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The impacts of government reimbursement negotiation on targeted anticancer medication price, volume and spending in China

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ABSTRACT

Introduction New targeted therapies have changed cancer treatment in the past decades. However, high prices of targeted anticancer medications have increased economic burden for both patients and health insurance systems. In July 2017, China implemented combined medication price negotiation and mandatory reimbursement policies for 15 targeted anticancer medications. This study assesses effects of the policy on hospital procurement prices, volumes and spending.

Methods Using a quasi-experimental interrupted time series design, we analysed procurement data from the Chinese Medical Economic Information of 789 public hospitals in 30 provinces between January 2016 and September 2018. The intervention group consisted of 15 targeted anticancer medications with negotiated prices in 2017. The comparison group consisted of six targeted anticancer medications without negotiated prices by 2018. The effective date of the policy was September 2017.

Results After the implementation of the 2017 medication price negotiation and reimbursement policy, cost per defined daily dose (DDD) of the 15 targeted anticancer medications dropped US$71.21 on average from an average US$169.24/DDD before (p=0.000). Compared with what would have happened without the intervention, cost/DDD of price-negotiated medications decreased by 48.9% (p=0.000), procurement volumes increased by 143.0% (p=0.000) and hospital medication spending decreased by 6.9% (p=0.146).

Conclusions The 2017 medication price negotiation and reimbursement policy decreased targeted medication procurement costs per DDD, increased volumes procured and at least temporarily contained spending. These changes should result in better access to and affordability of targeted anticancer medications in China.

Key questions

What is already known?

- As cancer burden is increasing across the world, high prices of new targeted anticancer medications have raised major concerns regarding access and affordability, especially in emerging and expanding universal coverage systems.
- It has been widely recommended that governments should use their bargaining power to reduce procurement prices of anticancer medicines.
- China has implemented in 2017 medication price negotiation as a criterion for mandatory insurance reimbursement. Impacts of the negotiation policy on targeted anticancer medication prices, volumes and spending are unknown.

What are the new findings?

- Using a quasi-experimental interrupted time series design, this study demonstrates that in China national medication price negotiation as a condition for mandatory insurance reimbursement decreased medication prices, increased volumes procured and controlled hospital spending on anticancer medications.

What do the new findings imply?

- China's approach to promoting affordability of new anticancer medications provides valuable experience for health policy decision-makers.

INTRODUCTION

With increasing incidence, cancers are a major public health problem worldwide.[1] Since 2010, cancers are the leading cause of death in China.[2] New targeted therapies have significantly changed the treatment of some cancers in the past decades.[3] However, high prices of targeted anticancer medications have increased economic burden for both patients and health insurance systems.[4]

To promote access to healthcare, including access to cancer care and anticancer medications, China has since 2009 implemented a series of linked policies (see box 1). As medications listed in the national reimbursement list must be paid at least in part by China's health insurance system,[5] including new medications in the National Reimbursement Drug List (NRDL) is the main approach for

Box 1 Main policies and actions of the Chinese government to promote medication access and affordability

March 2009: Beginning of comprehensive health system reforms
Aiming to establish an equitable and effective health system for all people (universal health coverage) by 2020,[44] the government established Basic Medical Insurance (BMI) coverage with a target of enrolling 90% of the population by 2010.[45]

November 2009: 2009 Edition of the National Reimbursement Drug List (NRDL) for the BMI
The NRDL is the guiding standard for BMI to pay for medications. Prior to 2017, experts created the NRDL based on safety, efficacy and need, without price negotiation of included products.[46]

February 2017: 2017 Edition NRDL[6]
Medications included in the February 2017 Edition NRDL were based on expert review.

July 2017: First-round of drug price negotiations for the 2017 Edition NRDL[17]
The Chinese government conducted price negotiations with manufacturers whose medications had been suggested for inclusion in the NRDL based on expert review. Thirty-six medications were listed in the NRDL after successful price negotiations in July 2017 with negotiated medication maximum procurement prices reduced by 44% on average.[47]

October 2018: Second round of drug price negotiations for the 2017 Edition NRDL[48]
The Chinese government conducted the second round of price negotiations in October 2018. Seventeen medications were added to the NRDL in October 2018 with negotiated medication maximum procurement prices reduced by 57%.[49]

December 2018: BMI enrolment
The BMI enrolled more than 95% of Chinese citizens by the end of 2018.[33]

improving access and patient affordability. Before 2017, medications were listed in the NRDL based on expert review and some would not be recommended due to high prices. Aiming to increase coverage by the Basic Medical Insurance (BMI) while containing BMI spending, China has since 2017 used medication price negotiation as one of the conditions for medication inclusion in the NRDL (box 1). Following national price negotiations and inclusion of medicines in the NRDL, provinces are required to update their Provincial Reimbursement Drug Lists (PRDLs).[6] All price-negotiated medications are mandated to be listed in the PRDLs.[7] Public sector hospitals must purchase these medications via the provincial procurement websites and negotiated prices are maximum prices. City or county-level insurance funding is then required to reimburse medication costs based on the negotiated prices (minus beneficiaries' copayments).

Effects of centralised negotiation or other regulation approaches on curbing medication prices have been described in China[8] and other countries.[8–11] Previous studies have also shown that insurance coverage of medications without price negotiation led to a rise in medication use volumes as well as expenditures.[12 13] Expectations are that China's combined price negotiation and mandatory reimbursement policies decrease procurement cost per medication unit and increase utilisation and thereby improve access to and affordability of expensive targeted anticancer medications. In this study, we used an interrupted time series (ITS) design and segmented regression analyses to assess the effects of the 2017 national price negotiations on targeted anticancer medication cost per defined daily dose (DDD), hospital procurement volumes and spending in China.

METHODS

Study design

We used an ITS design covering the period from January 2016 to September 2018 to analyse changes in daily costs and hospital purchasing volumes of and spending on 15 targeted anticancer medications for which procurement prices were negotiated in July 2017 and which were subsequently included in the NRDL and PRDLs.[14–16] The sample included all targeted anticancer medications identified from the total national price-negotiated medications in 2017.[17] To further strengthen the ITS design, we selected as comparison group all targeted anticancer medications approved by the National Medical Products Administration (NMPA) before 2016 and which were not price negotiated by the end of the study period. Provinces in mainland China were mandated to list the 2017 price-negotiated medications in their PRDLs before 31 July 2017. Considering that policy effects may lag, we selected September 2017 as the time point when price negotiation and mandatory reimbursement would have taken effect.

Data and outcome measures

We used hospital procurement data captured in the Chinese Medicine Economic Information (CMEI) database. The CMEI captures monthly medicines purchases reported by 594 tertiary and 195 secondary public sector hospitals,[18] which respectively accounted for 28.1% and 3.2% of tertiary and secondary public hospitals in China in 2017.[19]

In this study, we assessed three main outcome measures: cost per DDD, procurement volume and spending. We calculated cost per DDD of each product, for example, the ratio of procurement spending and volume procured (in DDDs), as a surrogate measure of actual medication price paid. DDDs, recommended by WHO for drug utilisation monitoring and research,[20] constituted the measure of purchased volumes. DDDs were the number of daily doses of each medication based on dosage regimens recommended in the manufacturers' product labels and as approved by the NMPA.[21] We prepared data for ITS analysis by summing up monthly hospital spending and DDDs of medications procured between January 2016 and September 2018 and calculated average cost per

DDD for each medication and across the intervention and comparison groups.[22] Hospital average procurement volumes and spending were calculated to reflect drug consumption. All expenditures were converted to 2016 US dollars using the Consumer Price Index and average annual exchange rates.[23 24]

Statistical analysis

Statistical model

We used segmented regression models to assess whether the 2017 national medication price negotiation policy affected hospital procurement costs and consumption of intervention and comparison group medications across 30 of 31 provinces (data of Qinghai province was not available).[14 25] The regression model assumes the following form.

$$Y_t = \beta_0 + \beta_1 T_t + \beta_2 X_t + \beta_3 T_t X_t + \beta_4 Z + \beta_5 Z T_t + \beta_6 Z X_t + \beta_7 Z X_t T_t + \varepsilon_t$$

Y_t is the dependent variable measured at each monthly time point t, T_t is the time since the start of the study, X_t is a dummy variable representing the intervention (preintervention periods 0, otherwise 1), and $X_t T_t$ is an interaction term of the time and intervention.[26] Z is a dummy variable to denote the cohort assignment (treatment or comparison group). When a comparison group is available, Z for the intervention group is set as 1.[27]

We performed the Durbin-Watson test to estimate residual autocorrelations[28] and used the Cochrane-Orcutt autoregression procedure to correct for first order serially correlated errors when needed.[29] The results of the segmented regression models are presented as changes in the levels and slopes of average daily cost, DDDs and spending after the implementation of 2017 medication price negotiation policy. In addition, based on level and trend change parameter estimates, we calculated absolute and relative differences in outcomes at 6 months after the intervention as well as at the end of the observation period compared with what would have happened without the policy (the counterfactual).[14 26]

To analyse policy impacts on use and costs of and spending on different medications, we conducted the ITS regression analyses separately for individual medications. Pearson correlation coefficient was also estimated to examine the correlation between relative price change at the intervention time and medication launch time in China.

Statistical analysis software

All models were run using the statistical software Stata/MP V.14.0 (Revision 2 April 2015), StataCorp.

Patient and public involvement

Patients were not involved in this study.

RESULTS

Fifteen targeted anticancer medications had price negotiations in 2017 and constituted the intervention group. The comparison group consisted of all six targeted anticancer medications included in the CMEI database for which prices were not negotiated and which were not listed in the NRDL by the end of the observation period (table 1, for more detailed information, please see online supplemental appendix 1). Launch years of the intervention and comparison group medications ranged from 2000 to 2015. The majority of intervention group medications were indicated for the most common solid tumours in China, such as lung cancer (N=3), breast cancer (N=2), kidney cancer (N=2). Prices of four medications for haematological malignancies including lymphoma and multiple myeloma treatment were also negotiated in 2017. As for the comparison group, 4 medications were indicated for solid tumours including lung cancer, colorectal cancer and kidney cancer, and two medications were leukaemia therapies.

Impacts on cost per DDD, volume and spending

The aggregated controlled ITS analysis showed that the cost per DDD of medications in the intervention group decreased abruptly and significantly in September 2017 while the cost of comparison group medications did not. (figure 1A). With the implementation of the negotiation policy, cost per DDD of the fifteen 2017 price-negotiated medications had dropped by US\$71.21 ($p<0.01$) on average from an average pre-policy cost of US\$169.24/DDD just before the policy change (table 2). At 6 months after the price-negotiation policy, cost per DDD of negotiated medications had dropped by US\$76.91 ($p<0.01$) and the relative change compared with expected cost without the policy was −48.9%. When the comparison group was included in the model, at the end of the observation period, average cost per DDD of the intervention group medications had declined by US\$88.36 ($p<0.01$) compared with the estimated cost without price negotiation. Table 2 lists coefficients for level and trend changes for all outcome measures.

After the negotiation policy, the procured volume of price-negotiated medications increased significantly in terms of level and trend (figure 1B)(). Meanwhile, the volume of comparison group medication was slightly decreasing ($p<0.05$). (table 2) At the intervention point, the consumption volume of the price-negotiated medications showed a significant increase ($p<0.01$). (figure 1B) Compared with what would have happened without the intervention, the volume of use (in DDDs) had increased by 85.6% at 6 months after the negotiation policy took effect and by 143.0% at the end of the observation period (table 2).

Figure 1C illustrates that, with the price decrease after the negotiation policy, medication spending dropped significantly at the time of the policy implementation. Given increasing consumption volumes, medication spending over time increased and the change in spending by the end of observation period was slightly less than predicted spending without the negotiation (p=0.146). Compared with what would have been expected without the negotiation, spending on intervention group medications had decreased by 19.6% at 6 months after the

Table 1 Characteristics of targeted anticancer medication in the intervention group and comparison group

No	Generic name	Launch time in China	Indication
Intervention group			
1	Rituximab	April 2000	Lymphoma
2	Trastuzumab	September 2002	Breast cancer; stomach cancer
3	Bortezomib	February 2005	Multiple myeloma; lymphoma
4	Recombinant Human Endostatin	September 2005	Lung cancer
5	Erlotinib	April 2006	Lung cancer
6	Sorafenib	September 2006	Liver cancer; kidney cancer; thyroid cancer
7	Nimotuzumab	April 2008	Nasopharynx cancer
8	Bevacizumab	February 2010	Colorectal cancer; lung cancer
9	Fulvestrant	June 2010	Breast cancer
10	Lapatinib	January 2013	Breast cancer
11	Everolimus	January 2013	Brain cancer; kidney cancer; pancreatic neuroendocrine tumor
12	Lenalidomide	January 2013	Multiple myeloma
13	Apatinib	October 2014	Stomach cancer
14	Chidamide	December 2014	Lymphoma
15	Abiraterone	May 2015	Prostate cancer
Comparison group			
1	Cetuximab	July 2006	Colorectal cancer
2	Sunitinib	October 2007	Kidney cancer; stomach cancer; pancreatic neuroendocrine tumor
3	Pegaspargase	January 2009	Leukaemia
4	Nilotinib	July 2009	Leukaemia
5	Crizotinib	January 2013	Lung cancer
6	Axitinib	April 2015	Kidney cancer

intervention and 6.9% by the end of the observation period. Spending on comparison group medications slightly increased before September 2017 and decreased after the intervention (table 2).

Impacts on individual medication costs per DDD, volumes, spending

For individual medications, our results show that all price-negotiated medications had significant decreases in cost per DDD, ranging from 23.4% to 69.9% by the end of the observation period. After implementation of the

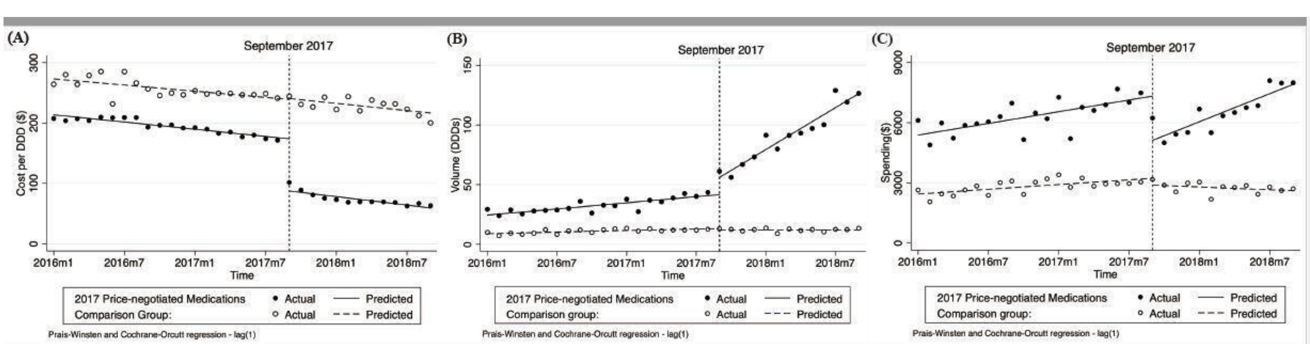

Figure 1 (A) Observed and predicted cost per DDD of 2017 price-negotiated and comparison group medications. (B) Observed and predicted hospital average volume (in DDDs) of 2017 price-negotiated and comparison group medications. (C) Observed and predicted hospital average spending ($) on 2017 price-negotiated and comparison group medications. DDDs, defined daily doses.

Table 2 Changes in levels and trends of and absolute and relative changes in medication cost per DDD, procurement volume and spending, for 2017 price-negotiated and comparison group medications

2017 negotiation medications	2017 price-negotiated medications			Comparison group medications			Change relative to comparison group		
	Coefficient	P value	95% CI	Coefficient	P value	95% CI	Coefficient	P value	95% CI
Cost per DDD (US$/DDD)*									
Baseline level	215.58	0.000	204.37 to 226.80	274.83	0.000	267.18 to 282.48	−59.16	0.000	−68.55 to −49.77
Baseline trend	−2.24	0.000	−3.11 to −1.37	−1.71	0.000	−2.35 to −1.07	−0.29	0.463	−1.08 to 0.50
Level change after intervention	−71.21	0.000	−81.56 to −60.85	1.54	0.801	−10.81 to 13.89	−87.69	0.000	−102.76 to −72.61
Trend change after intervention	−0.95	0.316	−2.85 to 0.95	−0.24	0.723	−1.63 to 1.14	−0.05	0.951	−1.75 to 1.64
Absolute change at 6 months after intervention	−76.91	0.000	−90.25 to −63.57	0.08	0.989	−11.60 to 11.76	−88.00	0.000	−102.32 to −73.68
Relative change at 6 months after intervention	−48.88	0.000	53.71 to 44.04	0.04	0.989	4.82 to 4.89	−32.94	0.000	−36.24 to −29.64
Absolute change by end of observation period	−83.56	0.000	−107.86 to −59.27	−1.62	0.848	−18.70 to 15.47	−88.36	0.000	−109.37 to −67.36
Relative change by end of observation period	−58.99	0.000	69.05 to 48.92	−0.74	0.846	8.19 to 6.71	−33.33	0.000	−38.55 to −28.11
Volume (no of DDDs)*									
Baseline level	23.69	0.000	20.01 to 27.37	8.76	0.000	7.83 to 9.70	14.92	0.000	11.21 to 18.64
Baseline trend	0.86	0.000	0.55 to 1.17	0.22	0.000	0.14 to 0.30	0.64	0.000	0.33 to 0.95
Level change after intervention	9.38	0.003	3.45 to 15.31	−1.11	0.143	−2.62 to 0.40	10.49	0.001	4.51 to 16.48
Trend change after intervention	4.99	0.000	4.33 to 5.66	−0.21	0.017	−0.38 to −0.04	5.20	0.000	4.53 to 5.88
Absolute change at 6 months after intervention	39.35	0.000	33.73 to 44.97	−2.36	0.002	−3.79 to −0.94	41.72	0.000	36.04 to 47.39
Relative change at 6 months after intervention	85.59	0.000	65.26 to 105.93	−16.41	0.000	−24.65 to −8.18	164.19	0.000	82.47 to 245.92
Absolute change by end of observation period	74.31	0.000	66.09 to 82.54	−3.83	0.001	−5.92 to −1.74	78.14	0.000	69.84 to 86.45

Continued

Table 2 Continued

2017 negotiation medications	2017 price-negotiated medications			Comparison group medications			Change relative to comparison group		
	Coefficient	P value	95% CI	Coefficient	P value	95% CI	Coefficient	P value	95% CI
Relative change by end of observation period	142.98	0.000	110.18 to 175.78	−24.04	0.000	−34.47 to −13.62	261.47	0.000	134.94 to 387.99
Spending (US$)*									
Baseline level	5279.02	0.000	4892.18 to 5665.86	2408.59	0.000	2199.23 to 2617.96	2879.15	0.000	2449.58 to 3308.72
Baseline trend	97.36	0.000	64.96 to 129.76	38.78	0.000	21.25 to 56.31	57.75	0.002	21.77 to 93.73
Level change after intervention	−2347.96	0.000	−2972.24 to −1723.67	−270.61	0.110	−606.29 to 65.07	−2061.56	0.000	−2754.26 to −1368.86
Trend change after intervention	135.79	0.000	65.81 to 205.77	−62.48	0.002	−100.30 to −24.65	198.35	0.000	120.66 to 276.05
Absolute change at 6 months after intervention	−1533.22	0.000	−2123.59 to −942.85	−645.46	0.000	−964.59 to −326.33	−871.43	0.010	−1526.98 to −215.87
Relative change at 6 months after intervention	−19.63	0.000	−25.72 to −13.54	−18.89	0.000	−26.46 to −11.32	−22.32	0.000	−34.13 to −10.51
Absolute change by end of observation period	−582.68	0.178	−1446.50 to 281.13	−1082.79	0.000	−1551.16 to −614.41	517.06	0.285	−442.46 to 1476.58
Relative change by end of observation period	−6.86	0.146	−16.12 to 2.39	−29.36	0.000	−38.99 to −19.72	12.00	0.346	−12.98 to 36.98

US$ in 2016
*Except for relative changes which are expressed in percent.
CI, confidence interval; DDD, defined daily doses.

negotiation policy, consumption volumes of 14 of the 15 medications (except bortezomib), trended significantly upward. (table 3 and online supplemental appendix 2) By the end of the observation period, the Pearson correlation coefficient between the relative price change and medication launch date was 0.309 (p=0.262, online supplemental appendix 2.1.2).

Before September 2017, 12 of 15 medications in the intervention group showed an increasing trend in procurement spending. After implementation of the negotiation policy, trends in spending on erlotinib, nimotuzumab and everolimus increased while spending on bortezomib decreased (online supplemental appendix 2.3). At 6 months after the intervention, spending on five price-negotiated medications was significantly lower than spending estimated without the policy (table 3).

DISCUSSION

Principal findings

Our results indicate that the introduction of the Chinese medication price negotiation and reimbursement policies led to significant decreases in cost per DDD and sharp increases in procured volumes of targeted anticancer medications, while at least temporarily containing overall spending on these medications.

The increasing economic burden of cancer treatments has become a source of worldwide concern for patients, prescribers, payers and policy-makers.[30] Various approaches have been proposed to mitigate effects of increasing drug prices.[31 32] Aiming to improve access to healthcare and medications, the Chinese government published the Opinions on Deepening Health System Reform in 2009, a political commitment to establishing an accessible, equitable, affordable, and efficient health system to cover all people by 2020.[33] Insurance coverage expansion and better medication access were two foci of the 2009 reforms.[34] The 2017 medication price negotiation and mandatory reimbursement policies jointly targeted both policy goals. Prior to 2017, most insured patients needed to pay for expensive targeted anticancer medications entirely out-of-pocket (OOP) except in few provinces or cities which had included the medications in their reimbursement lists.[5] To improve patient and system affordability and decrease health inequity, the Chinese government implemented a series of policies, including reimbursement-linked central medication price negotiations.[7]

We found that after national medication price negotiations in 2017, procurement volumes of all price-negotiated anticancer medications increased abruptly and significantly, except for bortezomib for which use increased initially and declined in 2018. Nonetheless, cost per DDD of all price-negotiated medication decreased between 17.3% and 78.5% by the end of the study period regardless of duration of the drugs on the Chinese market. Increased volumes of use suggest that patients' access to these cancer medications may have improved.[35]

In addition to price reduction, insurance coverage should have further improved affordability of expensive medications, as demonstrated before.[13 36] A previous study showed that estimated patient OOP spending decreased after a patient assistance programme in Zhejiang Province, China.[37] However, challenges to equitable access likely remain in China since insurance schemes differ in the amounts of patient copayments.[38 39] Further study, based on individual-level data, including claims data, is needed to evaluate equity in access to and quality of use of new anticancer medications following price and reimbursement negotiations.

With price reductions and volume increases, our study showed that spending on targeted anticancer medications in the intervention group did not increase 1 year after the policy took effect. Considering the significant increase in use of most of the sample medications, further follow-up is needed to estimate the long-term policy effects, including the impact on insurance budgets.

New anticancer medications come to markets at high and increasing prices and many with limited evidence of benefit at time of approval.[40 41] It is therefore imperative for payers to negotiate prices, to assess whether new cancer therapies result in the expected clinical benefits, and to estimate the opportunity costs of cancer therapy spending in health and social systems. Our results are consistent with previous studies that have demonstrated price negotiation as a strategy to improve medication affordability in both developed and low/middle-income countries.[42 43] With more bargaining power, centralised national price negotiation seems more effective in constraining medication prices.[9] While impacts of the policy changes on access to, quality, and outcomes of cancer care require further study, China's reimbursement-linked cancer medication price negotiation approach may constitute a valuable experience for healthcare decision-makers elsewhere.

Strengths and limitations

To our knowledge, this is the first analysis to evaluate impacts of national reimbursement-linked price negotiations on targeted cancer medication costs, volumes and spending in China. We used an ITS design, a quasi-experimental approach for evaluating the effects of interventions, increasing internal validity. In addition, we strengthened the ITS design by adding a comparison group to separate intervention effects from other potential influences on the outcomes that may have occurred at the same time as the price negotiations.

This study has several limitations related to its data source. First, our study is based on aggregated medication purchase data of hospitals. We, therefore, cannot assess access in terms of numbers of patients treated or affordability in terms of OOP spending. In addition, we cannot assess whether treatment for patients with indications for bortezomib changed to explain the volume decline of that medication in 2018. Third, few targeted anticancer medications were available in China before

Table 3 Changes in levels and trends of, and absolute and relative changes in individual price-negotiated medication cost per DDD, procurement volume and spending

	Baseline		Change after intervention		Change 6 months after intervention		Change at the end of observation	
Price-negotiated medications	**Level**	**Trend**	**Level**	**Trend**	**Absolute**	**Relative (%)**	**Absolute**	**Relative (%)**
Cost per DDD (US$/DDD)								
Trastuzumab	155.57***	−1.65***	−55.75***	−0.26***	−57.29***	−50.83	−59.08***	−58.40
Bortezomib	460.65***	−5.55***	−108.07***	−0.23***	−109.47***	−34.59	−111.11***	−40.02
Recombinant human endostatin	228.69***	−2.02***	−35.62***	0.58***	−32.12***	−18.24	−28.04***	−17.31
Erlotinib	94.15***	−1.87***	−22.69***	1.02***	−16.58***	−36.48	−9.46	−29.25
Sorafenib	246.21***	−1.23*	−111.12***	−2.51***	−126.16***	−58.87	−143.7***	−69.85
Nimotuzumab	146.75***	−1.98***	−26.46***	0.57***	−23.02***	−24.20	−19.01	−23.40
Rituximab	951.44***	−7.49***	−215.69***	3.79***	−192.94***	−25.50	−166.4***	−23.62
Bevacizumab	198.88***	−1.94***	−64.31***	−0.58***	−67.80***	−45.68	−71.88***	−53.30
Fulvestrant	26.83***	−0.08***	−13.30***	−0.05***	−13.63***	−55.05	−14.01***	−57.89
Lapatinib	86.40***	−0.10	−24.98***	−3.09***	−43.52***	−52.00	−65.15***	−78.52
Everolimus	75.30***	−0.33***	−27.16***	0.12***	−26.46***	−39.63	−25.63***	−39.76
Lenalidomide	185.76***	−0.02	−114.32***	−0.69***	−118.43***	−63.94	−123.23***	−66.59
Apatinib	105.38***	−0.24**	−35.50***	−0.15***	−36.43***	−36.74	−37.52***	−38.49
Chidamide	144.03***	−0.64***	−38.90***	−0.14***	−39.74***	−31.19	−40.73***	−33.13
Abiraterone	187.17***	−0.79***	−93.69***	0.72***	−89.38***	−53.67	−84.35***	−52.39
Volume (no of DDDs)								
Trastuzumab	93.35***	3.75	−23.27	33.63***	178.52***	93.59	413.94***	190.79
Bortezomib	7.89***	0.51***	17.98***	−1.34***	9.96***	47.00	0.60	2.41
Recombinant human endostatin	21.89***	0.31**	6.76**	0.4***	9.17***	30.70	11.99***	37.44
Erlotinib	30.23***	0.53***	2.35	1.37***	10.57***	24.09	20.17***	42.39
Sorafenib	21.67***	0.29	12.96	5.78***	47.64***	163.19	88.10***	282.22
Nimotuzumab	26.14***	0.34	17.74***	2.34***	31.77***	90.68	48.13***	128.60
Rituximab	8.41***	0.29***	2.34	1.53***	11.53***	72.11	22.26***	123.44
Bevacizumab	32.77***	1.97***	19.62***	15.05***	109.93***	130.83	215.3***	220.08
Fulvestrant	41.79***	0.38	34.09***	16.7***	134.26***	260.44	251.14***	463.54
Lapatinib	10.25*	0.75	−7.02	4.46***	19.77**	66.53	51.02***	145.97
Everolimus	13.27***	−0.10	−0.01	0.41***	2.44	22.74	5.30**	52.70
Lenalidomide	5.84***	0.21	−5.54*	2.3***	8.29***	72.69	24.42***	189.26
Apatinib	5.34***	1.47***	0.48	1.37***	8.69***	19.96	18.27***	33.94
Chidamide	−0.30	0.17**	4.29***	0.63***	8.07***	198.04	12.49***	237.57

Continued

Table 3 Continued

Price-negotiated medications	Baseline		Change after intervention		Change 6 months after intervention		Change at the end of observation	
	Level	Trend	Level	Trend	Absolute	Relative (%)	Absolute	Relative (%)
Abiraterone	3.92*	0.19	8.79**	6.56***	48.17***	549.62	94.12***	934.69
Spending (US$)								
Trastuzumab	15377.32***	310.38**	−12360.62***	1108.81***	−5707.79**	−24.34	2053.84	8.02
Bortezomib	3911.54***	128.15***	1507.93***	−423.41***	−1032.53**	−14.25	−3996.39***	−49.09
Recombinant human endostatin	4983.48***	21.99	−276.99	37.53***	−51.83	−0.93	210.86	3.69
Erlotinib	2970.76***	−32.48***	−833.64***	40.52***	−590.52**	−27.77	−306.87	−16.16
Sorafenib	5306.88***	37.32*	−1882.34***	281.62***	−192.60	−3.07	1778.75***	27.20
Nimotuzumab	3974.38***	−16.77	−0.72	157.25***	942.80	26.65	2043.57**	59.74
Rituximab	8350.76***	171.62***	−2785.27***	804.79***	2043.47***	15.95	7676.99***	54.78
Bevacizumab	6962.73***	258.54***	−4440.06***	719.03***	−125.89	−0.92	4907.31***	31.67
Fulvestrant	1126.59***	5.97	−247.60	164.26***	737.93***	57.57	1887.71***	142.63
Lapatinib	877.3***	64.37**	−682.04	−31.6***	−871.64***	−34.17	−1092.84	−36.41
Everolimus	997.63***	−11.09*	−296.67**	20.01***	−176.58	−24.89	−36.48	−5.77
Lenalidomide	1201.93***	29.48	−1353.46***	114.9***	−664.09	−33.74	140.19	6.45
Apatinib	596.74***	145.21***	−1171.08***	9.64***	−1113.27***	−25.46	−1045.82***	−19.41
Chidamide	−44.18	15.7**	443.86***	42.48***	698.76***	192.00	996.14***	210.24
Abiraterone	735.93***	30.16*	−54.39	483.01***	2843.68***	187.08	6224.77***	359.58

US$ in 2016.
*P<0.05, **p<0.01, ***p<0.001.
CI, confidence interval; DDD, defined daily doses.

2016 and the comparison group is imperfect in that intervention and comparison group targeted anticancer medications have different indications. Different incidences of the diseases for which the medications are indicated may influence changes in use and spending over time. However, the quasi-experimental design we used controls for preintervention levels and trends of medication costs, use and spending.

Further research is needed to evaluate the actual financial burden of new anticancer medications on households and the health system and clinical outcomes among patients after the implementation of the policy.

CONCLUSION

Our results suggest that the 2017 medication price negotiation policy, linked to mandatory reimbursement, significantly changed costs and use of and spending on selected anticancer medications. The decline in per-unit medication procurement costs combined with at least partial coverage by the BMI should improve patients' access to these anticancer medications, although this remains to be demonstrated.

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REFERENCES

1 GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the global burden of disease study 2016. *Lancet* 2017;390:1151–210.
2 Chen W, Zheng R, Baade PD, *et al*. Cancer statistics in China, 2015. *CA Cancer J Clin* 2016;66:115–32.
3 Sledge GW. What is targeted therapy? *J Clin Oncol* 2005;23:1614–5.
4 Shih Y-CT, Xu Y, Liu L, *et al*. Rising prices of targeted oral anticancer medications and associated financial burden on Medicare beneficiaries. *J Clin Oncol* 2017;35:2482–9.
5 Guan X, Zhang Y, Wushouer H, *et al*. Differences in reimbursement listing of anticancer therapies in China: an observational study. *BMJ Open* 2020;10:e031203–e03.
6 Notice of the Ministry of Human Resources and Social Security on Issuing the National Drug Catalog for Basic Medical Insurance, Work-Related Injury Insurance, and Maternity Insurance [updated 21 Feb 2017]. Available: http://www.mohrss.gov.cn/gkml/zlbmxgwj/ylbx_3063/201702/t20170223_266775.html [Accessed Jun 2021].
7 Tang M, Song P, He J. Progress on drug pricing negotiations in China. *Biosci Trends* 2020;13:464–8.
8 Guan X, Wushouer H, Yang M, *et al*. Influence of government price regulation and deregulation on the price of antineoplastic medications in China: a controlled interrupted time series study. *BMJ Open* 2019;9:e031658.
9 Berkemeier F, Whaley C, Robinson JC. Increasing divergence in drug prices between the United States and Germany after implementation of comparative effectiveness analysis and collective price negotiations. *J Manag Care Spec Pharm* 2019;25:1310–7.
10 Moye-Holz D, van Dijk JP, Reijneveld SA, *et al*. Policy approaches to improve availability and affordability of medicines in Mexico - an example of a middle income country. *Global Health* 2017;13:53.
11 Limwattananon C, Waleekhachonloet O. Access to and price trends of antidiabetic, antihypertensive, and antilipidemic drugs in outpatient settings of the universal coverage scheme in Thailand. *PLoS One* 2019;14:e0211759.
12 Peng Y-L, Lee C-T, Tain Y-L, *et al*. The impact of adoption of a new urate-lowering agent on trends in utilization and cost in practice. *PLoS One* 2019;14:e0221504.
13 Garabedian LF, Ross-Degnan D, Ratanawijitrasin S, *et al*. Impact of universal health insurance coverage in Thailand on sales and market share of medicines for non-communicable diseases: an interrupted time series study. *BMJ Open* 2012;2. doi:10.1136/bmjopen-2012-001686. [Epub ahead of print: 28 11 2012].
14 Wagner AK, Soumerai SB, Zhang F, *et al*. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther* 2002;27:299–309.
15 Sun J, Wei Q, Zhou Y, *et al*. A systematic analysis of FDA-approved anticancer drugs. *BMC Syst Biol* 2017;11:87.
16 Limaverde-Sousa G, Sternberg C, Ferreira CG. Antiangiogenesis beyond VEGF inhibition: a journey from antiangiogenic single-target to broad-spectrum agents. *Cancer Treat Rev* 2014;40:548–57.
17 Ministry of Human Resources and Social Security. Notice of the Ministry of Human Resources and Social Security on Including 36 Drugs in the National Reimbursement Drug List for Basic Medical Insurance, Work-Related Injury Insurance, and Maternity Insurance 2017 [updated July 19, 2017]. Available: http://www.mohrss.gov.cn/SYrlzyhshbzb/shehuibaozhang/zcwj/yiliao/201707/t20170718_274153.html [Accessed June 2021].
18 Guan X, Tian Y, Ross-Degnan D, *et al*. Interrupted time-series analysis of the impact of generic market entry of antineoplastic products in China. *BMJ Open* 2018;8:e022328–e28.
19 China National health accounts report: China National health development research center 2018.
20 WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2019. 2019.
21 National Medical Products Administration. Available: http://app1.sfda.gov.cn/datasearchcnda/face3/base.jsp?tableId=25&tableName=TABLE25&title=%B9%FA%B2%FA%D2%A9%C6%B7&bcId=152904713761213296322795806604 [Accessed Jan 2020].
22 O'Donnell A, Anderson P, Jané-Llopis E, *et al*. Immediate impact of minimum unit pricing on alcohol purchases in Scotland: controlled interrupted time series analysis for 2015-18. *BMJ* 2019;366:l5274.
23 National Bureau of Statistics of China. Available: http://data.stats.gov.cn/easyquery.htm?cn=A01 [Accessed Jun 2021].
24 Fu H, Li L, Yip W. Intended and unintended impacts of price changes for drugs and medical services: evidence from China. *Soc Sci Med* 2018;211:114–22.
25 Jandoc R, Burden AM, Mamdani M, *et al*. Interrupted time series analysis in drug utilization research is increasing: systematic review and recommendations. *J Clin Epidemiol* 2015;68:950–6.

26 Zhang F, Wagner AK, Soumerai SB, *et al*. Methods for estimating confidence intervals in interrupted time series analyses of health interventions. *J Clin Epidemiol* 2009;62:143–8.
27 Linden A. Conducting interrupted time-series analysis for single- and multiple-group comparisons. *Stata J* 2015;15:480–500.
28 Durbin J, Watson GS. Testing for serial correlation in least squares regression. I. *Biometrika* 1950;37:409–28.
29 Kutner MH, Nachtsheim C, Neter J. *Applied linear regression models*. 4th ed. New York; Boston: McGraw-Hill/Irwin, 2004.
30 World Health Organization. *Technical report: pricing of cancer medicines and its impacts: a comprehensive technical report for the world health assembly resolution 70.12: operative paragraph 2.9 on pricing approaches and their impacts on availability and affordability of medicines for the prevention and treatment of cancer*. Geneva: World Health Organization, 2018: 112.
31 Kantarjian H, Rajkumar SV. Why are cancer drugs so expensive in the United States, and what are the solutions? *Mayo Clin Proc* 2015;90:500–4.
32 Gómez-Dantés O, Wirtz VJ, Reich MR, *et al*. A new entity for the negotiation of public procurement prices for patented medicines in Mexico. *Bull World Health Organ* 2012;90:788–92.
33 Meng Q, Yin D, Mills A, *et al*. China's encouraging commitment to health. *BMJ* 2019;365:l4178.
34 Fang H, Eggleston K, Hanson K. Enhancing financial protection under China's social health insurance to achieve universal health coverage. *BMJ* 2019;365:l2378–l78.
35 Moye-Holz D, van Dijk JP, Reijneveld SA, *et al*. The impact of price negotiations on public procurement prices and access to 8 innovative cancer medicines in a middle-income country: the case of Mexico. *Value Health Reg Issues* 2019;20:129–35.
36 Emmerick ICM, Campos MR, Luiza VL, *et al*. Retrospective interrupted time series examining hypertension and diabetes medicines usage following changes in patient cost sharing in the 'Farmácia Popular' programme in Brazil. *BMJ Open* 2017;7:e017308.
37 Diao Y, Qian J, Liu Y, *et al*. How government insurance coverage changed the utilization and affordability of expensive targeted anti-cancer medicines in China: an interrupted time-series study. *J Glob Health* 2019;9:020702.
38 Meng Q, Fang H, Liu X, *et al*. Consolidating the social health insurance schemes in China: towards an equitable and efficient health system. *Lancet* 2015;386:1484–92.
39 Zhang A, Nikoloski Z, Mossialos E. Does health insurance reduce out-of-pocket expenditure? heterogeneity among China's middle-aged and elderly. *Soc Sci Med* 2017;190:11–19.
40 Davis C, Naci H, Gurpinar E, *et al*. Availability of evidence of benefits on overall survival and quality of life of cancer drugs Approved by European medicines agency: retrospective cohort study of drug approvals 2009-13. *BMJ* 2017;359:j4530–j30.
41 Tibau A, Molto C, Ocana A, *et al*. Magnitude of clinical benefit of cancer drugs Approved by the US food and drug administration. *J Natl Cancer Inst* 2018;110:486–92.
42 Kwon H-Y, Kim J. Consistency of new drug pricing in Korea: bridging variations among personnel in price negotiations. *Health Policy* 2020;124:965–70.
43 Kim S, Kim J, Cho H, *et al*. Trends in the pricing and reimbursement of new anticancer drugs in South Korea: an analysis of listed anticancer drugs during the past three years. *Expert Rev Pharmacoecon Outcomes Res* 2021;21:479–88.
44 Meng Q, Mills A, Wang L, *et al*. What can we learn from China's health system reform? *BMJ* 2019;365:l2349.
45 Guo Y, Shibuya K, Cheng G, *et al*. Tracking China's health reform. *Lancet* 2010;375:1056–8.
46 Liu W, Shi L, Sawhney M, *et al*. Evidence for the effectiveness of anti-hypertensive medicines included on the Chinese national reimbursement drug list. *BMC Health Serv Res* 2019;19:112.
47 Ministry of Human Resources and Social Security Releases Results of Negotiations on National Reimbursement Drug List Entry [updated July 19, 2017]. Available: http://www.mohrss.gov.cn/SYrlzyhshbzb/dongtaixinwen/buneiyaowen/201707/t20170719_274189.html [Accessed Jun 2021].
48 Notice of the National Healthcare Security Administration on the Inclusion of 17 Anticancer Medications in the Category B of National Reimbursement Drug List for Basic Medical Insurance, Work Injury Insurance, and Maternity Insurance [updated October 10, 2018]. Available: http://www.nhsa.gov.cn/art/2018/10/10/art_37_1057.html [Accessed Jun 2021].
49 Statistical Communiqué on the Development of National Basic Medical Insurance in 2018 [updated June 30, 2019]. Available: http://www.nhsa.gov.cn/art/2019/6/30/art_47_1476.html [Accessed Jun 2021].