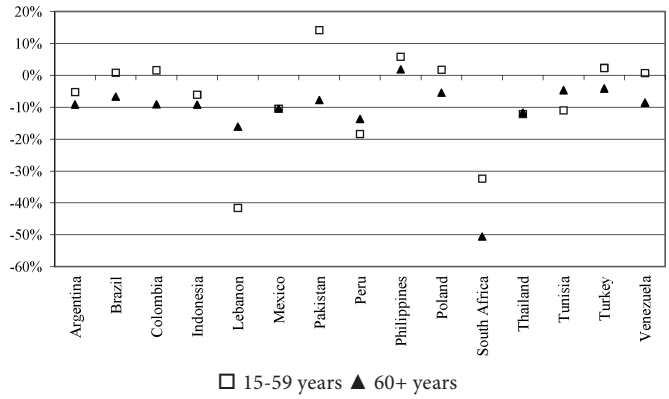
Gender differences by country grouping

No consistent results favouring men or women were seen when data were aggregated according to World Bank country income category or WHO Region (data not shown).

(A) Depression



(B) Diabetes



(C) Acute Respiratory Infection

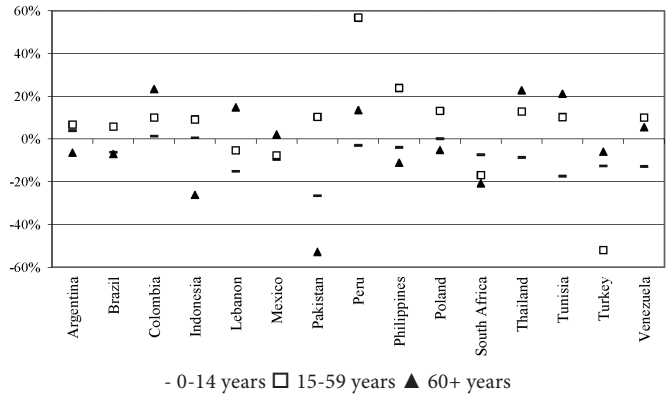


Figure 1: *Differences between observed and expected numbers of treated consultations for women (expressed as a percentage of the expected number). Positive numbers indicate that the observed is higher than expected. 0-14 year old data are excluded from depression and diabetes graphs due to small numbers. Higher than expected rates for women indicate lower than expected rates for men, and vice versa.*

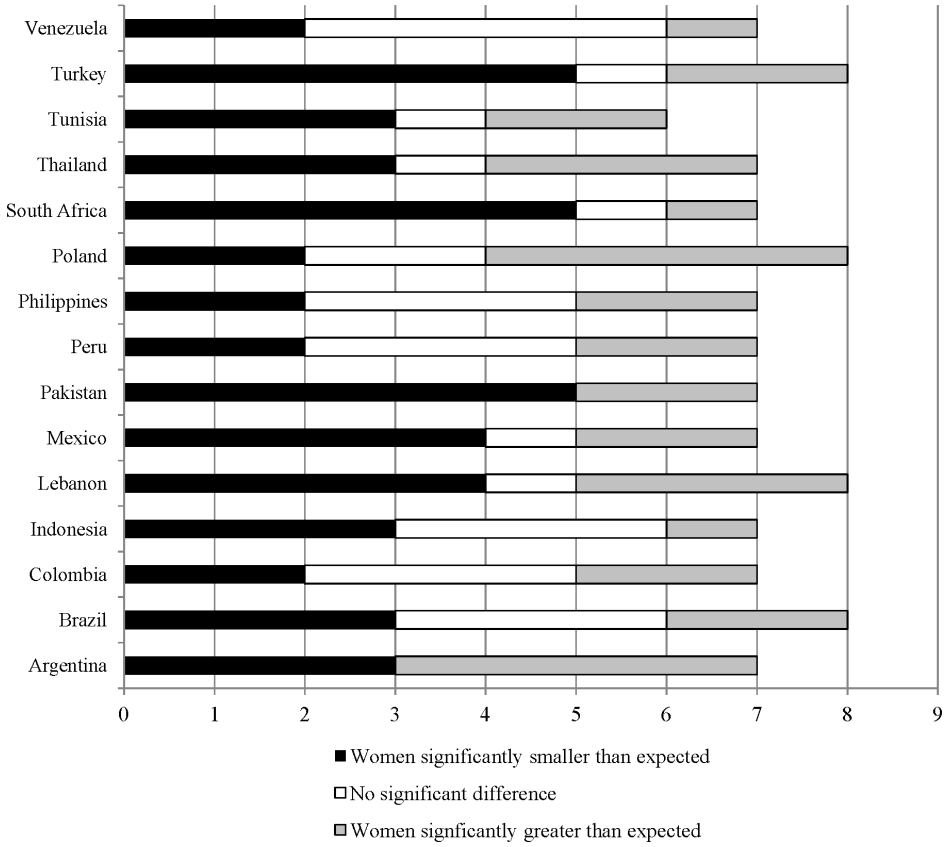


Figure 2: *Count of significant differences (p<0.05) between observed and expected numbers of treated consultations for women across all conditions and age groups combined by country. Comparisons with fewer than 100 treated consultations excluded from statistical analysis.*

In lower middle income countries, observed proportions of eligible consultations were significantly higher than expected for men in 15 comparisons, for women in 12 cases, and not different in 14 cases. The results for upper middle income countries were 28, 19 and 13 respectively. Observed proportions of eligible consultations were similar to expected across all three categories for the WHO Americas region, and in the three countries of the Eastern Mediterranean, observed proportions were significantly higher for men in 12 cases, for women in seven cases and not different in two cases. Other regions that contained data from one or two countries only are not described.

Although differences in favour of both men and women existed in each GGGI quartile, countries with wider gaps on the GGGI (in Quartiles 3 or 4) had a greater percentage of comparisons significantly in favour of men compared to those with narrower gender gaps (in Quartiles 1 or 2), 53% versus 37% respectively (data not shown). Visual inspection of Figures 1A-C indicates that there is no common pattern of gender differences among

countries with a higher or lower percentage of doctors or consultations treating private patients. For example, Poland and Turkey have similarly low proportions of private consultations (1% and 5%, respectively) but different patterns of gender differences.

Gender differences in type of prescribed medicines for diabetes

Differences in prescribing of new oral hypoglycaemics were not statistically significant (p=0.44) for women compared to men in the 15-59 and 60+ year categories. Consultations for the 0-14 age group were excluded because of too few observations. At a country level, only Brazil showed statistically significant differences favouring the use of the newer drugs in men (p=0.01) and older traditional oral hypoglycaemics in women (p=0.04) in the same age group (15-59) (data not shown).

DISCUSSION

This study suggests that gender differences in access to care and medicines are more complex than previously thought. Women in different health systems did not consistently have less access to care, as defined by eligible consultations with physicians where at least one prescription was written. Overall, the pattern of gender differences in consultations tends to be country, age- and condition-specific. Other studies of prescribing practice also indicate that discrimination against women at the physician level is not a consistent feature. A recently published study of physician behaviour in 6 low income countries in Africa and in Afghanistan suggests that in health facilities, men and women are treated similarly [21]. In all seven countries, doctors spent the same amount of time with patients, asked the same questions and completed the same number of examinations, regardless of the sex of the patient. A comparison of rates of infection and the use of antiretrovirals across a number of countries found over-representation of treated women in Thailand and Argentina, similar rates in Brazil and under-representation in India [22]. In addition, a recent analysis of 2002 World Health Survey (WHS) data from 53 countries found that women with arthritis, asthma or depression reported treatment more frequently than men, and that reported treatment access for angina, diabetes, and schizophrenia did not differ significantly between men and women [23].

Studies such as these seem to highlight a greater complexity of gender differences in use of medicines than had been assumed based on studies focused on gender differences in literacy, economic and political power, and health. Our study emphasizes that men can also be disadvantaged with respect to medicines prescribing for common conditions in different settings of care. This points to the continuing need for real-world evidence about gender-related differences in patterns of medicines prescribing and use within countries for patient groups defined by disease and age.

Our study has important limitations. IMS data represent a particular segment of the population, namely, those who have access to a physician and who were prescribed a medicine. In Colombia and Thailand, at least, it has been asserted that the majority of the

people with diabetes do not use medications for blood glucose control [7]. In seven upper middle income countries, 48% of people eligible for treatment for secondary prevention of cardiovascular disease did not take a drug and in four lower middle income countries, this proportion was 67.5%. Gender differences in terms of access to consultations where no prescription is written may be different to that which is described here, although the proportion of total consultations for the three diagnoses studied where a prescription was not provided was low (projected data 2008-11, 13 country median 1.22%, range (0.04%-3.52%)). Likewise there may be gender differences in terms of access to a physician or to care although a recent analysis of the World Health Survey conducted by the WHO in 2002 and 2003 in 70 countries indicates that there is, once again, no consistent pattern in differences in access to care by gender [23].

IMS also does not capture care provided outside of the physician practice setting. In addition IMS data in most countries are collected from samples of doctors that constitute a small proportion (<1%) of the total number of prescribers. While doctors that provide data to IMS are sampled by geographic area and specialty to represent each country's care providers, it is possible that they are not fully representative.

IMS data do not record deprivation, caste, ethnicity or other social markers, and they provide no information about the history or severity of the disease. Such information has been shown to explain much of the observed variation in the use of surgery or other treatments by gender for cardiovascular disease in the UK and Canada [24, 25] and higher rates of obesity have been postulated to explain a higher rate of insulin prescribing for women in Bahrain [26]. In a study among children in India on differences in diet and immunisations, gender was found to have little explanatory power (~2%) and maternal literacy (25%) and region (60%) better explained vaccination inequality between boys and girls [27]. In the absence of information on patient characteristics other than age and gender in the IMS data, we may thus over or underestimate gender differences. Other data will be needed to meet the WHO recommendation for a "more systematic examination of how gender intersects with economic inequality, racial or ethnic hierarchy, caste domination, differences based on sexual orientation, and a number of other social markers in the social patterning of health" [11].

We used the GBOD estimates as the benchmark for estimating the expected number of consultations. GBOD estimates do not take account of user-induced or supplier-induced demand. Individuals of either gender may present for treatment more often than the burden of disease estimates would lead one to expect, and physicians who focus on particular diseases may attract a larger proportion of men or women. In addition the population that has access to care for a specific condition may not reflect the gender mix of the total population with that condition. For these reasons, GBOD may not predict consultation rates accurately by gender. In addition, GBOD estimates in some of the study countries are derived from mortality data taken from other countries (for Indonesia, Lebanon, Pakistan and Tunisia) or in the case of unipolar depression, from a systematic review of 56 countries rather than all countries. However, to bias our results, inaccuracies in GBOD estimates would need to differ between women and men.

These limitations notwithstanding, our results suggest that donors and policy makers should not assume that inequities in medicines access affect women only. Medicines access may be inequitable for both men and women, and inequities may differ by age and condition. Policy makers should also bear in mind that physician prescribing is only one step for accessing medicines; dispensing and use patterns may also differ by gender. Gender mainstreaming policies and programmes should therefore seek to meet men's and women's need at different steps on the pathway to effective treatment.

CONCLUSIONS

This is the first study which uses prescribing data from doctors known to be working predominantly or partly in the private sector in fifteen LMICs to assess gender differences in access to and type of prescribed medicines. Gender differences in access to medicines do occur but the pattern is not consistent. Future research should assess the impact of other social determinants known to cause variation in access to care that interact with gender, as well as inequities in the quality of care for both men and women within countries.

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Table 1: Description of data sources and time periods

	Audit design		Time periods (Quarters of data)			Extent of private treatment of study diseases (2008-2010)	
	Period	No. doctors per period	Acute Respiratory Infection	Depression	Diabetes	% of doctors with 1 or more private* consultations	% of all consultations paid out of pocket or by private insurance*
Argentina	Quarter	470	Jan 07 - Sep 10 (15)	Jan 07 - Jun 10 (14)	Jan 08 - Sep 10 (11)	78%	35%
Brazil	Quarter	1315	Jan 08 - Sep 10 (11)	Jan 07 - Sep 10 (15)	Jan 08 - Sep 10 (11)	83%	88%
Colombia	Semester	385	Jan 07 - Dec 09 (12)	Jan 07 - Jun 10 (14)	Jan 07 - Dec 09 (12)	89%	73%
Indonesia	Semester	450	Jan 08 - Jun 10 (10)	Jan 07 - Jun 10 (14)	Jan 07 - Dec 09 (12)	NA	NA
Lebanon	Semester	265	Jan 07 - Jun 10 (14)	Jan 07 - Jun 10 (14)	Jan 08 - Jun 10 (10)	69%	100%
Mexico	Quarter	1050‡	Jan 08 - Sep 10 (11)	Jan 07 - Sep 10 (15)	Jan 08 - Sep 10 (11)	93%	77%
Pakistan	Semester	540	Jan 08 - Jun 10 (10)	Jan 07 - Jun 10 (14)	Jan 07 - Dec 09 (12)	NA	NA††
Peru	Semester	565	Jan 07 - Jun 10 (14)	Jan 07 - Jun 10 (14)	Jan 07 - Dec 09 (12)	75%	61%
Philippines	Semester	350†	Jan 08 - Dec 08 (4)	Jan 07 - Dec 08 (8)	Jan 07 - Dec 08 (8)	NA	NA††
Poland	Quarter	565	Jan 08 - Sep 10 (11)	Jan 07 - Sep 10 (15)	Jan 08 - Sep 10 (11)	12%	1%
South Africa	Quarter	384	Jan 08 - Sep 10 (11)	Jan 07 - Sep 10 (15)	Jan 08 - Sep 10 (11)	82%	21%
Thailand	Semester	440#	Jan 08 - Jun 10 (10)	Jan 07 - Jun 10 (14)	Jan 07 - Dec 09 (12)	NA	NA
Tunisia†	Semester	250	Jan 07 - Jun 09 (10)	Jan 07 - Jun 10 (14)	Jan 07 - Jun 09 (10)	NA	NA
Turkey	Quarter	705◊	Oct 09 - Sep 10 (4)	Jan 07 - Sep 10 (15)	Jan 08 - Sep 10 (11)	39%	5%
Venezuela	Semester	500	Jan 07 - Jun 09 (12)	Jan 07 - Dec 09 (12)	Jan 07 - Jun 09 (10)	70%	82%

† Sample included 600 doctors per audit period in 2008
‡ Sample included 990 doctors in Quarter 3 2009 only
# Sample size increased between Semester 1 and Semester 2, 2008
◊ Sample size increased from 640 to 705 in 2009
* Health system structure and definition of private treatment varies by country
†† In Pakistan ~80% of prescriptions from sample doctors are from the private sector. In Philippines, 97% of sample doctors work in the private sector

Table 2: Characteristics of countries included in the study

Country	WHO region	World Bank income category‡	GGGI rank (Composite)	GGGI quartile†	Private pharmaceutical expenditures as % of total pharmaceutical expenditures#	Year of data#
Argentina	Americas	Upper middle	29	1	66%	2006
Brazil	Americas	Upper middle	85	3	70%	2006
Colombia	Americas	Lower middle	55	2	78%	2006
Indonesia	SE Asia	Lower middle	87	3	94%	2006
Lebanon	E. Mediterranean	Upper middle	116	4	94%	1998
Mexico	Americas	Upper middle	91	3	74%	2006
Pakistan	E. Mediterranean	Low	132	4	41%	2001
Peru	Americas	Lower middle	60	2	77%	2006
Philippines	W. Pacific	Lower middle	9	1	90%	2006
Poland	European	Upper middle	43	1	61%	2006
South Africa	African	Upper middle	12	1	85%¤	2006
Thailand	SE Asia	Lower middle	57	2	12%	2006
Tunisia	E. Mediterranean	Lower middle	107	4	No data	No data
Turkey	European	Upper middle	126	4	41%	2006
Venezuela	Americas	Upper middle	64	2	95%	2006

† Quartile rank among countries included in this study, not among all GGGI-ranked countries
‡ As of July 2008
# Source: Lu Y, Hernandez P, Abegunde D and Edejer T. Medicines Expenditures. Medicines Expenditures Annex. World Medicines Situation Report. World Health Organisation, 2011
¤ Source: IMS Health
GGGI – Global Gender Gap Index

Table 3: Example calculation for expected proportion of treated consultations for diabetes

Country	Condition	Age group	Gender	DALYs	% of DALYs	Expected proportion of eligible consultations
			Females	54	58%	58%
Argentina	Diabetes mellitus	15-59	Males	39	42%	42%
			Total	93		

DALY – Disability Adjusted Life Year

Table 4: Number of doctors providing data and the number of treated consultations and drug items included in the study

	No. Doctors recording one or more consultations for:			Treated consultations			Drug items prescribed		
	Acute Respiratory Infection	Depression	Diabetes	Acute Respiratory Infection	Depression	Diabetes	Acute Respiratory Infection	Depression	Diabetes
Argentina	801	386	498	18,245	2742	5783	22,454	2803	6320
Brazil	1876	1677	1350	38,584	20,292	17,241	63,106	21,153	22,526
Colombia	342	197	258	6511	1639	2213	13,010	3798	2798
Indonesia	492	88	404	22,361	1193	6747	69,663	1238	9237
Lebanon	162	110	162	4026	1258	4782	8439	1419	7220
Mexico	1174	658	948	25,761	5507	11,518	56,916	5651	13,758
Pakistan	450	309	510	25,518	5837	19,480	49,802	6679	27,633
Peru	958	152	366	9722	738	1649	17,854	766	1941
Philippines	504	58	484	9840	1232	13,492	16,475	1283	18,207
Poland	813	685	842	19,596	6080	22,335	50,991	7135	35,940
South Africa	404	379	354	17,224	10,445	4835	39,402	11,970	6424
Thailand	518	92	474	12,701	1758	10,920	40,085	2233	18,445
Tunisia	279	37	202	2845	48	945	6196	48	1245
Turkey	635	894	809	34,731	33,553	19,794	84,558	38,551	29,020
Venezuela	604	108	307	4120	647	1353	8656	674	1754
Totals	10,012	5830	7968	251,785	92,969	143,087	547,607	105,401	202,468

CHAPTER 3.2

THE IMPACT OF PATIENT FACTORS ON USE OF ANTIFUNGAL MEDICINES IN ADULTS WITH LIFE-THREATENING ILLNESS - A CROSS-SECTIONAL STUDY IN 34 ENGLISH HOSPITALS

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ABSTRACT

Objectives

To describe the use of antifungal medicines in English hospitals in adults with life-limiting illness, and to investigate the association between socio-demographic variables and the use of high cost formulations.

Methods

Pseudonymised patient level information extracted from hospital pharmacy systems in 34 English acute general hospitals was linked to a National Health Service database of diagnoses and procedures. National Information Governance Board for England and Ethics approval was granted.

The impact of socio-demographic variables on the use of high cost formulations was assessed using stepwise logistic regression across 13 disease groups. Hospital guidelines on the use of antifungals were sourced and compared.

Results

People with haematological malignancies and unconfirmed infection formed the largest disease group (49.3%). Fungal infection was confirmed in an additional 12.6%. Guidelines focused on antifungal use in neutropenic patients. No guideline cited patient age, deprivation, gender or ethnicity as independent factors influencing treatment. Fluconazole dominated use (75% admissions). Significant associations were found between age, gender, deprivation and ethnicity and the use of high cost antifungals. However the direction of that association was not consistent across disease groups.

Conclusions

This study found widespread use of fluconazole, echoing results of earlier studies across Europe. It also found associations between patient factors and high cost antifungal use that are not easily explained by disease, co-morbidities, contra-indications, guidelines or any systematic bias against particular groups of patients. It is clear that the drivers of antifungal therapy in hospital are complex and that antifungal stewardship poses a significant challenge for pharmacy.

INTRODUCTION

The National Health Service (NHS) Constitution in England states that it will provide "a comprehensive service, available to all, irrespective of gender, race, disability, age, sexual orientation, religion or belief" [1]. Public bodies must publish information to demonstrate their compliance at least annually [2].

Access to the treatment of some life-threatening conditions has, however, been shown to vary by age and deprivation. Older people with cancer, for example, have been shown to be less likely to be given access to a clinical nurse specialist and are said to be less likely to receive standard cancer treatments such as surgery, radiotherapy and chemotherapy [3]. A survey suggested that "chronological age alone may be used as a proxy for wider biological factors, resulting in some patients [with cancer], being provided with less intense treatment than might be appropriate" [4]. More deprived patients are said to be more likely to receive late or no cancer treatment [5, 6].

Observational studies of the effect of socio-demographic factors on the treatment of life-threatening conditions can be confounded by patient choice. Not all cancer patients will wish to undergo the surgery or chemotherapy offered, for example, and will refuse treatment. Observational studies cannot take patient choice into account. Observational studies comparing the types of drug administered, on the other hand, are less likely to suffer from such confounding. This is because the decisions to provide and accept treatment have already been made.

This paper describes the use of antifungal treatments in people with life-limiting illnesses. Fungal and mould infections are a significant cause of morbidity and mortality, particularly in immunocompromised patients. Mortality rates can reach up to 60% for people with acute myelogenous leukaemia (AML) and up to 40% with severe acute pancreatitis. Mortality from fungal and mould infection is reported to be highest in people with haematopoietic stem cell transplants or bone marrow transplants, together with people being treated for solid tumours or cancers of the blood, and people with solid organ transplants [7]. Younger people survive better [8-10], and women with AML have been found to survive better than men [10].

Treatment strategies vary depending on whether treatment is empirical, pre-emptive or directed [11]. Rapid initiation of antifungal treatment is essential and has been shown to reduce mortality [8, 9, 12]. Antifungal stewardship is now deemed to be as critical as antibacterial stewardship [13].

An earlier study of the use of antifungals in 147 hospitals across Europe by the European Surveillance of Antimicrobial Consumption (ESAC) group in 2008-9 highlighted variation in the use of antifungals by age. Antifungal use increased up to the 60–75 year age group but decreased in patients >75 years, unlike antibacterials. This result was not anticipated by the authors. Older patients, they argued, have a lower level of immunity and are thus equally likely to acquire both bacterial and fungal infections. The authors found it surprising that the distribution of both antibacterial and antifungal agents did not follow similar trends across all age groups [14].

This paper describes the use of high and low cost antifungals in people with life-limiting illness in 34 hospitals in England and discusses the implications of the variations seen.

METHODS

Data sources – Pseudonymised data

Pseudonymised data were extracted from IMS Health's Hospital Treatment Insights (HTI). This is a database that combines hospital pharmacy transactions with the NHS Hospital Episode Statistics (HES) database at patient level in 34 English Hospitals for the period January 2010 to October 2012. Hospitals were included if local ethical approval had been granted and extraction of the data was able to be automated. The characteristics of these hospitals are summarized in Table 1. The hospitals are seen to be similar to other NHS hospitals in England in terms of the age and gender of those admitted, and in terms of the proportions of admissions for neoplasms, haematology and infectious disease. Table 1 also suggests that these hospitals also form a relatively homogenous group along these same dimensions [15].

The HES database contains details of all admissions to National Health Service hospitals in England and is created from patients' clinical records. Following a patient's discharge from hospital, the patient's records are examined by highly trained coders based at each acute hospital. These coders convert the diagnoses and procedures described by the treating physicians into internationally recognized classifications, for example the International Classification of Diseases [16].

Drugs dispensed by a hospital pharmacy are either issued directly to the patient or to the ward where the drug will be used ("ward stock"). Ward stock is not issued together with any patient details and so cannot be linked to the patient's records in the HES database. Discussions with pharmacists indicate that both high and low cost antifungal drugs are kept as ward stock, particularly on haematology wards. It is not likely, however, that use of ward stock will have varied by any of the socio-demographic variables of interest. It is unlikely for example that age makes the use of ward stock more or less likely. Systematic error thus seems unlikely.

Moreover, the extent of ward stock use, and thus the impact on the results of this study, can be estimated by comparing the total volumes dispensed with the total volume that is able to be linked to patients. Analysis across the range of molecules included in this study showed that the median percentage able to be linked to a patient was 88%, with fluconazole being the lowest at 60%. This study thus also reflects the use of the majority of antifungal use.

Deidentification is carried out by the Health and Social Care Information Centre before release of the data to IMS Health. The database is approved by the National Information Governance Board and by the National Research Ethics Service (NRES) Committee South West - Central Bristol Research and Ethics Committee. Approval for the collection of data on an ongoing basis is also granted by each hospital involved.

Data relate to January 2010 to October 2012. Not all hospitals were able to provide data for all months. Data were available for 89% of months across all hospitals and analysis was restricted to those months where data were available.

Table 1: Characteristics of hospitals (n=34)

		% of all admissions in England 2011-12					
	% episodes	**% male**	**% female**	**% >60 years old**	**% Neoplasms**	**% Clinical Haematology**	**% Infectious Disease**
Sample Hospitals	21%	20%	20%	22%	20%	19%	21%
All other hospital providers in England	79%	80%	80%	78%	80%	81%	79%

	Admissions 2011-2012				
	Episodes (Mean, IQR)†	**% male (Mean, IQR) †**	**% >60 years old (Mean, IQR) †**	**% Neoplasm (Mean, IQR) †**	**% Clinical Haematology (Mean, IQR) †**
Sample Hospitals	210,000 (50,000)	44% (3%)	47% (8%)	9% (5%)	2 % (3%)

† Mean and Inter Quartile Range (IQR) rounded to prevent identification of hospitals in sample
Source: Author analysis of Provider level analysis for HES admitted patient care 2010-11 and 2011-12. The Health and Social Care Information Centre.

Data sources – guidelines

Regulatory constraints prevent the identification of individual hospitals within the database and so guidelines specific to the hospitals included in this study could not be sourced. Some NHS hospitals publish their management guidelines for antifungal prophylaxis and treatment, however. 13 hospital guidelines were found and analysed, with some hospitals publishing more than one, these relating to different patient populations [17-30]. These guidelines were also compared to the guidelines of the European Conference on Infections in Leukaemia published in 2009 [31].

Participants and unit of analysis

Only records of adults were included in the study. Age is banded into groups prior to receipt of the data by IMS Health in order to help preserve patient confidentiality. This study included only those aged over 22 years of age.

The unit of analysis used in this study was the period during which the patient was in hospital ("admission"). In England, the period of time under the care of a particular consultant in a hospital is known as an "episode". If care is transferred from one consultant to another within the same hospital, then a new episode starts, and the combination of these episodes is known as a "spell". If the patient is later transferred to another hospital, but the difference between the end of care in one hospital and the beginning of care in another is shown as less than two days in the Hospital Episode Statistics database, then the period of care across the two hospitals is known as a "super-spell". In this study the "admission" is the same as the "super-spell".

If a patient was found to have been admitted more than once in the study period, then each of those admissions would be entered separately into the study. Drugs were linked to an admission if the date of dispensing of the drug to that patient fell on or between the start and end date of the admission.

Disease – classification and exclusions

Records showing anti-fungal use were grouped according to one of 14 disease groups (Figure 1). Group 14 ("Other") was excluded from the study, this consisting of a heterogeneous group of different indications, the vast majority of which were not thought to be life-threatening.

People were assigned to groups in a sequential fashion. For example people assigned to the first group (invasive aspergillosis) could not appear in any other group. The number of patients with a record of HIV/AIDS was very small, and all of these were assigned to other groups earlier in the classification sequence.

Records were assigned to the solid organ transplant group if there was a record of a solid organ transplant at any point from April 2005 (the earliest date for which a date of transplant was available). This is because fungal infections associated with transplants are reported up to more than five years after the actual transplant date [10]. All other records were assigned to a particular disease group only if there was a record of anti-fungal use and of that disease within that admission.

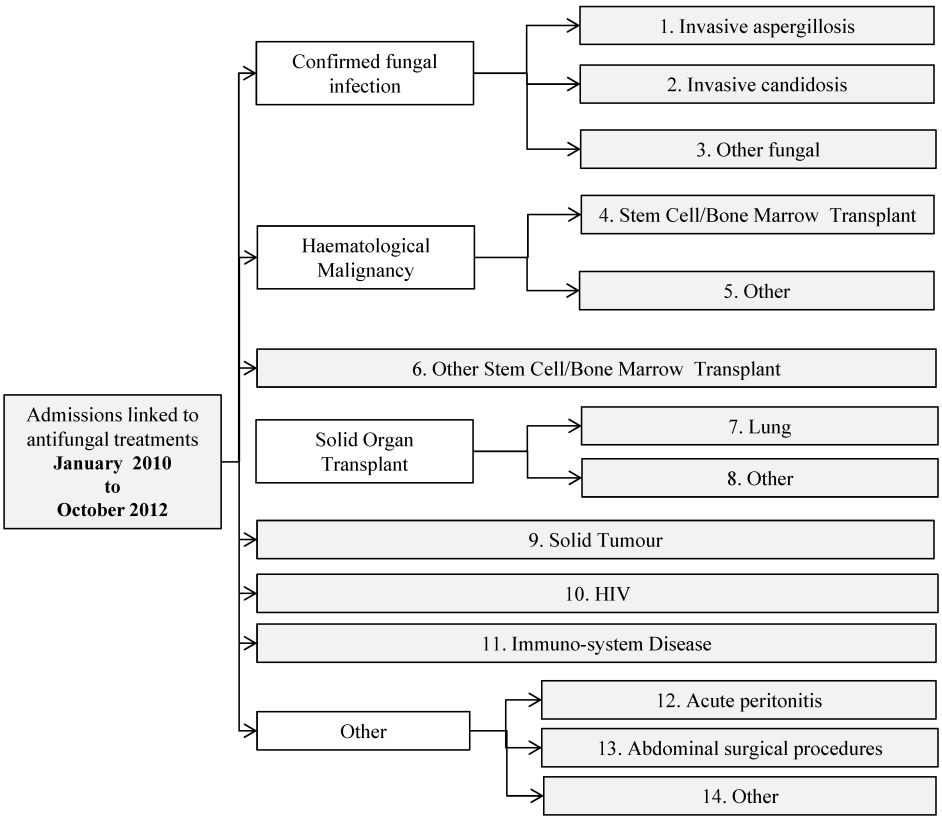

Figure 1: *Classification of diseases*

Diseases were categorized according to the likelihood of the patient receiving antifungal therapy as prophylaxis, treatment or both. Hospital guidelines indicate that antifungal prophylaxis should always be given to those at high risk of fungal infection, notably those undergoing stem cell transplant, those undergoing treatment for acute myeloid leukaemia, aplastic anaemia, myelodysplastic syndrome or acute lymphoblastic leukaemia [17-30]. A survey of lung transplant centres across Europe and the USA also revealed that antifungal prophylaxis is invariably given, sometimes in combination [32]. In addition it is almost certain that those with a confirmed diagnosis of fungal infection will have received treatment. Thus in terms of this study, those with confirmed aspergillosis, candidosis or other fungal infections will almost certainly have received treatment (in addition to prophylaxis potentially) and those undergoing stem cell transplants or lung transplants will almost certainly have received prophylaxis (in addition to treatment if fungal infection was suspected). Other disease groups cannot be grouped in this way.

Drugs administered – classifications and exclusions

The definition of high cost antifungals is provided by the NHS [33]. It includes voriconazole, liposomal amphotericin B, anidulafungin, caspofungin, and posaconazole. In addition micafungin was included by the NHS in Band 1 [high cost] from 2010/11.

Low cost anti-fungals are defined as conventional amphotericin B, fluconazole, itraconazole and flucytosine and micafungin prior to 2010/11. Fluctyosine was excluded from the study as it is rarely used, and then only in combination with other low cost antifungals.

Quantitative variables and statistical analysis

The dependent variable was the presence or absence of use of a high cost antifungal. The effect of each socio-demographic variable (age, gender, ethnicity or deprivation) on the dependent variable was investigated using binomial stepwise logistic regression. Age was grouped into bands, the Index of Multiple Deprivation (IMD) into deciles. IMD is an index of multiple deprivation experienced by people living in an area. It attempts to measure deprivation along several distinct dimensions – Income, Employment, Health, Education, Housing and Services, Environment and Crime, the index being a composite score derived from these [34]. Age and IMD were treated as ordinal variables within the logistic regression, gender and ethnicity as cardinal variables.

The logistic regression was carried out using the statistical package R version 2.14.0 (2011-10-31).

RESULTS

Table 2 shows that, by and large, the available NHS guidelines focus on treatment with antifungals in the neutropenic patient. In most cases, the guidelines recommend high cost treatments for both prophylaxis and treatment. A guideline also points out that liposomal amphotericin B should be avoided in people with renal impairment, voriconazole in people with liver impairment, that caspofungin requires dosage adjustment in people with liver impairment and levels of itraconazole should be monitored weekly [30]. It should be noted that none of the guidelines suggest that treatment should differ according to age, gender or deprivation.

Table 3 shows the characteristics of patients entered into the study. Both liver and renal impairment were notably higher in people with acute peritonitis or undergoing solid organ transplants (excluding lung), or major abdominal surgery. The definition of renal impairment is restricted to renal failure, as other degrees of impairment are not defined in the HES database. The recorded rate of renal impairment may therefore underestimate the actual number of people with sufficient renal impairment to affect choice of treatment.

Table 4 shows that fungal infection was confirmed in 12.6% of the admissions included in this study, the predominant pathogen being candida. 49% of the admissions related to people with haematological malignancy, with a further 33% relating to people with solid tumours. Fluconazole and itraconazole dominate usage, with high cost antifungals being more commonly used in confirmed aspergillosis and in people with lung transplant and

Table 2: Descriptive analysis of guidelines on the use of antifungals in life-limiting disease [17-30]

	Number of guidelines	Antifungal agents mentioned	% High cost#
Confirmed infection			
Aspergillosis	9	Liposomal amphotericin B (7), Voriconazole (9), Posaconazole (1), Caspofungin (1)	100%
Candidosis - Haematology	4	Liposomal amphotericin B (2), Caspofungin (3), Micafungin (1), Fluconazole (1)†	71%
Candidosis - Non Haematology	2	Liposomal amphotericin B (2), Caspofungin (1), Micafungin (1), Fluconazole (1)†	60%
Empiric treatment			
1st line - Haematology	8+	Liposomal amphotericin B (4), Voriconazole (3), Amphotericin B lipid complex (1)	88%
2nd line - Haematology		Caspofungin (4), Voriconazole (2), Liposomal amphotericin B (1), Micafungin (1)	88%
3rd line - Haematology		Liposomal amphotericin B (1)	
Intensive care	1	Liposomal amphotericin B (1), Micafungin (1), Fluconazole (1)	
Prophylaxis			
Haematology	11	Posaconazole (7), Itraconazole (4), Liposomal amphotericin B (4), Voriconazole (2), Fluconazole (1)	72%

† In one guideline use of fluconazole is an additional option if the organism is found to be fluconazole sensitive and neutrophils are increasing.
# Assumes micafungin is not a high cost drug although it was regarded by the NHS as a high cost drug in the first half of the study period
+ Total number of guidelines describing empiric treatment in Haematology

Table 3: Baseline characteristics

Disease	Patients (Number)	Admissions (Number)	% Male	% British (White)	% >68 years old	% least deprived	% most deprived	% Liver disease †	% Liver disease ¥	% Renal impairment#
1. Aspergillosis	457	845	56%	88%	36%	18%	28%	*	*	8%
2. Candidosis	2,577	2,936	52%	87%	57*	17%	24%	1%	2%	16%
3. Other confirmed fungal infection	13	19	77%	54%	*	*	*	0%	0%	*
4. Stem cell/Bone Marrow Transplant in Haematological Malignancy	433	440	65%	90%	9%	17%	18%	0%	0%	5%
5. Haematological Malignancy	5,326	14,361	59%	84%	48%	25%	17%	1%	1%	5%
6. Stem cell/Bone Marrow Transplant (no record of haematological malignancy)	26	29	58%	73%	0%	*	27%	0%	0%	0%
7. Lung Transplant	96	294	55%	96%	*	15%	23%	*	*	15%
8. Other solid organ transplant	159	255	55%	89%	*	18%	27%	11%	15%	34%
9. Solid Tumour	6,672	9,920	46%	89%	42%	18%	25%	*	1%	8%
11. Immuno-system disease	108	126	47%	74%	34%	11%	28%	*	*	16%
12. Acute peritonitis	294	331	47%	86%	33%	17%	30%	5%	9%	24%
13. Abdominal surgery	450	464	53%	85%	30%	13%	35%	5%	12%	26%
Total	16,611	30,020								

Asterisk (*): Small numbers are suppressed. Some patients can appear in more than one disease category if they were admitted more than once

† Defined as a record of Hepatic failure, not elsewhere classified (ICD10 K72)

¥ Defined as a record of Hepatic failure, not elsewhere classified (ICD10 K72), Toxic liver disease (K71), Chronic hepatitis, not elsewhere classified (K73), Fibrosis or cirrhosis of liver (K74)

Defined as Acute renal failure (N17), Chronic renal failure (N18), Unspecified renal failure (N19)

Table 4: Antifungal use as a proportion of admissions (n=30,020)

Disease	Amphotericin B	Anidulafungin	Caspofungin	Fluconazole	Itraconazole	Liposomal amphotericin B	Micafungin	Posaconazole	Voriconazole
1. Aspergillosis	2%	*	10%	6%	37%	22%	5%	7%	33%
2. Candidosis	0%	0%	8%	89%	1%	4%	1%	*	2%
3. Other confirmed fungal infection	*	*	*	*	0%	89%		*	*
4. Stem cell/Bone Marrow Transplant in Haematological Malignancy			15%	56%	33%	11%		4%	6%
5. Haematological Malignancy	0%	*	5%	71%	17%	7%	*	3%	5%
6. Stem cell/Bone Marrow Transplant (no record of haematological malignancy)			*	*	55%	*	*	*	7%
7. Lung Transplant	11%		10%	41%	28%	10%	7%	4%	16%
8. Other solid organ transplant		*	7%	84%	*	*	4%	*	7%
9. Solid Tumour	0%	0%	2%	97%	1%	1%	0%	*	0%
11. Immuno-system disease	*		*	82%	8%	*		*	*
12. Acute peritonitis		*	18%	80%	*	5%	3%		*
13. Abdominal surgery		*	11%	88%	*	2%	*		*
Total	0%	0%	4%	75%	10%	5%	0%	2%	4%

Asterisk (*): Small numbers are suppressed.

haematological malignancies (Table 2). Prophylactic use could not be distinguished from treatment in the pharmacy record.

The results of the logistic regression for the patient factors are shown in Table 5. These results are based on a total of 29,973 admissions, 237 having been excluded from the logistic regression due to unknown age and/or deprivation. Certain disease groups also contained too few patients on which to conduct a logistic regression. The remaining diseases are categorised according to the likelihood of prophylaxis or treatment having been given. Overall increasing age and ethnicity (black) appeared to be negatively associated with use of a high cost antifungal. Analysis within disease group, however, shows a lack of consistency. In 3 disease groups increasing age is negatively associated with use of a high cost antifungal but in two, confirmed aspergillosis and solid tumours, increasing age is positively associated with use of a high cost antifungal. At a disease level the effect of deprivation also appears to be significant, but again the direction of that association is not consistent.

DISCUSSION

NHS guidelines for the use of antifungal therapy in the neutropenic patient recommend the use of high cost antifungals in the majority of cases. This recommendation reflects European guidelines. The ELIC-3 guidelines "strongly recommend" the use of liposomal amphotericin B and caspofungin and "generally recommend" the use of other formulations of amphotericin, micafungin, voriconazole and itraconazole in people with leukaemia. Fluconazole is not recommended in either the NHS or European guidelines. Indeed in the ELIC-3 guidelines fluconazole is described only as an option, it being categorized as having either insufficient evidence for efficacy or with efficacy that does not outweigh possible adverse consequences [31].

It is surprising therefore that in this study fluconazole is found to be the most widely used antifungal, even in those with haematological malignancies, the largest group in the study. Fluconazole was, however, also found to be the most commonly used antifungal across the 147 hospitals in the ESAC study, and in addition, fluconazole constituted 58% of antifungal use within a study carried out in a tertiary centre in Spain [35]. In the ESAC study the authors commented that "the use of empiric fluconazole in intensive-care units in adults with risk factors for invasive candidiasis is widely practised despite the fact that it is not clearly proven to improve outcome compared with placebo" [14]. In the review of use of antifungals in the tertiary centre in Spain the authors found that the most common reason for inappropriate use of fluconazole was its prescription for mild oral or vaginal infections that could have been treated with topical antifungal agents. Both the ESAC authors, and indeed the ELIC-3 guidelines, also indicate that widespread use of fluconazole could lead to a rise in the prevalence of resistant fungi [14, 31]. For all these reasons, therefore, the apparent high use of fluconazole in this study is worthy of further investigation.

This study found a negative association between increasing age and the use of a high cost antifungal overall. None of the NHS guidelines however make any reference to age being a factor in treatment choice, and the direction of the association between age and use of an antifungal

Table 5: Results of logistic regression for patient factors

	Age (Older)	Gender (Male)	Deprivation (More)	Ethnicity
Overall				
All diseases†	P<0.001 OR 0.87 (0.86-0.88)			Black: p=0.00075 OR 0.61 (0.46-0.81)
Disease where guidelines indicate treatment with high cost drug on most occasions				
1. Aspergillosis	p=0.023 OR 1.06 (1.01-1.11)			
2. Candidosis	p<0.0005 OR 0.85 (0.83-0.88)		p<0.0005 OR 0.9 (0.87-0.94)	
Disease where guidelines indicate prophylaxis on most occasions				
4. Stem cell/Bone Marrow Transplant in Haematological Malignancy	p<0.0005 OR 0.82 (0.74-0.89)		p=0.00312 OR 1.13 (1.04-1.23)	
7. Lung Transplant		p<0.0002 OR 0.38 (0.23-0.64)	p=0.026 OR 0.9 (0.82-0.99)	
Disease where guidelines indicate prophylaxis depends on the risk factors present on presentation				
5. Haematological Malignancy	p<0.0005 OR 0.82 (0.81-0.83)			Black: p=0.005 OR 0.62 (0.44-0.86); Mixed: p=0.005 OR 2.44 (1.29-4.52)
8. Other solid organ transplant				
9. Solid Tumour	p=0.02 OR 1.06 (1.01-1.11)	p<0.0005 OR 1.99 (1.56-2.55)		
11. Immuno-system disease			p=0.04 OR 0.8 (0.65-0.98)	
12. Acute peritonitis				
13. Abdominal surgery				

† Disease groups were also included in the model. These results therefore indicate the association between patient factors and the use of a high cost antifungal independent of disease group
OR – Odds Ratio

was not consistent across disease groups. It seems unlikely therefore that there is any systematic bias against the elderly in the choice of treatment but, as described below, it is interesting to note that there would appear to be no simple explanation for the results seen in this study.

As noted earlier, the ESAC study found that patients over the age of 75 were prescribed relatively less antifungals in hospital than expected, and that fluconazole is sometimes used without there being strong evidence of efficacy [14]. If this pattern of use were repeated in English hospitals, then it could explain the negative association between increasing age and use of a high cost antifungal found here. Wider use of a fluconazole in younger patients would constrain antifungal choice in the event that empiric treatment were needed. Itraconazole for example, would not be an option. More high cost antifungals would therefore be needed to treat younger patients than old. However fluconazole prophylaxis is highly unlikely in people with haematological malignancy [35]. And yet it is precisely in this group that we find a negative association between age and use of a high cost antifungal. Fluconazole prophylaxis cannot therefore explain all of the results seen here.

Whilst empiric or prophylactic use of high cost antifungal treatments is common, microbiological confirmation of an azole-sensitive fungal infection should drive a switch of therapy to fluconazole or itraconazole, both low cost drugs [35]. As noted above, wider use of such drugs in the elderly would lead to the negative association between age and the use of high cost drugs seen in this study. Such a pattern of use would, however, require that microbiological confirmation of infection was more likely in the elderly. Moreover, microbiological confirmation of the infection would also have led to such patients being categorized in the confirmed infection groups, and not in any other group. As such, microbiological confirmation cannot be said to explain all of the results seen in this study. Having said that, it should be noted that microbiological confirmation of infections may be under-recorded in the HES database.

As noted earlier, colonization by candida species was the most common cause of inappropriate use of fluconazole in the study of antifungal use in Spain [35]. Use of fluconazole in leukaemic patients with gastrointestinal colonization is common, being recorded to be as high as high as 35% or more [31]. Potentially rates of suspected candida colonization may be higher in the elderly than in the young, or may have been found to be so in this study. However if this is a driver of the pattern of use seen in this study then some have argued that such use may still be inappropriate.

Contra-indications could also have played a part in the choice of therapy and thus in the nature of the relationship between patient factors and the use of high cost antifungals. Liposomal amphotericin B and voriconazole, two key high cost antifungals, are contraindicated in people with renal or liver impairment respectively. Renal impairment and chronic liver disease are more common in the elderly [36-37]. The choice of therapies available in the elderly is thus more constrained in the elderly than in the young. Co-morbidities may thus lead to a preference for lower cost antifungals in the elderly. A comparison between the patients with confirmed aspergillosis and confirmed candidosis in this study may indicate just such an effect. The rate of recorded renal impairment in

those with confirmed aspergillosis is almost half that in those with confirmed candidosis, whilst the rate of use of high cost antifungal is relatively higher in the elderly in those with aspergillosis than in those with confirmed candidosis. However not all high cost antifungals are contraindicated in people with liver or renal impairment, and liver disease is hardly recorded in the patients with confirmed aspergillosis in this study. Moreover the highest rates of renal and liver impairment recorded are in those with acute peritonitis or in those who are undergoing solid organ transplants or abdominal surgery. In none of these groups is any significant difference found between the use of high cost drugs and age.

This study has a number of limitations. To preserve patient confidentiality the identity of the hospital is concealed prior to the data being released to IMS. Differences in protocols and/or fungal resistance patterns could not thus be taken into account although analysis of available hospital guidelines indicates a degree of consistency. Also although an attempt was made to categorise disease groups according to the likelihood of use of prophylaxis and/or treatment this study was unable to distinguish between use of the drug as prophylaxis or treatment.

This study found widespread use of fluconazole, echoing results of earlier studies across Europe. It also found associations between patient factors and high cost antifungal use that are not easily explained by disease, co-morbidities, contra-indications, guidelines or any systematic bias against particular groups of patients. It is clear from this that the drivers of antifungal therapy in hospital are complex and that antifungal stewardship poses a significant challenge for pharmacy.

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CHAPTER 3.3

PRESCRIBING OF ANTIPSYCHOTICS IN PEOPLE WITH DEMENTIA IN ACUTE GENERAL HOSPITALS IN ENGLAND: 2010-2012

European Geriatric Medicine, 2014 (Accepted)

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ABSTRACT

Purpose

Antipsychotics are believed to be over-used in the control of the behavioural and psychological symptoms of dementia. Hospitals are encouraged to audit antipsychotic use in people with dementia.

The objectives of this study are to describe antipsychotic use in inpatients with dementia between 2010 and 2012 and to understand the impact of clinical and socio-demographic factors on their use.

Design

Retrospective and longitudinal analysis of antipsychotics dispensed to people with dementia in 34 English hospitals between January 2010 and October 2012. The unit of analysis was the period during which an inpatient was under the continuous care of one or more hospitals.

Results

16.6% (10,440/63,079) of inpatients with dementia received an antipsychotic in 13.9% of periods of care (13,643/97,902). Antipsychotic use was higher in inpatients with dementia and schizophrenia (57%) and in those inpatients with dementia and the symptoms and signs involving emotional state (38.2%). Antipsychotic use decreased between 2010 and 2012 (15.9% versus 12.1%, $p<0.001$). In people with dementia without schizophrenia, the absence of cerebrovascular or ischaemic heart disease (OR 1.16, 1.12-1.21)), the presence of signs or symptoms of emotional state (OR 3.71 (3.29-4.19)), increasing deprivation (OR 1.02 (1.01-1.03)) and male gender (OR 1.10 (1.06-1.15)) were significantly associated with increased antipsychotic use ($p<0.001$ in all cases). Increasing age (OR 0.88 (0.87-0.89)) was significantly associated with decreased antipsychotic use ($p<0.001$).

Conclusion

Antipsychotic use in inpatients with dementia is declining but still more than one in eight periods of care are associated with use of an antipsychotic.

INTRODUCTION

Dementia is often first diagnosed in hospital [1]. Pneumonia, eating disorders, urinary tract infections, fractured neck of femur and Parkinson's disease are all more common co-morbid disorders in patients admitted with dementia [2]. 25% of hospital beds are taken by people with dementia [1] and lengths of stay in hospital are longer, relative to those with the same conditions but without dementia [3]. In England 10% of people with dementia stay in hospital for more than 50 days [3].

More than 90% of people with dementia experience the behavioural and psychological symptoms associated with dementia (BPSD). BPSD is a significant contributor to the direct and indirect costs of caring for patients with dementia, even after the severity of cognitive disorder and other co-morbidities have been taken into account [4]. Antipsychotics confer benefits in the treatment of some symptoms of BPSD but are associated with side-effects including sedation, parkinsonism, gait disturbance, dehydration, falls, chest infections, accelerated cognitive decline, stroke and death [5]. The risk of death is elevated for at least 30 days post administration of the antipsychotic in particular populations, notably those of older age, male gender, more severe dementia and greater functional impairment [4]. Antipsychotic drugs may therefore help reduce behavioural and psychological symptoms, but this may be at the expense of quality of life [6].

Alternatives to antipsychotics for the treatment of BPSD include non-drug therapies (although the benefits may take time to appear), as well as the use of drugs to alleviate any underlying cause. Better pain management for example in people with dementia can reduce aggression and hostility. More research is, however, needed before antidepressants and anticonvulsants can be recommended in people with dementia [6].

Acute hospitals and the staff dealing with dementia are said not to be well prepared for the challenges that it brings [1]. Hospital staff are reported to feel that time pressure and staff shortages have a negative effect on their ability to deal with BPSD, and also on their ability to meet the needs of other patients. This is stated to lead to pressure on doctors to prescribe sedation, including antipsychotics, especially at night and in locations with a lower staff to patient ratio [7].

Whilst the best way to deliver care to people with dementia in hospital is still far from clear [7], one recommendation of the national audit in England was that hospitals put in place a process that separately audits prescribing of antipsychotics to people with dementia [3]. This paper describes changes in the prescribing of antipsychotics to people with dementia in acute general hospitals in England between 2010-2012.

MATERIALS AND METHODS

Objectives

The objectives were to describe change in the prescribing of antipsychotics in people with dementia treated as inpatients in England in 34 acute general hospitals between January 2010 and October 2012 and to understand the impact of clinical and socio-demographic factors on such use.

Data sources

Pseudonymised data were extracted from IMS Health's Hospital Treatment Insights database. This is a new database that combines hospital pharmacy transactions with information on diagnoses and procedures held within the Hospital Episode Statistics (HES) database. The HES database contains details of all admissions to National Health Service hospitals in England and is created from patients' clinical records. Following a patient's discharge from hospital, the patient's records are examined by highly trained coders based at each acute hospital. These coders convert the diagnoses and procedures described by the treating physicians into internationally recognized classifications, for example the International Classification of Diseases [8].

Drugs dispensed by a hospital pharmacy are either issued directly to the patient or to the ward where the drug will be used ("ward stock"). Ward stock is not issued together with any patient details and so cannot be linked to the patient's records in the HES database. Antipsychotics are issued both directly to patients and as ward stock. A survey of 10 Trusts supplying data to IMS carried out in October 2013 indicated, however, that the database would capture almost all hospital dispensing of atypical antipsychotics to people with dementia, but would miss most PRN (as required) use of haloperidol, should clinicians decide to use it outside of its license in the treatment of dementia-related behavioural disturbances [9].

Deidentification of the patient records is carried out by the Health and Social Care Information Centre before release of the data to IMS Health. The Health and Social Care Information Centre is the body established by the government in England to provide information, data and information technology guidance and services to the health and social care services. The database itself has received approval from the National Information Governance Board for England, is approved by the National Research Ethics Service Committee South West - Central Bristol Research and Ethics Committee and by the responsible authorities in each of the 34 acute general hospitals that provided data. The protocol for this study was also approved by the IMS Independent Scientific and Ethics Committee.

Data are grouped into age bands before release of the data to IMS by the Health and Social Care Information Centre. For example the band "58-63 years" includes all those patients between the age of 58 and 63.

The deidentified data are stored at IMS in an ISO27001 approved secure environment and within a stand-alone network to which access is strictly controlled and audited. Data were analysed using SQL Server 2008 Management Studio.

Data extracted relate to the period January 2010-October 2012. Not all Trusts were able to provide pharmacy data for all months. Data were available for 89% of months across all Trusts, and analysis restricted to data from those months only.

Participants

Adult patients aged over 58 years with a diagnosis of dementia recorded in their clinical record by their treating physician between January 2010 and October 2012 were included. Of these inpatients, those that could not be linked to any drug (not just antipsychotics) during their inpatient stay were excluded. 74% of those so excluded had a length of stay that

was less than or the same as one night. These patients did not differ from those remaining in terms of age, gender or Index of Multiple Deprivation decile. The Index of Multiple Deprivation (IMD) is an index of deprivation as experienced by people living in a defined area. It measures deprivation along several dimensions – Income, Employment, Health, Education, Housing and Services, Environment and Crime, the index being a composite score derived from these [10].

Unit of analysis

The unit of analysis used in this study was the period during which a patient was under continuous hospital care ("period of hospital care"). In England, the period of time under the care of a particular consultant in a hospital is known as an "episode". If care is transferred from one consultant to another within the same hospital, then a new episode starts, and the combination of these episodes is known as a "spell". If the patient is later transferred to another hospital, but the difference between the end of care in one hospital and the beginning of care in another is shown as less than two days in HES, then the period of care across the two hospitals is known as a "super-spell". The term "period of hospital care" as used in this study is thus the same as the "super-spell".

If a patient was linked to more than one period of hospital care during the study period, then each of those periods were entered separately into the study. Drugs were linked to a period of hospital care if the date of dispensing of the drug to that patient fell on or between the start and end date of that patient's period of hospital care.

The period of hospital care was chosen as the unit of analysis because some patients experienced different co-morbidities or symptoms at different times. However it should be noted that as some patients were linked to more than one period of care, units of analysis may not be independent of each other.

Classifications

Patients with dementia (International Classifications of Disease (ICD10: F00-F03)) were grouped according to the following diagnostic or symptomatic criteria – presence or absence of schizophrenia, schizotypal and delusional disorders (ICD10: F20-29), symptoms and signs involving emotional state (ICD10: R45) and cerebrovascular or ischaemic heart disease. Symptoms and signs involving emotional state (ICD10: R45) is a heterogeneous group, including nervousness, agitation, unhappiness, demoralisation and apathy, irritability, anger, hostility, physical violence, state of emotional shock and stress. It is nevertheless the closest diagnostic code to BPSD held within HES.

Patients were analysed by age group (using the 5 year bands into which the data are grouped, beginning with the age band 58-63 years, with those over 88 years of age forming one group), gender and IMD deciles.

Quantitative variables and statistical analysis

Trends were investigated both graphically and through statistical analysis. Graphical investigation is useful as sample numbers are very large, giving rise to the possibility that significance levels may be misleading. Graphical analysis was univariate, statistical analysis multivariate.

Significance at a univariate level was tested using the chi squared test for trend [11]. Backward stepwise logistic regression was used in the multivariate analysis to determine which, if any, of the diagnostic, symptomatic or socio-demographic variables (age, gender, ethnicity or deprivation) was predictive of use of an antipsychotic in three different groups – (1) people with schizophrenia, schizotypal and delusional disorders ("Schizophrenia"), (2) people without schizophrenia, schizotypal and delusional disorders but with a note of symptoms and signs involving emotional state ("Emotional state") and (3) people with neither schizophrenia or agitation. Age, length of stay, and the IMD decile were treated as ordinal variables, gender and the presence of particular diagnoses as cardinal variables. The logistic regression was carried out using the statistical package R version 2.14.0 (2011-10-31).

RESULTS

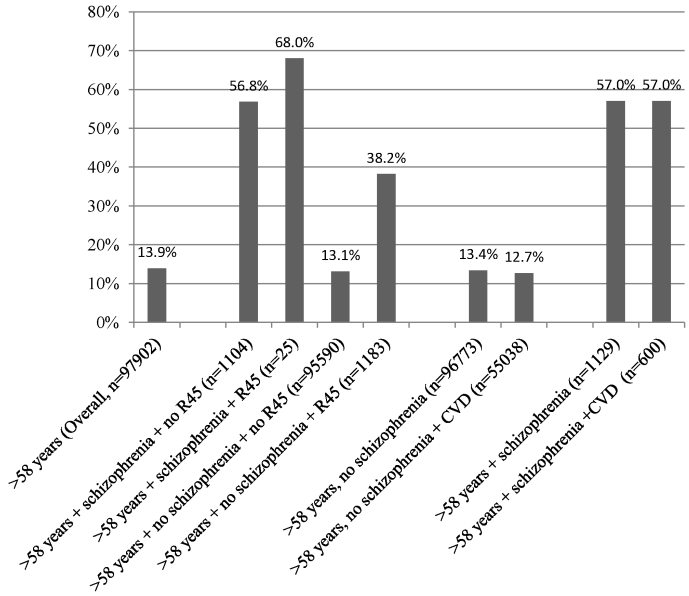
This study includes information on 63,079 inpatients with dementia, representing just under 7% of all inpatients of the same age range admitted to the 34 Trusts. Each inpatient was admitted on average 1.55 times over the study period, giving a total of 97,902 periods of hospital care. Most had no record of either schizophrenia or the signs or symptoms of emotional state (95,590/97,902). Median length of stay was 15 nights. Women were linked to 62% of the periods of hospital care, and people aged over 88 to 34%.

16.6% (10,440/63,079) of the inpatients with dementia included in this study were linked to at least one period of hospital care where an antipsychotic was dispensed. For every 100 periods of hospital care provided to this group, antipsychotics were used in 13.9%. This rate was found to be higher in both people with schizophrenia (57.0%) and in people with the signs and symptoms of emotional state (38.2%). For those with neither schizophrenia nor the signs or symptoms of emotional state, the rate was 13.1%. Co-morbid cerebrovascular or ischaemic heart disease was associated only with a slight reduction in the use of antipsychotics. These results are shown in Figure 1.

The use of antipsychotics in people with dementia decreased overall by almost a quarter across the 3 years of this study (15.9% in 2010 versus 12.1% in 2012**,** chi squared test for trend $p<0.001$). A similarly sized but non-significant decrease was seen in those inpatients with dementia and a concurrent record of signs and symptoms of emotional state (42.7% in 2010 versus 34.7% in 2012, chi-squared test for trend $p>0.01$) (Figure 2).

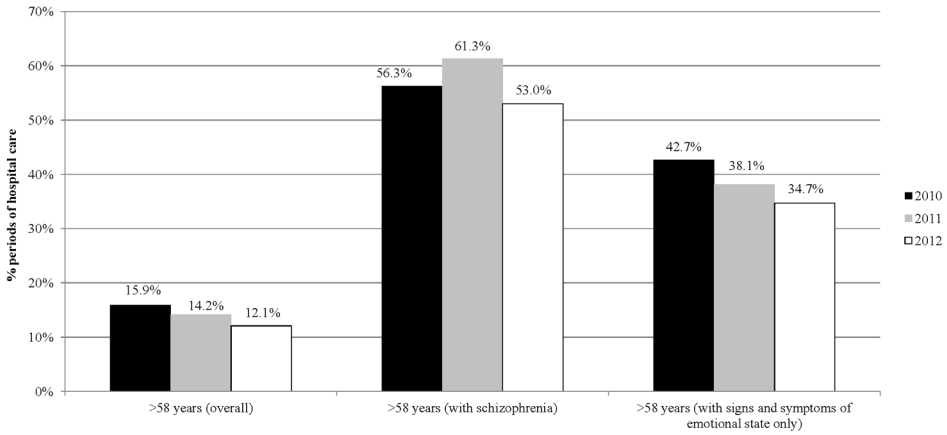
Variation by age is shown in Figure 3. Univariate analysis indicated that the effect of age and deprivation on the use of antipsychotics was significant overall (chi squared test for trend, $p<0.001$) but not in those inpatients with a note of both schizophrenia and dementia.

Stepwise logistic regression revealed that in inpatients with both dementia and schizophrenia, only length of stay was significantly associated with increased use of an antipsychotic ($p<0.001$,



R45: Signs and symptoms of emotional state (ICD code R45)
CVD: Cerebrovascular or ischaemic heart disease

Figure 1: *Percentage use of antipsychotics in different patient populations (% periods of hospital care)*



Total number of periods of care	2010	2011	2012	Total
>58 years of age (overall)	26,833	38,193	32,876	97,902
>58 years of age (with schizophrenia with or without emotional state)	309	431	389	1,129
>58 years of age (with signs and symptoms of emotional state)	309	485	389	1,183

Figure 2: *Change in the percentage of periods of hospital care showing use of antipsychotics in different patient populations over time*

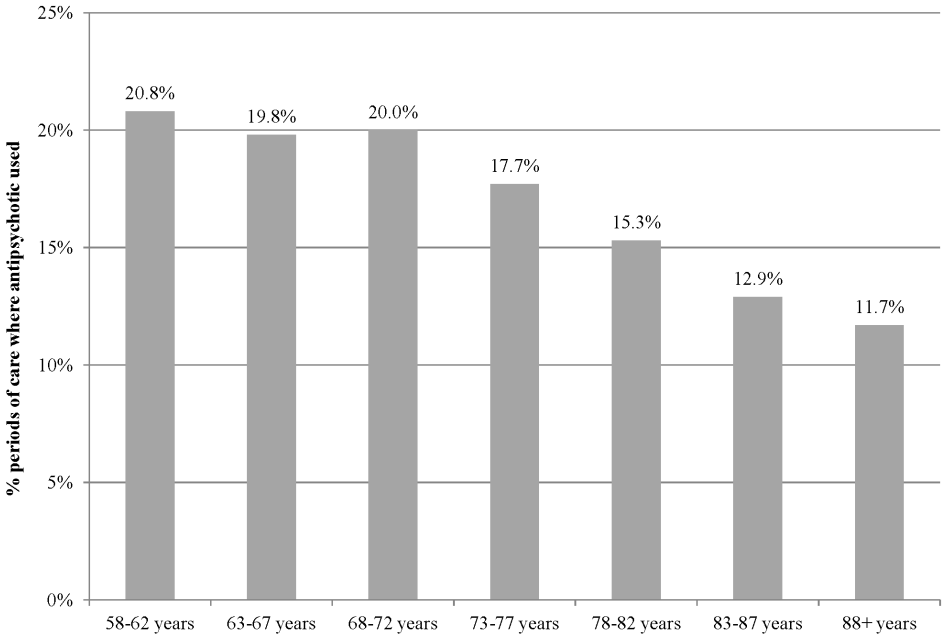


Figure 3: *Percentage of periods of care where an antipsychotic was used, broken down by age of person with dementia (n=97,902 periods of hospital care)*

Odds Ratio (OR) 1.015 (1.008-1.022). Due to the small numbers of people in this category, however, absence of a significant effect of other variables does not prove absence of any effect.

In people with dementia and no note of schizophrenia, however, all variables were associated with a change in the rate of use (Table 1). In this group, a note of the signs and symptoms of emotional state increases the likelihood of antipsychotic prescribing by more than three-fold. Older age was associated with a decrease in the rate of use whilst male gender was associated with a 10% increase.

DISCUSSION

In this study we have seen a reduction in the use of antipsychotics in people with dementia of just under a quarter between 2010 and 2012. The independent report into the treatment of people with dementia in England suggested that it ought to be possible to reduce the use of antipsychotics by two thirds within three years, or by October 2012 [12]. The recently published national audit of general hospitals in England reports a 10% drop in the percentage of admissions with a note of antipsychotic use (29% to 19%) and a 4% drop in the percentage of hospital initiated antipsychotic prescriptions (12% to 8%) [13]. This study therefore shows a similar pattern to that expected but across a much deeper sample of patients from the hospitals included.

This study also showed a decline in the use of antipsychotics with age. This is again consistent with findings in studies of people with dementia across multiple care settings – in

Table 1: Effects of diagnostic, symptomatic and socio-demographic variables on the use of antipsychotics in inpatients with no note of schizophrenia

	P value	Odds Ratio
Length of stay (Increase)	P < 0.001	1.01 (1.01-1.01)
Cerebrovascular or Ischaemic heart disease (Absence)	P < 0.001	1.16 (1.12-1.21)
Note of signs or symptoms of Emotional state (ICD10: R45)	P < 0.001	3.71 (3.29-4.19)
Age (Increase)	P < 0.001	0.88 (0.87-0.89)
Deprivation (Increase)	P < 0.001	1.02 (1.01-1.03)
Sex (Male)	P < 0.001	1.1 (1.06-1.15)

general practice [14], in home care, across countries [15] and in people under the care of specialist older people's mental health services [16].

Likewise the reduction seen in the rate of use of antipsychotics in people with a note of cerebrovascular or ischaemic heart disease is to be expected given the adverse event profile of antipsychotics in people with dementia. It is interesting to note, however, that male gender was associated with an increase in the rate of antipsychotic prescribing. As noted earlier the use of antipsychotics in men with dementia is associated with an elevated risk of death for at least 30 days post administration and perhaps for up to 2 years [4].

In this study the effect of deprivation on the use of antipsychotics was significant, although not strong. Increasing deprivation has not been associated with a change in antipsychotic use in community settings in England [14], but it may be that this study incorporates a wider range of people.

Antipsychotics were used in just over a third of all periods of hospital care of people with both dementia and the signs and symptoms of emotional state. This is almost three times as high as the rate overall. The signs and symptoms of emotional state include unhappiness and demoralisation, and although antipsychotics are sometimes used in the treatment of severe and persistent anxiety, the recommendations are clear – that the use of antipsychotics in dementia should be avoided, even for the treatment of severe and persistent anxiety [17]. As such the higher rate in people with both dementia and the signs and symptoms of emotional state is worthy of further investigation.

The rate of antipsychotic prescribing in this study is lower than that found in the national audit of 2010/11 (13.9% versus 28%) but closer to that found in the later study (2011/12) [3, 13]. Differences in the methodology may explain some of this variation. The national audit shows extensive variation in the use of antipsychotics in people with dementia across hospitals, and the audit draws on a sample of 40 patient records per site [3]. This study uses an average sample size per hospital of more than 1800 but covers 34 hospitals only. The national audit also excluded inpatient stays of less than 4 nights. If the same is done for the data used in this study, the observed rate of prescribing of antipsychotics increases from 13.9% to 15.4%. The national audit's case note review takes account of concurrent prescribing of antipsychotics in the community, which would not be reflected in the IMS database. As already noted the IMS database is unlikely

to record PRN use of haloperidol, although as discussed above, use of haloperidol is likely to be restricted in this population due to such use being outside of its license.

Weaknesses of this study include potential inaccuracy of diagnosis, incomplete recording and the difficulty of understanding the drivers of change in the rate of use of antipsychotics over time. The diagnosis of dementia is difficult, can require specialist expertise and in England at least is associated with increased out of pocket care costs on discharge as only care homes with specialist facilities will accept people with a diagnosis of dementia. Physicians in the acute general hospital may therefore be reluctant to give a diagnosis of dementia. The HES database may thus under-record the true prevalence of dementia, or include only those patients with dementia with more severe signs and symptoms. In addition the heterogeneity of the signs and symptoms of emotional states makes assessment of the appropriateness of the use of antipsychotics in this population more difficult. Moreover the apparent reduction in antipsychotic use in hospital may have a number of different causes. A reduction in the rate of in-hospital use may indicate improving practice in hospital but also reduction in community prescribing, and thus the admission of people with dementia using antipsychotics, or, alternatively, an increase in the numbers of people diagnosed with mild to moderate dementia, and thus an increase in the proportion of people with dementia with BPSD. A reduction in community prescribing and increased diagnosis of dementia are both expected outputs of recent policy initiatives but in this study it is not possible to distinguish between the effect of these on hospital use of antipsychotics and changes in hospital practice itself. In addition it should be noted that the rate of use of antipsychotics appears to vary considerably across different institutions, making it difficult to generalise these results either to particular institutions or to the rate in England overall [3,18].

In conclusion, this study confirms that in-hospital use of antipsychotics in people with dementia is declining over time, even in those with a record of the signs and symptoms of emotional state. Whilst it is difficult to generalize from this study to the UK as a whole, it remains true that in this study an antipsychotic is used to treat a person with dementia in more than one in eight episodes of hospital care.

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CHAPTER 4

GENERICS: MARKET DRIVERS

CHAPTER 4.1

THE MARKET DYNAMICS OF GENERIC MEDICINES IN THE PRIVATE SECTOR OF 19 LOW AND MIDDLE INCOME COUNTRIES BETWEEN 2001 AND 2011: A DESCRIPTIVE TIME SERIES ANALYSIS

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Kaplan WA, Wirtz VJ, Stephens P.

ABSTRACT

This observational study investigates the private sector retail pharmaceutical market of 19 low and middle income countries (LMICs) in Latin America, Asia and the Middle East/South Africa analyzing the relationships between volume market share of generic and originator medicines over a time series from 2001 to 2011.

Over 5000 individual pharmaceutical substances were divided into generic (unbranded generic plus branded generic medicines) and originator categories for each country, including the United States as a comparator. In 9 selected LMICs, the market share of those originator substances with the largest decrease over time was compared to the market share of their counterpart generic versions.

Generic medicines (branded generic plus unbranded generic) represent between 70% and 80% of market share in the private sector of these LMICs which exceeds that of most European countries. Branded generic medicine market share is higher than that of unbranded generics in all three regions and this is in contrast to the United States.

Although switching from an originator to its generic counterpart can save money, this narrative in reality is complex at the level of individual medicines. In some countries, the market behaviour of some originator medicines that showed the most temporal decrease, showed switching to their generic counterpart. In other countries such as in the Middle East/South Africa and Asia, the loss of these originators was not accompanied by any change at all in market share of the equivalent generic version. For those countries with a significant increase in generic medicines market share and/or with evidence of comprehensive "switching" to generic versions, notably in Latin America, it would be worthwhile to establish cause-effect relationships between pharmaceutical policies and uptake of generic medicines. The absence of change in the generic medicines market share in other countries suggests that, at a minimum, generic medicines have not been strongly promoted.

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INTRODUCTION

In recent years, the growth of government health programmes, coupled with major and disruptive shortfalls in financing, have forced governments to realize that the provision of low-cost, quality assured medicines will need to take on increasing importance [1, 2]. To lower total pharmaceutical expenditures, many high income countries have implemented a series of policies to promote the use of generic medicines [3]. In Europe, for example, generic medicines volume share [1] increased from 42% in 2005 to 49.0% in 2009 [4]. With respect to individual countries, increases in the market share of generic medicines have been documented in Germany, France and Sweden between 2006 and 2009 [4, 5]. In absolute terms, in 2009 generic medicines were 65% of the total market by volume in Germany, 60% in the UK, 40% in France and 30% in Spain and Italy [4].

The United States has also implemented policies to promote the use of generic medicines, most notably the Drug Price Competition and Patent Term Restoration Act, informally known as the "Hatch-Waxman Act" [6]. Between 1984 and 2005, generic medicines in the United States increased from 19% to 54% of the total pharmaceutical market volume [7] and in the last decade, of all United States prescriptions dispensed in retail pharmacies, 80% by volume were filled using generic medicines [8]. Strong support from Medicaid and private health insurances to contain costs, as well as from state laws requiring generic substitution [7], have been identified as the main factors for this increase.

Apart from these high income countries, many low and middle income countries (LMICs) have introduced policies to promote uptake of generic medicines (e.g. South Africa, Brazil, Philippines) [9]. Their impact could be substantial [10, 11] but we know far less about the effect of pro-generic medicine policies in LMICs than in high income countries [9]. Indeed, we know comparatively little about the private sector pharmaceutical market in LMICs as compared to the public sector LMIC pharmaceutical markets [12, 13, 14] and even less about the market dynamics between originator/brand name and generic versions of the same medicine.

In this observational, retrospective study, we provide data that answers the following questions: What are the trends of originator and generic medicines market share in the private sector of selected LMICs over the last 10 years? What patterns can we observe in the relationship between the market share of an originator and its generic medicine counterpart in the private sector of LMICs? We also suggest some potential drivers of these market relationships.

MATERIALS AND METHODS

Data sources

We obtained retail private sector sales data (prescription and over-the-counter (OTC)) from IMS Health (www.imshealth.com) on the aggregated volume of oral (including oral liquids) pharmaceutical products, excluding contraceptives, herbal medicines, vitamins, insulins and

[1] The data refers to the unprotected market of pharmaceuticals which includes only those products that have never been, or are no longer, protected by patents.

neurotonics for 19 LMICs and the United States from 2001 to 2011.[2] The LMICs (as defined by the World Bank [16]) are from three different geographical regions: Latin America and the Caribbean ("LAC": Argentina, Brazil, Chile, Colombia, Dominican Republic, Ecuador, Mexico, Peru, Uruguay, Venezuela); Middle East plus South Africa (MeSA) (Egypt, Jordan, Morocco, Tunisia, South Africa) and Asia (Bangladesh, Pakistan, Philippines, Thailand). The selection of the LMIC was guided by the availability of data from the retail sector in the three geographical regions. Even though this is not a representative sample of countries in each region, the countries chosen are important pharmaceutical markets in terms of their value in the respective regions. We used data from the United States as a comparator.[3] In the LMICs under review here, the data primarily reflect the private sectors that receive out-of-pocket payments although in some countries the private sector also includes the private insurance sector and governmental social security. Significantly, volume data represent either purchase or dispensing by the supply chain, rather than actual consumption by patients.

We excluded contraceptives, insulin, herbals, neurotonics and vitamins because the category includes many molecules that are not considered to be new active substances and therefore do not have an "originator" under our classification system (See next section).

The retail sales volume of oral solids and oral liquids was reported in "standard units" (SU). For oral solids one SU is one tablet or capsule. For oral liquids, one SU is 5ml. Our analysis focuses on market share expressed as percentage of retail market volume. The Defined Daily Dose (DDD) which is the standard method when studying medicines utilization was not used as converting SU into DDD for the substantial number of combination products is difficult. In interpreting the volume trends described below, it should be borne in mind that the exact same set of pharmaceutical products is not being compared. The range of products distributed in the private sector differs by country and has differed over time. What we are measuring are the various volume components of the private pharmaceutical market as a percentage of the total private pharmaceutical market volume.

Data on the private sector sales volume is country-specific and collected from various stages in the retail pharmaceutical supply chain (i.e. from pharmaceutical manufacturers and importers, wholesalers, distributors, and sub-distributors of medicines) depending on the country.

Data analysis

For each country, the database is populated with aggregated annual sales volumes coded for the following five categories of products: originator brands, licensed brands, "Other" brands, unbranded products and 'Patent Not Applicable" product categories. We regrouped

[2] The raw data is available upon request by third party researchers for non-commercial purposes at the approval of the IMS Health Global Health Research Program [15].

[3] The US market has the most well understood dynamics of the countries in our study and in 2011 it had about 34% of global pharmaceutical spending. It is the largest pharmaceutical market in the world and one of the largest of generic medicines markets. Per capita spending on pharmaceuticals (2005 dollars) in the US was 5 times that of Brazil (the largest market in the LAC) [17].

those five categories into four and renamed them ("other brands" as "branded generics" for consistency with the literature [18]):

(1) Originator products: "Originator" products are those products first authorized in a given country for marketing (normally as a patented product) on the basis of the documentation of its efficacy, safety, and quality, according to requirements at the time of authorization. Originator products that are marketed by a company under the terms of a licensing agreement with the originator are defined as "Licensed Brands". These two particular categories were combined for the present analysis and are combined and named hereafter as "originator" medicines.
(2) Unbranded generic products: Non-originator products sold under an international non-proprietary name (INN) (i.e., the generic name of the ingredient molecule(s)) rather than a brand name. That is, they are products that are off-patent without a trade name and from a single source or co-licensed.
(3) Branded generic products: Branded generics are non-originator products. They can be either novel dosage forms of off-patent products produced by a manufacturer that is not the originator of the molecule, or a molecule copy of an off-patent product with a trade name produced by a manufacturer not the originator. In other words, products sold under brand names by a company NOT the originator company and for which there is no evidence of a licensing agreement between them fall into this category.
(4) Patent N/A products: These are products whose patent status could not be, or has not been, defined under the IMS classification with any certainty and thus could not be placed into any of the other three categories. Because of this uncertainty, we did not use this category in our subsequent analysis of the market share. This introduced some limitations as discussed below.

We converted the standard unit volume of medicines for three categories (see above) into their respective percentages to obtain outcome measurements, as follows:

(i) "Total generic market share": the percentage of total annual private sector sales volume of branded generic medicines plus unbranded generic medicines divided by the total annual medicines private sector sales volume (originator plus licensed plus branded generic plus unbranded generic medicines).
Total generic market share = (unbranded + branded generic medicines)/ (unbranded + branded generic + originator + licensed medicines).
(ii) "Branded generic medicines market share": the percentage of annual private sector sales volume of branded generic medicines divided by total medicines private sector sales volume, as defined immediately above.
(iii) "Unbranded generic medicines market share": the percentage of annual private sector sales volume of unbranded generic medicines divided by total medicines private sector sales volume, as defined above.

We took as the "regional" market share the median value of the respective market shares for all countries in a given region (LAC, Asia, MeSA) of the different categories (unbranded,

branded generic, originator) in a given year. Thus, for the LAC region, the median regional branded generic market share is the median value of the branded generic market share for the 10 different LAC countries. For the metric "total generic market share" for the LAC, we calculated the median LAC market share for each individual category of generic (as described above) and summed median regional values of branded + unbranded markets.

Quantifying the volume relationships between 'originator' and 'generic' medicines

We tested whether a decrease in percent market share of an originator product and any concomitant increase in market share of the counterpart generic products (branded + unbranded generic versions) can be explained as an intentional "switch" of the same pharmaceutical substance from originator to generic. We chose those countries for which there was at least an overall 6% decrease in percentage market share of all originator products between 2001 and 2011: these countries being South Africa, Colombia, Brazil, Philippines, Peru, Ecuador, Venezuela, Mexico and Jordan. We used the United States as a comparator.

By looking at specific pharmaceutical substances per group (originator, branded generic, unbranded generic) we were able to determine if the decrease in market share of a specific originator pharmaceutical substance was accompanied by an increase in its counterpart unbranded and/or branded generic market share(s).

We used the disaggregated data on yearly volumes of a total of 5131 different pharmaceutical substances (molecules or combinations of molecules) for the 10 countries listed above for all years from 2001 to 2011. For each country, we calculated the difference in volume market share (as a % of the total volume of all pharmaceuticals for all categories (exclusive of the "Patent N/A" category)) between 2001 and 2011. For originator pharmaceutical substances, we ranked them by this so-called "delta originator" with the largest negative delta first, and selected for further analysis the top ranked 30 in this list (hereafter called the "top 30 list"). For each of these top 30 originator pharmaceutical substances, we compared its loss in market share with the change in market share (delta 2001-2011) of the exact counterpart unbranded and branded pharmaceutical substances ("delta unbranded" and "delta branded generic", respectively).

For each specific 'originator' pharmaceutical substance in the top 30 list for each country we calculated a simple diagnostic ratio: ((delta unbranded + delta branded generic)/ delta originator)) to detect whether there was a net growth, loss or no net change in market share for the generic counterparts to each of these top 30 pharmaceutical substances between 2001 and 2011. The magnitude of the diagnostic provides quantitative information about the relative magnitude of the respective change in market shares. See Table 1.

Inferences about patent protection

For Brazil and the United States, we had information on whether or not the top 30 pharmaceutical substances were under patent during the relevant time period 2001-2011. We did not have this information for the other countries. Instead, we developed some

Table 1: "Diagnostic ratios": definitions, examples and explanation

Delta (unbranded + branded generic)	Delta (Originator)	Delta (unbranded + branded generics)/delta (Originator)	Examples	Explanation of changes in market share
Positive= net gain in generics	Always negative	Positive	Ratio greater than zero but < 1 e.g., Ratio = +0.5	Generic growth half that of Originator loss (Category B)
		We divided the Delta (unbranded + branded generic) by the corresponding delta (originator) which is always a negative number and took the absolute value to yield a positive diagnostic.	Ratio =1	Generic growth matched by originator loss
			Ratio = >1, e.g., 3.5	Generic growth 3.5 times that of originator loss (Category A)
Negative =net loss in generics	Always negative	Negative We divided the Delta (unbranded + branded generic) by the corresponding delta (originator) and multiplied the fraction by minus 1 to yield a negative diagnostic.	Ratio less than zero, e.g. – 0.5	Loss of generic market share twice that of originator loss (Category C)
Zero=no generic on market at any time		Zero		Category D

inferences about the presence of patent protection by checking if the originator substances in the top 30 list for all other LMICs besides Brazil had a generic counterpart in Q4 2000. If so, this would suggest that the originator patents were either ignored or non-existent for these products over the subsequent period 2001-2011. Conversely, we looked for top 30 originator substances with no generic product marketed at the end of 2000 but for which there was a subsequent diagnostic ratio for 2001-2011 greater than 1 (i.e., subsequent rapid growth of generic market share greater than the decrease in originator market share). This would be a strong inference of rapid generic "replacement" of an originator.

Sensitivity analysis

As the retail data used for this study is based on audits from the distribution chain, it is almost inevitable that the number of outlets/entities in this chain would change over time and possibly impact the volume data. Such changes can be primarily due to inclusion of generic products from new companies, incorporation of sales of private label products that belong to pharmacy chains, or the addition of new data suppliers and new wholesalers into the audit. Reclassification of products according to official lists would not change the data sources but may possibly affect rates of generic uptake. Hence IMS routinely performs a validation of the retail sales data by comparing estimated yearly sales volumes for each product pack with the manufacturer's estimated or provided sales volumes supplied to the retail sector. For the countries under study here, the largest variation registered for the study period was for Jordan in which the manufacturer estimated total sales volume for all medicines categories over all years to be, on average, 22% percent more than the audits recorded (data not shown here). For Brazil the manufacturer estimated the actual total sales volume on average 5% higher. We chose Jordan because this apparent bias is the largest among the lower income countries and Brazil because this is the largest bias for upper middle income countries.

Although the 'bias' in this estimation probably varies between our categories, it is reasonable to assert that the manufacturers that supply data for validation are those that use the IMS data. In general this will tend to include a higher proportion of branded, larger manufacturers than unbranded. Our validation is thus more likely to be most representative of larger companies and less representative of the smaller companies. To estimate the possible impact of such bias on market share, we did a sensitivity analysis for Jordan in which we assumed that the volume of unbranded generics was actually 22% higher each year than reported. We recalculated the unbranded generic market share and computed the difference in market share with and without unbranded generic 'bias'. We did the same analysis for unbranded generics in Brazil assuming the volume was actually 5% higher each year.

RESULTS

Regional Market Share:

Total generic medicines market share

The temporal changes in total generic market, as defined above, are in Figure 1 (where n= number of countries in the region). Each point in the time series for a given region is the median value of the individual countries in that region (See also Figures 2-3, where "n" is the same as in Figure 1).

The share of the market volume of generic medicines (unbranded plus branded, excluding originator) in the LAC region increased from 66% to 78% during this 10-year period. These increases are about three times that of the Middle East plus SA (MeSA) and Asia countries studied. Although the Asian countries studied here had the highest absolute total generic market share over this time period (> 70%), they showed the smallest change over time. The United States market volume share of generic medicines shows the highest increase in comparison to the three regions studied (growth from 61% to 85%).

Branded generic medicines

The median market fraction of branded generic medicines in all regions is greater than 50% meaning that the majority of 'generic' medicines in the private sector of all 19 LMICs are branded medicines whose manufacture is not licensed by the maker of the corresponding originator product (Figure 2). This is in sharp contrast to the United States where less than 20% of the market share corresponds to this category of medicines and where this value decreased over time. Whereas the median volume share of branded generics in the MeSA and Asian countries increased during the study period, for the LAC region it slightly decreased over time but the LAC region is consistently the lowest compared to the MeSA and Asian countries.

Unbranded generic medicines

The median market fraction for unbranded generic medicines in the LAC countries studied here (although much lower than the United States in absolute terms) more than doubled from 13% to 27% 2001-2011at a rate of 1.46%/yr (Figure 3). In contrast, the volume share of unbranded generics slowly decreased in the Asian countries in the study period (from about 8% to 6%: rate of -0.27%/yr) and was very low and substantially unchanged in countries of the MeSA countries under study (3.6% to 2.9%: rate of -0.08%/yr). In contrast, the unbranded generic medicines volume in the United States over this same time period increased from 41% to 75% of the total market (at a rate of 2.90%/yr), with the highest market share and positive trend as compared to the three regions.

Changes in Private Sector Market share in individual countries

With respect to individual countries, twelve of them showed aggregate increases in percent market share of unbranded generics between 2001 and 2011 ("delta" range: 0.3% to 22.3%) (Table 2). Eight of these twelve countries were in the LAC region. Thirteen countries showed

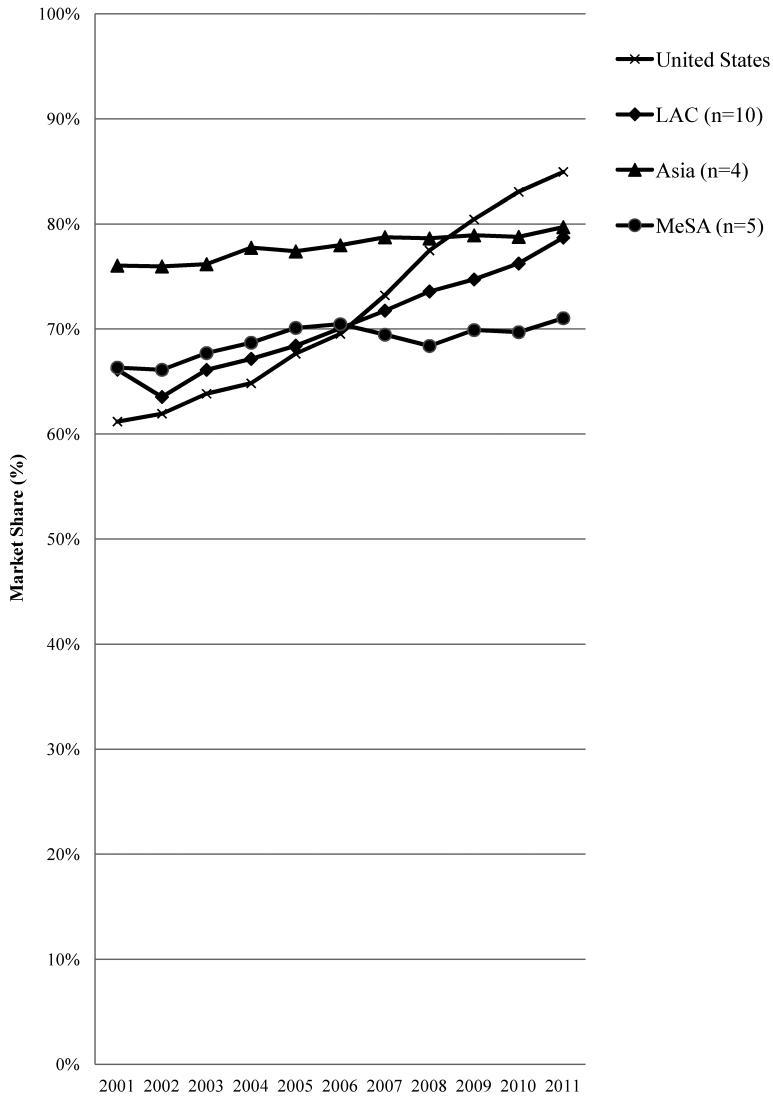

Figure 1: *Time series of "total generic market share" in 19 LMICs and the United States*

LEGEND: The trend (change in total generic market share /yr) was calculated using a simple linear regression model. Trend: United States 1.54%/yr; LAC 1.12%/yr; Middle East plus South Africa (MeSA) 0.38%/yr; Asia 0.31%/yr. A t test for regressions were all significant [p< 0.05].

aggregate increases in percent market share of branded generics ("delta" range: 2.8% to 26.7%), with three of the five countries from the Asian region (Philippines, Pakistan and Bangladesh). Six countries showed aggregate increases in both unbranded and branded generics (Mexico, Argentina, South Africa, Jordan, Morocco, Philippines). In 2011, the countries with the highest share of private sector originator medicines were Tunisia (37.2%),

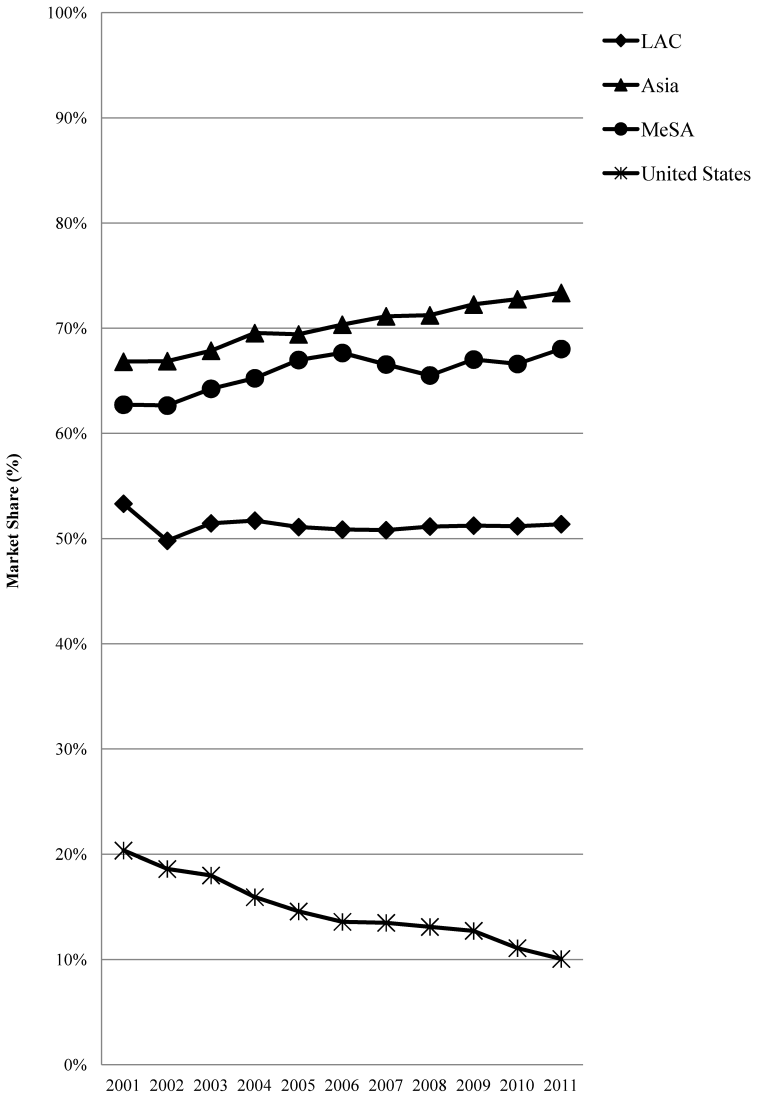

Figure 2: *Time series "branded generic" market share in 19 LMICs and the United States*

LEGEND: The trend (change in branded generic market share /yr) was calculated using a simple linear regression model.Trend: United States -1.15%/yr; LAC -0.34%/yr; Middle East plus South Africa (MeSA) 0.47%/yr; Asia 0.61%/yr. A t test for regressions were all significant [p< 0.05]. The number of countries in Figure 2 is the same as in Figure 1.

Pakistan (35.6%), Mexico (34.8%) and Morocco (31.9%). Nonetheless, the market share for the entire originator market decreased in all countries, with large decreases in certain countries in Latin America (e.g., Brazil, Mexico, Colombia, Peru, Venezuela, Ecuador, Uruguay) as well as Jordan and South Africa. These countries showed a more than 6% market share decrease in total originator market between 2001 and 2011 (Table 2).

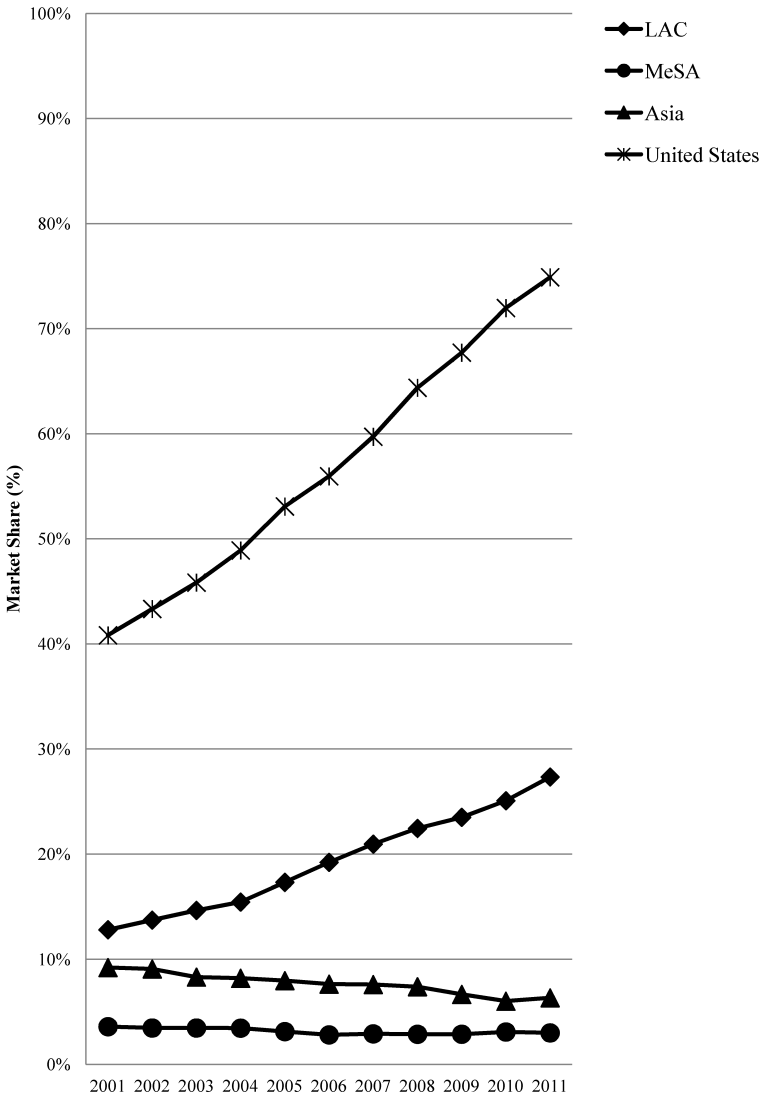

Figure 3: *Time series of "unbranded generic" market share in 19 LMICs and the United States*

LEGEND: The trend (change in branded generic market share /yr) was calculated using a simple linear regression model.Trend: United States 2.90%/yr; LAC 1.46%/yr; Middle East plus South Africa (MeSA) -0.08%/yr; Asia -0.27%/yr. A t test for regressions were all significant [p< 0.05]. The number of countries in Figure 3 is the same as in Figure 1.

Market dynamics of originator and generic versions of individual pharmaceutical substances

We calculated the 'diagnostic ratio' previously described to test whether the decrease in a given originator market share was matched by an increase in market share of its counterpart

Table 2: Market share of unbranded, "other" (branded generic), and originator products in 2001 and 2011 by country

	Unbranded generics market share % (2001)	Unbranded generics market share % (2011)	*Delta		Branded Generic share % (2001)	Branded Generic share % (2011)	*Delta		**Originator share % (2001)	**Originator share % (2011)	*Delta
Brazil	8.9	31.2	22.30%	Argentina	55.7	82.4	26.70%	Thailand	7.2	7	-0.20%
Colombia	38	57.7	19.70%	Mexico	41.5	51.2	9.70%	Argentina	29.5	29.1	-0.40%
Peru	19.6	38.6	19.00%	Philippines	61.7	70	8.30%	Pakistan	36.6	35.6	-1.00%
Venezuela	15	33	18.00%	Pakistan	53.2	60.3	7.10%	Chile	10	8.5	-1.50%
Mexico	1.2	14.1	12.90%	Bangladesh	86.6	92.2	5.60%	Dominican Republic	15.4	12.7	-2.70%
Ecuador	11.4	23.5	12.10%	South Africa	62.8	68.3	5.50%	Egypt	31.5	28.5	-3.00%
Uruguay	5.8	11.5	5.70%	Jordan	62.7	68	5.30%	Tunisia	40.9	37.2	-3.70%
Argentina	7.1	11.4	4.30%	Thailand	71.9	76.8	4.90%	Bangladesh	10.6	6.9	-3.70%
South Africa	5.5	8.9	3.40%	Morocco	60.8	65.2	4.40%	Morocco	37.5	31.9	-5.60%
Jordan	4.6	6.3	1.70%	Chile	42.5	46.8	4.30%	Uruguay	19.3	13.7	-5.60%
Morocco	1.8	2.9	1.10%	Tunisia	55.5	59.8	4.30%	Ecuador	31.5	25	-6.50%
Philippines	8.2	8.5	0.30%	Egypt	65.3	68.5	3.20%	Jordan	32.7	25.7	-7.00%
Egypt	3.1	3	-0.10%	Dominican Republic	70.4	73.2	2.80%	Venezuela	35.4	28	-7.40%
Dominican Republic	14.2	14.1	-0.10%	Uruguay	74.9	74.8	-0.10%	Philippines	30	21.5	-8.50%
Tunisia	3.6	3	-0.60%	Brazil	53.3	51.6	-1.70%	South Africa	31.7	22.8	-8.90%
Bangladesh	2.8	1	-1.80%	Ecuador	57	51.5	-5.50%	Peru	20.7	11.5	-9.20%
Chile	47.5	44.7	-2.80%	Peru	53.3	47.6	-5.70%	Colombia	23.5	10.3	-13.20%
Thailand	20.9	16.2	-4.70%	Colombia	38.6	32.0	-6.60%	Mexico	54.2	34.8	-19.40%
Pakistan	10.2	4.20	-6.00%	Venezuela	49.3	39.0	-10.30%	Brazil	37.8	17.3	-20.50%

Legend: *Delta= Difference between 2011 and 2001; **Originator market= includes licensed brands, as defined above.

generic version (branded and unbranded). In the 9 LMICs we selected for this analysis (Jordan, South Africa, Brazil, Mexico, Colombia, Peru, Venezuela, Ecuador, Uruguay), the top 30 originator pharmaceutical substances with the highest market share losses accounted for between 50% and 75% of the total loss of originator market share between 2001 and 2011.

Figure 4 shows the distribution of the diagnostic ratios (in the 4 categories) for each country's 30 originator pharmaceutical substances, including the United States. The number in each bar is the number of medicines falling into the respective category. In category A ("net generic gain"), the diagnostic ratio is 1 or more. Of the nine LMICs selected for analysis, South Africa displays the largest number of top 30 pharmaceutical substances in which the increase in generic market share of the substance was larger than the corresponding decrease in originator market share. Of all countries analyzed, the United States has the largest number of these category A pharmaceutical substances (12/30) and the largest total number of top 30 pharmaceutical substances (27/30) with a loss of originator and at least some corresponding increase in generic market share, i.e., sum of categories A and B. Brazil (23/30) and South Africa (22/30) are the LMICs with the largest number of category A and B pharmaceutical substances. Jordan was the only country of these nine LMICs which showed no generic replacement of any of the top 30 originator pharmaceutical substances over the study period (no "Category A" medicines). Indeed, for half of the top 30 originator substances on the Jordanian market between 2001 and 2011, there was also a loss of counterpart generic market share (15 "Category C" medicines).

In most countries, some of the top 30 originator substances that lost market share did not have a generic counterpart on the market at all during 2001-2011 ("Category D"). These category "D" substances are listed in Table 3. The only exception was Brazil, in which all the top 30 originator substances had a generic counterpart on the market during 2001-2011 (no "Category D" medicines) (Figure 4).

Some of the top 30 originator molecules were commonly found in several countries, e.g., glibenclamide (antidiabetic), diclofenac (anti-inflammatory), sulfamethoxazole plus trimethoprim (antibiotic), amoxicillin (antibiotic) and alprazolam (psycholeptic) were common in eight countries (for more detailed description for the common molecules see Supplementary Information). For some of these above-identified molecules, the increase in generic market share was larger than the corresponding decrease in market share of the counterpart originator indicating an originator-to-generic switch (e.g., glibenclamide in Venezuela, diclofenac in Colombia, Uruguay and South Africa, amoxicillin in Colombia).

We can make some inferences about the presence of patent protection. Most of the originator products in the top 30 list for all LMICs had a generic counterpart in Q4 2000, suggesting that originator patents were either non-existent or perhaps ignored for these products over the period 2001-2011. In Brazil, we know that all the top 30 originator products lacked patent protection during 2001-2011 (data not presented here). However, we did observe that in other countries, for several substances there was a top 30 originator with no generic product marketed at the end of 2000 but for which there was a subsequent diagnostic ratio for 2001-2011 greater than 1 (i.e., subsequent rapid growth of generic

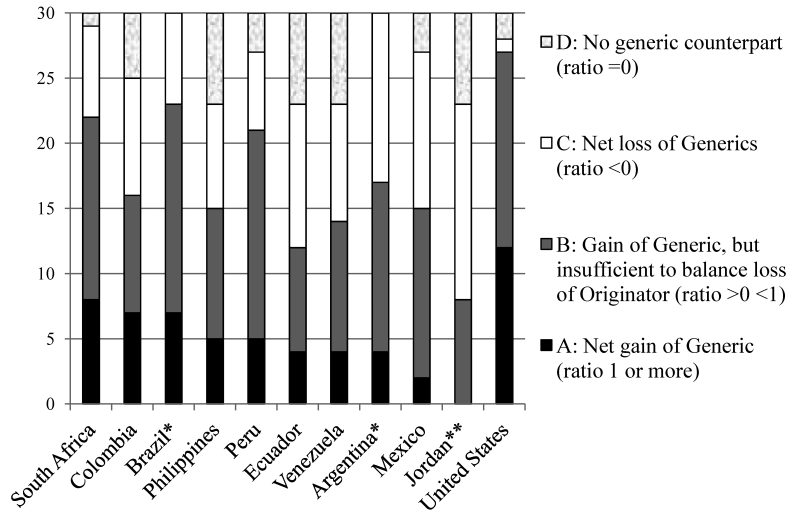

Figure 4: *The distribution of diagnostic ratios (in the 4 categories) for each country's 30 originator pharmaceutical substances. The number in each bar is the number of medicines falling into the respective category.*

*Notes: * In Brazil and Argentina all medicines had generic counterparts; ** In Jordan, no generic medicines showed a gain in market share exceeding the loss in Originator + Licensed product market share.*

market share greater than the decrease in originator market share): orlistat - Colombia; cyproheptadine - Ecuador; cefaclor and trimetazidine - Philippines; glibenclamide - Venezuela; loratadine; citalopram, meloxicam, omeprazole, simvastatin - all South Africa.

Sensitivity Analyses

For Brazil and Jordan, we assumed that, each year, the volume of unbranded generics was, respectively, 5% and 22% more than the audited volume. We calculated the potential error induced in the market share for these assumptions and for Brazil, the error is small (range: 0.28-1.1% underestimation of unbranded generic market share). For Jordan, the potential error induced is also fairly small (range: 0.71%-1.02% underestimation of unbranded generic market share).

DISCUSSION

To our knowledge, this is the first such longitudinal analysis of the private sector generic medicine market in a large number of LMICs. We wish to bring out several points.

Total generic medicines market share in some LMICs exceeds that of many European countries

In 2001 the volume market share of generic medicines (unbranded + branded) was over 65% in all three regions which means that the 19 LMICs studied generally initially (in 2001) had a higher percentage of generic medicines market share than the United States

Table 3: Pharmaceutical substances with decreasing originator market share (2001-2011) and no generic counterpart on market

PERU	COLOMBIA	ECUADOR	URUGUAY	PHILIPPINES
Acetylsalicylic acid/ chlorphenamine/ pseudoephedrine	Caffeine/ diphenhydramine/ ergotamine	Chlorphenamine/ salicylic acid	Diphenhydramine/ guaifenesin	Betamethasone/ dexchlorpheniramine
Dextromethorphan/ diphenhydramine	Fluphenazine/ nortriptylline	Diphenhydramine	Diphenhydramine/ paracetamol/ phenylpropanolamine	Betamethasone
	Metildigoxin	Dextromethorphan/ diphenhydramine		Betamethasone/ chlorphenamine
	Bromelains/ dihydrocholic acid/ dimeticone/ metoclopramide/ pancreatin	Chlorphenamine/ phenylephrine/ salicylamide		Diphenhydramine/ guaifenesin
	Hydrochlorthiazide/ propranolol	Acetylsalicylic acid/caffeine		Atropine diphenoxylate
		Rofecoxib		Guaifenesin/ terbutaline
		Calcium/copper/ dexpanthenol/iron /magnesium/ manganese/ molybdenum multivitamins/ phosphorus/ potassium/ vitamin E/zinc		Ketotifen

Legend: Ingredients separated by backslash (/) are part of the same combination

and many European countries [5]. However, there has been little temporal change in market share of generic medicines (unbranded + branded) in at least half of the 19 LMICs studied, specifically in Asia and countries in the MeSA (Figure 1). This is in contrast to many European countries and the United States [5], where the generic medicines market share over this time period has increased at least 25 percent. See also Figures 1 and 3 of this present paper. Our results are in line with others describing similar increasing trends in the utilization of generic medicines in the United States and Europe [19, 20].

Dominance of branded generics over unbranded generics as a class

In sharp contrast to the United States where the overwhelming majority of generic products are unbranded (Figure 3), branded generics by class are by far the dominant form of generic medicine in our private sector LMIC dataset (Figure 2). The countries in the MeSA we analyzed had by far the greatest preponderance of branded versus unbranded generics as a

VENEZUELA	SOUTH AFRICA	MEXICO	JORDAN	UNITED STATES
Betamethasone/ dexchlorpheniramine	Rofecoxib	Pseudoephedrine/ triprolidine	Amitriptyline	Celecoxib
Rofecoxib		Acetylsalicylic acid/ chlorphenamine/ pseudoephedrine	Biperiden	Rofecoxib
Celecoxib		Dexbrompheniramine/ pseudephedrine	Clobutinol/ orciprenaline	
Ephedrine/ hydroxyzine/ theophylline			Clonazepam	
Lorazepam			Flupentixol	
Metamizole sodium/ scopalamine butyl hydroxide			Clopamide/ dihydroertocristine/ reserpine	
Triazolam			Hydroxyzine	

volume ratio (trend 17:1 to 23:1), followed by the Asian countries (trend 7:1 to10:1) and the LAC countries (trend 5:1 to 2:1) (data not presented here).

From a business perspective, launching a "branded" generic product may be a good choice in certain middle income countries where the 'brand' provides some perceived signal of assured quality over time. For instance, almost all medicines in India are sold under a trade/brand name and not under an unbranded (INN) name [21]. Generic manufacturers aim to establish themselves in a particular product market by creating brand awareness, and, potentially, brand loyalty among prescribers and/or patients.

The promotion and marketing of branded generics by all these entities raises the question as to whether branded generics are likely to be more expensive than their unbranded counterparts. In Peru, for two ACE inhibitors (captopril, enalapril), three anti-ulcerants (lansoprazole, omeprazole, ranitidine) and two anti-diabetic agents (glibenclamide, metformin), the branded generic ranged from 26% more expensive (metformin) to 900% more expensive (enalapril) than its unbranded generic counterpart [22]. A study from Brazil

found that unbranded products were more expensive than branded ones, the explanation being that unbranded products have to prove bioequivalence, and this cost is added to the consumer price [1]. There appears, however, to be little data in the literature on this type of price comparison between branded and unbranded generic medicines.

Some evidence for originator to generic "switching" exists for certain medicines in these markets

The cost savings of increased use of generic medicines can be substantial in LMICs [11]. Potentially, it is possible to improve cost-effective medicine use in the private sector if originator brands were to be switched to the lowest-priced generic equivalents available at medicine outlets [11]. The amount of saving would depend on the price difference between originator and generic equivalent. However, as our data suggest when disaggregated into individual pharmaceutical substances, the actual situation appears more complex than simple "switching". One should not assume that, if market share of an originator has decreased, then its counterpart generic has increased. For many countries, this assumption does not hold.

In those nine LMICs whose private sector market shares we have disaggregated into their "diagnostic ratios" (Table 1), there appears to be a spectrum of market behaviours with respect to those originator medicines that lost market share, ranging from e.g., loss of originator market share without any generic counterpart on the market at all (Table 3, Figure 4: "Category D") to a growth of counterpart generic volume share sufficient to overcome the decrease in originator volume share (Figure 4: "Category A"). The United States also shows this spectrum of behaviour but in comparison to LMICs, in United States many more originators have been replaced by their counterpart generic versions (Figure 4). This same question of switching from originator to a counterpart generic medicine was studied in 10 European countries between 2002 and 2006 [23]. Briefly, for countries that have long promoted generics such as Germany, the UK and the Netherlands there was an increase in the volume consumption of generic medicines and a switch from an original to its counterpart generic version. For less mature markets, such as Spain, Italy, Belgium and Austria, they found only an increase in generic medicines consumption with no 'switching'. The same could be true for the LMICs studied; in markets such as Brazil and South Africa we found a higher number of originators which were replaced by their counterpart generic products.

In our view, increases in private sector LMIC generic market share for the medicines under study are not predominantly a response to patent expiries. Certainly in Brazil, we know that the top 30 molecules with the highest decrease in the originator group were off-patent so that the increase in generics by volume (Table 2) cannot be attributed to the 'release' of generics onto the market post-patent. In other countries (Colombia, Ecuador, Philippines, Venezuela, South Africa), very few top 30 originators (i.e., orlistat, cyproheptadine, cefaclor, trimetazidine, glibenclamide, loratadine, citalopram, meloxicam, omeprazole, simvastatin) had both diagnostic ratios >1 (indicating complete replacement by the generic) and no generic counterpart at the 2000/2001 boundary. We can certainly infer from this a rapid generic replacement of the originator. We are less certain that this

is a possible "signature" of patent expiry in-country sometime during 2001-2011 as we can neither confirm nor deny the patent expiration dates for these medicines.

It is thus tempting to assert that increases in generics in the LAC region over time (Figure 1, Table 1) and the majority of diagnostic values > 0 (categories A and B: (Figure 4)), result from comprehensive policies, at least in Latin America, to promote substitution of originators with counterpart generic medicines [24] and not from patent expiration.

There are alternative explanations for the increase in generic medicines in the LAC region. One is the relative importance of generic substitution within pharmacies, another is the direct demand for generic medicines by consumers who buy medicines without prescription. However, our data does not permit us to clearly distinguish these alternatives. The literature suggests that generic substitution in pharmacies in some Latin America countries is prohibited if the brand name of the product is mentioned on the prescription (e.g. Mexico [25]) and for some countries policies to promote INN prescribing has not resulted in a very significant uptake as they have not been enforced [26]. This suggests that the uptake of generic medicines in the private market may be more consumer-driven rather than driven by effective generic substitution policies. Thus, what may be driving the originator/generic dynamic is balance between a change to less costly options for consumers and a more profitable medicine because of better mark-ups and rebates.

Another explanation is safety and efficacy concerns that are possibly responsible for some of the observed market dynamics. Originators losing market share without a corresponding generic market ("Category D" Figure 4; Table 3) include medicines already taken off the market in the United States (cox-2 inhibitors like rofecoxib). The reason for this behaviour in other classes (e.g., alkylated antihistamines like diphenhydramine – sold as Benadryl® in the United States and halogenated derivatives e.g., chlorphenamine) may be due to removal of the originator from the market and /or substitution of another, more effective originator or even a substitutable, non-counterpart generic. We cannot at present distinguish between any of these possibilities.

Finally, as the population of a country ages and more non-communicable diseases are treated with medications, the consumer demand as well as demand by insurance schemes for less expensive and/or more cost-effective drug therapy has continued to grow. Elements driving the observed increase in generics in the LAC region, indeed in any country, are likely to be multifactorial.

Limitations

A possible limitation is that we cannot capture the entire pharmaceutical market (private and public) of a given country so that we are not attempting to generalize our findings to the entire pharmaceutical market of each of the 19 LMICs. At the same time it is worthwhile mentioning that the private sector in LMICs overall is often more than 60% of the total medicines market by value [26]. In the specific countries that are the subject of this analysis, the percent of the total pharmaceutical market by value allocated to the private sector is even higher, averaging 76 % (median: 80%) [IMS unpublished data] so we are capturing a clear majority of the total medicines market.

We eliminated the "patent N/A" category from our analysis as they cannot be placed into any IMS category (i.e., "INN", "originator", "branded generic"). This category averages across all countries about 12% of the total private market (including patent N/A). Thus, we are still capturing a substantial part of the total private sector pharmaceutical market in the 19 LMICs.

However, we are analyzing a limited number of countries for each region, aside from Latin America. Thus, we cannot really generalize the data geographically to Asia or the MeSA as a whole. Nonetheless, some of the largest sized pharmaceutical markets in each of the regions are included (e.g. Egypt, in the MeSA and the Philippines in Asia).

We assume there are systematic errors in our panel data. Any systematic errors in the panel data are due to several factors including: (1) Coverage: Some distribution channels are not captured in our data and therefore, not included in the analysis. Our study focuses on the private market and excludes the public sector. (2) Accuracy: Accuracy may vary by product size for sample-based data, as most audits are sample based. A more cogent limitation might be the fact that there are almost inevitable errors in the panel data due to changes in already existing distributors over time. We attempted to model the impact of changes in volume on outcome measurements which should be the most sensitive to such changes. We infer that the errors in outcome measures are rather small. We do not think that changes in market share that we see over time are caused by changes in the number of audited entities included in annual surveys. Unknown and/or uncorrected under/overestimations would have to occur continuously over multiple years in order to account for the trends we observe. This seems unlikely.

DDD is the more commonly used measure of medicines consumption in the scientific literature. However, as we represent the values as ratios, it is unlikely that analysis by DDD would produce different results.

Clearly differentiating between products that were off-patent from the beginning of the study period and those that lost their patent during the study period would add an additional insight into our results regarding the increase in generic medicines market share. We note that patent protection has not always been enforceable, or enforced, in all countries. This is a limitation of the study. However, for all the top 30 originators in each country under study, we were able to determine whether there were any generic competitors on the market prior to the beginning of the time series. Changes in generic market share thus occurred in some of the cases even in the presence of originator and within, not prior, to the study period.

Lastly, any inferences we draw regarding patent expiry should have been obtained from the respective LMIC Patent Offices but we did not have this information and this is almost always difficult in any case for LMICs [28].

CONCLUSION: FUTURE CHALLENGES AND POLICY IMPLICATIONS

There are few private retail sector analyses of generic medicines in LMICs. Our study shows that generic medicines (branded generic plus INN generic) represent between 70% and 80% of market share in the private sector of these LMICs which is greater than most European countries.

In contrast to high income markets such as the United States, branded generic medicine market share is much higher than unbranded generics, most notably in countries in the MeSA and Asia. Although switching from originator to generic counterparts saves money in principle [11], this narrative in reality is complex and nuanced at the level of individual medicines.

Our study is a first step analyzing generic medicines consumption in the private market in LMIC over time. For some countries with an originator medicines market share of around 30% we found less than 3% change in the generic medicines market share over time (e.g. Argentina, Pakistan, Egypt and Tunisia). For various reasons, generics may not be promoted, but the conditions under which we can say that generics would be taking more market share in these countries are not known with certainty. It is possible that there is a lack of effective policies promoting generic medicines. For other countries it is difficult to say from this analysis what is actually driving the decreasing market share of originators in, for instance, many Latin American countries, South Africa and the Philippines. Generic medicine policies such as specific pricing policies, aligning financial incentives of consumers and prescribers/dispensers, promoting generic medicines among consumers, economic forces (e.g., presence/absence of taxes, rebates, discounts), safety recalls and health care provision (e.g., presence/absence of health insurance coverage, presence of fragmented and complex distribution channels) might play a role.

A second important step would be a more rigorous and in-depth economic and policy analysis to establish cause-effect relationships between pharmaceutical policies and, for example, the data presented here. Those studies can support relevant recommendations on medicines policies and assist in modulating their implementation in-country. A comprehensive prospective picture that includes estimations of the number of generic competitors, penetration of generics after patent expiry, and national-level costs of purchasing branded versus unbranded generics will require accurate, validated price information as well as a well-described policies and their implementation process. In addition, the analysis should be complemented by a qualitative review of policy changes and their likely effect on the volume share. Interviews with policy makers, policy analysts and other stakeholders can provide valuable insight into the market dynamics.

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Table 1

Number of countries	Top 30 of Originator and Licensed (O+L)	O+L to generic Switch? Ratio greater than 1	Taken off market?
8	AMOXICILLIN†	Yes, Colombia	
8	ALPRAZOLAM	NO	
8	BROMAZEPAM	NO	
8	DICLOFENAC	Colombia, Uruguay, South Africa	
8	GLIBENCLAMIDE	Venezuela	
8	SULFAMETHOXAZOLE/TRIMETHOPRIM	NO	
6	LORATADINE†	South Africa, Ecuador, Venezuela	
6	BROMHEXINE	Venezuela	
6	CARBAMAZEPINE	NO	
5	DIPHENHYDRAMINE†	NO	
5	PHENYTOIN†	NO	
5	ROFECOXIB†	NO	Taken off market in US, S Africa, Venezuela
5	ENALAPRIL	Ecuador, South Africa	
5	LORAZEPAM	NO	Taken off the market in Venezuela
5	SALBUTAMOL	NO	
4	LORATADINE/PSEUDOEPHEDRINE†	NO	
4	AMITRIPTYLINE	Colombia	Taken off the market in Jordan
4	BIPERIDEN	NO	
4	CINNARIZINE	NO	
4	CLONAZEPAM	Uruguay	Taken off the market in Jordan
4	DIAZEPAM	NO	
4	IBUPROFEN	Venezuela	

4	LOPERAMIDE	Philippines	
3	SIMVASTATIN†	NO	
3	AMBROXOL	NO	
3	AMPICILLIN	NO	
3	ATENOLOL	Philippines	
3	BETAMETHASONE/DEXCHLORPHENIRAMINE	NO	Taken off the market in Venezuela, Philippines
3	CAPTOPRIL	NO	
3	CHLORPHENAMINE/PARACETAMOL/PSEUDOEPHEDRINE	NO	
3	ERYTHROMYCIN	NO	
3	METAMIZOLE SODIUM/SCOPOLAMINE BUTYL HYDROXIDE	NO	Taken off the market in Venezuela
3	NAPROXEN	NO	
3	NIFEDIPINE	NO	
3	NIMESULIDE	Ecuador	
3	PROPRANOLOL	NO	
2	ACETYLSALICYLIC ACID/CHLORPHENAMINE/PSEUDOEPHEDRINE	NO	Taken off the market in Peru and Mexico
2	AMILORIDE/HYDROCHLOROTHIAZIDE	NO	
2	AMLODIPINE†	NO	
2	ATORVASTATIN†	NO	
2	CEFACLOR	Philippines	
2	CEFRADINE	NO	
2	CELECOXIB†	NO	Taken off the market in US and Venezuela
2	CHLORPHENAMINE	Colombia	
2	CHLORPHENAMINE/PARACETAMOL/PHENYLPROPANOLAMINE	NO	
2	CHLORPROPAMIDE	NO	

Table 1: Continued

Number of countries	Top 30 of Originator and Licensed (O+L)	O+L to generic Switch? Ratio greater than 1	Taken off market?
2	CITALOPRAM†	South Africa	
2	DEXTROMETHORPHAN/DIPHENHYDRAMINE	NO	Taken off the market in Peru and Ecuador
2	DILTIAZEM	NO	
2	FEXOFENADINE†	NO	
2	FUROSEMIDE	NO	
2	HALOPERIDOL	NO	
2	HYDROXYZINE	NO	
2	LANSOPRAZOLE†	South Africa	
2	LISINOPRIL†	South Africa	
2	METOPROLOL†	Philippines	
2	METRONIDAZOLE	NO	
2	OMEPRAZOLE†	South Africa	
2	ORLISTAT	Uruguay, Colombia	
2	PENICILLIN V	NO	
2	PSEUDOEPHEDRINE/TRIPROLIDINE	NO	Taken off the market in Mexico
2	QUINAPRIL†	NO	
2	RANITIDINE	NO	
2	TIBOLONE	NO	
2	TRIMEBUTINE	Colombia	

† LMIC including the US; All others LMIC excluding the US

CHAPTER 4.2

THE IMPACT OF PATIENT AND DOCTOR CHARACTERISTICS ON THE PRESCRIBING OF LOW COST GENERIC FORMULATIONS IN BRAZIL

Submitted

Stephens P, Leufkens HG.

ABSTRACT

Objectives

To examine the impact of the characteristics of doctors and patients on the use of low cost generic formulations in Brazil in 2012.

Setting

This study examined 17,627 consultations in which a medicine known to have an unbranded generic formulation available was prescribed. These consultations were generated by a sample of 723 doctors working in both public and private sectors in 2012.

Results

74% of doctors prescribed both branded and unbranded formulations. Only 8/723 doctors never prescribed a generic of any sort. Doctors were found to prescribe less expensive formulations of medicines to those patients with co-morbid conditions and those needing treatment with higher priced medicines. Doctor and patient demographics had little effect although older age was significantly associated with less expensive formulations.

Conclusion

This study indicates that Brazil is a relatively mature generic market with most doctors prescribing a generic formulation. Doctors prescribe formulations that are relatively less expensive where the absolute price of the medicine is higher and where the patient is older or being treated for more than one diagnosis. This suggests that the economic burden of treatment may be being taken into account.

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INTRODUCTION

The Unified Health System (SUS) of Brazil was created to ensure universal, free and equal access to healthcare in Brazil [1]. In 2008, however, out of pocket expenditure on medicines constituted 66% of total health expenditure in Brazil [2], 25% of medicines obtained by those in the lowest economic quintile were purchased out of pocket [3], and one quarter of the population had private health insurance [3].

To reduce out of pocket expenditure on medicines, Brazil has introduced many different initiatives.

It offers a range of medicines free of charge through public facilities as well as discounted medicines through privately owned pharmacies accredited to the Farmacia Popular programme [4]. It has also introduced a range of initiatives to encourage the wider use of generic medicines [5].

Few low and middle income countries have been more successful at generic expansion than Brazil [6]. In Brazil there are three types of medicine – original or licensed brands, generics, and branded generics, known as "similares" [3]. Generics have proven equivalence with the original or licensed brand but cannot be sold under a brand name [3]. "Similares" are branded versions of original or licensed brands but, in contrast to generics, were not required, at first, to prove bioequivalence [3]. In this paper Brazilian generics are described as unbranded generics, and "similares" as branded generics. Unbranded generic medicines grew by 22% between 2001 and 2011 and in 2011 constituted 31% of total retail volume in Brazil, and branded generics a further 52% [6].

Given this success of generics in Brazil, the evolution of medicine prices in that country can seem counter-intuitive. Original brands have increased their prices faster than generics [7], and unbranded generics have in the past been found to be more expensive than branded generics [3]. It seems, however, that the pricing of original brands in Brazil conforms to the so-called "generic paradox". In the generic paradox the availability of cheaper generics causes price sensitive users of original brands to switch to less expensive formulations but less price sensitive users continue to use the original brand. As generic use expands, therefore, the remaining users of original brands are evidently less price sensitive and as a result, original brands are able to increase prices to some extent without additional loss of volume [8]. The pricing of branded and unbranded generics in Brazil, on the other hand, appears to be the result of a difference in the timing of the implementation of regulations requiring stringent pharmaceutical equivalence between unbranded generics and the originator brand. Unbranded generics were required to meet those tests from 1999, whilst branded generics were allowed to adapt gradually, according to a schedule that runs from 2003-2014 [5]. The costs of these additional tests, and indeed the competitive advantage that they may give, were thus applied to unbranded generics earlier than the branded generics.

Perhaps because of this complexity, studies of generic expansion in Brazil have tended to focus on patients' attitudes towards generics [9, 10, 11] rather than on actual prescribing practice. The most recently published study found that the following factors were most important in the decision to use or accept a generic: pharmacist recommendation (28%), posology (25%), prior

experience of the medicine (16%), doctor recommendation (15%), price (9%) and the name of the manufacturer (6%) [9]. Others have also commented on the complex set of interactions between the patient, their doctor, the pharmacist and market conditions affecting the decision to prescribe or dispense a generic in preference to a branded product [12,13].

Studies in other countries have also examined the association between attitudes of doctors and patients towards generics and a variety of socio-demographic and economic characteristics. Studies have often however produced conflicting results, in particular perhaps in relation to doctor age [14, 15, 16, 17] or the patients' economic circumstances [17, 18, 19, 20]. Nevertheless whilst findings may differ, several studies point to the importance of the interaction between patient and doctor, and between patient and pharmacist in determining the type of product dispensed [9, 21].

Given the extent of out of pocket expenditure on medicines and the rapidly changing nature of the market, there remains a need to understand the ongoing drivers of generic expansion in Brazil. This study uses actual prescribing data to examine the impact of patient and doctor characteristics on the prescribing of less expensive formulations of generic medicines in Brazil.

MATERIALS AND METHOD

Data sources

This study uses four different types of information – data about prices, availability, prescribing practices and type of product prescribed.

As noted above, the history of product pricing in Brazil indicates that it cannot be assumed that unbranded generics are necessarily always less expensive than branded generics. Actual price data must therefore be used. There are however no large scale studies of the out of pocket prices paid for medicines by consumers in Brazil, and the latest smaller scale study dates to 2008, some time prior to the full implementation of the regulations requiring stringent pharmaceutical equivalence between branded generics and the originator brand described earlier. These studies may not therefore reflect changes in pricing strategy as pharmaceutical equivalence is achieved.

Information on the prices paid by pharmacies for all products was however available from an audit created by IMS Health from a panel of 130 independent pharmacies, 35 chain pharmacy organisations and 16 delivery pharmacies. These prices reflect the commercial incentives available to pharmacists, which in turn, help to drive dispensing practice, and with that, patient experience and preference [13, 14, 21]. This audit was the source of the pricing data used in this study.

Information about availability was taken from an IMS audit of the volume of pharmacy purchases created from a panel of 417 wholesalers combined with invoice data from a panel of a further 130 independent pharmacies. This database was used to look at the presence on the market of unbranded generic, branded generic and originator forms of the same medicines prior to and during the study period.

Prescribing information was taken from an IMS audit created from a sample of 1,315 doctors working across all locations, stratified by region and specialty. Approximately

12% of these 1,315 doctors work exclusively in the public sector. Each doctor provides information on consultations made for one week every quarter. Patient variables recorded are age, sex, diagnosis, co-morbidities and consultation type. Consultation type is divided into two categories – consultations paid for by the health service and consultations paid for by the patient (either out of pocket or through private insurance). It should be noted that in Brazil private insurance does not cover the costs of medicines used in ambulatory care [3]. Prescription details recorded include concomitant prescriptions, brand name/molecule, form, strength and quantity prescribed as well as whether the prescription is new (to the doctor), a switch or a repeat. Doctor details recorded include age, sex and specialty.

Products were classified into four different types – a) those included within the list of products able to be dispensed under the Farmacia Popular scheme [22] b) those included on the Essential Medicine List for Brazil [23] c) those on both lists and d) those on neither. Products were classified into these types as it was felt possible that the higher demand for products on the Essential Medicine lists or the discounted prices for those products dispensed under the Farmacia Popular programme could potentially affect the number of manufacturers and/or the extent of competition between manufacturers and this would in turn affect pricing policies and price variation between different formulations.

Inclusion and Exclusion criteria

The study period was 2012. All therapy classes were eligible for inclusion in the study. Data were first grouped into medicines containing the same molecule, pharmaceutical form and strength (described here as "medicines"). All further analyses were carried out at this level. This ensured that any impact of posology on prescribing decisions, customer preference or pricing could be taken into account. Only those medicines with sales of at least one unbranded generic, at least one branded generic and the original brand in every quarter of 2010-2012 were included in the study. This ensured that availability of a type of product would not affect the prescribing decision and so distort the analysis.

The prescribing audit was filtered in order to select prescriptions for the medicines so identified above. Medicines were excluded if more than 10% of the prescriptions written for it could not be linked to price information within the sales audits. Medicines were also excluded if all were priced at exactly the same level (there then being no price variation to analyse). Prescriptions written generically (or in other words written with no indication of preferred brand or manufacturer) were given the minimum price for that medicine by default. Specialties linked to less than 20 doctors were removed in order to ensure adequate power within the multi-level model, and doctors linked to less than 10 prescriptions were also removed for the same reason. One record was excluded due to an unknown value for the type of consultation. The characteristics of the doctors and medicines included in the study are shown in Tables 1 and 2.

Statistical analysis

A two-level multilevel linear regression analysis was used to analyse the effect of doctor and patient characteristics on price ratio. The doctor is taken as one level, consultations as the

next. Multilevel analyses take the nested structure of the data into account (i.e. consultations nested in doctors) [24].

In this study a linear multi-level model was used. The model allowed the intercept to vary (random intercepts), but not the slope [24]. The appropriateness of the multi-level approach was tested by comparing the change (reduction) in the values of the -2 log-likelihood results achieved by ordinary multiple regression (no levels) with that of the multi-level model.

All multi-level analyses were carried out in SPSS20.

Dependent variable

The dependent variable ("price ratio") was the ratio between the minimum price of the particular medicine recorded in the sales audit and the price recorded in the same audit for the formulation of the medicine actually prescribed. The minimum price was given a value of 1. Thus if the lowest price of a particular medicine was 10, and the price of the actual formulation prescribed containing the same molecule, form and strength was 15, the ratio was calculated as 1.5. Prescriptions written generically (or in other words written with no indication of preferred brand or manufacturer) were given the minimum price for that medicine by default (i.e. a price ratio of 1).

Independent variables

The independent variables entered into the model can be divided into three types – Market variables, Doctor variables and Patient variables.

Market Variables

Three different characteristics of the medicines were included – inclusion on the Essential Medicines List, inclusion on the list of drugs able to be dispensed via the Farmacia Popular scheme and the minimum price of each medicine. The first two variables were included because of their potential impact on market competition and the price ratio as described above. The minimum price of each medicine was included in case the actual amount paid changed prescribing behaviour. For example imagine two medicines, both of which are calculated to have a price ratio of 1.5. If the minimum price of one of these products was $20 and for the other just $1, then the difference between the purchase price of the medicine prescribed and the minimum price would be $10 in one case and just $0.5 in the other. In the event of such a large difference a doctor might prescribe cheaper formulations where the minimum price of a product was larger.

Doctor variables

Doctor variables were included where evidence could be found in the literature indicating an effect on attitudes or use of generics, even if the results were not always consistent. Doctor specialty has been found to affect attitudes in Spain and Taiwan [14, 25]. Doctor age has been found to affect attitudes in Taiwan, Pakistan and Malaysia [14, 15, 16] and doctor gender in Pakistan [15]. The list of doctor variables included was thus specialty,

Table 1: Distribution of medicines by Anatomical Therapy Class (ATC)

ATC	Prescriptions (%)
A	3651 (21%)
B	516 (3%)
C	5582 (32%)
D	811 (5%)
G	162 (1%)
H	26 (0%)
J	1186 (7%)
L	8 (0%)
M	1177 (7%)
N	2535 (14%)
P	399 (2%)
R	1550 (9%)
S	24 (0%)
Total	17627

Table 2: Distribution of prescriptions by specialty

Specialty	Doctors (%)	Prescriptions (%)
Cardiology	82 (11%)	3792 (22%)
Dermatology	27 (4%)	489 (3%)
Gastroenterology	39 (5%)	1061 (6%)
General Medicine	311 (43%)	6854 (39%)
Geriatrics	26 (4%)	578 (3%)
Neurology	25 (3%)	454 (3%)
Obstetrics & Gynaecology	26 (4%)	392 (2%)
Orthopaedics	21 (3%)	389 (2%)
Otorhinolaryngology	20 (3%)	341 (2%)
Paediatrics	125 (14%)	2851 (16%)
Urology	21 (3%)	426 (2%)
Total	723	17627

age and gender. Age was related to the date of introduction of generics and considered as qualification pre or post the introduction of generics.

In addition, doctors working in the public sector must by law use only the generic name when prescribing [8]. In an attempt to control for the effect of public sector prescribing, those doctors that were seen only to prescribe unbranded generics were identified separately.

Patient variables

Patient variables included were those where evidence could be found of an effect on use or attitudes to generics. Patient age and gender has been associated with a change in use or attitudes in developed countries and in Brazil [11, 12, 26]. Economic circumstances have been associated with differences in use of generics by patients in Brazil [10, 11], and by doctors in Jamaica [18]. Custom or prior use of generics was also found to be a significant variable in Ireland [21]. The final list of patient variables was age and gender plus those variables giving an indication of the likely extent of out of pocket expenditure (consultation type and co-diagnoses). In addition, in order to take account of a patient's prior use of a particular brand or generic, the type of prescription (new, switch or repeat) was included.

RESULTS

This study included 17,627 prescriptions from 723 doctors. Of these, 9.8% prescribed only to patients whose consultations were paid for by the government, 55.6% only to those whose consultations were not paid for by the government, and 34.5% to a mix of consultation types. In total 12,674 prescriptions (72%) were written to patients paying for the consultation themselves.

8 doctors were observed only ever to write unbranded prescriptions, 14 were observed only ever to write prescriptions for original brands and 184 were observed only ever to write prescriptions for branded generics or original brands. The average price ratios for medicines identified as original brands and branded generics was 4.7 and 4.3 respectively. The unbranded generic was not always the least expensive. Medicines identified as unbranded generics were found to have a price ratio of 1.8. The breakdown by Anatomical Therapy Class (ATC) and by doctor specialty is shown in Tables 1 and 2.

Figure 1 shows the proportion of prescriptions written for medicines with a price ratio of less than 3 for each independent variable. Figure 1 thus gives an indication of the likely effect of each independent variable, although it will not reflect interactions between variables. Nevertheless the higher the percentage the more likely it is that prescriptions are being written for less expensive formulations. Figure 1 suggests therefore that (1) prescriptions for medicines included on both the Farmacia Popular and Essential Medicines list will tend to have a lower price ratio, (2) that prescriptions written for older patients or for patients diagnosed with more than one condition will tend to have a lower price ratio, (3) that patients whose consultations are paid for by the government or for whom the prescription is a repeat will tend to be prescribed medicines with a higher price ratio and (4) that doctor specialty can have a particularly strong effect. Figure 1 suggests, for example, that neurologists prescribe medicines with a price ratio of less than 3 in a third more consultations than do doctors that practise general medicine, geriatrics, obstetrics and gynaecology, urology, otorhinolaryngology and paediatrics.

Analysis showed that the addition of the doctor as a distinct level within the multi-level model improved the fit of the model significantly ($p<0.001$, Table A, Supplementary Material).

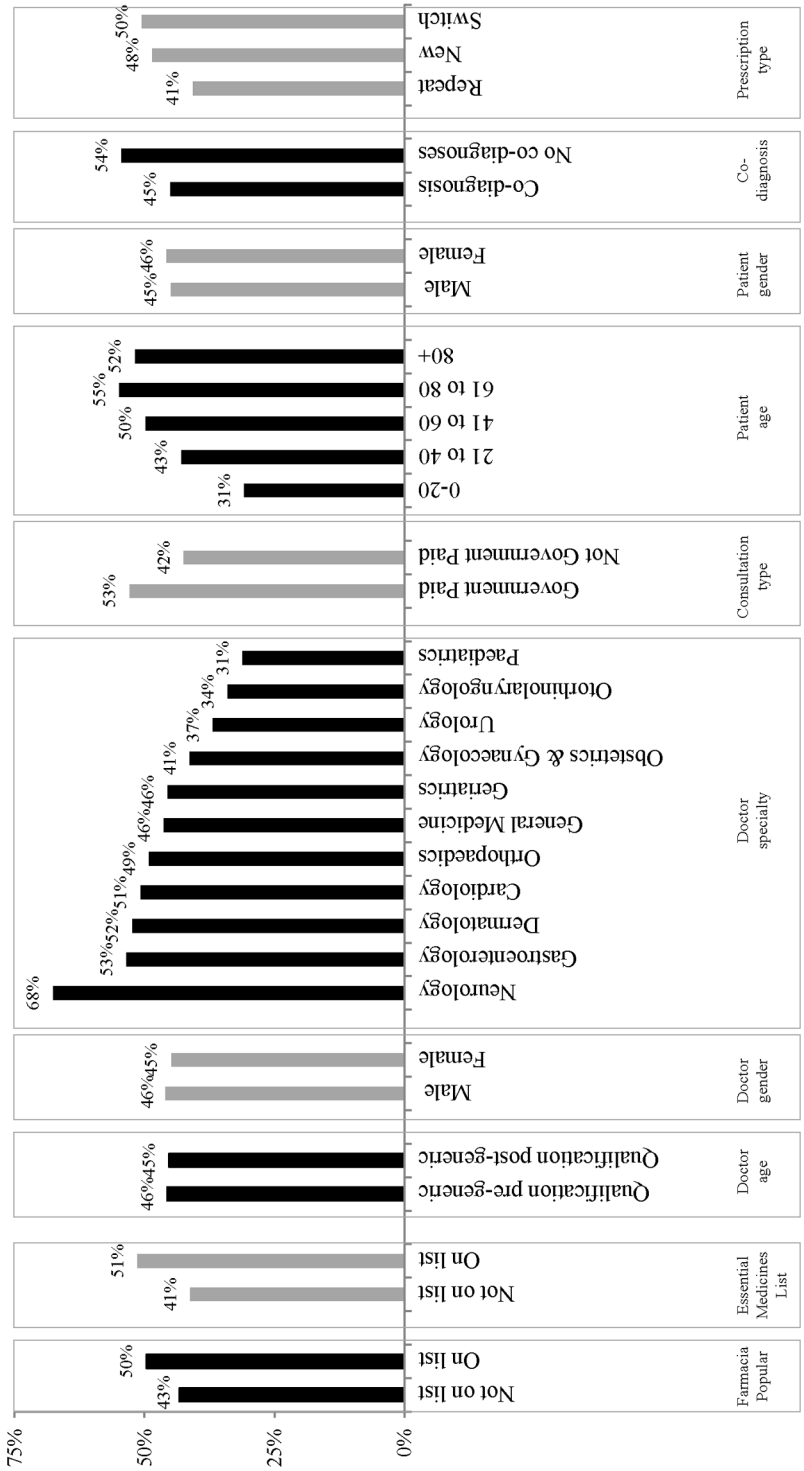

Figure 1: *Percentage of prescriptions written for formulations with a Price Ratio of less than 3*

A summary of the results of the multi-level model is given in Table 3 below, with more details available in the Supplementary Material (Table B and Table C, Supplementary Material).

The results of the multi-level model are generally consistent with those shown in Figure 1. As in Figure 1 doctor age, doctor gender and patient gender were not found to have a significant effect (p≤0.05). Similarly consultations not covered by the government and repeat prescriptions were found to have a higher price ratio (p≤0.001). In contrast, but

Table 3: Result of multi-level logistic regression showing the effect of doctor, patient and market variables on price ratio

Market variables	**Direction of effect**	**Estimate**	**Significance**
Medicine not included in Farmacia Popular scheme	—	-0.045	0.343
Medicine not included in National Essential Medicines List	↓	-0.255	0.000***
Lowest price observed for medicine formulation is higher	↓	-0.777	0.000***
Doctor variables			
Female gender	—	-0.018	0.863
Qualified after introduction of generic legislation	—	-0.031	0.771
Writes both branded and unbranded prescriptions	↑	2.771	0.000***
Doctor specialty***	↑		0.000***
Urology[a]	↑	1.282	0.001**
General Medicine[a]	↑	0.867	0.002**
Geriatrics[a]	↑	0.973	0.010**
Obstetrics & Gynaecology[a]	↑	0.975	0.011*
Otorhinolaryngology[a]	↑	0.898	0.027*
Orthopaedics[a]	—	0.719	0.078
Gastroenterology[a]	—	0.429	0.211
Dermatology[a]	—	0.418	0.264
Paediatrics[a]	—	0.301	0.312
Cardiology[a]	—	0.231	0.450
Patient variables			
Consultation covered by government insurance	↓	-0.303	0.000***
Male gender	—	0.039	0.279
Older Age	↓	-0.009	0.000***
Only one diagnosis in consultation	↑	0.193	0.050*
Type of prescription (new, switch or repeat) ***	↑		0.000***
New[b]	—	0.009	0.913
Repeat[b]	↑	0.328	0.000***

a Effect relative to Neurology
b Effect relative to Switch
* p≤0.05 ** p≤0.01 ***p≤0.001

again as shown in Figure 1, older age ($p \leq 0.001$), more than one diagnosis ($p \leq 0.05$), and the absolute level of the lowest price for a medicine ($p \leq 0.001$) were found to reduce the price ratio significantly. These latter results suggest that economic circumstances or likely total burden of out of pocket expenditure were being taken into account.

The multi-level analysis also confirms the effect of specialty. Relative to the prescribing of a neurologist, five types of specialist were found to prescribe medicines with a higher price ratio (those practising urology, general medicine, geriatrics, obstetrics and gynaecology and otorhinolaryngology).

Of note, however, is the fact that whilst both the univariate analysis described in Figure 1 and the multi-level model described in Table 3 indicate that inclusion within the Essential Medicines List had an effect, the direction of that effect is seen to be different. Figure 1 shows that prescriptions written for products in the Essential Medicines List are more likely to have a price ratio of less than 3. This, in turn, would suggest that exclusion of a product from the Essential Medicines List increases the price ratio. However the multivariate analysis suggests the opposite. Exclusion from the Essential Medicines List is associated with a decrease in the price ratio. Further analysis suggests a reason why we find such differing results. Medicines included in the Essential Medicines List have a higher proportion of price ratios of more than 6 (14% versus 8%). The multivariate analysis considers the price ratio as a continuous variable, and thus all values across all categories, the univariate analysis considers only one category (price ratio less than 3). This difference in method, combined with the distribution of price ratios, may thus explain the differences seen.

DISCUSSION

In this study, 74% of doctors wrote prescriptions for both brands and generics. Only 2% never wrote a prescription for generic of any sort. This compares to the 2007 study carried out in the state of Santa Catarina in Brazil where 35% of doctors were said never to write prescriptions for generics of any sort [10]. The majority of these doctors prescribed to patients whose consultations were not paid for by the government. Nevertheless awareness of this sample of doctors of generics seems thus to be high, although it is clear that some doctors, and in particular some doctors in particular specialties, continue to prescribe branded and/or more expensive formulations of particular medicines on some occasions.

This is despite the evidence in this study that the price of the medicine and likely extent of out of pocket payments affects prescribing, even after consultation type is taken into account. Doctors prescribed closer to the minimum possible price where the price of the medicine prescribed was higher, where the patients needed medicines to treat more than one diagnoses and where the patient was older. It is not known whether the doctor or the patient raised concerns about the costs of treatment but in the UK, price concerns were not found to be something that patients felt able to raise with their doctor [19]. Given the apparent awareness of the majority of doctors of generic or lower cost formulations, and the evidence in this study of the impact of price or total out of pocket expenditure amongst certain segments of

the population, it may be that the next phase of generic expansion in Brazil should be to help patients raise concerns over price with their doctor, where this is appropriate.

In this study repeat prescriptions were found to have a significantly higher price ratio than new or switch prescriptions. This is as may be expected but it highlights the complexity of calculating realistic and realisable out of pocket savings through generic expansion. Doctors and patients can be resistant to a change of brand [20]. Studies of generic expansion should analyse repeat prescriptions separately from new or switch prescriptions.

Overall patient and doctor demographics were found to have little effect. Only patient age was found to have a significant effect. However it should be noted that a limited set of patient and doctor demographics was included in this study. Neither the socio-economic circumstances nor ethnicity of each patient, for example is recorded in the IMS data.

The main weakness of this study, however, is the lack of information relating to the actual price paid by the patient or, more particularly, the patient's or doctor's perception at the point of prescribing of the price that will be paid. It is possible that the doctors' or patients' perceptions are different to the prices shown in the audit, particularly as the prices of branded generics appear to have changed over time. Perceptions of actual price may therefore be outdated. In this study the average price ratio of original brands and branded generics was more than 4 times that of the unbranded generics. When compared to earlier price studies this is a surprising result. In earlier studies, the price of branded generics was more similar to the unbranded generics [3]. Earlier studies were, however, carried out before branded generics were required to meet the more exacting manufacturing standards. By 2012 most branded generics would have been required to comply with these standards. Branded generics thus appear to have changed pricing strategy, although we should note that the prices used in this study reflect the prices paid by pharmacies, not by consumers. It is therefore, an assumption that the prices used in this study are related to the price paid by consumers.

CONCLUSION

This study describes prescribing of medicines where the availability of unbranded generic formulations is known. It uses multi-level modelling to take account of the interaction between patient and doctor, and logistic regression within each level controls for market variables and consultation type. The study indicates that the market for generics in Brazil is relatively mature, with the majority of doctors prescribing at least one branded or unbranded generic formulation. Doctors prescribe formulations that are relatively less expensive where the absolute price of the medicine is higher and where the patient is older or being treated for more than one diagnosis. This suggests that the economic burden of treatment may be being taken into account.

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SUPPLEMENTARY INFORMATION

Table A: Significant effect of including doctor as a level within the multi-level model

	All variables	Addition of doctor as level
-2 Log Likelihood	83038.83	80005
Change in -2 Log likelihood		-3033.54
Degrees freedom (parameters)	24	25
Change in Degrees freedom (parameters)		1
Improvement in model		p<0.001

Table B: Summary results of multi-level logistic regression showing the effect of doctor, patient and market variables on price ratio

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	902.577	130.894	.000
Medicine included in Farmacia Popular scheme or not	1	17395.390	.901	.343
Medicine included in Essential Medicine List or not	1	17418.319	30.957	.000
Lowest price observed for that formulation	1	17468.131	799.106	.000
Doctor qualified pre or post generic legislation	1	718.489	.085	.771
Doctor gender	1	713.099	.030	.863
Doctor writes only unbranded prescriptions or not	1	786.079	32.061	.000
Doctor specialty	10	745.880	4.054	.000
Consultation covered by government insurance or not	1	10058.431	23.228	.000
Patient gender	1	17266.495	1.170	.279
Patient age (older)	1	17598.214	105.500	.000
Co-diagnosis	1	17461.042	3.826	.050
Type of prescription (new, switch or repeat)	2	17393.280	25.544	.000

Table C: Result of multi-level logistic regression showing the effect of doctor, patient and market variables on price ratio

Parameter		Estimate
Intercept		1.002657
Medicine included in Farmacia Popular scheme or not	Farmacia Popular - No	-.045382
	Farmacia Popular - Yes	0[a]
Medicine included in Essential Medicine List or not	EML - No	-.255458
	EML - Yes	0[a]
Lowest price observed for that formulation		-.777051
Doctor qualified pre or post generic legislation	Post generic	-.031347
	Pre-generic	0[a]
Doctor gender	Female	-.018298
	Male	0[a]
Doctor writes only unbranded prescriptions or not	100% unbranded - No	2.770882
	100% unbranded - Yes	0[a]
Doctor specialty	General Medicine	.867179
	Paediatrics	.300532
	Geriatrics	.973439
	Gastroenterology	.428919
	Cardiology	.231138
	Dermatology	.418187
	Obstetrics & Gynaecology	.974999
	Otorhinolaryngology	.897922
	Urology	1.282056
	Orthopaedics	.718565
	Neurology	0[a]
Consultation covered by government insurance or not	Government covered - Yes	-.303010
	Government covered - No	0[a]
Patient gender	Male	.039084
	Female	0[a]
Patient Age (Older)		-.008878
Co-diagnosis in consultation	1 diagnosis	.192806
	>1 diagnosis	0[a]
Type of prescription (new, switch or repeat)	Prescription - New	.008512
	Prescription - Repeat	.327535
	Switch	0[a]

a. This variable is the reference group for this categorical variable

				95% Confidence Interval	
Std. Error	df	t	Sig.	Lower Bound	Upper Bound
.581214	873.965	1.725	.085	-.138081	2.143394
.047823	17395.390	-.949	.343	-.139119	.048355
0	.	.	.	.	.
.045914	17418.319	-5.564	.000	-.345454	-.165463
0	.	.	.	.	.
.027488	17468.131	-28.268	.000	-.830930	-.723171
.107570	718.489	-.291	.771	-.242537	.179842
0	.	.	.	.	.
.105893	713.099	-.173	.863	-.226197	.189601
0	.	.	.	.	.
.489360	786.079	5.662	.000	1.810274	3.731489
0	.	.	.	.	.
.281525	757.800	3.080	.002	.314516	1.419841
.296751	765.251	1.013	.312	-.282011	.883075
.375004	737.137	2.596	.010	.237237	1.709642
.342714	735.129	1.252	.211	-.243895	1.101733
.306039	732.703	.755	.450	-.369680	.831957
.374338	760.265	1.117	.264	-.316671	1.153046
.382875	792.817	2.547	.011	.223431	1.726567
.406453	768.919	2.209	.027	.100033	1.695811
.402200	750.144	3.188	.001	.492485	2.071628
.407272	784.005	1.764	.078	-.080908	1.518038
0	.	.	.	.	.
.062871	10058.431	-4.820	.000	-.426251	-.179770
0	.	.	.	.	.
.036133	17266.495	1.082	.279	-.031741	.109908
0	.	.	.	.	.
.000864	17598.214	-10.271	.000	-.010573	-.007184
.098575	17461.042	1.956	.050	-.000411	.386022
0	.	.	.	.	.
.077481	17508.515	.110	.913	-.143358	.160382
.080331	17524.144	4.077	.000	.170078	.484991
0	.	.	.	.	.

CHAPTER 5

SCALE UP: THE POTENTIAL OF RING - FENCED FUNDING AND SOCIAL MARKETING

CHAPTER 5.1

THE CANCER DRUG FUND ONE YEAR ON – SUCCESS OR FAILURE?

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On October 1st 2010 the English Government introduced ring-fenced funding for the procurement of cancer medicines not funded by the NHS, worth an additional £650m over three and a half years as "a means of improving patient access to cancer drugs" [1] and as the start of "plans to address the disparity in patients' access to cancer drugs in England compared to other countries" [2]. These monies, collectively known as the Cancer Drug Fund (CDF), were additional to existing NHS funding flows, and allocated at regional level, through Strategic Health Authorities (SHA).

Some feared that demand would outstrip funding [3], others that the so-called "postcode lottery" would worsen [4]. In December 2011, however, a national newspaper claimed that millions had not been spent, and that "patients were paying the price" [5].

So what is the real impact of the CDF? Here we examine actual drug usage, and compare such usage against expectations.

CDF monies are spent on relatively few medicines. Five – bevacizumab, cetuximab, everolimus, lapatinib and sorafenib - constituted 59% of applications between April - December 2011, each receiving more than 350 applications [6].

Figure 1 illustrates the dramatic growth in volume of these drugs following the introduction of the CDF as recorded in utilisation data collected by IMS Health from almost all English hospitals. Mean volumes dispensed within SHAs post launch, in the year to November 2011, were significantly higher than those in the year prior to the CDF ($p<0{\cdot}05$). Variability between SHAs also declined (Figure 2) and differences between the 10th and 90th percentile for each drug appear to be at levels described as "normal" in earlier reports of variation in the uptake of NICE approved cancer medicines [7].

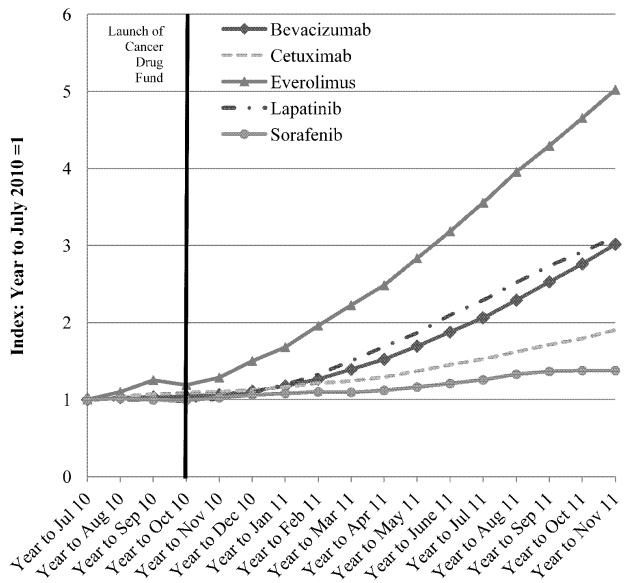

Figure 1: *Growth in use (mg) per capita in England of five cancer medicines following the launch of the Cancer Drug Fund, indexed to use in the year to July 2010*

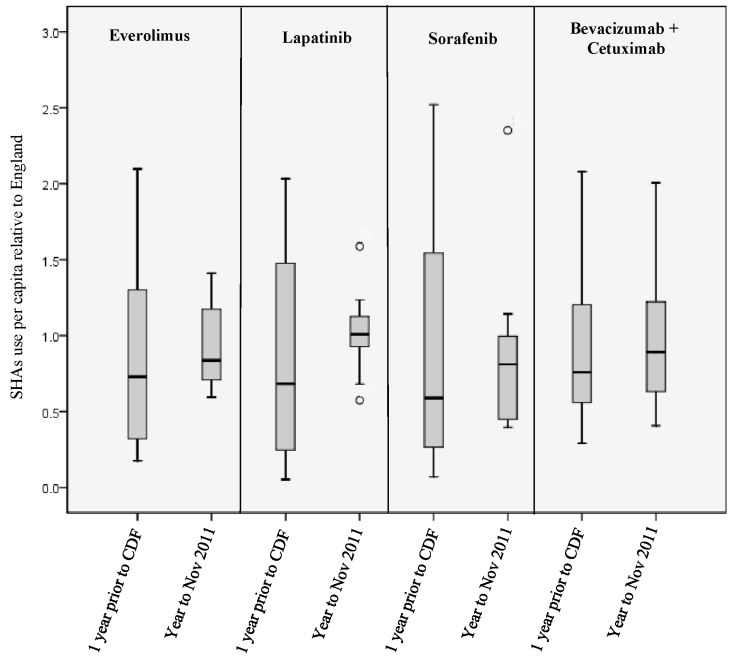

Figure 2: *SHAs' per capita usage (mg) of five cancer medicines pre and post the launch of the Cancer Drug Fund. SHAs compared to the average for England. Bevacizumab and Cetuximab are combined as in some SHAs it appeared that high use of one led to lower use of the other.*

Volume growth is, however, less than would be expected. If each application to the CDF led to a treatment dose and duration similar to those used in clinical trials then growth should be almost 4 times as high as that actually found for sorafenib, more than double that for bevacizumab and about 1.3 times higher than that for lapatinib and cetuximab. Similar results are obtained if information on dose and duration collated by IMS Health from questionnaires describing clinical practice in the year to March 2011 are used instead (see appendix for description). Actual growth is again lower than expected ($p<0{\cdot}05$) for all drugs, apart from lapatinib (see appendix for methodology). Two potential explanations for this difference between actual and expected growth – a shorter duration of treatment than expected and/or a switch of funding from the NHS to the CDF – raise a number of important questions about the value of the CDF, about the funding of cancer drugs and about the data required to understand the use of cancer medicines better.

As stated previously, in our analysis, the differences between actual and expected growth are derived from the assumption that dose and duration of treatment are similar to either those used in clinical trials or those declared in studies describing intended treatment. However, if a shorter duration of therapy or a reduced dose is assumed to be used in practice, this would have led to the observed growth rates being in line with that expected. If, however, we have to assume that duration and dose of these drugs are different

from their use in trials, and/or records of intended clinical practice then the Department of Health's impact assessment for the CDF may have to be challenged.

The Department's impact assessment assumed that the cost per Quality of Life Year gained (QALY) of drugs funded through the CDF was twice as high as that of other drugs reimbursed under the NHS (£50,000 versus £25,000). This difference was calculated to lead to a net health loss to the NHS worth £646 million [8] (estimated as an additional 25,840 QALYs that could have been generated if the money had not been spent by the CDF).

We have suggested however that drugs funded through the CDF may be being used for shorter periods of time or at a lower dose than those seen in clinical trials, trial data being the underlying basis for the Department's calculations. In clinical practice, the most likely causes of shorter therapy duration or reduced dose are earlier disease progression or adverse events. If these are the explanation for the difference between actual and expected volume growth, then it is likely that the cost per QALY of drugs funded through the CDF is higher than that anticipated in the impact assessment. This is because whilst shorter duration of therapy leads to lower drug cost, such a cost reduction is unlikely to compensate for the loss of survival benefit and/or the higher frequency or impact of adverse events. It seems likely, therefore, that the cost per QALY of drugs funded through the CDF is not £50,000 but rather more. The health loss to the NHS is thus even greater.

This, in turn, has implications for access to cancer drugs come the closure of the CDF in 2014 and the advent of Value Based Pricing. If the cost per QALY for drugs funded through the CDF is higher in clinical practice than originally assumed then access to cancer drugs may only be maintained if health gains for people with cancer are valued closer to three times as highly as those provided to others.

An alternative or additional explanation for the difference between actual and expected volume growth is, however, a switch of funding for these agents from the NHS to the CDF. In this case, not all CDF applications would generate "additional" growth. Growth in one area would be cancelled out by losses in another. Guidance from the Department of Health in England states that the CDF should be "additional funding for new activity". This would prevent any such switch. However, prior to the launch of the CDF anecdotal evidence suggests that at least some of these medicines were being funded by some Primary Care Trusts either via Individual Funding Requests (IFR) or commissioning policies. A negative NICE appraisal may have forced a review of such IFRs or commissioning policies with the result that funding by these PCTs may have ceased and then been sought from the CDF. Sorafenib, bevacizumab and everolimus all received negative NICE decisions for particular indications in this time period, although the same cannot be said for cetuximab or lapatinib.

It should also be noted that there are limitations to the IMS Health information. These limitations are discussed elsewhere but as an example, IMS is unable to collect information from all homecare providers [7]. IMS data may therefore miss some growth.

Whatever the reason for the differences, it is clear that more complete data are needed to understand how cancer medicines are used in NHS England and what their real impact is – particularly with regards to clinical outcomes. This view is reinforced by the differences

in volume per capita use seen between England and other European countries. In the year to November 2011, for the five drugs examined here, England used just 17% of the average volume per head of four European countries combined (France, Germany, Italy and Spain – data not shown). It is clear that clinicians in England use these drugs very differently to their European neighbours. At one time such differences may have been caused by reimbursement barriers in England not present in other systems. Such considerations have, however, been removed for these drugs in their licensed indications with the advent of the CDF.

Are we in England then less willing to offer chemotherapy or accept its associated toxicities? Or are the differences in volume due to use earlier or later in treatment, a smaller number of eligible patients, off label usage or use outside guidelines? As yet we cannot identify the drivers, and better data are urgently needed, some of which may be provided by the newly commissioned audit of the CDF and the roll out of the Systemic Anti-Cancer Dataset.

At this point though it is clear that the CDF has had a statistically significant impact on access to the new cancer drugs investigated here and that it has reduced the "postcode lottery" at SHA level, even if there may be some indication that not all CDF monies are being spent on "new activity". Nevertheless it is also clear that total usage remains well below that of some countries in Europe, raising the question of whether NHS England wishes to continue to measure itself against such countries or not, without a precise understanding of the details of usage in these countries. The final question that remains is what will happen to cancer patients' access to these medicines when the CDF closes in 2014? The only answer that we can give is that if access to new cancer medicines is to remain at their current levels, it appears that society may have to value effective treatments for cancer more than twice as highly as those provided by other treatments.

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APPENDIX METHODOLOGY

Data sources

Utilisation data were supplied by IMS. Data from England relates to drugs dispensed by NHS hospitals containing more than 99% of acute beds. Drugs dispensed to private patients in NHS hospitals are excluded.

Data from France, Germany, Italy and Spain includes dispensing by hospital pharmacies and specialist cancer pharmacies found in the community. Data are collected according to a stratified sampling frame, reflecting region, type and size of hospital, and then projected to give national totals.

Population numbers for each SHA were sourced from the NHS Health and Social Care Information Centre (http://www.ic.nhs.uk/pubs/gpregpop10) and for the other countries, from the CIA World Factbook (https://www.cia.gov/library/publications/the-world-factbook/fields/2119.html)

Analyses

We undertook a number of analyses in order to understand the impact of the CDF in NHS England.

1. Uptake in NHS England between July 2010 and November 2011

Volume (milligrams) per capita dispensed of each drug by month, aggregated into Moving Annual Totals (MATs).

2. Assessment of variation in usage between SHAs in NHS England

Volume (milligrams) per capita dispensed in each SHA in the year prior to the CDF launch (October 2010) compared to that dispensed in the year to November 2011.

Volumes of cetuximab and bevacizumab were combined for the SHA analysis, it appearing that, at least in some SHAs, high growth in one drug correlated with low growth in the other. Volumes of each drug were first converted to the number of treatments and then combined, each drug assumed to be being used at an average dose appropriate to the treatment of metastatic colorectal cancer.

The distribution of within SHA differences was assessed for Normality using the Shapiro-Wilk statistic in SPSS® 16.0. Differences for all were found to be Normally distributed, although differences for cetuximab almost reached significance (p=0.09). The "T test" was used to determine the confidence interval for the means for all drugs except cetuximab. A non-parametric test (Sign Test) was used to test for cetuximab within SHA differences.

The ratio of the 90th percentile to the 10th percentile of the distribution of usage per capita by SHA was used to provide a single measure of variability for each drug. This analysis mirrors prior studies of cancer drug variability at network level (http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4083895.pdf).

3. Estimated growth due to the CDF compared to actual number of CDF applications

The National Cancer Action Team (NCAT) provided the number of CDF applications by drug and month. Some applications, however, were not attributed by NCAT to month, but to the period April-November 2011 (52 for bevacizumab and one for cetuximab). Bevacizumab applications were distributed equally across these six months, the cetuximab application attributed to April 2011. It was assumed, given that 95% or more CDF applications are approved, that applications equals approvals.

Estimated growth due to the CDF was defined as the estimated number of patients benefiting from the CDF. We calculated this from four figures:

- The difference in cost at national level between the year prior to the CDF launch (October 2010) and the year to November 2011.
- The estimated average total amount, and cost, of each treatment. Average treatment length and dose used the Cancer Network Pharmacy Forum's earlier work (http://www.bopawebsite.org/publications/docs/position-statements). This in turn used data from clinical trials. Weighted averages were used where funding anticipated use across multiple indications, drawing on incidence data cited in the same source, these from NICE Technology Appraisals and/or manufacturers' data on file.
- Alternative estimates of average treatment size for specific indications were also created from pseudonymised record data (IMS Health Oncology Analyzer) for the year to March 2011. These data describe planned duration, current dose, line of therapy, diagnosis and cycle length and are derived from a routine questionnaire based survey of physicians treating cancer. Sample numbers as follows: Bevacizumab, 1st line metastatic colorectal cancer (mCRC), n=472; cetuximab, 2nd line mCRC, n=68; everolimus, 2nd line advanced renal cell carcinoma, n=9, lapatinib, 2nd line metastatic breast cancer, n=10; sorafenib, 1st line liver cancer, n=69. Average treatment size for bevacizumab used as 1st line for mCRC was also compared to its use as 2nd line treatment for mCRC (n= 106) but no significant difference was found. Similarly no significant difference was found in average treatment size between cetuximab used 2nd line or cetuximab used 3rd line in mCRC (n=18). Data were aggregated from five countries (France, Germany, Italy, Spain and the UK) due to low numbers in the UK alone in the specific indications of interest. Length of therapy was rounded up to the nearest pack in the case of oral treatments, and to the nearest whole vial (100% waste) per cycle in the case of the injectable preparations. Figures were also calculated for zero wastage.
- The proportion of total treatment completed within the year under consideration. This was calculated from the number of people starting treatment each month (based on the number of applications per month) and the average length of treatment (based on both data from clinical trials and IMS Health Oncology Analyzer).

We then compared the estimated number of people benefiting from the CDF ("estimated growth") to the actual number of applications received.

4. Uptake comparison with France, Germany, Italy and Spain

To standardise comparisons between countries, volumes (milligrams) dispensed per capita for each month between September 2009 and October 2011 were calculated for each country for each drug, converted into £ Sterling using a weighted average UK drug tariff price per mg and these figures then multiplied by the population of England. The four other countries are broadly comparable in terms of economic development, level of gross domestic product (GDP) and proportion of GDP spent on healthcare.

CHAPTER 5.2

INTERACTIONS BETWEEN SUBSIDISED AND UNSUBSIDISED ORAL CONTRACEPTIVES IN 5 FRANCOPHONE WEST AFRICAN COUNTRIES: A DESCRIPTIVE STUDY

To be submitted

Stephens P.

ABSTRACT

Objectives

To explore the interaction between the distribution of subsidised oral contraceptives and the sales of unsubsidised product through the private sector in 5 countries in francophone West Africa, and to discuss the implications for wider access and sustainability of family planning programmes.

Setting

Analysis focuses on the sale of subsidised and unsubsidised oral contraceptives. Demographic and Health survey data, subsidised and unsubsidised product sales data, and population data are combined to create two indicators.

Propositions

(1) That the potential of the private sector and social marketing organisations to work together to increase access and/or reduce countries' reliance on donor funds may be constrained if the supply of subsidised product leaves little room for unsubsidised product growth ("over-supply"); (2) That the potential of the private sector to reduce countries' reliance on donor funds is constrained if users switch from unsubsidised product to subsidised product ("substitution").

Results

There is no convincing evidence for over-supply but there are indications of substitution. Unsubsidised product volumes fell by 12% and 16% in Côte d'Ivoire and Senegal respectively.

Conclusion

Indicators point to the need for a closer understanding between social marketing organisations and the private sector supply chain if the potential role of the private sector in widening access and reducing countries' reliance on donor funds is to be realised. In addition there is a need to investigate possibilities for more complete data collection across all sectors so as to better monitor and manage social marketing programmes.

Acknowledgements

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INTRODUCTION

Family planning is regarded as one of the most cost effective interventions to improve health and accelerate development [1]. Estimates provided for 9 countries in francophone West Africa suggest that investment in family planning would avert 7,400 maternal deaths and 500,000 child deaths in the next 10 years [1, 2]. The costs of maternal and child health care in these same countries would also reduce by US$182 million in the same time period and by US$1.9 billion by 2040 [1, 2].

Donor support for family planning is substantial. Many country programmes rely on donated and/or subsidised supplies [3]. There remains, however, interest in the ability of the private sector to reduce countries' reliance on donor subsidies [3] and to improve access to health services [4, 5]. It is argued that there are advantages to working with a pre-existing, self-sustaining supply chain that is an important source of care, even for poor and disadvantaged groups within low and middle income countries [4]. In francophone West Africa, moreover, it is said that the private sector "... should be viewed as an indispensable partner in meeting reproductive health needs" [1]. The national plans for family planning of Burkina Faso, Guinea and Senegal also list greater integration of the private sector as a key action [6-8].

Attempts to integrate with, or capitalise upon, the private sector have tended to include at least one of three different characteristics – consumer information campaigns, new regulatory mechanisms to provide oversight and a means of consumer redress and the provision of subsidies to make services or products more affordable or free in the private sector [9]. Social marketing falls into the latter category. Social marketing is the application of private sector marketing techniques to the promotion and sale of subsidised products.

In many developing countries, social marketing programmes have become a critical component of national family planning and HIV prevention strategies [10]. In 2012 social marketing organisations were said to have provided contraceptives to approximately 25% of couples in the developing world that use modern contraceptives [11]. In parts of francophone West Africa, moreover, social marketing organisations have distributed contraceptives since at least 1991 [12].

Two types of social marketing model have been described in relation to reproductive health – the Non Governmental Organisation (NGO) model and the manufacturer model. Under the NGO model, the aim is to maximise the number of users. Donors fund the purchase of product and those products are then sold by social marketing organisations at prices that only allow for partial recovery of procurement, marketing and distribution costs. Sustainability of such programmes is thus entirely dependent on donor funding. Under the manufacturer model, manufacturers reduce their prices but those prices allow for full cost recovery, as well as profit. In return social marketing organisations take on other responsibilities and costs, for example, promotional campaigns. Manufacturer models are believed to be inherently more sustainable over the long term [13, 14].

Given resource constraints, donors have put in place programmes to monitor the potential of countries to graduate from the NGO model to the manufacturer model and

so work towards sustainability [14, 15]. Interest in sustainability is growing given the anticipated growth in the so-called middle class in Africa [16, 17].

Key to the question of sustainability is the health of the private sector supply chain. Recent initiatives propose that the social marketing organisations and manufacturers work together in what has been termed a "Total Market Approach" [18]. Under this approach, full priced (unsubsidised) and subsidised product both play a part in ensuring that services reach all segments of society and that donor funds are spent efficiently.

Evidence also suggests that in some cases the availability of both subsidised and unsubsidised product may be synergistic [19]. An early study in the 1980s, for example, showed that in the Dominican Republic 60 new users of unsubsidised oral contraceptives were created for every 100 served by social marketing organisations [20]. In other cases, however social marketing distribution of subsidised product has been shown to replace, rather than add to, unsubsidised product sales. In Honduras, for example, a study from the 1980s showed that half of the new customers using oral contraceptives served by social marketing came from the private sector [21]. More recently a study of condom use in Kenya from 2009 suggested that whilst social marketing of free, low and mid-priced condoms was associated with an uplift in total volumes distributed, the average subsidy per condom distributed increased and unsubsidised product volumes reduced. Unsubsidised product market share reduced from 1% of volumes to 0.6% [18].

Francophone West Africa stands at the cusp of a renewed focus and investment in family planning programmes. The Ouagadougou Partnership, a group of 9 countries, lists a series of actions that each will take, ranging from advocacy and communications through to measures to improve contraceptive security. Distribution of subsidised contraceptives was carried out by social marketing organisations in 2013 in all but one of these countries (Mauritania) [12]. The question of how social marketing programmes interact with the private sector, and whether that interaction promotes wider access and/or sustainability thus remains important to address.

This paper explores the interaction between the distribution of subsidised oral contraceptives and the sales of unsubsidised product through the private sector in 5 countries in francophone West Africa, all members of the Ouagadougou Partnership.

Analyses are based on two propositions:

1. That the potential of the private sector and social marketing organisations to work together to increase access and/or reduce countries' reliance on donor funds may be constrained if the supply of subsidised product leaves little room for unsubsidised product growth ("over-supply").
2. That the potential of the private sector to reduce countries' reliance on donor funds is constrained if users switch from unsubsidised product to subsidised product ("substitution"). In this case substitution leads to increased reliance on donor funds.

These propositions are used to develop two indicators, the combination of which may help to monitor social marketing interventions in order to improve access and sustainability.

MATERIALS AND METHODS

Setting

Data from 5 countries in francophone West Africa were used in this study - Burkina Faso, Côte d'Ivoire, Guinea, Mali and Senegal. All countries have signed the Ouagadougou Declaration. Countries were selected on the grounds that private sector sales data were available, social marketing of subsidised contraceptives through private sector channels was evident, and discussions with social marketing organisations indicated that the available data on subsidised product sales related to supply to the private sector only.

The median contraceptive prevalence rate across these 5 countries for 2008-12 is estimated as 12.9% (range 5.6%-18.2%). Contraceptive prevalence was calculated as the percentage of women in union aged 15-49 years currently using contraception. The Total Fertility Rate (TFR) for 2011, calculated as the number of children that would be born per woman if she were to live to the end of her child-bearing years and bear children at each age in accordance with prevailing age-specific fertility rates, is 5 (range 4-6). This compares to a contraceptive prevalence rate of 23.9% and a TFR of 5 for sub Saharan Africa as a whole [22].

The analysis is restricted to the use of oral contraceptives. Oral contraceptives were used by a median of 33% (range 20%-46%) of all women aged 15-49 years using modern contraceptives, according to the most recent Demographic and Health survey in each country [23]. Oral contraceptives thus play an important role in the delivery of modern contraceptives in these countries. Other contraceptive methods were not studied for three reasons: (1) Unsubsidised injectables, intrauterine devices and implants do not appear to be distributed in any great number in the private sector. These commodities thus offer little possibility of monitoring interactions between subsidised and unsubsidised product; (2) Distribution of subsidised emergency contraceptives was only evidenced in one country (Côte d'Ivoire) and this only from 2012 [12]. As such there is insufficient data for meaningful analysis of the interactions between subsidised and unsubsidised emergency contraceptives; and (3) no data were available on unsubsidised sales of condoms.

Data sources and definitions

Four different types of information were used in this study – (1) household surveys, (2) population statistics, (3) social marketing sales statistics relating to sales of subsidised product to the private sector, and (4) sales of unsubsidised product in the private sector supply chain.

The household survey data was extracted from the Demographic and Health Survey (DHS) programme. This collects accurate and representative data on population, health, HIV and nutrition. Of particular interest for this study were the DHS estimates of the numbers of women aged 15-49 using modern contraceptives, the number using each type of contraceptive method and the information relating to the source of the last contraceptive used [23]. DHS are carried out on a periodic basis. Data relate to the year of the survey. The longest gap between surveys was 13 years (Côte d'Ivoire). Information for the years between surveys was filled using linear interpolation.

Population statistics were drawn from data published by the United Nations Department of Economic and Social Affairs Population Division. The World Population 2012 Prospects: 2012 Revision produces estimates based on a variety of data sources including censuses, demographic surveys and registration systems. Of particular relevance to this study were the estimates of the numbers of women aged 15-49 years [24].

Total volumes of subsidised product delivered by social marketing organisations were taken from the data compiled by the social marketing organisation DKT International. These include statistics for all social marketing programmes reported to DKT International that have delivered more than 10,000 Couple Years of Protection (CYP) in a single year [12]. A CYP is the amount of contraceptive needed to protect a couple for a year. Fifteen cycles of an oral contraceptive are estimated to be needed to provide one CYP [25]. The DKT Contraceptive Social Marketing Statistics record information on the sales of subsidised product by the following social marketing organisations: Agence Ivoirienne de Marketing Social (AIMAS) (Côte d'Ivoire), Agence pour le developpement du marketing social (ADEMAS) (Senegal), GSMF International (Senegal), Marie Stopes International (Burkina Faso), Population Services International (Burkina Faso, Côte d'Ivoire, Guinea, Mali and Senegal) and USAID (for SOMARC and The Futures Group in Mali and Senegal). The volumes needed to provide a CYP vary by contraceptive method and these definitions have varied over time [25]. The DKT Contraceptive Social Marketing Statistics were re-based according to the latest definitions where data allowed.

Volumes of subsidised and unsubsidised product distributed by private sector wholesalers were measured using data collected from IMS Health from 13 wholesalers working across the 5 countries. A survey of manufacturers distributing product into the private sector in these countries was carried out at the end of 2013. IMS estimates were found to differ by a median of 0.3% from manufacturer's estimates in terms of value, although it should be noted that IMS' data for Guinea was found to under-estimate the market by approximately one third. IMS data were converted to CYP using the same definitions as those noted above.

Indicators

Indicator 1

Indicator 1 looks to determine if the supply of subsidised product leaves little room for unsubsidised product growth ("over-supply"). It compares the total number of women estimated to obtain any oral contraceptive from the private sector with the number of women that are estimated to have been provided subsidised product via that route.

An estimate for the number of women obtaining oral contraceptives from the private sector was calculated in two stages: (1) The percentage of women aged 15-49 using oral contraceptives in each country was extracted from available DHS. Values for each year between DHS were estimated by linear interpolation. These percentages were then multiplied by estimates of the total number of women aged 15-49 in each year, taken from the World Population 2012 Prospects: 2012 Revision. This provides an estimate of the number of women using oral contraceptives for each year; (2) these estimates were then

multiplied by the proportion of women using oral contraceptives that obtained it from the private sector, this latter figure being found in the final DHS reports for each country [26-36]. This provides an estimate of the number of women obtaining an oral contraceptive from the private sector in each year.

The private sector is defined by the DHS. It includes the private medical sector (hospitals, clinics, family planning centres, individual doctor practices, pharmacies and health workers) and other private sources (friends, shops and itinerant vendors) [26-36].

Estimates for the number of women receiving subsidised oral contraceptive from social marketing organisations was calculated from the volumes of product delivered, as shown in the DKT Social Marketing Statistics. It was assumed that one oral contraceptive CYP (15 cycles) was the equivalent of one woman indicating use of an oral contraceptive in the DHS. A sensitivity analysis was also carried out that took into account known discontinuation rates. First year discontinuation rates are known for Senegal (53.1%) and Burkina Faso (23.1%). Discontinuation was assumed to be spread evenly through the year. A discontinuation rate of 53.1% was calculated to increase the assumed number of cycles needing to be delivered to each woman in a year by 26% (i.e. from 15 to 18.85 cycles). A discontinuation rate of 23.1% was calculated to decrease the assumed number by 8%.

Indicator 1 shows the number of women estimated to have been supplied with a subsidised oral contraceptive as a percentage of the number of women estimated to obtain oral contraceptives from the private sector. Theoretically no country should be higher than 100%, although given the construction of this Indicator some imprecision is to be expected.

5.2

Indicator 2

Indicator 2 looks to determine if the potential of the private sector to reduce countries' reliance on donor funds is constrained by users switching from unsubsidised product to subsidised product ("substitution"). It compares the absolute growth of subsidised and unsubsidised product in the sales data provided by private sector wholesalers monitored by IMS. Volumes for the years 2009-10 were compared to the years 2012-13. 2009 and 2010 data, and 2012 and 2013 data, were combined in order to help eliminate distortion caused by peaks and troughs in the supply chain. Growth is expressed as the increase in CYP delivered per 1000 women aged 15-49 in each country.

Brand names were used to distinguish subsidised from unsubsidised products. The brand names of subsidised oral contraceptives were identified through internet searches and discussions with social marketing organisations. 4 brands were so identified (Confiance (Côte d'Ivoire and Burkina Faso), Planyl (Guinea), Pilplan (Mali) and Securil (Senegal)). No sales of subsidised products were found in the IMS data for Burkina Faso and Guinea, indicating distribution of these products via channels not monitored by IMS. Total unsubsidised product growth over the same period as shown in the DKT Contraceptive Social Marketing Statistics is therefore shown for comparison.

RESULTS

Figure 1 shows the results for Indicator 1. Figure 2 shows the results for Indicator 2. Indicator 2 looks for evidence of substitution or, in other words, evidence that users of unsubsidised product are switching from unsubsidised to subsidised product. The combination of these two indicators provides an interesting perspective on the interactions between subsidised and unsubsidised oral contraceptives.

As Figure 1 shows, in Burkina Faso, Côte d'Ivoire and Senegal there is plenty of room for growth of unsubsidised product and indeed it appears that unsubsidised product already plays an important role in the provision of oral contraceptives in the private sector. For example in Senegal, it is calculated that women supplied with subsidised product only make up between 23% and 32% of the whole.

Figure 1 would suggest, however, that the volumes of subsidised product distributed in Guinea and Mali exceeds the number of women estimated to obtain their oral contraceptive from the private sector. Given that Indicator 2 indicates that that there is private sector distribution of unsubsidised product in these countries as well, this suggests that Indicator 1, at least in these countries, should be used with caution. Indeed Indicator 2 would suggest that in Mali at least there is not only distribution of unsubsidised product but also growth of the unsubsidised product post 2010. In Guinea Indicator 2 would suggest an absolute

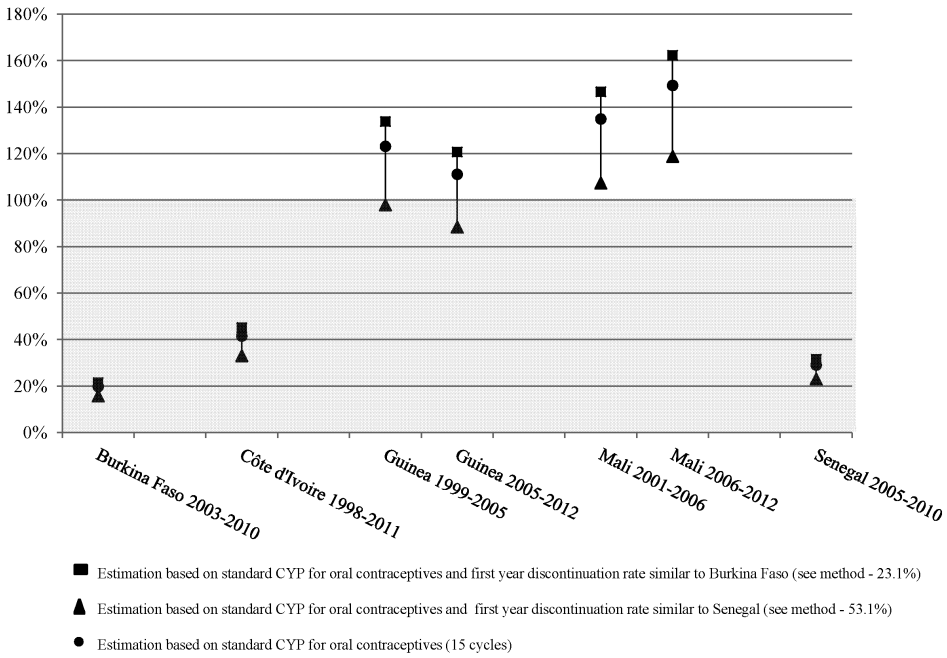

Figure 1: *Estimate of the proportion of women using oral contraceptives obtained from the private sector supplied with subsidised product*

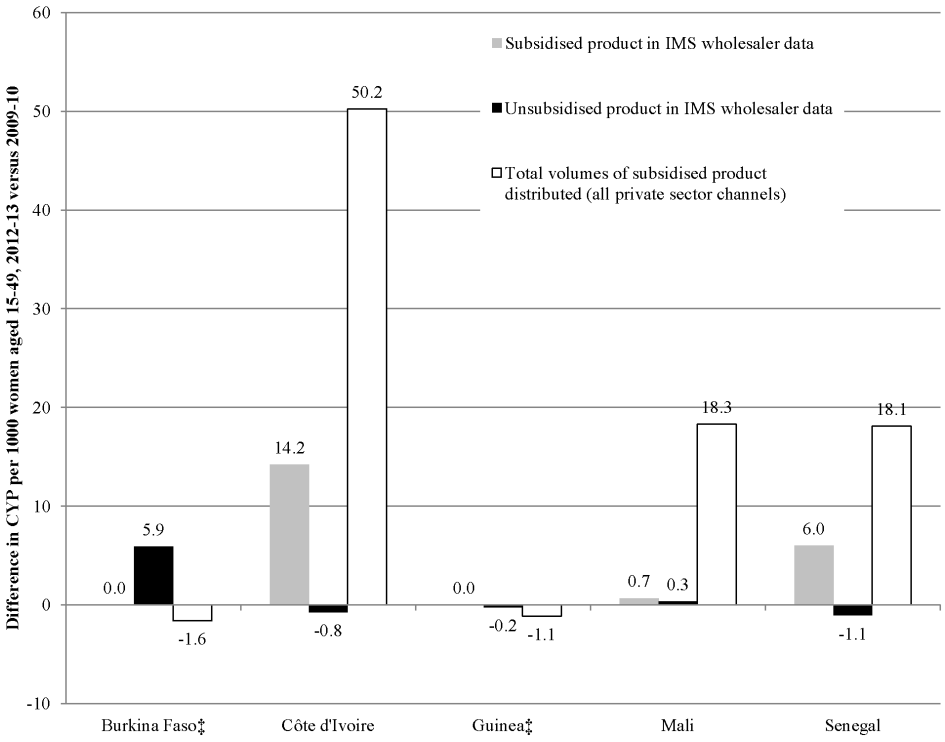

Figure 2: *Comparison of volume growth (CYP) between 2012-13 and 2009-10, split by subsidised and unsubsidised product. ‡ No subsidised brand sales were detected in the IMS wholesaler data for Burkina Faso or Guinea.*

decline in both unsubsidised and subsidised product volumes. Overall though there would seem to be no convincing evidence of over-supply in any country.

Indicator 2 does suggest however a pattern consistent with the replacement of unsubsidised product by subsidised product in Côte d'Ivoire and in Senegal. In both of these countries there is an absolute decline in unsubsidised product volumes. Unsubsidised volumes declined by 12% in Côte d'Ivoire and 16% in Senegal, whilst subsidised volumes increased by 28% and 94% respectively.

Alternative explanations for these same trends would include replacement of unsubsidised product by oral contraceptives sourced from the public sector, or relatively higher discontinuation rates by users of unsubsidised products. One driver of discontinuation would be a change in sale price or users' ability to pay. In this respect however it should be noted that cost is given as the reason for discontinuation of oral contraceptives by just 0.6% of women in Senegal and 1.4% of women in Burkina Faso [23]. In addition, in Côte d'Ivoire, if not in Senegal, there is no evidence of public sector expansion in the delivery of oral contraceptives. In Côte d'Ivoire DHS indicate that the percentage of women obtaining their oral contraceptive from the private sector increased by 15.3% (from 44.6% to 59.9%) between 1998-9 and 2011

[28, 29]. In Senegal this percentage decreased by 8% (from 25.1% to 17.1%) [35, 36], but it is not known whether this decline continued into the current study period. Indicator 1 and Indicator 2 suggest that in Burkina Faso there is both room for growth and actual growth of the unsubsidised product. To this extent Burkina Faso seems to show the ideal combination, although it should be noted that subsidised product volumes seem to have declined.

DISCUSSION

This paper describes the interaction between the distribution of subsidised and unsubsidised oral contraceptives in 5 francophone countries in West Africa. It proposes two indicators that might be used to monitor the impact of social marketing distribution of subsidised product and the effect on the private sector's ability to widen access and reduce countries' reliance on donor funds. Indicator 1 appears to be a relatively imprecise measure and should be used with caution. Nevertheless there seems to be no convincing evidence of over-supply, although trends are consistent with substitution of unsubsidised product with subsidised product in Senegal and Côte d'Ivoire.

It should be noted that the substitution of unsubsidised product with a cheaper product may actually promote wider access over the longer term. Purchase of an unsubsidised product will impose a greater economic burden on the consumer than purchase of a subsidised product. That greater economic burden may affect compliance. As noted above though, it should be noted that cost is given as the reason for discontinuation of oral contraceptives by just 0.6% of women in Senegal and 1.4% of women in Burkina Faso [23].

Likewise where analysis suggests there is little room for growth for the unsubsidised product this may actually be because the private sector is failing to provide oral contraceptives at a price that users can afford. Little room for growth therefore does not necessarily imply that there needs to be a change in social marketing strategy only that perhaps further investigations should take place to determine what, if any, can be the role of the private sector to widen access or promote sustainability.

Nevertheless it may be that in Côte d'Ivoire and Senegal it is time to think about the potential for alternative models of social marketing. The manufacturer model of social marketing has been deemed appropriate for middle income countries and both Senegal and Côte d'Ivoire were classified as lower middle income countries from 2008-9 [37]. On the other hand it may only require that social marketing organisations work more closely with the private sector to better segment the market, much as has been proposed in Kenya in the face of evidence for substitution there [18].

These indicators do however have several weaknesses: (1) In order to combine the different data sources a number of assumptions have to be made, not the least of which is that the number of oral contraceptives that provide a CYP is constant across countries and that one CYP of product distributed is equivalent to one woman indicating use of an oral contraceptive in the DHS. As we have seen these assumptions lead to certain countries appearing to deliver more subsidised product than the total of that actually obtained from

the private sector; (2) gaps between the DHS have been filled using linear interpolation whilst changes may actually have been more abrupt; (3) the IMS data is derived from a sample of wholesalers. Although there is good correlation between manufacturer and IMS estimates generally, in Guinea IMS underestimated the market by one third. Comparison between the IMS datasets and the social marketed volumes suggests also that there are other channels of supply for subsidised product not monitored by IMS. (4) the DKT Contraceptive Social Marketing Statistics only represent the sales reported to them. These may be an underestimate; (5) trends in one dataset may be associated with change in another but one cannot determine causality. and (6) absolute volumes of oral contraceptives distributed through the private sector are relatively small compared to the unmet need. Minimal changes in the supply of subsidised or unsubsidised product chain may thus appear to have apparently large effects. Whilst this is to some extent taken into account in this study by focussing on absolute rather than percentage change, interactions can be difficult to determine and studies using aggregate volume data should probably be carried out on a routine basis.

Many of the weaknesses described above relate to a lack of data, or a lack of confidence around the data. If these indicators are deemed useful, it would seem important to investigate the possibilities for regular market data collection and analysis, across all sectors of the market. This is of course a point that has been echoed by social marketing organisations themselves. Social marketing organisations have called for a "Total Market Approach", and highlighted the need to collect and use information that can be used to actively manage interventions in the market. By doing this they argue, social marketing will benefit vulnerable groups and markets will develop to serve all segments of the population [18].

In conclusion, it is clear that family planning is regarded as one of the most cost effective interventions to improve health and accelerate development, and that the use of modern contraceptives in francophone West Africa is amongst the lowest in the world. Donor support for family planning is substantial and social marketing programmes, funded by donors, have become a critical component of national family planning initiatives in many developing countries. The interaction between social marketing distribution of subsidised product and the private sector is key to the sustainability of donor programmes and cost-effective expenditure. This study proposes two indicators that may be used to monitor and manage social marketing programmes. These indicators point to the need for a closer understanding between social marketing organisations and the private sector supply chain as well as the need for the collection of more routine and complete data across both public and private sectors.

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CHAPTER 6

GENERAL DISCUSSION

INTRODUCTION

The Evidence-Based Policy Movement believed both that policy makers make little use of evidence, and that more use of evidence would improve policy [1]. Policy makers were urged to move from policy development based on common sense or ideology to one based on scientific fact [2]. For a while quantitative techniques ruled the roost, but over time the centrality of quantitative techniques was challenged and a new so-called realism emerged. This suggested that evidence informs, rather than determines, policy, and recognises that mixed methods, including qualitative techniques, are needed if complex policy problems are to be understood. This new realism was in turn born of a growing understanding of the limitations of research in general and of the emerging paradox that the more we seem to know, the more we become aware of the gaps in our knowledge [3].

Proposals for a new framework of evidence specific to policy gained ground. Unlike Evidence-Based Medicine it sets no one type of evidence above another but gives primacy to the requirements of the policy maker, and in particular, to how certain the policy maker needs to be before they come to a decision.

This evidence framework divides studies into three types – adequacy assessments, plausibility assessments and probability assessments [4]. Adequacy and plausibility assessments tell the policy maker that an intervention is associated with an effect, but not that the intervention and effect are causally related. Only probability assessments, similar to randomised controlled trials, can determine causality, and even then with a certain degree of uncertainty. Plausibility statements differ from adequacy assessments in that they attempt to eliminate, either through testing or discussion, other plausible explanations for the results seen. Adequacy statements hope simply to show that the impact of the intervention is as expected.

Probability assessments are rare in policy evaluation, for practical, methodological and ethical reasons. It may be unethical to deny a sub-population an intervention in order only that the effect of that intervention can be studied. Probability assessments can also be expensive to establish, and can take time to accumulate the necessary volumes of data to establish differences between interventions. More than this, probability assessments require a stable environment, and by and large the policy environment is not stable. In developing country institutions, we are told, the organisations that determine and implement policy are only partially functional, and the rules of engagement change rapidly [5]. To a degree this is also true of the developed world. In 2009, for example, it was pointed out that the NHS in the United Kingdom had undergone 14 major reorganisations in the previous 35 years [6]. That rate of change has continued unabated.

This thesis is founded on quantitative analysis, and constitutes a mix of adequacy and plausibility assessments. We can characterise the papers describing research and development, generic uptake in low and middle income countries and the impact of social marketing as adequacy assessments. On the other hand we can characterise the impact of patient factors on the uptake of generics in Brazil, of age on prescribing in dementia and life limiting illnesses, and on the uptake of drugs reimbursed through the Cancer Drug Fund in England as plausibility assessments. The limitations of these types of studies are generally well known. Confounding is the main drawback, confounding being the

possibility that variables other than the intervention may be independently associated with both the intervention and the desired outcome [7]. Nevertheless this thesis raises other methodological issues, notably in relation to measurement.

METHODOLOGICAL CHALLENGES

In the General Introduction, we noted the accepted wisdom that pharmaceutical R&D is in need of re-orientation towards diseases of poverty and that productivity is in decline. This thesis suggests no different. Vaccine R&D for example was shown to have suffered almost a four-fold decline over the most recent 5 years, this in turn on top of a three-fold decline in the previous 15 years or so. Pharmaceutical "gaps" remain, with several examples of a striking disparity between need and investment being highlighted. In recent months, however, this conventional view has been challenged. Other commentators spurn data relating to the early phases of pharmaceutical development. Rather they focus on the nature and revenue potential of products that have been launched. From this perspective pharmaceutical R&D seems to correlate with global disease burden [8, 9] and productivity has recovered, doubling between 2008 and 2013 [10]. And yet R&D policy, and indeed much of some countries' economic policy [11], has been founded on the view that pharmaceutical R&D is both lucrative and in trouble. So have we been measuring the wrong thing for all this time?

Or do we sometimes measure the right thing at the wrong time? In Chapter 4.2 we noted the impact of the so-called generic paradox in unregulated markets. Under the generic paradox, wider availability of cheaper generics leads to an increase in the price of the original brand. Measurement of the difference between the price of the original brand and the lowest priced generic, as is common in the WHO-HAI price surveys [12], may be appropriate at some stages of the generic lifecycle but not at others. Likewise we noted that in Brazil the gradual application of regulations requiring bioequivalence between branded generics and the original brand may have led to a slow reversal of pricing strategies. At one time only unbranded generics were required to meet these new standards and the unbranded generics were found to be priced higher than branded generics. Now it would appear that normal service has been resumed. Branded generics are found to be priced higher than unbranded generics, at least in some parts of the supply chain. In such circumstances, therefore, the past may be no guide to the future – a conclusion that echoes the main finding of this thesis' study on vaccine R&D.

If, however, it is sometimes difficult to predict the future from the past, this thesis also highlights that it can be wrong to extrapolate from one aspect of social policy into health, or even across countries. Chapter 3.1 revealed a greater complexity of gender differences in the use of medicines than had been assumed based on studies focused on gender differences in literacy, economic and political power and maternal and child health. Chapter 5.1 comments that despite the removal of funding restrictions in England, the use of certain cancer medicines in England is just one fifth of that found in similar countries in Europe. Benchmarking across countries is commonly used to compare performance [13], but in this case we wondered at its appropriateness.

The cross-country examination of gender differences described in Chapter 3.1, and indeed the studies relating to the impact of patient factors on prescribing for people with dementia and life-threatening fungal infections use databases that are either new or have rarely been used in policy research. In its use of new data sources, this thesis continues a theme of recent years. In the developing world the drive for transparency has culminated in the fact that donor proposals, grant disbursements and procurements are now readily disclosed and made publicly available, if not always though reliably or accurately. In the developed world transparency is perhaps characterised best by "Big Data", and in particular in linked "Big Data" [14, 15]. Much is expected of these new data sources. They are viewed as having "untapped potential" [16] or presenting new opportunities. However no database, not even "Big Data" can escape the fundamental problem of confounding, and no data can escape from the possibility of bias in collection or in interpretation. In this we should perhaps remember that "Scientific findings do not fall on blank minds that get made up as a result; Science engages with busy minds that have strong views about how things are and ought to be" [17].

From this perspective it is legitimate then to question the role of evidence in health policy. If bias or confounding cannot be overcome outside of probability assessments, what is the role of evidence? Are we in danger of being able only to conclude that "nothing works" or that the evidence is "too thin to suggest reliable approaches" [3]?

To analyse this it may be helpful to return to the evidence framework described earlier. Under this framework what matters is not certainty or causality but the level of certainty that policy makers require, or in other words the costs of making a wrong decision. Research can help to quantify those costs and the likelihood that policies will, or are, working. It can form a body of evidence that makes it more plausible that the impact of an intervention is as expected. The study presented here for example on the prescribing of antipsychotics in dementia within hospitals is reinforced by similar changes in the community. It is acknowledged that changes in one care setting will affect results in another and so causality is unclear. Nonetheless the fact that prescribing of antipsychotics in people with dementia can be shown to be declining in both the community and in hospital suggests that recent policy initiatives have been effective.

We should also remember that research may act as a conduit between policy and reality. In the opinion of at least one respondent to a survey in the developing world, for example, "Policy makers sit at the top of the health ministry and do not know the reality of their communities...they sit there in their air-conditioning...they are not in touch with reality" [2]. Whilst, therefore, research may not necessarily reflect reality in its totality, it may help to describe reality in ways that policy makers will understand.

In short this thesis serves to reinforce some well known facts - that no data collection is perfect, no study design all-encompassing and no interpretation necessarily without bias. At the same time it highlights new issues of measurement for policy makers to consider in their drive to increase access to medicines – notably questions of timing, granularity and extrapolation.

POLICY IMPLICATIONS

Policy making is sometimes divided into a series of distinct stages – agenda setting, formulation, implementation and evaluation [18]. This classical approach to policy making has been somewhat overtaken in recent years by a realisation that policy making is rarely linear, and that networks and political transitions play their part. Nevertheless the model still provides a useful conceptual framework and the policy implications are considered under these different headings:

Agenda setting

This thesis began by stating that the extent to which gender or age discrimination affected access to medicines was unknown. In the case of gender, inequity had been assumed to exist, this being based on studies largely focused on gender differences in literacy, economic and political power and maternal and child health. This thesis helps to inform that agenda. It is now clear that gender differences in access to care and medicines are more complex than previously thought. Gender differences in consultations tend to be country, age and condition specific. Moreover, despite the difficulties of isolating the effect of age on prescribing in dementia and in the treatment of life threatening fungal analysis, it remains plausible that age discrimination, even in a high income country, plays a part in the prescribing decision.

Policy formulation: Interactions with the private sector

This thesis describes multiple interactions with the private sector. It describes the interaction between the academic and private sectors in R&D; it comments on the interaction between social marketing organisations and the private sector in the delivery of oral contraceptives in francophone West Africa; and it notes the success of the Farmacia Popular programme in terms of the delivery of essential medicines in Brazil. These interactions reflect the view that the private sector has talents and capacity that can complement those of the public sector.

These examples come from very different fields, but it is not evident that such interactions are inevitably synergistic. Both academic and private sector R&D organisations are seen to migrate towards the more lucrative markets of the developed world. Academic and private sector R&D may then be seen to duplicate rather than to complement. Social marketing organisations are seen to distribute product in such volumes that they may threaten the sustainability of the supply chain on which they rely.

In the absence of evidence of synergy, it is possible to argue that there remains a need to better understand how to work with, as opposed to against, the private sector. Some examples may serve as pointers. Manufacturer-led social marketing models work by splitting roles and responsibilities. The social marketing organisation may take on promotion, the manufacturer distribution. Social marketing organisations and manufacturers thus agree to work together but apart, profit margins having been agreed [19]. Public-Private Development partnerships (PDPs) work in a similar way. PDPs are seen as a promising solution to address the challenges in pharmaceutical innovation [8]. PDPs agree on price and roles. Medicines for Malaria Venture for example enter into agreements with pharmaceutical companies

only where it is agreed that products sold in developing countries are preferentially priced, at profit margins more comparable to those traditionally associated with generic products than those associated with new products [20].

Public sector organisations may continue to hope that private sector organisations will devote resources to the diseases of the poor through a sense of corporate social responsibility. And many do. But like donor funding, the focus of corporate social responsibility funding can change. Long term programmes involving the private sector will be more sustainable if the private sector has a financial as well as social incentive. This does not mean that the interactions with the private sector should be seen as a panacea. There is little evidence that the private sector can serve the poorest populations at scale [21]. Manufacturer-led social marketing also involves a trade off between equity, sustainability, coverage and sometimes, quality [22, 23].

Nevertheless several commentators have stated that the private sector should be seen as an indispensable partner in the drive to widen access to medicines [24, 25]. If then such a relationship is necessary, then we should aim for synergy, not duplication or addition. A pre-requisite would appear to be an agreement on profit.

Policy formulation: The role of the patient

Payors have long recognised the power of the patient. Payors have, for example, launched public campaigns to help reduce antibiotic prescribing and to increase the uptake of generics, with some success [26, 27]. Such campaigns aim to educate, in the one case to emphasise that antibiotics will not work in viral infections, in the other that generics are equivalent to the original brand.

This thesis' examination of the use of lower cost formulations in Brazil describes the influence of the patient in a different light, however. This study found that the majority of prescribers used both generics and branded formulations on different occasions. Of itself this suggests that the patient may influence the choice of product. That much, however, is not new. Of more interest perhaps is the fact that doctors are shown to prescribe formulations that are relatively less expensive to those for whom the total burden of prescribing is likely to be higher. In the light of evidence from other countries that patients can sometimes be reluctant to raise financial concerns with prescribers, this raises a new possibility for pro-generic policies. If doctors are cognizant of the patient's economic circumstances but patients are reluctant to raise financial concerns with their doctor, then it may be that wider use of generics can be encouraged if patients can be encouraged to raise financial concerns with their prescriber.

Such a situation would, moreover, have other consequences for policy makers. We have noted elsewhere the existence of the so-called generic paradox, or in other words the existence of a segment of a population prepared to pay much higher prices for original brands. As long as the purchase of original brands does not cause financial hardship there seems no reason for policy makers to prioritise the elimination of original brands. Policy makers can only be sure however that the purchase of original brands does not lead to financial hardship if patients are able to access lower cost formulations when they want them and also feel able to raise financial concerns with both the prescriber and dispenser.

Policy Evaluation: The need for local knowledge and capacity

Research often ends with a call for more data or more rigorous research. Indeed in Chapter 4.1 it was proposed that "a more rigorous and in-depth economic and policy analysis to establish cause-effect relationships between pharmaceutical policies and, for example, the data presented here" should be carried out if generic use in lower and middle income countries was to be understood.

But more data does not really seem to be the answer. This thesis uses datasets that have rarely, if ever, been used for policy analysis before. Others also have trumpeted the emergence of new datasets in the recent past as we have seen. We are in effect living with more data than ever before.

What may therefore be needed is not more data but more "context". Context, and in particular the ability to identify or control for other plausible explanations of the phenomena seen, depends upon local knowledge and capacity. In the Developing World that capacity is said to be weak [28]. Others have gone further. Others have argued that the demands of globally driven research are stifling the use of research designs and multi-disciplinary methodologies that are needed to respond to context-specific health problems [2].

In 2006, as was mentioned in Chapter 2.1, the Commission on Intellectual Property Rights, Innovation and Public Health concluded that ..."In the longer term, the development of innovative capacity for health research in developing countries will be the most important determinant of their ability to address their own need for appropriate health-care technologies"[29]. The Commission was speaking here in relation to pharmaceutical R&D but it would appear to apply equally well to the development of health policy research.

Policy implementation: The "Politics Stream"

Policy has been described as the product of different "streams" – the Problem Stream, the Policy Stream and the Politics Stream. The Problem Stream contains the issues facing society, the Policy Stream the range of possible interventions, and the Politics Stream, the political transitions and social pressures that lead to certain problems being addressed and particular interventions being preferred [18].

In this thesis we see the Politics Stream reflected in the adoption and continuation of the Cancer Drug Fund in England. In Chapter 5.1 we noted that the Cancer Drug Fund (CDF) in England is based on the premise that society values effective treatments for cancer twice as highly as those for other disorders. It was launched as "a means of improving patient access to cancer drugs" and as the start of "plans to address the disparity in patients' access to cancer drugs in England compared to other countries" [30, 31].

In this thesis, however, we noted that early data suggests that the cost per Quality of Adjusted Life Year of drugs funded by the CDF is higher than expected and that as such the health loss to other parts of the NHS is even higher than anticipated. In this view this paper has not been a lone voice. The announcement of the CDF itself was met with accusations of inequity [32]. More recent analyses suggest that the CDF may be hindering the uptake of more cost-effective drugs [33]. And yet the CDF continues [34].

This thesis does not purport to study the Politics Stream. Nevertheless the creation of the CDF does seem to be a reflection of it. Other medicines had been subject to a range of reports indicating lower levels of use than expected. Other therapy areas have been the focus of special attention from clinicians appointed as so-called Tsars [35]. And yet we have only a Cancer Drug Fund – and this launched immediately following electoral debate.

It seems therefore that the Cancer Drug Fund can serve to illustrate a point of significance – that policies can be the product of a fortuitous confluence of evidence, social pressure, individual actors and political exigency.

CONCLUSION

This thesis asked whether access to medicines could be characterised in terms of common problems and common solutions. In doing so it has addressed four cross-cutting controversies relating to pharmaceutical R&D, equity, generics policies and scale up.

This thesis finds there are certainly common problems. Declining pharmaceutical productivity affects everyone. Gender inequality is found across multiple countries, even if the picture is rather more complex than first seemed. Age discrimination appears to persist even where resources are greatest. Private sector relations, whether that be in R&D or in healthcare delivery, are not as productive as they might be. And confounding confounds us all.

Plus lessons have been learned. We have learnt that several prior assumptions in policy research cannot now be sustained. We cannot now for example assume that all women in low and middle income countries have consistently low access to medicines; we cannot now assume that social marketing will always strengthen the private sector; and we cannot now assume that historical or cross country benchmarks are necessarily appropriate measures of performance.

More than this, this thesis has reinforced certain themes related to policy setting, formulation, evaluation, and implementation. In particular it provides pointers to the ways in which it may be appropriate to work with the private sector and how one might harness the power of the patient over the prescribing decision. It also echoes the calls for greater investment in local research capacity and greater awareness amongst policy researchers of the so-called Politics Stream.

But if there are common problems and common lessons, however, one should be wary of suggesting that there exist common solutions. This thesis has described variation between countries, between diseases and between different sectors of the health system. It has emphasised the importance of context in methodology, measurement, and interpretation. Against such a background common solutions or common methodologies may be entirely inappropriate.

Others in the PhD programme at the WHO Collaborating Centre for Pharmaceutical Policy and Regulation within the Utrecht Institute for Pharmaceutical Sciences have similarly emphasised the importance of context and the need to match methodology to local circumstance. We have been urged to recognise the importance of "adequate information on the pharmaceutical policy context" [36]. We are reminded that "Any intervention must therefore be based on a clear understanding of the underlying issues in the national

context" in relation to understanding the impact of interventions in low and middle income countries [37]. And as the dynamics of pharmaceutical markets are reviewed, we note that "Multidisciplinary approaches need to be developed and adapted as the global health and policy landscapes evolve" [16].

When faced with the need for a multidisciplinary approach or the sharing of knowledge, the academic community has often called for, or established, networks of like-minded institutions or individuals. For example to realise the potential of stratified medicine, it is stated that a funded EU research network could help in identifying "opportunities in research, strengthening collaborations within Europe, contributing to standardization processes, and organizing educational and scientific conferences" [8]. In relation to pricing and reimbursement in Europe it is argued that it is "critical to build and support a research infrastructure that is able to create a research network that links all stakeholders and existing networks..." [8]. To unlock the value of real world evidence data collection policy makers are asked to fund "a European research network for comparative effectiveness and health policy evaluation", the key focus of which would be methodology development and the facilitation of a dialogue about the availability and use of real life data [8]. Health policy networks are also hardly rare, and many are of long standing. Some at least have been established or adapted in such a way as to promote a multidisciplinary approach [38].

A common response to the need for multidisciplinary working and methodological development appears thus to be a call for a network to be established. Health policy appears to require detailed information on local context and methodological development. But do we really need another network?

The calls for funded networks seem to reflect two beliefs – first that a network is essential if the requisite experience is to be brought to bear, and second that without funding such networks will collapse or fail in their objectives. This much seems clear but at this point it is perhaps worth pausing to examine the Innovative Medicines Initiative (IMI). The IMI aims to boost pharmaceutical R&D through networks or collaborations between large pharmaceutical companies and other key actors in the healthcare ecosystem, notably academic institutions, small and medium enterprises, patients, and regulatory authorities. Not always easy bedfellows, these organisations have come together to focus on what is termed "pre-competitive" research. Pre-competitive research is research that is useful to all but leads to no direct competitive advantage [39].

Health policy and academia may not be as competitive as pharmaceutical R&D but competition does exist – for staff, students, grants and other forms of funding, within and across countries [40]. Given this level of competition across all sectors interested in pharmaceutical policy, both public and private, perhaps health policy also needs to define what might fall into pre-competitive research and to use this knowledge to create networks that draw on the experience and expertise of all sectors. Certainly it would seem that information on local context, and perhaps on certain methodological advice, would be candidates.

But we have to return to the question of funding. The IMI is after all funded to the tune of more than €2bn. Such sums are unlikely to be found for health policy networks, these being

rather more divorced from industrial policy. A reliance on funding may, moreover, restrict the numbers of those willing to contribute. Experts may not wish to contribute free of charge if their peers are being paid. For pre-competitive health policy research perhaps we need a different route and for this we might learn from "Wikipedia", an online encyclopaedia that presents the "wisdom of crowds". As of December 2013 it contains 30 million articles written in more than 287 language editions [41]. If nothing else Wikipedia tells us that certain people want to write about what they know. Could they write about context relevant to health policy evaluation? And if so could a Wikipedia for policy be an answer?

Academics however are said not to contribute to Wikipedia. Whatever the reason, and some have argued it is a combination of the academic ego and the lack of incentives to contribute [42], the lack of academic expertise in contextual information will lead to inaccuracies and perhaps a lack of an appropriate frame. Private sector contributions may also be rare, again because of the lack of incentives and also perhaps due to the potential for conflict of interest. And citizens can hardly be expected to provide information on methodologies specific to health policy research. There is though a spin-off from Wikipedia that may provide a pointer. "Citizendium" requires contributors to use their real names and whilst expert authors can be recognized with a special role, membership is open to all [42]. In Citizendium therefore the academic ego and the private sector need for recognition and image can be satisfied at the same time as citizens can provide personal experiences or opinions. Perhaps Citizendium, or something like it, is the platform for pre-competitive health policy research. It is established, cheap and more than this would provide a medium for critical information and methodologies to be shared, through the lens of both academic and personal experience. Moreover health policy researchers are urged to provide information to policy makers relevant to their needs and in a format useful to them [44]. Policy makers could reciprocate by providing information on policy initiatives in a format that was more easily digestible through such a forum. Health policy researchers would also value the policy makers viewpoint on the policy background. An on-line forum like Citizendium may thus provide the necessary incentives for valuable information on context to be shared over the long-term.

A question might be then how to start such a forum. Again we might look to Wikipedia. It appears that in at least one case Wikipedia is being used as a teaching resource [42]. At the University of Hull's Scarborough school of arts and new media, students write or update pages about practitioners and broad concepts in the field. Is there then a role for Universities and in particular some of the departments of global health? Certainly it would appear from an analysis of editing of Wikipedia that once a core set of information is established, the majority of maintenance and updating is carried out by a smaller set of willing volunteers [45]. In the case of a health policy forum, those volunteers might come from academia, some from the private sector and some from the civil service or government.

So common problems, common lessons, no common solutions, but perhaps a common platform.

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CHAPTER 7

SUMMARY AND SAMENVATTING

CHAPTER 7.1

SUMMARY

At least one third of the world's population has no regular access to medicines. Even in the developed world achieving equitable access to good quality care is difficult. Two main challenges have been highlighted - first how to increase access to existing medicines and second how to promote the development of new medicines.

Investigators are encouraged to take a systems approach to the study of medicines access. Here the health sector is seen as part of a wider system, one where social and cultural conventions as well as political and economic forces drive access and innovation. Environmental trends include the dramatic increases in funding for AIDS, TB and malaria, the drive towards data transparency and economic growth in Africa. As regards the latter it is claimed that East Africa will reach Middle Income status in the next 10 years if current trends continue.

This thesis investigates four cross-cutting controversies in access to medicines – aspects of pharmaceutical R&D, equity, generics policy and scale up. It asks whether access to medicines can be characterised in terms of common problems and common solutions.

Chapter 1 places these four challenges in context. Pharmaceutical R&D is said to be in decline with some going so far as to say that the capacity for R&D is being progressively dismantled. Declining innovation poses challenges for health and economic policy alike. Equity, or the absence of avoidable or remediable differences among groups of people, is considered from the perspective of gender and age. Here the evidence is described as weak or absent, but equity remains at the forefront of policy formulation. Generic policies are, on the other hand, widely implemented and described and form a key component of policies to counter high prices. Little however is known about generic markets in low and middle income countries or the impact of patient or doctor factors on product choice in such markets. Attitudinal studies had given conflicting results. Successful scale up of pilot programmes requires adequate budgets, absorptive capacity at macroeconomic, health system and community levels, planning and implementation ability, and a focus on equity and quality. Ring-fenced funding can provide the budgetary focus, or so it is argued, whilst interactions with the private sector are viewed as being indispensable if targets for high priority disease programmes are to be met. Social marketing is one such private sector strategy and while it is said to show promise, it has been argued that the evidence relating to impact, feasibility and equity is unclear.

This thesis examines these four challenges through a multi-country lens. Like others it takes the view that there is a commonality of interests driven in part by the increasing burden of non-communicable disease. It also argues that given the paucity of some types of data, notably patient data, in the developing world, the developed world may be able to provide policy makers in other countries pointers of what to do, or more likely what not to do, and of what to be aware. Each study or theme is therefore placed within its own context, whether that be national, regional or country income level but the thesis attempts to highlight cross-cutting themes that will be relevant to policy makers in multiple settings.

Chapter 2 sets out the current state of pharmaceutical research and development (R&D), and in particular addresses issues of productivity, focus and interactions between the public and private sectors. Such analyses form the basis of policies to address the second major challenge highlighted above – how to promote the development of new medicines. **Chapter**

2.1 examines the susceptibility of drug development to failure by examining the progress of molecules in active development at particular points in time. It finds that overall failure rates remain high with for example only 11% of compounds in pre-clinical development progressing beyond that phase. It also finds that the vast majority of molecules in development are for non-communicable disease (~85%), and that there remain some striking discrepancies between disease burden and R&D activity, despite the industry's growing role in the funding of research into treatments for neglected disease. Public and private sector R&D are also found to duplicate rather than complement. There would appear to be no difference between academic and private sector activity. Non-communicable disease R&D predominates with a similar emphasis on malignant neoplasms and neuropsychiatric conditions. Chapter 2.1 concludes with a summary of future issues, notably that with productivity stable or declining, the escalating costs of pharmaceutical R&D will make investments unaffordable for many diseases affecting both low and middle income countries. This is one of the reasons why the Commission on Intellectual Property Rights, Innovation and Public Health concluded in 2006 that "In the longer term, the development of innovative capacity for health in research in developing countries will be the most important determinant of their ability to address their own need for appropriate health-care technologies."

Chapter 2.2 investigates one particular area of pharmaceutical R&D in more depth. It examines activity as it relates to vaccines. Vaccines have been said to offer the most cost-effective solution to prevent both communicable and non-communicable disease in poor countries. Like pharmaceutical R&D overall, published analyses point to a declining success in vaccine research. This study updates those latest analyses, finding that the observed probability of market entry between 2003 and 2013 was just 1.8%, almost a fourfold decline over 5 years. The study highlights however that this decline occurred within the context of a very different product portfolio from that seen earlier. New technologies, notably DNA vaccines, have emerged. There is now a focus on both prophylactic and therapeutic vaccines with the latter making up 38% of the total in this latest study. Success rates were shown to differ by type of vaccine (prophylactic or therapeutic), by disease target (infectious disease versus cancer) and by technology (DNA or other). Given the change in portfolio the paper argues that the past is no guide to the future. Nonetheless a probability of market entry of just 1.8% is very low and has to be of concern. Literature suggested that the reasons for the failures in vaccine research included the scale of the scientific challenge, the shrinking levels of investment and a lack of co-operation between and within academia and industry. This latter seems to be the greatest challenge with some arguing that vaccine development has not kept pace with breakthroughs in basic science and technological development.

Chapter 3 addresses the question of inequity of access to medicines in terms of age and gender. Gender equity has been a concern in many social and economic domains, including health, but information on the effect of gender is sparse. The same is true of the effect of age. In the case of gender, policies have been created on an assumption that there is systematic bias against women. Chapter 3 suggests that the situation is rather more complex, and that the potential for confounding is large. In **Chapter 3.1** gender differences in access

to prescribed medicines in 15 lower and middle income countries are examined. The proportion of consultations with at least one prescription for women with acute respiratory tract infections, depression and diabetes is compared to the expected proportion calculated from the WHO Global Burden of Disease estimates. Overall the pattern of gender differences in consultations tends to be country, age and condition-specific. The results challenge prevailing hypotheses of systematic disparities in access to care for women. **Chapter 3.2** also finds significant associations between age, gender, deprivation and ethnicity and the use of the high cost antifungal medicines in the treatment of life-limiting illness but the direction of those associations is not found to be consistent across disease groups. The study analyses the dispensing of low and high cost formulations of antifungal treatments. It uses a database of pseudonymised patient records extracted from hospital pharmacy systems in 34 English acute general hospitals that had been linked to a National Health Service database of diagnoses and procedures. It compares the use of high and low cost formulations of antifungal medicines across different disease and age groups. Stepwise regression is used in an attempt to disentangle the effect of disease, age, gender and deprivation whilst literature review is used to discuss the potential impact of co-morbidities, contra-indications and guidelines on the results seen. A negative association between increasing age and the use of a high cost antifungal is found overall but the direction of this association is not consistent across all disease groups. No simple explanation for the results seen could be found and the study concludes that the drivers of antifungal therapy in hospital are complex, that antifungal stewardship poses a significant challenge for pharmacy, but that systematic bias against the elderly seems unlikely. **Chapter 3.3** uses the same database to examine the prescribing of antipsychotics in people with dementia. Antipsychotics have been used to control the behavioural and psychological symptoms associated with dementia but their use is associated with side-effects including sedation, parkinsonism, gait disturbance, dehydration, falls, chest infections, accelerated cognitive decline and death. Their use is generally discouraged with an independent report into the treatment of people with dementia in England suggesting that it ought to be possible to reduce the use of antipsychotics by two thirds within three years. Over-use of antipsychotics is viewed as an indicator of denial of more appropriate (non-drug) treatments to the elderly. The study shows that there was a significant decline ($p<0.001$) in the use of antipsychotics in inpatients with dementia between 2010 and 2012, that almost one third of patients with signs and symptoms of emotional state are treated with an antipsychotic, and that, in this study at least, an antipsychotic is still used to treat a person with dementia in more than one in eight episodes of hospital care.

Chapter 4 attempts to shed light on the success and drivers of pro-generics policies in low and middle income countries. Pro-generic policies are used in high, middle and low income countries to lower total pharmaceutical expenditures. They are regarded as being a key component of access to medicines policy. Having said that, like many other areas addressed in this thesis, there was much that was unknown. It remained true for example that comparatively little was known about the private sector pharmaceutical market in low and middle income countries and even less about the market dynamics between originator and generic versions

of the same medicine. Likewise whilst few lower and middle income country studies used actual prescribing data, attitudinal studies had produced conflicting results as to the impact of patient and doctor characteristics on the prescribing choice. **Chapter 4.1** attempts therefore to answer two questions – first what are the trends of originator and generic medicines in the private sector of selected low and middle income countries and second, what patterns can be observed in the relationship between the market shares of originators and their generic counterpart? In this study generic market share varies markedly across countries. Generic market share in Latin America is approximately three times that of the Middle East and Asian countries studied, and branded generics dominate. Decline in the share of the originator is sometimes taken to indicate savings for patient or payor. Closer analysis of these data at least suggests that the actual situation is rather more complex. One cannot now simply assume that if the market share of an originator has decreased then its counterpart generic has increased. For many countries this assumption is found not to hold.

Few low and middle income countries have been as successful as Brazil at generic expansion. **Chapter 4.2** aims to investigate the impact of the characteristics of doctors and patients on the use of low cost formulations of generic medicines in Brazil, attitudinal studies both within and across countries having given conflicting results, as noted above. The study employs a combination of univariate analysis and multi-level modelling to investigate the records of individual consultations by doctors across multiple specialties working in both the public and private sectors. Doctors are found to prescribe less expensive formulations of medicines to those patients with co-morbid conditions and those needing treatment with higher priced medicines. Doctor and patient demographics had little effect, although age is found to be significantly associated with a lower price ratio. The fact that the extent of out of pocket payment seems to affect choice of brand is thought to be important. At least one other study in another country indicates that patients are reluctant to raise financial concerns with their doctors. In Brazil it is clear that the majority of doctors use both generic and/or low cost brands. It is suggested therefore that the next phase of generic expansion in Brazil may be to help patients raise concerns over price with their doctor, where this is appropriate.

Chapter 5 concerns itself not with the policy itself but how it should be financed and implemented. In particular it looks at the impact of ring-fenced funding and interactions with the private sector supply chain. **Chapter 5.1** looks at the impact of the Cancer Drug Fund in England, a ring-fenced fund for the procurement of cancer drugs not funded by the National Health Service but nevertheless deemed clinically, if not cost, effective. It compares actual growth rates with that expected given the number of patients provided with drug by the Fund. Actual growth is found to be lower than expected, giving rise to the hypothesis that dose and/or duration of the drug is somewhat less than had been found in clinical trials or in studies describing intended treatment length and dose. Further analysis suggests that whilst the Fund had been established with the view that society values cancer treatments more than twice as much as treatments for other diseases, one explanation for the results seen was that the ring-fenced fund had actually led to a greater health loss to the NHS than envisaged. This study suggests therefore that ring-fenced funding may worsen inequality between disease

groups, even if, as was also demonstrated in this study, variation between geographic regions in the delivery of the cancer medicines themselves reduced. **Chapter 5.2** examines the impact of one particular strategy for capitalising upon the strengths and capacity of the private sector. It investigates the delivery of subsidised and unsubsidised oral contraceptives in 5 francophone West African countries through the private sector. Analyses are based on two propositions: (1) That the potential of the private sector and social marketing organisations to work together to increase access and/or reduce countries' reliance on donor funds may be constrained if the supply of subsidised product leaves little room for unsubsidised product growth ("over-supply"); and (2) That the potential of the private sector to reduce countries' reliance on donor funds is constrained if users switch from unsubsidised product to subsidised product ("substitution"). These propositions are used to develop two indicators, the combination of which may help to monitor social marketing interventions in order to improve access and sustainability. Results show no convincing evidence for over-supply but there are indications of substitution. Unsubsidised product volumes fell by 12% and 16% in Côte d'Ivoire and Senegal respectively. The study suggests that at a minimum there is a need for a closer understanding between social marketing organisations and the private sector supply chain if the potential role of the commercial sector in widening access and reducing countries' reliance on donor funds is to be realised. This may include a change in the social marketing model used. In addition there is a need to investigate possibilities for more complete data collection across all sectors so as to better monitor and manage social marketing programmes.

The chapters outlined above address particular controversies in access to medicine policy. **Chapter 6** discusses the methodological and policy implications of these studies.

Methodological implications raised relate mainly to measurement - what to measure, when to measure and how or when one can extrapolate from other disciplines, other countries or even the past. These considerations lead to a discussion as to the role of evidence in health policy and to a commentary on the use of information and evidence by policy makers. That commentary describes the emergence of a new framework of evidence, one based around adequacy assessments, plausibility assessments and probability assessments.

Policy implications are considered within the linear framework of agenda setting, formulation, implementation and evaluation. This remains a useful conceptual framework even if it is acknowledged that it has been overtaken in recent years by a realisation that policy making is rarely linear and that networks and political transitions play their part.

Several studies in this thesis are seen to inform the policy setting agenda, but most notably those that consider the extent to which gender or age discrimination affects access to medicines. It is clear that the situation is more complex than may have been assumed, and that isolating the effects of age and/or gender will be difficult. Nonetheless differences between age groups and between men and women exist, and whilst systematic bias can be ruled out it remains plausible that they play a part in the prescribing decision.

Two areas are highlighted in relation to policy formulation – the role of the private sector and the role of the patient. Different models of working with the private sector are described and an argument is made that if nothing else, successful, sustainable relationships require

an agreement on margins and/or price. As for patients, whilst it is acknowledged that policy makers have long attempted to harness the power of the patient in their attempts to constrain the actions of prescribers and dispensers, it is suggested that the extent to which patients' financial concerns can be raised with doctors may usher in a new phase in generic expansion.

The extent to which local knowledge and expertise is needed to evaluate policy results was evident in many of the studies. Lack of detailed knowledge of systems and policies within and across countries will hinder interpretation. Policy evaluation requires local knowledge and capacity. Other commentators have argued that that capacity is weak in the developing world. It is therefore argued that the strengthening of local research capacity in the developing world is important if the barriers to access to medicines are to be overcome. Implementation is also considered from the perspective of the so-called "Politics Stream", the political and social pressures that lead to certain problems being addressed and particular problems being preferred. This thesis does not purport to study the Politics Stream but we are reminded of its importance by the description of the origin and continuing debates over the Cancer Drug Fund in England. It is clear from this description that policy implementation can be the product of a fortuitous confluence of evidence, social pressure, individual actors and political exigency.

This thesis asked whether access to medicines could be characterised in terms of common problems and common solutions. It finds that certainly there are common problems – including declining pharmaceutical R&D productivity, gender inequality, age discrimination and the question of how to work with the private sector. We have also found common themes or lessons. Complexity looms large. Gender discrimination appears to affect both women and men, and varies by age and condition. The success of social marketing depends on the stage of market and economic growth, as well as closer relations with the private sector. And given this complexity, we echo the call for greater investment in local research capacity.

This complexity warns against proposing common solutions. The thesis emphasises the importance of context in methodology, measurement and interpretation. The question remains however as to how such contextual information can be generated.

Chapter 6 points out that faced with similar situations the academic community has often called for, or established, networks of like-minded institutions or individuals. Funding for such networks is, however, likely to be in short supply. The thesis ends therefore with the proposal that contextual information might fall into a category of "pre-competitive" research, in other words research that is useful to all but leads to no direct competitive advantage. If contextual information does fall into the pre-competitive research category, other opportunities emerge, most notably those that utilise the "wisdom of crowds". It is proposed that Citizendium, a spin off of Wikipedia (itself an on-line encyclopaedia written collaboratively by the people who use it), may provide a pointer. Like Wikipedia, Citizendium is an on-line forum to which people contribute information. Unlike Wikipedia, however, Citizendium would appear to satisfy both the academic and private sector need for recognition. Membership is open to all but expert authors can be recognized with a special role, and all contributions are attributed. Citizendium, or something like it, may therefore provide a common platform to which all would contribute. And by doing that health policy research would be enhanced.

CHAPTER 7.2

SAMENVATTING

Tenminste een derde van de wereldbevolking heeft geen directe toegang tot geneesmiddelen. Ook in ontwikkelde landen is het moeilijk om universele toegang tot kwalitatief hoogstaande zorg te waarborgen. Twee belangrijke uitdagingen zijn het verbeteren van de toegang tot bestaande geneesmiddelen en het stimuleren van de ontwikkeling van nieuwe geneesmiddelen.

Het is van belang dat onderzoek naar toegang tot geneesmiddelen een systeembenadering kent. Hierbij wordt de gezondheidssector als onderdeel van een meer omvattend systeem bestudeerd. Zowel sociale en culturele conventies als politieke en economische factoren vormen daarin de drijvende krachten achter toegang tot geneesmiddelen en innovatie. Tot de belangrijkste maatschappelijke ontwikkelingen behoren de toegenomen kosten voor de behandeling van AIDS, tuberculose en malaria, de roep om meer openbaarheid van gegevens en de economische groei in Afrika. Als de huidige trend wat dat laatste punt betreft doorzet, zullen landen in Oost-Afrika binnen tien jaar tot de middeninkomenlanden gaan behoren.

In dit proefschrift worden vier 'cross-cutting' controverses met betrekking tot toegang tot geneesmiddelen bestudeerd - onderzoek en ontwikkeling (R&D), rechtvaardige verdeling, beleid ten aanzien van generieke (merkloze) geneesmiddelen en opschaling van zorgprogramma's. Daarbij staat de vraag centraal of er gewone, algemene problemen en algemene oplossingen kunnen worden geïdentificeerd.

Hoofdstuk 1 plaatst deze vier uitdagingen in een bredere context. De algemene teneur is dat farmaceutische R&D zou afnemen en de huidige R&D capaciteit zelfs in hoog tempo zou worden ontmanteld. Minder innovatie leidt tot nieuwe uitdagingen voor zowel de volksgezondheid als voor het economische beleid. Een rechtvaardige verdeling, oftewel de afwezigheid van te voorkómen of niet te repareren verschillen in het aanbieden van zorg tussen groepen mensen, wordt vaak bekeken vanuit de vraag of er verschillen zijn tussen mannen en vrouwen of leeftijdsgroepen. Hoewel er niet of nauwelijks bewijs is dat er sprake zou zijn van een onrechtvaardige verdeling binnen de gezondheidszorg, staat dit thema desalniettemin hoog op de politieke beleidsagenda. Beleid ten aanzien van generieke geneesmiddelen is daarentegen op grote schaal geïmplementeerd en bestudeerd en maakt een wezenlijk deel uit van beleid om hoge geneesmiddelenprijzen tegen te gaan. Er is echter weinig bekend over de generieke markt in lage- en middeninkomenlanden en de invloed van patiënt- of artsgerelateerde factoren op de keuze voor een bepaald product in die landen. Onderzoek naar attitudes van patiënten en artsen heeft daarbij tot nu toe tegenstrijdige resultaten opgeleverd. Tot slot vraagt een succesvolle opschaling van pilot programma's in de zorg voldoende budget en personele capaciteit op alle niveaus, van macro-economie tot op de werkvloer, het vermogen tot planning en implementatie en een focus op een rechtvaardige verdeling en kwaliteit. Het reserveren van financiële middelen voor specifieke doeleinden zou de noodzakelijke budgettaire focus kunnen geven, terwijl samenwerking met de private sector onontbeerlijk lijkt om de doelen van de belangrijkste zorgprogramma's te kunnen bereiken. Daarbij is 'social marketing' een mogelijk veelbelovende strategie, waarvan de impact, haalbaarheid en rechtvaardigheid echter onduidelijk zijn.

Dit proefschrift bestudeert deze vier uitdagingen in verschillende landen. Evenals in eerder onderzoek wordt er vanuit gegaan dat deze landen een gemeenschappelijk belang

hebben, met name door de wereldwijde toenemende ziektelast ten gevolge van chronische aandoeningen. Onderzoek uit ontwikkelde landen kan beleidsmakers in andere landen mogelijk aanknopingspunten bieden wat zij zouden kunnen doen, moeten laten of waar ze bedacht op moeten zijn. Dit is met name van belang omdat goede gegevens, en dan vooral gegevens op patiëntniveau, vaak ontbreken in ontwikkelingslanden. Elk onderzoek of thema wordt daarom binnen de eigen nationale of regionale context geplaatst, terwijl er tevens wordt beoogd om 'cross-cutting' thema's te beschrijven die relevant zijn voor beleidsmakers in verschillende settings.

Hoofdstuk 2 analyseert de stand van zaken binnen het huidige farmaceutische onderzoek- en ontwikkelingsprogramma (R&D) en gaat daarbij in op thema's als productiviteit, focus en samenwerking tussen de publieke en private sector. Dit vormt de basis voor verder onderzoek naar de tweede uitdaging die hierboven is beschreven; het stimuleren van de ontwikkeling van nieuwe geneesmiddelen. In **Hoofdstuk 2.1** werd door het in de tijd volgen van moleculen in hun ontwikkelingsfase onderzocht in hoeverre geneesmiddelenontwikkeling vatbaar is voor mislukkingen. Dit onderzoek bevestigde dat veel middelen in de eindstreep uiteindelijk niet halen. Slechts 11% van de geneesmiddelen in pre-klinisch onderzoek kwam bijvoorbeeld voorbij deze fase. De overgrote meerderheid van de moleculen (~85%) in ontwikkeling bleek voor chronische ziekten zijn. Er waren daarnaast opvallende discrepanties tussen wat er wordt ontwikkeld en wereldwijde ziektelast, ondanks de toenemende rol van de farmaceutische industrie in de financiering van onderzoek naar tropische ziekten die tot nu toe weinig aandacht kregen. Het onderzoek binnen de publieke en private sector bleek elkaar vaak te overlappen in plaats van complementair aan elkaar te zijn. Het onderzoek naar chronische ziekten waaronder maligniteiten en neuropsychiatrische ziekten overheerste in beide sectoren. Dit hoofdstuk eindigt met de conclusie dat de snel stijgende kosten voor R&D met de huidige of afnemende productiviteit verdere investeringen voor ziekten die in lage- en middeninkomenlanden voorkomen onbetaalbaar maken. Dit is één van de redenen dat de Commission on Intellectual Property Rights, Innovation and Public Health in 2006 concludeerde dat "op de langere termijn de ontwikkeling van voldoende innovatieve capaciteit voor gezondheidsonderzoek in ontwikkelingslanden de bepalende factor zal zijn in hun vermogen om tegemoet te komen aan hun eigen behoeften aan geschikte technologieën."

In **hoofdstuk 2.2** wordt een specifiek deelgebied binnen de farmaceutische R&D, de ontwikkeling van vaccins, nader bestudeerd. Van vaccins wordt gezegd dat zij de meest kosten-effectieve methode zijn om zowel besmettelijke als chronische ziekten in arme landen te voorkomen. Eerdere studies wezen op een mogelijk afnemend succes in onderzoek en ontwikkeling van vaccins. Dit onderzoek geeft meer recente resultaten en laat zien dat de kans dat een vaccin op de markt kwam in de periode 2003 tot 2013 slechts 1,8% bedroeg. Dit is een viervoudige afname binnen een periode van slechts 5 jaar. De ziekten waarvoor deze vaccins werden ontwikkeld waren echter aanzienlijk anders dan in voorgaande periodes. Nieuw technologieën zoals met name DNA vaccins zijn in opkomst en er is naast profylactische vaccins ook aandacht voor de ontwikkeling van therapeutische

vaccins (38% van alle vaccins in dit onderzoek). Slagingspercentages werden in deze studie berekend voor verschillende type vaccins (profylactisch of therapeutisch), ziektegebieden (infectieziekten versus kanker) en technologie (DNA versus andere technologieën). Omdat er de laatste jaren nieuwe typen vaccins in ontwikkeling zijn, kunnen lessen uit het verleden lastig worden toegepast in de toekomst. Een kans van 1,8% om op de markt te komen is echter bijzonder klein en daarom zorgwekkend. Uit de literatuur blijkt dat een grote mate van wetenschappelijke uitdaging, afnemende investeringen en de afwezigheid van samenwerking tussen en binnen de universiteiten en industrieën tot de mogelijke oorzaken van de lage slagingspercentages behoren. Dit laatste lijkt de grootste uitdaging, waarbij het erop lijkt dat vaccinontwikkeling achterloopt bij grote doorbraken binnen de basale wetenschap en ontwikkeling van nieuwe technologieën.

In **hoofdstuk 3** wordt de mogelijke onrechtvaardige verdeling in toegang tot geneesmiddelen tussen mannen en vrouwen en tussen verschillende leeftijdsgroepen bestudeerd. Hoewel er binnen zowel sociale als economische vraagstukken, inclusief de gezondheidszorg, bezorgdheid bestaat over mogelijke verschillen tussen deze groepen, is informatie hierover slechts beperkt beschikbaar. Bij de ontwikkeling van beleid is men er tot nu toe echter vanuit gegaan dat vrouwen stelselmatig worden achtergesteld. Hoofdstuk 3 laat zien dat de situatie complexer is en dat de kans op vertekening van resultaten groot is. Verschillen in toegang tot geneesmiddelen tussen mannen en vrouwen zijn in **hoofdstuk 3.1** in 15 lage- en middeninkomenlanden geanalyseerd. Het percentage artsenbezoeken voor een acute luchtweginfectie, depressie of diabetes mellitus dat resulteerde in het voorschrijven van tenminste één geneesmiddel bij vrouwen werd vergeleken met het verwachte percentage dat werd berekend aan de hand van wereldwijde gegevens over ziektelast van de Wereldgezondheidsorganisatie (WHO). De gevonden verschillen tussen mannen en vrouwen bleken afhankelijk te zijn van het land, de leeftijd van de patiënten en de ziekte. Deze resultaten betwijfelen de gangbare veronderstelling dat vrouwen stelselmatig minder toegang tot zorg hebben. In het onderzoek in **hoofdstuk 3.2** werd het gebruik van goedkope en van nieuwe, dure antischimmel middelen die worden voorgeschreven ter behandeling van levensbedreigende aandoeningen geanalyseerd. Geanonimiseerde patiëntengegevens waren afkomstig uit ziekenhuisapotheken van 34 Engelse ziekenhuizen voor acute zorg die gekoppeld waren aan de National Health Services database met informatie over diagnoses en procedures. Het gebruik van zowel goedkope als dure antischimmel middelen werd vergeleken tussen verschillende ziekten waarvoor deze middelen werden voorgeschreven en leeftijdsgroepen. Om het effect van de ziekte, leeftijd, geslacht en armoede te kunnen bepalen werden regressietechnieken gebruikt, terwijl informatie over het mogelijke effect van co-morbiditeiten, contra-indicaties en behandelrichtlijnen uit de literatuur werd verkregen. In zijn algemeenheid werd een omgekeerd verband gevonden tussen leeftijd en het gebruik van dure middelen, maar (de richting van) dit verband varieerde tussen de verschillende ziektes. Ook werden verbanden gevonden tussen geslacht, armoede en etniciteit en het gebruik van dure antischimmel middelen, die eveneens varieerden per bestudeerde aandoening. Er kon derhalve geen eenvoudige conclusie worden getrokken; de factoren die van invloed zijn op

het gebruik van dure antischimmel middelen zijn complex en het gebruik trekt een zware financiële wissel op de apotheken, maar het lijkt onwaarschijnlijk dat ouderen stelselmatig worden achtergesteld. In **hoofdstuk 3.3** is dezelfde database gebruikt om het voorschrijven van antispychotica aan patiënten met dementie te evalueren. Antipsychotica worden bij deze patiënten ingezet om gedrag- en psychologische problemen die samenhangen met dementie tegen te gaan, maar het gebruik is geassocieerd met bijwerkingen als sedatie, parkinsonisme, bewegingsstoornissen, dehydratie, vallen, luchtweginfecties, versnelde cognitieve achteruitgang en mortaliteit. Het gebruik van antipsychotica wordt daarom afgeraden bij patiënten met dementie en uit een Engels rapport blijkt dat het mogelijk zou moeten zijn het gebruik binnen drie jaar met twee derde terug te kunnen dringen. Het te veel gebruiken van antipsychotica onder ouderen wordt ook wel gezien als een indicator dat patiënten betere (niet-medicamenteuze) zorg wordt onthouden. Dit onderzoek liet zien dat er in de periode 2010-2012 in ziekenhuizen een significante afname ($p<0,001$) was van het gebruik van antipsychotica door demente ouderen, dat bijna een derde van de patiënten met stemmingsstoornissen werd behandeld met een antipsychoticum en dat in meer dan één van de acht ziekenhuisepisodes een demente patiënt werd behandeld met een antipsychoticum.

Hoofdstuk 4 tracht inzicht te geven in factoren die leiden tot succesvolle beleidsmaatregelen om het gebruik van generieke middelen in lage- en middeninkomenlanden te stimuleren. Dergelijke beleidsmaatregelen worden wereldwijd gebruikt om de totale uitgaven aan geneesmiddelen te verminderen en worden gezien als een cruciaal onderdeel van het beleid om toegang tot geneesmiddelen te vergroten. Net zoals voor de andere onderwerpen in dit proefschrift geldt dat er weinig bekend is over dit specifieke onderwerp. Zo is er bijvoorbeeld relatief weinig informatie bekend over de farmaceutische markt in de private sector in lage- en middeninkomenlanden en zelfs nog minder over de marktdynamiek die er is tussen de originele en generieke versies van hetzelfde product. Het beperkte aantal studies uit deze landen gebruikte daarnaast in veel gevallen geen echte voorschrijfgegevens. Tot slot heeft onderzoek naar attitudes van patiënten en artsen tot nu toe tegenstrijdige resultaten opgeleverd ten aanzien van een mogelijke verband tussen patiënt- en artskarakteristieken en keuzes voor een bepaald product. In **hoofdstuk 4.1** werd daarom getracht twee vragen te beantwoorden - ten eerste welke trends er zijn in het gebruik van originele en generieke producten in de private sector van een select aantal lage- en middeninkomenlanden en ten tweede welke patronen er kunnen worden ontdekt in het verband tussen het marktaandeel van originele producten en hun generieke tegenhangers. Het marktaandeel van generieken bleek opvallend te verschillen tussen landen. Het generieke marktaandeel was drie keer hoger in Latijns-Amerika dan in de onderzochte landen in het Midden-Oosten en Azië en het gebruik van zogenaamde 'branded' generieken (generieken met een eigen merknaam) overheerste. Hoewel een afname in het marktaandeel van originele producten vaak wordt gezien als een teken van betere betaalbaarheid voor de betaler (patiënt of de zorgverzekeraar), laat dit onderzoek zijn dat de situatie complexer is. De aanname dat een daling in het marktaandeel van een origineel product samengaat met een stijging van het marktaandeel van de generieke producten kon voor veel landen in deze studie namelijk niet worden bevestigd.

Er zijn slechts weinig landen die zo succesvol zijn in het stimuleren van het gebruik van generieke geneesmiddelen als Brazilië. Het doel van **hoofdstuk 4.2** was daarom het effect van patiënt- en artskarakteristieken op het gebruik van goedkope generieke geneesmiddelen in Brazilië te onderzoeken, omdat eerder onderzoek zoals gezegd tegenstrijdige resultaten had laten zien. In dit onderzoek is een combinatie van enkelvoudige analyses en modelleren met behulp van "multi-level" technieken toegepast om gegevens over individuele bezoeken aan artsen met verschillende specialismen en werkzaam in zowel de publieke als private sector te bestuderen. Hieruit bleek dat artsen goedkopere preparaten voorschreven aan patiënten met meerdere aandoeningen en aan patiënten die met dure geneesmiddelen moesten worden behandeld. Patiënt- en artskarakteristieken hadden over het algemeen weinig invloed op de keuze, hoewel oudere patiënten significant vaker een goedkoper preparaat kregen voorgeschreven. De bevinding dat de mate waarin de patiënt zelf financieel moet bijdragen een effect heeft op de keuze voor een bepaald product is belangrijk, omdat tenminste één onderzoek uit een ander land heeft laten zien dat patiënten terughoudend zijn met het bespreken van hun financiële zorgen met hun arts. De volgende stap in de verdere uitbreiding van het gebruik van generieke geneesmiddelen in Brazilië zou zich daarom moeten richten op het helpen van patiënten om deze zorgen te uiten, daar waar dat van toepassing is.

Hoofdstuk 5 richt zich op de vraag hoe beleid zou moeten worden gefinancierd en geïmplementeerd. Het hoofdstuk richt zich met name op het reserveren van financiële middelen voor specifieke doeleinden en op samenwerking met geneesmiddelendistributie in de private sector. In **hoofdstuk 5.1** werd het effect van het instellen van het Cancer Drug Fund in Engeland bestudeerd. In dit fonds worden financiële middelen gereserveerd voor antikanker middelen die niet door de National Health Service worden vergoed, maar wel klinisch effectief (maar niet kosten-effectief) gebleken zijn. In het onderzoek werd het percentage groei in het gebruik van een aantal van deze middelen vergeleken met de verwachte groei op basis van het aantal patiënten dat aanspraak zou kunnen maken op het fonds. De gevonden groei bleef achter bij de verwachte groei. Dit zou mogelijk verklaard kunnen worden door het gebruik van een iets lagere dosis of korter gebruik in de klinische praktijk in vergelijking met doseringen en behandelduur zoals die in klinisch onderzoek zijn toegepast. Bij de oprichting van het Cancer Drug Fund ging men er vanuit dat de samenleving de behandeling van kanker twee keer zo veel waard zou vinden als de behandeling van andere aandoeningen. Het specifiek toekennen van middelen aan dit fonds heeft echter mogelijk geleid tot minder gezondheidswinst in de National Health Service, wat de gevonden resultaten in dit onderzoek zou kunnen verklaren. Dit onderzoek suggereert dus dat het specifiek toekennen van financiële middelen ongelijkheid tussen patiënten met verschillende aandoeningen kan vergroten, zelfs als de variatie in het gebruik van antikanker middelen tussen regio's is verminderd, zoals eveneens uit dit onderzoek bleek. **Hoofdstuk 5.2** beschrijft het effect van een specifieke strategie die uitgaat van de sterke punten en specifieke mogelijkheden van de private sector. Het betreft onderzoek naar het afleveren met en zonder subsidie van orale anticonceptiva door de private sector in 5 Franstalige West-Afrikaanse landen. De analyses waren gebaseerd op twee veronderstellingen: (1) dat het vermogen

van samenwerking tussen de private sector en 'social marketing' organisaties om meer toegang tot geneesmiddelen en/of minder afhankelijkheid van financiële donoren te krijgen wordt beperkt, als de toevoer van gesubsidieerde producten weinig ruimte laat voor verdere groei van de markt voor ongesubsidieerde producten (overbevoorrading) en (2) dat het vermogen van de private sector om afhankelijkheid van financiële donoren te verminderen wordt beperkt als gebruikers wisselen van ongesubsidieerde naar gesubsidieerde producten (substitutie). Deze veronderstellingen zijn gebruikt om 2 indicatoren te ontwikkelen, die samen kunnen helpen om 'sociale marketing' interventies te volgen die toegang tot geneesmiddelen en duurzaamheid trachten te verbeteren. De resultaten van het onderzoek lieten geen overtuigend bewijs voor overbevoorrading zien, maar er zijn wel aanwijzingen voor substitutie. Het volume ongesubsidieerde producten nam met 12% af in Ivoorkust en met 16% in Senegal. Dit onderzoek geeft aan dat er minimaal beter inzicht moet komen in de samenwerking tussen 'social marketing' organisaties en geneesmiddelendistributie in de private sector, als men optimaal gebruik wil maken van de potentiële rol van de commerciële sector bij het vergroten van de toegang tot geneesmiddelen en het verminderen van de afhankelijkheid van financiële donoren. Hiertoe zou ook een verandering van het huidige 'social marketing' model kunnen behoren. Daarnaast moeten mogelijkheden voor het verzamelen van meer complete gegevens uit alle sectoren om 'social marketing' programma's beter te kunnen volgen en beheersen nader worden onderzocht.

De bovenstaande hoofdstukken beschrijven specifieke uitdagingen in het geneesmiddelenbeleid. In **hoofdstuk 6** worden de methodologische en beleidsmatige implicaties van dit onderzoek bediscussieerd.

De methodologische implicaties hebben voornamelijk betrekking op het meten – wat te meten, wanneer te meten en hoe en wanneer er kan worden geëxtrapoleerd vanuit andere disciplines, landen of oude gegevens. Deze overwegingen leidden tot een discussie over de rol van wetenschappelijk bewijs in beleid binnen de gezondheidszorg en tot een beschouwing over het gebruik van informatie en wetenschappelijk bewijs door beleidsmakers. Deze beschouwing beschrijft de opkomst van een nieuw kader voor wetenschappelijk bewijs, gebaseerd op beoordeling van werkzaamheid, aannemelijkheid en waarschijnlijkheid.

Implicaties voor het beleid worden bezien vanuit een lineair kader van agendering, formulering, implementatie en evaluatie. Dit blijft een bruikbaar kader, hoewel er wordt erkend dat dit concept in de laatste jaren is achterhaald door de bewustwording dat het maken van beleid zelden lineair is en dat netwerken en politieke transities een rol spelen.

Verscheidene studies in dit proefschrift kunnen een bijdrage leveren aan de beleidsagenda. Dit geldt met name voor de studies die hebben onderzocht in welke mate discriminatie naar leeftijd of geslacht invloed heeft op de toegang tot geneesmiddelen. Het moge duidelijk zijn dat de situatie complexer is dan gedacht en het isoleren van het effect van leeftijd en/of geslacht is moeilijk. Desalniettemin zijn er verschillen tussen leeftijdscategorieën en tussen mannen en vrouwen en hoewel een stelselmatige achterstelling van bepaalde groepen kan worden uitgesloten, blijft het waarschijnlijk dat leeftijd en geslacht een rol spelen bij het besluit om geneesmiddelen voor te voorschrijven.

Met betrekking tot het formuleren van beleid worden de rol van de private sector en de rol van de patiënt benadrukt. Er worden verschillende modellen voor samenwerking met de private sector beschreven en er wordt beargumenteerd dat voor succesvolle en duurzame relaties minimaal overeenstemming over financiële marges en/of prijzen nodig is. Beleidsmakers proberen reeds langere tijd de macht van patiënten aan te wenden om het doen en laten van artsen en apothekers te beheersen. De mate waarin patiënten hun financiële zorgen met hun arts kunnen bespreken zal echter van doorslaggevend belang zijn bij het ingaan van een nieuwe fase in het uitbreiden van het gebruik van generieke geneesmiddelen.

In veel van het gepresenteerde onderzoek was het evident dat lokale kennis en expertise onontbeerlijk is bij het evalueren van beleidsmaatregelen. Het ontbreken van gedetailleerde kennis van systemen en beleidsmaatregelen binnen en tussen landen bemoeilijkt de interpretatie van verkregen resultaten. Daarom is voor de evaluatie van beleidsmaatregelen lokale kennis en mankracht nodig, wat volgens sommigen een zwak punt is in ontwikkelingslanden. Het versterken van de lokale onderzoekscapaciteit in die landen is derhalve van groot belang om de barrières voor toegang tot geneesmiddelen te kunnen slechten. De implementatie van beleid wordt ook bekeken vanuit het perspectief van de zogenaamde 'Politics Stream', de politieke en sociale druk die leidt tot het aan de orde stellen van bepaalde problemen en de voorkeur voor specifieke problemen. Dit proefschrift heeft niet tot doel deze 'Politics Stream' te onderzoeken, maar herinnert ons aan het belang ervan bij de beschrijving van het ontstaan van de Cancer Drug Fund in Engeland en de aanhoudende debatten rondom dit fonds. De implementatie van beleid blijkt het product te zijn van een toevallige samenloop van wetenschappelijk bewijs, sociale druk, individuele actoren en politieke noodzaak.

In dit proefschrift stond de vraag centraal of toegang tot geneesmiddelen kan worden gekarakteriseerd door gewone, algemene problemen en algemene oplossingen. Er zijn zeker algemene problemen, zoals de afgenomen farmaceutische R&D productiviteit, discriminatie op basis van leeftijd en geslacht en de vraag hoe kan worden samengewerkt met de private sector. Ook zijn gewone, algemene thema's en lessen geïdentificeerd, maar complexiteit dreigt daarbij. Discriminatie op basis van geslacht treft zowel vrouwen als mannen en varieert per leeftijdscategorie en onderliggende ziekte. Het succes van 'social marketing' hangt af van de stadium en economische groei en van nauwere banden met de private sector. En vanwege deze complexiteit wordt wederom een oproep gedaan voor meer investeringen in lokale onderzoekscapaciteit.

Deze complexiteit waarschuwt ook voor gewone oplossingen. Dit proefschrift benadrukt het belang van het geven van context met betrekking tot de methodologie, de metingen zelf en de interpretatie daarvan. De vraag blijft echter hoe dergelijke context op een zinnige wijze kan worden gegenereerd.

Hoofdstuk 6 wijst erop dat de academische gemeenschap in dergelijke situaties vaak een oproep heeft gedaan voor netwerken van gelijkgestemde instituten of individuen of deze netwerken heeft opgezet. Financiering van dergelijke netwerken zal echter vaak tekort schieten. Daarom eindigt dit proefschrift met het voorstel dat informatie over de context in de categorie van precompetitief onderzoek zou kunnen vallen, met andere woorden

onderzoek dat zinvol is voor allen maar geen direct (financieel) voordeel oplevert. Als informatie over de context in deze categorie zou vallen, ontstaan nieuwe mogelijkheden waaronder met name initiatieven waarbij gebruik gemaakt wordt van de 'wisdom of crowds' ("samen slimmer"). Citizendium, een spin off van Wikipedia (zelf een online encyclopedie die gezamenlijk geschreven wordt door gebruikers), zou hierbij een eerste aanzet kunnen zijn. Citizendium is net als Wikipedia een online forum waar mensen informatie een bijdragen. In tegenstelling tot Wikipedia zou Citizendium echter tegemoet kunnen komen aan de behoefte van de academie en de private sector aan erkenning. Lidmaatschap staat open voor iedereen, maar experts kunnen worden herkend en bijdragen worden aan de auteurs toegeschreven. Citizendium, of een vergelijkbaar forum, kan daarom een algemeen platform vormen waaraan eenieder kan bijdragen. En op die manier kan onderzoek binnen de gezondheidszorg worden versterkt.

CHAPTER 8

ADDENDUM

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