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Evidence-Based Public Policy Making for Medicines across countries; findings and implications for the future

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Abstract

Background: Global expenditure on medicines is rising up to 6% per year driven by increasing prevalence of non-communicable diseases (NCDs) and new premium priced medicines for cancer, orphan diseases and other complex areas. This is difficult to sustain without reforms. **Methods:** Extensive narrative review of published papers and contextualizing the findings to provide future guidance. **Results:** New models are being introduced to improve the managed entry of new medicines including managed entry agreements, fair pricing approaches and monitoring prescribing against agreed guidance. Multiple measures have also successfully been introduced to improve the prescribing of established medicines. This includes encouraging greater prescribing of generics and biosimilars versus originators and patented medicines in a class to conserve resources without compromising care. In addition, reducing inappropriate antibiotic utilisation. Typically, multiple measures are the most effective. **Conclusions:** Multiple measures will be needed to attain and retain universal healthcare.

Keywords: Antimicrobials, biosimilars, COVID-19, demand-side measures, generics, guidelines, managed entry, orphan medicines, oncology, quality indicators, statins.

Key points

- Expenditure on medicines continues to grow and estimated to reach US\$1.5trillion by 2023. The increase in expenditure on medicines is being driven principally by increased prices and expenditure on new medicines for complex diseases including cancer and orphan diseases and will become unsustainable
- European health authorities and others have introduced new models to better manage the entry of new medicines, which start pre-launch and continue post-launch. Post-launch activities include monitoring the effectiveness and safety of new medicines in routine clinical care as well as against agreed guidance
- Peri-launch activities include critiquing managed entry agreements (MEAs) from companies to enhance reimbursement for their new medicines. However, growing concerns with MEAs need to be addressed to accelerate their use
- There have been activities among health authorities to increase the prescribing of generics and biosimilars versus originators to save monies without compromising care. Typically, multiple co-ordinated activities are needed to maximising savings
- There have also been numerous activities among health authorities to enhance the prescribing of multiple sourced products in a class or related class versus considerably higher priced patented medicines. Again, multiple and co-ordinated demand-side measures are needed to maximise savings
- Co-ordinated activities are also needed to reduce inappropriate prescribing and dispensing of antibiotics in ambulatory care to reduce rising resistance rates. This includes educational activities among physicians, pharmacists and patients
- Coordinated activities are also need to reduce the level of misinformation and associated consequences for treatment of patients with COVID-19

1. Introduction

Global expenditure on medicines has risen appreciably in recent years, and is estimated to reach US\$1.5 trillion by 2023. This represents an annual compounded growth rate of 3–6% in recent years [1]. This growth rate is driven by many factors, which include the increasing prevalence of non-communicable chronic diseases (NCDs) including cancer, coronary vascular disease (CVD), diabetes, and hypertension, and with it an associated increase in medicine use, increasing prices and costs of new medicines especially for cancer and orphan diseases, and changes in clinical practice [2-6]. This increase in expenditure on medicines has additional ramifications among lower- and middle-income countries (LMICs) where expenditure on medicines can be as high as 60% of total healthcare expenditure, much of which is out-of-pocket, with potentially catastrophic consequences on families when members become ill [7-10]. Concurrent with this, the World Health Organization (WHO) estimates that more than half of all medicines are prescribed or dispensed inappropriately [8,11], and inappropriate prescribing increases adverse drug reactions as well resistance with antimicrobials, increasing mortality, morbidity and costs [12-17]. Misinformation has also played a key role with

increasing antimicrobial prescribing and dispensing for patients with COVID-19 including hydroxychloroquine, which is a concern [18,19].

Concerns with the potential value of new medicines, and their role, even in high income countries, especially for oncology and orphan diseases, is leading to the development of new models and approaches to better manage their introduction [3,20-22]. These developments are seen as critical since, unless addressed, expenditure on specialty medicines, including those for chronic, complex, or rare diseases including cancer, will approach 50% of total expenditure on medicines by 2023 in most developed markets [1]. Regional and national health authorities across Europe, who have budget responsibilities for their citizens with the goal of maximising the health of their populations within finite resources [23,24], have instigated a number of activities to improve the introduction of new medicines given rising expenditures [3,21,24]. Activities typically start pre-launch with horizon scanning, progress to peri-launch including assessing reimbursement and funding at requested prices, and finish with post-launch activities including evaluating the effectiveness and safety of new medicines in routine clinical care as well as evaluating prescribing against agreed criteria [3,25-27].

Ongoing initiatives among health authorities to improve the quality and efficiency of prescribing of established medicines include initiatives to increase the prescribing of multiple sourced medicines versus originators and patented medicines in the same or related classes, as well as biosimilars, without compromising care [24, 28-31]. In addition, encouraging disinvestment in technologies where there are concerns with their effectiveness and value, enhanced by the recent formalization of potential approaches towards disinvestment among countries [32-36].

We are aware that there are examples where reforms have been introduced but have failed to reach their desired objective since not all scenarios were considered before their introduction. This includes initiatives to enhance INN (International Non-Proprietary Name) prescribing in Abu Dhabi to conserve resources without encouraging physicians to preferentially prescribe multiple sourced products in the class instead of more expensive patented medicines or encourage pharmacists to preferentially dispense the cheapest multiple sourced medicine [37]. Such outcomes can be avoided by comprehensive planning before the introduction of potential new measures, building on published successful approaches.

There have also been increasing concerns with the level of misinformation that can exist regarding medicines especially if this increases morbidity, mortality and/ or costs [38,39]. This has been the case surrounding the prescribing and dispensing of hydroxychloroquine for the prevention and treatment of COVID-19 across countries. In this situation, despite concerns with the lack of evidence including the lack of control arms in the early studies with hydroxychloroquine, the initial hype resulted in endorsements from governments, which led to increases in prices, shortages and suicides arising from cardiac side-effects [19,40-43]. The concerns were endorsed by the fact that subsequent studies failed to show any clinical benefit from hydroxychloroquine resulting in a lack of any endorsement [44,45].

Consequently, in view of concerns with rising expenditures on medicines and finite budgets, alongside concerns with rising rates of antimicrobial resistance (AMR) due to inappropriate prescribing and dispensing of antimicrobials, we believe there is a need to document examples of activities principally instigated by health authorities across countries, and their impact, to provide guidance on evidence-based activities that can be instigated to improve the future quality and efficiency of prescribing and dispensing of both new and established medicines. This was the objective behind this perspective paper, i.e., to provide guidance especially to health authorities on potential initiatives that can be instigated to improve future quality and efficiency of prescribing. Alongside this, possible pitfalls to avoid including the impact of no or limited demand-side measures to influence future prescribing. We will start with ongoing activities regarding new medicines before discussing established medicines to provide future guidance.

2. Materials and Methods

During the last decades, the authors of this perspective paper have been involved in multiple studies researching measures to influencing the quality of prescribing and dispensing in many different countries across the world. In the extensive narrative review of the literature, we have sought to document multiple examples of the impact of activities to influence future prescribing and dispensing of medicines across sectors, as well as the underlying infrastructure where pertinent, which we believed could be helpful to policy makers in the future. This includes activities that have not secured the intended consequences, and the rationale behind this, and incorporates both high-income as well as middle- and lower-income countries (LMICs) across continents.

We adopted this approach rather than undertaking an extensive literature search of peer-reviewed publications, as well as distinguishing between different countries in terms of their income levels, since our objective was principally to document examples of government and health authority activities and decision making across countries and their impact based, as mentioned, on the considerable knowledge of the co-authors. Subsequently, contextualise the findings to provide future direction. We have undertaken similar approaches before when debating key areas principally from a health authority perspective. This includes key issues surrounding new medicines including managed entry agreements (MEAs), minimum effectiveness criteria and potential approaches for new oncology medicines to improve the assessment of their role and value, key issues surrounding generics, biosimilars, upper respiratory tract infections, fixed-dose combinations and shortages of medicines as well as key reforms to enhance prescribing efficiency [20,21,23,28,29,46-53].

We concentrated on medicines rather than other technologies such as public health interventions given increasing expenditure on medicines, their significant contribution to total healthcare expenditure especially in LMICs, and limited evaluations to date of technologies such as lifestyle interventions [1,7,54].

We have not specified a time scale for the publications since initiatives span a number of years starting with those to enhance the prescribing of generics versus originators and patented medicines in a class without compromising care when the first multiple-sourced proton pump inhibitors (PPIs) and statins became available in the early 2000s [55], as well as patented angiotensin receptor blockers (ARBs) [56], up to the current times with misinformation surrounding treatments for patients with COVID-19 and the consequences thereof [19]. We have not assessed the quality of the documented papers including the methodology using scales such as the modified Jadad scale, Egger's test or the Newcastle-Ottawa scale, since as stated, our objective was to provide guidance to principally health authority personnel based on the considerable expertise of the co-authors [57-60]. In addition, we have only used examples from published papers in peer-reviewed journals. As mentioned, we have adopted this approach before when providing guidance to key stakeholder groups [3,23,28,50].

We will first review ongoing activities among Governments and health authorities to improve the quality and efficiency of prescribing of new medicines starting pre-launch and continuing post-launch. This will be followed by reviewing a range of activities that have been instigated by health authorities and others to improve the quality and efficiency of prescribing and dispensing of established medicines across sectors including activities to improve antimicrobial utilization including reducing pertinent misinformation. In both situations, demand-side measures will be captured under the 4Es: Education, Engineering, Economics and Enforcement [24,61]. Table 1A in the Appendix contains the definitions of the 4Es and gives illustrative examples. In brief, Education includes developing and communicating formularies and guidelines, as well as educational activities in hospitals typically coordinated by Drug and Therapeutic Committees (DTCs) to improve the quality and efficiency of care [61-64]. This also includes auditing compliance with guidelines in routine clinical care [65]. Engineering includes managerial or organizational interventions including instigating and monitoring prescribing against targets [24,61]. Economics includes financial incentives to key stakeholder groups including physicians, pharmacists and patients including payment to physicians for attaining agreed prescribing targets as well as fining pharmacists for illegally dispensing an antibiotic without a prescription [24,66,67]. Enforcement includes regulations by law [24,61]. Examples include national policies to instigate DTCs in hospitals, as seen in South Africa, compulsory generic substitution as seen in Sweden as well as laws banning the dispensing of antibiotics in pharmacies without a prescription [68-70].

We chose to principally concentrate on a health authority/ payer perspective for this paper as they are the key personnel typically charged with maximizing the health gain of their population within available resources [24]. In addition, typically the key drivers for initiating public policy initiatives.

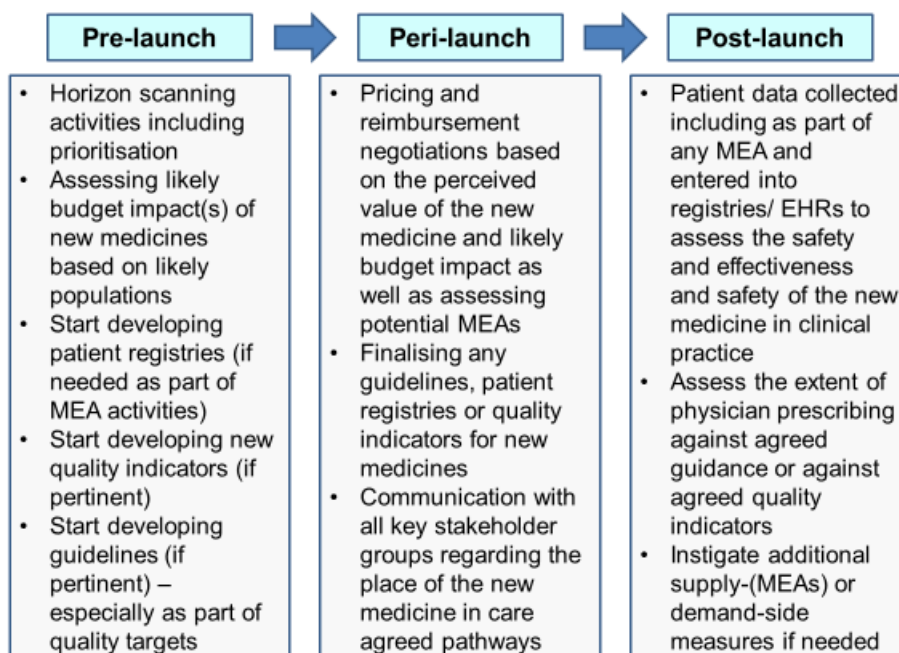
3. Results

We will first review initiatives that have been instigated principally by health authorities to try and improve the quality and efficiency of the prescribing of new medicines given concerns before discussing initiatives for established medicines. This includes their prescribing and dispensing across sectors and countries.

3.1. New medicines

We have seen new models developed across Europe to optimise the managed entry of new medicines in response to concerns with their safety and value including those for cancer and orphan diseases [3,20,71,72]. These models can be divided into three pillars: namely pre-, peri- and post launch activities (Figure 1). They build on initial initiatives in Stockholm County Council, Sweden (Regional health authority), as well as across Europe with respect to dabigatran [20,70]. Dabigatran was the catalyst for the development of this model as horizon scanning activities had documented concerns with the potential budget impact versus warfarin. In addition, there were concerns that the manufacturer was suggesting reduced monitoring of patients with this newer anticoagulant, which was seen as an issue especially in the elderly with poor renal function as this could potentially increase morbidity and mortality [20,73,74].

Figure 1 – Ongoing model to optimise the managed entry of new drugs across Europe incorporating national and regional stakeholder groups (Based on [20,21,26,75,76])



NB: MEA = Managed entry agreement; EHR = Electronic health records

Pre-launch activities, including horizon scanning activities, are growing across countries given the number of new medicines in development including new oncology medicines and likely high price expectations [71,77-80]. Horizon scanning is defined as “*identifying new medicines or new uses of existing medicines that are expected to receive marketing authorisation from the Regulatory Authority in the near future and estimating their potential impact on patient care*” [81,82]. Horizon scanning activities can include budget forecasts in all or some populations to guide health authorities with future planning activities including budgeting activities [26,75,83]. Such activities typically start with a

prioritisation/ filtering process based on agreed criteria (Box 1 A - Appendix) before undertaking early assessments and monitoring the information provided [3,75,84].

Horizon scanning activities among health authorities across Europe and wider typically start up to 24 to 36 months before likely approval by regulatory agencies such as the European Medicines Agency (EMA), with more complete data provided pre-launch to key stakeholder groups as additional data becomes available [3,75]. These activities are increasingly seen as critical with for instance new cancer medicines increasingly being launched with only Phase II data and concerns about potentially limited health gain including survival [85-87]. Key Horizon Scanning groups include the EuroScan International Network, which is a global network of publicly funded early awareness and alert (EAA) system bodies for new health technologies across countries [88,89]. This builds on early alert systems in individual countries including Italy, Sweden and the UK [26,90-92].

Table 1 contains of the activities of early awareness systems (Horizon Scanning) among two European countries. EuroScan have also researched pertinent topic areas including key factors driving innovation in new medicines with limited correlation with the actual burden of disease [93].

Table 1 – Horizon Scanning Activities and their impact among two European countries

Country	Impact
Sweden [78]	<ul style="list-style-type: none"> • The Swedish Early Awareness and Alert System is seen as robust as it identified all new medicines that would go on to have substantial economic impact (21 medicines) and subsequently prioritized most of these medicines (71 medicines were prioritized by the System) • The sensitivity and positive predictive value of the medicines identified were 76.2% and 22.5%, respectively • Subgroup analyses showed that the accuracy of prioritization, in terms of sensitivity, was 100% for antineoplastic/ immunomodulating medicines, which is important given their envisaged budget impact
United Kingdom [91]	<ul style="list-style-type: none"> • The UK early warning system appears to have performed well in terms of sensitivity over the past decade (0.92 based on new medicines subject to a NICE appraisal) • However, a false positive rate of 60% indicates the filtration criteria for medicines needs to be tightened for increased efficiency

However, it is recognized that horizon scanning activities can be costly in terms of manpower and available resources leading to proposals among the Ministers of Health of the BeNeLuxA consortium of countries, i.e. Belgium, Netherlands, Luxembourg, and Austria, to contract out such activities [79,94].

The rationale for these activities was illustrated, as mentioned, by concerns among health authorities that care was needed among physicians when prescribing dabigatran in the elderly with atrial fibrillation as dabigatran is principally excreted in the kidneys, and excessive blood levels arising from poor renal function could potentially be catastrophic [20]. This was indeed the case in some patients when dabigatran was first launched with lack of guidance from the Company [73]. However, there were no excessive bleeding rates in regions and localities where health authority educational and other initiatives had taken place pre-launch [25,95].

Independent willingness-to-pay (WTP) as well as other preference elucidation studies are also being conducted pre-pricing deliberations in some countries to help health authorities with subsequent pricing deliberations especially given increasing concerns with the lack of transparency with suggested prices [96-100]. We have seen WTP activities grow in countries such as Brazil with important implications for future pricing deliberations [96,98,101].

Within peri-launch activities (Figure 1), countries have adopted different approaches to the pricing and reimbursement of new medicines; however, typically considerations such as requested prices and the

level of health gain versus current standards are core considerations [76,102-106]. A recent development has been an attempt by the Italian reimbursement agency to better define innovation for new medicines [107], as well as by the European Commission to better define value in 'value-based healthcare' to improve transparency in this area [108].

The general concerns regarding the continuing increases in the prices of new cancer medicines have resulted in a number of initiatives and developments. These include establishing minimum effectiveness levels for new oncology medicines to be seen as an advance and therefore able to command a premium price [51,109-111]. In addition, the development of new pricing models for new oncology medicines including the potential for differential pricing and price caps across countries [23,112,113]. Other ongoing activities to address concerns with pricing, affordability and potential reimbursement of new medicines include the instigation of MEAs or risk sharing arrangements [50,114,115], the development of multicriteria decision analyses models (MCDAs) [21,116-119], which have recently been adapted for LMICs [120], discussions around fair and transparent pricing for new medicines including models being developed by European health insurance companies and others [23,112,120-124], evaluating possible annuity payment models especially for advanced and complex treatments such as cell therapies as well as de-linking the costs of R&D from a medicine's price to enhance their affordability especially in LMICs [103,110,125,126]. Section 3.1.1 discusses some of the key issues regarding MEAs especially some of the concerns from a health authority perspective that need to be addressed to enhance their use under evidenced-based approaches.

Post-launch activities (Figure 1) include monitoring the effectiveness and safety of new medicines in routine clinical practice using information in either patient registries or Electronic Health Records (EHRs). However, this typically requires patient-level systems to be embedded within healthcare systems [50]. Individual patient registries for new biological medicines in Italy have proved challenging, which has resulted in limited clinical data being collected in practice [127]. This compares with the comprehensive patient-level systems in Catalonia, Spain, where for instance the follow-up of patients prescribed dabigatran showed that a number of elderly patients were not being prescribed the recommended dose, renal function was also not being recorded in an appreciable number of patients (30%) and there were concerns that 17% of patients prescribed dabigatran had previous ischemic heart disease, which is a contraindication [128]. Educational activities are ongoing to address these identified concerns to improve future prescribing and patient care. Post launch studies with these novel oral anticoagulants (NOACs) in countries with suitable patient databases have now evolved to examine differences in key areas. Key areas include assessing the effectiveness, safety and adherence in routine clinical care between the different NOACs now that several NOACs are available to guide future prescribing [129,130].

In a different disease area, longer term studies in Sweden have shown that patients with rheumatoid arthritis treated with biological drugs are not at increased risk of invasive melanoma despite initial concerns although care is needed in patients at high risk of melanoma [3,131]. This was a concern with biological medicines when first launched. Alongside this, Frisk *et al.* (2018) have demonstrated an estimated overall cure rate of 96% with second-generation direct-acting antivirals (DAAs) in patients with chronic hepatitis C in routine care, with high levels of prescribing adherence noted to the introduction protocol across Sweden [27]. This is especially important as there were major concerns with the potential budget impact of DAAs when they were first launched given the potential number of patients across countries and their price [132,133].

We are also seeing increased monitoring of physician prescribing against agreed guidance or quality indicators as part of ongoing activities within hospitals to improve the quality and efficiency of prescribing of new and established medicines [65,75,134-136]. Such activities typically centre around Drug and Therapeutic Committees (DTCs), also known as Pharmacy and Therapeutics Committees (PTCs), within hospitals, which are seen as a pivotal model to promote the rational use of medicines (RUM) in hospitals [64,137-139]. DTCs within hospitals can provide the necessary leadership and activities to select the most appropriate medicines to prescribe as well as educate physicians on RUM and evidence-based medicine thereby helping optimise expenditure on medicines and improve patient outcomes within available resources [62,64,68,139]. An example of this concerns the management of patients with ipilimumab for malignant melanoma within the Karolinska University Hospitals. Treating all possible patients would have caused severe budgetary issues without necessarily appreciably improving patient outcomes. Key stakeholders, including those involved with the DTC activities, jointly developed agreed patient criteria for its usage ahead of its launch to restrict prescribing to those patient

sub-populations most likely to benefit. Follow-up activities revealed agreed patient criteria were being followed, which resulted in only 15 patients being prescribed ipilimumab in the first year of its availability compared with potential expectations of over 50 patients a year [140]. As a result, these combined activities at the Karolinska University Hospital helped to conserve appreciable funds without compromising care.

In Brazil, there is the National List of Essential Medicines (Rename), a technical-scientific element that guides the supply, prescription and dispensing of medicines in the Brazilian NHS [141]. In 2011, the National Commission for Incorporation of Health Technology (Conitec) became responsible for proposing updates of Rename including new medicines based on a thorough evaluation including their efficacy, effectiveness, safety, cost, cost-effectiveness and availability versus current standards based on available published evidence [142]. Adherence to any published treatment guidance incorporating new medicines is enhanced by 100% co-pay for patients when their prescription does not follow national guidance, with ongoing academic detailing activities in some regions of Brazil to further enhance guidance to published guidelines [143,144].

However, there are concerns with the lack of active DTCs within hospitals in many LMICs even in tertiary hospitals [145]. This is a concern with DTC activities typically including adding to- or removing medicines from formulary lists principally based on Essential Medicines Lists and Standard Treatment Guidelines (EMLs/ STG), enhancing RUM within the hospital, providing guidance on possible alternative medicines in times of shortage, and encouraging pharmacovigilance activities given ongoing concerns as well as using agreed indicators to monitor DTC performance [65,68.146-150]. Consequently, where pertinent, DTC activities should be encouraged in hospitals. South Africa with its government policies and guidelines surrounding DTC activities as well as formulary development, management, and use within health facilities, provides examples to other LMICs seeking to instigate evidence-based approaches [68,149-151].

This model for the introduction of new medicines across Europe (Figure 1) has been further refined in Stockholm County Council, Sweden, with extensive follow-up activities to ensure the envisaged value of new medicines is being seen in routine clinical care using their comprehensive patient-level databases and that physicians are adhering to agreed prescribing guidance building on the examples with dabigatran and ipilimumab [26,27,140,152].

3.1.1. Managed Entry Agreements (MEAs)

MEAs are typically a set instruments that are used by health authorities to reduce the uncertainty and high prices associated with the majority of new medicines and, as such, help provide access to new premium priced medicines that would otherwise struggle to be reimbursed at requested prices [50,153,154]. Health Technology Assessment International (HTAi) defines MEAs as “*an arrangement between a manufacturer and payer or provider that enables coverage or reimbursement of a health technology subject to specific conditions*” [50,155,156].

MEAs can typically be broken down to either financial-based schemes, typically involving discounts, rebates, or price volume agreements or performance- or outcome-based schemes including outcome guarantee schemes [76,104,115,154,157]. Outcome- or performance-based agreements are generally seen as more problematic than financial schemes since they typically require robust and sophisticated systems to collect and analyse the data, and many confounders may influence patient outcomes in real life [50,157,158].

However, there are a number of issues that are causing concern to payers that ideally need to be addressed going forward. These include a lack of transparency with most financial based agreements, especially confidential discounts, as well as published data on their outcomes to guide future evidenced-based decisions [50,115]. Confidential discounts can be seen as undemocratic as debates within parliaments are not possible when Ministers have already negotiated confidential discounts.

Box 2A in the Appendix discusses key issues regarding both financial- and outcome-based schemes in more detail. In any event, we are likely to see an increase in the number of MEAs in the future with the continued launch of new high-priced medicines coupled with continued pressure on resources, exacerbated by the current COVID-19 pandemic [3,50,115,159].

3.2. Established medicines

There have been numerous activities by health authorities over the years to enhance the quality and efficiency of prescribing of established medicines. These include encouraging prescribing against agreed guidance, increasing the prescribing of generics and biosimilars versus originators given numerous publications demonstrating no difference in outcomes [136,160-171], encouraging the prescribing of multiple sourced medicines within a class or related class without compromising care [28,172], as well as improving appropriate prescribing and dispensing of antibiotics to reduce antibiotic resistance (AMR) with its impact on morbidity, mortality and costs [15-17,173].

3.2.1 Health authority activities to enhance adherence to prescribing guidance

There are ongoing concerns whether the current World Health Organisation/International Network for Rational Use of Drugs (WHO/INRUD) indicators, which are used extensively across LMICs including Africa, actually assess the quality of prescribing in practice [174-177]. In their recent study, Niaz *et al.* (2019) found sub-optimal levels for prescribing among ambulatory care facilities for the indicator levels established by WHO/ INRUD [174] (Table 2A). Of equal concern is that they found the majority of current WHO/INRUD indicators had low sensitivity and/or specificity when assessing the quality of prescribing versus adherence to national STGs, with the WHO/INRUD indicators typically having poor accuracy in predicting rational prescribing [174]. Consequently, the authors called for more specific quality indicators to be developed to enable Governments and health authorities across Africa to more accurately assess the quality of prescribing in ambulatory care [174]. Box 3A contains key attributes that health authorities and others need to apply to any new quality indicators developed for ambulatory care facilities across Africa and wider to improve future prescribing.

This controversy contrasts with multiple studies that have shown that adherence to robust clinical guidelines improves patient outcomes [178-182]. Table 2 contains details of activities across countries to enhance adherence to guidelines and their impact to guide future activities.

Table 2 – Published studies assessing strategies among health authorities to enhance adherence to guidelines and their impact

Author and Year	Intervention/ Activity	Impact where known
Wettermark <i>et al.</i> , 2009 [183]; Gustafsson <i>et al.</i> (2011) [63], Bjorkhem-Bergman <i>et al.</i> (2013) [62], and Eriksen <i>et al.</i> (2017) [184]	<ul style="list-style-type: none"> Developing a condensed list of well-known medicines covering the vast majority of prescribing needs in ambulatory care (the 'Wise List' of Stockholm Country Council, Sweden) based on sound evidence-based principles with strong conflicts-of-interest regulations 'Wise List' updated annually with the help of multidisciplinary Expert Groups with physicians able to question the developers to justify their choices Regular benchmarking of prescribing against suggested medicines coupled with physicians writing an annual quality report regarding their prescribing habits and areas for improvement 	<ul style="list-style-type: none"> Adherence to prescribing recommendations for the core list of recommended medicines increased from 80% of all prescriptions in 2005 to 90% in 2015 There was decreasing variation among the ambulatory care practices over the years - 32% down to 13%
Fitzgerald <i>et al.</i> 2014 [185]	Review of principally health authority activities exploring key initiatives including: <ul style="list-style-type: none"> Mailed dissemination for improving guideline uptake Computerised decision-support systems 	Overall, variable impact: <ul style="list-style-type: none"> Mailed dissemination – variable impact Computerised decision-support systems – variable impact Educational meetings – variable impact

	<ul style="list-style-type: none"> • Educational meetings to enhance adherence • Educational outreach visits • Audit and feedback 	<ul style="list-style-type: none"> • Educational outreach visits – shown to be effective with improving adherence rates • Audit and feedback – generally positive impact
Jeffery <i>et al.</i> 2015 [182]	<p>Review of principally health authority activities exploring key initiatives including:</p> <ul style="list-style-type: none"> • Educational interventions • Audit and feedback • Academic detailing (outreach visits) 	<p>Overall, variable impact:</p> <ul style="list-style-type: none"> • Educational interventions – Overall positive impact. Outcomes evaluated included disease specific targets, hospitalisations and mortality • Audit and feedback as well as Academic detailing - Overall positive impact on disease specific targets as well as adherence rates to the guidelines
Niaz <i>et al.</i> (2020) [186]	<p>Assessment of programmatic activities including comprehensive of Namibian Standard Treatment Guidelines (BSTGs), simple indexing/ ease of understanding and access, routine availability of suggested medicines and updated/ relevant information</p>	<ul style="list-style-type: none"> • 73% of analysed prescriptions complied with the NSTGs • 94.6% of prescribers were aware of/ had access to the NSTGs • The NSTGs were typically easy to use and regularly referred to, with the main drivers of compliance being programmatic including access to up-to date and objective guidelines and ease of referencing.

3.2.2. Health authority and other initiatives to enhance the prescribing of generics versus originators

The United Kingdom (UK) has high rates of voluntary INN prescribed, with activities starting in medical school to educate students regarding the INN name of medicines rather than originator/ patented names, and continuing post qualification through health authority activities including education, monitoring of prescribing and prescribing support systems [31,67,187]. This has resulted in high rates of INN prescribing in practice in the UK (Appendix Table 3A) apart from a limited number of well-known situations (Appendix Box 4A) [187,188]. Originator name dispensing is enhanced by the fact that pharmacists in the UK are not allowed to substitute an originator with a generic [31,188,189]. Possible confusion in product names between packages for multiple sourced medicines and the originator are addressed in the UK by just having the INN name on packages of generic medicines. This is different to a number of other European countries where packages can contain the name of different branded generics alongside the originator. This can cause confusion among patients especially when different branded generics are being dispensed as a result of procurement practices. The resultant confusion can result in potential under- and over-dosing unless the prescribing physicians and/ or dispensing pharmacist spend time with patients re-assuring them that the medicines are the same [190-192].

National, regional, and local authorities in the UK are involved in addressing concerns with generics including when there are different salts to the originator with a lower number of indications. Typically provided bioequivalence has been demonstrated between the generic and the originator, as seen with generic clopidogrel when it became available, there are no problems with health authorities in the UK advocating INN prescribing, similar to other countries [193]. This was different from the situation with pregabalin when generics first became available. The pharmaceutical company threatened legal action if general practitioners prescribed pregabalin by INN for neuropathic pain, which was still under patent compared with the indication for epilepsy, with similar activities in other European countries [46]. However, this was not the case recently with generic oral oncology medicines with their multiple

indications [194], which is encouraging given the rising costs of medicines for patients with cancer. We have also seen originator companies try and argue against the prescribing of generics as seen with Sanofi when generic clopidogrel was first launched. Concerns though with the level of misinformation provided eventually resulted in a fine from the French Health Authority [193,195].

Changes in the pricing approach for generics in the United Kingdom (UK) resulted in increased transparency in the manufacturing costs as well as the extent of discounts and rebates given by manufacturers to wholesalers and pharmacists. These measures combined with high volumes appreciably lowered the prices of generics over time in the UK (Table 3A) [67,187].

Other European countries have introduced either compulsory INN prescribing such as Lithuania or compulsory generic substitution apart from agreed medicines including Sweden, alternatively, physicians specifically writing no substitution in Finland, to enhance generic utilization [70,196,197].

We are aware though that there are examples where reforms have been introduced but have failed to reach their desired objective since not all scenarios were considered before their introduction. This includes initiatives to enhance INN prescribing in Abu Dhabi to conserve resources. However, as mentioned, there were no initiatives to encourage pharmacists to preferentially dispense the cheapest multiple sourced medicine available. In addition, no initiatives to encourage physicians to preferentially prescribe multiple sourced products in the class, with the manufacturers of the still patented medicines questioning the quality of generics [37]. Consequently, the desired savings were not achieved. In South Korea, policies to increase pricing competition among generics and originators in the multiple sourced market to enhance future savings from generic availability had the opposite effect. In fact, the ratio of originator to generic prescribing actually increased in the absence of demand-side measures to encourage the physicians to preferentially prescribe generics first rather than originators [198]. The authors concluded that simple, efficient and well thought out measures are typically more desirable to achieve stated goals than complex measures [198,199], providing direction to others.

There are also concerns that if patients are dispensed different branded generics on different occasions with compulsory generic substitution as seen in Sweden. As mentioned, such practices could lead to patient confusion with the potential for over-dosing, under-dosing or increased adverse reactions unless patients are educated regarding this possibility of different brand names by either the physician or the pharmacist [70,190,200]. INN prescribing can help to address this coupled with only the INN name appearing on the packages of multiple sourced medicines. Having said this, there are concerns with the quality of generics in many LMICs, which challenges routine INN prescribing [201-204]. The launch of the Lomé initiative in Africa in January 2020 to address substandard as well as falsified medicines is a key step forward to enhance physician and patient trust in generic medicines across countries building on earlier WHO initiatives [205-207].

Encouragingly, the extensive price reductions seen for generics in the United Kingdom versus pre-patent loss prices (Table 2A) have also been seen in other European countries including Sweden [70,208,209]. Alongside this, reimbursed prices for generics in Lithuania and the Republic of Srpska have also matched those of other European countries despite their small population sizes, which was seen as a barrier [196,210]. Increasing competition among generic manufacturers in the Netherlands led to price reductions of 98% versus pre-patent loss prices for generic omeprazole and generic simvastatin, greater than those seen in the UK (Table 3A) [211]. However, as seen in Sweden there can be confusion if different branded generics are launched with different names and there is regular switching without informing patients that the medicines are similar [212]. Encouragingly as well, a recent study analysing prices of generic oral oncology medicines among 25 European countries found that prices were not influenced by the population size of the country or its locality; with prices principally dependent on the regulations within the country regarding the pricing of generics [194]. However, there are concerns with potential shortages if prices of generics are too low, exacerbating current concerns with shortages of medicines across countries [48,213,214]. This must be avoided where possible

Low prices for generic PPIs and statins were also associated with changes in reimbursement policies among a number of Central and Eastern European countries enhancing their utilization and subsequent patient care [28,210,215].

The low prices for generic oncology medicines seen in the recent study of Godman *et al.* (2019) mirror the findings of Hill *et al.* regarding low manufacturing costs for oral cancer medicines [194,216,217]. These low prices for multiple source medicines should lead to a revision of the prices or discounts for still patented oncology medicines that used these multiple sourced medicines during pricing negotiations [23,113]. However, this rarely happens currently, although this may start to change [194].

3.2.3. Biosimilars

We are seeing biological medicines becoming an increasing proportion of global drug expenditure with their high costs at launch [3,6,218]. In Europe in 2018, over 30% of all spending on medicines was on biological medicines, of which 1.5% was biosimilars and growing [218], and by 2023, as mentioned, it is estimated that global spending on medicines will reach US\$1.5 trillion, with 50% of total expenditure on specialty medicines including biological medicines, including those for chronic, complex, or rare diseases, and growing [1]. These growth rates, alongside the consequences of the recent COVID-19 pandemic on the management of both infectious and non-infectious diseases, is a concern for countries seeking to attain or retain universal healthcare [219-221].

Alongside this, there are also concerns generally with the cost of biologicals across a number of Central and Eastern European countries as well as LMICs, which has appreciably limited their prescribing in practice [222-226]. As a result, denying patients access to effective therapies. Biosimilars are a way forward given their lower costs [227]. By 2018, 16 biological molecules had biosimilar products and this figure is growing rapidly given the prices for biological medicines across countries, the growing number losing their patent, and potential savings [218,227,228].

Acceptance of biosimilars is now growing across countries as more studies are published demonstrating similar effectiveness and safety between originators and biosimilars coupled with growing knowledge that originator companies themselves regularly change their manufacturing processes [167,229-234]. This builds on the landmark NOR-SWITCH study with infliximab sponsored by the Ministry of Health in Norway [167]. In addition, recent reviews have suggested no major concerns with immunogenicity with switching between originators and biosimilars, with potential concerns heightened by the nocebo effect [235,236]. This is manifested by Abbvie reducing the price of HUMIRA by 80 - 89% in some markets across Europe to deter biosimilar entry although this was not universal [237,238]. However, this has been countered in a number of countries by health authorities and other organisations preferentially contracting with biosimilar manufacturers, as well as introducing quality targets and other measures, to encourage the preferential prescribing of biosimilars versus originators where pertinent [29,30,140,239]. Table 3 contains details of a number of activities by health authorities across Europe to enhance the prescribing of biosimilars and their impact. In addition, Tesar *et al.* (2020) recently calculated that the health fund in Slovakia could have saved an estimated €35 to 50 million per year if biosimilars with marketing authorisations had been readily available and promoted [240], and such savings are likely to grow. It is imperative though that patients are involved in any switching programme to help negate any potential nocebo effect as well as provide feedback regarding any concerns with the effectiveness and safety of the biosimilars [235,241].

Table 3 – Demand-side measures undertaken among countries to accelerate the prescribing of biosimilars and their outcome

Country	Initiative	Outcome where known
Catalonia – Spain [237,242,243]	<ul style="list-style-type: none"> • Education including materials, workshops <ul style="list-style-type: none"> ○ Workshops, meetings, materials and recommendations coupled with prioritizing biosimilars where feasible in regional guidelines and formularies • Engineering including the development of agreed indicators for biosimilar use and benchmarking physicians (hospital and ambulatory care) • Economics – including financial incentives linked to indicators, possible penalties for over-budget situations and increasingly aggressive contracting with companies 	<p>% biosimilar use in 2019 as a % of total biological:</p> <ul style="list-style-type: none"> • Adalimumab - 26% (influenced by contracts with the originator company) • Etanercept – 35.2% • Rituximab - 37.3%
Denmark – Adalimumab [237,244]	<ul style="list-style-type: none"> • Engineering – initially no automatic substitution for biosimilars but changed following the availability of adalimumab biosimilars • Engineering/ Economics - single purchaser of medicines for all hospitals in Denmark with the choice of biological depending on the outcome of national tenders • Enforcement - Typically only biosimilars can be dispensed if they win the contract 	<ul style="list-style-type: none"> • 3 biosimilars won the adalimumab tender - one biosimilar for children and two for adults depending on the Region • The proportion of biosimilar prescribing reached 95.1% of total adalimumab by December 2018 • Expenditure on adalimumab decreased by 82.8% (September 2018 to December 2018)
Norway – Infliximab and Etanercept [140,245,246]	<ul style="list-style-type: none"> • Engineering and Economics <ul style="list-style-type: none"> ○ The hospitals in Norway combine together in an annual bidding process ○ Normally there is one winner of the contracts covering 12 months – which included biosimilars for infliximab and etanercept when first available 	<ul style="list-style-type: none"> • In 2014, biosimilar infliximab won the contract initially priced 33–39% lower than the reference product • In 2015 prices were further reduced resulting in prices of infliximab 51–69% lower than the reference product • In 2016, biosimilar infliximab was still the cheapest alternative - 60% lower than the originator price • In 2016, biosimilar etanercept was offered for tender at 47% lower than the regular price of the originator

<p>United Kingdom (England) – various biosimilars</p>	<ul style="list-style-type: none"> • Education - Variety of educational and other booklets discussing biosimilars [247-249] • Engineering – various including: <ul style="list-style-type: none"> ○ Target of 90% for all new patients to be prescribed the lowest priced biological medicine within 3 months of the availability of a biosimilar [250] ○ Local health authorities actively encouraging switching to meet the goal of 80% biosimilar prescription rates within one year of launch [250,251] ○ Regular benchmarking with biosimilar adoption rates closely monitored through regional teams [252] 	<ul style="list-style-type: none"> • In 2017 estimated savings were [251]: <ul style="list-style-type: none"> ○ infliximab GB£99.4 million ○ etanercept GB£60.3 million ○ rituximab GB£50.4 million <p>The uptake of biosimilars has increased with multiple activities over the years [253]:</p> <ul style="list-style-type: none"> • Biosimilar infliximab took 28 months to reach 80% penetration vs. biosimilar rituximab which took 10 months to reach 80% of total rituximab and biosimilar trastuzumab took 8 months to reach target penetration rates • In their study, Kim et al found that infliximab biosimilar accounted for 89% of total infliximab by March 2018 through multiple activities [248] • Expenditure on adalimumab is envisaged to fall by 75% following the availability of biosimilars coupled with aggressive contracting [251]
<p>United Kingdom Scotland [237,254-256] – various biosimilars</p>	<ul style="list-style-type: none"> • Education - Multiple educational initiatives among all key stakeholder groups • Engineering - Prescribing targets for biosimilar use (new and existing patients) and Health Boards (Regions) regularly benchmarked against each other • Economics – Continual pressure to prescribed lower costs biosimilars where possible with ongoing pressure on budgets and the desire to treat more patients with biological medicines 	<ul style="list-style-type: none"> • Etanercept and infliximab biosimilars reached 84% and 94% of total utilisation of these biologicals by December 2017; rituximab 74% - its first year of availability • By December 2019, biosimilars for trastuzumab had accounted for 92% of all trastuzumab and biosimilar adalimumab 87% of all adalimumab and growing
<p>United Kingdom [257,258]</p>	<p>Multiple demand-side measures introduced by national and regional health authorities including education and prescribing targets (Engineering)</p>	<p>By 2017, infliximab and etanercept biosimilars accounted for 79% and 54% of the UK market share respectively</p>

Overall, demand-side measures (Table 3) including addressing physician and patient concerns combined with supply-side measures are the key to increasing the prescribing of biosimilars and any associated savings. This was further seen in South Korea where the predominance of supply-side policies based on price-linking, coupled with limited demand-side policies compared to most countries, resulted in appreciably increased utilisation of originator infliximab and limited increase in the utilisation of biosimilar infliximab following its availability [248]. In addition, appreciably lower uptake of biosimilar rituximab and trastuzumab at just 12.9% and 13.9% respectively of total utilization the second year of their market entry [259]. This lack of demand-side measures and the resultant impact mirrors the situation with limited prescribing of oral generic medicines versus originators in South Korea in the absence of extensive demand-side measures [198,199].

However, we are aware there are biosimilars where there is still caution regarding their use versus originators. This includes insulin glargine where health authorities in England and Scotland currently recommend prescribing by brand name including brand names for biosimilars for new patients due to concerns with different devices potentially increasing hypoglycaemia [227,260-262]. This is in view of concerns that switching between devices could increase the rate of hypoglycaemia [263,264]. This though was not universal as seen for instance in Bangladesh and the USA with increased prescribing of biosimilar insulin glargine versus the originator [265,266]. Lower cost biosimilars will be essential to increase funding and utilisation of long-acting insulin analogues in countries where affordability even to insulins is a key issue [267].

Overall, we will expect to see countries learning from each other as more biosimilars become available at lower prices given the envisaged increasing contribution of biological medicines to overall drug expenditure, continued unmet need to effectively manage immunological diseases and cancer, and the need to conserve costs where possible [30,226,268,269]. For instance, it has been estimated that the in USA alone greater fostering of biosimilars for commonly prescribed biologics could lead to estimated savings of US\$54 billion over the next 10 years without compromising patient care [270].

3.3.3. Health authority and other initiatives to enhance the prescribing of multiple sourced medicines in a class or related class

Different activities undertaken by health authorities across Europe to enhance the preferential prescribing of generic omeprazole and generic simvastatin versus more expensive patented statins in the class and their impact to conserve resources without compromising care will first be reviewed [28,172,271], before discussing multiple activities and their impact regarding renin-angiotensin inhibitors. Finally, the findings with other classes of medicines including those for mental health and the implications will also be reviewed along with the implications for future policy making.

3.3.3.1 Proton pump inhibitors (PPIs) and statins

Multiple demand-side activities (Education, Economics and Engineering) in Sweden to encourage the preferential prescribing of generic omeprazole and generic simvastatin versus patented medicines in the class when these first became available produced considerable savings when compared with Ireland with more limited demand-side measures (Table 4). In both countries, there was an appreciable increase in the prescribing of PPIs and statins, with the increase in statin prescribing driven by increasing rates of coronary vascular disease and a greater understanding of the role of statins in preventing further cardiac events [172,271-273]. Multiple demand-side measures also appreciably improved prescribing efficiency in Scotland for both the PPIs and lipid-lowering medicines (Table 4).

Table 4 – Impact of multiple demand-side measures on the utilization and expenditure of PPIs and statins/lipid lowering medicines in Ireland, Scotland and Sweden once multiple sources became available in the class (Adapted from [31,172,274])

Product Areas	Findings
Proton Pump Inhibitors (PPIs)	<ul style="list-style-type: none"> <li data-bbox="491 1167 638 1205">• Sweden <ul style="list-style-type: none"> <li data-bbox="587 1205 1364 1413">○ Multiple demand side measures appreciably increased the prescribing of omeprazole once generics became available up to 74.2% of total PPI utilisation and limited the utilisation of patented esomeprazole to less than 14.2% of total PPIs by the end of 2007. This coupled with low prices for generic PPIs in Sweden resulted in expenditure decreasing by 49% in 2007 versus 2001 despite a 53% increase in utilisation <li data-bbox="587 1413 1364 1480">○ By 2007, expenditure on PPIs was €5832/1000 inhabitants/ year <li data-bbox="491 1480 622 1518">• Ireland <ul style="list-style-type: none"> <li data-bbox="587 1518 1364 1749">○ Limited demand-side measures resulted in utilisation of omeprazole decreasing from 46.4% of total PPIs in 2001 to 36.5% in 2007 and patented esomeprazole increasing from 12.2% of total PPIs in 2001 to 30.5% in 2007. This coupled with higher prices for generics in Ireland versus Sweden resulted in both utilisation and expenditure increasing utilisation by 2.4 fold and 2.6 fold respectively between 2001 and 2007 <li data-bbox="587 1749 1364 1816">○ By 2007, expenditure on PPIs was over €60,000/ 1000 inhabitants/ year <li data-bbox="491 1816 646 1854">• Scotland <ul style="list-style-type: none"> <li data-bbox="587 1854 1364 2029">○ Multiple demand-side measures (Education, Engineering and Economics) in Scotland coupled with initiatives to lower the prices of generics (Table 2A) resulted in total expenditure on PPIs in Scotland 66.7% lower in 2017 compared with 2001 despite a 3.06-fold increase in the utilization of PPIs during this period

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- The reduction in expenditure was also helped by a reduction in the prescribing of higher strength PPIs given concerns with long term safety
- Statins
- Sweden
 - Multiple demand-side measures in Sweden resulted in simvastatin utilisation increasing to 74% of total statin utilisation by the end of 2007 with the utilization of patented statins (atorvastatin and rosuvastatin) limited to 21% total utilisation by 2007. This coupled with low prices for generic statins in Sweden resulted in a 39% reduction in reimbursed expenditure in 2007 versus 2001 despite a 3.2 fold increase in utilisation during this period
 - By 2007, expenditure on statins was €5192 /1000 inhabitants/ year
 - Ireland
 - Limited demand-side measures resulted in simvastatin accounting for just 4.7% of total statin utilization by 2007 with the utilization of patented atorvastatin and rosuvastatin accounting for 75.4% of total statins by 2007. As a result, both utilization and expenditure increased by 7.3-fold and 4.9-fold respectively between 2001 and 2007
 - By 2007, expenditure on statins was over €60,000/1000 inhabitants/ year
- Lipid lowering therapies (Scotland)
- Multiple demand-side measures, including initiatives to reduce the prescribing of ezetimibe due to concerns with its actual effectiveness in reducing cardiac events, resulted in a 50% reduction in expenditure on lipid-lowering therapies between 2001 and 2015 despite a 412% increase in their utilization
 - The lower costs were despite ongoing educational and other activities to appreciably increase the prescribing of higher dose statins to enhance their effectiveness

Different European countries have also introduced prescribing restrictions (Enforcement) to limit the prescribing of patented PPIs and statins. However, their impact has been variable depending on the extent of follow-up activities and the timing of the prescribing restrictions (Table 5).

Table 5 - Impact of prescribing restrictions on the utilisation of patent protected PPIs and statins (adapted from [197,275-277])

Country	Nature of the restriction	Overall change in utilisation of patent protected products	% change over time (patented medicines)
Austria – Atorvastatin only (prescribing of rosuvastatin restricted from outset)	Physicians must have the permission of the Chief Medical Officer of the patient's Social Insurance Fund for atorvastatin to be reimbursed otherwise 100% co-payment	<ul style="list-style-type: none"> • 31.6% of total statin utilisation in 2003 (year before restrictions) to 10.9% in 2007 • Simvastatin increased to 64.4% of total statins by 2007 	66% reduction
Finland – Atorvastatin and rosuvastatin	Physicians in Finland have to specify that atorvastatin or rosuvastatin is for a 'treatment resistant disorder of lipid metabolism' otherwise no reimbursement	44.2% of statin utilisation before restrictions to 18.7% 1.2 years after restrictions, with simvastatin increasing to 73.5% of total usage	59% reduction
Norway – only atorvastatin (rosuvastatin not reimbursed during the study period)	Physicians typically trusted to write the rationale for atorvastatin in the patient's notes. This could be followed up by the health authority if wished (limited)	46.2% of total statins in 2004 (full year before restrictions) to 26.2% in 2008, with simvastatin increasing from 34.7% in 2004 to 67.4% in 2008	44% reduction
Sweden – restrictions on patented statins	Restricted reimbursement on higher strength atorvastatin and rosuvastatin (low doses not reimbursed) to second line in 2009 (6 years after generic simvastatin with accompanying demand side measures – Table 4)	Continued increase in the utilisation of restricted statins (considerable reduction in those not reimbursed)	
Norway - Esomeprazole	Lansoprazole, omeprazole and pantoprazole should be prescribed first line as 'preferred products' with esomeprazole restricted. However, hospital specialists have to verify the diagnosis and recommend therapy before PPIs are reimbursed and they are not subject to the restrictions	Utilisation of esomeprazole decreased from 59.6% of total PPI utilisation the year before restrictions to 40.9% 2 years after the restrictions	31.5% reduction

Prescribing restrictions also severely limited the prescribing of PPIs and statins in Lithuania compared with other European countries (Box 1) and compared with the utilisation of renin-angiotensin inhibitors in Lithuania where prescribing rates were similar to other European countries [196,215,271]. Prescribing of reimbursed PPIs and statins appreciably increased once restrictions were eased following the availability of low cost generics [215]. These findings again re-enforce the conclusion that aggressive prescribing restrictions can appreciably influence physician prescribing.

Box 1 – Impact of prescribing restrictions and other measures on the utilisation of PPIs and statins in Lithuania (adapted from [196,215,271]).

PPIs

- PPIs in Lithuania had a 50% co-payment for reimbursement, with reimbursement restricted to patients with reflux oesophagitis, duodenal ulcers, or for *Helicobacter pylori* eradication - enforced via bar coding system in pharmacies. Otherwise 100% co-pay
- Until 2006 omeprazole, rabeprazole and esomeprazole were reimbursed. From 2006, only omeprazole was reimbursed in view of the higher requested prices of essentially similar PPIs. Other PPIs 100% co-payment
- Utilisation of PPIs in Lithuania in 2004 was 0.7 DIDs, and 2.3 in 2007. This compared in 2007 with 36.7 DIDs in Sweden, 49.0 DIDs in Austria, 76.9 DIDs in Scotland and 101.0 DIDs in Ireland

Statins

- There was a 20% co-payment for reimbursed statins. They were only reimbursed for secondary prevention up to 2008, and up to 2006 only for the first 6 months, enforced through a bar coding system in pharmacies. In addition up to 2006, statins could only be prescribed by cardiologists for reimbursement
- Since 2006, the first prescription must still be issued by a cardiologist although GPs are subsequently allowed to continue prescribing, which is enforced through an active gatekeeper system in Lithuania. Otherwise 100% co-pay
- The prescribing restrictions were lifted for generic statins at the end of May 2009, with family physicians now allowed to prescribe generic statins
- Utilisation of statins in Lithuania in 2004 was 0.6 DIDs and 0.8 DIDs in 2007. This compared with 36.2 DIDs in Austria, 53.5 DIDs in Sweden, 114.7 DIDs in Scotland, and 144.3 DIDs in Ireland

NB: DIDs = Defined Daily Doses per 1000 inhabitants per day; PPIs = Proton pump inhibitors

3.3.3.2 Renin-angiotensin inhibitors

In 1997, British Columbia in Canada introduced a reference pricing system for ACEIs as they believed these were all essentially similar [278]. Under this scheme, certain ACEIs were subject to cost sharing leading to switching to avoid co-payments. Overall, the authors found that reference pricing for ACEIs was not associated with any changes in key outcome measures including rates of visits to physicians, admissions to long-term care facilities, hospitalisations, or mortality [278]. As a result, helping to conserve resources without compromising care.

ACEIs can produce a cough in a minority of patients, which was used by the manufacturers of ARBs to justify their prescribing at appreciably higher costs than generic ACEIs despite similar effectiveness and safety of [56,279,280]. Overall, prospective clinical studies had shown that coughing only occurs in approximately 10% of patients prescribed ACEIs with only 2% to 3% of patients in ACEI clinical trials discontinuing treatment due to coughing [56,280]. This resulted in European countries introducing a variety of measures to limit the prescribing in ARBs. Initiatives included prescribing restrictions in Austria and Croatia, and multiple demand-side measures (Education, Economics and Engineering) in Scotland, contrasting with limited demand-side measures in Portugal combating ARB manufacturers' marketing activities [56,187,281]. These differences in initiatives resulted in appreciable differences in the subsequent utilisation of ARBs as a percentage of total renin-angiotensin inhibitors among the four countries (Table 6) as well as overall expenditure on renin-angiotensin inhibitors.

Table 6 – Impact of multiple initiatives on ARB utilisation and overall renin-angiotensin expenditure between 2001 to 2007 (adapted from [56,187]).

Country	% ARB utilisation versus total renin-angiotensin utilisation based on DDDs		Expenditure - €/1000inhabitants/ year	
	2001	2007	2001	2007
Austria	15.3%	24.8%	13270.7	16305.2
Croatia	2.1%	13.2%	6951.1	8459.2
Portugal	19.8%	44.5%	18853.8	26620.2
Scotland	11.6%	18.8%	9359.3	11256.3

NB: DDDs = Defined Daily Doses

The greater follow-up of prescribing restrictions among GPs by the authorities in Croatia compared with Austria, which included access to patients' histories, with the potential fines for physicians in Croatia if abuse of the restrictions was suspected, resulted in more limited utilisation of ARBs in Croatia compared with Austria during the study period (Table 6) [56,187]. Encouragingly, the multiple demand-side measures introduced in Scotland appeared to be as effective as the prescribing restrictions introduced in Austria and Croatia with limiting ARB prescribing (Table 6), which is important for countries that are unable to introduce prescribing restrictions [187].

There were similar increases in the utilisation of renin-angiotensin inhibitors in Scotland between 2001 and 2007 (159%) as Portugal (155%) (Table 6). However, overall expenditure was appreciably lower in Scotland compared with Portugal when adjusting for population size following the instigation of multiple demand-side measures in Scotland to limit ARB prescribing without compromising care (Table 6) [56,187].

However, there was a different outcome in the United Kingdom when the Better Care Better Value (BCBV) indicators were launched in 2009 to try and further enhance the prescribing of generic ACEIs versus patented ARBs [282]. The proportion of monthly ACEIs prescribed as a total of all anti-hypertensive medicines was 71.2 % in April 2006 but declined to 70.7 % in March 2012. The BCBV policy helped to reduce the rate of decline in the prescribing of ACEIs, with ARB prescribing stable post BCBV implementation. Overall though, failing to achieve the 80% BCBV target set for March 2012 with the potential cost-saving of 23.9% of total renin-angiotensin expenditure [282]. The failure to achieve established targets with associated cost savings was attributable to a lack of any comprehensive communication programme and financial incentives among GPs, GPs had already been targeted for several years to limit ARB prescribing (Table 5) and a reluctance among GPs for therapeutic switching even between related classes due to concerns around deteriorating patient outcomes even though published studies had shown there appeared to be no negative impact on patient adherence to renin-angiotensin inhibitors or clinical outcomes with switching [283,284].

Health authorities across Europe again introduced a variety of measures when losartan became the first ARB to lose its patent (Box 5A), which resulted in different rates for the utilisation of losartan versus other ARBs, with all ARBs seen as similarly effective at comparable doses [285]. Lifting prescribing restrictions for losartan but not for other patented ARBs enhanced its prescribing in Austria and Belgium; however, the increase was more limited compared to multiple measures in Sweden and delisting of patented ARBs in Denmark, which rapidly resulted in losartan utilisation reaching 92.3% of total ARBs (Table 4A). As seen, there was no difference in losartan utilisation in Scotland (Table 4A) in the absence of any demand-side measures compared with the previous situation limiting ARB prescribing, which again confirms that multiple demand-side measures are needed by health authorities to influence physician prescribing (Table 6).

However, the situation changed in one Primary Care Group in the UK versus Scotland (Table 4A) where multiple measures were introduced to enhance the prescribing of generic losartan versus patented ARBs to conserve valuable resources. Measures introduced included educational initiatives among both GPs and patients helped by pharmacists, regular monitoring of patients including their blood pressure following switching as well as financial incentives (Economics) for GPs reaching agreed prescribing targets [191]. By the end of the study period, losartan accounted for 65% of all single ARB items dispensed up from 24% pre the multiple initiatives. Total ARB expenditure was 59% below pre-study levels by the end of the study period helped by a 92% reduction in expenditure per item for losartan. Annual net savings were estimated at over eight-times the cost of implementing the

measures without compromising care [191]. This multiple programme was seen as appreciably more effective than the previous BCBV initiative encouraging greater prescribing of ACEIs in view of the instigation of multiple measures involving all key stakeholder groups coupled with a sense of urgency to rapidly realise savings [191].

3.3.3.3. Other medicine classes

Health authorities recognize that there are classes of medicines where it can be difficult to instigate measures to encourage the preferential prescribing of low-cost multiple sourced products first line versus patented products in a class. This includes the atypical antipsychotic drugs for treating schizophrenia and bipolar disease where in view of the differences in patients' profiles, it is acknowledged that treatment should be tailored to individual patients [286-288]. The only exception could be for different formulations of the same molecule where there are considerable cost differences. This happened in Belgium where the price difference between oral and long-acting injections of risperidone widened following the availability of low-cost generics [289]. The regulations were tightened regarding specific prior authorisation for the prescribing of long-acting injections, otherwise 100% co-payment, resulting in their reduced utilisation in recent years, which is continuing [289].

The same considerations are generally seen with antidepressants [290]. However, there were ongoing activities in Scotland to switch patients from premium priced escitalopram to multiple sourced citalopram alongside continued monitoring of patients given the considerable cost differences and perceived limited difference in clinical outcomes in practice [291]. These activities, alongside continued promotion of INN prescribing in Scotland and low costs for generics (Table 2A), resulted in a 73.7% reduction in the expenditure on selective serotonin re-uptake inhibitors (SSRIs) in Scotland between 2001 and 2017 despite a 2.34-fold increase in SSRI utilisation during this period [291].

Prescribing restrictions for duloxetine were introduced in Sweden due to concerns with its effectiveness and value compared with other multiple-sourced anti-depressants. These restrictions resulted in significantly increased prescribing of generic venlafaxine [292]. In addition, 3 monthly expenditure on the newer anti-depressants in August 2011 was 55% below expenditure in January 2009 prior to the availability of generic venlafaxine [292].

3.3.4 Improving antibiotic utilisation in ambulatory care

There is still appreciable over-utilisation of antibiotics across countries increasing AMR rates and with it associated morbidity, mortality and costs [16,52,293-295]. Concerns with growing resistance rates have resulted in multiple activities among authorities and other key stakeholder groups across countries, with typically multiple activities needed to reduce prescribing and dispensing of antibiotics as well as limit increases where there is already low prescribing rates [52,296-298]. This contrasts with Poland where limited activities among the authorities and other groups have resulted in Poland continuing having one of the highest rates of antibiotic consumption in Europe between 2007 and 2016 [299].

A particular issue is excessive prescribing and dispensing of antibiotics for respiratory tract infections (RTIs) in ambulatory care, which are predominantly viral in origin. This is a concern since RTIs are not only one of the most prevalent infection seen in ambulatory care but they are also the most prevalent condition associated with inappropriate prescribing and dispensing of antibiotics [52,300-303]. This overuse drives up AMR rates within countries [52,304-306], and needs to be addressed going forward based on published evidence-based studies.

Dyar *et al.* in 2016 described a number of strategies that health authorities can instigate among physicians in high-middle as well as high-income countries to reduce inappropriate prescribing of antibiotics in ambulatory care [302]. There have been several publications since then across countries to provide further evidence-based guidance to relevant authorities seeking to further improve antibiotic prescribing in ambulatory care in their country. Some of these are captured in Table 7. Prescribing restrictions were also successful in Slovenia resulting in an average 42% reduction in the utilisation of restricted antibiotics between 1999 and 2012 [297].

Table 7 – Initiatives across countries to improve antibiotic prescribing in ambulatory care in patients with respiratory tract infections

Country and Year	Intervention and Impact
Australia (2018) [307]	<ul style="list-style-type: none"> • Between 2009 and 2015, a series of comprehensive educational campaigns combined with advertising campaigns were undertaken with general practitioners and patients across Australia to help reduce antibiotic prescriptions for URTIs • Overall, the authors believed there was a 14% reduction in dispensed prescriptions following the multifaceted interventions
China (2019) [305]	<ul style="list-style-type: none"> • Clinical guidelines, monthly prescribing review meetings, doctor–patient communication skills training, and education materials for caregivers were instigated to try and reduce antibiotic prescription rates (ABR) among children with URTIs • The multiple interventions resulted in a 49% reduction in ABR after 6 months in the intervention arm having adjusted for patient and prescribing doctor covariates • These reductions still persisted after 18 months but at lower rates (-36%)
Netherlands (2016) [308]	<ul style="list-style-type: none"> • An intervention study was undertaken to improve the management of patients with respiratory tract and ear infections (respiratory tract infections) in ambulatory care consisting of physician education and audit/feedback on the quantity and quality of their antibiotic prescribing, with the results analysed up to 2 years after the intervention • The over prescribing of antibiotics for RTIs decreased from 44% of prescriptions for these ARIs to 28% following the intervention
United Kingdom - England (2016) [309]	<ul style="list-style-type: none"> • Every GP in the intervention group (overall 1581 GP practices were involved in the study) was sent a letter from England's Chief Medical Officer stating the extent of their over prescribing of antibiotics versus colleagues - accompanied by a leaflet on appropriate antibiotics for use with patients • The rate of antibiotic items dispensed per 1000 population decreased from 131.25 in the control group to 126.98 in the intervention group – a decrease of 4.27 (3.3%; $p < 0.0001$), representing an estimated 73,406 fewer antibiotic items dispensed for a limited cost of the intervention • The study concluded that social norm feedback from a senior governmental source reduced inappropriate antibiotic prescribing at low costs
United States of America [310]	<ul style="list-style-type: none"> • McDonagh et al (2018) evaluated twenty-six interventions regarding their potential effectiveness to reduce inappropriate prescribing of antibiotics for patients with ARIs • Four interventions had moderate-strength evidence of improved prescribing including: <ul style="list-style-type: none"> ○ Parent education: 21% reduction in antibiotic prescribing, no increase in return visits ○ Combined patient/clinician education: 7% reduction in antibiotic prescribing, no change in complication or satisfaction rates ○ Procalcitonin testing for adults: 12%–72% reduction in antibiotic use, no increased adverse consequences

	<ul style="list-style-type: none"> ○ Electronic decision support systems: 24%–47% improvement in appropriate prescribing, 5%–9% reduction in inappropriate use of antibiotics, no increase in complication rates
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There have been similar studies to assess the impact of interventions to reduce self-purchasing of antibiotics, which is particularly common among LMICs accounting for up to 93% of dispensed antibiotics [52,303,311-313]. A number of these initiatives and their outcomes are discussed in Table 8 to provide future guidance. We are aware that self-purchasing of antibiotics is not possible particularly in high-income countries. Table 7 provides guidance on potential approaches in these countries to improve future antibiotic utilisation.

Table 8 – Summary of examples of initiatives to reduce self-purchasing of antibiotics in pharmacies including tightening of regulations (adapted from [52,69,314])

Country and Year	Activity
Brazil and Mexico (2013) – private pharmacies [315]	<p>Variable results were seen between 2007 and 2012 assessing the impact of legislation banning the sales of antibiotics to patients in private pharmacies without a prescription in Brazil and Mexico (always been the case among public pharmacies in Brazil [316,317]:</p> <ul style="list-style-type: none"> • Total antibiotic usage consumption increased in Brazil (from 5.7 to 8.5 DDD/TID) but decreased in Mexico (10.5 to 7.5 DDD/TID) • Interrupted time series analysis showed a change in level of consumption of - 1.35 DDD/TID ($p < 0.01$) for Brazil and - 1.17 DDD/TID ($p < 0.00$) for Mexico. In Brazil, there was a decrease in the level of consumption of the penicillins, sulfonamides and macrolides consumption of 0.64 DDD/TID ($p = 0.02$), 0.41 DDD/TID ($p = 0.02$) and 0.47 DDD/TID ($p = 0.01$) respectively • The authors concluded that whilst the effect of the restrictions was similar across the countries; in Brazil, the trend of increased consumption of antibiotics was tempered after the restrictions whilst in Mexico the trend of decreased consumption was accelerated
Brazil – Both private and public pharmacies	<ul style="list-style-type: none"> • Moura <i>et al.</i> (2015) showed a decrease in antibiotic use of 1.87 DDD/TID ($p < 0.001$) immediately after restrictions banning the sales of antibiotics without a prescription among private pharmacies (2008 to 2012), with a greater decrease in the more developed regions as well as in the State Capitals versus other localities in the region. Not surprisingly, there was no difference in sales in the public pharmacies where there were always restrictions and it is generally impossible to sell antibiotics without a prescription ($p=0.643$) [317] • Lopes-Junior <i>et al.</i> (2015) using sales data were from approximately 3000 private pharmacies pre and post the new legislation in Brazil found that sales of amoxicillin (commonly sold antibiotic) fell by approximately 30% post legislation despite a general growth in the pharmaceutical market, with falls in sales of other popular antibiotics including tetracyclines (30.5% decrease), sulfonamides (28.5% decrease), and macrolides (25% decrease) [318] • Mattos <i>et al.</i> (2017) documented an increase in antibiotic sales from 2008 to 2011 including cephalosporin: 216.8%, quinolones: 170.9%, and aminopenicillins: 140.9%. This was followed by a decrease in sales in 2012 of cephalosporin (- 19.4%), quinolones (- 12.7%) and aminopenicillins (- 11.1%) following restrictions in private pharmacies. There was no significant change in sales of nitrofurans during the study period [319] <p>The differences in the findings in the various findings in Brazil between the different studies before and after the changes in legislation may well reflect differences in data sets and methodologies</p>

Kenya – 2018 [320]	<ul style="list-style-type: none"> Monitoring of antibiotics dispensed among pharmacies allied to the University of Nairobi showed a low level of dispensing of antibiotics without a prescription, with 94.1% of antibiotics dispensed with a valid prescription No antibiotics were dispensed for patients with influenza or a common cold or influenza with OTC medicines such as cough and cold syrups and lozenges often dispensed A more recent study during the COVID-19 pandemic also showed no dispensing of either antimalarials or antibiotics without a prescription [43]
Republic of Srpska - 2017 [321,322]	<ul style="list-style-type: none"> A series of interventions including guidelines for pharmacists and greater enforcement of the regulations banning self-purchasing of antibiotics resulted in self-purchasing of antibiotics for self-diagnosed URIs significantly decreasing from 58% of requests to 18.5% among the pharmacies visited Encouragingly, the most common reason for not dispensing an antibiotic was that antibiotics cannot be dispensed without a prescription
Romania – 2018 onwards [323,324]	<ul style="list-style-type: none"> A National Committee for Limiting AMR was formed in 2018 - responsible for issuing recommendations to relevant institutions on the training of human healthcare and veterinary staff on the judicious use of antibiotics, testing AMR, reporting resistance rates, as well as general communication in the field of AMR including informing the public about the judicious use of antibiotics and the risks associated with their inappropriate use The first evidence brief for policy produced in Romania (2020) discussed three options for tackling inappropriate antibiotic use and AMR: (1) consolidate and coordinate the legal framework for AMR in Romania, focusing on two layers (first, the legal framework for controlling AMR at the national level, and second, a national ASP at the operational level); (2) align funding arrangements to facilitate AMR control, ASPs and infection prevention and control programmes; and (3) develop and implement programmes to provide information, improve education and strengthen communication among medical professionals and the public. The outcomes will be closely monitored to provide future direction
Saudi Arabia - 2020 [314]	<ul style="list-style-type: none"> In May 2018 in Saudi Arabia, the law and regulations surrounding self-purchasing without a prescription were enforced alongside fines Before enforcement, 70.7% of pharmacies reported that self-purchasing was common, with 96.6% and 87.7% of participating pharmacies dispensed antibiotics without a prescription for pharyngitis and urinary tract infections (UTIs) respectively Following law enforcement and fines, only 12.9% reported self-purchasing is still common, with only 12.1% and 5.2% dispensing antibiotics without prescriptions for pharyngitis and UTIs respectively When antibiotics were dispensed, typically this only happened following considerable pressure from patients
Thailand - 2015 [325]	<ul style="list-style-type: none"> A multidisciplinary intervention was instigated among grocery stores in a rural province in Thailand using trained community leaders Grocery stores in the intervention group had 87% fewer antibiotics available postintervention compared with preintervention, whereas the control group had only an 8% reduction in antibiotic availability between the 2 time periods

NB: AMR = Antimicrobial resistance; ASP = Antimicrobial Stewardship Programmes; DDDs = defined daily dose; DDD/ TID = DDDs/1000 inhabitants per day; OTC = over-the-counter; URI: Upper respiratory tract infection

Similar to the situation with PPIs and statins (Table 5), the extent of ‘enforcement’ impacts on the outcome. In Venezuela, the government implemented policies to reduce self-purchasing of antibiotics among three antibiotic groups namely macrolides, quinolones and third generation cephalosporins. However, there were no public awareness campaigns. Besides, ‘enforcement’ was made only via formal government publications and was not followed up by the authorities with for instance any increase in pharmacy supervision, any pharmacy closures or any financial sanctions for non-

compliance. As a result, there was no decrease in consumption levels, in fact there was an increase in antibiotic utilisation during the study period [326].

Similarly in Colombia, whilst initial enforcement banning self-purchasing in 2005 had a modest impact on overall retail sales in the first three years (-1.00 DDDs/ 1000 inhabitants per day) following the regulations, a follow up study five years after implementation found that 80.3% of pharmacies were not complying with the regulations with lax monitoring prompting calls for greater enforcement of the law to achieve appreciable reductions [326,327]. This contrasts with appreciable reductions in antibiotics dispensed without a prescription in a number of countries following multiple interventions, e.g. Saudi Arabia (Table 8).

It is recognized though that it can be difficult to enforce regulations banning the self-purchasing of antibiotics especially in rural areas in LMICs with high co-payment rates, limited health insurance among patients and limited number of government personnel to enforce any regulations including fines. Alongside this, where pharmacies may be the only health service delivery points available [303], it would be problematic to ban self-purchasing of antimicrobials. In this situation, trained pharmacists can help reduce inappropriate dispensing of antibiotics alongside health authorities potentially monitoring pharmacy activities using mobile technologies and instigating IT surveillance systems to track antibiotics through the supply chain to further reduce inappropriate dispensing [303,320]. This may mean improving pharmacists' knowledge regarding AMR and its causes where there are concerns starting in pharmacy school and continuing post qualification [328-331]. In addition, helping ensure that any antibiotic dispensed for RTIs and other common conditions must be from the Access group of antibiotics including the beta-lactams from the WHO AWaRE list [306,332], and not antibiotics on the 'Watch' or 'Reserve' list.

3.3.5 COVID-19 misinformation

As mentioned, there have been concerns about the level of misinformation regarding treatments for COVID-19 including hydroxychloroquine [19,40,43]. To date, only dexamethasone has been shown to improve outcomes in hospitalised patients, with concerns with hydroxychloroquine, lopinavir/ritonavir and remdesivir [45,333,334]. However the initial hype surrounding hydroxychloroquine with or without antibiotics resulted in appreciable shortages, price rises and deaths due to suicides in a number of countries [40,42,43]. This though was not the case in countries with strict regulations and activities surrounding the dispensing of antimicrobials including Kenya, Namibia and Vietnam providing direction to others [42,43,335].

Concerns with the misinformation with hydroxychloroquine and its consequences, alongside concerns with misinformation generally surrounding COVID-19, has already resulted in African countries including Botswana and Zimbabwe starting to fine companies, with potentially a prison sentence, for such activities [41]. We are also aware that the US Federal Trade Commission has sent letters to companies they believed were falsely advertising product capabilities for the management of patients with COVID-19 violating federal laws by indicating that claims were "deceptive or scientifically unproven" [336,337]. It is likely that such government activities will grow in the future.

4. Discussion

There is continued unmet need for new medicines especially new medicines for cancer and orphan diseases as well as immunological disease. However, there are concerns that ever increasing prices for new medicines, which coupled with increasing prevalence rates of NCDs, will appreciable increase expenditure on medicines unless addressed [1,3]. These concerns have resulted in greater pro-activity among health authorities to improve the managed entry of new medicines (Figure 1). Key activities include horizon scanning pre-launch, continued growth in MEAs to help with the financing of new premium priced medicines as well as the increased monitoring of their effectiveness and safety in routine clinical care and against agreed guidance. The latter is seen as particularly important given concerns when dabigatran was first launched in terms of potentially increased morbidity and mortality if physicians were unaware of potential problems in the elderly with poor renal function as well as the launch of new medicines for cancer and orphan diseases often with only limited data available at launch for decision making coupled with high requested prices [20,25,73,74,85].

The growth in MEAs, especially financially-based MEAs, is likely to lead increased discussions among authorities whether such discounts should continue within public healthcare systems especially as

they would appear undemocratic [113]. In addition, discussions surrounding who should cover the costs of data collection as part of any outcome-based scheme (Box 2A). It is also likely that improvements in EHRs and registries will enhance the design of future outcome-based MEAs resulting in the generation of meaningful clinical data addressing earlier concerns [127,338]. Alongside this, there will be greater discussions regarding fair and transparent prices for new medicines enhanced by greater knowledge among health authorities of the likely cost-of-goods of new medicines [22,121,122, 339], coupled with increasing knowledge of the low prices seen for generics and biosimilars in some markets and considerable discounts offered by the manufacturers of biological medicines to help retain market share in the face of biosimilar competition (Table 3A) [194,217,238,244].

There is also likely to be increasing research around different approaches to the financing of new medicines especially from the standpoint of payers with increasing availability of more complex treatments including advanced therapy medicinal products (ATMPs) and gene therapies, which are being launched at high prices [3,23,126,340,341]. Examples include onasemnogene abeparvovec (Zolgensma) for spinal muscular atrophy, approved by FDA and recently by EMA, with an entry price of US\$2.125 million/ patient [342-344]. In addition, it is increasingly likely we will see the re-evaluation of prices or discounts for patented medicines when the standards used for pricing negotiations become available as either low-cost generics or biosimilars to enhance the affordability and funding for new medicines [23,194], and we will continue to monitor this.

We are already seeing DTC activities grow across countries to improve the quality and efficiency of prescribing among hospital facilities, and this will continue [3,68]. However, the principal issue for many LMICs are concerns with the availability and access to essential medicines as defined by the WHO and others [3,345]. We have already seen considerably lower utilisation of biological medicines to treat patients with immunological conditions such as rheumatoid arthritis and inflammatory bowel disease in CEE countries versus higher income European countries due to issues of affordability [222-224], with this situation likely to continue with high prices for new patented biological [71,72]. The increasing availability of biosimilars at low costs should help in this regard as seen with biosimilars for insulin glargine in Bangladesh [227,346].

Adherence to guidelines and other potential quality indicators appear more beneficial in actually assessing the quality of prescribing than current WHO/ INRUD criteria, and we are likely to see changes in the future (Table 2). Box 3A gives direction to health authorities and others on key considerations when seeking to develop new quality indicators. A key challenge though is to limit their number. This was the philosophy in Scotland when generic losartan became available with encouraging physicians to concentrate on existing indicators rather than introduce an additional one which could cause concern [347]. The 'Wise List' in Stockholm County Council, Sweden (Table 2), is also an exemplar for countries seeking to introduce a limited number of medicines in ambulatory care building on the WHO EML concept. Robust processes including good communication and follow-up were keys to the success of the 'Wise List', providing guidance to other health authorities.

Typically, increasing the use of multiple sourced medicines as well as biosimilars versus originators and patented medicines is essential to maintain universal healthcare (UHC) where this exists as well as help countries attain UHC as part of attaining Sustainable Development Goal 3 [348,349]. Countries are learning from each other regarding healthcare reforms, and this will continue [28]. The first step towards enhancing the prescribing of generic medicines is to ensure only good quality generics are available for patients as seen for instance in Europe and the US. There are ongoing steps to attain this [205], which include strengthening the registration system and quality tests [350], and these will continue. The aim is to achieve high INN prescribing rates as seen in the UK (Table 3A) for non-controversial medicines (Box 4A), close to the 100% target established by the WHO (Table 2A) [176]. Encouraging INN prescribing helps reduce patient confusion with different branded generics. However, this only works well if patients are warned beforehand that they may be dispensed different packages with different names; alternatively, only the INN name is listed on the packages of multiple sourced medicines as currently seen in the UK. The pricing of generics is also a key consideration especially in LMICs given the increasing prevalence of chronic NCDs especially in sub-Saharan Africa [4,351]. However, if prices of generics become too low then, as mentioned, they potentially become uneconomic to produce exacerbating drug shortages [213,352,353].

There are also multiple initiatives that health authorities can introduce to enhance the prescribing of multiple-sourced medicines first line versus patented medicines in a class or related class (Section 3.3.3). Typically, multiple measures and initiatives are needed to maximise efficiency along with low prices for generics as seen for instance with Sweden versus Ireland for PPIs and statins (Table 4), Scotland versus Portugal for renin-angiotensin inhibitors (Table 6), a primary care group for ARBs in the UK [191], and Sweden versus Scotland (Box 5A, Table 4A). We also see this when evaluating initiatives to reduce inappropriate prescribing of antibiotics (Section 3.3.4). However, it is recognized that there are certain classes where such activities are difficult including the anti-psychotics [286,354]. In addition, the timing of initiatives is important as seen with the limited impact on the prescribing of ACEIs versus ARBs in the UK following additional BCBV indicators some years after initial multiple measures (Table 6) [282].

There are similar considerations when it comes to appraising the impact of prescribing restrictions instigated by health authorities including their timing (Box 1, Table 5) as well as measures to reduce self-purchasing of antibiotics through laws to prevent this. For instance, greater follow-up in the Republic of Srpska and Saudi Arabia, including potential fines (Table 8), had a considerably greater impact in reducing self-purchasing of antibiotics than that seen in either Colombia and Venezuela with their limited follow-up activities. However, adequate policing is needed to fully enforce any regulations. Care is also needed especially in rural areas of LMICs where community pharmacies may be the principal healthcare professional available for patients. Different approaches are needed in this situation including the presence of appropriately trained pharmacists.

Finally, adherence to guidelines and other potential quality indicators would appear to be more beneficial in actually assessing the quality of prescribing compared with the current WHO/ INRUD criteria, and we are likely to see changes in the future. Box 4 gives direction to health authorities and others on key considerations when seeking to develop new quality indicators. A key challenge though is to limit their number. This was the philosophy in Scotland when generic losartan became available with encouraging physicians to concentrate on existing indicators rather than introduce an additional one which could cause concern [347]. The 'Wise List' in Stockholm, Sweden (Section 3.2.5) is also an exemplar for countries seeking to introduce a limited number of medicines in ambulatory care building on the WHO EML concept. Robust processes including good communication and follow-up are keys to success as seen in Sweden.

We are also likely to see a growth in disinvestment opportunities as any investment in new or established technologies typically involves a disinvestment. Suggested methods for undertaking such activities and their potential impact have been described in a number of published papers to provide direction [32-35].

We accept there are limitations with this paper. This includes the fact that we did not undertake a systematic review, nor give specific dates for inclusion or exclusion of examples, for the reasons stated. However, we believe the examples documented across multiple disease areas and countries provide examples of evidence-based approaches instigated by health authorities that countries could learn from, including situations where initiatives did not work, given ever increasing pressures on their resources.

5. Conclusions

In conclusion, we are likely to see ongoing initiatives among health authorities to better manage the entry of new medicines given concerns with ever increasing prices, which includes a growth in MEAs. Alongside this, continued measures and initiatives to enhance the utilization of multiple sourced medicines and biosimilars versus more expensive patented medicines where this will not compromise care. The resources released will fund increased medicine volumes as well as new premium priced medicines that address areas of unmet need given finite resources within countries. Coupled with this, there will be increasing measures to improve the prescribing and dispensing of antibiotics to curb rising AMR rates. Whatever the focus, the illustrated case histories have shown that typically multiple activities involving the 4Es have a greater impact than initiatives involving only a limited number of measures.

Overall, multiple evidence-based measures are essential to attain or retain UHC as well as increase affordability of medicines, exacerbated by the impact of COVID-19 including its unintended consequences. Countries are learning from each other, and this will necessarily continue.

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References

1. IQVIA. The Global Use of Medicine in 2019 and Outlook to 2023 - Forecasts and Areas to Watch (2019). Available at URL: <https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/the-global-use-of-medicine-in-2019-and-outlook-to-2023.pdf>.
2. OECD. Health at a Glance 2019: OECD INDICATORS. OECD Publishing, Paris (2019). Available at URL: <https://doi.org/10.1787/4dd50c09-en>.
3. Godman B, Bucsecs A, Vella Bonanno P et al. Barriers for Access to New Medicines: Searching for the Balance Between Rising Costs and Limited Budgets. *Front Public Health*. 6,328 (2018).
4. Godman B, Basu D, Pillay Y et al. Review of Ongoing Activities and Challenges to Improve the Care of Patients With Type 2 Diabetes Across Africa and the Implications for the Future. *Frontiers in pharmacology*. 11,(108) (2020).
5. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA*. 68(6), 394-424 (2018).
6. Morgan SG, Bathula HS, Moon S. Pricing of pharmaceuticals is becoming a major challenge for health systems. *BMJ*. 368, l4627 (2020).
7. Cameron A, Ewen M, Ross-Degnan D, Ball D, Laing R. Medicine prices, availability, and affordability in 36 developing and middle-income countries: a secondary analysis. *Lancet*. 373(9659), 240-249 (2009).
8. Ofori-Asenso R, Agyeman AA. Irrational Use of Medicines—A Summary of Key Concepts. *Pharmacy*. 4, 35 (2016).
9. Kastor A, Mohanty SK. Disease-specific out-of-pocket and catastrophic health expenditure on hospitalization in India: Do Indian households face distress health financing? *PloS one*. 13(5), e0196106-e (2018).
10. Rahman MM, Zhang C, Swe KT et al. Disease-specific out-of-pocket healthcare expenditure in urban Bangladesh: A Bayesian analysis. *PloS one*. 15(1), e0227565-e (2020).
11. World Health Organization. The pursuit of responsible use of medicines: Sharing and learning from country experiences. World Health Organization (2012). Available at URL: https://apps.who.int/iris/bitstream/handle/10665/75828/WHO_EMP_MAR_2012.3_eng.pdf;jsessionid=D819046B9E21DE48A1391A19A07770CC?sequence=1.
12. Mouton JP, Njuguna C, Kramer N et al. Adverse Drug Reactions Causing Admission to Medical Wards: A Cross-Sectional Survey at 4 Hospitals in South Africa. *Medicine*. 95(19), e3437 (2016).
13. Batel Marques F, Penedones A, Mendes D, Alves C. A systematic review of observational studies evaluating costs of adverse drug reactions. *ClinicoEconomics and outcomes research*. 8, 413-426 (2016).
14. Formica D, Sultana J, Cutroneo PM et al. The economic burden of preventable adverse drug reactions: a systematic review of observational studies. *Expert opinion on drug safety*. 17(7), 681-695 (2018).
15. Haque M, Godman B. Potential Strategies to Improve Antimicrobial Utilisation in Hospitals in Bangladesh Building on Experiences Across Developing Countries. *Bangladesh Journal of Medical Science*. 19 (3): 469-477 (2021).
16. Hofer U. The cost of antimicrobial resistance. *Nature reviews Microbiology*. 17(1), 3 (2019).
17. Founou RC, Founou LL, Essack SY. Clinical and economic impact of antibiotic resistance in developing countries: A systematic review and meta-analysis. *PloS one*. 12(12), e0189621 (2017).
18. Hsu J. How covid-19 is accelerating the threat of antimicrobial resistance. *BMJ*. 369, m1983 (2020).

-
19. Godman B. Combating COVID-19: Lessons learnt particularly among developing countries and the implications. *Bangladesh Journal of Medical Science, Special Issue on Covid19*. 2020; S103-8 (2020).
 20. Malmstrom RE, Godman BB, Diogene E et al. Dabigatran - a case history demonstrating the need for comprehensive approaches to optimize the use of new drugs. *Frontiers in pharmacology*. 4, 39 (2013).
 21. Godman B, Malmstrom RE, Diogene E et al. Are new models needed to optimize the utilization of new medicines to sustain healthcare systems? *Expert review of clinical pharmacology*. 8(1), 77-94 (2015).
 22. Morgan SG, Bathula HS, Moon S. Pricing of pharmaceuticals is becoming a major challenge for health systems. *BMJ*. 368, l4627-l (2020).
 23. Godman B, Hill A, Simoens S et al. Potential approaches for the pricing of cancer medicines across Europe to enhance the sustainability of healthcare systems and the implications. *Expert review of pharmacoeconomics & outcomes research*. 1-14 (2021)
 24. Godman B. Health authority activities to enhance the quality and efficiency of medicine use and their impact. *Adv Hum Biol*. 11, 11-16 (2021).
 25. Godman B, Malmstrom RE, Diogene E et al. Dabigatran - a continuing exemplar case history demonstrating the need for comprehensive models to optimize the utilization of new drugs. *Frontiers in pharmacology*. 5, 109 (2014).
 26. Eriksson I, Wettermark B, Persson M et al. The Early Awareness and Alert System in Sweden: History and Current Status. *Frontiers in pharmacology*. 8, 674 (2017).
 27. Frisk P, Aggefors K, Cars T et al. Introduction of the second-generation direct-acting antivirals (DAAs) in chronic hepatitis C: a register-based study in Sweden. *European journal of clinical pharmacology*. 74(7). 971-978 (2018).
 28. Godman B, Wettermark B, van Woerkom M et al. Multiple policies to enhance prescribing efficiency for established medicines in Europe with a particular focus on demand-side measures: findings and future implications. *Frontiers in pharmacology*. 5, 106 (2014).
 29. Moorkens E, Vulto AG, Huys I et al. Policies for biosimilar uptake in Europe: An overview. *PloS one*. 12(12), e0190147 (2017).
 30. Godman B, Allocati E, Moorkens E. Ever-Evolving landscape of biosimilars in Canada; findings and implications from a global perspective. *GABI Journal*. 8 (3), 93-97 (2019)
 31. Leporowski A, Godman B, Kurdi A et al. Ongoing activities to optimize the quality and efficiency of lipid-lowering agents in the Scottish national health service: influence and implications. *Expert review of pharmacoeconomics & outcomes research*. 18(6), 655-666 (2018).
 32. Parkinson B, Sermet C, Clement F et al. Disinvestment and Value-Based Purchasing Strategies for Pharmaceuticals: An International Review. *PharmacoEconomics*. 33(9), 905-924 (2015).
 33. Guerra-Junior AA, Pires de Lemos LL, Godman B et al. HEALTH TECHNOLOGY PERFORMANCE ASSESSMENT: REAL-WORLD EVIDENCE FOR PUBLIC HEALTHCARE SUSTAINABILITY. *International journal of technology assessment in health care*. 33(2), 279-287 (2017).
 34. Lemos LLP, Guerra Junior AA, Santos M et al. The Assessment for Disinvestment of Intramuscular Interferon Beta for Relapsing-Remitting Multiple Sclerosis in Brazil. *PharmacoEconomics*. 36(2), 161-173 (2018).
 35. Esandi ME, Gutiérrez-Ibarluzea I, Ibarгойen-Roteta N, Godman B. An evidence-based framework for identifying technologies of no or low-added value (NLVT). *International journal of technology assessment in health care*. 36(1), 50-57 (2020).
 36. Costa S, Bentley C, Regier DA et al. Public perspectives on disinvestments in drug funding: results from a Canadian deliberative public engagement event on cancer drugs. *BMC public health*. 19(1), 977 (2019).
 37. Abuelkhair M, Abdu S, Godman B, Fahmy S, Malmstrom RE, Gustafsson LL. Imperative to consider multiple initiatives to maximize prescribing efficiency from generic availability: case history from Abu Dhabi. *Expert review of pharmacoeconomics & outcomes research*. 12(1),115-124 (2012).
 38. Hill JA, following HGS, Agewall S, Baranchuk A et al. Medical Misinformation: Vet the Message! *European heart journal*. 40(5):404-405 (2019).
 39. Swire-Thompson B, Lazer D. Public Health and Online Misinformation: Challenges and Recommendations. *Annual Review of Public Health*. 41(1), 433-451 (2020).
 40. Abena PM, Declodt EH, Bottieau E et al. Chloroquine and Hydroxychloroquine for the Prevention or Treatment of COVID-19 in Africa: Caution for Inappropriate Off-label Use in Healthcare Settings. *Am J Trop Med Hyg*. 102(6), 1184-1188 (2020).

-
41. Ogunleye OO, Basu D, Mueller D et al. Response to the Novel Corona Virus (COVID-19) Pandemic Across Africa: Successes, Challenges, and Implications for the Future. *Frontiers in pharmacology*. 11, 1205 (2020).
 42. Godman B, Haque M, Islam S et al. Rapid Assessment of Price Instability and Paucity of Medicines and Protection for COVID-19 Across Asia: Findings and Public Health Implications for the Future. *Frontiers in Public Health*. 8, 744 (2020).
 43. Sefah I, Ogunleye O, Essah D et al. Rapid assessment of the potential paucity and price increases for suggested medicines and protection equipment for COVID-19 across developing countries with a particular focus on Africa and the implications. *Frontiers in pharmacology*. 11, 2055 (2021).
 44. Horby P, Mafham M, Linsell L et al. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. *N Engl J Med*. EPrint (2020).
 45. WHO Solidarity trial consortium. Repurposed antiviral drugs for COVID-19 –interim WHO SOLIDARITY trial results. MedRxiv (October 15) version available at URL: <https://doi.org/10.1101/2020.10.15.20209817>
 46. Godman B, Wilcock M, Martin A et al. Generic pregabalin; current situation and implications for health authorities, generics and biosimilars manufacturers in the future. *GABI Journal*. 4(3):125-135 (2015).
 47. Godman B, Wettermark B, Bishop I et al. European payer initiatives to reduce prescribing costs through use of generics. *GABI Journal*. 1(1):22-7 (2012).
 48. Bochenek T, Abilova V, Alkan A et al. Systemic Measures and Legislative and Organizational Frameworks Aimed at Preventing or Mitigating Drug Shortages in 28 European and Western Asian Countries. *Frontiers in pharmacology*. 8, 942 (2017)
 49. Mijlković N, Godman B, Kovačević M et al. Prospective Risk Assessment of Medicine Shortages in Europe and Israel: Findings and Implications. *Frontiers in pharmacology*. 11, 357 (2020).
 50. Zampirolli Dias C, Godman B, Gargano LP et al. Integrative Review of Managed Entry Agreements: Chances and Limitations. *PharmacoEconomics*. 38(11), 1165-1185 (2020).
 51. Wild C, Grossmann N, Bonanno PV et al. Utilisation of the ESMO-MCBS in practice of HTA. *Annals of oncology*. 27(11), 2134-2136 (2016).
 52. Godman B, Haque M, McKimm J et al. Ongoing strategies to improve the management of upper respiratory tract infections and reduce inappropriate antibiotic use particularly among lower and middle-income countries: findings and implications for the future. *Current medical research and opinion*. 36(2):301-327 (2020).
 53. Godman B, McCabe H, Leong TD. Fixed dose drug combinations - are they pharmaco-economically sound? Findings and implications especially for lower- and middle-income countries. *Expert review of pharmacoeconomics & outcomes research*. 20(1), 1-26 (2020).
 54. Stojanovic J, Wübbeler M, Geis S, Reviriego E, Gutiérrez-Ibarluzea I, Lenoir-Wijnkoop I. Evaluating Public Health Interventions: A Neglected Area in Health Technology Assessment. *Frontiers in Public Health*. 2020;8(106) (2020).
 55. Godman B, Shrank W, Wettermark B et al. Use of Generics-A Critical Cost Containment Measure for All Healthcare Professionals in Europe? *Pharmaceuticals*. 3(8), 2470-2494 (2020).
 56. Voncina L, Strizrep T, Godman B et al. Influence of demand-side measures to enhance renin-angiotensin prescribing efficiency in Europe: implications for the future. *Expert review of pharmacoeconomics & outcomes research*. 11(4), 469-479 (2011).
 57. Caires de Souza AL, de Assis Acurcio F, Guerra Junior AA, Rezende Macedo do Nascimento RC, Godman B, Diniz LM. Insulin glargine in a Brazilian state: should the government disinvest? An assessment based on a systematic review. *Applied health economics and health policy*. 12(1), 19-32 (2014).
 58. Almeida P, Silva TBC, de Assis Acurcio F et al. Quality of Life of Patients with Type 1 Diabetes Mellitus Using Insulin Analog Glargine Compared with NPH Insulin: A Systematic Review and Policy Implications. *The patient*. 11(4), 377-389 (2018).
 59. de Lemos LLP, Carvalho de Souza M, Pena Moreira D et al. Stage at diagnosis and stage-specific survival of breast cancer in Latin America and the Caribbean: A systematic review and meta-analysis. *PloS one*. 14(10), e0224012 (2019).
 60. Kurdi A, Abutheraa N, Akil L, Godman B. A systematic review and meta-analysis of the use of renin-angiotensin system drugs and COVID-19 clinical outcomes: What is the evidence so far? *Pharmacology research & perspectives*. 8(6), e00666 (2020).
 61. Wettermark B, Godman B, Jacobsson B, Haaijer-Ruskamp FM. Soft regulations in pharmaceutical policy making: an overview of current approaches and their consequences. *Applied health economics and health policy*. 7(3):137-147 (2009).

-
62. Bjorkhem-Bergman L, Andersen-Karlsson E, Laing R et al. Interface management of pharmacotherapy. Joint hospital and primary care drug recommendations. *European journal of clinical pharmacology*. 69 Suppl 1, 73-78 (2013).
63. Gustafsson LL, Wettermark B, Godman B et al. The 'wise list'- a comprehensive concept to select, communicate and achieve adherence to recommendations of essential drugs in ambulatory care in Stockholm. *Basic & clinical pharmacology & toxicology*. 108(4), 224-233 (2011).
64. Hoffmann M. The right drug, but from whose perspective? A framework for analysing the structure and activities of drug and therapeutics committees. *European journal of clinical pharmacology*. 69(Suppl 1), 79-87 (2013).
65. Nakwatumbah S, Kibuule D, Godman B et al. Compliance to guidelines for the prescribing of antibiotics in acute infections at Namibia's national referral hospital: a pilot study and the implications. *Expert review of anti-infective therapy*. 15(7), 713-721 (2017).
66. Campbell SM, Reeves D, Kontopantelis E, Sibbald B, Roland M. Effects of pay for performance on the quality of primary care in England. *N Engl J Med*. 361(4):368-378 (2009).
67. McGinn D, Godman B, Lonsdale J, Way R, Wettermark B, Haycox A. Initiatives to enhance the quality and efficiency of statin and PPI prescribing in the UK: impact and implications. *Expert review of pharmacoeconomics & outcomes research*. 10(1), 73-85 (2010).
68. Matlala M, Gous AGS, Meyer JC, Godman B. Formulary Management Activities and Practice Implications Among Public Sector Hospital Pharmaceutical and Therapeutics Committees in a South African Province. *Frontiers in pharmacology*. 11, 1267 (2020).
69. Jacobs TG, Robertson J, van den Ham HA, Iwamoto K, Bak Pedersen H, Mantel-Teeuwisse AK. Assessing the impact of law enforcement to reduce over-the-counter (OTC) sales of antibiotics in low- and middle-income countries; a systematic literature review. *BMC health services research*. 19(1), 536 (2019).
70. Godman B, Wettermark B, Hoffmann M, Andersson K, Haycox A, Gustafsson LL. Multifaceted national and regional drug reforms and initiatives in ambulatory care in Sweden: global relevance. *Expert review of pharmacoeconomics & outcomes research*. 9(1), 65-83 (2009).
71. Cohen D. Cancer drugs: high price, uncertain value. *BMJ*. 359, j4543 (2017).
72. Luzzatto L, Hyry HI, Schieppati A et al. Outrageous prices of orphan drugs: a call for collaboration. *Lancet*. 392(10149), 791-794 (2018).
73. Cohen D. Dabigatran: how the drug company withheld important analyses. *BMJ*. 349, g4670 (2014).
74. Moore TJ, Cohen MR, Mattison DR. Dabigatran, bleeding, and the regulators. *BMJ*. 349, g4517 (2014).
75. Godman B, Joppi R, Bennie M, Jan S, Wettermark B. Managed introduction of new drugs. Chapter 20: 210-221 in Elseviers M, Wettermark B et al (eds). *Drug Utilization Research: Methods and Applications*. John Wiley & Sons, Chichester ISBN: 978-1-118-94978-8 (2016).
76. Vogler S, Paris V, Panteli D. European Observatory Policy Briefs. In: Richardson E, Palm W, Mossialos E, editors. *Ensuring access to medicines: How to redesign pricing, reimbursement and procurement?* Copenhagen (Denmark): European Observatory on Health Systems and Policies (c) World Health Organization (2018).
77. Waters R, Urquhart L. EvaluatePharma® World Preview. Outlook to 2024. (2019). Available at URL: https://info.evaluate.com/rs/607-YGS-364/images/EvaluatePharma_World_Preview_2019.pdf.
78. Eriksson I, von Euler M, Malmström RE, Godman B, Wettermark B. Did we see it Coming? An Evaluation of the Swedish Early Awareness and Alert System. *Applied health economics and health policy*. 17(1), 93-101 (2019).
79. KCE REPORT 283. HORIZON SCANNING FOR PHARMACEUTICALS: PROPOSAL FOR THE BENELUXA COLLABORATION (2017). Available at URL: https://beneluxa.org/sites/beneluxa.org/files/2017-07/Horizon%20scanning_ScientificReport_full.pdf.
80. Tefferi A, Kantarjian H, Rajkumar SV et al. In Support of a Patient-Driven Initiative and Petition to Lower the High Price of Cancer Drugs. *Mayo Clin Proc*. 90(8), 996-1000 (2015)
81. Wild C, Langer T. Emerging health technologies: informing and supporting health policy early. *Health policy*. 87(2), 160-71 (2008).
82. Wild C, Simpson S, Douw K, Geiger-Gritsch S, Mathis S, Langer T. Information service on new and emerging health technologies: identification and prioritization processes for a European union-wide newsletter. *International journal of technology assessment in health care*. 25 Suppl 2, 48-55 (2009).
83. Wettermark B, Persson ME, Wilking N et al. Forecasting drug utilization and expenditure in a metropolitan health region. *BMC health services research*. 10, 128 (2010).

-
84. Godman B, Paterson K, Malmstrom RE, Selke G, Fagot JP, Mrak J. Improving the managed entry of new medicines: sharing experiences across Europe. *Expert review of pharmacoeconomics & outcomes research*. 12(4), 439-441 (2012).
 85. Pontes C, Zara C, Torrent-Farnell J et al. Time to Review Authorisation and Funding for New Cancer Medicines in Europe? Inferences from the Case of Olaratumab. *Applied health economics and health policy*. 18(1), 5-16 (2020).
 86. Gyawali B, Addeo A. Negative phase 3 randomized controlled trials: Why cancer drugs fail the last barrier? *Int J Cancer*. 143(8), 2079-2081 (2018).
 87. Jonker DJ, Nott L, Yoshino T et al. Napabucasin versus placebo in refractory advanced colorectal cancer: a randomised phase 3 trial. *The lancet Gastroenterology & hepatology*. 3(4), 263-270 (2018).
 88. Packer C, Simpson S, de Almeida RT. EUROSCAN INTERNATIONAL NETWORK MEMBER AGENCIES: THEIR STRUCTURE, PROCESSES, AND OUTPUTS. *International journal of technology assessment in health care*. 31(1-2), 78-85 (2015).
 89. Simpson S, Packer C, Carlsson P et al. Early identification and assessment of new and emerging health technologies: actions, progress, and the future direction of an international collaboration--EuroScan. *International journal of technology assessment in health care*. 24(4), 518-25 (2008).
 90. Joppi R, Dematte L, Menti AM, Pase D, Poggiani C, Mezzalira L. The Italian Horizon Scanning Project. *European journal of clinical pharmacology*. 65(8), 775-781 (2009).
 91. Packer C, Fung M, Stevens A. Analyzing 10 years of early awareness and alert activity in the United kingdom. *International journal of technology assessment in health care*. 28(3), 308-314 (2012).
 92. Scottish Medicines Consortium. Horizon Scanning Activities. (2021). Available at URL: <https://www.scottishmedicines.org.uk/about-us/horizon-scanning/>.
 93. Martino OI, Ward DJ, Packer C, Simpson S, Stevens A. Innovation and the burden of disease: retrospective observational study of new and emerging health technologies reported by the EuroScan Network from 2000 to 2009. *Value in health*. 15(2), 376-380 (2012).
 94. O'Mahony JF. Beneluxa: What are the Prospects for Collective Bargaining on Pharmaceutical Prices Given Diverse Health Technology Assessment Processes? *PharmacoEconomics*. 37(5), 627-630 (2019).
 95. Sinigoj P, Malmstrom RE, Vene N et al. Dabigatran Concentration: Variability and Potential Bleeding Prediction In "Real-Life" Patients With Atrial Fibrillation. *Basic & clinical pharmacology & toxicology*. 117(5):323-329 (2015).
 96. Godoi IP, Santos AS, Reis EA et al. Consumer Willingness to Pay for Dengue Vaccine (CYD-TDV, Dengvaxia(R)) in Brazil; Implications for Future Pricing Considerations. *Frontiers in pharmacology*. 8, 41 (2017).
 97. Weernink MGM, Janus SIM, van Til JA, Raisch DW, van Manen JG, Ijzerman MJ. A Systematic Review to Identify the Use of Preference Elicitation Methods in Healthcare Decision Making. *Pharmaceutical Medicine*. 28(4), 175-185 (2014).
 98. Muniz Júnior RL, Godói IP, Reis EA et al. Consumer willingness to pay for a hypothetical Zika vaccine in Brazil and the implications. *Expert review of pharmacoeconomics & outcomes research*. 19(4), 473-82 (2019).
 99. Vogler S, Paterson KR. Can Price Transparency Contribute to More Affordable Patient Access to Medicines? *PharmacoEconomics - open*. 1(3), 145-147 (2017).
 100. Annemans L. A proposal for value informed, affordable ("via") prices for innovative medicines. *Journal of medical economics*. 22(11), 1235-1239 (2019).
 101. Athie TS, Nascimento GC, Labis da Costa MJ et al. Consumer willingness to pay for a hypothetical Chagas disease vaccine in Brazil: a cross-sectional study and the implications. *Journal of comparative effectiveness research*. 10(8), 659-672 (2021).
 102. Permanand G, Pedersen H. Managing new premium-priced medicines in Europe. *Journal of Pharmaceutical Policy and Practice*. 8(Suppl 1), K2 (2015).
 103. Godman B, Oortwijn W, de Waure C et al. Links between Pharmaceutical R&D Models and Access to Affordable Medicines. A Study for the ENVI COMMITTEE. (2016) Available at URL: [http://www.europarl.europa.eu/RegData/etudes/STUD/2016/587321/IPOL_STU\(2016\)587321_EN.pdf](http://www.europarl.europa.eu/RegData/etudes/STUD/2016/587321/IPOL_STU(2016)587321_EN.pdf)
 104. Vogler S, Paris V, Ferrario A et al. How Can Pricing and Reimbursement Policies Improve Affordable Access to Medicines? Lessons Learned from European Countries. *Applied health economics and health policy*. 15(3), 307-321 (2017).
 105. Paris V, Belloni A. Value in Pharmaceutical Pricing. (2013). Available at URL: http://www.oecd-ilibrary.org/social-issues-migration-health/value-in-pharmaceutical-pricing_5k43jc9v6knx-en

-
106. Emanuel EJ, Zhang C, Glickman A, Gudbranson E, DiMugno SSP, Urwin JW. Drug Reimbursement Regulation in 6 Peer Countries. *JAMA Intern Med.* 180(11), 1510-1517 (2020)
107. Fortinguerra F, Tafuri G, Trotta F, Addis A. Using GRADE methodology to assess innovation of new medicinal products in Italy. *British journal of clinical pharmacology.* 86(1), 93-105 (2020).
108. European Commission. DEFINING VALUE IN "VALUE BASED HEALTHCARE". Report of the Expert Panel on effective ways of investing in Health (EXPH) (2019). Available at URL: https://ec.europa.eu/health/sites/health/files/expert_panel/docs/024_defining-value-vbhc_en.pdf.
109. Ferguson JS, Summerhayes M, Masters S, Schey S, Smith IE. New treatments for advanced cancer: an approach to prioritization. *Br J Cancer.* 83(10), 1268-1273 (2000).
110. WHO. Access to new medicines in Europe: technical review of policy initiatives and opportunities for collaboration and research. (2015). Available at URL: http://www.euro.who.int/__data/assets/pdf_file/0008/306179/Access-new-medicines-TR-PIO-collaboration-research.pdf?ua=1
111. Godman B, Wild C, Haycox A. Patent expiry and costs for anti-cancer medicines for clinical use. *GABI Journal.* 6(3), 105-106 (2017).
112. Uyl-de Groot CA, Lowenberg B. Sustainability and affordability of cancer drugs: a novel pricing model. *Nature reviews Clinical oncology.* 15(7), 405-406 (2018).
113. World Health Organization. Pricing of cancer medicines and its impacts. (2018). Available from URL: <https://apps.who.int/iris/bitstream/handle/10665/277190/9789241515115-eng.pdf?ua=1>.
114. Carlson JJ, Chen S, Garrison LP, Jr. Performance-Based Risk-Sharing Arrangements: An Updated International Review. *PharmacoEconomics.* 35(10), 1063-1072 (2017).
115. Ferrario A, Arāja D, Bochenek T et al. The Implementation of Managed Entry Agreements in Central and Eastern Europe: Findings and Implications. *PharmacoEconomics.* 35(12), 1271-1285 (2017).
116. Ezeife DA, Dionne F, Fares AF et al. Value assessment of oncology drugs using a weighted criterion-based approach. *Cancer.* 126(7), 1530-1540 (2020).
117. Sculpher M, Claxton K, Pearson SD. Developing a Value Framework: The Need to Reflect the Opportunity Costs of Funding Decisions. *Value in health.* 20(2), 234-239 (2017).
118. Hughes-Wilson W, Palma A, Schuurman A, Simoens S. Paying for the Orphan Drug System: break or bend? Is it time for a new evaluation system for payers in Europe to take account of new rare disease treatments? *Orphanet journal of rare diseases.* 7, 74 (2012).
119. Angelis A, Linch M, Montibeller G et al. Multiple Criteria Decision Analysis for HTA across four EU Member States: Piloting the Advance Value Framework. *Social Science & Medicine.* 246, 112595 (2020).
120. Inotai A, Nguyen HT, Hidayat B et al. Guidance toward the implementation of multicriteria decision analysis framework in developing countries. *Expert review of pharmacoeconomics & outcomes research.* 18(6), 585-592 (2018).
121. Suleman F, Low M, Moon S, Morgan SG. New business models for research and development with affordability requirements are needed to achieve fair pricing of medicines. *BMJ.* 368, I4408-I (2020).
122. AIM. AIM PROPOSES TO ESTABLISH A EUROPEAN DRUG PRICING MODEL FOR FAIR AND TRANSPARENT PRICES FOR ACCESSIBLE PHARMACEUTICAL INNOVATIONS. (2019) Available at URL: <https://www.aim-mutual.org/wp-content/uploads/2019/12/AIMs-proposal-for-fair-and-transparent-prices-for-pharmaceuticals.pdf>.
123. Moon S, Mariat S, Kamae I, Pedersen HB. Defining the concept of fair pricing for medicines. *BMJ.* 368, I4726-I (2020).
124. WHO. WHO guideline on country pharmaceutical pricing policies, second edition. Geneva: World Health Organization (2020). Available at URL: <https://apps.who.int/iris/bitstream/handle/10665/335692/9789240011878-eng.pdf>.
125. Workman P, Draetta GF, Schellens JH, Bernards R. How Much Longer Will We Put Up With \$100,000 Cancer Drugs? *Cell.* 168(4), 579-583 (2017).
126. Jönsson B, Hampson G, Michaels J, Towse A, von der Schulenburg JMG, Wong O. Advanced therapy medicinal products and health technology assessment principles and practices for value-based and sustainable healthcare. *The European journal of health economics.* 20(3), 427-438 (2019).
127. Garattini L, Curto A. Performance-Based Agreements in Italy: 'Trendy Outcomes' or Mere Illusions? *PharmacoEconomics.* 34(10), 967-969 (2016).
128. Troncoso A, Diogene E. Dabigatran and rivaroxaban prescription for atrial fibrillation in Catalonia, Spain: the need to manage the introduction of new drugs. *European journal of clinical pharmacology.* 70(2), 249-50 (2014).

-
129. Maura G, Pariente A, Alla F, Billionnet C. Adherence with direct oral anticoagulants in nonvalvular atrial fibrillation new users and associated factors: a French nationwide cohort study. *Pharmacoepidemiol Drug Saf.* 26(11), 1367-1377 (2017).
130. Mueller T, Alvarez-Madrado S, Robertson C, Wu O, Bennie M. Comparative safety and effectiveness of direct oral anticoagulants in patients with atrial fibrillation in clinical practice in Scotland. *British journal of clinical pharmacology.* 85(2), 422-431 (2019).
131. Raaschou P, Simard JF, Holmqvist M, Askling J. Rheumatoid arthritis, anti-tumour necrosis factor therapy, and risk of malignant melanoma: nationwide population based prospective cohort study from Sweden. *BMJ.* 346, f1939 (2013).
132. Brennan T, Shrank W. New expensive treatments for hepatitis C infection. *Jama.* 312(6), 593-594 (2014).
133. de Bruijn W, Ibanez C, Frisk P et al. Introduction and Utilization of High Priced HCV Medicines across Europe; Implications for the Future. *Frontiers in pharmacology.* 7, 197 (2016).
134. Campbell SM, Godman B, Diogene E et al. Quality indicators as a tool in improving the introduction of new medicines. *Basic & clinical pharmacology & toxicology.* 116(2), 146-157 (2015).
135. Sofat R, Cremers S, Ferner RE. Drug and therapeutics committees as guardians of safe and rational medicines use. *British journal of clinical pharmacology.* 86(1), 10-12 (2020)
136. Godman B. Ongoing initiatives to improve the prescribing of medicines across sectors and the implications. *Adv Hum Biol.* 10 (3), 85-89 (2020).
137. Holloway K, Green T. Drug and therapeutics committees. A practical guide on behalf of the WHO in collaboration with MSH. (2003). Available at URL: https://apps.who.int/iris/bitstream/handle/10665/68553/WHO_EDM_PAR_2004.1.pdf?sequence=1&isAllowed=y
138. Office of Director of Pharmaceutical Services (ODPS) Ministry of Health Ghana. Strengthening of Drug and Therapeutics Committees in Public and Private Health Facilities in Ghana. (2015). Available at URL: <https://apps.who.int/medicinedocs/documents/s22376en/s22376en.pdf>.
139. Lima-Dellamora Eda C, Caetano R, Gustafsson LL, Godman BB, Patterson K, Osorio-de-Castro CG. An analytical framework for assessing drug and therapeutics committee structure and work processes in tertiary Brazilian hospitals. *Basic & clinical pharmacology & toxicology.* 115(3), 268-276 (2014).
140. Matuszewicz W, Godman B, Pedersen HB et al. Improving the managed introduction of new medicines: sharing experiences to aid authorities across Europe. *Expert review of pharmacoeconomics & outcomes research.* 15(5), 755-758 (2015).
141. Ministry of Health BRASIL. Relação Nacional de Medicamentos Essenciais – Rename. (2020). Available: <https://saude.gov.br/saude-de-a-z/rename>.
142. Ministry of Health BRASIL. Relação Nacional de Medicamentos Essenciais. (2020). Available: http://bvsmms.saude.gov.br/bvs/publicacoes/relacao_medicamentos_rename_2020.pdf.
143. Costa JO, Almeida-Brasil CC, Godman B et al. Implementation of clinical guidelines in Brazil: Should academic detailing be used? *Jn Pharm Health Services Res.* 7, 105-115 (2016)
144. Carvalho Borin M, Kakehasi AM, Dartnell J et al. Academic detailing program for rheumatoid arthritis: a contribution to Brazilian public health system sustainability. *Journal of Pharmaceutical Health Services Research.* 11(3), 249-254 (2020).
145. Fadare JO, Ogunleye O, Obiako R et al. Drug and therapeutics committees in Nigeria: evaluation of scope and functionality. *Expert review of clinical pharmacology.* 11(12), 1255-62 (2018).
146. Modisakeng C, Matlala M, Godman B, Meyer JC. Medicine shortages and challenges with the procurement process among public sector hospitals in South Africa; findings and implications. *BMC health services research.* 20(1), 234 (2020)
147. Giardina C, Cutroneo PM, Mocciano E et al. Adverse Drug Reactions in Hospitalized Patients: Results of the FORWARD (Facilitation of Reporting in Hospital Ward) Study. *Frontiers in pharmacology.* 9, 350 (2018).
148. Terblanche A, Meyer JC, Godman B, Summers RS. Impact of a pharmacist-driven pharmacovigilance system in a secondary hospital in the Gauteng Province of South Africa. *Hospital practice.* 46(4), 221-228 (2018).
149. Mashaba TP, Matlala M, Godman B, Meyer JC. Implementation and monitoring of decisions by pharmacy and therapeutics committees in South African public sector hospitals. *Expert review of clinical pharmacology.* 12(2), 159-168 (2019).
150. Matlala M, Gous AG, Godman B, Meyer JC. Structure and activities of pharmacy and therapeutics committees among public hospitals in South Africa; findings and implications. *Expert review of clinical pharmacology.* 10(11), 1273-1280 (2017).

-
151. Meyer JC, Schellack N, Stokes J et al. Ongoing Initiatives to Improve the Quality and Efficiency of Medicine Use within the Public Healthcare System in South Africa; A Preliminary Study. *Frontiers in pharmacology*. 8, 751 (2017).
152. Cars T, Lindhagen L, Malmstrom RE et al. Effectiveness of Drugs in Routine Care: A Model for Sequential Monitoring of New Medicines Using Dronedarone as Example. *Clinical pharmacology and therapeutics*. 103(3), 493-501 (2018).
153. Ferrario A, Kanavos P. Dealing with uncertainty and high prices of new medicines: a comparative analysis of the use of managed entry agreements in Belgium, England, the Netherlands and Sweden. *Soc Sci Med*. 124, 39-47 (2015).
154. Adamski J, Godman B, Ofierska-Sujkowska G et al. Risk sharing arrangements for pharmaceuticals: potential considerations and recommendations for European payers. *BMC health services research*. 10, 153 (2010).
155. Robinson MF, Mihalopoulos C, Merlin T, Roughead E. CHARACTERISTICS OF MANAGED ENTRY AGREEMENTS IN AUSTRALIA. *International journal of technology assessment in health care*. 34(1), 46-55 (2018).
156. Van Wilder P, Pirson M, Dupont A. Impact of health technology assessment and managed entry schemes on reimbursement decisions of centrally authorised medicinal products in Belgium. *European journal of clinical pharmacology*. 75(7), 895-900 (2019).
157. KCE. HOW TO IMPROVE THE BELGIAN PROCESS FOR MANAGED ENTRY AGREEMENTS? (2017). Available at URL: <https://kce.fgov.be/sites/default/files/atoms/files/Download%20the%20synthesis%20in%20English%20%2840%20p.%29.pdf>.
158. Annemans L, Panie L. Dynamic outcomes based approaches to pricing and reimbursement of innovative medicines. (2017). Available at URL: <https://www.eurordis.org/sites/default/files/FIPRA.pdf>.
159. Nazareth T, Ko JJ, Sasane R et al. Outcomes-Based Contracting Experience: Research Findings from U.S. and European Stakeholders. *Journal of managed care & specialty pharmacy*. 23(10), 1018-1026 (2017).
160. Lessing C, Ashton T, Davis P. The impact on health outcomes and healthcare utilisation of switching to generic medicines consequent to reference pricing: the case of lamotrigine in New Zealand. *Applied health economics and health policy*. 12(5), 537-546 (2014).
161. Kesselheim AS, Misono AS, Lee JL et al. Clinical equivalence of generic and brand-name drugs used in cardiovascular disease: a systematic review and meta-analysis. *Jama*. 300(21), 2514-2526 (2008).
162. Corrao G, Soranna D, Merlino L, Mancina G. Similarity between generic and brand-name antihypertensive drugs for primary prevention of cardiovascular disease: evidence from a large population-based study. *European journal of clinical investigation*. 44(10), 933-939 (2014).
163. Corrao G, Soranna D, Arfe A et al. Are generic and brand-name statins clinically equivalent? Evidence from a real data-base. *European journal of internal medicine*. 25(8), 745-750 (2014).
164. Manzoli L, Flacco ME, Boccia S et al. Generic versus brand-name drugs used in cardiovascular diseases. *European journal of epidemiology*. 31(4), 351-368 (2016).
165. Paton C. Generic clozapine: outcomes after switching formulations. *The British journal of psychiatry*. 189, 184-185 (2006).
166. Godman B, Baumgartel C. Are generic immunosuppressants safe and effective? *BMJ*. 350, h3248 (2015).
167. Jorgensen KK, Olsen IC, Goll GL et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. *Lancet*. 389(10086), 2304-2316 (2017).
168. Pivot X, Bondarenko I, Nowecki Z et al. A phase III study comparing SB3 (a proposed trastuzumab biosimilar) and trastuzumab reference product in HER2-positive early breast cancer treated with neoadjuvant-adjuvant treatment: Final safety, immunogenicity and survival results. *Eur J Cancer*. 93, 19-27 (2018).
169. Blair HA. GP2013: A Rituximab Biosimilar. *BioDrugs*. 31(5), 465-468 (2017).
170. Egeberg A, Ottosen MB, Gniadecki R et al. Safety, efficacy and drug survival of biologics and biosimilars for moderate-to-severe plaque psoriasis. *The British journal of dermatology*. 178(2), 509-519 (2018).
171. Blevins TC, Barve A, Raiter Y et al. Efficacy and safety of MYL-1501D versus insulin glargine in people with type 1 diabetes mellitus: Results of the INSTRIDE 3 phase 3 switch study. *Diabetes, obesity & metabolism*. 22(3), 365-372 (2020).

-
172. Godman B, Shrank W, Andersen M et al. Comparing policies to enhance prescribing efficiency in Europe through increasing generic utilization: changes seen and global implications. *Expert review of pharmacoeconomics & outcomes research*. 10(6):707-722 (2010).
173. The World Bank. Final Report - DRUG-RESISTANT INFECTIONS. A Threat to Our Economic Future. (2017). Available at URL: <http://documents1.worldbank.org/curated/en/323311493396993758/pdf/final-report.pdf>.
174. Niaz Q, Godman B, Masseur A et al. Validity of World Health Organisation prescribing indicators in Namibia's primary healthcare: findings and implications. *International journal for quality in health care*. 31(5), 338-345 (2019).
175. Bilal AI, Osman ED, Mulugeta A. Assessment of medicines use pattern using World Health Organization's Prescribing, Patient Care and Health facility indicators in selected health facilities in eastern Ethiopia. *BMC health services research*. 16, 144 (2016).
176. Ofori-Asenso R, Brhlikova P, Pollock AM. Prescribing indicators at primary health care centers within the WHO African region: a systematic analysis (1995-2015). *BMC public health*. 16, 724 (2016).
177. Atif M, Sarwar MR, Azeem M et al. Assessment of WHO/INRUD core drug use indicators in two tertiary care hospitals of Bahawalpur, Punjab, Pakistan. *Journal of Pharmaceutical Policy and Practice*. 9, 27 (2016)
178. Lui G, To HKW, Lee N et al. Adherence to Treatment Guideline Improves Patient Outcomes in a Prospective Cohort of Adults Hospitalized for Community-Acquired Pneumonia. *Open Forum Infectious Diseases*. 7(5) (2020).
179. Wathne JS, Harthug S, Kleppe LKS et al. The association between adherence to national antibiotic guidelines and mortality, readmission and length of stay in hospital inpatients: results from a Norwegian multicentre, observational cohort study. *Antimicrobial Resistance & Infection Control*. 8(1), 63 (2019).
180. Hubbard IJ, Harris D, Kilkenny MF, Faux SG, Pollack MR, Cadilhac DA. Adherence to clinical guidelines improves patient outcomes in Australian audit of stroke rehabilitation practice. *Archives of physical medicine and rehabilitation*. 93(6), 965-971 (2012).
181. Krittayaphong R, Winijkul A, Kunjara-Na-Ayudhya R et al. Adherence to Anticoagulant Guideline for Atrial Fibrillation Improves Outcomes in Asian Population: The COOL-AF Registry. *Stroke*. 51(6):1772-1780 (2020).
182. Jeffery RA, To MJ, Hayduk-Costa G et al. Interventions to improve adherence to cardiovascular disease guidelines: a systematic review. *BMC Fam Pract*. 16:147 (2015)
183. Wettermark B, Pehrsson A, Juhasz-Haverinen M et al. Financial incentives linked to self-assessment of prescribing patterns: a new approach for quality improvement of drug prescribing in primary care. *Quality in primary care*. 17(3), 179-189 (2009)
184. Eriksen J, Gustafsson LL, Ateva K et al. High adherence to the 'Wise List' treatment recommendations in Stockholm: a 15-year retrospective review of a multifaceted approach promoting rational use of medicines. *BMJ open*. 7(4), e014345 (2017).
185. A Fitzgerald AL, M Cikalo, J Glanville, H Wood Review of Systematic Reviews Exploring the Implementation/Uptake of Guidelines. York Health Economics Consortium. (2014). Available at URL: <https://www.nice.org.uk/guidance/ph56/evidence/evidence-review-2-431762366>
186. Niaz Q, Godman B, Campbell S, Kibuule D. Compliance to prescribing guidelines among public health care facilities in Namibia; findings and implications. *International journal of clinical pharmacy*. 42(4), 1227-1236 (2020).
187. Godman B, Bishop I, Finlayson AE, Campbell S, Kwon HY, Bennie M. Reforms and initiatives in Scotland in recent years to encourage the prescribing of generic drugs, their influence and implications for other countries. *Expert review of pharmacoeconomics & outcomes research*. 13(4), 469-482 (2013).
188. Duerden MG, Hughes DA. Generic and therapeutic substitutions in the UK: are they a good thing? *British journal of clinical pharmacology*. 70(3), 335-341 (2010)
189. Ferner RE, Lenney W, Marriott JF. Controversy over generic substitution. *BMJ*. 340, c2548 (2010).
190. Olsson E, Wallach-Kildemoes H, Ahmed B, Ingman P, Kaae S, Kalvemarm Sporrang S. The influence of generic substitution on the content of patient-pharmacist communication in Swedish community pharmacies. *The International journal of pharmacy practice*. 25(4), 274-281 (2017).
191. Martin A, Godman B, Miranda J et al. Measures to improve angiotensin receptor blocker prescribing efficiency in the UK: findings and implications. *Journal of comparative effectiveness research*. 3(1), 41-51 (2014).

-
192. Olsson E, Källemark Sporrang S. Pharmacists' experiences and attitudes regarding generic drugs and generic substitution: two sides of the coin. *The International journal of pharmacy practice*. 20(6), 377-383 (2012).
193. Baumgärtel C, Godman B, Malmström R et al. What lessons can be learned from the launch of generic clopidogrel? *GaBI Journal*. 1(2), 58-68 (2012)
194. Godman B, Hill A, Simoens S et al. Pricing of oral generic cancer medicines in 25 European countries; findings and implications. *GaBI Journal*. 8(2), 49-70 (2019)
195. Editorial. Generic bashing: effective but illegal. *Rev Prescrire*. 33(360), 773 (2013)
196. Garuoliene K, Godman B, Gulbinovic J, Wettermark B, Haycox A. European countries with small populations can obtain low prices for drugs: Lithuania as a case history. *Expert review of pharmacoeconomics & outcomes research*. 11(3), 343-349 (2011)
197. Martikainen JE, Saastamoinen LK, Korhonen MJ, Enlund H, Helin-Salmivaara A. Impact of restricted reimbursement on the use of statins in Finland: a register-based study. *Medical care*. 48(9), 761-766 (2010).
198. Kwon HY, Kim H, Godman B, Reich MR. The impact of South Korea's new drug-pricing policy on market competition among off-patent drugs. *Expert review of pharmacoeconomics & outcomes research*. 15(6), 1007-1014 (2015).
199. Kwon HY, Godman B. Drug Pricing in South Korea. *Applied health economics and health policy*. 15(4), 447-453 (2017).
200. Olsson E, Ingman P, Ahmed B, Källemark Sporrang S. Pharmacist-patient communication in Swedish community pharmacies. *Research in social & administrative pharmacy*. 10(1):149-155 (2014).
201. Fadare JO, Adeoti AO, Desalu OO et al. The prescribing of generic medicines in Nigeria: knowledge, perceptions and attitudes of physicians. *Expert review of pharmacoeconomics & outcomes research*. 16(5), 639-650 (2016).
202. Khan B, Godman B, Babar A, Hussain S, Mahmood S, Aqeel T. Assessment of active pharmaceutical ingredients in the registration procedures in Pakistan: implications for the future. *GaBI Journal*. 5(4), 156-163 (2016).
203. Arnet I, Altermatt M, Roggo Y, Schnetzler G. Pharmaceutical quality of eight generics of ceftriaxone preparation for injection in Eastern Asia. *Journal of chemotherapy*. 27(6), 337-42 (2015).
204. Redfern J, Kaur H, Adedoyin RA et al. Equivalence in Active Pharmaceutical Ingredient of Generic Antihypertensive Medicines Available in Nigeria (EQUIMEDS): A Case for Further Surveillance. *Global heart*. 14(3), 327-333 (2019).
205. WHO. Launch of the Lomé Initiative. (2020). Available at URL: <https://www.who.int/dg/speeches/detail/launch-of-the-lom%C3%A9-initiative>.
206. Gwaza L, Gordon J, Welink et al. Adjusted indirect treatment comparison of the bioavailability of WHO-prequalified first-line generic antituberculosis medicines. *Clinical pharmacology and therapeutics*. 96(5), 580-588 (2014).
207. Editorial. Generic medicines - Interchangeability of WHO-prequalified generics. *WHO Drug Information*. 30 (3), 370-375 (2016).
208. Godman B, Wettermark B, Miranda J, Bennie M, Martin A, Malmstrom RE. Influence of multiple initiatives in Sweden to enhance ARB prescribing efficiency following generic losartan; findings and implications for other countries. *International journal of clinical practice*. 67(9), 853-862 (2013).
209. Godman B, Persson M, Miranda J et al. Can authorities take advantage of the availability of generic atypical antipsychotic drugs:? Findings from Sweden and potential implications. *Journal of Pharmaceutical Health Services Research*. 4, 139-150 (2013).
210. Markovic-Pekovic V, Skrbic R, Godman B, Gustafsson LL. Ongoing initiatives in the Republic of Srpska to enhance prescribing efficiency: influence and future directions. *Expert review of pharmacoeconomics & outcomes research*. 12(5), 661-671 (2012).
211. Woerkom M, Piepenbrink H, Godman B et al. Ongoing measures to enhance the efficiency of prescribing of proton pump inhibitors and statins in The Netherlands: influence and future implications. *Journal of comparative effectiveness research*. 1(6), 527-538 (2012).
212. Glerum PJ, Maliepaard M, de Valk V, Burger DM, Neef K. Drug switching in the Netherlands: a cohort study of 20 active substances. *BMC health services research*. 20(1), 650 (2020).
213. Dylst P, Vulto A, Godman B, Simoens S. Generic medicines: solutions for a sustainable drug market? *Applied health economics and health policy*. 11(5), 437-43 (2013).
214. Acosta A, Vanegas EP, Rovira J, Godman B, Bochenek T. Medicine Shortages: Gaps Between Countries and Global Perspectives. *Frontiers in pharmacology*. 10, 763 (2019).

-
215. Garuoliene K, Godman B, Gulbinovic J, Schiffers K, Wettermark B. Differences in utilization rates between commercial and administrative databases: implications for future health-economic and cross-national studies. *Expert review of pharmacoeconomics & outcomes research*. 16(2), 149-152 (2016).
216. Hill A, Gotham D, Fortunak J et al. Target prices for mass production of tyrosine kinase inhibitors for global cancer treatment. *BMJ open*. 6(1), e009586 (2016).
217. Hill A, Redd C, Gotham D, Erbacher I, Meldrum J, Harada R. Estimated generic prices of cancer medicines deemed cost-ineffective in England: a cost estimation analysis. *BMJ open*. 7(1), e011965 (2017).
218. IQVIA. The Impact of Biosimilar Competition in Europe. (2019). Available at URL: <https://ec.europa.eu/docsroom/documents/38461>.
219. Kluge HHP, Wickramasinghe K, Rippin HL et al. Prevention and control of non-communicable diseases in the COVID-19 response. *Lancet*. 395(10238), 1678-1680 (2020)
220. United Nations. Policy Brief: COVID-19 and Universal Health Coverage - OCTOBER 2020. Available at URL: https://www.un.org/sites/un2.un.org/files/sg_policy_brief_on_universal_health_coverage.pdf.
221. Molyneux D, Bush S, Bannerman R et al. Neglected tropical diseases activities in Africa in the COVID-19 era: the need for a "hybrid" approach in COVID-endemic times. *Infectious diseases of poverty*. 10(1), 1 (2021).
222. Baumgart DC, Misery L, Naeyaert S, Taylor PC. Biological Therapies in Immune-Mediated Inflammatory Diseases: Can Biosimilars Reduce Access Inequities? *Frontiers in pharmacology*. 10, 279 (2019).
223. Putrik P, Ramiro S, Kvien TK et al. Inequities in access to biologic and synthetic DMARDs across 46 European countries. *Annals of the rheumatic diseases*. 73(1), 198-206 (2014).
224. Kostic M, Djakovic L, Sujic R, Godman B, Jankovic SM. Inflammatory Bowel Diseases (Crohn's Disease and Ulcerative Colitis): Cost of Treatment in Serbia and the Implications. *Applied health economics and health policy*. 15(1), 85-93 (2017).
225. Al-Ziftawi NH, Shafie AA, Mohamed Ibrahim MI. Cost-effectiveness analyses of breast cancer medications use in developing countries: a systematic review. *Expert review of pharmacoeconomics & outcomes research*. 1-11 (2020).
226. Dutta B, Huys I, Vulto AG, Simoens S. Identifying Key Benefits in European Off-Patent Biologics and Biosimilar Markets: It is Not Only About Price! *BioDrugs*. 2020;34(2):159-70 (2020).
227. Godman B. Biosimilars are becoming indispensable in the management of multiple diseases although concerns still exist. *Bangladesh Journal of Medical Science*. 20 (1); 5-10 (2021).
228. Derbyshire M, Shina S. Patent expiry dates for biologics: 2017 update. *GaBI Journal*. 7(1), 29-34 (2018).
229. Gisondi P, Bianchi L, Calzavara-Pinton P, Conti A, Chiricozzi A, Fimiani M, et al. Etanercept biosimilar SB4 in the treatment of chronic plaque psoriasis: data from the Psobiosimilars registry. *The British journal of dermatology*. 180(2). 409-410 (2019).
230. Stebbing J, Baranau YV, Baryash V et al. Double-blind, randomized phase III study to compare the efficacy and safety of CT-P6, trastuzumab biosimilar candidate versus trastuzumab as neoadjuvant treatment in HER2 positive early breast cancer (EBC). *Journal of Clinical Oncology*. 35(15_suppl), 510 (2017)
231. Pegram MD, Bondarenko I, Zorzetto MMC et al. PF-05280014 (a trastuzumab biosimilar) plus paclitaxel compared with reference trastuzumab plus paclitaxel for HER2-positive metastatic breast cancer: a randomised, double-blind study. *Br J Cancer*. 120(2), 172-182 (2019).
232. Jimenez-Pichardo L, Gazquez-Perez R, Sierra-Sanchez JF. Degree of prescriber's knowledge about variability in biological drugs "innovators" in manufacturing process. *European journal of clinical pharmacology*. 74(4), 505-511 (2018).
233. Vezer B, Buzas Z, Sebeszta M, Zrubka Z. Authorized manufacturing changes for therapeutic monoclonal antibodies (mAbs) in European Public Assessment Report (EPAR) documents. *Current medical research and opinion*. 32(5), 829-834 (2016).
234. Høivik ML, Buer LCT, Cvancarova M et al. Switching from originator to biosimilar infliximab - real world data of a prospective 18 months follow-up of a single-centre IBD population. *Scandinavian journal of gastroenterology*. 53(6), 692-699 (2018).
235. Barbier L, Ebberts HC, Declerck P, Simoens S, Vulto AG, Huys I. The Efficacy, Safety, and Immunogenicity of Switching Between Reference Biopharmaceuticals and Biosimilars: A Systematic Review. *Clinical pharmacology and therapeutics*. 108(4), 734-755 (2020).
236. Colloca L, Panaccione R, Murphy TK. The Clinical Implications of Nocebo Effects for Biosimilar Therapy. *Frontiers in pharmacology*. 10, 1372 (2019)

-
237. Moorkens E, Godman B, Huys I et al. The expiry of Humira ® market exclusivity and the entry of adalimumab biosimilars in Europe: An overview of pricing and national policy measures. *Frontiers in pharmacology*. 11, 1993 (2021).
238. Sagonowsky E. AbbVie's massive Humira discounts are stifling Netherlands biosimilars: report. (2019). Available at URL: <https://www.fiercepharma.com/pharma/abbvie-stifling-humira-biosim-competition-massive-discounting-dutch-report>.
239. NHS Scotland. Secondary Care National Therapeutic Indicators 2018/19. (2018) Available at URL: <https://www.therapeutics.scot.nhs.uk/wp-content/uploads/2018/08/Secondary-Care-National-Therapeutic-Indicators-Version-1.0.pdf>.
240. Tesar T, Golias P, Kobliskova Z, Wawruch M, Kawalec P, Inotai A. Potential Cost-Savings From the Use of the Biosimilars in Slovakia. *Frontiers in Public Health*. 8, 431 (2020).
241. Pouillon L, Socha M, Demore B et al. The nocebo effect: a clinical challenge in the era of biosimilars. *Expert review of clinical immunology*. 14(9), 739-749 (2018)
242. Catalan Health Authority. Què són els medicaments biosimilars? (2020). Available at URL: <http://medicaments.gencat.cat/ca/ciutadania/informacio-i-consells/preguntes-frequents/que-son-els-medicaments-biosimilars/>.
243. CatSalut. Medicaments biosimilars. (2019). Available at URL: http://medicaments.gencat.cat/web/.content/minisite/medicaments/professionals/Informes_tecnics/Document-informatiu-biosimilars_Area-del-Medicament_desembre-2019.pdf.
244. Jensen TB, Kim SC, Jimenez-Solem E, Bartels D, Christensen HR, Andersen JT. Shift From Adalimumab Originator to Biosimilars in Denmark. *JAMA Internal Medicine*. 180(6), 902-903 (2020)
245. Dörner T, Strand V, Cornes P et al. The changing landscape of biosimilars in rheumatology. *Annals of the rheumatic diseases*. 75(6), 974-982 (2016)
246. IQVIA. Country Scorecards for Biosimilar Sustainability. (2020). Available at URL: <https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/country-scorecards-for-biosimilar-sustainability/iqvia-institute-scorecards-appendix-orb2520.pdf?la=en>.
247. NHS England. Biosimilar medicines. (2020). Available at URL: <https://www.england.nhs.uk/medicines-2/biosimilar-medicines/>.
248. Kim Y, Kwon H-Y, Godman B, Moorkens E, Simoens S, Bae S. Uptake of Biosimilar Infliximab in the UK, France, Japan, and Korea: Budget Savings or Market Expansion Across Countries? *Frontiers in pharmacology*. 11, 970 (2020)
249. NHS England and NHS Improvement. What is a Biosimilar Medicine? (2019). Available at URL: <https://www.england.nhs.uk/wp-content/uploads/2019/05/what-is-a-biosimilar-medicine-guide-v2.pdf>.
250. NHS England. Commissioning framework for biological medicines (including biosimilar medicines). (2017). Available at URL: <https://www.england.nhs.uk/wp-content/uploads/2017/09/biosimilar-medicines-commissioning-framework.pdf>.
251. Davio K. After Biosimilar Deals, UK Spending on Adalimumab Will Drop by 75%. (2018). Available at URL: <https://www.centerforbiosimilars.com/news/after-biosimilar-deals-uk-spending-on-adalimumab-will-drop-by-75>.
252. NHS England - Regional Medicines Optimisation Committees Operating Model. (2019). Available from: <https://www.england.nhs.uk/publication/regional-medicines-optimisation-committee-operating-guidance-and-recruitment-information/>.
253. Tyler D. Biosimilars in the UK: where are we now and where does the NHS want to go? (2019). Available at URL: <https://pharmaphorum.com/views-analysis-market-access/biosimilars-in-the-uk/>.
254. Godman B, Allocati E, Moorkens E, Kwon H-Y. Can local policies on biosimilars optimize the use of freed resources – experiences from Italy. *GABI Journal*. 9 (4), 183-187 (2020)
255. Health Improvement Scotland (NHS Scotland). Biosimilar Medicines: A National Prescribing Framework. (2018). Available at URL: http://www.healthcareimprovementscotland.org/our_work/technologies_and_medicines/programme_resources/biosimilar_medicines_framework.aspx
256. NHS Scotland. Secondary Care National Therapeutic Indicators 2019/20. (2019). Available at URL: http://www.healthcareimprovementscotland.org/our_work/technologies_and_medicines/programme_resources/biosimilar_medicines_framework.aspx#:~:text=Biosimilar%20medicines%3A%20A%20national%20prescribing%20framework.%20This%20updated,safe%20use%20of%20biosimilar%20medicines%3B%20promote%20prescriber%20confidence
257. IQVIA Report 2018: The impact of biosimilar competition in Europe. (2018). Available at URL: <https://ec.europa.eu/docsroom/documents/31642>

-
258. Kim H, Alten R, Avedano L et al. The Future of Biosimilars: Maximizing Benefits Across Immune-Mediated Inflammatory Diseases. *Drugs*. 80(2), 99-113 (2020).
259. Lee HJ, Han E, Kim H. Comparison of Utilization Trends between Biosimilars and Generics: Lessons from the Nationwide Claims Data in South Korea. *Applied health economics and health policy*. 18(4), 557-566 (2020).
260. Greater Glasgow and Clyde. Medicines Update - Prescribing Medicines by Brand. (2020). Available at URL: <http://www.ggcprescribing.org.uk/blog/prescribing-medicines-brand/>
261. Lothian Formulary. 6.1.1 Insulins. (2020). Available at URL: <https://www.ljf.scot.nhs.uk/LothianJointFormularies/Adult/6.0/6.1/6.1.1/Pages/default.aspx>.
262. South Staffordshire Joint Formulary. Biosimilar insulins. (2017). Available at URL: <http://www.southstaffordshirejointformulary.nhs.uk/docs/misc/Biosimilar%20insulins%20FINAL.pdf?UPLID=670264570202091911152>.
263. Aladul MI, Fitzpatrick RW, Chapman SR. Healthcare professionals' perceptions and perspectives on biosimilar medicines and the barriers and facilitators to their prescribing in UK: a qualitative study. *BMJ open*. 8(11), e023603 (2018)
264. Greener M. Why isn't the NHS making the most of biosimilar insulin? *Prescriber August 2019*. 21-24 (2019).
265. Haque M, Islam S, Kamal ZM et al. Ongoing efforts to improve the management of patients with diabetes in Bangladesh and the implications. *Hospital practice*. EPrint (2021).
266. Hernandez I, Good CB, Shrank WH, Gellad WF. Trends in Medicaid Prices, Market Share, and Spending on Long-Acting Insulins, 2006-2018. *Jama*. 321(16), 1627-1629 (2019).
267. Opanga S, Njeri LW, Kimonge D, Godman B, Oluka M. Assessing Utilisation and Expenditure on Long-Acting Insulin Analogues in Kenya; Findings and Implications for the Future. *Sch Acad J Pharm*. 10(4), 63-70 (2021).
268. Simoens S, Le Pen C, Boone N et al. How to realize the potential of off-patent biologicals and biosimilars in Europe? Guidance to policymakers. *GaBI Journal*. 7(2), 70-74 (2018).
269. AIFA. Rapporto sulle politiche di assistenza farmaceutica attuate dalle Regioni in Piano di Rientro. (2020). Available at URL: <https://www.aifa.gov.it/web/guest/-/rapporto-sulle-politiche-di-assistenza-farmaceutica-attuate-dalle-regioni-in-piano-di-rientro>.
270. Claytor JD, Gellad W. Decreasing Health Care Spending Through Market Competition-a Case for the Rapid Adoption of Adalimumab Biosimilars. *JAMA Intern Med*. 180(6), 903-904 (2020).
271. Godman B, Shrank W, Andersen M et al. Policies to enhance prescribing efficiency in europe: findings and future implications. *Frontiers in pharmacology*. 1, 141 (2010).
272. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 360(9326), 7-22 (2002).
273. Strandberg TE, Pyorala K, Cook TJ, Wilhelmsen L, Faergeman O, Thorgeirsson G, et al. Mortality and incidence of cancer during 10-year follow-up of the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 364(9436), 771-777 (2004).
274. Godman B, Kurdi A, McCabe H et al. Ongoing activities to influence the prescribing of proton pump inhibitors within the Scottish National Health Service: their effect and implications. *GaBI Journal*. 7(4), 142-151 (2018).
275. Godman B, Sakshaug S, Berg C, Wettermark B, Haycox A. Combination of prescribing restrictions and policies to engineer low prices to reduce reimbursement costs. *Expert review of pharmacoeconomics & outcomes research*. 11(1), 121-129 (2011).
276. Godman B, Burkhardt T, Bucsecs A, Wettermark B, Wieninger P. Impact of recent reforms in Austria on utilization and expenditure of PPIs and lipid-lowering drugs: implications for the future. *Expert review of pharmacoeconomics & outcomes research*. 9(5), 475-484 (2009).
277. Pettersson B, Hoffmann M, Wandell P, Levin LA. Utilization and costs of lipid modifying therapies following health technology assessment for the new reimbursement scheme in Sweden. *Health policy*. 104(1). 84-91 (2012).
278. Schneeweiss S, Walker AM, Glynn RJ, Maclure M, Dormuth C, Soumerai SB. Outcomes of Reference Pricing for Angiotensin-Converting-Enzyme Inhibitors. *NEJM*. 346(11), 822-829 (2002).
279. Kalaba M, Godman B, Vuksanovic A, Bennie M, Malmstrom RE. Possible ways to enhance renin-angiotensin prescribing efficiency: Republic of Serbia as a case history? *Journal of comparative effectiveness research*. 1(6), 539-549 (2012).
280. Godman B, Bucsecs A, Burkhardt T, Schmitzer M, Wettermark B, Wieninger P. Initiatives to enhance renin-angiotensin prescribing efficiency in Austria: impact and implications for other countries. *Expert review of pharmacoeconomics & outcomes research*. 10(2), 199-207 (2010).

-
281. Godman B, Acurcio F, Guerra Junior AA et al. Initiatives among authorities to improve the quality and efficiency of prescribing and the implications. *J Pharma Care Health Sys.* 1(3), 1-15 (2014).
282. Baker A, Chen LC, Elliott RA, Godman B. The impact of the 'Better Care Better Value' prescribing policy on the utilisation of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for treating hypertension in the UK primary care setting: longitudinal quasi-experimental design. *BMC health services research.* 15, 367 (2015).
283. Kurdi AIB, Elliott RA, Chen LC. Clinical and economic implications of therapeutic switching of angiotensin receptor blockers to angiotensin-converting enzyme inhibitors: a population-based study. *Journal of hypertension.* 37(6), 1285-1293 (2019).
284. Kurdi A, Elliott RA, Chen LC. Lessons from the failure of implementing the 'Better Care Better Value' prescribing indicator for renin-angiotensin system drugs in England: a qualitative study of general practitioners' perceptions using behavioural change framework. *BMJ open.* 10(6), e035910 (2020).
285. Moon JC, Godman B, Petzold M et al. Different initiatives across Europe to enhance losartan utilization post generics: impact and implications. *Frontiers in pharmacology.* 5, 219 (2014).
286. Parks J, Radke A, Parker G et al. Principles of antipsychotic prescribing for policy makers, circa 2008. Translating knowledge to promote individualized treatment. *Schizophrenia bulletin.* 35(5), 931-936 (2009).
287. Leucht S, Cipriani A, Spineli L et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet.* 382(9896), 951-962 (2013).
288. Godman B, Petzold M, Bennett K et al. Can authorities appreciably enhance the prescribing of oral generic risperidone to conserve resources?: Findings from across Europe and their implications. *BMC medicine.* 12(1), 98 (2014).
289. Godman B, De Bruyn K, Miranda J et al. Generic atypical antipsychotic drugs in Belgium: their influence and implications. *Journal of comparative effectiveness research.* 2(6):551-561 (2013).
290. Godman B, Bucsecs A, Burkhardt T et al. Potential to enhance the prescribing of generic drugs in patients with mental health problems in Austria; implications for the future. *Frontiers in pharmacology.* 3:198 (2012).
291. Godman B, Kurdi A, McCabe H et al. Ongoing initiatives within the Scottish National Health Service to affect the prescribing of selective serotonin reuptake inhibitors and their influence. *Journal of comparative effectiveness research.* 8(7), 535-547 (2019).
292. Godman B, Persson M, Miranda J et al. Changes in the utilization of venlafaxine after the introduction of generics in Sweden. *Applied health economics and health policy.* 11(4):383-93 (2013).
293. Klein EY, Van Boeckel TP, Martinez EM et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proceedings of the National Academy of Sciences of the United States of America.* 115(15), E3463-e70 (2018).
294. Laxminarayan R, Van Boeckel T, Frost I et al. The Lancet Infectious Diseases Commission on antimicrobial resistance: 6 years later. *The Lancet Infectious diseases.* 20(4), e51-e60 (2020).
295. Nyabuti AO, Okalebo FA, Guantai EM. Examination of WHO/INRUD Core Drug Use Indicators at Public Primary Healthcare Centers in Kisii County, Kenya. *Advances in pharmacological and pharmaceutical sciences.* 2020, 3173847 (2020).
296. Abilova V, Kurdi A, Godman B. Ongoing initiatives in Azerbaijan to improve the use of antibiotics; findings and implications. *Expert review of anti-infective therapy.* 16(1), 77-84 (2018).
297. Furst J, Cizman M, Mrak J, Kos D, Campbell S, Coenen S, et al. The influence of a sustained multifaceted approach to improve antibiotic prescribing in Slovenia during the past decade: findings and implications. *Expert review of anti-infective therapy.* 13(2), 279-289 (2015).
298. Bojanic L, Markovic-Pekovic V, Skrbic R et al. Recent Initiatives in the Republic of Srpska to Enhance Appropriate Use of Antibiotics in Ambulatory Care; Their Influence and Implications. *Frontiers in pharmacology.* 9, 442 (2018).
299. Wojkowska-Mach J, Godman B, Glassman A et al. Antibiotic consumption and antimicrobial resistance in Poland; findings and implications. *Antimicrobial Resistance & Infection Control.* 7(1), 136 (2018).
300. Little P, Stuart B, Francis N et al. Effects of internet-based training on antibiotic prescribing rates for acute respiratory-tract infections: a multinational, cluster, randomised, factorial, controlled trial. *Lancet.* 382(9899), 1175-1182 (2013).
301. Lee ML, Cho CY, Hsu CL et al. Recent trends in antibiotic prescriptions for acute respiratory tract infections in pediatric ambulatory care in Taiwan, 2000-2009: A nationwide population-based study. *Journal of microbiology, immunology, and infection.* 49(4), 554-560 (2016).

-
302. Dyar OJ, Beovic B, Vlahovic-Palcevski V, Verheij T, Pulcini C. How can we improve antibiotic prescribing in primary care? *Expert review of anti-infective therapy*. 14(4), 403-413 (2016).
303. Kalungia A, Godman B. Implications of non-prescription antibiotic sales in China. *The Lancet Infectious diseases*. 19(12), 1272-1273 (2019).
304. Llor C, Bjerrum L. Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem. *Therapeutic advances in drug safety*. 5(6), 229-241 (2014).
305. Wei X, Zhang Z, Hicks JP et al. Long-term outcomes of an educational intervention to reduce antibiotic prescribing for childhood upper respiratory tract infections in rural China: Follow-up of a cluster-randomised controlled trial. *PLoS Med*. 16(2), e1002733 (2019).
306. Saleem Z, Hassali MA, Godman B et al. Sale of WHO AWaRe groups antibiotics without a prescription in Pakistan: a simulated client study. *Journal of Pharmaceutical Policy and Practice*. 13(1), 26 (2020).
307. Wu J, Taylor D, Ovchinnikova L et al. Relationship between antimicrobial-resistance programs and antibiotic dispensing for upper respiratory tract infection: An analysis of Australian data between 2004 and 2015. *The Journal of international medical research*. 46(4), 1326-1338 (2018).
308. van der Velden AW, Kuyvenhoven MM, Verheij TJ. Improving antibiotic prescribing quality by an intervention embedded in the primary care practice accreditation: the ARTI4 randomized trial. *The Journal of antimicrobial chemotherapy*. 71(1), 257-263 (2016).
309. Hallsworth M, Chadborn T, Sallis A et al. Provision of social norm feedback to high prescribers of antibiotics in general practice: a pragmatic national randomised controlled trial. *Lancet*. 387(10029), 1743-1752 (2016).
310. McDonagh MS, Peterson K, Winthrop K, Cantor A, Lazur BH, Buckley DI. Interventions to reduce inappropriate prescribing of antibiotics for acute respiratory tract infections: summary and update of a systematic review. *The Journal of international medical research*. 46(8), 3337-3357 (2018).
311. Auta A, Hadi MA, Oga E et al. Global access to antibiotics without prescription in community pharmacies: A systematic review and meta-analysis. *The Journal of infection*. 78(1), 8-18 (2019).
312. Ocan M, Obuku EA, Bwanga F et al. Household antimicrobial self-medication: a systematic review and meta-analysis of the burden, risk factors and outcomes in developing countries. *BMC public health*. 15, 742 (2015).
313. Nepal G, Bhatta S. Self-medication with Antibiotics in WHO Southeast Asian Region: A Systematic Review. *Cureus*. 2018;10(4):e2428.
314. Alrasheedy AA, Alsalloum MA, Almuqbil FA et al. The impact of law enforcement on dispensing antibiotics without prescription: a multi-methods study from Saudi Arabia. *Expert review of anti-infective therapy*. 18(1), 87-97 (2020).
315. Santa-Ana-Tellez Y, Mantel-Teeuwisse AK, Dreser A, Leufkens HG, Wirtz VJ. Impact of over-the-counter restrictions on antibiotic consumption in Brazil and Mexico. *PloS one*. 8(10), e75550 (2013).
316. Godman B, Fadare J, Kibuule D, Irawati L, Mubita M, Ogunleye O, et al. Initiatives Across Countries to Reduce Antibiotic Utilisation and Resistance Patterns: Impact and Implications. In: Arora G, Sajid A, Kalia VC, editors. *Drug Resistance in Bacteria, Fungi, Malaria, and Cancer*. Cham: Springer International Publishing 539-76 (2017).
317. Moura ML, Boszczowski I, Mortari N et al. The Impact of Restricting Over-the-Counter Sales of Antimicrobial Drugs: Preliminary Analysis of National Data. *Medicine*. 94(38), e1605 (2015).
318. Lopes-Junior R, de Sa Del Fiol F, Araujo JL, de Toledo MI, Barberato-Filho S. Decrease in penicillin Sales in Brazil after over-the-counter restrictions. *Antimicrob Agents Chemother*. 59(9), 5862-5863 (2015).
319. Mattos KPH, Visacri MB, Quintanilha JCF et al. Brazil's resolutions to regulate the sale of antibiotics: Impact on consumption and Escherichia coli resistance rates. *Journal of global antimicrobial resistance*. 10, 195-199 (2017).
320. Mukokinya M, Opanga S, Oluka M, Godman B. Dispensing of antimicrobials in Kenya: A cross-sectional pilot study and its implications. *J Res Pharm Pract*. 7(2), 77-82 (2018).
321. Markovic-Pekovic V, Grubisa N, Burger J, Bojanic L, Godman B. Initiatives to Reduce Nonprescription Sales and Dispensing of Antibiotics: Findings and Implications. *J Res Pharm Pract*. 6(2), 120-125 (2017).
322. Markovic-Pekovic V, Grubisa N. Self-medication with antibiotics in the Republic of Srpska community pharmacies: pharmacy staff behavior. *Pharmacoepidemiol Drug Saf*. 21(10), 1130-1133 (2012).

-
323. Government of Romania. Decision No. 879/2018 on the establishment of a national committee for limiting antimicrobial resistance. Official Gazette, 20 November 2018 (in Romanian). Available at: https://www.gov.ro/fisiere/subpagini_fisiere/NF_HG_879-2018.pdf
324. WHO. Evidence brief for policy - Romania's health system to address antimicrobial resistance. EviNet Europe, No. 6, 2020. Available at URL: <https://www.euro.who.int/en/countries/romania/publications/evidence-brief-for-policy.-number-6-strengthening-romanias-health-system-to-address-antimicrobial-resistance-2020>.
325. Arparsithongsagul S, Kulsomboon V, Zuckerman IH. Multidisciplinary perspective intervention with community involvement to decrease antibiotic sales in village groceries in Thailand. *Asia-Pacific journal of public health*. 27(2), Np 2480-2488 (2015).
326. Wirtz VJ, Herrera-Patino JJ, Santa-Ana-Tellez Y, Dreser A, Elseviers M, Vander Stichele RH. Analysing policy interventions to prohibit over-the-counter antibiotic sales in four Latin American countries. *Trop Med Int Health*. 18(6), 665-673 (2013).
327. Vacca CP, Nino CY, Reveiz L. [Restriction of antibiotic sales in pharmacies in Bogota, Colombia: a descriptive study]. *Revista panamericana de salud publica*. 30(6), 586-591 (2011).
328. Hoxha I, Malaj A, Kraja B et al. Are pharmacists' good knowledge and awareness on antibiotics taken for granted? The situation in Albania and future implications across countries. *Journal of global antimicrobial resistance*. 13, 240-245 (2018).
329. Roque F, Soares S, Breitenfeld L, López-Durán A, Figueiras A, Herdeiro MT. Attitudes of community pharmacists to antibiotic dispensing and microbial resistance: a qualitative study in Portugal. *International journal of clinical pharmacy*. 35(3), 417-424 (2013).
330. Barker AK, Brown K, Ahsan M, Sengupta S, Safdar N. What drives inappropriate antibiotic dispensing? A mixed-methods study of pharmacy employee perspectives in Haryana, India. *BMJ open*. 7(3), e013190 (2017).
331. Saleem Z, Hassali MA, Hashmi FK, Godman B, Saleem F. Antimicrobial dispensing practices and determinants of antimicrobial resistance: a qualitative study among community pharmacists in Pakistan. *Family medicine and community health*. 7(3), e000138 (2019).
332. Sharland M, Gandra S, Huttner B et al. Encouraging AWaRe-ness and discouraging inappropriate antibiotic use-the new 2019 Essential Medicines List becomes a global antibiotic stewardship tool. *The Lancet Infectious diseases*. 19(12), 1278-1280 (2019).
333. Horby P, Lim WS, Emberson JR et al. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med*. 384(8), 693-704 (2021).
334. Dyer O. Covid-19: Remdesivir has little or no impact on survival, WHO trial shows. *BMJ*. 371, m4057 (2020)
335. Opanga SA, Rizvi N, Wamaitha A, Sefah IA, Godman B. Availability of Medicines in Community Pharmacy to Manage Patients with COVID-19 in Kenya; Pilot Study and Implications. *Sch Acad J Pharm*. 10(3), 36-42 (2021).
336. Price M. FTC sends more than 120 warnings about false coronavirus treatments. (2020). Available at URL: <https://www.cnet.com/news/scam-coronavirus-treatments-are-on-the-rise>
337. Bramstedt KA. Unicorn Poo and Blessed Waters: COVID-19 Quackery and FDA Warning Letters. *Ther Innov Regul Sci*. 55(1), 239-244 (2021).
338. OECD. Addressing Challenges in Access to Oncology Medicines - Analytical Report. (2020). Available at URL: <https://www.oecd.org/health/health-systems/Addressing-Challenges-in-Access-to-Oncology-Medicines-Analytical-Report.pdf>
339. Gotham D, Barber MJ, Hill A. Production costs and potential prices for biosimilars of human insulin and insulin analogues. *BMJ global health*. 3(5), e000850 (2018).
340. CATAPULT. Summary findings from: "ATTCs, clinical infrastructure requirements and adoption of ATMPs" workshop. (2018). Available at URL: https://ct.catapult.org.uk/sites/default/files/publication/ATTCs%2C%20clinical%20infrastructure%20requirements%20and%20adoption%20of%20ATMPs%20workshop_FINAL.pdf.
341. Eder C, Wild C. Technology forecast: advanced therapies in late clinical research, EMA approval or clinical application via hospital exemption. *J Mark Access Health Policy*. 7(1), 1600939 (2019).
342. US FDA. FDA approves innovative gene therapy to treat pediatric patients with spinal muscular atrophy, a rare disease and leading genetic cause of infant mortality. 24 march 2019. Available at URL: <https://www.fda.gov/news-events/press-announcements/fda-approves-innovative-gene-therapy-treat-pediatric-patients-spinal-muscular-atrophy-rare-disease>.
343. Stein R. At \$2.1 Million, New Gene Therapy Is The Most Expensive Drug Ever. 24 May 2019. Available at URL: <https://www.npr.org/sections/health-shots/2019/05/24/725404168/at-2-125-million-new-gene-therapy-is-the-most-expensive-drug-ever?t=1598996800132>.

-
344. European Medicines Agency. Zolgensma. May 2020. Available at URL: <https://www.ema.europa.eu/en/medicines/human/EPAR/zolgensma>.
345. Godman B, Basu D, Pillay Y et al. Ongoing and planned activities to improve the management of patients with Type 1 diabetes across Africa; implications for the future. *Hospital practice*. 48(2), 51-67 (2020).
346. Haque M, Islam S, Kamal ZM et al. Ongoing efforts to improve the management of patients with diabetes in Bangladesh and the implications. *Hospital practice*. 1-7 EPrint (2021)
347. Bennie M, Bishop I, Godman B et al. Are prescribing initiatives readily transferable across classes: the case of generic losartan in Scotland? *Quality in primary care*. 21(1), 7-15 (2013).
348. UN. Sustainable Development Goal 3 - Ensure healthy lives and promote well-being for all at all ages. (2019). Available at URL: <https://sustainabledevelopment.un.org/sdg3>.
349. Cerf ME. Sustainable Development Goal Integration, Interdependence, and Implementation: the Environment-Economic-Health Nexus and Universal Health Coverage. *Glob Chall*. 3(9), 1900021 (2019).
350. Kaplan WA, Ritz LS, Vitello M, Wirtz VJ. Policies to promote use of generic medicines in low and middle income countries: a review of published literature, 2000-2010. *Health policy*. 106(3), 211-224 (2012).
351. Hamid S, Groot W, Pavlova M. Trends in cardiovascular diseases and associated risks in sub-Saharan Africa: a review of the evidence for Ghana, Nigeria, South Africa, Sudan and Tanzania. *The aging male*. 2019:1-8 (2019).
352. Kalo Z, Holtorf AP, Alfonso-Cristancho R et al. Need for multicriteria evaluation of generic drug policies. *Value in health*. 18(2), 346-351 (2015).
353. Bogaert P, Bochenek T, Prokop A, Pilc A. A Qualitative Approach to a Better Understanding of the Problems Underlying Drug Shortages, as Viewed from Belgian, French and the European Union's Perspectives. *PloS one*. 10(5), e0125691 (2015).
354. Godman B, Petzold M, Bennett K et al. Can authorities appreciably enhance the prescribing of oral generic risperidone to conserve resources? Findings from across Europe and their implications. *BMC medicine*. 12, 98 (2014).