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How can pricing and reimbursement policies improve affordable access to medicines? lessons learned from European countries

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How can pricing and reimbursement policies improve affordable access to medicines?

Lessons learned from European countries

Short title: Lessons from pricing and reimbursement policies in Europe

Key points for Decision Makers:

- European countries apply different pharmaceutical pricing and reimbursement policies.
- These policies are frequently assessed against their financial consequences and their ability to contain costs but less so in terms of access to medicines. Policies should be accompanied by regular evaluations, facilitated by the use of the appropriate methodology and access to the relevant data.
- There appears to be a need for additional changes beyond traditional pharmaceutical pricing and reimbursement policies. Collaborative approaches (e.g. between countries or between regulatory authorities, pricing and reimbursement agencies) and more transparency in terms of real medicine prices, R+D costs and medicines in the pipeline are considered as possible pathways for the future.

Abstract

The paper discusses pharmaceutical pricing and reimbursement policies in European countries with regard to their ability to ensure affordable access to medicines. A frequently applied pricing policy is external price referencing. While it provides some benchmark for policy-makers and has shown to be able to generate savings, it may also contribute to delay in product launch in countries where medicine prices are low. Value-based pricing has been proposed as a policy that promotes access while rewarding useful innovation, however implementing it has proven quite challenging. For high-priced medicines, managed-entry agreements are increasingly used. These agreements allow policy-makers to manage uncertainty and obtain lower prices. They can also facilitate earlier market access in case of limited evidence about added therapeutic value of the medicine. However, these agreements raise transparency concerns due to the confidentiality clause. Tendering as used in the

hospital and offpatent outpatient sectors has proven to reduce medicine prices but it requires a robust framework and appropriate design with clear strategic goals in order to prevent shortages. These pricing and reimbursement policies are supplemented by the widespread use of Health Technology Assessment to inform decision-making, and by strategies to improve the uptake of generics, and also biosimilars. While European countries have been implementing a set of policy options, there is a lack of thorough impact assessments of several pricing and reimbursement policies on affordable access. Increased cooperation between authorities, experience sharing, and improving transparency on price information, including the disclosure of confidential discounts, are opportunities to address current challenges.

1. Introduction

In recent years, access to essential medicines has become an issue even in the wealthiest parts of Europe. In particular, the proliferation of high-priced medicines has pushed the issue of access to new medicines high on the policy agenda of all European countries, including in high-income economies [1-4]. At the same time, pharmaceutical spending is rising again, boosted in 2014 by the entry of new hepatitis C treatments [5]. Apart from prices, payers are increasingly concerned that some of these high-priced medicines only deliver limited therapeutic added benefits to patients [6-8].

While in most European countries all residents benefit from comprehensive coverage of health care costs, including costs related to medicines [9] and a major part of spending on medicines comes from public programmes, there is considerable variation in public funding on medicines between countries [10]. In addition, important variation in access to medicines exists between European countries, in particular between Western and Eastern countries. This is due to differences in marketing of medicines and their inclusion in national reimbursement lists, country's gross domestic product, government expenditure on health, and also due to medicine prices and utilization (for further information on differences between countries related to availability [11-14], prices [5, 15-22] and utilization [23-30] of medicines see A1 in the Supplementary Materials).

This paper provides a critical discussion of selected pharmaceutical reimbursement and pricing policies used in European countries and their ability to ensure affordable access to medicines. In line with existing frameworks [31-34], availability (marketing of a medicine in national markets) and indicators such as inclusion of medicines in reimbursement, public spending and medicine prices are considered as key determinants for affordable access to medicines. This understanding of affordable access to medicines also fits within the Universal Health Coverage and access to medicines target under Sustainable Development Goal 3 on Good health [35].

Over the last three decades a number of initiatives have been developed to better characterize and measure the situation in countries and globally on the access to, regulation and use of medicines. These initiatives were developed in collaboration with numerous international and national organisations, academia, experts and fed with country experiences and often consolidated in WHO documents and guidelines [36]. They normally contain a set of structure, process, output and outcome indicators. In parallel many countries developed and used their own set of indicators to more specifically measure their national situation. The latest effort has been the development of set of 100 indicators, jointly by WHO and the World Bank to monitor progress on UHC, and this also contains some indicators across disease programmes as well as health system development [37].

The presented findings are based on an iterative search of the published and grey literature, using the bibliographic database PubMed, alongside Google Scholar and reviewing reference lists of flagship reports (e.g. a WHO Euro report on access to new medicines [3] and the WHO Priority Medicines for Europe and the World report, with the background chapter on pricing and reimbursement [11]). The literature search was complemented by the input from co-authors, all expert on the topic. Key search terms were the names of the pricing and reimbursement policies, as listed in the WHO report on access to new medicines [3]; searches were run between 25 May and 26 June 2016. When co-authors learned about relevant updated literature that was published later, this was also included in the first draft and revised paper. In order to have access to up-to-date information about policies in Europe that might not have been covered in literature, we included descriptive information about the existence of the discussed policies in Europe as of 2016 based on information obtained from policy surveys done with representatives of competent authorities involved the Pharmaceutical Pricing and Reimbursement Information /PPRI network.

To keep the review focused, this paper focuses on key policies out of the larger menu of pharmaceutical pricing and reimbursement policies, as described in literature [3, 18, 38]. Policies included were those commonly been applied in European countries for several years, some of which (e.g. health technology assessment, external price referencing) have also

been intensively discussed in literature. In addition, recently introduced policies (e.g. managed-entry agreements, horizon scanning) that have been seen as major policy options in the menu of policies for high-priced medicines are included [3]. For definitions of key policies used see Table 1.

Insert Table 1 here

2. Health technology assessments to inform pricing and reimbursement policies

In Europe, decisions about reimbursement of medicines are taken at the national level. These are often implemented through positive or negative lists, even in health systems with competing health insurers such as the Netherlands or Switzerland. Patients usually have to contribute to the costs of outpatient medicines; however various mechanisms exist to protect patients from excessive out-of-pocket payments [9]. Typically, marketing authorisations' holders have to file an application if they want their medicine to be included in the positive list of reimbursed medicines. European countries use one of the following processes to make reimbursement and pricing decisions: In some countries, health technology assessment (HTA) is used to inform reimbursement and/or pricing decisions (e.g. France, Italy, the Czech Republic, Switzerland). In other countries, HTA (and appraisal) results in a decision to reimburse a new product (with or without restrictions) or to reject funding (e.g. England, Sweden, Norway; see A2 on different models).

In many European countries, HTA is used either systematically for all new medicines or only for those raising specific problems such as high prices, uncertain clinical benefits or high budget impact. There are usually more than one or two HTA institutions per country (for an overview see [3]). HTA is focused on the assessment of clinical benefits but may also include economic aspects. It determines the therapeutic value of a medicine, the added therapeutic value by comparison to existing treatments, and frequently its cost-effectiveness. Medicines which are more effective than existing comparators can get a higher price, while others tend to be priced at a similar or lower level. Medicines used in the treatment of very severe diseases and/or orphan diseases without treatment alternatives are very often

accepted for reimbursement even though they do not meet the cost-effectiveness threshold [39]. This suggests that cost-effectiveness is not the only criteria taken into account by decision makers and also that the negotiation power of payers is very limited in such cases.

HTA is a tool to support prioritization, with the aim to help policy-makers obtain better value for money. This would arguably ensure a more rational and targeted investment of funds, thus contributing to access to cost-effective medicines. A study that compared HTA and internal price referencing suggested that HTA appears to be the superior strategy for obtaining value for money because it addresses both price and appropriate indications for the use of the medicine and the relation between additional value and additional costs [40]. Overall, no clear pattern of the impact of HTA on prices could be determined [41]. Still, policy-makers consider HTA as one of the two key tools (the other one being managed-entry agreements) to deal with new high-priced medicines [42].

3 Selected pricing and reimbursement policies

Most European countries regulate the prices of medicines via a mix of instruments, applied to different market segments (outpatient / inpatient medicines, onpatent / offpatent, innovative / medicines with no added therapeutic value, etc.). Even though, all these instruments have advantages and drawbacks that are described below, it is difficult to isolate the impact of any single policy on availability and affordability of medicines since countries typically use several of these policies simultaneously.

3.1 External price referencing

All EU Member States but two (Sweden, United Kingdom) refer to the price in other countries to set the price of medicines in their own country, a practice known as external price referencing (EPR). EPR is also used in further European countries (e.g. Norway, Iceland, Switzerland, Turkey) [43]. However, the scope, relevance and methodological design vary across countries. In Denmark, for instance, EPR only applies in the hospital sector. In Germany, EPR exists in the legislation but is not used in practice [43]. EPR is typically applied to regulate the price of new products, less often in offpatent markets. This

international price comparison offers a reference, or benchmark, for policy-makers, to understand where the prices proposed by industry for their country are relatively ranked. The price information achieved through EPR is frequently seen as a starting point for public payers to further negotiate and conclude agreements to reach a more acceptable, and somewhat affordable price that will be funded.

The Organisation for Economic Co-operation and Development (OECD) described EPR as a policy that is 'readily gameable by the pharmaceutical industry and – by reducing firms' willingness to price to market – contributes to access and affordability problems' [44]. EPR incentivizes marketing authorization holders to launch medicines first in countries with higher prices, and delay, or not to launch, in lower-priced countries. This is in order to not reduce the medicine's international reference price [38, 45-53]. Countries with lower prices or lower market volume were found to have fewer medicines available and longer delays in medicines launches [48, 54, 55]. Pharmaceutical companies have systematically delayed dossier submissions in Belgium in order to avoid that the lower Belgian prices affect other European countries [56]. While studies highlighted the ability of EPR to negatively impact the availability of medicines on the market, it remains difficult to isolate the impact of EPR from other factors, such as 'parallel trade' (see Table 1) that is a legal practice within the European Union [49, 57] or pricing regulation in Germany and Italy that allow free pricing for some medicines in the first year to improve earlier market access in their country but thus signal a high price to other EPR-applying countries. Overall, available literature on the impact of EPR is limited [41, 48]. Evaluations focused on cost-containment, showing how EPR was able to contribute to savings under specific conditions [21, 58-61], whereas aspects such as availability and uptake have not been sufficiently addressed. One study showed that, using a limited sample of new patented medicines, EPR-applying countries had, in general, lower list prices than countries not using EPR [60].

To mitigate the negative impact of EPR (and parallel trade) on availability in lower-income countries in Europe, it has been argued that public payers could keep a high 'list price' and get confidential discounts through product-specific agreements [46, 62]. This would allow

industry to provide medicines at lower prices to low-income countries without negatively impacting the average reference price. While confidential arrangements (frequently subsumed under the umbrella term of managed-entry agreements/MEA, see below) have increasingly been used, also by higher-income countries as an instrument to ensure affordable access to medicines [3, 63], there is no evidence that access has improved in lower-income countries since they continue to experience delayed and limited availability. On the negative side, confidential discounts and rebates are blurring the price transparency of the market, and they limit the ability of payers to determine what a 'reasonable and fair' price would be.

3.2 Value-based pricing

Value-based pricing (VBP) consists in setting a price according to the added therapeutic value of a new product by comparison to existing treatments. Seeking to pay for medicines in relation to the 'value' they bring to their own health system and society has been considered as one approach to ensure value in pharmaceutical spending (static efficiency) and to send appropriate signals to companies for further investments in R&D (dynamic efficiency)[44].

In a narrow approach, VBP (in the context of the English National Health Service /NHS) is defined as '(the price) that ensures that the expected health benefits [of a new technology] exceed the health predicted to be displaced elsewhere in the NHS, due to their additional cost' [64]. It thus relies on cost-effectiveness analysis and the setting of an ICER threshold beyond which a new medicine is not funded. Sweden has such a 'real' VBP system. Introduced in 2002, pricing and reimbursement processes are completely integrated, and eligibility for reimbursement is assessed against three criteria: the human value principle to guard against discrimination of individuals, the need and solidarity principle that gives priority to those in greatest need, and the cost-effectiveness principle [11, 65].

Applying a broader approach, any policy linking the price of a medicine to its added therapeutic value can be considered within the category of value-based pricing. With such a definition, many European countries use such policies [3, 39].

However, value-based pricing has proven difficult to implement, especially in therapeutic areas where no alternative treatment is available and patients suffer from severe life-threatening or debilitating disease, such as oncology or rare diseases. In such cases, payers face a strong public pressure and often accept to pay high prices for limited clinical benefits. To some extent, it can be argued that the value of such products cannot be reduced to clinical benefits and some analysts have developed frameworks to take other criteria into account, such as the absence of alternative treatment for orphan diseases for instance [66]. However, such frameworks do not provide any simple rule to set the price of a new medicine. A major argument for using a value-based pricing policy is that it might create an incentive for the development of products that generate more added value [11, 65]. It could also support a new approach of policy-makers to signal more explicitly their priorities which medicines would be reimbursed if they are developed as proposed in the WHO Priority Medicines for Europe and the World study in 2004 [67]. Currently, the pharmaceutical policy framework appears to be supply-driven, and a more pro-active approach has been suggested [68, 69]. In principle, medicines with perceived high value are likely to obtain higher prices, providing a reward for innovation, which might explain the preference of the industry for this policy [70]. However, VBP also presents opportunities to industry for 'gaming', in particular related to the choice of the comparator and the threshold [53]. For instance, a manufacturer will try to avoid genericised molecule as a comparator, even if this means positioning their product as a second or third line therapy. In such a case, the population target will be smaller but the price premium will be set in relation to the price of an on-patent medicine. In addition, where an explicit cost-effectiveness threshold is published, marketing authorization holders tend to price up to the threshold [71].

It has been argued that VBP would encourage access to needed medicines, in line with the prioritization of policy-makers. Still, it can also result in limited, or delayed, access due to the resource-intensive and time-intensive character of underlying value assessments, and discussions between the authority and the manufacturer on different perceptions of value [53]. Until now, VBP has been proposed as a logical and fair policy to promote access as

well as reward useful innovation, however implementing this policy has proven very challenging.

3.3 Managed-entry agreement

European countries have increasingly been using managed-entry agreements (MEA) to deal with high-priced medicines and uncertainty around the medicine's value [3]. These agreements take many forms such as simple confidential discounts and price-volume agreements in financial-based schemes (non-health outcome-based schemes). These also include more sophisticated performance-based (or health outcome-based) schemes, where the final price of a product is linked to health outcomes observed in real life. Performance-based schemes include outcome guarantees (i.e. an agreement where the manufacturer provides rebates, refunds, or price adjustments if the product fails to meet the agreed outcome target), coverage with evidence development (i.e. reimbursement where additional data gathered in the context of clinical care would further clarify the impact of the medicines, and patient eligibility linked to patient registries to measure post-marketing clinical outcomes).

In some countries, the existence of such agreements is not disclosed to the public (e.g. in France) while in others the existence and the content of the agreements is public (e.g. Scotland, England, Belgium). In all cases, the final discount to payers is unknown. The EMINet survey as of 2013 [72] confirmed other research [73-75] that MEA were particularly used for specific (high-priced) indications such as cancer and that some European countries (e.g. Italy, UK) used them at a much higher scale than others. It also showed that most countries opted for financial MEA that are easier to handle, than performance-based MEA [76]. Since that study, more MEA have been implemented for new products, and even European countries (e.g. Bulgaria, Romania) that had not applied them before started to use them [3, 77].

For patients and industry, MEA are an opportunity to facilitate early market access to medicines, even if added therapeutic value has not yet been fully proven. They also allow for price discrimination without changing list prices. For policy-makers, MEA are a tool to

manage uncertainty [78] and obtain lower prices than the list prices; how much lower is unknown as the prices are confidential. When performance-based MEA have been set up, together with patients registries, for instance, this allows collecting real-life clinical data that are needed to assess the treatment effect and take a more sound decision based on more robust evidence. Still, even if updated data may urge for a discontinuation of funding (at high prices) of a medicine under a MEA, it might be difficult in reality to implement it if expectations of patients have been created [79]. Due to public pressure, funding may be continued, as observed in the cases of agalsidase alfa and agalsidase beta for Fabry disease and alglucosidase alfa for Pompe disease in the Netherlands [80].

The confidentiality of MEA is a major drawback, particularly given the widespread use of EPR. As a result, European countries refer to the official list price of a high-priced medicine that is under MEA in several countries. It was argued that by opting for MEA payers implicitly accepting high (list) prices [81].

Despite continuously wide-spread use of MEA, there is some [82] but comparably little knowledge about their functioning nor results in terms of improving affordability and access.

3.4 Tendering

In Europe, tendering has traditionally been applied in the hospital sector, at the level of individual hospitals and hospital groups, or through voluntary pooling of regional procurement at national level by procurement agencies (in Denmark and Norway) acting on behalf all public hospitals [83-85]. In the outpatient offpatent sector, some European countries (e.g. Germany, the Netherlands, Slovenia, Romania) have implemented tender systems and auction elements to enhance competition (cluster-tendering) and thus achieve lower medicine prices [86-88].

National procurement agencies in Denmark (AMGROS) and Norway (LIS) have been reporting efficiency gains and lower prices through their centralised hospital tendering compared to other countries [83-85]. This is in part attributed to the shift of the balance of

power in favour of the national procurement agency that procures for a much larger market as well as use of new types of tendering procedures.

Tendering in the outpatient sector has also proven its ability to considerably reduce prices through competition [88-90]. Concerns have been raised that, if tender pushed prices too low, the sustainability of the generic industry would suffer, and some companies could withdraw from the market, this reducing competition in the longer term [91]. However, a recent study did not find any evidence for Dutch offpatent market that tendered medicines would be more affected by shortages than non-tendered medicines [88]. Still, in case of shortages of tendered medicines alternative medicines might also not be available or only at substantially higher prices. Tendering requires a clear and robust framework, as apparently observed for the tender-like system in the Danish outpatient system [88], particularly aiming at keeping several suppliers in the market, including backup strategies to deal with possible supply problems. If tendering is not well designed and based on a sound framework, there are risks of neutralization of savings (lower prices for one medicine are met with higher prices for similar medicines), of stakeholders going to court to challenge the legal provisions and the non-availability of medicines. These developments were observed in Belgium which, as a result, withdrew its tendering policy for offpatent medicines [88, 92].

3.5 Generic policies

European countries have increasingly been implementing generic policies [93, 94] (see Table 1 for definitions of generic policies listed below). They are particularly aimed at ensuring swift market entry of high-quality generics, bring down the prices of multi-source products (off-patent originator medicines and generic medicines) and improve generics' acceptance and uptake of lower-priced medicines. As a result, generic policies are considered as a valuable instrument to generate savings for public payers which can be used for affording more expensive medicines and for treating more patients. European countries use a mix of policies related to pricing, reimbursement and enhancement of uptake of generics.

Twenty-two EU Member States (as of 2016) use 'internal reference pricing', i.e. maximum reimbursement amounts for clusters of medicines. In 9 of these countries, clusters of medicines with the same active ingredient have been established, while in 13 countries a reference price is applied to therapeutic substitutes (e.g. Germany, the Netherlands) [95]. Most EU Member States set the price of generics in relation to originator prices, whereas fewer countries (e.g. Finland, Germany, Norway, Sweden, UK) exclusively rely on competition [96]. As explained above, tendering, or an auction-like system for generics, is used by some European countries for the procurement of generics in the inpatient and, to a lesser extent, in the outpatient sector. Generic substitution by the pharmacist is allowed in 24 EU Member States and even mandatory in ten (2016 data [95]). Doctors are encouraged to prescribe in International Non-Proprietary Name (INN) in 25 EU Member States, and even mandated to do so in 10 of them [95]. These demand-side measures are supplemented by education and information activities targeted at patients and health professionals. Financial incentives are also applied, but to a far lesser extent. For instance, different co-payment rates for originator and generic medicines had been in place in Portugal and were abolished [97], and Austria ran a pilot of lower co-payment in one health insurance fund [98]. In recent times, more countries are moving towards mandatory generic substitution and mandatory INN prescribing instead of the voluntary form they had introduced earlier [99]. This may be in fact an approach to ensure better enforcement of the measures.

As a result, several European countries have been successful in bringing down generic prices and increasing their generic market share even if, apart from a few countries (Germany, the United Kingdom, Slovak Republic and the Netherlands) generic uptake is lower in Europe than in the United States and generic prices in European countries tend to be higher than in the US [100]. Overall, competitive pricing policies, including tendering, as used in some Nordic European countries, appear to be more successful than other, more regulated generic policies in reducing the price levels of generics as well as of competitor originators as well as increasing generics' uptake, in particular if coupled them with demand-side measures [96, 101]. The quality of generics is ensured in the EU Member States and

neighbouring European countries, but lack of trust into the quality of generics by patients and even health professionals is still an issue [94, 102, 103]. It has been noted, e.g. by the Pharmaceutical Sector Inquiry of the European Commission [104] that benefits of generics were not always fully realised because of delays in market entry. Industry strategies of 'evergreening' have been observed, trying to link intellectual property issues to marketing authorization, pricing and reimbursement of medicines [105, 106].

There is a large body of literature, including on European countries, that confirmed the savings' potential through lower prices by implementing generics policies [101, 107-109]. Evidence shows that generics have contributed to increased utilization of medicines [101, 110]. In contrast to other policies described above, generics policies describe an area for which evidence on their effectiveness to ensure affordable access is available.

3.6 Biosimilar medicines' policies

Given the high prices of new biological medicines, authorities and payers have high expectations regarding offpatent successors [3]. At the time of writing, 20 biosimilar medicines have been approved in Europe [111], with substantial cost savings [112], compared to two biosimilar medicines in the US [113]. Studies about the clinical impact of switches from originators to biosimilars are being performed in European countries [114]. The recently published first results of the Norwegian NOR SWITCH study suggested that a switch from originator infliximab to biosimilar infliximab is safe [115].

Policies to encourage the uptake of biosimilars differ from policies to encourage to uptake of generic medicines because of the perception that biosimilar medicines should not be treated as 'generics' [116]. For instance, prices of biosimilars are linked to originator prices, the required difference between the biosimilar and the originator price is lower compared to generics (e.g., 30% for generics and 15% for biosimilars in Croatia; and 50% for generics and 30% for biosimilars in Lithuania) [117]. While generic substitution has been widely implemented in European countries, this is not the case for biosimilar substitution at pharmacy level [118, 119]. Though European countries seem to be advanced related to

biosimilar medicines compared to the rest of the world, overall governments in European countries appear to be still struggling to develop the best policy option mix for best benefitting from biosimilar medicines. At the same time, there is the best-practice example of Norway that combines several policies (pricing, uptake enhancement, education): In the areas of biological and biosimilar medicines, Norway has been following up on its successful policy of tendering through a public procurement agency for medicines used in public hospitals [120] and closely works with the clinicians to educate and encourage them to prescribe the tendered, lower-priced medicines. Figures about price reductions that Norway achieved in tenders are impressive (e.g. discounts of up to 80 percent between originator and biosimilar medicines)[121], and this is used to ensure that in total more patients can be treated.

4. Suggestions for improvement

European countries developed a range of pricing and reimbursement policies, with the aim to ensure affordable access to medicines, protect citizens against financial hardship and to generate public savings and/or to contain costs. Despite several achievements, countries continue to struggle to meet policy objectives. This is in particular the case in the context of market entry of new high-priced medicines. Policy-makers in Europe identified an imbalance of (negotiation) power in the pharmaceutical sector, as stated in the ‘Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States’ published under the Dutch EU Presidency in June 2016 [122]. In order to address this perceived imbalance, some new approaches, including cooperation between countries and between different agencies (e.g. responsible for marketing authorization, HTA body, pricing and reimbursement authorities), improved information sharing and data generation as well as revised incentives and frameworks, have been discussed and also partially been implemented in European countries. They aim to improve capacity, knowledge and negotiation power of governments. They are thus intended to enable payers to take more informed decisions and to achieve negotiation results with industry that lead to a more affordable access to medicines for patients while keeping a ‘healthy market’. These

approaches are not policies per se, but rather processes and tools to support and further develop pharmaceutical policy.

4.1 Cooperation and stakeholder involvement

During the last decade, European countries have seen increased cross-national cooperation activities between public authorities at technical level, using platforms such as the Network of Competent Authorities on Pricing and Reimbursement (CAPR) and the Pharmaceutical Pricing and Reimbursement Information (PPRI) network (information on these and further networks see Appendix A3 in the Supplementary Materials).

These networks mainly serve for building capacity and improving the exchange of experiences between authorities. Any further-reaching collaboration beyond information sharing, such as joint negotiations or joint procurement, were for long not considered as feasible policy options for EU Member States which take the decisions about medicines' prices and funding at their national levels. The sofosbuvir case, however, appeared to have been a trigger for a change. A French initiative in 2014 sought collaborative approaches with other European countries to get a lower price for sofosbuvir but it was not successful. Some EU Member States hoped that the specific 'Joint Procurement Agreement (JPA) of medical countermeasures' as of 2014 [123] (i.e. procurement of vaccines, for instance, to be prepared for an outbreak of a serious cross-border threat to health such as a pandemic) could be extended to a joint procurement of high-priced medicines against cancer, multiple sclerosis, and orphan medicines. But the European Commission clarified that this would be beyond of the scope of this agreement [43]. Collaborative approaches such as joint negotiations and procurements were sought since Member States wanted to increase their negotiation power in order to achieve lower prices, in return for – the predictability of – larger volumes for industry, and also to achieve earlier and improved access to medicines for lower-priced countries and small markets that were not supplied with some high-priced medicines. In this respect, the issue of 'fair prices' was also discussed since prices in lower-priced European countries were found to be as high as in higher-priced countries and thus unaffordable ([5], see also Appendix A1). Discussions also included considerations about a

differential pricing policy within the EU in order to ensure that medicine prices were better linked to the economic situation of a country. A study [43] commissioned by the European Commission to explore the feasibility of differential pricing in Europe concluded that a fully-fledged differential pricing system would require addressing major obstacles, including measures to prevent leakage due to parallel trade and the wide-spread use of EPR, and political commitment of the EU Member States to agreeing on principles and mechanisms.

While this far-reaching EU-wide cooperation appeared not to be implementable in the short term, a number of the countries started to cooperate in this area. For instance, in 2015, Belgium, the Netherlands and Luxembourg announced a cooperation initiative aiming to jointly negotiate with pharmaceutical companies [124], and another country (Austria) joined this cooperation platform (Beneluxa) in 2016 [125]. These collaborations appear to be at early stages and thus cannot be assessed. Joint negotiations are expected to strengthen the purchasing power of the collaborating countries; and technical cooperation in areas of Health Technology Assessment or horizon scanning is planned that helps governments get improved evidence base for more informed decisions in a more resource-efficient way compared to doing this individually and separately.

In addition, joining forces in the fragmented pharmaceutical systems in European countries also requires vertical (cross-agency) cooperation in countries and at European level. In order to overcome working in 'silos' at different stages of a medicine's life-cycle, awareness has been raised for enhancing national and international cooperation between different authorities along the management of market entry of new medicines (i.e. regulatory authorities, HTA organisations, pricing authorities, reimbursement agencies), possibly with the involvement of other stakeholders like industry, patients and academia [3]. Supported by a legal framework and EU funding, EUNetHTA that is a large network of HTA organisations and public authorities, with the involvement of external stakeholders such as industry, has already been active for nearly a decade [126]. Since 2010, the European Medicines Agency (EMA) has been offering parallel scientific advice with HTA bodies that allows pharmaceutical companies to receive simultaneous feedback from both regulators (EMA)

and HTA bodies on their development plans for new medicines [127] and to be better able to respond to expectations of regulators and payers. Furthermore, the project of the Adaptive Pathways (adaptive licensing) of EMA foresees a staged approach to the collection of evidence and consequent licence adaptations [128]. However, it is still in the pilot phase, and the impact on pricing and reimbursement is not clear.

The involvement of patients, and, even more broader, of citizens in priority-setting for health and social care, including aspects of pricing and reimbursement policies, has been urged for several years [67]. Patients are the ‘experts’ for their diseases, and they can bring in aspects of quality of life and different perspectives about medicines, e.g. on their observed and expected impracticalities [129]. Despite the acknowledged importance of patient involvement, this has been hardly implemented in the area of pricing and reimbursement in European countries [130]. This might also be linked to authorities’ lack of knowledge and experience of how to address patients and integrate them in committees, for instance. Few examples in this field include activities of the National Institute for Health and Care Excellence (NICE) in England [129] and the Scottish Medicines Agency [131] that have been involving the public in their processes.

4.2 Transparency

While pricing and reimbursement decisions are, as described, the responsibility of the national competent authorities in the EU Member States, the EU Transparency Directive [132] obliges Member States to comply with defined specifications of the processes, including time-lines and a clear definition of criteria taken into account to make reimbursement and pricing decisions and of processes (e.g., justifications of the decisions, possibility for marketing authorization holders to appeal). This Directive impose obligations to competent authorities, not companies, and confidential arrangements between payers and companies do not fall under the scope of this regulation.

As shown, confidential discounts and further managed-entry agreements have been increasingly used, particularly for high-priced medicines. Industry has been arguing that,

given the widespread use of external price referencing, price discrimination through confidential discounts was the only way to ensure affordable access to medicines (see also [133]). Policy-makers have increasingly become aware about the impact of their confidentiality agreements to other countries, but they are in a kind of prisoners' dilemma [43]. In recent years, authorities [134] increasingly joined the call of researchers and international institutions [3, 16, 48] for more price transparency. A disclosure of discounts would allow EPR-applying countries to refer to actual, thus lower prices and contain costs by not overpaying. But even payers that do not apply EPR, or only as supplementary policy, reported that knowledge about real prices would be helpful to have some kind of benchmark for decision-making (information provided by PPRI network members). However, no European country has pioneered in disclosing discounted prices [43], also for the concern that lower or no discounts would be offered by industry. As a first step, since 2016 Austria has been labelling the medicines in its reimbursement list for which a discount agreement has been arranged, without disclosing the extent of the discount. Such practice is also common in Australia [135]. While a routine disclosure of discounts does not appear feasible for European countries at the time being, a possible solution could lie in cooperative approaches of public authorities, as discussed in the previous section and also encouraged by the Council Conclusions in June 2016 [122] ('enhancing voluntary cooperation between Member States aimed at greater transparency'). Even the cooperation of few countries can be expected to have an impact: given the improved knowledge and capacity of the cooperating countries, prices will likely reduce, and due to stronger purchasing power and larger markets in case of joint negotiations or even joint procurement, access can arguably be improved. Another option for countries could be to assume a certain extent of discount and thus insist on lowering the 'list price' that would be used everywhere as a starting point for negotiation.

Discussions about transparency are not only about price transparency and disclosure of discounts. To be prepared for new medicines and to develop appropriate strategies to manage their market entry (including taking prioritisation in resource-restrained settings),

public authorities need to know which medicines are in the pipeline. Horizon scanning and forecasting tended to be implemented rather as an academic exercise disconnected to the policy practice [3]. The horizon scanning project in Veneto (Italy) [136], the English National Horizon Scanning Centre [137] and activities at regional level Stockholm County Council in Sweden [138] were among the rare exceptions in Europe where horizon scanning was used to support decision-making of public authorities. While horizon scanning is not a tool to immediately ensure access to medicines or bring down prices, it surely supports the prioritization process. The sofosbuvir case to which policy-makers and payers of several countries were not prepared [81] could be seen as a trigger, and some countries (e.g. Norway, France) started building horizon scanning systems [3]. Also, above-mentioned cooperation platforms such as Beneluxa or the Nordic Pharmaceutical Forum aim to work together on horizon scanning [125, 139].

Furthermore, long-lasting discussions about knowledge of production costs, including research and development costs [69, 140], have also reached Europe. In some US states 'pharmaceutical cost transparency acts' were passed in spring 2016. Under these acts, it is mandatory for manufacturers to disclose their production costs of some high-priced medicines [141]. However, no concrete steps regarding a disclosure of R + D costs have been yet implemented either in Europe or in the US.

4.3 New funding models

As access to new high-priced medicines has become a challenge for high-income countries in Europe as well, the ability of current pricing and reimbursement policies to ensure affordable access to medicines has been questioned. Incremental changes that are envisaged may not be enough to respond to all policy objectives, i.e. provide access, encourage innovation and ensure sustainability. There has been a call for new rules and frameworks, in particular new methods to develop and market medicines (by de-linking the price from the return on investment into R + D): While at global levels the WHO, policy-advisers and academics have been discussing new models of funding R&D for many years [142-148], this debate has started in Europe only recently, fuelled by the Dutch Presidency of

the EU [4], the Review on Antimicrobial Resistance [149] and interventions at conferences (e.g. European Health Forum Gastein 2015 – statement by Josef Probst, Austrian Main Association of Social Security Institution, or the PPRI Conference 2015 [81]). In September 2016, the UN High Level Panel on Access to Medicines report was published and also called for de-linking the R+D cost from the price of a medicine [150]. The Lancet Commission Essential Medicines for UHC goes one step further in calling for an Essential Medicines Patent Pool (EMPP) by which patent owner's refusal to license an essential medicine to the EMPP would satisfy the condition for granting a compulsory licence [151]. A medicines patent pool provides a legal mechanism through which the availability of a generic medicine can be increased and negative effects of market monopolies be reduced.

Still within the scope of the current pricing and reimbursement framework, some European countries introduced funding models that aim bridging the hospital and ambulatory sectors. This was done in response to the fragmentation in health care systems (different payers responsible for funding medicines, e.g. outpatient medicines reimbursed by social health insurance and medicines in hospitals covered by hospitals or regional authorities). This set-up incentivized payers to shift patients, treatments and thus costs between sectors. The transfer could have negative clinical outcomes, and in turn may even increase overall healthcare costs [152]. In the Netherlands, defined high-priced medicines used in hospitals are funded by the health insurers (instead out of the hospital budget). Since 2006, Norway has been increasingly transferring the funding responsibility for a selected number of medicines (TNF alpha inhibitors, medicines for the treatment of Multiple Sclerosis, anti-cancer medicines) to hospitals even if these medicines were used in the outpatient sector [3, 83]. However, to the knowledge of the authors, impact assessments as to whether these new funding approaches were able to address the observed limitations have not been made.

5. Conclusions

The paper discussed selected pharmaceutical policies that aim to contribute to improve affordable access to medicines. The analysis concluded that there is an overall lack of evidence on the impact of pricing and reimbursement policies on affordable access in many

settings. This is partially due to the lack of a well-established methodological evaluation framework, and the challenges in attribution, demonstrating the causal relation between the implementation of a single policy and the observed results in medicines availability and affordability [153, 154]. Furthermore, access to relevant data is a common limitation [151, 155].

However, an exception are policies to promote generics where there is strong evidence on price reduction resulting into substantial savings that allow investing into treating overall more patients. As other work has shown [156], an important precondition is that generic medicines in fact are lower-priced than originators, quality assured and accepted by patients and health professionals. The entry of a number of biosimilars offers the opportunity to increase access to biological medicines and to contain expenditure. To take advantage of the the benefits offered by biosimilars, studies such as the NOR SWITCH study [115] are essential to build trust among the medical and patient communities on the safety of switching. Further, the analysis showed the relevance of tools that allow prioritization on which medicines (and patient groups) money should be spent not only in making them more affordable through pricing policies. There is a need for improved prioritization techniques in HTA and evaluations, and for capacity-building of technical staff. Countries pioneering in this area could support other countries through sharing of methods and techniques.

This analysis found that sharing information and exchanging experiences about policy implementation and procurement, including failures, between policy-makers is very beneficial for countries. This allows to take better informed decisions and to negotiate more strategically. Eventually, this could increase transparency around negotiated prices in case that cross-border collaborations agreed to jointly negotiate and procure.

Our analysis, though limited to selected policies, covered both existing policies as well as discussions and initiatives for new models, including proposals for funding and incentivizing R + D and patent pooling. While we identified a strong interest of some policy-makers and Non-Governmental Organisations in more far-reaching changes, the analysis also showed

that there is still space for improvement in the development and implementation of traditional pricing and reimbursement policies, such as a better enforcement of demand-side measures to promote generic uptake (e.g. generic substitution) and methodological adaptations in external price referencing (e.g. related to country baskets).

Regular reviews and evaluations of the impact of pricing and reimbursement policies, with subsequent adaptation based on the findings, if necessary are critical to inform whether, or not, the policies were effective in achieving the intended aims (e.g. more affordable access to medicines). In addition, evaluations are necessary to determine areas for improvement including increase efficiencies. In particular, there is a need for impact assessments of managed-entry agreements, value-based pricing and HTA.

While this paper was limited to European policies, the conclusions about the impacts of some of the discussed policies, and possible avenues for the future are also of relevance in the global context.

Ethical standards

No funding was received for the writing of the manuscript.

SV, VP, AF, VW, KdJ, PS, HBP, GD and ZUB have no conflict of interest to declare. All authors submitted a signed Conflict of Interest disclosure form.

Author Contributions

All authors fulfill the authorship criteria. All authors are aware of the submission and agree with the manuscript. SV had the lead in drafting and revising the manuscript. VP drafted the chapter on health technology assessments, KdJ drafted the section about measurement of policies, and PS drafted the Appendix on networks. AF had the lead in providing literature. VP, AF, VW, KdJ, PS, HBP, GD and ZUB critically reviewed several versions of the manuscript.

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