PEER REVIEW HISTORY

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ARTICLE DETAILS

Title (Provisional)

R&D investment of Chinese chemical medicines companies under the national pooled procurement: a retrospective panel data analysis, 2013-2022

Authors

Lei, Qianrun; Wu, Qiyou; Wang, Zhitao; SUN, Jing; Liu, Yuanli

VERSION 1 - REVIEW

Reviewer	1
Name	Zhaohui, Zhu
Affiliation	Zhejiang Gongshang University
Date	23-Nov-2023
COI	None

The paper examines whether the recently implemented policy of National Pooled Procurement of off-patent medicines achieved its objective of fostering a competitive

pharmaceutical industry in China Though the authors make a lot of effort in this manuscript, it is unsuitable for publication in the BMJ Open for the following reasons:

1. Introduction

The introduction needs to adequately discuss how and why we planned to conduct this research, the future benefits of this research to upcoming scholars, and what the findings of this study are

2. Methods

The period involved in the study is long, and the model is too simple to avoid the impact of other factors on enterprise R&D and then test the impact of procurement policy on enterprise R&D; The control variables is relatively simple and may miss some important variables such as companies' corporate governance and the regional economic development.

3. Results and Discussion

(1) There is a big deviation between the research content and the research goal. The paper's objective is to exam "whether the recently implemented policy of National Pooled Procurement of off-patent medicines achieved its objective of fostering a competitive pharmaceutical industry in China". But in the first part of results "Average trends of financial performances of target companies", the average trends of financial performance among the target companies is analyzed firstly. Even if these financial indicators are related to the National Pooled Procurement, it cannot prove that these changes are due to the procurement policy through descriptive statistics analysis. So, the result "Interestingly, there was a reversal in the average ROA between 2020 and 2021, coinciding with the time when the procurement was institutionalized. This implies that the institutionalization of the procurement may have positively influenced the companies' profitability and output efficiency, leading to a favorable change in the ROA during that period (P14, 22-32) " is unreliable.

(2) In the second part of results "Average trends of R&D investment intensities among subgroups", the paper compares the average R&D investment intensity of successful bidders and that of unsuccessful bidders. And then the paper compares the average R&D investment intensity of companies engaged and not engaged in TCM production, and the companies engaged and not engaged in API production, which have little relevance to the objective of the paper.

(3) This study did not account for factors that may have influenced the results during the COVID-19 epidemic, it may have an important impact on the R&D investment and performance of the pharmaceutical industry.

(4) Though the the paper suggests "the intensified competition in the generics market

could play a significant role in reducing transaction costs and creating economies of scale for successful bidders through committed market share and advanced payment. Consequently, this dynamic incentivizes local pharmaceutical companies to prioritize R&D, positioning themselves for enhanced market competitiveness", the paper lacks further research on how National Pooled Procurement promotes R&D Investment Of the successful bidders.

Reviewer	2
Name	Hong, Xuezhi
Affiliation management	Beijing University of Chinese Medicine, school of
Date	26-Dec-2023
COI	no

It is suggested to further demonstrate the representativeness of 76 listed companies in the selected samples.

VERSION 1 - AUTHOR RESPONSE

Reviewer: 1

Dr. Zhu Zhaohui, Zhejiang Gongshang University

Comments to the Author:

The paper examines whether the recently implemented policy of National Pooled Procurement of off-patent medicines achieved its objective of fostering a competitive pharmaceutical industry in China Though the authors make a lot of effort in this manuscript, it is unsuitable for publication in the BMJ Open with the following reasons:

1. Introduction

The introduction needs to adequately discuss how and why we planned to conduct this research, the future benefits of this research to upcoming scholars, and what the findings of this study are

Authors' response:

The author revised the Introduction by strengthening the rationale and objective, and added the potential benefits of this study.

2. Methods

The period involved in the study is long, and the model is too simple to avoid the impact of other factors on enterprise R&D and then test the impact of procurement policy on enterprise R&D; The control variables is relatively simple and may miss some important variables such as companies' corporate governance and the regional economic development.

Authors' response:

First of all, the authors included seven covariates (ITR=inventory turnover rate, ATR= Asset turnover rate, ROA= Rate of return on total assets, capital density= net fixed assets/total assets, leverage ratio=total liabilities/total assets, enterprise size, and government subsidy) in the panel regression models. These covariates might influence the R&D investment and were selected based on existing literature. These covariates were listed in Table 1 with detailed explanations one by one, but not presented one by one in Table 2, in which we reported the regression results. This is mainly due to the considerations that, firstly, these variables were not the explanatory variables of interest; secondly, to make Table 2 more concise.

It is true that corporate governance and the regional economic development of individual companies were not included in the models, as well as many other variables that might potentially affect the R&D investment of companies. One reason is that these variables were not included in our cited reference literature; the other is that we do not have data access for these variables. However, non-inclusion of these variables in the regression models does not mean that the analyses were biased unacceptably. The panel regression allows controlling the effects of unobserved missing variables. The analytical approaches of fix-effect models help to reduce the bias due to the missing confounders to a certain extent. As presented in Table 2, the company fixed-effect regression (Model 2) automatically omitted all the time-invariant variables that reflect the inherent characteristics of the target companies, including corporate governance, etc. In addition, the time fixed-effect regression (Model 3) and the company fixed-effect model introduced with the year dummies (Model 4) also help to control the time-variant variables, like regional economic development.

3. Results and Discussion

(1) There is a big deviation between the research content and the research goal. The paper's objective is to exam "whether the recently implemented policy of National Pooled Procurement of off-patent medicines achieved its objective of fostering a competitive pharmaceutical industry in China". But in the first part of results "Average trends of financial

performances of target companies", the average trends of financial performance among the target companies is analyzed firstly. Even if these financial indicators are related to the National Pooled Procurement, it cannot prove that these changes are due to the procurement policy through descriptive statistics analysis. So, the result "Interestingly, there was a reversal in the average ROA between 2020 and 2021, coinciding with the time when the procurement was institutionalized. This implies that the institutionalization of the procurement may have positively influenced the companies' profitability and output efficiency, leading to a favorable change in the ROA during that period (P14, 22-32)" is unreliable.

Authors' response:

The authors revised the expression of the objective of this study at the end of the Introduction as follows: "There have been increasing concerns that significant price reductions might negatively affect R&D investment, which is not conducive to the sustainable and healthy development of the Chinese pharmaceutical industry. This study attempted to respond to such concerns with evidence about the changes in R&D investment before and after the procurement implementation. It is expected that the findings of this study will help to facilitate evidence-based decision-making for the improvement of the national pooled procurement policy."

The authors agree with the point raised by the reviewer that it is not reliable to conclude a causal effect simply based on the descriptive analysis of the trends. We revised the Results section and the Discussions section by removing the descriptions of the inventory turnover, asset turnover, and rate of return on total assets, as well as the original Figure 1. The original Figure 2 was renamed as Figure 1, which also showed the trend of R&D investment intensity of 76 target companies in each graph.

(2) In the second part of results "Average trends of R&D investment intensities among subgroups", the paper compares the average R&D investment intensity of successful bidders and that of unsuccessful bidders. And then the paper compares the average R&D investment intensity of companies engaged and not engaged in TCM production, and the companies engaged and not engaged in API production, which have little relevance to the objective of the paper.

Authors' response:

The authors have different opinions about the relevance of the subgroup analysis in terms of bidding status and engagement of TCM and API productions. As the reviewer pointed out in the previous points, many factors could potentially influence the R&D investment of the target companies, including bidding status and the engagement of TCM and API productions. The author noticed these variables were statistically significant from the time fixed-effect regression results (Model 3) (Table 2). Comparing the average trends of these variables among subgroups could help address the target companies' heterogeneity. Existing literature that analyzed the R&D investment intensity of Chinese pharmaceutical companies also considered these covariates.

(3) This study did not account for factors that may have influenced the results during the COVID-19 epidemic, it may have an important impact on the R&D investment and performance of the pharmaceutical industry.

Authors' response:

The authors fully agree with the point raised by the reviewer that the COVID-19 epidemic had an important impact on the R&D investment and the performance of the Chinese

pharmaceutical industry. And this was discussed in the Limitations. The authors considered that the impact of COVID-19 might be different for different types of Chinese pharmaceutical companies. During the epidemic, the companies that produce vaccines, test regent, and medical consumables might gain more significant market opportunities; the companies of chemical medicines were affected by the reduced volumes of medical diagnostics and treatments in health facilities due to the reduced number of health facility visits. The products included in the national pooled procurement are mainly chemical medicines, and the target companies of this study are also chemical medicines producers. Therefore, the target companies might experience similar macro influence of the epidemic, which could be controlled by the time fixed-effect. The panel regression with the time fixed-effect model could help to reduce the bias brought by the macro influence factors to certain extents.

(4) Though the paper suggests "the intensified competition in the generics market could play a significant role in reducing transaction costs and creating economies of scale for successful bidders through committed market share and advanced payment. Consequently, this dynamic incentivizes local pharmaceutical companies to prioritize R&D, positioning themselves for enhanced market competitiveness", the paper lacks further research on how National Pooled Procurement promotes R&D Investment of the successful bidders.

Authors' response:

The authors strengthened the discussions about how the national pooled procurement policy promotes R&D Investment of the successful bidders in the 4th, 5th and 6th paragraphs of the Discussion section. The successful bidders gain the advantages mainly from two points: One is the committed stable market share, and the other is the advanced payment. These enable them to achieve economy of scale with reduced unit production costs by alleviating personnel and the cost burden associated with the traditional decentralized marketing model. The economy of scale could help to reinforce the market position of the leading companies, potentially leading to a virtuous circle where their enhanced R&D capabilities and competitive pricing contribute to further market expansion and dominance.

The other point is the promised advance payments of 30-50% of the order value, providing successful bidders with a capital edge. The enhanced financial performances with quick sales and improved output efficiency reinforce the successful budders' market competitiveness, leading to a more concentrated market, which may further enhance the economy of scale for the dominant players.

Reviewer: 2

Dr. Xuezhi Hong, Beijing University of Chinese Medicine

Comments to the Author:

1. It is suggested to further demonstrate the representativeness of 76 listed companies in the selected samples.

Authors' response:

The target companies of this study were A-share listed Chinese chemical medicines companies that produce generics with validated quality and efficacy. This was due to the consideration of the considerable heterogeneity across all the Chinese pharmaceutical companies in terms of R&D. The other important reason is the data availability. A-share listed companies generally have a specific capacity for R&D, representing the core of a viable local pharmaceutical industry. The successful bidders had ever won the bidding of at least one round of the six national pooled procurements of chemical medicines by the end of 2022. The other suppliers were those who never participated in the pooled procurement or never won in any round of the national pooled procurement of chemical medicines by the end of 2022. The authors added a table in the Appendix to show the number of chemical medicines and the bidding status of the six rounds of national pooled procurement.

Reviewer: 3

Dr. Zoe Kelson, University of Exeter

Comments to the Author:

This retrospective study examines whether the recently implemented policy of National Pooled Procurement of off-patent medicines achieved its objective of fostering a competitive pharmaceutical industry in China.

Reviewer comments:

Abstract:

"Our panel data analysis investigated the association between the implementation of the National Pooled Procurement policy and the change in research and development (R&D) investment by Chinese pharmaceutical companies". The aim of the study is clearly stated.

"Fixed-effect panel regressions were then performed to explore the association between implementing the procurement and changes in the R&D investment intensity of the target companies" and "the Bootstrap hypothesis test method was employed to assess potential variations in the impact of procurement implementation across different subgroups. " The methods are succinctly described. "The findings indicate that the intensified competition in the generics market could play a significant role in reducing transaction costs and creating economies of scale for successful bidders through committed market share and advanced payment. Consequently, this dynamic incentivizes local pharmaceutical companies to prioritize R&D, positioning themselves for enhanced market competitiveness." [Abstract, Conclusions].

1. Can the authors please consider whether the stated conclusions are within scope of the data and analysis

undertaken in this study?

Authors' response:

The authors revised the stated conclusions in the Abstract and at the end of the manuscript: "This study found that the enthusiasm of Chinese chemical medicines companies to invest in R&D following the medicines regulatory reforms was not suppressed when the pilot pooled procurement was expanded and continued. The overall level of R&D investment intensity following the pilot was even higher than before the pilot during the whole observation time. The enhanced investment in R&D has been a distinctive feature of Chinese chemical medicines companies that position themselves with more substantial market competitiveness."

Methods:

2. "To account for potential heterogeneity among these companies, the same analysis was employed for different subgroups". Did the authors also consider adjusting for subgroups as covariates in a (random- or fixed- effects) multilevel model?

Authors' response:

Yes, as presented in Table 2, the authors included a series of covariates in the basic pooled OLS regression model and the time fixed-effect model. These covariates included bidding status, engagement of TCM and API productions, as well as the financial performance covariates of inventory turnover rate (ITR), asset turnover rate (ATR), return on total assets (ROA), capital density, leverage ratio, company size, and government subsidy. An explanation of these covariates was presented in Table 1. The time-invariant variables (bidding status, engaged in TCM production, and engaged in API production) were not included in the company fixed-effect model, as these were automatically omitted in the individual fixed-effect model.

3. "Bidding results from each round of the procurement were collected from the Sunshine Medical Procurement System". Financial performance data were retrieved from the China Stock Market & Accounting Research Database 20. Information about a company's involvement in TCM and API production was retrieved from WIND economic database". Can the authors please confirm if there was any missing data, and if so, how this was handled in the analysis?

Authors' response:

The authors added the following data description in the 2nd paragraph of the Samples and data source under the Methods section: "76 companies were included in the analyses. Among these, 52 were listed in the A-share in 2013, 61 were listed in 2014, 64 were listed in 2015, 65 were listed in 2016, and all 76 were listed in 2017. A total of 62 company*year observation units were not available for analysis. As soon as the target companies were listed, data of the dependent and the independent variables were all available for analysis. Considering that potential bias might be brought by the imputation of many missing data, we did not make any

imputation. In addition, the fixed-effects estimations help to mitigate the bias caused by the missing values to a certain extent."

4. "One pivotal component of the policies aimed at promoting generics competition is the national pooled procurement of off-patent medicines, hereafter referred to as 'the procurement'. This was initially piloted in 11 large cities during 2018 and 2019 and subsequently rolled out nationwide. As of June 2023, eight rounds of procurement have been implemented. The scope of procured products has progressively broadened, starting with a selected number of generics with validated quality and efficacy and their originators, and eventually encompassing products with high volume and value consumptions in the Chinese market" [Introduction]

and "The primary dependent variable of this study is R&D investment intensity, defined as the ratio of the amount of R&D investment to total revenue. The primary independent binary variable is the implementation of the procurement, categorized as 'before' and 'after'." Can the definition of the procurement variable please be clarified? For instance: What time period makes up 'before' and 'after'? Does this vary by city? How are rounds and scope of procurement accounted for and included in the analysis?

Authors' response:

The authors revised the definition of the national pooled procurement variable in the Variables section under the Methods as follows: "The primary independent binary variable was the implementation of the national pooled procurement, piloted in 2019, expanded nationwide and continued with another five rounds afterward, categorized as 'before 2019

' (assigned with 0) and 'after 2019' (assigned with 1)." This variable does not vary by

city; it only divided the observation time from 2013 to 2022 into two parts. The study design was a simple multiple panel regression, not an event study. The coefficient of this variable of the company fixed-effect regression was an estimation of the overall difference of the R&D investment intensity between the observation time before 2019 and after 2019, by controlling the inherent time-invariant variables (including the city level characteristics) and the time-variant covariates.

As for the rounds and the scope of the pooled procurement, as presented in the Appendix, there were two rounds of pooled procurement implemented in 2019 and 2021 respectively, and the scope of all six rounds of pooled procurements focused only on off-patent chemical medicines with competition of quality and efficacy re-validated generics. The target chemical entities vary in different rounds of the national pooled procurement, but the suppliers might be duplicated for different target entities and in different rounds of procurement. As some target entities are registered with multiple suppliers, and some companies might be involved in several rounds of procurement. With the available annual data and the current study design, it is not feasible to perform an event study to account for the effect of different rounds of procurement and different target entities.

5. With range, rounds, and scope of procurement in mind, did the authors consider modelling procurement as a restricted cubic spline rather than a binary variable?

Authors' response:

The authors agree with the reviewer's proposal that restricted cubic spline modeling can help analyze non-linear relationships. For many clinical risk factor estimations, when the relationship between the interested variables is a U-shape or in even more complicated scenarios, the restricted cubic spline modeling can describe the relationship accurately. However, the purpose of this study was not to distinguish the effect of different rounds of procurement. The overall difference in the R&D investment intensity before and after the pilot procurement already responded to the concerns as described in the Introduction section as follows: "significant price reductions might negatively affect R&D investment, which is not conducive to the sustainable and healthy development of the Chinese pharmaceutical industry."

In addition, since the target companies might be involved in any of the six rounds of the national pooled procurement, among which two rounds of procurement were implemented in 2019 and 2021, it is difficult to create an appropriate treatment group and control group with the available annual data to perform the causal effect estimation with the quasi-experimental study design. It is also difficult to identify appropriate knots to divide the range of values of the predictor, so as to fit separate regression lines between the knots.

6. "Several controlled variables were considered in the analysis. The first controlled variable is bidding results, categorized as '0' for unsuccessful bidders, indicating companies that have not been successful in any round of bidding during 2013 and 2022, and '1' for successful bidders, representing companies that have been successful in at least one round of bidding. Companies engaged in the production of TCM are defined as '1', while those not engaged in TCM production are defined as '0'. Similarly, companies involved in API production are labeled '1', and those not are labeled '0'. To account for other factors that might influence R&D investment performance, we included several financial performance variables as covariates based on existing studies. These variables include inventory turnover rate (ITR), asset turnover rate (ATR), and return on total assets (ROA)... Additionally, covariates such as capital density, leverage, enterprise size, and government subsidy were also incorporated". The authors do well to include control covariates in the model.

"Performed the ordinary least square (OLS) regression (Model 1) using the pooled unbalanced panel data from 2013 to 2022" and "To account for inherent attributes of companies that might affect R&D investment intensity differently in response to implementing the procurement, we introduced individual fixed-effect (Model 2)." and "To address the potential influence of macro-environment changes over time, we fitted the time fixed-effect model (Model 3)." The methods are clearly described, with model formulation shown. Can the authors please clarify why they chose to use fixed-effects and not random-effects?

Authors' response:

The fixed-effect model was selected based on the Hausman test result. The authors added one sentence at the beginning of the paragraph in front of Model 2 in the Statistical analysis under the Methods section as follows: "We adopted the fixed-effect model based on the result of the Hausman test (P<0.001)."

"To reduce the potential bias arising from small sample sizes in the subgroups, we employed the Bootstrap hypothesis test method with 1000 repeated sampling (with replacement)." and "These subgroups included successful bidders versus the other suppliers, companies engaged in TCM production versus those not, and companies involved in API production versus those not." A range of insightful subgroup analyses have been satisfactorily explored by the authors.

Results:

7. "Figure 1 displays the average trends of financial performance among the target companies from 2013 to 2022. Over this period, the average R&D investment intensity demonstrated an

overall increasing trend. However, there was a decline between 2018 and 2019, followed by a resumption of the growing trend (Figure 1a)." Additionally, did the authors consider further exploring the time-series nature of the data, to model and compare what might be expected over time versus what was observed after implementation of procurement?

Authors' response:

The authors agree with the point raised by the reviewer that the time-series data may help estimate the level and trend change of R&D investment and may also help compare what might be expected over time versus what was observed after the implementation of procurement. The authors had considered adopting the interrupted time series regression model to estimate the level and trend changes. However, the data were only available for 10 time points, and there were only three time points after 2019. It is not feasible to fit the appropriate ITS model, and it is also not feasible to project the trend after 2019. The authors added discussions about these in the Limitation.

8. "Table 2 Regression results of the target companies" and "Table 3 Results of subgroup regressions and bootstrap hypothesis tests". Can numbers and parentheses please be explained in each column heading?

Authors' response:

The authors added explanations of the numbers in the notes, and kept the explanations of the numbers in parentheses in the note. This is to avoid duplications and to keep concise of Table 2 and Table 3.

9. Can the authors please comment on the R² values, which appear to be quite small for all

three models?

Authors' response:

The R² values were the within-group R² for the fixed--effects panel data models. The values were basically around 0.4 to 0.5 for our study. Considering that the fixed effect regressions were based on panel data, these R² values were ok. R² of the fixed-effects panel data models differs from that of the linear regression models. As reported in other studies adopting the robust fixed-effect models, for example, Sarı E, Şencan Karakuş B, Demir E. Economic uncertainty and mental health: Global evidence, 1991 to 2019. SSM Popul Health. 2024 Jun 14;27:101691. doi: 10.1016/j.ssmph.2024.10169, which reported R² valued around 0.1 and even <0.1 for the fixed-effect models.

Moreover, the R^2 of the company fixed-effect model was larger than that of the pooled OLS regression model, and the R^2 of the company fixed-effect model with the year dummies was larger than 0.5. This suggested that the company fixed-effect model that controlled the individual inherent time-invariant characteristics achieved better fitness.

10. "NOTES: Cluster robust standard error in parentheses". Can the use of cluster robust standard errors please also be specified in the methods section?

Authors' response:

The authors added one sentence in the last paragraph of the Statistical analysis: "All the standard errors were reported as cluster robust standard errors."

11. "Figure 1 Average trends of financial performances of the target companies (2013-2022)" and "Figure 2 Average trends of R&D investment intensities of subgroups (2013-2022)". Can vertical lines indicating the range, rounds, and scope of procurement implementation please be included in these plots (or perhaps in a separate figure)?

Authors' response:

The authors considered that there were six rounds of national pooled procurement, and in 2019 and 2021, two rounds of procurement were implemented; it might be too complex to have all relevant information presented in one graph. The authors added a Table as an Appendix to present detailed information about the range, rounds, and scope of six rounds of pooled procurement.

Discussion:

12. "a more comprehensive analysis is required to establish a clear causal relationship between the institutionalization of procurement and the observed improvement in ROA" and "This study has several limitations. First, the target companies consisted exclusively of Chinese A-share listed pharmaceutical companies engaged in the production of generics with qualified quality and efficacy. As a result, these companies tend to be larger in size, better funded and have a stronger ability to invest in R&D compared to other types of Chinese pharmaceutical manufacturing companies. Therefore, caution should be exercised when generalizing the conclusions of this study to the broader pharmaceutical industry. Future studies that include non-listed companies will help enrich the evidence. Secondly, this study did not account for factors that may have influenced the results during the COVID-19 epidemic or the effects of the market authorization reforms for novel medicines. Additionally, internal factors, including the product portfolio, ownership structure, and composition of board members in the target companies, were not considered, which could introduce potential bias in the estimation". The authors acknowledge some substantial study limitations in the discussion, which may confound the analysis and interpretation of the model outcomes. Can a sensitivity analyses be conducted to help demonstrate the robustness of the study findings to the COVID-19 pandemic (analysing up to the start of the epidemic, for instance)?

Authors' response:

This study did not account for factors that might have influenced the R&D investment of Chinese chemical medicines companies during the COVID-19 epidemic. The authors introduced the year dummies into the company fixed-effect model and found that the coefficients of the year dummy in 2017 and afterward generally increased over time, with an exception in 2020. 2020 coincided with the emergence of the COVID-19 epidemic in China. However, the persistent increasing trend after 2019 did not seem consistent with the ups and downs of the epidemic in 2021 and 2022. Considering that the epidemic might generally have a common negative influence on Chinese chemical medicines companies due to reduced health facility visits, the panel regression with the time fixed-effect could help reduce the potential bias from the common macro-environment factors. Further studies are needed to validate this speculation. The authors added descriptions of Model 4 in the Statistical analysis under the Methods section, reported the results of the regression of Model 4 in the 3rd paragraph of the Methods section, and discussed the coefficients of the year dummies in the Limitation.

Conclusions:

13. "This study highlights its potential to stimulate R&D investment in Chinese pharmaceutical manufacturing companies that possess the required R&D and financial capacities." It is not clear that the study in its current form has been able to highlight this potential. Additional and alternative analyses, as mentioned in the reviewer comments above, may help to demonstrate the validity of this conclusion.

Authors' response:

The authors fully agree with the points raised by the reviewer, and the current data and study design cannot make any causal estimation between the implementation of the national pooled procurement and the R&D investment intensity of the target companies. The authors revised

the conclusions' statements, added feasible additional and alternative analyses, as suggested by the reviewer in the above comments, and attempted to validate the conclusions.

VERSION 2 - REVIEW

Reviewer	3
Name	Kelson, Zoe
Affiliation	University of Exeter, Mathematics
Date	16-Oct-2024
COI	

Many thanks to the authors for their considered responses, satisfactory clarifications, and appropriate revisions. I have no further comments.