A Systematic Review of Zero-markup Policy for Essential Drugs Effect on Medical Treatment

CURRENT STATUS: POSTED

Wen-Yi Liu
Shanghai Bluecross Medical Science Institute

Chia-Hsien Hsu
Kaohsiung Medical University

Ting-Jun Liu
Tai Kang Institute of Healthcare Management

Pei-En Chen
aiwan Association of Health Industry Management and Development

Tao-Hsin Tung
Cheng Hsin General Hospital

ch2876@gmail.com Corresponding Author

Ching-Wen Chien
Tsing Hua University

DOI: 10.21203/rs.3.rs-15650/v1

SUBJECT AREAS
Health Economics & Outcomes Research  Health Policy

KEYWORDS
zero-markup policy, medical expenditure, systematic review, China
Abstract
Objective. This systematic review is conducted to synthesize recent empirical evidence of Zero-markup Policy for Essential Drugs Effect on Medical Treatment in China.

Methods. We searched the PubMed, Embase, Scopus, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) for all related studies published from inception to 30 April 2019 without restriction on language. In addition, grey literatures were captured through other sources, such as OpenGrey and Open Access Theses and Dissertations (OATD), to avoid selection bias. Methodological quality were evaluated using the PRISMA statement the Newcastle Ottawa Scale Collaboration tool.

Results. Thirty-four full texts were initially searched, but only nine studies met our inclusion criteria. Most of studies indicated the significant reduction for both the total expense and drug expense per visit. Additionally, outpatient and inpatient services indicated increasing trends in annual patient-visits.

Conclusions. In conclusion, the available limited, relative low-quality evidence does not support the long-term association between zero-markup policy for essential drugs and reduced medical expenditure. Further longitudinal studies that provide data for hospitals over a wider range of regions would make the economic effects more discursive.

Background
In 1954, Policy on Drug Markups (PoDM) announced by Chinese government granted medical institutions to raise pharmaceuticals price by maximum to 15% cap [1]. Since 1980s lacking enough fiscal subsidy and facing raised drug price, patients were struggling with health care [2]. To alleviate these challenges, Medical health reform was initiated by Chinese government and Zero-markup Policy for Essential Drugs (ZPED) was published in 2009. ZPED demonstrated that markup from pharmaceutical bills would no longer exist and 10% of original 15% markup under PoDM would be replaced by fiscal subsidy. The solution of rest payment would be deemed a ridiculous way that diagnosis costs would be raised to cover 80% of original markup. The rest was subject to medical institutions themselves [3].

Although ZPED was critical to limit rapid increasing drug price, it could not avoid financial burden of
patients transferred gradually from drug price to other medical payment at last. For example, at the beginning (2009–2011) per visit patient medication expense was reduced, especially in rural area and county. Zhou et. al. also believed dependence on drug revenue to subsidize the deficit of hospitals could be controlled by ZPED [4]. From 2011 to 2015, ZPED was not longer a pilot program and gradually applied to all the county medical institutions in China. However, Yang et. al, found that medical expenditure was still increasing, although its rising trend was restrained [2]. This might be that medical institutions were entitled to raise other medical expenditure, such as diagnosis payment, nursing fees, surgery expense and treatment fees, under ZPED [2].

Most studies focus on long-term effects of ZPED on per visit expenditure, especially drug expense, but ignore the whole payment of one course of treatment. Therefore, this study utilize systematic review to explore the effect of ZPED on annual medical expense of per citizen and expenditure of one course of treatment.

Methods

Data source and searches

The literature search was conducted using PubMed, Embase, Scopus, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) for all related studies published until 30 April 2019 without restriction on language. In addition, grey literatures were captured through other sources, such as OpenGrey and Open Access Theses and Dissertations (OATD), to avoid selection bias. A search strategy was developed for the aforementioned electronic databases, using key words as follows: (“pharmaceutical*” [Title/Abstract] OR “drug*” [Title/Abstract] OR “medicine*” [Title/Abstract]) AND (“zero” [Title/Abstract]) AND (“markup” [Title/Abstract] OR “mark-up” [Title/Abstract])). The reference lists of the screened related articles were manually examined to further identify additional similar studies (Table 1). In addition, no patients were involved in this study. We used data from published papers only. IRB approval was not required for the study.

Study selection

Two reviewers independently screened eligible studies that focused on the impacts of ZEPD on annual medical expense of per citizen and expenditure of one course of treatment. The disagreements resolved via discussion with a third author. These studies should be original articles instead of letters
to the editor or conference abstracts. Also, the outcomes which these included studies investigated should be linked to financial indicators of healthcare institutions, for example, total expenditure per inpatient/outpatient visit, drug expenditure per inpatient/outpatient visit, number of inpatient/outpatient visits, and so forth.

Data extraction and quality assessment of methodology

Two reviewers independently abstracted the following characteristics of included studies based on a normalized data collection form: author, publication year, study design, area, hospital accreditation, outcomes, statistical methods, and conclusions. As for quality assessment, the Newcastle Ottawa Scale (NOS) [5], a recommended and validated tool for evaluating methodologic quality in non-randomized studies, was used to assess the quality of the included studies independently by the same two reviewers. Regarding the quality ratings as shown in Table 2, each asterisk represents one point and the total NOS score is the sum of the points (a maximum of 9), which are assigned for selection (4 points), comparability (2 points), and outcome (3 points).

Data synthesis and analysis

There were four broad outcome variables: 1. Total expenses (inpatient/outpatient service); 2. Drug expenses (inpatient/outpatient service); 3. Number of patients’ visit. Outcome variables were assessed at baseline and intervention point.

Results

Characteristics of the included trials

As illustrated in Fig. 1, our search identified 34 records after removing duplicates. We excluded 25 records that did not meet our inclusion criteria. Nine studies (included time series study, retrospective cohort study, and quasi-experimental study) were included in this systematic review [1-4, 6-10]. The characteristics of the included studies are summarized in Table 3. These studies were published between 2015 and 2019. All selected studies were from China. In addition, all nine of the studies were rated less than seven stars on the NOS scale and were considered of relative low quality. As shown in Table 3, various sets of outcomes were measured.

Total expenses

Based on the quasi-experimental design, the total expense per visit reduced by 3.12 USD and 65.6 USD for outpatient and inpatient services, respectively. The expense per visit was estimated 11%
reduction for both outpatient and inpatient services [4]. A retrospective longitudinal study indicated that in absolute terms, there were increased annual patient-visits [6]. Yang et al (2017) indicated the statistically significant decreasing of monthly hospitalization expenditure [2]. Fu et al (2018) showed that a rise in expenditures for medical services and no changes in total health expenditures [8]. In addition, He et al (2018) showed the results that pharmaceutical reform could not reduce total health expenditure in long term [3]. There was a statistical significantly positive correlation between the rate of services compensation and the proportion of medical service revenue [1]. However, Mao et al (2019) concluded that no significant change of the average medical expenditure per prescription was observed [10].

Drug expenses
Zhou, et al (2015) showed that the drug expense per visit dropped by 4.47 USD and 45.75 USD for outpatient and inpatient services, respectively. They also found that the proportion of drug expense out of total expense per visit dropped by 11.73% and 3.92% in outpatient and inpatient visits, respectively [4]. Yin et al (2018) indicated that ZPED could improve rational use of antibiotic were related to the reduction of antibiotic consumption [9]. Fu et al (2018) found the policy change led to a decreased in drug expenditures [8]. He et al (2018) showed the results that pharmaceutical reform only could short term reduced drug expenditure [3]. Mao et al (2019) also found that the average number of medicines per prescription, use of antibiotics, intramuscular injections and intravenous injections decreased while the use of hormones increased [10].

Number of patients’ visits
Tian et al (2016) found that ratios of medicine-to-healthcare-charges decreased in outpatient and inpatient services. Both outpatient and inpatient services showed increasing trends in annual patient-visits [6]. Wei et al (2017) concluded that ZPED may be correlated to reductions in outpatient antibiotic prescribing and intravenous infusions [7].

Others
The inpatient physician work-days increased and inpatient mortality-rate reduced, physician work-days decreased and physician-workload and inflation-adjusted per-visit healthcare charges increased in outpatient service [6].
Discussion
Clinical implications

From the best of our knowledge, this is the first systematic review to explore the ZPED on medical treatment in China. According to the selected studies, we found the significant reduction for both the total expense and drug expense per visit. In addition, outpatient and inpatient services indicated increasing trends in annual patient-visits. In China, economic incentive and profits from prescribing medicines was the most frequently mentioned potential influential factor due to previous systematic review showed that irrational use of medicines was severe [11]. However, the improvement on the rational use of medicine still has many unexpected challenge. ZPED is a national level’s medicines, then lower level governments extend the list based on the demands. Medicines without lists are not allowed in prescriptions [7]. The main consequence for the medical policy is that hospitals are not only never sufficiently compensated, but also face many financial difficulties based on the complex medical environment [12].

It implied that the structure of inpatient and outpatient utilization may be changed because ZPED decreased healthcare costs for patients. The patients’ medical decision making on whether to utilize inpatient services are determined by factors other than outpatient price [13]. Evidenced findings from behavioral economics studies showed that subjects usually make decisions not only based on absolute, but also on relative changes in price [4, 14]. This appearance is at the central of relative thinking theory, which indicates that people are influenced more by relative changes than absolute changes in a given base line [14].

From the policy viewpoint, these findings of selected studies concerns about the health care cost containment policy that changes prices for drugs and clinical services. To change prices for drugs and medical services is a widely used policy instrument in western countries [8]. The price regulations alone would not yield the satisfactory cost reduction due to health providers would circumvent the regulations by information advantage. It is inevitable that China also faced great pressures to health care. To increase the provisions of other medical services with higher price-cost margins may compensate for the revenue loss in Chinese public hospitals [8]. In addition, Diagnosis-Related Group
(DRG) may be considered to address the inappropriate utilization of drugs and services and to reduce healthcare expenditure. The experience in Beijing had indicated that the introduction of DRG payment system decreased expenditures and out-of-pocket spending per admission [15].

**Clinical practice**

This systemic review found that despite there is some heterogeneity in total expense, there is significant improvement of drug expenses and number of patients’ visits. Based on the results, medical teams should develop the customized protocol to control or reduce medical expenses from the heart of ZPED because the increase or decrease of the medicine or healthcare charges is mainly dependently on the hospital levels [16]. Such as both outpatient and inpatient charges were decreased in township health centers but not of country levels or above [6]. For better expenditures improvement, the monitor system should long-term evaluation with progressive and alternative strategies.

**Methodological considerations**

Several limitations should be considered when interpreting the results of this study. Firstly, the small number of included studies limits the strength of the conclusions that were drawn. Secondly, the selected studies are of variable methodological quality, which introduced the risk of bias (Table 2). Thirdly, we were unable to conduct meta-analysis analyses based on selected studies because the included studies did not provide consistent information. Finally, the results might not be generalizable to other hospitals, as the studies we reviewed were conducted in just some regions in China. The external validity also should be further discussed.

**Conclusion**

Although the positive effects were demonstrated of ZPED, the available limited and relative low-quality evidence does not support the long-term association between zero-markup policy for essential drugs and reduced medical expenditure. Further longitudinal studies that provide data for hospitals over a wider range of regions in China would make the economic effects more discursive.

**Abbreviations**

Zero-markup Policy for Essential Drugs (ZPED)

Policy on Drug Markups (PoDM)
Cumulative Index to Nursing and Allied Health Literature (CINAHL)

Open Access Theses and Dissertations (OATD)

Newcastle Ottawa Scale (NOS)

Diagnosis-Related Group (DRG)

Declarations

**Ethics approval and consent to participate**

Not applicable

**Consent to publish**

Not applicable

**Availability of data and materials**

All data underlying the findings are within the paper.

**Competing interests**

The authors have no proprietary interest in any aspect of this study.

**Funding**

There was no additional financial support from public or private sources.

**Authors' Contributions**

Liu WY, Hsu CH, Liu TJ, Chen PE, Tung TH, and Chien CW conducted the study and drafted the manuscript. Liu WY, Hsu CH, Liu TJ participated in the design of the study and performed statistical analyses. Chen PE, Tung TH, and Chien CW conceived the study, and participated in its design and coordination. All of the authors read and approved the final manuscript.

**Acknowledgements**

Not applicable

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Tables

| Table 1. Search strategy in PubMed up until April 2019 (similar search run in other databases) |
|---------------------------------------------------------------------------------------------|
| 1. “pharmaceutical*” [Title/Abstract]                                                        |
| 1. “drug*” [Title/Abstract]                                                                 |
| 1. “medicine*” [Title/Abstract]                                                             |
| 1. 1 OR 2 OR 3                                                                             |
| 1. “zero” [Title/Abstract]                                                                  |
| 1. “markup” [Title/Abstract]                                                                |
| 1. “mark-up” [Title/Abstract]                                                               |
| 1. 6 OR 7                                                                                  |
| 1. 5 AND 8                                                                                 |
| 1. 4 AND 9                                                                                 |
### Table 2. Quality assessment of included studies using the Newcastle-Ottawa Scale (NOS)

| Source | Selection | Comparability | Exposure | Total NOS Score |
|--------|-----------|---------------|----------|----------------|
| Zhou et al., 2015 [4] | ☆ | ☆☆ | ☆ | 5 |
| Tian et al., 2016 [6] |  |  | ☆ | 2 |
| Wei et al., 2017 [7] | ☆ | ☆ |  | 6 |
| Yang et al., 2017 [2] | ☆ |  |  | 3 |
| Fu et al., 2018 [8] |  | ☆☆ |  | 5 |
| He et al., 2018 [3] |  |  |  | 3 |
| Tang et al., 2018 [1] |  |  |  | 2 |
| Yin et al., 2018 [9] |  |  |  | 3 |
| Mao et al., 2019 [10] |  |  |  | 3 |

**Selection**
1. Representativeness of the exposed cohort
2. Selection of the non-exposed cohort
3. Ascertainment of exposure
4. Demonstration that outcome of interest was not present at start of study

**Comparability**
1. Comparability of cohorts on the basis of the design or analysis

**Exposure**
1. Assessment of outcome
2. Was follow-up long enough for outcomes to occur
3. Non-Response rate

### Table 3. Characteristics of included studies in China

| Author | Publication year | Study design | Area | Hospital accreditation | Outcomes | Statistical methods | Conclusions |
|--------|------------------|--------------|------|------------------------|----------|---------------------|-------------|
| Zhou et al. [4] | 2015 | Quasi-experimental study | Ningshan County and Zhenping County, Shaanxi Province | Secondary | Total expense per visit (inpatient/outpatient service) Drug expense per visit (inpatient/outpatient service) | Hospital data difference-in-differences Individual data regressions | The absolute monetary reduction of the per-visit inpatient expense is 20 times of that in outpatient care The relative reductions are the same for outpatient and inpatient visits The incentive to utilize outpatient or inpatient care |
| Study          | Year | Study Design                           | Location | Setting   | Methods                                                                 | Findings                                                                 |
|---------------|------|----------------------------------------|----------|-----------|-------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Tian et al. [6] | 2016 | Descriptive study (retrospective longitudinal study) | Beijing  | Tertiary  | Annual patient-visits Ratios of medicine-to-healthcare-charges (RMOH) Physician work-days (inpatient/outpatient service) Physician-workload (inpatient/outpatient service) Inflation-adjusted per-visit healthcare charges (inpatient/outpatient service) Mortality-rate (inpatient/outpatient service) Rank-sum tests Join-point regression analyses | Implementation of Universal Zero-Markup Drug Policy: Increase annual patient-visits Reduce RMOH Have different impacts on outpatient and inpatient services |
| Wei et al. [7]  | 2017 | Natural experiment                      | Guangxi  | N/A       | Antibiotic prescribing rate (outpatients with a primary diagnosis of upper respiratory tract infection) Difference-in-difference analyses | The national essential medicines scheme and zero-mark-up policy may be associated with reductions in outpatient antibiotic prescribing and intravenous infusions. |
| Yang et al. [2] | 2017 | Time series study                       | Shaanxi Province | Primary | Monthly average hospitalization expenditure (AHE) Monthly average hospitalization expenditure after reimbursement (AHER) Segmented regression analysis of interrupted time series data | A statistically significant absolute decrease in the level or trend of monthly AHE and AHER was detected after the introduction of the zero-markup drug policy in western China. However, hospitalization |
expenditure and hospitalization expenditures were still increasing. More effective policies are needed to prevent these costs from continuing to rise.

Fu et al. [8] 2018 Penal study 1,880 counties N/A Outpatient care Total expenditure per visit Drug expenditure per visit Expenditure for diagnostic tests/medical consumables per visit Expenditure for medical services per visit Outpatient visits Inpatient care Total expenditure per admission Drug expenditure per admission Expenditure for diagnostic tests/medical consumables per admission Expenditure for medical services per admission Inpatient admissions Average length of inpatient stay Pre-trend test based on linear regressions The policy change led to a reduction in drug expenditures, a rise in expenditures for medical services, and no measurable changes in total health expenditures. However, this study also found an increase in expenditures for diagnostic tests/medical consumables at hospitals that had a greater reliance on drug revenues before the reform, which is unintended by policymakers. Further, these results were more likely to be driven by the supply side, suggesting that hospitals offset the reductions in drug revenues by increasing the provision of services and products with higher price-cost margins.

He et al. [3] 2018 Time series study Sanming City, Fujian Province Secondary (n=4) and Tertiary (n=21) Outpatient drug expenditure Outpatient total health expenditure Inpatient drug expenditure Interrupted time series analysis with three segments divided by two intervention points Although the pharmaceutical reform could control or reduced drug expenditure and total health
Inpatient total health expenditure in short term, expenditures gradually resumed growing again and reached or even exceeded their baseline levels of pre-reform period, indicating the effect became weakened or even faded out in long term.

Tang et al. [1] 2018 N/A Nanjing City, Jiangsu Province Secondary and Tertiary The markup ratio of drug sales The growth rate of medical service revenue Simple linear interrupted time series regressions Nanjing’s pricing and compensation reform has basically achieved the policy targets of eliminating the drug markups, promoting the growth of medical services revenue, and adjusting the structure of medical revenue. However, the growth rate of service revenue of hospitals varied significantly from one another.

Yin et al. [9] 2018 Time series study Shandong Province Secondary, tertiary, and urban/rural primary healthcare centers (PHCs) Total annual antibiotic expenditure Antibiotic expenditure per person per year Descriptive statistics The overall antibiotic expenditure increased over time in Shandong, China. However, the increase rate of expenditure began to decline in 2016, possibly related to the implementation of antibiotic stewardship initiatives.

Mao et al. [10] 2019 Penal study Hangzhou City, Zhejiang Province Primary (n=6), secondary (n=2), and tertiary (n=9) Average number of medicines Average number of antibiotics Average expenditure T test or Fisher exact test The average number of medicines per prescription, use of antibiotics, intramuscular (IM) injections
From 1995 to 2000, the number of prescriptions per prescription and intravenous (IV) injections decreased while the use of hormones increased. No significant change of the average medicine expenditure per prescription was observed. The problems of polypharmacy, overuse of antibiotics, intramuscular (IM) injections and intravenous (IV) injections and hormones still existed, however mitigated after the implementation of The National Essential Medicine Policy and the Zero Mark-up Policy.

Figures
Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

(CINAHL: Cumulative Index to Nursing and Allied Health Literature; OATD: Open Access Theses and Dissertations)

Figure 1

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram. (CINAHL: Cumulative Index to Nursing and Allied Health Literature; OATD: Open Access Theses and Dissertations)

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