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Interrupted Time Series Analysis of the Impact of Generic Market Entry of Antineoplastic Products in China

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Abstract

Objectives: The rapid growth of pharmaceutical costs is a major health care issue all over the world. The high prices of drugs are also a concern for stakeholders. Generic drugs are a major price-reducing opportunity for consumers. The aim of this research is to analyze the impact of generic entry on the volume and cost of antineoplastic agents in China.

Methods: An interrupted time-series design examined monthly sales of three antineoplastic drugs (capecitabine, decitabine, imatinib) from 699 public hospitals during January 2011 – June 2016. The first generic entry times (December 2012, December 2013, August 2013, respectively) were regarded as the intervention time points. We estimated changes in volume (DDDs) and cost (DDDc) following the generic entry.

Results: We found that generic entry was associated with increases in the volume of three antineoplastic agents and decreases in their costs. In terms of volume, generic entry was associated with increases in use of capecitabine, decitabine and imatinib by 745.2 (95%CI: -260.8 to 1751.2, p>0.10), 11.0 (95%CI: 2.8 to 19.2, p=0.009), and 2046.6 (95%CI: 1541.3 to 2551.9, p<0.001) units. The entry of generic antineoplastic drugs reduced the daily cost trend of three agents by CNY3.2 (95%CI: -3.1 to -2.9, p<0.001), CNY82.5 (95%CI: -97.5 to -67.5, p<0.001), and CNY22.4 (95%CI: -24.5 to -20.4, p<0.001) per month, respectively. The entry of generic drugs attenuated the upward trend in the volume of three brand-name drugs and even triggered reductions in the volume of brand-name Capecitabine. The entry of generics was accompanied by significant increase in the DDDc of brand-name Decitabine of CNY2.6 (95%CI: 0.2 to 5.1, p=0.04) per month.

Conclusion: Our findings suggested that entry of generic drugs impacted use and cost of antineoplastic medicines in China. Generic drugs may improve the availability and the

affordability of antineoplastic agents, which would benefit more patients.

Article Summary

Strengths and limitations of this study

1. Interrupted time series analysis is a well-established method to analyze drug utilization.
2. To our knowledge, this is the first quantitative study to determine the impact of generic entry on the antineoplastic markets in China.
3. Drug consumption data presented in DDDs only gives an estimate of consumption and does not present a precise picture of actual use.

Introduction

The rising cost of health care is an issue for almost every country, [1] for consumers and stakeholders alike. Patent protection entitles brand-name drug exclusivity in the market, permitting patent holders to maintain high prices to recover research and development costs and maintain profitability.[2] The entry of less expensive generic products and the subsequent availability of a greater selection of substitutes for consumers are expected to trigger lower prices for brand-name products.

High quality generic drugs offer a major opportunity for economic efficiency due to their lower prices and similar quality. Many countries adopt policies to increase the use of generic medicines.[3-5] The literature has shown mixed evidence about the impact of generic entry on brand-name price. Researchers have shown that the prices have tended to fall following the entry of generic alternatives.[6-11] However, other studies have shown that brand-name manufacturers continue to increase their prices at the same rate as prior to the introduction of generic drugs.[12-14] This contradiction is known as Generic Competition Paradox.[15] From the perspective of the utilization of brand-name drugs, some studies showed that after generic entry, much more patients were switched the generic substitution,[16,17] while others showed that the brand-name still be used more than generic drugs.[18] Evidence related to changes in overall therapeutic market limited. Published analyses showed the average cost per user for medicine decreased after generic entry from the perspective of overall therapeutic market.[19,20] Evidence related to changes in utilization following the entry of generic medicines highlighted the contribution of generic medicines to an increased availability of medicines in overall therapeutic market.[21-23]

In China, high pharmaceutical prices have attracted a great deal of attention from the public and the government. Medicine prices, particularly for brand-name drugs, remain significantly higher

than the international reference prices.[24,25] Patent protection for originator products and perceptions about lower safety and efficacy of generics have contributed to the prices of patent originals (and even off-patent originals) remaining higher than those of generic alternative.[26-28] Hu et al. illustrated a consistent average price difference of approximately 40% between off-patent brand-names and generics in the ten-year period from 2002 to 2011.[24] Using data from Shaanxi province, Jiang et al. showed that in private sector retail pharmacies, the median price for original brands was 5.5 times the price of lowest price of generic drugs, while in public sector health facilities, the ratio can be 11.3 or more.[26] There has been little empirical evidence about the impact of generic market entry in China.[27,28] Thus the objective of this study is to analyze the effect of the market entry of generic alternatives for three antineoplastic medications in China on utilization and cost in order to provide evidence about how the market responds to generic alternatives for expensive innovator medications in China.

Methods

Data source

Data were derived from China Medicine Economic Information (CMEI), a large database of drug procurement records covering 699 tertiary hospitals (accounting for 40% of all tertiary hospitals) in mainland China. We analyzed the records of 115 antineoplastic agents from January 2011 to June 2016 and found three antineoplastic agents (capecitabine, decitabine and imatinib) for which the first generic substitutes entered the market during the observation period. Records included the purchasing volume and cost of individual drugs, and basic information on the date of purchasing, the Anatomical Therapeutic Chemical code of the product as well as the manufacturer; 66 monthly values of expenditure and consumption for each of the three

antineoplastic agents comprised our samples. Table 1 provides the descriptive information for these three drugs.

Outcome measures

This study assessed the effect of generic entry on both volume and procurement cost of the study medications (total medication and brand-name drug for each antineoplastic agents). The defined daily doses (DDD) used in this paper were the recommended daily amounts for each study medication based on instructions of three product approved by China Food and Drug Administration (CFDA). The DDD of capecitabine, decitabine and imatinib were 1250mg, 15mg and 500mg respectively. We used these DDD to calculate DDDs (a standardized measure of the volume of each product procured) and DDDc (a standardized measure of the procurement cost of each product), respectively.

Statistical analysis

We first created graphic displays of the monthly procurement volume and cost of each study medication in order to observe and describe patterns over time. We then summed the monthly volumes and procurement costs of each medication to determine total monthly volume (total DDDs) and total cost; we calculated the average monthly cost per DDD (average DDDc) as the total monthly volume divided by the total monthly cost.

We used interrupted time-series (ITS) analysis of each study medication to assess the change in total DDDs and average DDDc associated with generic entry of substitute products. ITS is a commonly used approach for evaluating changes in longitudinal series following a quasi-experimental intervention occurring at a fixed point in time, such as the date of market entry of generic alternatives. The first generic entry date (December 2013, December 2012 and August 2013 for Capecitabine, Decitabine and Imatinib, respectively, see supplement table 1) was

regarded as the intervention time point for ITS analyses. We used segmented regression models that control for baseline trends to estimate changes in the levels and trends of total DDDs and average DDDc after the intervention.

The following model was used for the analysis:

$$Y_t = \beta_0 + \beta_1 * time_t + \beta_2 * entry_t + \beta_3 * timeafterentry_t + \varepsilon_t$$

Y_t is the independent outcome variable (total DDDs or average DDDc). β_0 estimates the level of the outcome at the beginning of the observation period. β_1 estimates the linear trend during the pre-intervention period where $time_t$ is an integer variable indicating the time in months at time t from the beginning of the study period. β_2 which is coded as $time_t = 0$ is before generic entry and $time_t = 1$ is after the entry estimates the change in the outcome immediately following the market entry. β_3 estimates the change in trend in the outcome in the post-entry period compared to baseline. ε_t is an estimate of the random error at time t. We set the time point immediately following first market entry to missing in these models in order to allow time for market adjustment and used the Durbin-Watson statistic to test for a serial autocorrelation of the error terms in the regression models. We performed the ITS analysis using STATA version 13.0.

Results

Descriptive analysis of changes in volume and cost

The monthly sales of the all three antineoplastic agents increased over time following market entry of generics, although increases in the volume of the brand-name medications tended to attenuate (Supplementary Figure 1A, 1C, 1E). For capecitabine, the brand medication remained the dominant product throughout the study period exceeding the total volume of all generic substitutes; for decitabine and imatinib, one of the generic alternatives increased to the same

volume as the brand medicine, and total volume of generic alternatives exceeded the brand product.

The prices of all three brand-name antineoplastic drugs remained nearly constant or experienced only a small decrease following market entry of generics, while most of the prices of generic drugs decreased over time (Supplementary Figure 1B, 1D, 1F). The prices of all generic drugs were consistently lower than the price of brand-name drugs. By the end of the observation period, all generic substitutes for capecitabine were priced at roughly half of the brand product, while all substitutes for imatinib were only 10%-20% of the brand price; the generic substitutes for decitabine experienced the largest price reductions, and by the end of follow-up, they ranged in price from 40% to 60% of the brand product.

ITS analysis of change in total volume and average treatment cost

The entry of generic drugs triggered increases in the total volume of decitabine and imatinib, as well as reductions in the average cost of treatment of three drugs (Figure 1, Table 1). Capecitabine volume was increasing by 1752.5 DDDs per month prior to generic entry. There was no significant change in either level or trend of capecitabine volume observed following the launch of generic versions of the drug. For decitabine, prior to generic entry, the overall volume was increasing by 8.8 DDDs per month. There was a significant increase of 11.0 DDDs (95%CI: 3.7 to 18.3, p=0.004) per month in overall volume after the entry of generic drugs. The volume was 437.7 DDDs (95%CI: 193.6 to 681.7) higher than expected at the end of observation period. Similarly, the entry of generic substitution was associated with the acceleration in the upward pre-generic increase of 817.8 DDDs of imatinib. Following generic entry, total volume of imatinib increased by an additional 2145.5 DDDs per month (95%CI: 1784.1 to 2506.9, p<0.001), resulting in an estimated increase of 82559.3 DDDs in the last month of the

observation period (95%CI: 61461.9 to 103656.9). There was no significant change in either the level or the trend of the capecitabine volume following the launch of generic versions of the drug. The trend in average daily cost of all three agents was stable prior to generic entry with the downward trend of capecitabine (-1.0 per month, 95%CI: -1.3 to -0.7), decitabine (-3.3 per month, 95%CI: -22.0 to 15.3) and imatinib (-0.1 per month, 95%CI: -2.3 to 2.1). The entry of generics was accompanied by significant monthly reductions in the DDDc of capecitabine, decitabine and imatinib of CNY3.1 (95%CI: -3.6 to -2.6, p<0.001), CNY84.7 (95%CI: -104.7 to -64.6, p<0.001) and CNY21.3 (95%CI: -24.2 to -18.4, p<0.001) per month, respectively. By the end of the study period, this led to estimated reductions in average daily treatment cost of the three antineoplastic medications of CNY130.3 (95%CI: -142.6 to -118.0), CNY3266.4 (95%CI: -3459.9 to -3073.0) and CNY986.1 (95%CI: -1055.8 to -916.3), respectively.

ITS analysis of change in brand-name drugs volume and average treatment cost

The entry of generic drugs attenuated the upward trend in the volume of three brand-name drugs and even triggered reductions in the volume of brand-name Capecitabine. Meanwhile, there were no significant changes of average treatment cost of the brand-name Capecitabine and Imatnib, while the downward trend of brand-name Decitabine cost was attenuated following the generic entry (Figure 2, Table 2). Before generic entry, volume of brand-name Capecitabine, Decitabine and Imatnib experienced increasing trend by 1752.5, 8.5 and 815.1 DDDs per month. Generic entry led to an immediate increase of 8278.3DDDs in brand-name Imatinib volume (95%CI: 2396.6 to 14160.1, p=0.007). There was a significant increasing trend in the volume of brand-name Capecitabine, Decitabine and Imatinib, respectively (95%CI: -3206.8 to -1644.8, p<0.001; 95%CI: -13.1 to -3.4, p<0.001; 95%CI: -1022.7 to -391.2, p<0.001) after the entry of generic

drugs. This resulted in an estimated decrease of 99342.2 DDDs, 283.8 DDDs and 22227.6 DDDs in the volume of these three brand-name drugs in the last month of the observation period (95%CI: -133858.0 to -64826.9, p<0.001; 95%CI: -497.3 to -70.2, p=0.009; 95%CI: -37807.7 to -6647.4, p=0.005). The downward trend in DDDc of brand-name Capecitabine and Decitabine was stable (95%CI: -1.4 to -0.6, p<0.001; 95%CI: -5.4 to -0.8, p=0.008) while the decreasing trend of brand-name Imatinib was not significant. The entry of generics was accompanied by significant increase in the DDDc of brand-name Decitabine of CNY2.6 (95%CI: 0.2 to 5.1, p=0.04) per month. By the end of the study period, generic entry led to the estimated increase in average daily treatment cost of brand-name Capecitabine and Decitabine of CNY28.8 and CNY124.6 (95%CI: 19.9 to 37.6, p<0.001; 95%CI: 9.5 to 239.8, p=0.03) while led to the estimated reduction in the cost of Imatinib of CNY109.7 (95%CI: -168.0 to -51.4, p<0.001).

Discussion

Our study showed that generic entry was associated with increases in the total volume of antineoplastic agents, while with decreases in volume of the brand-name. Rather than simply replacing the reductions of brand utilization with lower priced generics, generic entry resulted in the increases in the overall market volume. The increased overall use of three antineoplastic agents suggested the generic entry had a positive effect on the availability, financial accessibility, and overall utilization of the agents. The growing number of users for these important medications showed that generic entry improved patient access for those who may have been unable to afford the more expensive brand-name drugs.[24,30] Additionally, the entry of generic medicines might also lead to more optimal treatment of some diseases and additional patients will benefit from access to the medicines.[24,31,32]

Because generic prices tended to be much lower than brand-name drugs, the average cost per treatment declined substantially after generic entry. This confirmed that generic entry can increase the affordability of pharmaceuticals for patients. Thanks to the entry of generic drugs, those who could not have afforded expensive brand-name drugs might gain access to less costly generic versions. The entry of generic drugs encouraged the use of generics to realize considerable savings and more efficient resource allocation for the Chinese healthcare system, consistent with previous studies.[33,34]

Consist with previous researches, generic entry also had impact on brand-name drugs in our study.[18-20] The increasing volume of brand-name drugs experienced attenuation following the entry of generic alternative. The downward trend in the daily treatment cost of the three brand-name drugs tended to remained stable after the entry of generic alternatives, or decrease only slightly. This illustrates that brand-name manufacturers did not tend to decrease the price of their products when facing generic competition. Segmentation of the market [29] might explain this phenomenon. 'Loyal consumers' continuing to use these prodicts – in this case oncologists who prefer these products - allowed brand-name manufacturers to maintain their high price level with relatively stable volumes. Information asymmetry may be a contributing cause for this phenomenon; some oncologists may have been more familiar with the brand product than the newer generic substitutes, and they may have been motivated by economic incentives. Furthermore, physicians may have felt a responsibility to ensure that patients received the best therapy; local generics are not required to be bioequivalent and may be of lower quality, so doctors preferred brand-name products in clinical use.[28] Patients' preferences for brand-name drugs could also constitute a barrier to generic substitution, although this may be a less likely explanation for antineoplastic medications.[35] Hospital procurement practices could be a further

factor in the observed effects. Incentivized by a 15% mark-up rule, hospitals might seek to evade price ceilings by switching to more expensive drugs.[36]

The results of this study should be interpreted in light of several limitations. First, drug consumption data presented in DDDs only gives an estimate of consumption and does not present a precise picture of actual use. Second, we only find three antineoplastic drugs in the observation period which may not represent the whole market. Meanwhile, we only focused on the antineoplastic market so that we cannot generalize conclusions about the impact of generic entry to other markets, especially those that do not share the unique features of oncology treatment. Third, we failed to consider the institutional factors that affect prescription and prices in the Chinese health system.

Conclusions

This study demonstrated that the generic entry had substantial positive impacts on the antineoplastic market in China. Generic entry improved the availability of antineoplastic therapy, increased affordability, and generated cost-savings through reduced average treatment costs, which will benefit more patients. However, this study also showed that the generic entry seemed have a negative impact on brand-name drugs sales, and the expected competition on brand-name price did not occur.

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Table 1 Estimates from interrupted time series models of changes in total antineoplastic volume and average treatment cost following generic market entry (baseline trend, post-entry level and trend changes, and absolute changes at the end of observation period)

	Total Volume (DDDs)			Average Cost (DDDc)		
	β	95%CI	P	β	95%CI	P
capecitabine						
baseline level	73847.2	62503.6 to 85190.8	<0.001	589.5	582.8 to 596.3	<0.001
trend before generic entry	1752.5	1207.1 to 2297.9	<0.001	-1.0	-1.3 to -0.7	<0.001
level change after generic entry	-1927.4	-18519.0 to 14664.2	0.82	3.7	-6.0 to 13.4	0.44
trend change after generic entry	815.0	-66.5 to 1696.5	0.07	-3.1	-3.6 to -2.6	<0.001
absolute changes at the end of observation period	32260.9	-6366.3 to 70888.0	0.10	-130.3	-142.6 to -118.0	<0.001
decitabine						
baseline level	85.2	-8.6 to 179.1	0.07	10154.4	9888.8 to 10420.0	<0.001

trend before generic entry	8.8	2.0 to 15.6	0.01	-3.3	-22.0 to 15.3	0.72
level change after generic entry	-30.2	-142.0 to 81.6	0.59	266.4	-37.3 to 570.2	0.08
trend change after generic entry	11.0	3.7 to 18.3	0.004	-84.7	-104.7 to -64.6	<0.001
absolute changes at the end of observation period	437.7	193.6 to 681.7	<0.001	-3266.4	-3459.9 to -3073.0	<0.001
imatinib						
baseline level	10903.9	5883.6 to 15924.2	<0.001	1185.7	1143.9 to 1227.5	<0.001
trend before generic entry	817.8	544.7 to 1090.9	<0.001	-0.1	-2.3 to 2.1	0.90
level change after generic entry	-6343.7	-13187.1 to 499.6	0.07	-43.1	-98.2 to 12.0	0.12
trend change after generic entry	2145.5	1784.1 to 2506.9	<0.001	-21.3	-24.2 to -18.4	<0.001
absolute changes at the end of observation period	82559.3	61461.9 to 103656.9	<0.001	-986.1	-1055.8 to -916.3	<0.001

Table 2 Estimates from interrupted time series models of changes in brand-name antineoplastic volume and cost following generic market entry (baseline trend, post-entry level and trend changes, and absolute changes at the end of observation period)

	Volume (DDDs)			Cost (DDDc)		
	β	95%CI	P	β	95%CI	P
Capecitabine						
baseline level	73849.7	63800.4 to 83899.1	<0.001	590.3	581.6 to 599.0	<0.001
trend before generic entry	1752.5	1269.2 to 2235.7	<0.001	-1.0	-1.4 to .0.6	<0.001
level change after generic entry	2333.7	-12366.5 to 17034.0	0.75	5.4	-6.6 to 17.4	0.37
trend change after generic entry	-2425.8	-3206.8 to -1644.8	<0.001	0.6	-0.1 to 1.2	0.054
absolute changes at the end of observation period	-99342.2	-133858.0 to -64826.9	<0.001	28.8	19.9 to 37.6	<0.001
Decitabine						
baseline level	92.2	31.0 to 153.5	0.004	10150.7	10119.4 to 10182.0	<0.001

trend before generic entry	8.5	4.0 to 12.9	<0.001	-3.1	-5.4 to -0.8	0.008
level change after generic entry	63.4	-12.4 to 139.1	0.10	10.3	-26.8 to 47.4	0.58
trend change after generic entry	-8.3	-13.1 to -3.4	<0.001	2.6	0.2 to 5.1	0.04
absolute changes at the end of observation period	283.8	-497.3 to -70.2	0.009	124.6	9.5 to 239.8	0.03
Imatinib						
baseline level	11171.1	6806.0 to 15536.3	<0.001	1190.6	1139.6 to 1241.6	<0.001
trend before generic entry	815.1	577.0 to 1053.3	<0.001	-0.4	-3.0 to 2.3	0.79
level change after generic entry	8278.3	2396.6 to 14160.1	0.007	-41.7	-107.6 to 24.2	0.21
trend change after generic entry	-706.9	-1022.7 to -391.2	<0.001	-0.3	-3.8 to 3.2	0.87
absolute changes at the end of observation period	-22227.6	-37807.7 to -6647.4	0.005	-109.7	-168.0 to -51.4	<0.001

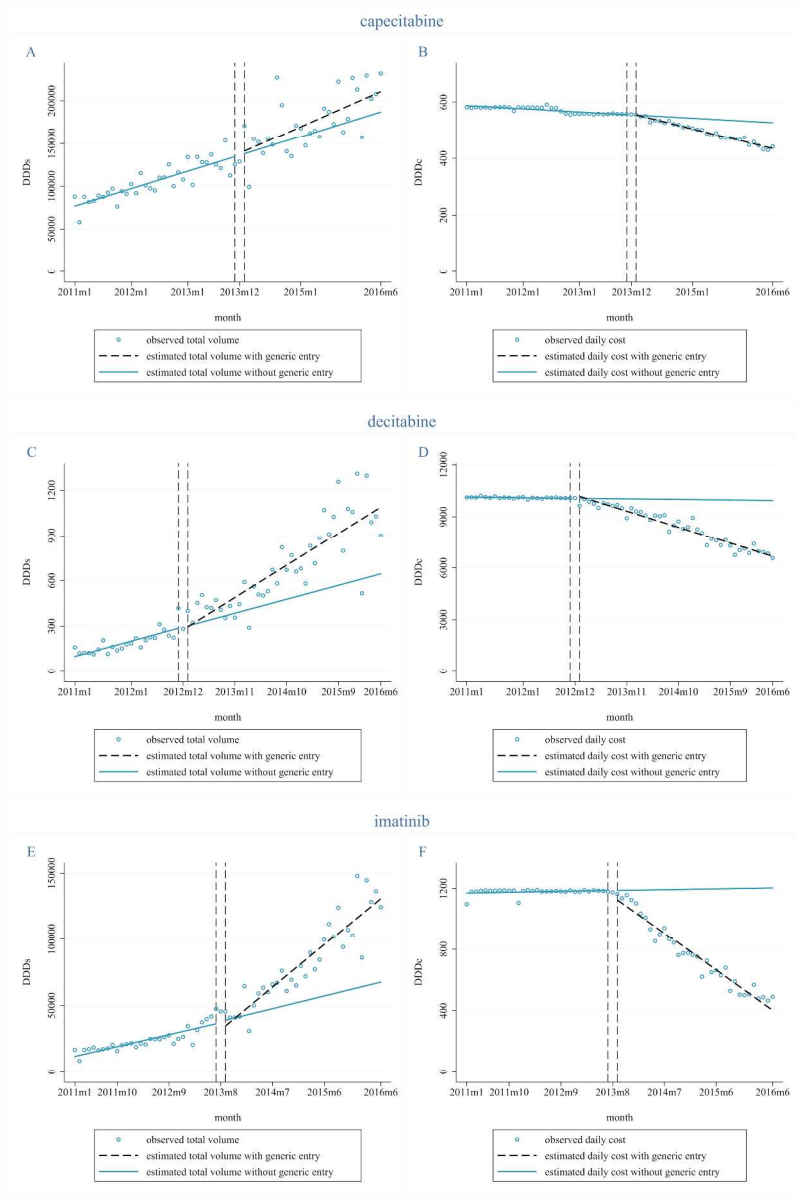


Figure 1 Change in total volume and daily cost for three antineoplastic agents before and after generic entry

203x304mm (300 x 300 DPI)

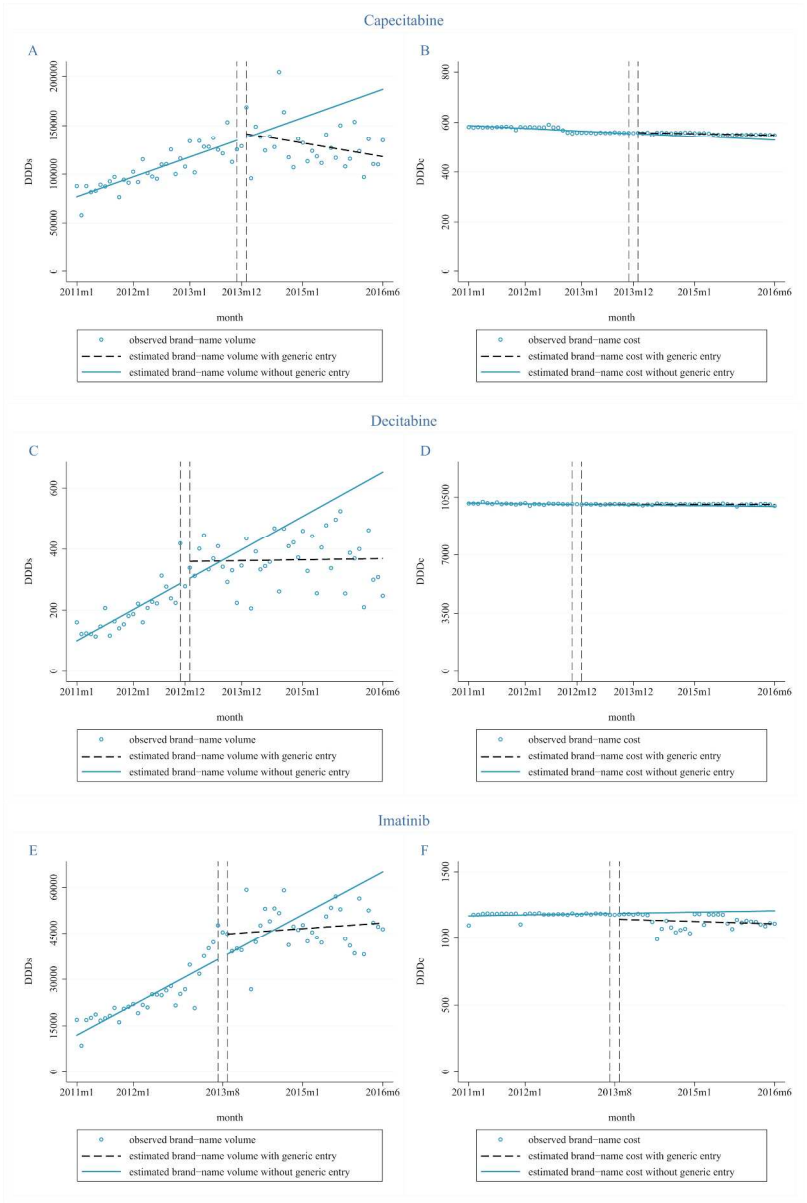
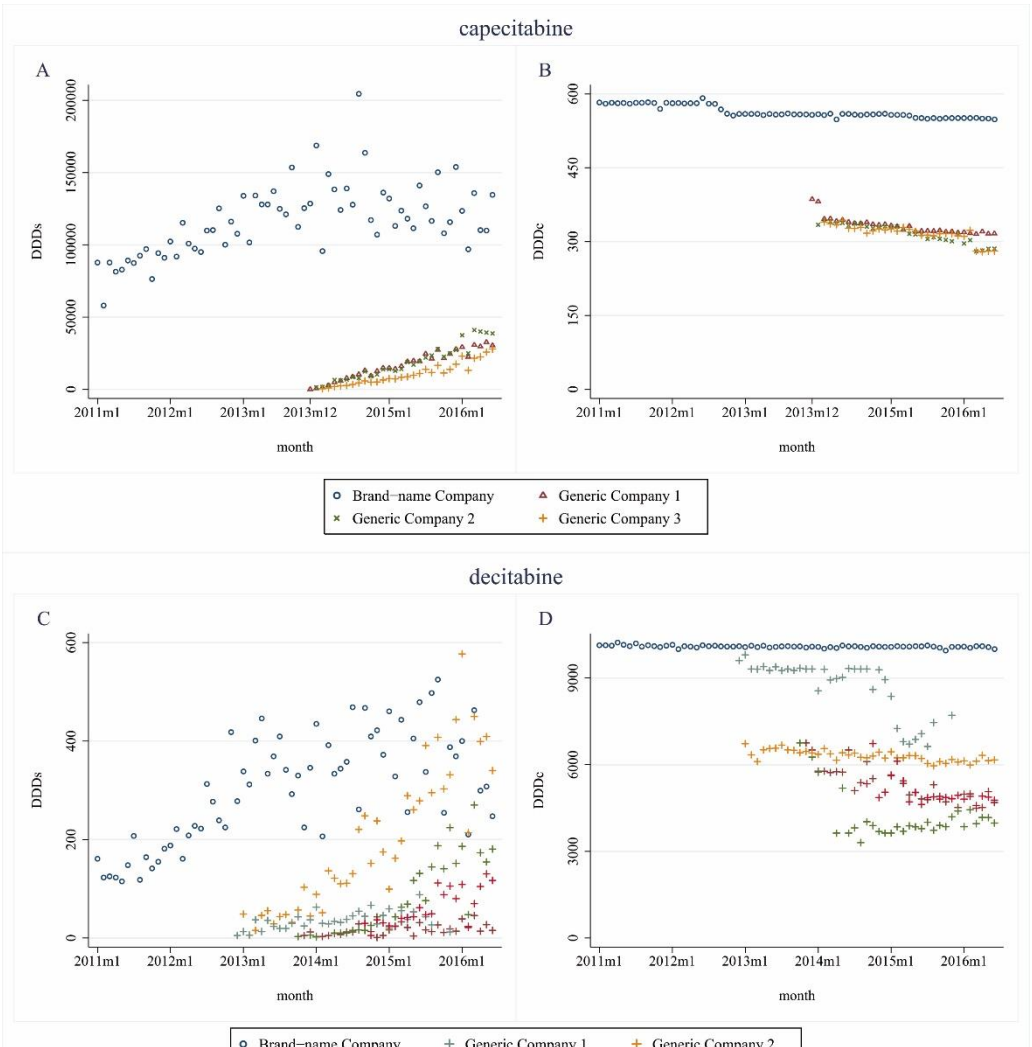


Figure 2 Change in volume and daily cost for three brand-name drugs before and after generic entry

203x304mm (300 x 300 DPI)

Supplement Table 1 Descriptive summary of three antineoplastic study drugs

ATC	Generic name	Indication	Brand-name producer	First entry of generic	Numbers of generic entrants
L01BC06	capecitabine	Breast cancer, gastric cancer and colorectal cancer	Genentech (Roche)	2013-12	3
L01BC08	decitabine	Myelodysplastic syndromes	Pharmachemie	2012-12	5
L01XE01	imatinib	CML, ALL, GIST	Novartis	2013-08	3



Supplement figure1: Volume and cost of three antineoplastic agents from January 2011 to June 2016

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Interrupted Time Series Analysis of the Impact of Generic Market Entry of Antineoplastic Products in China

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Interrupted Time Series Analysis of the Impact of Generic Market Entry of Antineoplastic Products in China

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Abstract

Objectives: The rapid growth of pharmaceutical costs is a major health care issue all over the world. The high prices of new drugs, especially those for cancer, are also a concern for stakeholders. Generic drugs are a major price-reducing opportunity and provide more societal value. The aim of this research is to analyze the impact of generic entry on the volume and cost of antineoplastic agents in China.

Methods: An interrupted time-series design examined monthly sales of three antineoplastic drugs (capecitabine, decitabine, imatinib) from 699 public hospitals during January 2011 – June 2016. The first generic entry times (December 2012, December 2013, August 2013, respectively) were regarded as the intervention time points. We estimated changes in volume (DDDs) and cost (DDDc) following the generic entry.

Results: We found that generic entry was associated with increases in the volume of three antineoplastic agents and decreases in their costs. In terms of volume, generic entry was associated with increases in use of capecitabine, decitabine and imatinib by 815.0 (95%CI: -66.5 to 1696.5, p>0.05), 11.0 (95%CI: 3.7 to 18.3, p=0.004) and 2145.5 (95%CI: 1784.1 to 2506.9, p<0.001) units. The entry of generic antineoplastic drugs reduced the monthly cost trend of three agents by 3.1 CNY (95%CI: -3.6 to -2.6, p<0.001), 84.7 CNY (95%CI: -104.7 to -64.6, p<0.001) and 21.3 CNY (95%CI: -24.2 to -18.4, p<0.001), respectively. The entry of generic drugs attenuated the upward trend in volume of three brand-name drugs and even triggered reductions in the volume of brand-name capecitabine. The entry of generics was accompanied by significant increase of 2.6 CNY in monthly brand-name decitabine cost (95%CI: 0.2 to 5.1, p=0.04).

Conclusion: Our findings suggest that entry of generic drugs impacted use and cost of antineoplastic medicines in China. Generic drugs may improve the availability and the

affordability of antineoplastic agents, which would benefit more patients.

Article Summary

Strengths and limitations of this study

1. This study used complete drug procurement records from 699 hospitals in the China Medicine Economic Information Database to present the first analysis of the impact of generic entry in the antineoplastic market in China.
2. We used interrupted time series analysis to evaluate trends before and after generic market entry, a well-established method to analyze changes in drug utilization and cost after an intervention at a defined point in time.
3. One limitation of this study was unable to assess drug utilization by individual patients, and it could only give an overview of drug utilization trend over time.
4. The second limitation was although we conducted a search of all antineoplastic agents in the database, and only found three antineoplastic drugs that had a generic enter the market in the observation period, which may not represent the whole market.

Introduction

The rising cost of health care is an issue for consumers and stakeholders alike in almost every country. Patent protection entitles brand-name drug exclusivity in the market, permitting patent holders to maintain high prices to maximize profit.[1] The entry of less expensive generic products and the subsequent availability of a greater selection of substitutes for consumers may trigger lower prices for brand-name products.[2] Additionally, the entry of generic medicines might also lead to more optimal treatment of some diseases with additional patients benefitting from access to the medicines.[3]

High quality generic drugs offer a major opportunity for economic efficiency due to their lower prices and similar quality.[4,5] Many countries adopt policies to increase the use of generic medicines.[6-8] Some studies have shown that after generic entry, more patients are switched to the generic substitutes,[9,10] while others have shown that the brand-name products are still used more than the generic alternatives.[11] The literature has shown mixed evidence about the impact of generic entry on brand-name price. Some research has indicated that brand-name prices have tended to fall following the entry of generic alternatives,[12-14] while others have found that brand-name manufacturers continue to increase their prices at the same rate as prior to the introduction of generics.[15-17] This contradiction is known as the Generic Competition Paradox.[18] Evidence related to changes in the overall therapeutic market is limited. Some analyses have found that the average cost per user for medicines decreased after generic entry.[19,20] Evidence related to changes in utilization following the entry of generic medicines has highlighted the contribution of generics to increased availability of medicines in overall therapeutic market.[21,22]

China still faces challenges in transforming from a profit-oriented public hospital-centered system to an integrated primary care-based delivery system.[23] Health care facilities customarily

obtain medicines from eligible suppliers through a centralized province-wide supply system at agreed prices negotiated by the provincial government and suppliers.[24] A zero-markup policy was introduced which prevents hospitals from marking up essential medicines in order to remove perverse economic incentives for over-prescription.[25] Nevertheless physicians are still incentivized to make a profit from medicines.[26]

High pharmaceutical prices have attracted a great deal of attention from the public and the government in China. Medicine prices, particularly for brand-name drugs, remain significantly higher than the international reference prices.[27,28] Patent protection for originator products and perceptions about lower safety and efficacy of generics have contributed to the prices of patent originals (and even off-patent originals) remaining higher than those of generic alternative.[29-31] Hu et al. illustrated a consistent average price difference of approximately 40% between off-patent brand-names and generics in the ten-year period from 2002 to 2011.[29] Using data from Shaanxi province, Jiang et al. showed that in private sector retail pharmacies, the median price for original brands was 5.5 times the price of the lowest price generic equivalents, while in public sector health facilities, the ratio can be 11.3 or more.[27]

There has been little empirical evidence about the impact of generic market entry in China.[30,31] Thus the objective of this study is to analyze the effect of the market entry of generic alternatives for three antineoplastic medications on utilization and cost in order to provide evidence about how the market responds in terms of price and utilization.

Methods

Data source

Data were derived from China Medicine Economic Information (CMEI), a large database

covering procurement records of 1117 hospitals in 2016 in mainland China. We conducted a search of 115 antineoplastic agents (all antineoplastic agents in the database) from January 2011 to June 2016, and only found three antineoplastic agents (capecitabine, decitabine and imatinib) that experienced first entry of a generic substitute in the study period. A total of 699 tertiary hospitals had complete procurement records in this period and these were included in our study. Records included the purchasing volume and cost of individual drugs, and basic information on the date of purchasing, the Anatomical Therapeutic Chemical (ATC) code of the product, as well as the manufacturer; 66 monthly values of expenditure and consumption for each of the three antineoplastic agents comprised our samples. Supplement Table 1 provides the descriptive information for these three drugs.

Outcome measures

This study assessed the effect of generic entry on both volume and procurement cost of the study medications (total medication and brand-name drug for each antineoplastic agents). The defined daily doses (DDD) used in this paper were the recommended daily amounts for each study medication based on dosage regimen recommended in the manufacturers' instructions of the three products, as approved by China Food and Drug Administration (CFDA). The maintenance dose of capecitabine, decitabine and imatinib which we used in this study were 1250mg, 15mg and 500mg, respectively. We used maintenance dose to calculate DDDs (a standardized measure of the volume of each product procured) and DDDc (a standardized measure of the procurement cost of each product), respectively.

Statistical analysis

We first created graphic displays of the monthly procurement volume and cost of each study medication in order to observe and describe patterns over time. We then summed the monthly

volumes and procurement costs of each medication to determine total monthly volume (total DDDs) and total cost; we calculated the average monthly cost per DDD (average DDDc) as the total monthly volume divided by the total monthly cost. The expense data were reported in both Chinese Yuan and US Dollars (1 Chinese yuan (CNY) = 0.155 USD based on the 2011 exchange rate).[32]

We used interrupted time-series (ITS) analysis of each study medication to assess the change in total DDDs and average DDDc associated with generic entry of substitute products. ITS is a commonly used approach for evaluating changes in longitudinal series following a quasi-experimental intervention occurring at a fixed point in time, such as the date of market entry of generic alternatives. The first generic entry date (December 2013, December 2012 and August 2013 for capecitabine, decitabine and imatinib, respectively, see Supplement Table 1) was regarded as the intervention time point for ITS analyses. We used segmented regression models that control for baseline trends to estimate changes in the levels and trends of total DDDs and average DDDc after generic market entry.

The following model was used for the analysis:

$$Y_t = \beta_0 + \beta_1 * time_t + \beta_2 * entry_t + \beta_3 * timeafterentry_t + \varepsilon_t$$

Y_t is the independent outcome variable (total DDDs or average DDDc). β_0 estimates the level of the outcome at the beginning of the observation period. β_1 estimates the linear trend during the pre-intervention period where $time_t$ is an integer variable indicating the time in months at time t from the beginning of the study period. β_2 which is coded as $time_t = 0$ is before generic entry and $time_t = 1$ is after the entry estimates the change in the outcome immediately following the market entry. β_3 estimates the change in trend in the outcome in the post-entry period compared to baseline. ε_t is an estimate of the random error at time t. We set the time point immediately

following first market entry to missing in these models in order to allow time for market adjustment and used the Durbin-Watson statistic to test for a serial autocorrelation of the error terms in the regression models. We performed the ITS analysis using STATA version 13.0.

Patient and public statement

Patients or public were not involved in this study, and ethical approval was not required according to the relevant requirements for conducting this type of survey in China.

Results

Descriptive analysis of changes in volume and cost

The monthly sales of the all three antineoplastic agents increased over time following market entry of generics, although increases in the volume of the brand-name medications tended to attenuate (Supplement Figure 1A, 1B, 1C). For capecitabine, the brand medication remained the dominant product throughout the study period exceeding the total volume of all generic substitutes; for decitabine and imatinib, one of the generic alternatives increased to approximately the same volume as the brand medicine, and total volume of generic alternatives exceeded the brand product.

The prices of all three brand-name antineoplastic drugs remained nearly constant or experienced only a small decrease following market entry of generics, while most of the prices of generic drugs decreased over time (Supplement Figure 1D, 1E, 1F). The prices of all generic drugs were consistently lower than the price of brand-name drugs. By the end of the observation period, all generic substitutes for capecitabine were priced at roughly half of the brand product, while all substitutes for imatinib were only 10%-20% of the brand price. The generic substitutes for decitabine experienced the largest price reductions and by the end of follow-up they ranged in

price from 40% to 60% of the brand product.

ITS analysis of changes in total volume and average treatment cost

The entry of generic drugs triggered increases in the total volume of decitabine and imatinib, as well as reductions in the average cost of treatment for the three drugs (Figure 1, Table 1). Capecitabine volume was increasing by 1,752.5 DDDs per month prior to generic entry. There was no significant change in either level or trend of capecitabine volume observed following the launch of the generic versions of the drug. For decitabine, prior to generic entry, the overall volume was increasing by 8.8 DDDs per month. There was a significant increase of 11.0 DDDs (95%CI: 3.7 to 18.3, p=0.004) per month in overall volume after generic entry. The volume was 437.7 DDDs (95%CI: 193.6 to 681.7) higher than expected at the end of observation period. Similarly, the entry of a generic substitute was associated with the acceleration in the upward pre-generic increase of 817.8 DDDs of imatinib. Following generic entry, the total volume of imatinib increased by an additional 2,145.5 DDDs per month (95%CI: 1,784.1 to 2,506.9, p<0.001), resulting in an estimated increase of 82,559.3 DDDs in the last month of the observation period (95%CI: 61,461.9 to 103,656.9). There was no significant change in either the level or the trend of capecitabine volume following the launch of its generic alternative. The trend in average cost of all three agents was stable prior to generic entry with the downward trend of capecitabine (-1.0 CNY per month, 95%CI: -1.3 to -0.7), decitabine (-3.3 CNY per month, 95%CI: -22.0 to 15.3) and imatinib (-0.1 CNY per month, 95%CI: -2.3 to 2.1). The entry of generics was accompanied by significant monthly reductions in the DDDc of capecitabine, decitabine and imatinib of 3.1 CNY (0.2 USD; 95%CI: -3.6 to -2.6 CNY, p<0.001), 84.7 CNY (13.1 USD; 95%CI: -104.7 to -64.6 CNY, p<0.001) and 21.3 CNY (3.3 USD; 95%CI: -24.2 to -18.4 CNY, p<0.001) per month, respectively. By the end of the study period, this led to estimated

reductions in average daily treatment cost of the three antineoplastic medications of 130.3 CNY (20.2 USD; 95%CI: -142.6 to -118.0 CNY), 3,266.4 CNY (506.3 USD; 95%CI: -3459.9 to -3073.0 CNY) and 986.1 CNY (152.8 USD; 95%CI: -1,055.8 to -916.3 CNY), respectively.

ITS analysis of changes in volume and average treatment cost for brand-name drugs

The entry of generic drugs attenuated the upward trend in the volume of three brand-name drugs and even triggered reductions in the volume of brand-name capecitabine. Meanwhile, there were no significant changes of average treatment cost of the brand-name capecitabine and imatinib, while the downward trend of brand-name decitabine cost was attenuated following the generic entry (Figure 2, Table 2). Before generic entry, the volume of brand-name capecitabine, decitabine and imatinib experienced increasing trend by 1,752.5, 8.5 and 815.1 DDDs per month. Generic entry led to an immediate increase of 8,278.3 DDDs in brand-name imatinib volume (95%CI: 2,396.6 to 14,160.1, p=0.007). There was a significant decreasing trend in the volume of brand-name capecitabine, decitabine and imatinib, respectively (95%CI: -3,206.8 to -1,644.8, p<0.001; 95%CI: -13.1 to -3.4, p<0.001; 95%CI: -1,022.7 to -391.2, p<0.001) after the entry of generic drugs. This resulted in an estimated decrease of 99,342.2 DDDs, 283.8 DDDs and 22,227.6 DDDs in the volume of brand-name capecitabine, decitabine and imatinib in the last month of the observation period (95%CI: -133,858.0 to -64,826.9, p<0.001; 95%CI: -497.3 to -70.2, p=0.009; 95%CI: -37807.7 to -6647.4, p=0.005). The downward trend in DDDc of brand-name capecitabine and decitabine was stable (95%CI: -1.4 to -0.6, p<0.001; 95%CI: -5.4 to -0.8, p=0.008) while the decreasing trend of brand-name imatinib was not significant. The entry of generics was accompanied by significant increase in the DDDc of brand-name decitabine of 2.6 CNY (0.4 USD; 95%CI: 0.2 to 5.1 CNY, p=0.04) per month. By the end of the study period,

generic entry led to the estimated increase in average daily treatment cost of brand-name capecitabine and decitabine of 28.8 CNY (4.5 USD; 95%CI: 19.9 to 37.6 CNY, p<0.001) and 124.6 CNY (19.3 USD; 95%CI: 9.5 to 239.8 CNY, p=0.03), respectively, while led to the estimated reduction in the cost of imatinib of 109.7 CNY (17.0 USD; 95%CI: -168.0 to -51.4 CNY, p<0.001).

Discussion

Our study showed that generic entry was associated with increases in the total volume of antineoplastic agents for each of the three study medications, with decreases in volume of the brand-name product. Rather than simply replacing the reductions of brand utilization with lower priced generics, generic entry resulted in increases in the overall market volume. The increased overall use of the three antineoplastic agents suggested that generic entry had a positive effect on the availability, financial accessibility, and overall utilization of the agents. The growing number of users for these important medications showed that generic entry improved patient access for those who may have been unable to afford the more expensive brand-name drugs.[3,33]

Because generic prices tended to be much lower than the prices of brand-name drugs, the average cost per treatment declined substantially after generic entry. This confirmed that generic entry can increase the affordability of pharmaceuticals for patients. The entry of generic drugs resulted in considerable savings and more efficient resource allocation for the Chinese healthcare system, consistent with previous studies.[34,35]

Consistent with previous research, generic entry also had impact on use of brand-name drugs in our study.[19,20] The increasing volume of brand-name decitabine and imatinib experienced attenuation following the entry of generic alternatives, while the volume of brand name capecitabine began to decrease. The latter may have been because capecitabine was the only drug

of the three listed in National Reimbursement Drug List since 2009. Under the pressure of increasing deficits in China's medical insurance system,[23] physicians are forced to prescribe generic drugs. This might explain why uptake of generic capecitabine differs from the other two drugs studied. Current studies have demonstrated that insurance coverage enhances medicine adherence and access.[35,36] Although China has reached near-universal coverage after health reform since 2009, [37] only twenty targeted antineoplastic agents were approved by CFDA before 2017 and none was listed in the National Reimbursement Drug List.[38,39] Thus a strategy to reduce the out-of-pocket cost for these high-cost medicines in China is urgently needed.

We also found that daily treatment cost of the three brand-name drugs tended to remain stable after the entry of generic alternatives, or to decrease only slightly. This illustrates that brand-name manufacturers did not tend to decrease the prices of their products when facing generic competition. Segmentation of the market might explain this phenomenon.[34] 'Loyal consumers' continuing to use these products - in this case oncologists who prefer them - allowed brand-name manufacturers to maintain their high price levels with relatively stable volumes. Information asymmetry may be a contributing cause for this phenomenon; some oncologists may have been more familiar with the brand product than the newer generic substitutes, or they may have been motivated by economic incentives. Furthermore, physicians may have felt a responsibility to ensure that patients received the best therapy. Local generics are not required to be bioequivalent and may be of lower quality, so doctors prefer brand-name products in clinical use.[26,40] Moreover, incentivized by a 15% mark-up rule, hospitals might seek to evade price ceilings by switching to more expensive drugs during the study period.[41] Patients' preferences for brand-name drugs could also constitute a barrier to generic substitution, although this may be a less likely explanation for antineoplastic medications.[42]

However, the results of this study should be interpreted in light of several limitations. First, we were unable to assess drug utilization by individual patients, since only aggregate consumption data were available. Drug consumption data presented in DDDs only provide an estimate of the volume of medications consumed and do not present a precise picture of actual use. Second, we found only three antineoplastic drugs that had a generic enter the market in the observation period, and these three examples may not represent all antineoplastic medications. In addition, we only focused on the antineoplastic market, so our conclusions may not generalize to other product classes, especially those that do not share the unique features of oncology treatment. Finally, we were unable to measure institutional factors that may have affected prescribing patterns and prices in the Chinese health system during the observation period.

Conclusions

This study demonstrated that the generic entry had substantial positive impacts on the antineoplastic market in China. Generic entry improved the availability of antineoplastic therapy, increased affordability, and generated cost-savings through reduced average treatment costs, which will benefit more patients. However, this study also showed that generic entry had a negative impact on brand-name drugs sales, although the expected reduction in brand-name prices due to competition did not occur.

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Contributors Xiaodong Guan, Dennis Ross-Degnan and Luwen Shi conceptualised and

designed the study. Ye Tian screened and completed data extractions. Ye Tian and Chunxia Man contributed to analysis of the data. Xiaodong Guan, Dennis Ross-Degnan and Ye Tian conducted the final analysis and drafted the initial manuscript. All authors contributed to the critical revision of the paper and approved the final manuscript.

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Table 1 Estimates from interrupted time series models of changes in total volume and average treatment cost for all versions of three antineoplastic medications following generic market entry (baseline trend, post-entry level and trend changes, and absolute changes at the end of observation period)

	Total Volume (DDD)			Average Cost (CNY)		
	β	95%CI	P	β	95%CI	P
All products of capecitabine						
baseline level	73847.2	62503.6 to 85190.8	<0.001	589.5	582.8 to 596.3	<0.001
baseline trend	1752.5	1207.1 to 2297.9	<0.001	-1.0	-1.3 to -0.7	<0.001
level change	-1927.4	-18519.0 to 14664.2	0.82	3.7	-6.0 to 13.4	0.44
trend change	815.0	-66.5 to 1696.5	0.07	-3.1	-3.6 to -2.6	<0.001
total change by end of observation	32260.9	-6366.3 to 70888.0	0.10	-130.3	-142.6 to -118.0	<0.001
All products of decitabine						
baseline level	85.2	-8.6 to 179.1	0.07	10154.4	9888.8 to 10420.0	<0.001
baseline trend	8.8	2.0 to 15.6	0.01	-3.3	-22.0 to 15.3	0.72
level change	-30.2	-142.0 to 81.6	0.59	266.4	-37.3 to 570.2	0.08
trend change	11.0	3.7 to 18.3	0.004	-84.7	-104.7 to -64.6	<0.001

total change by end of observation	437.7	193.6 to 681.7	<0.001	-3266.4	-3459.9 to -3073.0	<0.001
All products of imatinib						
baseline level	10903.9	5883.6 to 15924.2	<0.001	1185.7	1143.9 to 1227.5	<0.001
baseline trend	817.8	544.7 to 1090.9	<0.001	-0.1	-2.3 to 2.1	0.90
level change	-6343.7	-13187.1 to 499.6	0.07	-43.1	-98.2 to 12.0	0.12
trend change	2145.5	1784.1 to 2506.9	<0.001	-21.3	-24.2 to -18.4	<0.001
total change by end of observation	82559.3	61461.9 to 103656.9	<0.001	-986.1	-1055.8 to -916.3	<0.001

Table 2 Estimates from interrupted time series models of changes in volume and cost for three brand-name antineoplastic medications following generic market entry (baseline trend, post-entry level and trend changes, and absolute changes at the end of observation period)

	Volume (DDD)			Cost (CNY)		
	β	95%CI	P	β	95%CI	P
Brand-name capecitabine						
baseline level	73849.7	63800.4 to 83899.1	<0.001	590.3	581.6 to 599.0	<0.001
baseline trend	1752.5	1269.2 to 2235.7	<0.001	-1.0	-1.4 to -0.6	<0.001
level change	2333.7	-12366.5 to 17034.0	0.75	5.4	-6.6 to 17.4	0.37
trend change	-2425.8	-3206.8 to -1644.8	<0.001	0.6	-0.1 to 1.2	0.054
total change by end of observation	-99342.2	-133858.0 to -64826.9	<0.001	28.8	19.9 to 37.6	<0.001
Brand-name decitabine						
baseline level	92.2	31.0 to 153.5	0.004	10150.7	10119.4 to 10182.0	<0.001
baseline trend	8.5	4.0 to 12.9	<0.001	-3.1	-5.4 to -0.8	0.008
level change	63.4	-12.4 to 139.1	0.10	10.3	-26.8 to 47.4	0.58
trend change	-8.3	-13.1 to -3.4	<0.001	2.6	0.2 to 5.1	0.04

total change by end of observation	-283.8	-497.3 to -70.2	0.009	124.6	9.5 to 239.8	0.03
Brand-name imatinib						
baseline level	11171.1	6806.0 to 15536.3	<0.001	1190.6	1139.6 to 1241.6	<0.001
baseline trend	815.1	577.0 to 1053.3	<0.001	-0.4	-3.0 to 2.3	0.79
level change	8278.3	2396.6 to 14160.1	0.007	-41.7	-107.6 to 24.2	0.21
trend change	-706.9	-1022.7 to -391.2	<0.001	-0.3	-3.8 to 3.2	0.87
total change by end of observation	-22227.6	-37807.7 to -6647.4	0.005	-109.7	-168.0 to -51.4	<0.001

Figure legend

Figure 1 Change in total volume and daily cost for three antineoplastic agents before and after generic entry. (A) total volume of all products of capecitabine; (B) average cost of all products of capecitabine; (C) total volume of all products of decitabine; (D) average cost of all products of decitabine; (E) total volume of all products of imatinib; (F) average cost of all products of imatinib

Figure 2 Change in volume and daily cost for three brand-name drugs before and after generic entry. (A) volume of brand-name capecitabine; (B) average cost of brand-name capecitabine; (C) total volume of brand-name decitabine; (D) average cost of brand-name decitabine; (E) total volume of brand-name imatinib; (F) average cost of brand-name imatinib

Supplement Figure 1 Volume and cost of three antineoplastic agents from January 2011 to June 2016. (A) volume of brand-name capecitabine and three generic substitutions; (B) volume of brand-name decitabine and five generic substitutions; (C) volume of brand-name imatinib and three generic substitutions; (D) cost of brand-name capecitabine and three generic substitutions; (E) cost of brand-name decitabine and five generic substitutions; (F) cost of brand-name imatinib and three generic substitutions

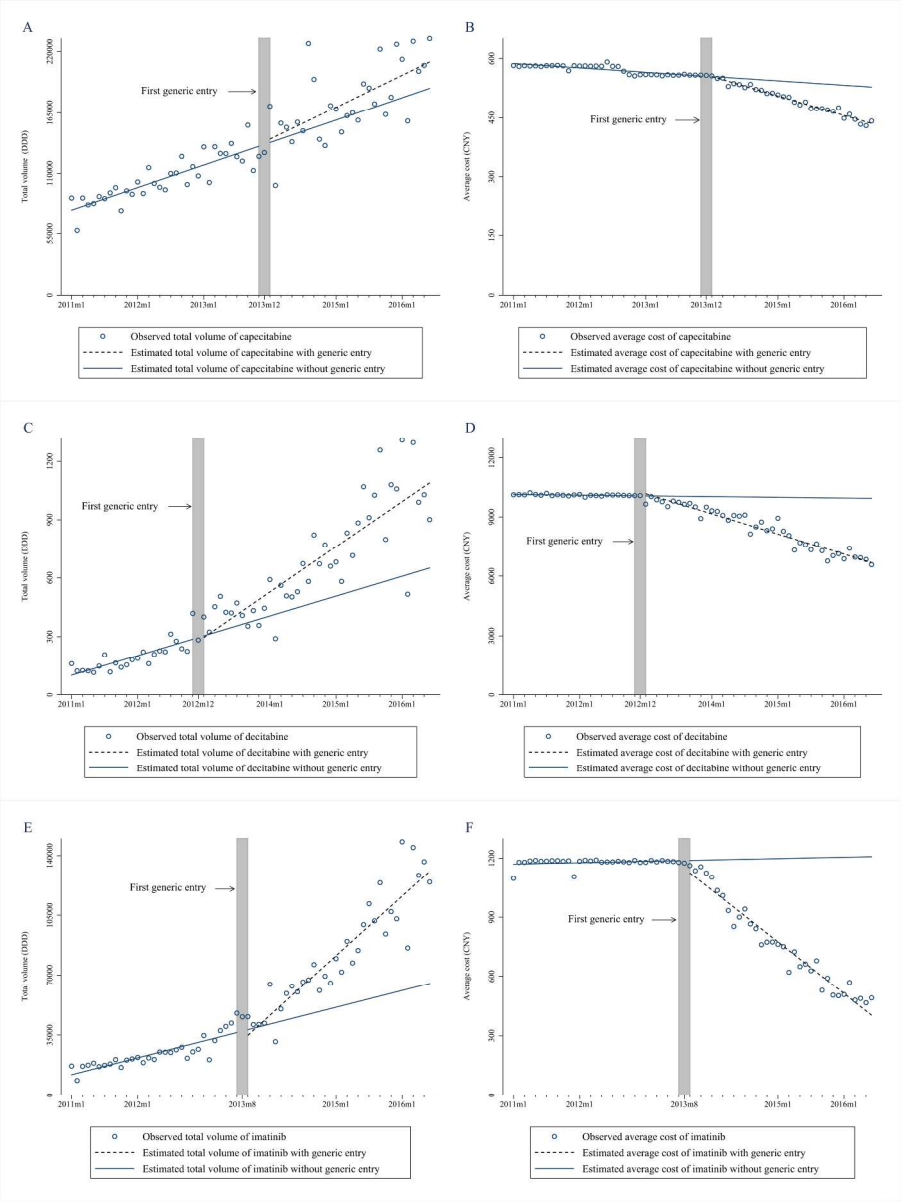

Figure 1 Change in total volume and daily cost for three antineoplastic agents before and after generic entry. (A) total volume of all products of capecitabine; (B) average cost of all products of capecitabine; (C) total volume of all products of decitabine; (D) average cost of all products of decitabine; (E) total volume of all products of imatinib; (F) average cost of all products of imatinib

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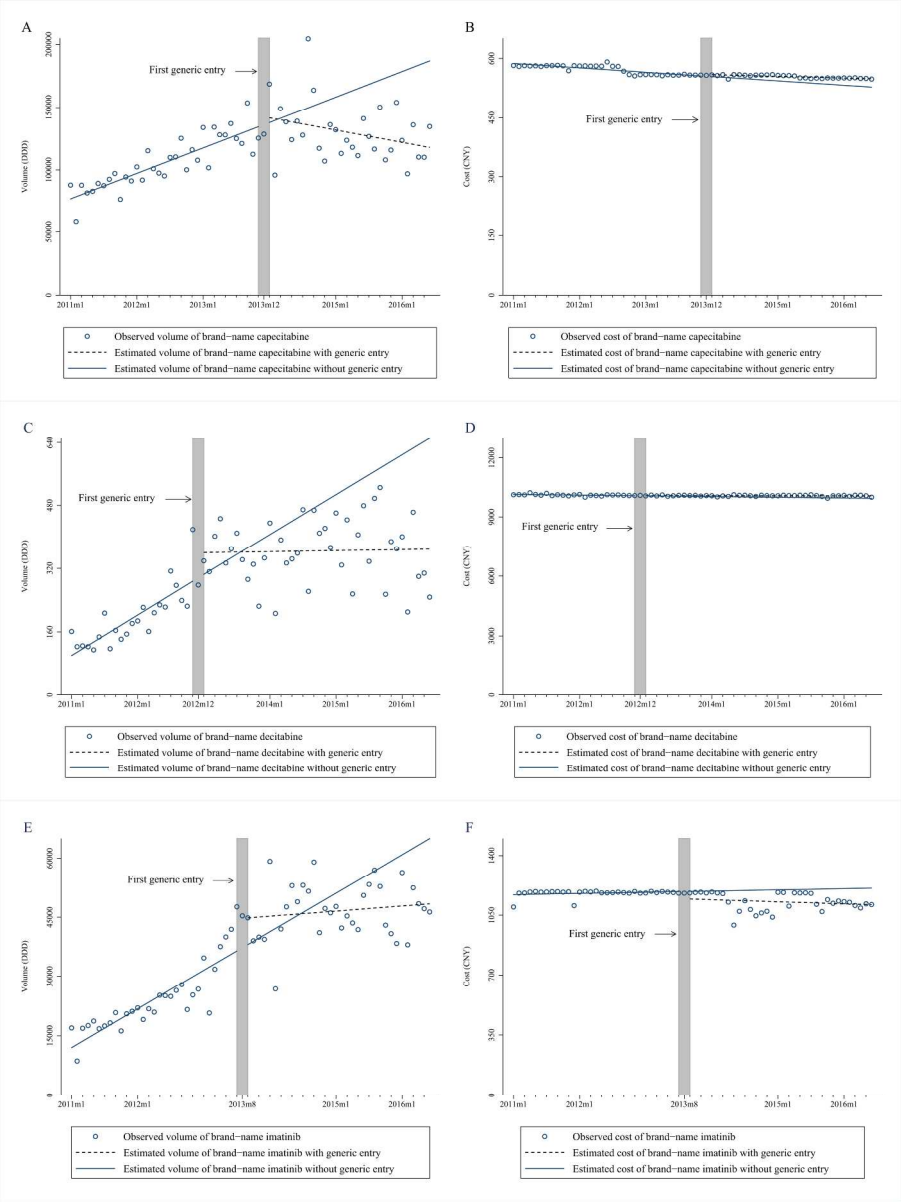

Figure 2 Change in volume and daily cost for three brand-name drugs before and after generic entry. (A)volume of brand-name capecitabine; (B) average cost of brand-name capecitabine; (C) total volume of brand-name decitabine; (D) average cost of brand-name decitabine; (E) total volume of brand-name imatinib; (F)average cost of brand-name imatinib

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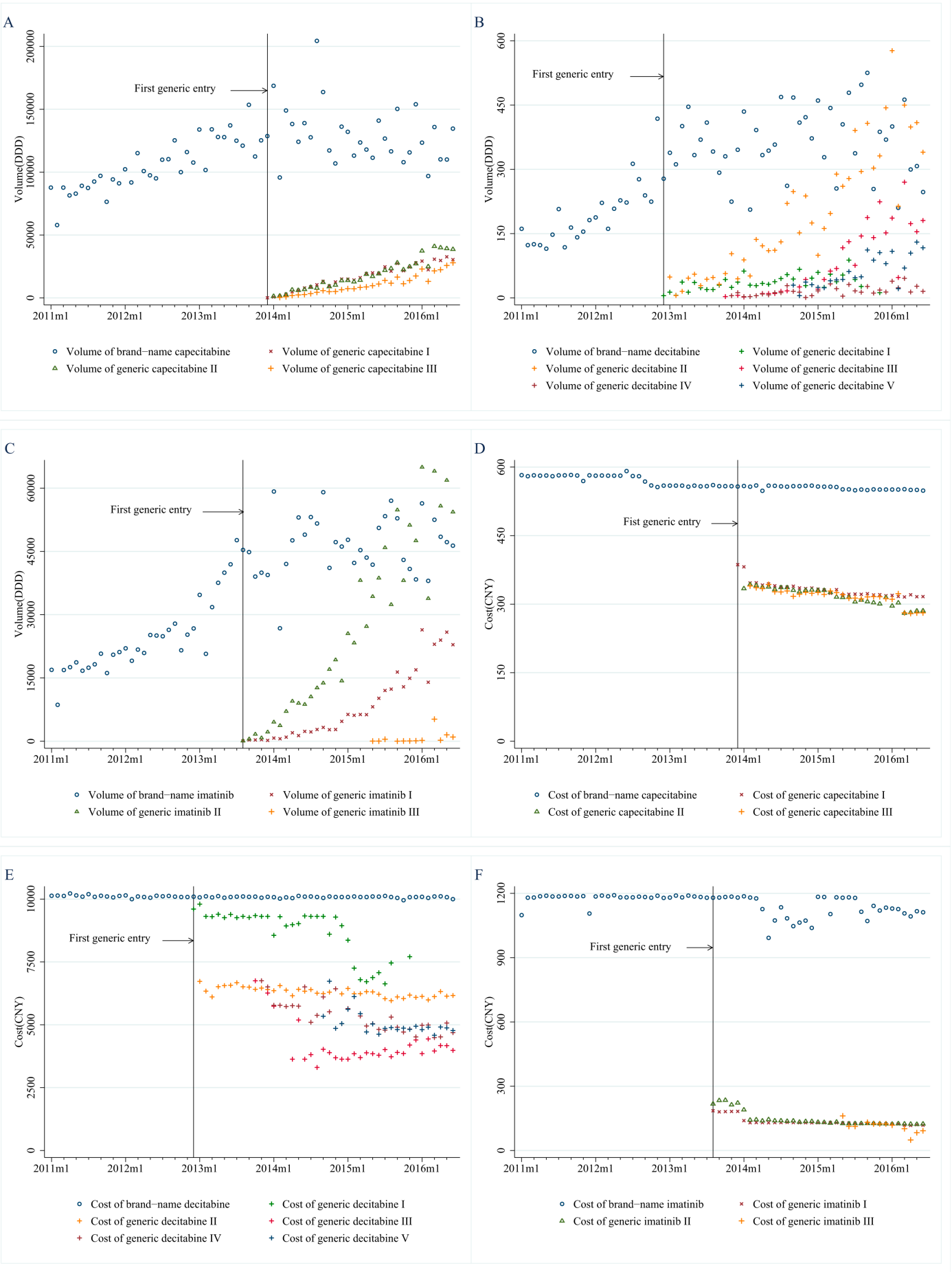
Supplement Table 1 Descriptive summary of three antineoplastic study drugs

ATC	Generic name	Indication	Brand-name producer	First entry of generic	Number of generic entrants
L01BC06	capecitabine	Breast cancer, gastric cancer and colorectal cancer	Genentech (Roche)	2013-12	3
L01BC08	decitabine	Myelodysplastic syndromes	Pharmachemie	2012-12	5
L01XE01	imatinib	Chronic myelocytic leukemia, acute lymphoblastic leukemia, gastrointestinal Stromal Tumor	Novartis	2013-08	3



Supplement Figure 1 Volume and cost of three antineoplastic agents from January 2011 to June 2016. (A) volume of brand-name capecitabine and three generic substitutions; (B) volume of brand-name decitabine and five generic substitutions; (C) volume of brand-name imatinib and three generic substitutions; (D) cost of brand-name capecitabine and three generic substitutions; (E) cost of brand-name decitabine and five generic substitutions; (F) cost of brand-name imatinib and three generic substitutions

CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force,* provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Page 1, line 3-6
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Page 2-3
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Page 5-6, page 7 line 3-17
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	NA
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Page 7, line 26-31
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	NA
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	NA
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	NA
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	NA
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Page 8, line 8-29
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	NA

	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	NA
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	NA
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 8, line 45-50
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Page 8, line 52-54
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	NA
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Page 8, line 52-54 page 9,line 3-45
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Page 9,line 52-54 page 10-12
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	NA
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	

		of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	NA
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	NA
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Page 13-14, page 15 line 3-41
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Page 16, line 35-38
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

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Interrupted Time Series Analysis of the Impact of Generic Market Entry of Antineoplastic Products in China

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Keywords: generic entry; access; utilization; cost

Word count: 2868

Abstract

Objectives: The rapid growth of pharmaceutical costs is a major health care issue all over the world. The high prices of new drugs, especially those for cancer, are also a concern for stakeholders. Generic drugs are a major price-reducing opportunity and provide more societal value. The aim of this research is to analyze the impact of generic entry on the volume and cost of antineoplastic agents in China.

Methods: An interrupted time-series design examined monthly sales of three antineoplastic drugs (capecitabine, decitabine, imatinib) from 699 public hospitals during January 2011 – June 2016. The first generic entry times (December 2012, December 2013, August 2013, respectively) were regarded as the intervention time points. We estimated changes in volume and cost following the generic entry.

Results: We found that generic entry was associated with increases in the volume of three antineoplastic agents and decreases in their costs. In terms of volume, generic entry was associated with increases in use of capecitabine, decitabine and imatinib by 815.0 (95%CI: -66.5 to 1696.5, p>0.05), 11.0 (95%CI: 3.7 to 18.3, p=0.004) and 2145.5 (95%CI: 1784.1 to 2506.9, p<0.001) units. The entry of generic antineoplastic drugs reduced the monthly cost trend of three agents by 3.1 CNY (95%CI: -3.6 to -2.6, p<0.001), 84.7 CNY (95%CI: -104.7 to -64.6, p<0.001) and 21.3 CNY (95%CI: -24.2 to -18.4, p<0.001), respectively. The entry of generic drugs attenuated the upward trend in volume of three brand-name drugs and even triggered reductions in the volume of brand-name capecitabine. The entry of generics was accompanied by significant increase of 2.6 CNY in monthly brand-name decitabine cost (95%CI: 0.2 to 5.1, p=0.04).

Conclusion: Our findings suggest that entry of generic drugs impacted use and cost of antineoplastic medicines in China. Generic drugs may improve the availability and the

affordability of antineoplastic agents, which would benefit more patients.

Article Summary

Strengths and limitations of this study

1. This study used complete drug procurement records from 699 hospitals in the China Medicine Economic Information Database to present the first analysis of the impact of generic entry in the antineoplastic market in China.
2. We used interrupted time series analysis to evaluate trends before and after generic market entry, a well-established method to analyze changes in drug utilization and cost after an intervention at a defined point in time.
3. This study only gave an overview of drug utilization trend over time without assessing drug utilization by individual patient.
4. We only found three antineoplastic agents with first generic entry in the observation period, which may not represent the whole market.

Introduction

The rising cost of health care is an issue for consumers and stakeholders alike in almost every country. Patent protection entitles brand-name drug exclusivity in the market, permitting patent holders to maintain high prices to maximize profit.[1] The entry of less expensive generic products and the subsequent availability of a greater selection of substitutes for consumers may trigger lower prices for brand-name products.[2] Additionally, the entry of generic medicines might also lead to more optimal treatment of some diseases with additional patients benefitting from access to the medicines.[3]

High quality generic drugs offer a major opportunity for economic efficiency due to their lower prices and similar quality.[4,5] Many countries adopt policies to increase the use of generic medicines.[6-8] Some studies found that after generic entry, more patients are switched to the generic substitutes,[9,10] while others showed that the brand-name products are still used more than the generic alternatives.[11] The literature has shown mixed evidence about the impact of generic entry on brand-name price. Some research has indicated that brand-name prices have tended to fall following the entry of generic alternatives,[12-14] while others have found that brand-name manufacturers continue to increase their prices at the same rate as prior to the introduction of generics.[15-17] This contradiction is known as the Generic Competition Paradox.[18] Evidence related to changes in the overall therapeutic market is limited. Some analyses have found that the average cost per user for medicines decreased after generic entry.[19,20] Evidence related to changes in utilization following the entry of generic medicines has highlighted the contribution of generics to increased availability of medicines in overall therapeutic market.[21,22]

China still faces challenges in transforming from a profit-oriented public hospital-centered system to an integrated primary care-based delivery system.[23] Health care facilities customarily

obtain medicines from eligible suppliers through a centralized province-wide supply system at agreed prices negotiated by the provincial government and suppliers.[24] A zero-markup policy was introduced which prevents hospitals from marking up essential medicines in order to remove perverse economic incentives for over-prescription.[25] Nevertheless physicians are still incentivized to make a profit from medicines.[26]

High pharmaceutical prices have attracted a great deal of attention from the public and the government in China. Medicine prices, particularly for brand-name drugs, remain significantly higher than the international reference prices.[27,28] Patent protection for originator products and perceptions about lower safety and efficacy of generics have contributed to the prices of patent originals (and even off-patent originals) remaining higher than those of generic alternative.[29-31] Hu et al. illustrated a consistent average price difference of approximately 40% between off-patent brand-names and generics in the ten-year period from 2002 to 2011.[29] Using data from Shaanxi province, Jiang et al. showed that in private sector retail pharmacies, the median price for original brands was 5.5 times the price of the lowest price generic equivalents, while in public sector health facilities, the ratio can be 11.3 or more.[27]

There has been little empirical evidence about the impact of generic market entry in China.[30,31] Thus the objective of this study is to analyze the effect of the market entry of generic alternatives for three antineoplastic medications on utilization and cost in order to provide evidence about how the market responds in terms of price and utilization.

Methods

Data source

Data were derived from China Medicine Economic Information (CMEI), a large database

covering procurement records of 1117 hospitals in 2016 in mainland China. We conducted a search of 115 antineoplastic agents (all antineoplastic agents in the database) from January 2011 to June 2016, and only found three antineoplastic agents (capecitabine, decitabine and imatinib) that experienced first entry of a generic substitute in the study period. A total of 699 tertiary hospitals had complete procurement records in this period and these were included in our study. Records included the purchasing volume and cost of individual drugs, and basic information on the date of purchasing, the Anatomical Therapeutic Chemical (ATC) code of the product, as well as the manufacturer; 66 monthly values of expenditure and consumption for each of the three antineoplastic agents comprised our samples. Supplement Table 1 provides the descriptive information for these three drugs.

Outcome measures

This study assessed the effect of generic entry on both volume and procurement cost of medicine in this study (total medication and brand-name drug for each antineoplastic agent). The daily dose (DD) in this paper was the daily amounts based on dosage regimen recommended in the manufacturers' instructions of the three products, as approved by China Food and Drug Administration (CFDA). The maintenance dose of capecitabine, decitabine and imatinib in this study were 1250mg, 15mg and 500mg, respectively. We used maintenance dose to calculate numbers of daily dose (a standardized measure of the volume of each product procured) and cost per daily dose (a standardized measure of the procurement cost of each product), respectively.

Statistical analysis

We first created graphic displays of the monthly procurement volume and cost of each study medication in order to observe and describe patterns over time. We then summed the monthly volumes and procurement costs of each medication to determine total monthly volume and total

cost; we calculated the average monthly cost as the total monthly volume divided by the total monthly cost. The expense data were reported in both Chinese Yuan and US Dollars (1 Chinese yuan (CNY) = 0.155 USD based on the 2011 exchange rate).[32]

We used interrupted time-series (ITS) analysis of each study medication to assess the change in total volume and average cost associated with generic entry of substitute products. ITS is a commonly used approach for evaluating changes in longitudinal series following a quasi-experimental intervention occurring at a fixed point in time, such as the date of market entry of generic alternatives. The date of first generic product entering the market (December 2013, December 2012 and August 2013 for capecitabine, decitabine and imatinib, respectively, see Supplement Table 1) was regarded as the intervention time point for ITS analyses. We used segmented regression models that control for baseline trends to estimate changes in the levels and trends of total volume and average cost after generic market entry.

The following model was used for the analysis:

$$Y_t = \beta_0 + \beta_1 * time_t + \beta_2 * entry_t + \beta_3 * timeafterentry_t + \varepsilon_t$$

Y_t is the independent outcome variable (total volume or average cost). β_0 estimates the level of the outcome at the beginning of the observation period. β_1 estimates the linear trend during the pre-intervention period where $time_t$ is an integer variable indicating the time in months at time t from the beginning of the study period. β_2 which is coded as $time_t = 0$ is before generic entry and $time_t = 1$ is after the entry estimates the change in the outcome immediately following the market entry. β_3 estimates the change in trend in the outcome in the post-entry period compared to baseline. ε_t is an estimate of the random error at time t. We set the time point immediately following first market entry to missing in these models in order to allow time for market adjustment and used the Durbin-Watson statistic to test for a serial autocorrelation of the error

terms in the regression models. We performed the ITS analysis using STATA version 13.0.

Patient and public statement

Patients or public were not involved in this study, and ethical approval was not required according to the relevant requirements for conducting this type of survey in China.

Results

Descriptive analysis of changes in volume and cost

The monthly sales of the all three antineoplastic agents increased over time following market entry of generics, although increases in the volume of the brand-name medications tended to attenuate (Supplement Figure 1A, 1B, 1C). For capecitabine, the brand medication remained the dominant product throughout the study period exceeding the total volume of all generic substitutes; for decitabine and imatinib, one of the generic alternatives increased to approximately the same volume as the brand medicine, and total volume of generic alternatives exceeded the brand product.

The cost of all three brand-name antineoplastic drugs remained nearly constant or experienced only a small decrease following market entry of generics, while the cost of most generic drugs decreased over time (Supplement Figure 1D, 1E, 1F). The cost of all generic drugs were consistently lower than the cost of brand-name drugs. By the end of the observation period, the cost of all generic capecitabine were roughly half of the brand product, while all generic imatinib were only 10%-20% of the brand. The cost of generic decitabine, though with high cost variance, were 40% to 60% of the brand product by the end of the observation period.

ITS analysis of changes in total volume and average treatment cost

The entry of generic drugs triggered increases in the total volume of decitabine and imatinib, as

well as reductions in the average cost of treatment for the three drugs (Figure 1, Table 1). Capecitabine volume was increasing by 1,752.5 DDs per month prior to generic entry. There was no significant change in either level or trend of capecitabine volume observed following the launch of the generic versions of the drug. For decitabine, prior to generic entry, the overall volume was increasing by 8.8 DDs per month. There was a significant increase of 11.0 DDs (95%CI: 3.7 to 18.3, p=0.004) per month in overall volume after generic entry. The volume was 437.7 DDs (95%CI: 193.6 to 681.7), higher than expected at the end of observation period. Similarly, the entry of a generic substitute was associated with the acceleration in the upward pre-generic increase of 817.8 DDs of imatinib. Following generic entry, the total volume of imatinib increased by an additional 2,145.5 DDs per month (95%CI: 1,784.1 to 2,506.9, p<0.001), resulting in an estimated increase of 82,559.3 DDs in the last month of the observation period (95%CI: 61,461.9 to 103,656.9). There was no significant change in either the level or the trend of capecitabine volume following the launch of its generic alternative. The trend in average cost of all three agents was stable prior to generic entry with the downward trend of capecitabine (-1.0 CNY per month, 95%CI: -1.3 to -0.7), decitabine (-3.3 CNY per month, 95%CI: -22.0 to 15.3) and imatinib (-0.1 CNY per month, 95%CI: -2.3 to 2.1). The entry of generics was accompanied by significant monthly reductions in the cost of capecitabine, decitabine and imatinib of 3.1 CNY (0.2 USD; 95%CI: -3.6 to -2.6 CNY, p<0.001), 84.7 CNY (13.1 USD; 95%CI: -104.7 to -64.6 CNY, p<0.001) and 21.3 CNY (3.3 USD; 95%CI: -24.2 to -18.4 CNY, p<0.001) per month, respectively. By the end of the study period, this led to estimated reductions in average daily treatment cost of the three antineoplastic medications of 130.3 CNY (20.2 USD; 95%CI: -142.6 to -118.0 CNY), 3,266.4 CNY (506.3 USD; 95%CI: -3459.9 to -3073.0 CNY) and 986.1 CNY (152.8 USD; 95%CI: -1,055.8 to -916.3 CNY), respectively.

ITS analysis of changes in volume and average treatment cost for brand-name drugs

The entry of generic drugs attenuated the upward trend in the volume of three brand-name drugs and even triggered reductions in the volume of brand-name capecitabine. Meanwhile, there were no significant changes of average treatment cost of the brand-name capecitabine and imatinib, while the downward trend of brand-name decitabine cost was attenuated following the generic entry (Figure 2, Table 2). Before generic entry, the volume of brand-name capecitabine, decitabine and imatinib experienced increasing trend by 1,752.5, 8.5 and 815.1 DDs per month. Generic entry led to an immediate increase of 8,278.3 DDs in brand-name imatinib volume (95%CI: 2,396.6 to 14,160.1, p=0.007). There was a significant decreasing trend in the volume of brand-name capecitabine, decitabine and imatinib, respectively (95%CI: -3,206.8 to -1,644.8, p<0.001; 95%CI: -13.1 to -3.4, p<0.001; 95%CI: -1,022.7 to -391.2, p<0.001) after the entry of generic drugs. This resulted in an estimated decrease of 99,342.2 DDs, 283.8 DDs and 22,227.6 DDs in the volume of brand-name capecitabine, decitabine and imatinib in the last month of the observation period (95%CI: -133,858.0 to -64,826.9, p<0.001; 95%CI: -497.3 to -70.2, p=0.009; 95%CI: -37807.7 to -6647.4, p=0.005). The downward trend in cost of brand-name capecitabine and decitabine was stable (95%CI: -1.4 to -0.6, p<0.001; 95%CI: -5.4 to -0.8, p=0.008) while the decreasing trend of brand-name imatinib was not significant. The entry of generics was accompanied by significant increase in the cost of brand-name decitabine of 2.6 CNY (0.4 USD; 95%CI: 0.2 to 5.1 CNY, p=0.04) per month. By the end of the study period, generic entry led to the estimated increase in average daily treatment cost of brand-name capecitabine and decitabine of 28.8 CNY (4.5 USD; 95%CI: 19.9 to 37.6 CNY, p<0.001) and 124.6 CNY (19.3 USD; 95%CI: 9.5 to 239.8 CNY, p=0.03), respectively, while led to the estimated reduction in the cost

of imatinib of 109.7 CNY (17.0 USD; 95%CI: -168.0 to -51.4 CNY, p<0.001).

Discussion

Our study showed that generic entry was associated with increases in the total volume of antineoplastic agents for each of the three study medications, with decreases in volume of the brand-name product. Rather than simply replacing the reductions of brand utilization with lower priced generics, generic entry resulted in increases in the overall market volume. The increased overall use of the three antineoplastic agents suggested that generic entry had a positive effect on the availability, financial accessibility, and overall utilization of the agents. The growing number of users for these important medications showed that generic entry improved patient access for those who may have been unable to afford the more expensive brand-name drugs.[3,33]

Because generic prices tended to be much lower than the prices of brand-name drugs, the average cost per treatment declined substantially after generic entry. This confirmed that generic entry can increase the affordability of pharmaceuticals for patients. The entry of generic drugs resulted in considerable savings and more efficient resource allocation for the Chinese healthcare system, consistent with previous studies.[34,35]

Consistent with previous research, generic entry also had impact on use of brand-name drugs in our study.[19,20] The increasing volume of brand-name decitabine and imatinib experienced attenuation following the entry of generic alternatives, while the volume of brand name capecitabine began to decrease. The latter may have been because capecitabine was the only drug of the three listed in National Reimbursement Drug List since 2009. Under the pressure of increasing deficits in China's medical insurance system,[23] physicians are forced to prescribe generic drugs. This might explain why uptake of generic capecitabine differs from the other two drugs studied. Current studies have demonstrated that insurance coverage enhances medicine

adherence and access.[35,36] Although China has reached near-universal coverage after health reform since 2009,[37] only twenty targeted antineoplastic agents were approved by CFDA before 2017 and none was listed in the National Reimbursement Drug List.[38,39] Thus a strategy to reduce the out-of-pocket cost for these high-cost medicines in China is urgently needed.

We also found that daily treatment cost of the three brand-name drugs tended to remain stable after the entry of generic alternatives, or to decrease only slightly. This illustrates that brand-name manufacturers did not tend to decrease the prices of their products when facing generic competition. Segmentation of the market might explain this phenomenon.[34] 'Loyal consumers' continuing to use these products - in this case oncologists who prefer them - allowed brand-name manufacturers to maintain their high price levels with relatively stable volumes. Information asymmetry may be a contributing cause for this phenomenon; some oncologists may have been more familiar with the brand product than the newer generic substitutes, or they may have been motivated by economic incentives. Furthermore, physicians may have felt a responsibility to ensure that patients received the best therapy. Local generics are not required to be bioequivalent and may be of lower quality, so doctors prefer brand-name products in clinical use.[26,40] Moreover, incentivized by a 15% mark-up rule, hospitals might seek to evade price ceilings by switching to more expensive drugs during the study period.[41] Patients' preferences for brand-name drugs could also constitute a barrier to generic substitution, although this may be a less likely explanation for antineoplastic medications.[42]

However, the results of this study should be interpreted in light of several limitations. First, we were unable to assess drug utilization by individual patients, since only aggregate consumption data were available. Drug consumption data presented in daily dose only provide an estimate of the volume of medications consumed and do not present a precise picture of actual use. Second,

we found only three antineoplastic drugs that had a generic enter the market in the observation period, and these three examples may not represent all antineoplastic medications. In addition, we only focused on the antineoplastic market, so our conclusions may not generalize to other product classes, especially those that do not share the unique features of oncology treatment. Finally, we were unable to measure institutional factors that may have affected prescribing patterns and prices in the Chinese health system during the observation period.

Conclusions

This study demonstrated that the generic entry had substantial positive impacts on the antineoplastic market in China. Generic entry improved the availability of antineoplastic therapy, increased affordability, and generated cost-savings through reduced average treatment costs, which will benefit more patients. However, this study also showed that generic entry had a negative impact on brand-name drugs sales, although the expected reduction in brand-name prices due to competition did not occur.

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Contributors Xiaodong Guan, Dennis Ross-Degnan and Luwen Shi conceptualised and designed the study. Ye Tian screened and completed data extractions. Ye Tian and Chunxia Man contributed to analysis of the data. Xiaodong Guan, Dennis Ross-Degnan and Ye Tian conducted the final analysis and drafted the initial manuscript. All authors contributed to the critical revision of the paper and approved the final manuscript.

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Table 1 Estimates from interrupted time series models of changes in total volume and average treatment cost for all versions of three antineoplastic medications following generic market entry (baseline trend, post-entry level and trend changes, and absolute changes at the end of observation period)

	Total Volume (DD)			Average Cost (CNY)		
	β	95%CI	P	β	95%CI	P
All products of capecitabine						
baseline level	73847.2	62503.6 to 85190.8	<0.001	589.5	582.8 to 596.3	<0.001
baseline trend	1752.5	1207.1 to 2297.9	<0.001	-1.0	-1.3 to -0.7	<0.001
level change	-1927.4	-18519.0 to 14664.2	0.82	3.7	-6.0 to 13.4	0.44
trend change	815.0	-66.5 to 1696.5	0.07	-3.1	-3.6 to -2.6	<0.001
total change by end of observation	32260.9	-6366.3 to 70888.0	0.10	-130.3	-142.6 to -118.0	<0.001
All products of decitabine						
baseline level	85.2	-8.6 to 179.1	0.07	10154.4	9888.8 to 10420.0	<0.001
baseline trend	8.8	2.0 to 15.6	0.01	-3.3	-22.0 to 15.3	0.72
level change	-30.2	-142.0 to 81.6	0.59	266.4	-37.3 to 570.2	0.08
trend change	11.0	3.7 to 18.3	0.004	-84.7	-104.7 to -64.6	<0.001

total change by end of observation	437.7	193.6 to 681.7	<0.001	-3266.4	-3459.9 to -3073.0	<0.001
All products of imatinib						
baseline level	10903.9	5883.6 to 15924.2	<0.001	1185.7	1143.9 to 1227.5	<0.001
baseline trend	817.8	544.7 to 1090.9	<0.001	-0.1	-2.3 to 2.1	0.90
level change	-6343.7	-13187.1 to 499.6	0.07	-43.1	-98.2 to 12.0	0.12
trend change	2145.5	1784.1 to 2506.9	<0.001	-21.3	-24.2 to -18.4	<0.001
total change by end of observation	82559.3	61461.9 to 103656.9	<0.001	-986.1	-1055.8 to -916.3	<0.001

Table 2 Estimates from interrupted time series models of changes in volume and cost for three brand-name antineoplastic medications following generic market entry (baseline trend, post-entry level and trend changes, and absolute changes at the end of observation period)

	Volume (DD)			Cost (CNY)		
	β	95%CI	P	β	95%CI	P
Brand-name capecitabine						
baseline level	73849.7	63800.4 to 83899.1	<0.001	590.3	581.6 to 599.0	<0.001
baseline trend	1752.5	1269.2 to 2235.7	<0.001	-1.0	-1.4 to -0.6	<0.001
level change	2333.7	-12366.5 to 17034.0	0.75	5.4	-6.6 to 17.4	0.37
trend change	-2425.8	-3206.8 to -1644.8	<0.001	0.6	-0.1 to 1.2	0.054
total change by end of observation	-99342.2	-133858.0 to -64826.9	<0.001	28.8	19.9 to 37.6	<0.001
Brand-name decitabine						
baseline level	92.2	31.0 to 153.5	0.004	10150.7	10119.4 to 10182.0	<0.001
baseline trend	8.5	4.0 to 12.9	<0.001	-3.1	-5.4 to -0.8	0.008
level change	63.4	-12.4 to 139.1	0.10	10.3	-26.8 to 47.4	0.58
trend change	-8.3	-13.1 to -3.4	<0.001	2.6	0.2 to 5.1	0.04

total change by end of observation	-283.8	-497.3 to -70.2	0.009	124.6	9.5 to 239.8	0.03
Brand-name imatinib						
baseline level	11171.1	6806.0 to 15536.3	<0.001	1190.6	1139.6 to 1241.6	<0.001
baseline trend	815.1	577.0 to 1053.3	<0.001	-0.4	-3.0 to 2.3	0.79
level change	8278.3	2396.6 to 14160.1	0.007	-41.7	-107.6 to 24.2	0.21
trend change	-706.9	-1022.7 to -391.2	<0.001	-0.3	-3.8 to 3.2	0.87
total change by end of observation	-22227.6	-37807.7 to -6647.4	0.005	-109.7	-168.0 to -51.4	<0.001

Figure legend

Figure 1 Change in total volume and daily cost for three antineoplastic agents before and after generic entry. (A) total volume of all products of capecitabine; (B) average cost of all products of capecitabine; (C) total volume of all products of decitabine; (D) average cost of all products of decitabine; (E) total volume of all products of imatinib; (F) average cost of all products of imatinib

Figure 2 Change in volume and daily cost for three brand-name drugs before and after generic entry. (A) volume of brand-name capecitabine; (B) average cost of brand-name capecitabine; (C) total volume of brand-name decitabine; (D) average cost of brand-name decitabine; (E) total volume of brand-name imatinib; (F) average cost of brand-name imatinib

Supplement Figure 1 Volume and cost of three antineoplastic agents from January 2011 to June 2016. (A) volume of brand-name capecitabine and three generic substitutions; (B) volume of brand-name decitabine and five generic substitutions; (C) volume of brand-name imatinib and three generic substitutions; (D) cost of brand-name capecitabine and three generic substitutions; (E) cost of brand-name decitabine and five generic substitutions; (F) cost of brand-name imatinib and three generic substitutions

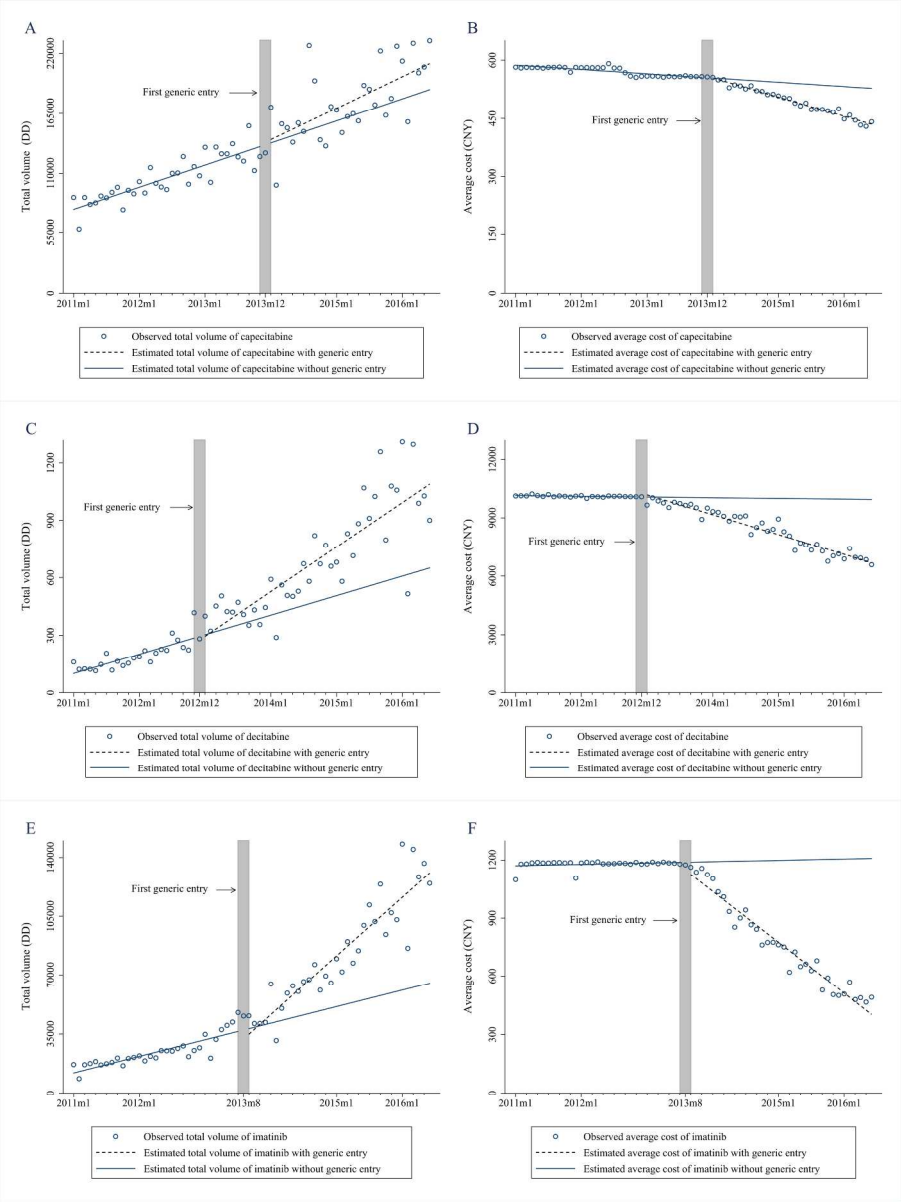

Figure 1 Change in total volume and daily cost for three antineoplastic agents before and after generic entry. (A) total volume of all products of capecitabine; (B) average cost of all products of capecitabine; (C) total volume of all products of decitabine; (D) average cost of all products of decitabine; (E) total volume of all products of imatinib; (F) average cost of all products of imatinib

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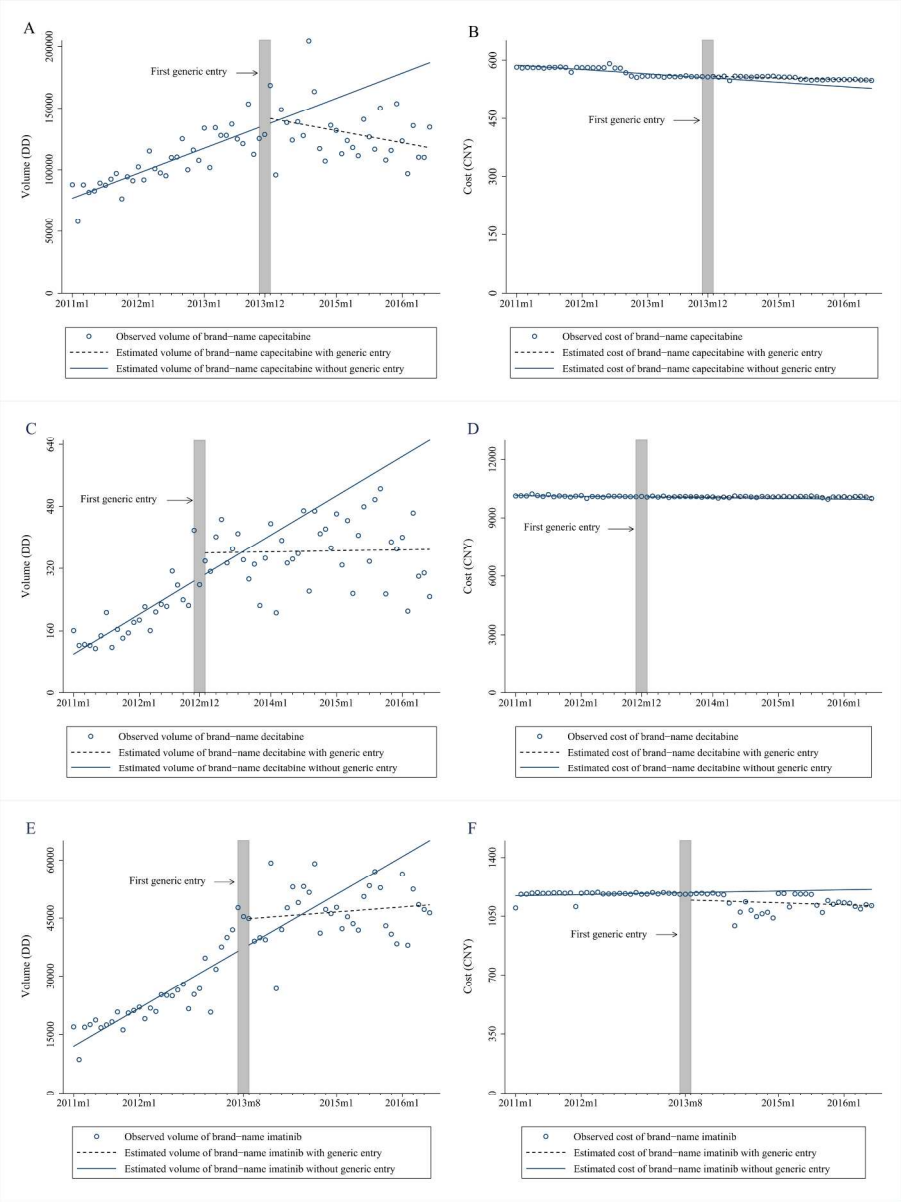

Figure 2 Change in volume and daily cost for three brand-name drugs before and after generic entry. (A)volume of brand-name capecitabine; (B) average cost of brand-name capecitabine; (C) total volume of brand-name decitabine; (D) average cost of brand-name decitabine; (E) total volume of brand-name imatinib; (F)average cost of brand-name imatinib

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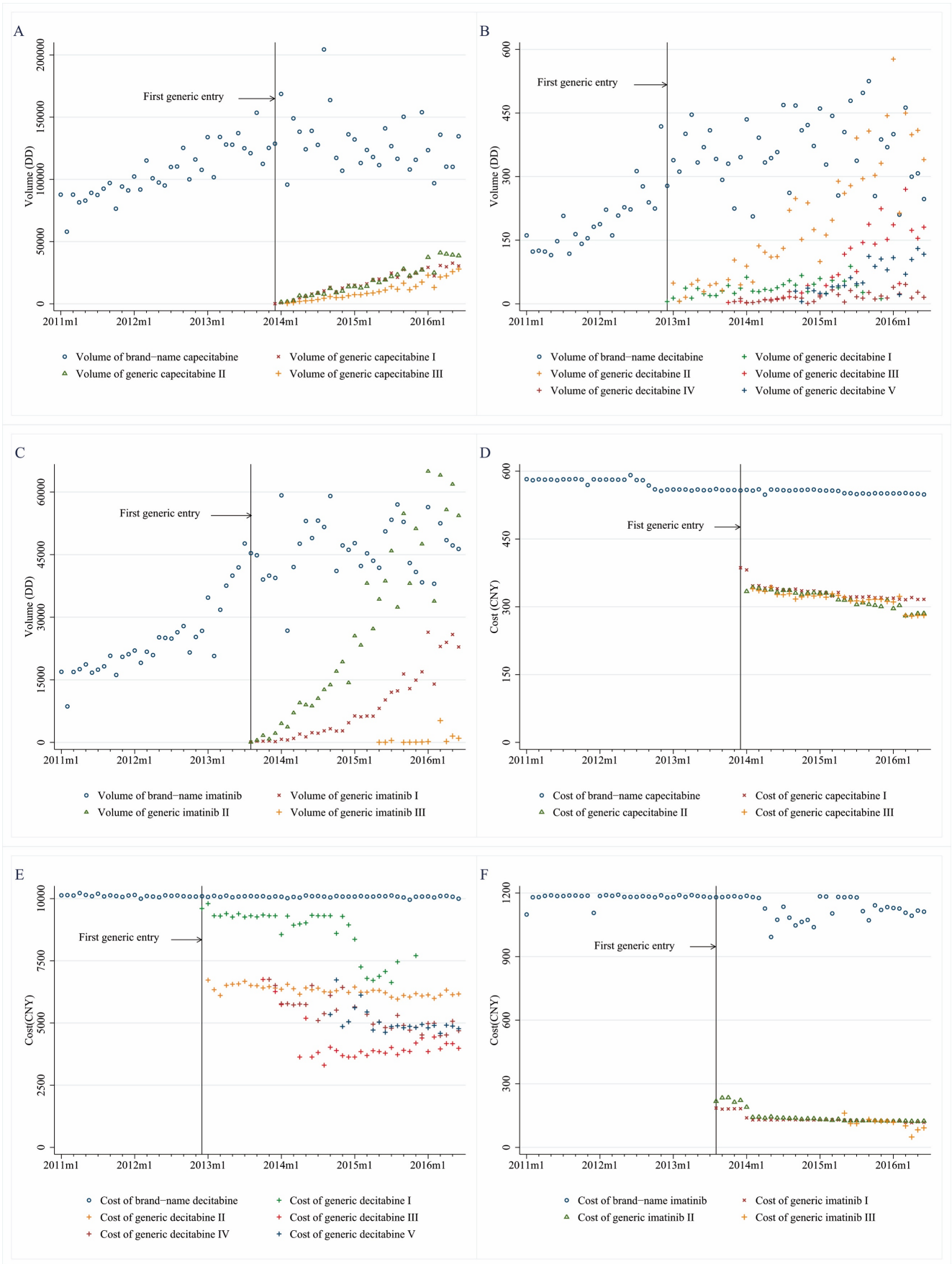
Supplement Table 1 Descriptive summary of three antineoplastic study drugs

ATC	Generic name	Indication	Brand-name producer	First entry of generic	Number of generic entrants
L01BC06	capecitabine	Breast cancer, gastric cancer and colorectal cancer	Genentech (Roche)	2013-12	3
L01BC08	decitabine	Myelodysplastic syndromes	Pharmachemie	2012-12	5
L01XE01	imatinib	Chronic myelocytic leukemia, acute lymphoblastic leukemia, gastrointestinal Stromal Tumor	Novartis	2013-08	3



Supplement Figure 1 Volume and cost of three antineoplastic agents from January 2011 to June 2016. (A) volume of brand-name capecitabine and three generic substitutions; (B) volume of brand-name decitabine and five generic substitutions; (C) volume of brand-name imatinib and three generic substitutions; (D) cost of brand-name capecitabine and three generic substitutions; (E) cost of brand-name decitabine and five generic substitutions; (F) cost of brand-name imatinib and three generic substitutions

CHEERS Checklist

Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force*, provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Page 1, line 3-6
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Page 2-3
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Page 5-6, page 7 line 3-17
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	NA
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Page 7, line 26-31
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	NA
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	NA
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	NA
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	NA
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Page 8, line 8-29
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	NA

	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	NA
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	NA
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 8, line 45-50
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Page 8, line 52-54
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	NA
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Page 8, line 52-54 page 9,line 3-45
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Page 9,line 52-54 page 10-12
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	NA
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	

		of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	NA
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	NA
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Page 13-14, page 15 line 3-41
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Page 16, line 35-38
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

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