Health Authority Activities to Enhance the Quality and Efficiency of Medicine Use and Their Impact

In the previous commentary paper, we discussed the growing expenditure on medicines. This growth arose from the continued launch of new premium-priced medicines, especially for oncology and orphan diseases, growth in non-communicable diseases (NCDs) assisted by ageing populations with associated increased use of medicines as well as changing clinical guidelines.[1-5] As a result, global sales of medicines are likely to exceed $1.5 trillion by 2023, with compounded annual growth rates estimated at 3%–6% per annum.[6] This is a concern not only for high-income countries struggling to fund new premium-priced medicines for cancer and orphan diseases but also for lower- and middle-income countries (LMICs) where expenditure on medicines can account for over 60% of total health-care expenditure affecting key issues such as access and affordability.[7-9] There are also concerns how governments can attain or retain universal health care given ongoing pressures on available resources, enhanced by the COVID-19 pandemic and its unintended consequences. In addition, concomitantly strive to reduce morbidity and mortality of NCDs as part of agreed Sustainable Development Goals (SDGs).[10-13] Alongside this address concerns with rising rates of antimicrobial resistance (AMR), which increases morbidity, mortality, and costs, as a result of inappropriate prescribing and dispensing of antibiotics especially in ambulatory care.[14-17]

These concerns have resulted in the development of new models to better manage the entry of new medicines, including addressing safety concerns with new medicines where these exist, alongside multiple initiatives to improve the quality and efficiency of prescribing and dispensing in ambulatory care.[1,16,18-20] The possible range of health authority activities can be collated under the 4Es, namely education, engineering, economics and enforcement.[21] Education includes developing guidelines or formularies, with adherence to well-constructed guidelines increasingly seen as indicating good quality care in both ambulatory care and hospitals.[2,20-24] Educational initiatives also include the development of the WHO AWaRe list of antibiotics, i.e., 'access', 'watch' and 'reserve', to guide future antibiotic prescribing and dispensing to reduce rising rates of AMR.[25,26] the development of the 'Wise List' in Stockholm, Sweden, with its limited list of well proven medicines to guide physician prescribing.[2,27] In addition, initiatives by health authorities to limit inappropriate prescribing of dabigatran where there were concerns initially that physicians would prescribe dabigatran in patients with atrial fibrillation with co-existing poor renal function and not be aware of the consequences.[28] Health authorities across Europe and New Zealand instigated multiple educational activities to address their concerns arising from misinformation from the company,[29] which worked in practice to limit major bleeding and deaths.[18,30] Other examples include campaigns by health authorities and others in Europe to address misinformation surrounding generic clopidogrel, which was initially launched as a different salt to the originator.[31,32] Cardiologists and others had expressed unfounded concerns regarding generic clopidogrel, which eventually resulted in the authorities in France fining the Company for the extent of their misinformation and the consequences.[32,33] We have seen a similar situation regarding potential medicines and other technologies to prevent and treat patients with COVID-19. A number of governments and health authorities now have the potential to fine pertinent companies and individuals for broadcasting misinformation, with such activities likely to grow.[34,35]

Engineering includes organisational or managerial interventions such as prescribing targets and quality targets.[20] Prescribing targets can include ratios such as the percentage of patients prescribed a multiple sourced medicine within a class or related class, or a biosimilar versus the initial originator, without compromising care.[3,36,37] In addition, removing ezetimibe from local formulary lists as seen in Scotland due to concerns with its effectiveness and value versus low-cost multiple sourced statins.[3] Alongside this, encourage the prescribing of low versus high dose proton pump inhibitors (PPIs) to reduce their long-term side effects and costs.[38] Economics includes financial incentives to physicians, pharmacists or patients, i.e., providing financial incentives to physicians for reaching agreed prescribing targets, fining pharmacists for illegally dispensing an antibiotic without a prescription or charging patients for a more expensive originator versus a lower cost generic where care will not be compromised.[20,39-41] We have also seen Stockholm regional health authority provide financial incentives to ambulatory care physicians to produce an annual quality report highlighting areas of prescribing that can be

improved as well as for attaining agreed adherence rates to the 'Wise List'.[27,42]

Enforcement includes regulations by law. Examples include restricting the prescribing of certain medicines to second line due to concerns with their value, e.g., patented versus considerably less expensive multiple sourced PPIs and patented duloxetine versus generic venlafaxine in Sweden,[40,43] or safety, e.g., restricting the prescribing of dabigatran to specialist centres and regularly monitoring patients.[18] In addition, instigating compulsory generic substitution, e.g., Sweden.[44] Alongside this delisting medicines from national reimbursement lists due to concerns with their value as seen in Denmark when patented angiotensin receptor blockers (ARBs) were removed from the reimbursement list following the availability of low cost generic losartan.[45] Patented ARBs were only subsequently reimbursed in Denmark if physicians could justify their prescribing otherwise 100% co-pay.[45]

Concerns with physicians prescribing dabigatran without sufficient knowledge, coupled with the potential budget impact, resulted in health authorities across Europe developing new models to better manage the entry of new medicines.[28] These centred on three pillars including prelaunch activities incorporating horizon scanning and budgeting, peri-launch activities including assessing the value of the new medicine versus existing standards as well as post-launch activities, which include assessing the effectiveness and safety of a new medicine in routine care as well as its prescribing against agreed guidance.[1,28] A good exemplar is seen in Sweden with their comprehensive horizon scanning activities coupled with assessing the likely budget impact of new medicines without any prescribing guidance.[19,46,47] Post-launch activities in Sweden include assessing the effectiveness of medicines in routine clinical care and against agreed guidance as seen with new medicines for hepatitis C and ovarian cancer.[48,49] Concerns with the potential budget impact of ipilimumab for malignant melanoma in Stockholm, Sweden, resulted in agreed guidance with physicians to limit its prescribing to target patient populations, given potential costs of approximately 40 million SEK (Euro 4.3 million) in the first year. As a result, costs were limited to 12 million SEK for 15 patients.[30] Peri-launch activities across countries also include the development of managed entry schemes (MEAs) to enhance the value and affordability of new medicines, given ever increasing prices.[50-52] MEAs include both financial-based schemes incorporating discounts and rebates and outcome-based schemes including payments based on achieving agreed outcomes.[53,54] However, there are concerns among health authorities, especially with outcome-based MEAs. These include the availability of robust databases to collect patient-level data, as well as the potential length of time of some schemes in practice before any funding decisions can be reviewed and refined.[50,54,55] Despite these concerns, we are likely to see a growth in such MEAs, given the number of new medicines in development expecting premium prices to address current unmet need.[56,57]

Multiple initiatives including education, engineering and economics, in Sweden, when generic omeprazole and generic simvastatin first became available, coupled with measures to obtain low prices for these generics through compulsory generic substitution, resulted in expenditure on PPIs and statins in Sweden being less than one tenth of that seen in Ireland in 2007 when adjusted for population size. These differences arose due to limited supply-and demand-side measures in Ireland at the time.[36] Similarly, in Scotland, multiple measures to improve the quality and efficiency of prescribing of lipid-lowering medicines, including limiting the prescribing of ezetimibe, resulted in a 50% reduction in expenditure on lipid-lowering medicines between 2001 and 2015 despite a 412% increase in utilisation (items dispensed). This was despite encouraging the prescribing of high- versus low-dose statins to improve outcomes.[3,58] We have seen a similar situation resulting from initiatives to limit the prescribing of patented ARBs versus lower cost generic angiotensin-converting enzyme inhibitors (ACEIs) where possible since the occurrence of coughing was limited in practice.[59] Expenditure on renin–angiotensin inhibitors in Portugal in 2007 with its limited demand-side measures was 2.4 times higher than Scotland when adjusted for population size following their multiple demand-side measures.[59,60] Of interest was that the multiple demand-side measures in Scotland (Education, Engineering, and Economics) had the same impact in limiting the prescribing of ARBs compared with prescribing restrictions in Austria and Croatia.[59,60] Similarly, the lack of demand-side measures in Scotland to encourage the preferential prescribing of generic losartan versus still patented ARBs when it first became available resulted in no increased use of losartan as a percentage of all ARBs.[61] These utilisation patterns contrasted with Sweden where multiple demand-side measures, including switching programmes, resulted in appreciable growth in the prescribing of losartan as a percentage of all ARBs post-generic losartan.[62] In addition, in one regional health authority in England, multiple educational and other activities quickly increased the prescribing of generic losartan to 65% of all single ARB prescriptions. This resulted in appreciable savings without compromising care, with net savings estimated at over eight times the cost of implementing the multiple programme.[39]

Of particular note regarding the renin–angiotensin inhibitors was that greater follow-up of prescribing restrictions among ambulatory care physicians by the authorities in Croatia to limit ARB prescribing with the potential for fines if concerns resulted in reduced ARB utilisation versus Austria with their less stringent follow-up.[59,60] In 2007, ARB utilisation in Croatia was only 13.2% of total renin–angiotensin inhibitors (defined daily dose basis) versus 24.8% in Austria.[59,63] The timing of prescribing restrictions is also important to maximise their impact. There was limited impact on subsequent utilisation patterns from the introduction of prescribing restrictions for still patented statins in Sweden 6 years after successful multiple demand-side measures had already limited their prescribing.[64]

It is recognised that there are disease areas where it is difficult for health authorities to be as prescriptive in their direction as for the PPIs and statins. This includes anti-depressants and anti-psychotics for the treatment of schizophrenia where it is recognised by health authorities and others that treatments should be tailored to patient characteristics.[65-67] The limited number of situations include limiting the prescribing of appreciably more expensive patented intramuscular formulations of atypical antipsychotics versus cheaper multiple sourced oral formulations unless there is good reason.[68] In addition, limiting the prescribing of patented duloxetine as a second line anti-depressant due to concerns with its effectiveness in practice as well as costs versus other effective second-line multiple-sourced anti-depressants such as venlafaxine,[40] as well as limiting the prescribing of citalopram and escitalopram following safety concerns.[69]

We have also seen multiple demand-side measures instigated by health authorities to increase the prescribing of lower cost biosimilars versus originators when these become available without compromising care.[70,71] This is essential with limited use initially of biological medicines among LMICs due to their high costs and patient co-payments.[72-74] Multiple activities in Scotland including prescribing targets for biosimilars have resulted in their rapid uptake.[37] For instance, utilisation of biosimilar infliximab reached 94% of total infliximab utilisation by December 2017.[37] By December 2019, biosimilar adalimumab had already reached 87% of all adalimumab and biosimilar trastuzumab 92% of all trastuzumab.[75] These uptake rates are growing to increase savings. Multiple initiatives in Denmark resulted in low prices for biosimilar adalimumab, which coupled with active switching programmes resulted in almost total prescribing of adalimumab biosimilar within a short time of its launch and expenditure on adalimumab rapidly falling by 82.8%.[76] Similar to the situation with oral medicines, multiple supply- and demand-side measures are needed to secure desired savings with biosimilars once available.[20,77] However, we are aware of situations where switching between biosimilars can be an issue. This is seen with insulin glargine where regional health authorities in England and Scotland recommend prescribing by brand name.[78-80] This is in view of concerns that switching between devices could increase the rate of hypoglycaemia.[81,82] This works in the UK because pharmacists are not allowed to substitute an originator for a generic or biosimilar.[3,83] However, this is less of an issue with high rates of voluntary International Non-proprietary Name prescribing in practice in the UK.[3,38,60] Greater education of physicians and patients regarding biosimilar insulin glargine, as well as education regarding the different devices, should help realise potential savings from increasing use of biosimilar insulin glargine. This is because published studies have demonstarted no difference in effectiveness and safety between the biosimilars and the originator.[82,84-87] Greater discounts associated with biosimilar insulin glargine could accelerate its usage with limited discounts to date,[88] and we are already seeing this in Bangladesh and India.

Finally, we have seen health authorities successfully tighten regulations as well as introduce fines to reduce self-purchasing of antibiotics without a prescription.[41,89] This is important as non-prescription sales of antibiotics can account for up to 93% of dispensed antibiotics in LMICs.[17,90] However, this may not always be possible or practical, especially in rural areas in LMICs where pharmacists may be the principal health-care professional available and where there are concerns with affordability and availability of physicians and their fee as well as paying for any medicines. Potential ways to address this situation include initiatives by health authorities to ensure the presence of pharmacists when antibiotics are dispensed, improving the education of pharmacists where there are concerns, making simple-to-use guidelines routinely available for common diseases such as upper respiratory tract infections and limiting the list of antibiotics that can be dispensed without a prescription. This could be be based on for instance the WHO AWaRe List. Finally, instigating IT surveillance systems and potentially using mobile technologies to track antibiotic dispensing habits.[17,91-94]

In conclusion, there are multiple activities that health authorities can introduce across countries in both ambulatory and hospital care to improve future prescribing. Such activities are growing in importance with increases in both infectious and non-infectious across countries, the desired to attain agreed SDGs as well as continuing pressure on resources exacerbated by COVID-19. We will continue to monitor health authority activities to provide direction to others.

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