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A systematic review of policies regulating or removing mark-ups in the pharmaceutical supply and distribution chain

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ABSTRACT

The regulation of mark-ups throughout the pharmaceutical supply and distribution chain may be a valuable approach to control prices of medicines and to achieve broader access to medicines. As part of a wider review, we aimed to systematically determine whether policies regulating mark-ups are effective in managing the prices of pharmaceutical products. We searched for studies published between January 1, 2004 and October 10, 2019, comparing policies on regulating mark-ups against other interventions or a counterfactual. Eligible study designs included randomized trials, and non-randomized or quasi-experimental studies such as interrupted time-series (ITS), repeated measures (RM), and controlled before-after studies. Studies were eligible if they included at least one of the following outcomes: price (or expenditure as a proxy for price and volume), volume, availability or affordability of pharmaceutical products. The quality of the evidence was assessed using the GRADE methodology. A total of 32,011 records were retrieved, seven of which were eligible for inclusion for this review. The limited body of evidence cautiously suggests that policies regulating mark-ups may be effective in reducing medicine prices and pharmaceutical expenditures. However, the design of mark-up regulations is a critical factor for their potential success. Additional research is required to confirm the effects of these policies on the availability, affordability or usage patterns of medicines and in low- and middle-income countries.

1. Introduction

Access to medicines is influenced by several factors such as affordability, rational use, sustainable financing and reliable supply systems [1]. One of the elements currently restricting patients' access to medicines is unaffordable medicine prices [2]. Both high- as well as low- and middle-income countries are challenged by these high prices, whether for innovative medicines or essential (originator or generic) medicines. The regulation of mark-ups throughout the pharmaceutical supply and distribution chain has been proposed as an approach to manage the price of medicines [3,4].

A mark-up represents the additional charges and costs which are applied to medicines by wholesalers, retailers and pharmacies to cover overhead costs, distribution or dispensing fees, and to provide a profit [5]. Mark-ups are distinct from (profit) margins as the latter only reflect the revenue gained after deduction of costs made. Mark-ups are usually applied as a percentage or a fixed amount on top of the purchase price. Although mark-ups can reflect the dynamics in supply and demand of a medicine in a competitive market [3], a lack of regulation could result in excessive mark-ups. Experiences from medicine price surveys demonstrate that mark-ups can, in extreme cases, account for up to 90 % of the final price of a medicine (i.e. consecutive mark-ups together constituting 900 % of ex-factory price) [5–9]. It is expected that regulating (maximum) mark-ups throughout the pharmaceutical distribution chain could lead to more affordable medicines. Measures to manage mark-up levels may include fixed percentage mark-ups and regressive mark-ups.

Regulating prices in the distribution chain is not a new approach and is already applied in many countries. A recent (2018) study in 47 high- and upper-middle-income countries demonstrated that wholesale mark-ups were regulated in 32 of these countries and 43 countries reported controlling pharmacy remuneration [10]. Likewise, about 60 % of low-income countries regulated wholesale or retail mark-ups in the

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public and private sector in 2007 [11]. Policies regulating mark-ups were also included in the first World Health Organization (WHO) Guideline on Country Pharmaceutical Pricing Policies [12], which recommended the use of mark-up regulations for wholesalers and retailers, as part of an overall pharmaceutical pricing policy.

A working paper on the regulation of mark-ups by Ball et al. from 2011 noted that, despite the use of mark-up regulations in many countries, there was a lack of evidence on the effects of these regulations [5]. More specifically, the effectiveness of mark-up regulations alone on medicine prices was mostly anecdotal or opinion-based. Furthermore, the authors noted there was no evidence on unintended consequences of mark-up regulations on the availability, sale or consumption patterns of medicines. A third gap in the evidence was the lack of information from low- and middle-income countries.

To reflect the evidence generated since the last systematic literature review in 2010, the 2020 update of the WHO Guideline on Country Pharmaceutical Pricing Policies sought to identify and reassess the available evidence on policies regulating mark-ups, as part of a larger review together with nine other pricing policies [13]. Accordingly, the aim of this systematic review is to determine whether policies regulating mark-ups are effective in managing the prices of pharmaceutical products, and to assess their impact on the volume, availability and affordability of medicines. Additionally, this review describes any reported contextual factors or implementation strategies that may impact the effects of mark-up regulations.

2. Methods

As part of a broader review on ten pharmaceutical pricing policies (i.e. I) cost-plus pricing, II) policies promoting the use of generic and biosimilar medicines, III) policies regulating mark-ups across the pharmaceutical supply and distribution chain, IV) pooled procurement, V) price discounts for single source pharmaceuticals, VI) (external and internal) reference pricing, VII) tax exemptions or tax reductions for pharmaceuticals, VIII) tendering and negotiation, IX) policies promoting price transparency and X) value-based pricing), this paper only addresses policies regulating mark-ups at any point along the pharmaceutical supply and distribution chain. Within this context, policies could involve the specification of a percentage or fixed mark-up at wholesale or retail level (including a 0 % mark-up), as well as pharmaceutical fee-for-service remuneration, in line with the definition used by WHO [12,13]. This definition does not include policies related to the setting of price thresholds (also referred to as price caps or price ceilings).

This systematic review was undertaken according to the principles of systematic reviewing embodied in the Cochrane Handbook and guidance document published by the Centre for Reviews and Dissemination (CRD) [14,15]. The methodology and search strategies have been described in detail previously [16], but a summary of key-points is provided below.

2.1. Search strategy

An extensive literature search was performed between September 5 and October 10, 2019, for relevant articles published from 2004 to the search date in a large number of databases including but not limited to MEDLINE (Ovid), Embase (Ovid), Social Science Citation Index, EconLit, and the NHS Economic Evaluations Database (NHS EED). A variety of grey literature sources were also searched. The main structure of the search strategy comprised concepts pertaining to [1] non-specific pharmaceutical pricing policies or to [2] pharmaceuticals and one of ten specific pricing policies, amongst which were policies regulating mark-ups. Supplementary search approaches included reference-list checking and contacting experts. Full details of the search strategy are reported separately [16].

2.2. Selection criteria

This systematic review only included studies that used robust experimental or observational study designs comparing policies regulating mark-ups to at least one comparator or counterfactual. Randomized trials and non-randomized or quasi-experimental studies (including interrupted time-series (ITS), repeated measures (RM), panel data analyses, and controlled before-after (CBA) studies) were considered robust designs. Single policies, or combinations of policies, were considered eligible. Studies reporting at least one of the primary outcomes of interest, i.e. price (or expenditure as a proxy), volume, availability or affordability, were eligible for inclusion. Price outcomes were selected to capture the expected, direct effects of policies; volume (e.g. prescription and utilization patterns), availability (at health facility level), and (health system and patient) affordability outcomes were selected to reflect indirect policy effects relevant to patients and society. Definitions of outcome parameters are provided in Appendix 1. Public, private and mixed public-private settings were of interest.

2.3. Study selection

A single researcher assessed all titles and abstracts identified from the database searches and removed the obviously irrelevant records based on titles and abstracts. Two reviewers independently screened the titles and abstracts of potentially eligible records, with disagreements adjudicated by a third reviewer. The full texts of studies identified as potentially relevant were then subjected to an eligibility check by two reviewers independently (IRJ and HAvdH) before data extraction. Disagreements about study selection were resolved by discussion until consensus was reached.

2.4. Data extraction and quality assessment

Data from included studies was extracted by one reviewer (IRJ) using a standardized data extraction form, including information on study design, setting and subjects, interventions including implementation strategies, outcomes, and results including contextual factors. Extracted data was verified by a second reviewer (HAvdH) for accuracy.

The risk of bias in each included study was assessed by the extracting reviewer and checked by a second reviewer. Any disagreements were resolved by discussion until a consensus was reached. The assessment was done according to the Cochrane EPOC (Effective Practice and Organisation of Care) guidelines, in which bias assessment criteria were adapted to study design [17]. Randomized-, non-randomized trials and controlled before-after studies were assessed on nine criteria; ITS and RM studies were assessed on eight criteria; and a set of four assessment criteria applied to all other study types. An explanation of the bias criteria is presented in Appendix 2.

The quality of the evidence was assessed using the GRADE methodology [18]. GRADE evidence levels were determined by considering the body of evidence available for each (sub-)intervention. Domains of scoring were the risk of bias, inconsistency of results, indirectness of evidence, imprecision of results, and 'other' (Appendix 3). Studies were upgraded in the 'other' domain if strong observational study designs were used (ITS, RM, panel data/regression analysis), according to precedent in literature [19]. The resultant certainty of the evidence was expressed as high, moderate, low or very low.

2.5. Data analysis

Substantial expected differences in the characteristics and contexts of included studies meant we did not aim to undertake a meta-analysis. Instead, we provided a narrative summary describing the quality of the studies, the relationship between interventions and patterns discerned in the data.

3. Results

Published and grey literature searches yielded 43,693 records for the combined review of ten pharmaceutical pricing policies. An additional 2345 records were identified through the checking of relevant reference lists and other sources. After removal of duplicates, 32,011 records were screened on title and abstract, of which 1000 articles remained for full-text screening. Thirty-eight of these articles were specific to policies regulating mark-ups. After full-text screening, only seven scientific articles were retained in this section of the systematic review (Fig. 1). Reasons for exclusion were ineligible study designs ($n = 25$) including four systematic reviews, ineligible interventions ($n = 3$), and primary

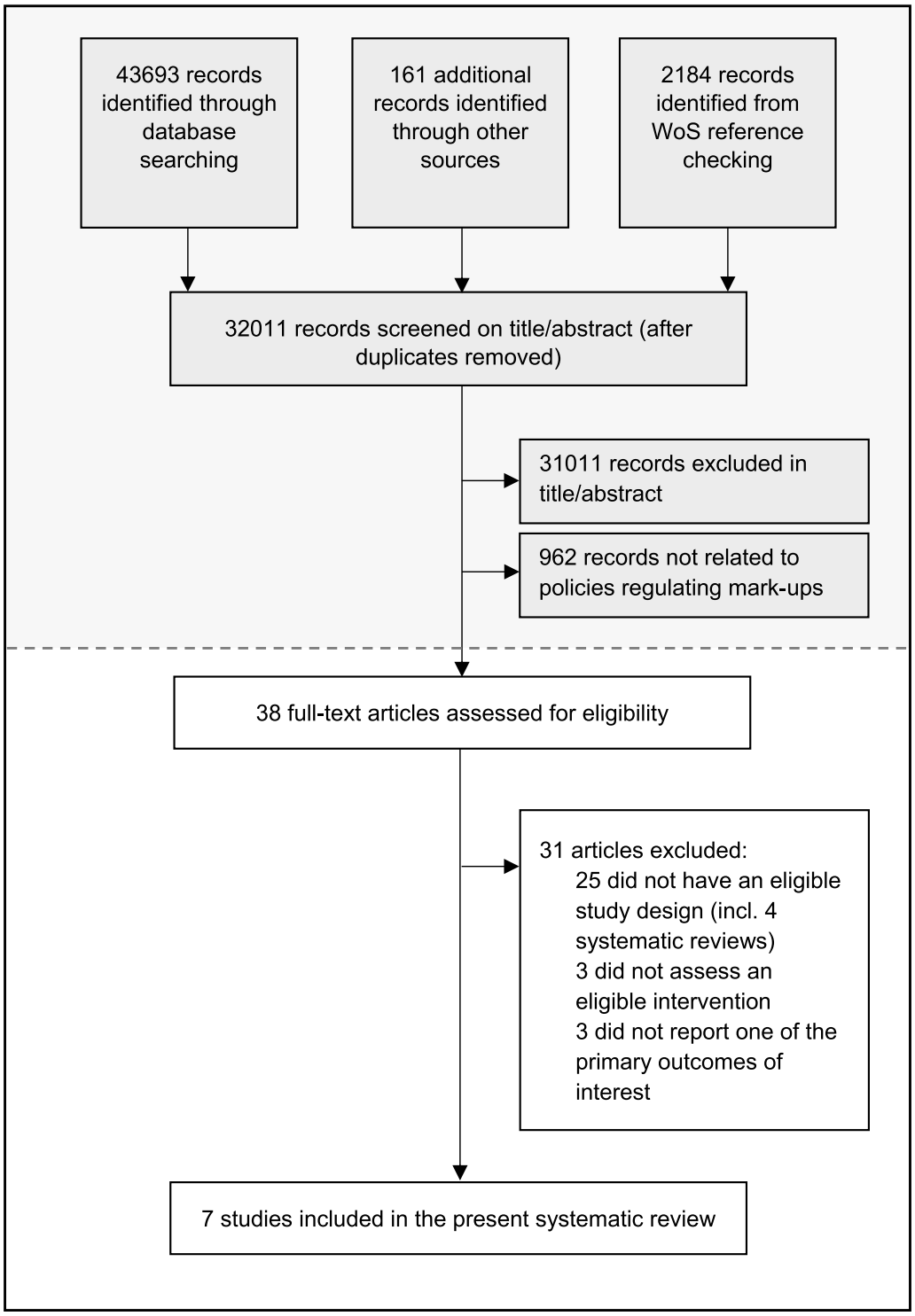

Fig. 1. Flow chart of study selection.
The number of articles identified through database searching and screening by title and abstract shown in grey apply to the overall search; as per protocol the database search included search terms for all ten specific pricing policies amongst which policies regulating mark-ups was one. The lower part of the flow chart shown in white is specific to the selection of studies on policies setting price and mark-up thresholds across the pharmaceutical supply and distribution chain. WoS=Web of Science.

outcomes not reported ($n = 3$).

Table 1 provides an overview of the characteristics of the included studies, published between 2008 and 2018 [20–26]. Notably, five of the seven studies included [22–26] examined the effects of a single policy in China, known as the 'zero mark-up' drug policy (ZMDP), implemented in different regions and at different times. Reported outcomes in all included studies comprise price ($n = 3$), expenditure ($n = 4$) and volume ($n = 1$) outcomes.

3.1. Quality assessment

The results of the risk of bias assessment are presented in Table 2. Three studies reporting on price outcomes [20,21,25] were each associated with a major limitation, and the overall risk of bias was thus considered to be high across these studies. This led to a downgrading of the certainty of the evidence on price outcomes to low quality.

The controlled before-after study by Cheng et al. [26] was associated with a risk of bias across several domains, which is inherent to its non-randomized study design. The studies by Fu et al., Yang et al., and Zhou et al. [22–24] demonstrated only minor limitations, none of which were considered to have a major influence on the results. Overall, the risk of bias was considered to be low for studies reporting expenditure outcomes. The certainty of the evidence was assessed as low.

The study by Moreno-Torres et al. also provided evidence on the outcome volume and was associated with a high risk of bias, as mentioned above [20]. Because the number of prescriptions per capita is considered a proxy for volume, the certainty of the evidence was downgraded to very low due to serious indirectness. Detailed assessments of the overall quality assessment (GRADE) are provided in Appendix 4.

3.2. Summary of findings

The summary of findings of policies regulating mark-ups are presented in Table 3.

3.2.1. Regressive pharmacy mark-ups

One study by Von der Schulenberg et al. assessed the effects of regressive pharmacy mark-ups [21]. They studied the association between regressive pharmacy mark-ups and originator prices of angiotensin converting enzyme (ACE) inhibitors in a sample of European countries (Denmark, France, Germany, Netherlands, Sweden, United Kingdom). The impact of a mix of other supply- and demand-side measures to reduce pharmaceutical expenditures were studied as well, each included as a dummy variable in the regression model. The estimated coefficients for regressive pharmacy mark-ups were negative (−0.259 to −0.303, $p<0.01$), implying mark-up regulation lowered medicine prices throughout Europe.

3.2.2. The 'zero mark-up' drug policy

Five studies [22–26] each studied the impact of implementing the ZMDP in China. With the ZMDP, public hospitals and primary healthcare centers were required to procure essential medicines via government pooled tendering and dispense these at the procurement price, removing the previously allowed 15 % mark-up on dispensed medicines. Previously, hospitals were able to use profits on medicine sales to reward prescribers, thus providing an indirect and perverse incentive to overprescribe drugs [27]. With the ZMDP, the Chinese government aimed to de-couple hospital profits from medicine prescribing, with a view to countering excessive drug use and reducing the financial burden on patients. The ZMDP was piloted and successively implemented across the country in phases between 2007 and 2015. The studies included in this review cover different (pilot) phases of the policy and various strategies to compensate for health centers' losses in revenue.

Li et al. examined the short-term effects of ZMDP implementation on the costs per prescription, in an early pilot of the policy [25]. In this

Table 1
Summary of included studies.

Name of study	Study type	Setting	Medicines studied	Intervention	Outcomes
Cheng 2012 [26]	CBA	Beijing, China	All medicines	The ZMDP implemented in 2007, which removed the previously allowed 15 % profit margin for drug sales at public hospitals.	Expenditure outcome (cost per outpatient visit)
Fu 2018 [22]	DID	Shaanxi province, China	All medicines	The ZMDP implemented between 2012 and 2015, which removed the previously allowed 15 % profit margin for drug sales at public hospitals.	Expenditure outcomes (cost per outpatient visit; cost per inpatient visit)
Li 2008 [25]	Regression analysis	Chengdu, China	All medicines	The ZMDP implemented in 2007, which removed the previously allowed 15 % profit margin for drug sales at public hospitals.	Price outcome (cost per prescription)
Moreno-Torres 2011 [20]	Other	Catalonia, Spain	All medicines	Five reductions of wholesale and retail mark-ups between 1997 and 2006	Price outcome (price per prescription); volume outcome (number of prescriptions per capita)
Von der Schulenberg 2011 [21]	Panel data analysis	Six European countries*	ACE inhibitors	Regressive pharmacy mark-ups, to make dispensing cheaper products more profitable for pharmacists, hence encouraging them to dispense generics rather than originators.	Price outcome (originator price)
Yang 2017 [23]	ITS	Shaanxi province, China	All medicines	The ZMDP implemented in 2010, which removed the previously allowed 15 % profit margin for drug sales at public hospitals.	Expenditure outcome (monthly hospitalization expenditure per patient)
Zhou 2015 [24]	DID	China	All medicines	The ZMDP implemented in 2010, which removed the previously allowed 15 % profit margin for drug sales at public hospitals.	Expenditure outcomes (cost per outpatient visit; cost per inpatient visit)

ACE=Angiotensin Converting Enzyme, CBA=controlled before-after study, DID=Difference-in-differences, ITS=Interrupted time series, ZMDP=zero mark-up drug policy.
* Denmark, France, Germany, Netherlands, Sweden, United Kingdom.

Table 2
Risk of bias assessment of included studies.

Bias type		Cheng 2012	Fu 2018	Li 2008	Moreno-Torres 2011	Von der Schulenberg 2011	Yang 2017	Zhou 2015
Random sequence allocation	**RCT, NRCT and CBA studies***	⊖	–	–	–	–	–	–
Allocation concealment		⊖	–	–	–	–	–	–
Baseline outcome measurements similar		?	–	–	–	–	–	–
Baseline characteristics similar		⊖	–	–	–	–	–	–
Protection against contamination		⊕	–	–	–	–	–	–
Intervention independent	**ITS and RM studies**	–	–	–	–	–	⊕	–
Appropriate analysis		–	–	–	–	–	⊕	–
Pre-specified shape of effect		–	–	–	–	–	⊕	–
Intervention to affect data collection		–	–	–	–	–	⊕	–
Incomplete outcome data	**All study types**	?	⊕	?	?	?	?	?
Knowledge of allocated intervention		⊕	⊕	⊕	⊕	⊕	⊕	⊕
Selective outcome reporting		⊖	⊕	⊖	⊕	⊕	⊕	⊕
Other bias		⊖	?	⊖	⊖	⊖	⊕	?

CBA=controlled before-after study, ITS=interrupted time series, NRCT=non-randomized controlled trial, RCT=randomized controlled trial, RM=repeated measures. A CBA study by Cheng et al. [26] was associated with a risk of bias across several domains, as is inherent to the study design. Additionally, there seemed to be some selectiveness in the reporting of results and data sources were segmented, possibly leading to differences in data collection. A DID study by Fu et al. presented only minor limitations [22]. It appeared the model used in Li et al. [25] did not take into account several potential confounding factors and did not include volume-related outcomes, regarded as a high risk. Moreno-Torres et al. raised concerns about the independent occurrence of the interventions [20]. There were also doubts about the validity of the model used because assumptions in the model were left untested and sensitivity analyses were not performed. The risk of multicollinearity in the model was assessed as high in Von der Schulenberg et al. [21]. The ITS study by Yang et al. [23] presented only minor limitations, as did the DID study by Zhou et al. [24].
†Bias domains only applicable to ITS and RM studies.
‡Bias domains applicable to all study types.
* Bias domains only applicable to RCT, NRCT and CBA studies.

pilot, the community health centers (CHCs) were compensated for their loss in drug revenue by a government subsidy. ZMDP implementation was associated with a negative coefficient estimate (-0.417, $p = 0.001$), implying reduced costs for patients. Although volume-related outcomes were only analysed using descriptive statistics, a reduction in prescription volume was observed.

Cheng et al. investigated the effects of ZMDP implementation and three distinct compensation methods for CHCs in a 2007 pilot [26]. A first group of CHCs was compensated through a fixed subsidy, providing full financial support, but these CHCs were not allowed to keep any surplus. The second group relied on an income-linked subsidy that covered staff expenses, but not the full operational costs. The amount of subsidy relied on the revenue of the facility. Within the third group, CHCs were self-financed and were compensated for the mark-up loss based on historical medicines sales.

Large differences were observed between groups. In CHCs receiving a fixed subsidy, medicine costs per visit were reduced by 18.7 % ($p<0.001$) in 2007, before increasing again with 17.1 % in 2008 and 6.3 % in 2009 compared to the year before. The impact of the policy was less pronounced in CHCs receiving an income-linked subsidy, with consecutive relative changes in medicines costs per visit of −1.9 % ($p<0.001$), +7.6 % and +8.5 %. Compensation based on historical medicines sales led to increasingly higher costs despite the implementation of the policy, with a yearly increase between 16.7 % to 25.2 %. Of note, medicines targeted by the ZMDP were intended to meet the majority of medicine needs, but in reality they accounted for ~75 % of total medicine costs per visit in CHCs receiving a fixed subsidy between 2007 and 2009. These proportions were even smaller in the other CHC groups (48.9–60.5 %).

The outcomes 'drug expenditure per inpatient admission', and 'per outpatient visit' were included in two studies [22,24]. Zhou et al. investigated the effects of ZMDP implementation on medical expenses for patients at county hospitals, where the policy had been piloted in most provinces between 2010 and 2011. Data from two county hospitals were analysed, one functioning as control. Fu et al. examined the effects of ZMDP implementation on medical expenses for patients in a large sample of public general county hospitals in mainland China between 2009 and 2014, where the policy was finally implemented in phases between 2012 and 2015. In the final policy, instead of providing subsidies, the loss of revenue was compensated by the government by raising fees for medical services, which had previously been set far below actual costs of providing the services, resulting in cross-subsidization from revenue generated from dispensed medicines. ZMDP implementation was associated with a −6.3 % ($p<0.01$) and −7.4 % ($p<0.01$) change in per-visit drug expenditure and a −9.0 % ($p<0.01$) and −3.9 % ($p<0.01$) change in per-admission drug expenditure [22,24]. Meanwhile, expenditures on medical services for outpatient visits and inpatient admissions increased by 8.2 % ($p<0.01$) and 8.0 % ($p<0.01$), respectively. Taken together, total expenditures per visit and admission were lowered only slightly by 2.5 % ($p>0.1$) and 1.2 % ($p>0.1$). Interestingly, in hospitals with a greater reliance on drug sales before the ZMDP, increased expenditures for diagnostic tests and medical consumables were observed ($p<0.01$).

Yang et al. examined the effect of ZMDP implementation in primary health institutions in the rural county of Fufeng, Shaanxi province, on monthly average hospitalization expenditure [23]. Health institutions received subsidies to compensate for their loss of potential drug revenue in this 2010 pilot. In this study with an ITS design, ZMDP implementation was associated with a −6.30 US$ ($p = 0.366$) immediate change in expenditure (reported as change in level) and a −2.58 US$ ($p = 0.009$) change in trend.

3.2.3. *Other mark-up regulations*

Moreno-Torres et al. examined the impact of five mark-up reductions

Table 3
Summary of findings of policies regulating mark-ups.

Policies regulating mark-ups compared to no policy or fixed mark-ups				
Medicines: ACE inhibitors; all medicines Settings: China; Spain; Denmark, France, Germany, Netherlands, Sweden, United Kingdom Intervention: Policies regulating mark-ups Comparison: No policy or fixed mark-ups				
Outcomes	Impacts	No. of studies	Certainty of the evidence (GRADE*)	Comments
Price				
Originator drug price	Regressive pharmacy mark-ups may lead to price reductions.	1	Low	–
Price/cost per prescription	Wholesale and retail mark-up reductions may lead to decreased prices. A zero-mark-up policy‡ may lead to decreased costs.	2	⨁⨁◯◯	Wholesale and/or retail mark-up reductions as well as the zero-mark-up drug policy were associated with significant negative coefficient estimates, indicating reduced costs.
Drug expenditure per outpatient visit	A zero-mark-up policy‡ may decrease drug expenditure.	3	Low ⨁⨁◯◯	The zero mark-up drug policy was associated with considerable decreases in drug expense per outpatient visit in two studies. In a third study, a small decrease was initially observed before the trend in drug expenditure increased again.
Drug expenditure per inpatient admission	A zero mark-up policy‡ may lead to a reduction in drug expenditure.	2		–
Monthly hospitalisation expenditure	A zero mark-up policy‡ may not lead to a difference in expenditure immediately after implementation. It may reduce expenditure long-term.	1		The zero mark-up drug policy was associated with a non-significant decrease in average monthly hospitalisation expenditure immediately after implementation. A significant negative change in trend was observed after the policy, indicating long-term benefits.
Volume				
No. of prescriptions per capita	It is uncertain if mark-up reductions result in a change in utilization, because the certainty of the evidence is very low.	1	Very low ⨁◯◯◯	The reduction of mark-ups was associated with a significant positive coefficient, indicating an increase in the number of prescriptions. Coefficients were positive but not significant for four similar measures that followed.
Availability				
–	No studies meeting the inclusion criteria were found	0	–	–
Affordability				
–	No studies meeting the inclusion criteria were found	0	–	–

* GRADE Working Group grades of evidence.

High = This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.**Moderate** = This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.**Low** = This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.**Very low** = This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

† Substantially different = a large enough difference that it might affect a decision.

‡ A zero mark-up policy is studied in five distinct studies, each regarding the Chinese Zero Mark-up Drug Policy. Results should be interpreted together.

implemented between 1997 and 2006 in Catalonia, Spain, as well as eleven other interventions to reduce pharmaceutical expenditures [20]. The authors did not describe the scope and extent of the mark-up reductions. Regardless, estimated coefficients were negative for all mark-up reductions for the outcome price per prescription (March 1997 −0.033, $p<0.01$; June 1999 −0.028, $p<0.05$; August 2000 −0.023, $p<0.01$; March 2005 −0.030, $p<0.01$; March 2006 −0.015, $p>0.1$). Notably, pharmaceutical expenditure per capita (including costs for the public insurer and respective co-payment by patients) were only (significantly) reduced after implementation of two of the five mark-up reductions. Savings achieved through reduced prices per prescriptions were offset by an increase in the number of prescriptions (March 1997 + 0.029, $p<0.1$; June 1999 + 0.031, $p>0.1$; August 2000 + 0.000, $p>0.1$; March 2005 + 0.009, $p>0.1$, March 2006 + 0.025, $p>0.1$).

There was no evidence on the impact of policies regulating mark-ups on the availability or affordability of medicines, because these outcomes were not studied in any of the included studies.

4. Discussion

Following extensive searches, we found seven studies examining the effects of policies regulating mark-ups eligible for inclusion in this review. Pricing policies, including policies regulating mark-ups, are implemented by government bodies as part of broader health policies, but there is limited established tradition for rigorous evaluation of such policies by those who enact and enforce them. Occasionally, academic research groups undertake and publish policy evaluations using rigorous observational designs. The choice for researching specific policies, however, does not always seem to be driven by the most pressing evidence gaps or areas of greatest potential societal impact, but by other factors such as research opportunities. While mark-up regulations are frequently encountered, limited attention has been paid to robust evaluation. This gap between what is implemented and what is researched could lead to the general lack of rigorous evidence observed here. The evidence that has been identified, although of low quality, shows that policies regulating mark-ups may indeed lead to reductions in drug prices and pharmaceutical expenditures. Whether policies regulating mark-ups also have an effect on the utilization of medicines remains unclear, because the certainty of the evidence is very low. There is currently no evidence on the impact of mark-up policies for the outcomes availability and affordability.

We considered policies prohibiting mark-ups on medicines (i.e. the ZMDP) to be eligible as the specification of a zero percent mark-up – and thus removing mark-ups – is in line with the definition used in this review. However, we acknowledge that different definitions may be used and controversies on the eligibility of this policy exist. Regardless, this particular type of mark-up regulation – similar to a regulation in South Korea where pharmacies are prohibited from charging mark-ups on essential medicines [28] – should be considered separately from other regulations that do not entirely eliminate mark-ups. Each of the five studies that examined the effects of the Chinese ZMDP support the prior hypothesis that these kind of policies may to some extent be effective in reducing pharmaceutical expenditures [22–26]. However, removing the previously allowed 15 % mark-up did not lead to a similar reduction in prices or expenditures. In fact, a decrease of less than 15 % implies that hospitals compensated the expected losses in drug revenue by other mechanisms. That facilities sought to offset their losses in drug revenue is probable, as results from the study by Fu et al. have shown that pharmaceutical expenditures were reduced by a greater extent (−6.3 % and −9.0 % vs. −2.5 % and −1.2 %) than total expenditures [22]. Similarly, only a modest slowing in growth rate of hospitalization expenditures was observed by Yang et al. (−2.58 US$ per month) [23].

A possible mechanism to compensate for losses in drug revenue is the dispensing of medicines outside of the scope of the ZMDP. Evidence for the use of this compensation mechanism is found in the study by Cheng et al., in which medicines targeted by the policy accounted for only 60 % of the total medicine costs [26]. This effect was more distinct in facilities with a stronger incentive to generate revenue, although even facilities on a fixed budget procured medicines outside of the list. The dispensing of medicines outside of the scope of the policy may thus not only be used as a compensation strategy, but could also indicate that medicines targeted by the ZMDP were unable to meet the majority of patients' needs. Along the same line, Li et al. hypothesized that the policy may have restricted patient choices, resulting in fewer patients visiting these health centers and explaining the reduced prescription volumes [25]. A second mechanism is the increased use of medical services or medical consumables. Fu. et al. observed that hospitals showed increased expenditures for medical services and for medical consumables and diagnostics [22]. The increased expenditures for medical services were intended by policy-makers, who raised the fees for medical services as part of the policy that was finally implemented nation-wide, to counterbalance losses in drug revenue and to better reflect actual costs of providing these services. Unintended, however, were the increases in expenditures for diagnostic tests and medical consumables, that imply increased use of these commodities with a higher price-cost margin. This effect was more pronounced in hospitals with a greater reliance on drug revenue before the ZMDP. Overall, reductions in expenditures on medicines achieved by reducing mark-ups were almost completely offset by increases in expenditures on medical services and medical consumables, without any significant changes in total expenditures [22]. A third potential compensation mechanism is the dispensing of larger quantities of medicines, although no specific evidence of that was found in the studies included in this systematic review.

Since the literature search for this systematic review was performed, additional studies meeting the eligibility criteria of this review have been published. In this regard, four studies assessing the impact of the Chinese ZMDP were (not systematically) identified. Three of these studies confirm that drug-related expenses may decrease due to the policy [29–31], although the magnitudes of the effects are probably limited [30]. The fourth study found that drug-related expenses did not change significantly, but the ZMDP did lead to a considerable increase in medical expenditures [32]. By circumventing the ZMDP and providing medicines or services outside of the scope of the policy, the results of the studies included in our review confirm that health system administrations and prescribers by extension act as imperfect agents due to financial incentives, as noted previously [33,34]. The results of these studies also imply that mark-up control of only selected drugs or medical services is not sufficient to control healthcare expenditures as higher price-cost margins on other medicines and services can indirectly still induce overprescription, despite governments offering subsidies or other compensation strategies. A comprehensive and well-designed approach that takes into account potential undesirable effects is thus expected to achieve better results.

The 2020 WHO Guidelines on Country Pharmaceutical Pricing Policies [13] note that mitigating undesirable effects in the design of policies regulating mark-ups is critical. The guidelines suggest the use of mark-up regulations across the supply and distribution chain, if implemented in conjunction with other pricing policies, and if regressive in structure rather than using a fixed percentage mark-up structure. The results of the present systematic review, although based on a single study that was limited in scope and that provided little detail on the structure of the regulation, confirm that regressive mark-ups may lead to reduced medicine prices [21]. Additionally, it is possible that a policy abolishing all mark-ups may lead to more unintended effects than policies simply reducing them, by eliciting stronger incentives to compensate losses. Overall, mark-up regulation is favored because the policy could facilitate broader access to medicines through incentivizing supply of specific medicines such as lower-priced medicines, generics, low volume medicines and reimbursable medicines [5,13]. The recommendations on mark-up regulations in the 2020 Guideline on Country Pharmaceutical Pricing Policies are in line with those in the 2015 Guideline [12].

It is remarkable that the evidence gaps noted by Ball et al. in 2011 still remain [5], implying that little new, robust evidence has been produced in recent years, as evidenced by the limited number of studies included in this review despite our wide ranging search of published and grey literature. The relatively large proportion of studies excluded during the review process due to study design and outcomes of interest indicates that there may be a mismatch between the type of evidence needed to inform policy-making through WHO guidelines and the evidence that has been produced. The remaining uncertainties are a clear call for further research, to both researchers and policy-makers. Researchers should better align their research agenda with the needs of policy-makers and in return policy-makers could contribute by planning for the evaluation of pricing policies and collection of the required data during the design and piloting of policies.

A strength of our systematic review is the use of a rigorous methodology based on the principles described in the Cochrane Handbook and CRD guidance documents [14,15], including prospective publication of a protocol [16]. Our methodology involved a sensitive search strategy that included a wide range of search terms designed to retrieve both published and grey literature. This was complemented by reference list checking and expert contact to identify any studies potentially missing. The risk of bias and strength of the evidence were assessed in duplicate and following validated guidelines [17,18], which were adapted to match the study design types encountered in this field of research.

Some limitations of our review are inherent to the nature of policy research. Firstly, although grey literature can be particularly valuable within this field of research, search and exporting functionalities of many grey literature databases are often poor. This demanded a more pragmatic search approach that included a smaller range of search terms than used in the major bibliographic databases. Although this could have resulted in missing potentially relevant literature, this limitation should be regarded within the wider search strategy that was used. Another limitation arises from the incomplete or missing description of the intervention or the context in which it was implemented in several of the studies included in the present review. We did not consult additional resources to clarify any questions, which hampered interpretation of some of the evidence. This is especially true for the studies by Moreno-Torres et al. and Von der Schulenberg et al. [20,21], as both studies present evidence on policies not encountered elsewhere in the included studies. In contrast, the collective evidence from five publications on the Chinese ZMDP provides a comprehensive overview of the policy. This has aided our interpretation of the results and may also facilitate evidence-informed policy making. Generalizability of our findings on ZMDP implementation is nevertheless limited as it was studied in one country only and study results were not consistent across included and later published studies.

5. Conclusion

The limited and low-grade evidence identified by this systematic review cautiously suggests that policies regulating mark-ups may be effective in reducing medicine prices and pharmaceutical expenditures. However, the majority of the evidence was on the ZMDP from a single country, further narrowing the applicability of these findings. Nonetheless, the available evidence suggests that the design of mark-up regulations is a critical factor for their potential success, as a supply side driven demand for medicines or services with higher price-cost margins may offset the impact of mark-up regulations. Further studies should include the effects of mark-up regulations on the availability, affordability or consumption patterns of medicines in countries covering different health care system designs and in resource constrained settings.

Declaration of Competing Interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.healthpol.2023.104919.

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