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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-022328
Article Type:	Research
Date Submitted by the Author:	13-Feb-2018
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Keywords:	Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, HEALTH SERVICES ADMINISTRATION & MANAGEMENT, PUBLIC HEALTH

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3 **Interrupted Time Series Analysis of the Impact of Generic Market Entry of Antineoplastic**
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5 **Products in China**
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35 **Keywords:** generic entry; access; utilization; cost
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42 **Word count:** 2483
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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

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affordability of antineoplastic agents, which would benefit more patients.

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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

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3 than the international reference prices.^{24,25} Patent protection for originator products and
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5 perceptions about lower safety and efficacy of generics have contributed to the prices of patent
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7 originals (and even off-patent originals) remaining higher than those of generic alternative.²⁶⁻²⁸
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10 Hu et al. illustrated a consistent average price difference of approximately 40% between off-
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12 patent brand-names and generics in the ten-year period from 2002 to 2011.²⁴ Using data from
13
14 Shaanxi province, Jiang et al. showed that in private sector retail pharmacies, the median price
15
16 for original brands was 5.5 times the price of lowest price of generic drugs, while in public sector
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18 health facilities, the ratio can be 11.3 or more.²⁶ There has been little empirical evidence about
19
20 the impact of generic market entry in China.^{27,28} Thus the objective of this study is to analyze the
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22 effect of the market entry of generic alternatives for three antineoplastic medications in China on
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24 utilization and cost in order to provide evidence about how the market responds to generic
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26 alternatives for expensive innovator medications in China.
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33 **Methods**

34 *Data source*

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37 Data were derived from China Medicine Economic Information (CMEI), a large database of drug
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39 procurement records covering 699 tertiary hospitals (accounting for 40% of all tertiary hospitals)
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41 in mainland China. We analyzed the records of 115 antineoplastic agents from January 2011 to
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43 June 2016 and found three antineoplastic agents (capecitabine, decitabine and imatinib) for
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45 which the first generic substitutes entered the market during the observation period. Records
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47 included the purchasing volume and cost of individual drugs, and basic information on the date
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49 of purchasing, the Anatomical Therapeutic Chemical code of the product as well as the
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51 manufacturer; 66 monthly values of expenditure and consumption for each of the three
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3 antineoplastic agents comprised our samples. Table 1 provides the descriptive information for
4 these three drugs.
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6 *Outcome measures*

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

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30 We first created graphic displays of the monthly procurement volume and cost of each study
31 medication in order to observe and describe patterns over time. We then summed the monthly
32 volumes and procurement costs of each medication to determine total monthly volume (total
33 DDDs) and total cost; we calculated the average monthly cost per DDD (average DDDc) as the
34 total monthly volume divided by the total monthly cost.
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42 We used interrupted time-series (ITS) analysis of each study medication to assess the change in
43 total DDDs and average DDDc associated with generic entry of substitute products. ITS is a
44 commonly used approach for evaluating changes in longitudinal series following a quasi-
45 experimental intervention occurring at a fixed point in time, such as the date of market entry of
46 generic alternatives. The first generic entry date (December 2013, December 2012 and August
47 2013 for Capecitabine, Decitabine and Imatinib, respectively, see supplement table 1) was
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3 regarded as the intervention time point for ITS analyses. We used segmented regression models
4 that control for baseline trends to estimate changes in the levels and trends of total DDDs and
5 average DDDc after the intervention.
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10 The following model was used for the analysis:

$$11 \quad Y_t = \beta_0 + \beta_1 * time_t + \beta_2 * entry_t + \beta_3 * timeafterentry_t + \varepsilon_t$$

12 Y_t is the independent outcome variable (total DDDs or average DDDc). β_0 estimates the level of
13 the outcome at the beginning of the observation period. β_1 estimates the linear trend during the
14 pre-intervention period where $time_t$ is an integer variable indicating the time in months at time t
15 from the beginning of the study period. β_2 which is coded as $time_t = 0$ is before generic entry and
16 $time_t = 1$ is after the entry estimates the change in the outcome immediately following the market
17 entry. β_3 estimates the change in trend in the outcome in the post-entry period compared to
18 baseline. ε_t is an estimate of the random error at time t . We set the time point immediately
19 following first market entry to missing in these models in order to allow time for market
20 adjustment and used the Durbin-Watson statistic to test for a serial autocorrelation of the error
21 terms in the regression models. We performed the ITS analysis using STATA version 13.0.
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40 **Results**

41 *Descriptive analysis of changes in volume and cost*

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

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

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28 The entry of generic drugs triggered increases in the total volume of decitabine and imatinib, as
29
30 well as reductions in the average cost of treatment of three drugs (Figure 1, Table 1).
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32 Capecitabine volume was increasing by 1752.5 DDDs per month prior to generic entry. There
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34 was no significant change in either level or trend of capecitabine volume observed following the
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36 launch of generic versions of the drug. For decitabine, prior to generic entry, the overall volume
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38 was increasing by 8.8 DDDs per month. There was a significant increase of 11.0 DDDs (95%CI:
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40 3.7 to 18.3, $p=0.004$) per month in overall volume after the entry of generic drugs. The volume
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42 was 437.7 DDDs (95%CI: 193.6 to 681.7) higher than expected at the end of observation period.
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44 Similarly, the entry of generic substitution was associated with the acceleration in the upward
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46 pre-generic increase of 817.8 DDDs of imatinib. Following generic entry, total volume of
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48 imatinib increased by an additional 2145.5 DDDs per month (95%CI: 1784.1 to 2506.9,
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50 $p<0.001$), resulting in an estimated increase of 82559.3 DDDs in the last month of the
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3 observation period (95%CI: 61461.9 to 103656.9). There was no significant change in either the
4 level or the trend of the capecitabine volume following the launch of generic versions of the
5 drug. The trend in average daily cost of all three agents was stable prior to generic entry with the
6 downward trend of capecitabine (-1.0 per month, 95%CI: -1.3 to -0.7), decitabine (-3.3 per
7 month, 95%CI: -22.0 to 15.3) and imatinib (-0.1 per month, 95%CI: -2.3 to 2.1). The entry of
8 generics was accompanied by significant monthly reductions in the DDDc of capecitabine,
9 decitabine and imatinib of CNY3.1 (95%CI: -3.6 to -2.6, $p<0.001$), CNY84.7 (95%CI: -104.7 to
10 -64.6, $p<0.001$) and CNY21.3 (95%CI: -24.2 to -18.4, $p<0.001$) per month, respectively. By the
11 end of the study period, this led to estimated reductions in average daily treatment cost of the
12 three antineoplastic medications of CNY130.3 (95%CI: -142.6 to -118.0), CNY3266.4 (95%CI: -
13 3459.9 to -3073.0) and CNY986.1 (95%CI: -1055.8 to -916.3), respectively.

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

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32 The entry of generic drugs attenuated the upward trend in the volume of three brand-name drugs
33 and even triggered reductions in the volume of brand-name Capecitabine. Meanwhile, there were
34 no significant changes of average treatment cost of the brand-name Capecitabine and Imatinib,
35 while the downward trend of brand-name Decitabine cost was attenuated following the generic
36 entry (Figure 2, Table 2). Before generic entry, volume of brand-name Capecitabine, Decitabine
37 and Imatinib experienced increasing trend by 1752.5, 8.5 and 815.1 DDDs per month. Generic
38 entry led to an immediate increase of 8278.3 DDDs in brand-name Imatinib volume (95%CI:
39 2396.6 to 14160.1, $p=0.007$). There was a significant increasing trend in the volume of brand-
40 name Capecitabine, Decitabine and Imatinib, respectively (95%CI: -3206.8 to -1644.8, $p<0.001$;
41 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
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3 drugs. This resulted in an estimated decrease of 99342.2 DDDs, 283.8 DDDs and 22227.6 DDDs
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5 in the volume of these three brand-name drugs in the last month of the observation period
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7 (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
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9 -6647.4, $p=0.005$). The downward trend in DDDc of brand-name Capecitabine and Decitabine
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11 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
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13 trend of brand-name Imatinib was not significant. The entry of generics was accompanied by
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15 significant increase in the DDDc of brand-name Decitabine of CNY2.6 (95%CI: 0.2 to 5.1,
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17 $p=0.04$) per month. By the end of the study period, generic entry led to the estimated increase in
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19 average daily treatment cost of brand-name Capecitabine and Decitabine of CNY28.8 and
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21 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
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23 estimated reduction in the cost of Imatinib of CNY109.7 (95%CI: -168.0 to -51.4, $p<0.001$).
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32 Discussion

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34 Our study showed that generic entry was associated with increases in the total volume of
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36 antineoplastic agents, while with decreases in volume of the brand-name. Rather than simply
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38 replacing the reductions of brand utilization with lower priced generics, generic entry resulted in
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40 the increases in the overall market volume. The increased overall use of three antineoplastic
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42 agents suggested the generic entry had a positive effect on the availability, financial accessibility,
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44 and overall utilization of the agents. The growing number of users for these important
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46 medications showed that generic entry improved patient access for those who may have been
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48 unable to afford the more expensive brand-name drugs.^{24,30} Additionally, the entry of generic
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50 medicines might also lead to more optimal treatment of some diseases and additional patients
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52 will benefit from access to the medicines.^{24,31,32}
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3 Because generic prices tended to be much lower than brand-name drugs, the average cost per
4 treatment declined substantially after generic entry. This confirmed that generic entry can
5 increase the affordability of pharmaceuticals for patients. Thanks to the entry of generic drugs,
6 those who could not have afforded expensive brand-name drugs might gain access to less costly
7 generic versions. The entry of generic drugs encouraged the use of generics to realize
8 considerable savings and more efficient resource allocation for the Chinese healthcare system,
9 consistent with previous studies.^{33,34}

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

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3 factor in the observed effects. Incentivized by a 15% mark-up rule, hospitals might seek to evade
4 price ceilings by switching to more expensive drugs.³⁶
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8 The results of this study should be interpreted in light of several limitations. First, drug
9 consumption data presented in DDDs only gives an estimate of consumption and does not
10 present a precise picture of actual use. Second, we only find three antineoplastic drugs in the
11 observation period which may not represent the whole market. Meanwhile, we only focused on
12 the antineoplastic market so that we cannot generalize conclusions about the impact of generic
13 entry to other markets, especially those that do not share the unique features of oncology
14 treatment. Third, we failed to consider the institutional factors that affect prescription and prices
15 in the Chinese health system.
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28 **Conclusions**

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30 This study demonstrated that the generic entry had substantial positive impacts on the
31 antineoplastic market in China. Generic entry improved the availability of antineoplastic therapy,
32 increased affordability, and generated cost-savings through reduced average treatment costs,
33 which will benefit more patients. However, this study also showed that the generic entry seemed
34 have a negative impact on brand-name drugs sales, and the expected competition on brand-name
35 price did not occur.
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47 **Acknowledgements:** We acknowledge all the participants in the study. We are also grateful for
48 the support and cooperation of the staff from the Scientific Development Center of China
49 Pharmacy Association.
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52 **Contributors:** Xiaodong Guan, Dennis Ross-Degnan and Luwen Shi conceptualised and
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3 designed the study. Ye Tian screened and completed data extractions. Ye Tian and Chunxia Man
4
5 contributed to analysis of the data. Xiaodong Guan, Dennis Ross-Degnan and Ye Tian conducted
6
7 the final analysis and drafted the initial manuscript. All authors contributed to the critical
8
9 revision of the paper and approved the final manuscript.
10

11
12 **Funding** This research received no specific grant from any funding agency in the public,
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14 commercial or not-for-profit sectors.
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17 **Competing interests** None declared.
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20 **Provenance and peer review** Not commissioned; externally peer reviewed.
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23 **Data sharing statement** No additional data are available.
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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

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3	trend before generic	8.8	2.0 to 15.6	0.01	-3.3	-22.0 to 15.3	0.72
4							
5	entry						
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8	level change after	-30.2	-142.0 to 81.6	0.59	266.4	-37.3 to 570.2	0.08
9							
10	generic entry						
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12							
13	trend change after	11.0	3.7 to 18.3	0.004	-84.7	-104.7 to -64.6	<0.001
14							
15	generic entry						
16							
17							
18	absolute changes at	437.7	193.6 to 681.7	<0.001	-3266.4	-3459.9 to -3073.0	<0.001
19							
20	the end of						
21							
22	observation period						
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24							
25							
26	imatinib						
27							
28							
29	baseline level	10903.9	5883.6 to 15924.2	<0.001	1185.7	1143.9 to 1227.5	<0.001
30							
31	trend before generic	817.8	544.7 to 1090.9	<0.001	-0.1	-2.3 to 2.1	0.90
32							
33	entry						
34							
35							
36	level change after	-6343.7	-13187.1 to 499.6	0.07	-43.1	-98.2 to 12.0	0.12
37							
38	generic entry						
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40							
41	trend change after	2145.5	1784.1 to 2506.9	<0.001	-21.3	-24.2 to -18.4	<0.001
42							
43	generic entry						
44							
45							
46	absolute changes at	82559.3	61461.9 to 103656.9	<0.001	-986.1	-1055.8 to -916.3	<0.001
47							
48	the end of						
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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

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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

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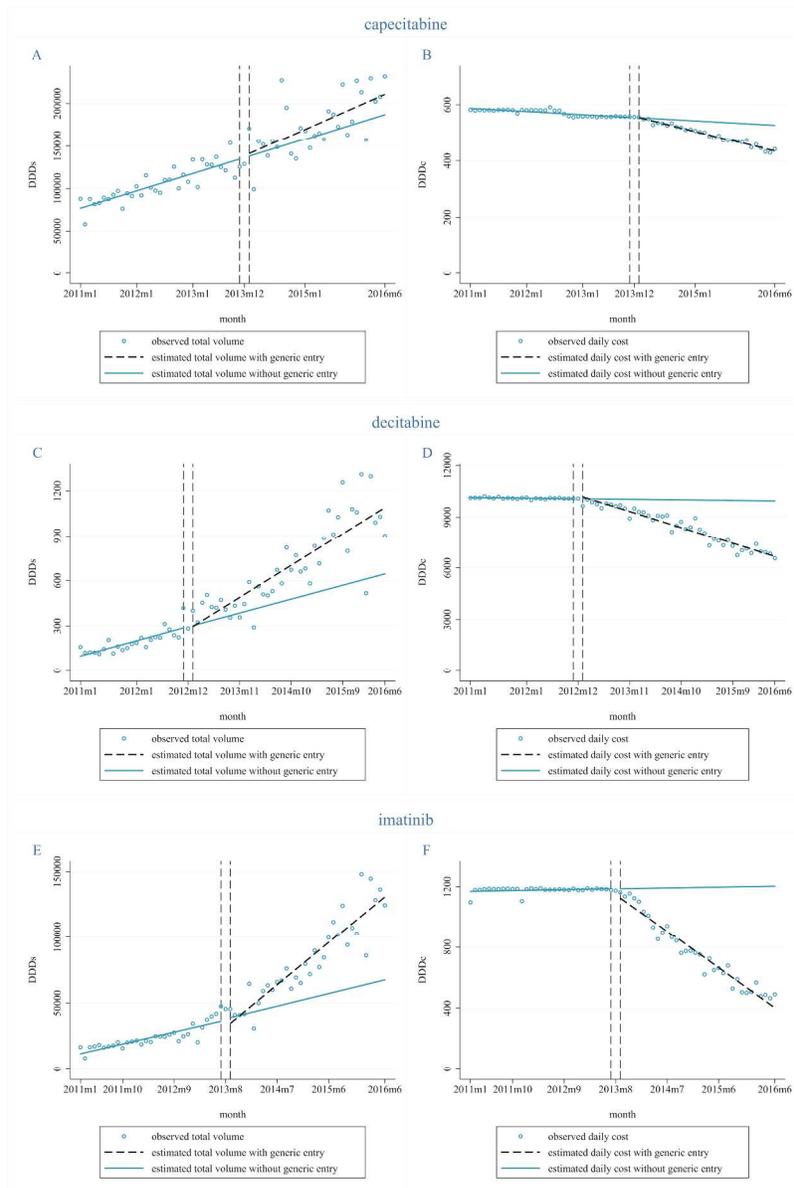


Figure 1 Change in total volume and daily cost for three antineoplastic agents before and after generic entry

203x304mm (300 x 300 DPI)

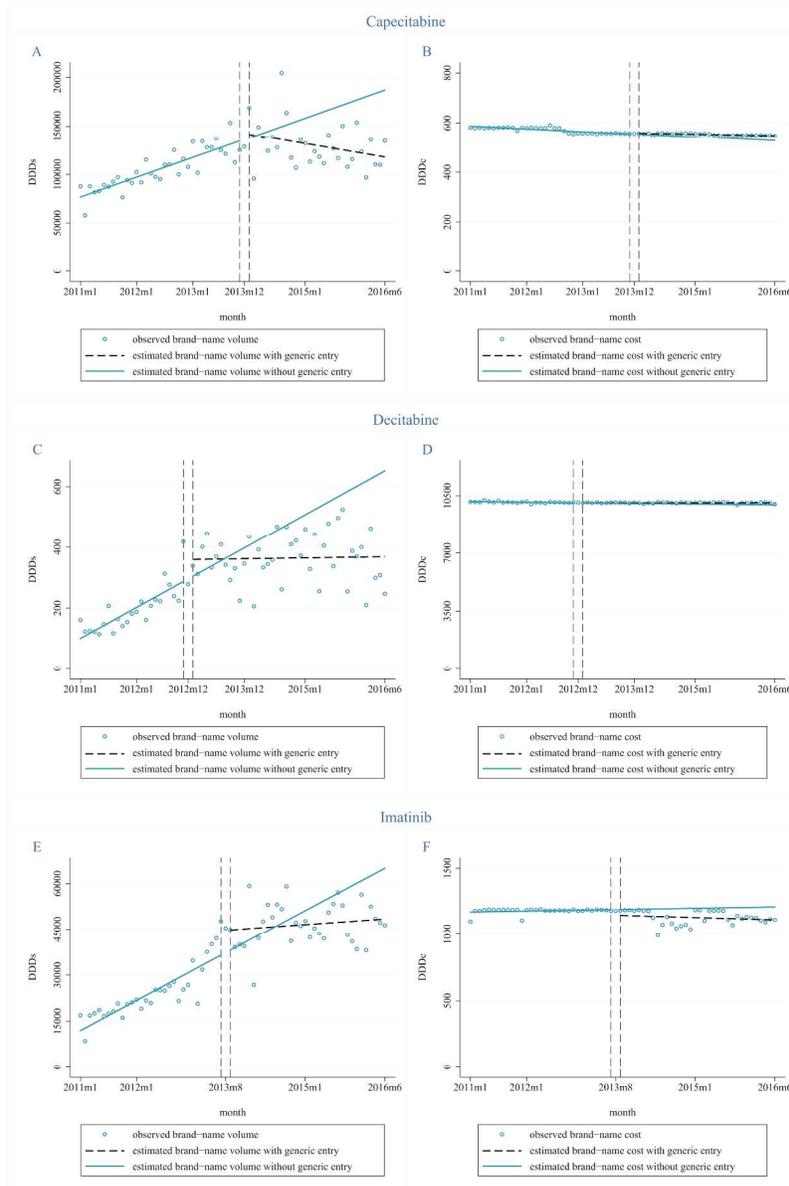
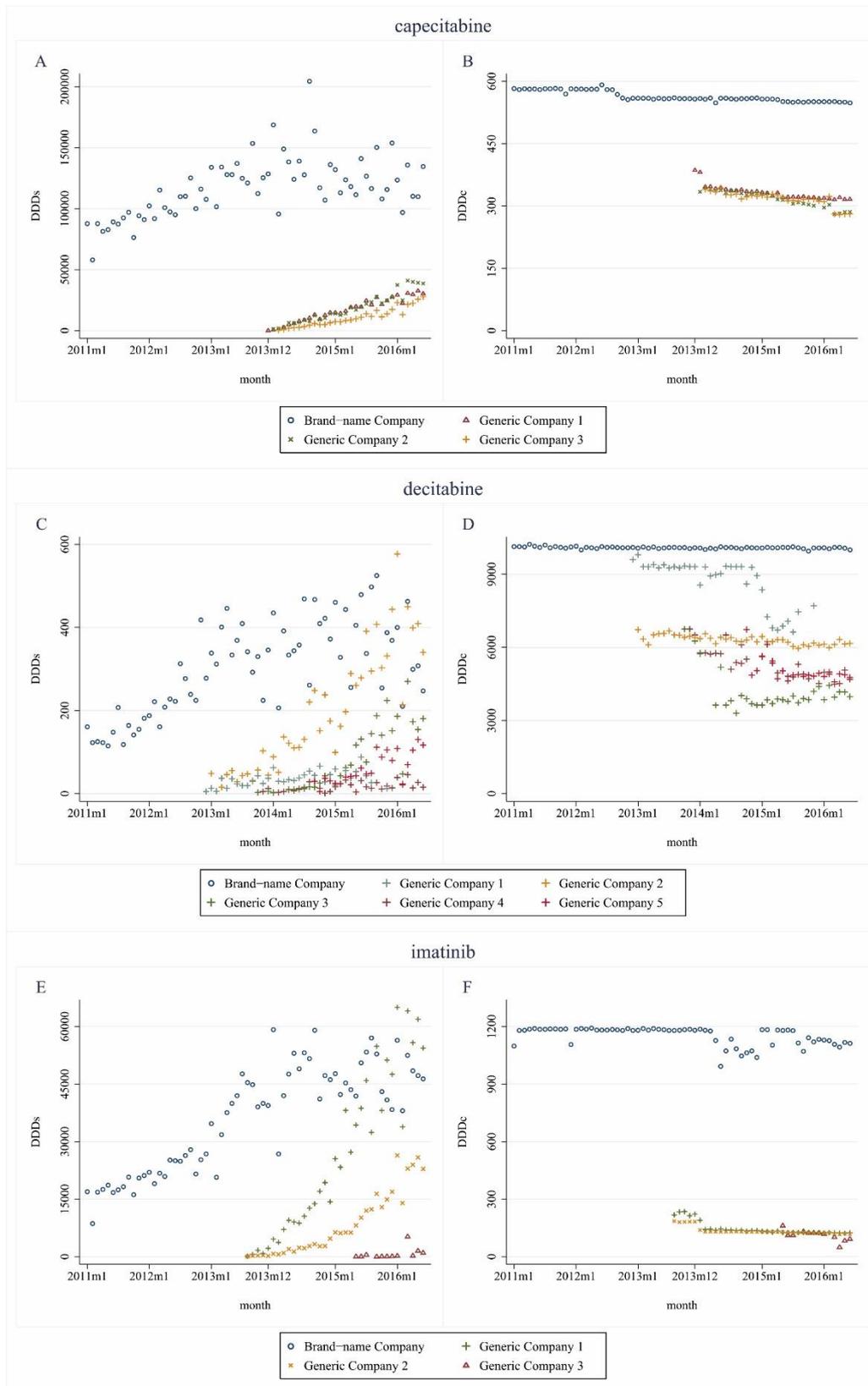


Figure 2 Change in volume and daily cost for three brand-name drugs before and after generic entry

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

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-022328.R1
Article Type:	Research
Date Submitted by the Author:	12-May-2018
Complete List of Authors:	Guan, Xiaodong; Department of Pharmacy Administration and Clinical Pharmacy, School of Pharmaceutical Sciences, Peking University; International Research Center for Medicinal Administration, Peking University Tian, Ye; Department of Pharmacy Administration and Clinical Pharmacy, School of Pharmaceutical Sciences, Peking University Ross-Degnan, Dennis; Harvard Medical School and Harvard Pilgrim Health Care Institute, Department of Population Medicine Man, Chunxia; Department of Pharmacy Administration and Clinical Pharmacy, School of Pharmaceutical Sciences, Peking University Shi, Luwen; Department of Pharmacy Administration and Clinical Pharmacy, School of Pharmaceutical Sciences, Peking University; International Research Center for Medicinal Administration, Peking University
Primary Subject Heading:	Public health
Secondary Subject Heading:	Health policy
Keywords:	Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, HEALTH SERVICES ADMINISTRATION & MANAGEMENT, PUBLIC HEALTH

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3 **Interrupted Time Series Analysis of the Impact of Generic Market Entry of Antineoplastic**
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35 **Keywords:** generic entry; access; utilization; cost
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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

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affordability of antineoplastic agents, which would benefit more patients.

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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

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3 obtain medicines from eligible suppliers through a centralized province-wide supply system at
4 agreed prices negotiated by the provincial government and suppliers.²⁴ A zero-markup policy
5 was introduced which prevents hospitals from marking up essential medicines in order to remove
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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

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

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

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51 We first created graphic displays of the monthly procurement volume and cost of each study
52 medication in order to observe and describe patterns over time. We then summed the monthly
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3 volumes and procurement costs of each medication to determine total monthly volume (total
4 DDDs) and total cost; we calculated the average monthly cost per DDD (average DDDc) as the
5 total monthly volume divided by the total monthly cost. The expense data were reported in both
6 Chinese Yuan and US Dollars (1 Chinese yuan (CNY) = 0.155 USD based on the 2011 exchange
7 rate).³²

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10 We used interrupted time-series (ITS) analysis of each study medication to assess the change in
11 total DDDs and average DDDc associated with generic entry of substitute products. ITS is a
12 commonly used approach for evaluating changes in longitudinal series following a quasi-
13 experimental intervention occurring at a fixed point in time, such as the date of market entry of
14 generic alternatives. The first generic entry date (December 2013, December 2012 and August
15 2013 for capecitabine, decitabine and imatinib, respectively, see Supplement Table 1) was
16 regarded as the intervention time point for ITS analyses. We used segmented regression models
17 that control for baseline trends to estimate changes in the levels and trends of total DDDs and
18 average DDDc after generic market entry.

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21 The following model was used for the analysis:

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

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 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

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3 following first market entry to missing in these models in order to allow time for market
4 adjustment and used the Durbin-Watson statistic to test for a serial autocorrelation of the error
5 terms in the regression models. We performed the ITS analysis using STATA version 13.0.
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8 9 10 *Patient and public statement*

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12 Patients or public were not involved in this study, and ethical approval was not required
13 according to the relevant requirements for conducting this type of survey in China.
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16 17 18 19 **Results**

20 21 *Descriptive analysis of changes in volume and cost*

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23 The monthly sales of the all three antineoplastic agents increased over time following market
24 entry of generics, although increases in the volume of the brand-name medications tended to
25 attenuate (Supplement Figure 1A, 1B, 1C). For capecitabine, the brand medication remained the
26 dominant product throughout the study period exceeding the total volume of all generic
27 substitutes; for decitabine and imatinib, one of the generic alternatives increased to
28 approximately the same volume as the brand medicine, and total volume of generic alternatives
29 exceeded the brand product.
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34 The prices of all three brand-name antineoplastic drugs remained nearly constant or experienced
35 only a small decrease following market entry of generics, while most of the prices of generic
36 drugs decreased over time (Supplement Figure 1D, 1E, 1F). The prices of all generic drugs were
37 consistently lower than the price of brand-name drugs. By the end of the observation period, all
38 generic substitutes for capecitabine were priced at roughly half of the brand product, while all
39 substitutes for imatinib were only 10%-20% of the brand price. The generic substitutes for
40 decitabine experienced the largest price reductions and by the end of follow-up they ranged in
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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

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3 reductions in average daily treatment cost of the three antineoplastic medications of 130.3 CNY
4 (20.2 USD; 95%CI: -142.6 to -118.0 CNY), 3,266.4 CNY (506.3 USD; 95%CI: -3459.9 to -
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6 3073.0 CNY) and 986.1 CNY (152.8 USD; 95%CI: -1,055.8 to -916.3 CNY), respectively.
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10 11 12 *ITS analysis of changes in volume and average treatment cost for brand-name drugs*

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14 The entry of generic drugs attenuated the upward trend in the volume of three brand-name drugs
15 and even triggered reductions in the volume of brand-name capecitabine. Meanwhile, there were
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17 no significant changes of average treatment cost of the brand-name capecitabine and imatinib,
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19 while the downward trend of brand-name decitabine cost was attenuated following the generic
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21 entry (Figure 2, Table 2). Before generic entry, the volume of brand-name capecitabine,
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23 decitabine and imatinib experienced increasing trend by 1,752.5, 8.5 and 815.1 DDDs per month.
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25 Generic entry led to an immediate increase of 8,278.3 DDDs in brand-name imatinib volume
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27 (95%CI: 2,396.6 to 14,160.1, p=0.007). There was a significant decreasing trend in the volume
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29 of brand-name capecitabine, decitabine and imatinib, respectively (95%CI: -3,206.8 to -1,644.8,
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31 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
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33 generic drugs. This resulted in an estimated decrease of 99,342.2 DDDs, 283.8 DDDs and
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35 22,227.6 DDDs in the volume of brand-name capecitabine, decitabine and imatinib in the last
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37 month of the observation period (95%CI: -133,858.0 to -64,826.9, p<0.001; 95%CI: -497.3 to -
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39 70.2, p=0.009; 95%CI: -37807.7 to -6647.4, p=0.005). The downward trend in DDDc of brand-
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41 name capecitabine and decitabine was stable (95%CI: -1.4 to -0.6, p<0.001; 95%CI: -5.4 to -0.8,
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43 p=0.008) while the decreasing trend of brand-name imatinib was not significant. The entry of
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45 generics was accompanied by significant increase in the DDDc of brand-name decitabine of 2.6
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47 CNY (0.4 USD; 95%CI: 0.2 to 5.1 CNY, p=0.04) per month. By the end of the study period,
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3 generic entry led to the estimated increase in average daily treatment cost of brand-name
4 capecitabine and decitabine of 28.8 CNY (4.5 USD; 95%CI: 19.9 to 37.6 CNY, $p<0.001$) and
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6 124.6 CNY (19.3 USD; 95%CI: 9.5 to 239.8 CNY, $p=0.03$), respectively, while led to the
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8 estimated reduction in the cost of imatinib of 109.7 CNY (17.0 USD; 95%CI: -168.0 to -51.4
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10 CNY, $p<0.001$).

15 **Discussion**

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18 Our study showed that generic entry was associated with increases in the total volume of
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20 antineoplastic agents for each of the three study medications, with decreases in volume of the
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22 brand-name product. Rather than simply replacing the reductions of brand utilization with lower
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24 priced generics, generic entry resulted in increases in the overall market volume. The increased
25
26 overall use of the three antineoplastic agents suggested that generic entry had a positive effect on
27
28 the availability, financial accessibility, and overall utilization of the agents. The growing number
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30 of users for these important medications showed that generic entry improved patient access for
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32 those who may have been unable to afford the more expensive brand-name drugs.^{3,33}

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

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46 Consistent with previous research, generic entry also had impact on use of brand-name drugs in
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48 our study.^{19,20} The increasing volume of brand-name decitabine and imatinib experienced
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50 attenuation following the entry of generic alternatives, while the volume of brand name
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52 capecitabine began to decrease. The latter may have been because capecitabine was the only drug
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3 of the three listed in National Reimbursement Drug List since 2009. Under the pressure of
4 increasing deficits in China's medical insurance system,²³ physicians are forced to prescribe
5 generic drugs. This might explain why uptake of generic capecitabine differs from the other two
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10 drugs studied. Current studies have demonstrated that insurance coverage enhances medicine
11 adherence and access.^{35,36} Although China has reached near-universal coverage after health
12 reform since 2009,³⁷ only twenty targeted antineoplastic agents were approved by CFDA before
13 2017 and none was listed in the National Reimbursement Drug List.^{38,39} Thus a strategy to
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19 reduce the out-of-pocket cost for these high-cost medicines in China is urgently needed.

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21 We also found that daily treatment cost of the three brand-name drugs tended to remain stable
22 after the entry of generic alternatives, or to decrease only slightly. This illustrates that brand-
23 name manufacturers did not tend to decrease the prices of their products when facing generic
24 competition. Segmentation of the market might explain this phenomenon.³⁴ 'Loyal consumers'
25 continuing to use these products - in this case oncologists who prefer them - allowed brand-name
26 manufacturers to maintain their high price levels with relatively stable volumes. Information
27 asymmetry may be a contributing cause for this phenomenon; some oncologists may have been
28 more familiar with the brand product than the newer generic substitutes, or they may have been
29 motivated by economic incentives. Furthermore, physicians may have felt a responsibility to
30 ensure that patients received the best therapy. Local generics are not required to be bioequivalent
31 and may be of lower quality, so doctors prefer brand-name products in clinical use.^{26,40}
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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

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

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30 This study demonstrated that the generic entry had substantial positive impacts on the
31 antineoplastic market in China. Generic entry improved the availability of antineoplastic therapy,
32 increased affordability, and generated cost-savings through reduced average treatment costs,
33 which will benefit more patients. However, this study also showed that generic entry had a
34 negative impact on brand-name drugs sales, although the expected reduction in brand-name
35 prices due to competition did not occur.
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47 **Acknowledgements** We acknowledge all the participants in the study. We are also grateful for
48 the support and cooperation of the staff from the Scientific Development Center of China
49 Pharmacy Association.
50
51

52 **Contributors** Xiaodong Guan, Dennis Ross-Degnan and Luwen Shi conceptualised and
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3 designed the study. Ye Tian screened and completed data extractions. Ye Tian and Chunxia Man
4
5 contributed to analysis of the data. Xiaodong Guan, Dennis Ross-Degnan and Ye Tian conducted
6
7 the final analysis and drafted the initial manuscript. All authors contributed to the critical
8
9 revision of the paper and approved the final manuscript.
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11
12 **Funding** This research received no specific grant from any funding agency in the public,
13
14 commercial or not-for-profit sectors.
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17 **Competing interests** None declared.
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20 **Provenance and peer review** Not commissioned; externally peer reviewed.
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23 **Data sharing statement** No additional data are available.
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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

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3 total change by end 437.7 193.6 to 681.7 <0.001 -3266.4 -3459.9 to -3073.0 <0.001
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5 of observation
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9 **All products of imatinib**

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11 baseline level 10903.9 5883.6 to 15924.2 <0.001 1185.7 1143.9 to 1227.5 <0.001
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14 baseline trend 817.8 544.7 to 1090.9 <0.001 -0.1 -2.3 to 2.1 0.90
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17 level change -6343.7 -13187.1 to 499.6 0.07 -43.1 -98.2 to 12.0 0.12
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20 trend change 2145.5 1784.1 to 2506.9 <0.001 -21.3 -24.2 to -18.4 <0.001
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23 total change by end 82559.3 61461.9 to 103656.9 <0.001 -986.1 -1055.8 to -916.3 <0.001
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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 10182.0	to <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

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5 Figure 1 Change in total volume and daily cost for three antineoplastic agents before and after generic
6 entry. (A) total volume of all products of capecitabine; (B) average cost of all products of capecitabine;
7 (C) total volume of all products of decitabine; (D) average cost of all products of decitabine; (E) total
8 volume of all products of imatinib; (F) average cost of all products of imatinib
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14 Figure 2 Change in volume and daily cost for three brand-name drugs before and after generic entry. (A)
15 volume of brand-name capecitabine; (B) average cost of brand-name capecitabine; (C) total volume of
16 brand-name decitabine; (D) average cost of brand-name decitabine; (E) total volume of brand-name
17 imatinib; (F) average cost of brand-name imatinib
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24 Supplement Figure 1 Volume and cost of three antineoplastic agents from January 2011 to June 2016. (A)
25 volume of brand-name capecitabine and three generic substitutions; (B) volume of brand-name decitabine
26 and five generic substitutions; (C) volume of brand-name imatinib and three generic substitutions; (D)
27 cost of brand-name capecitabine and three generic substitutions; (E) cost of brand-name decitabine and
28 five generic substitutions; (F) cost of brand-name imatinib and three generic substitutions
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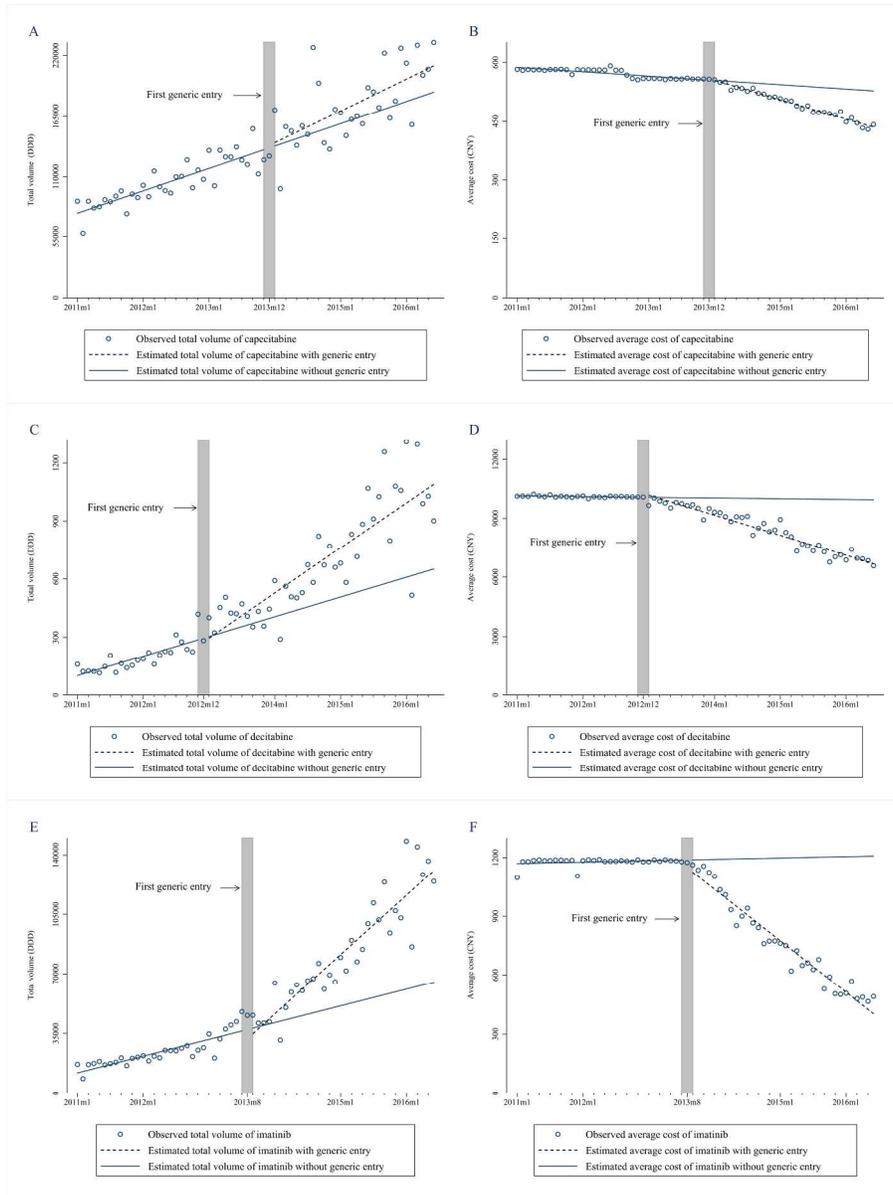


Figure 1 Change in total volume and daily cost for three antineoplastic agents before and after generic entry. (A) total volume of all products of capecitabine; (B) average cost of all products of capecitabine; (C) total volume of all products of decitabine; (D) average cost of all products of decitabine;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

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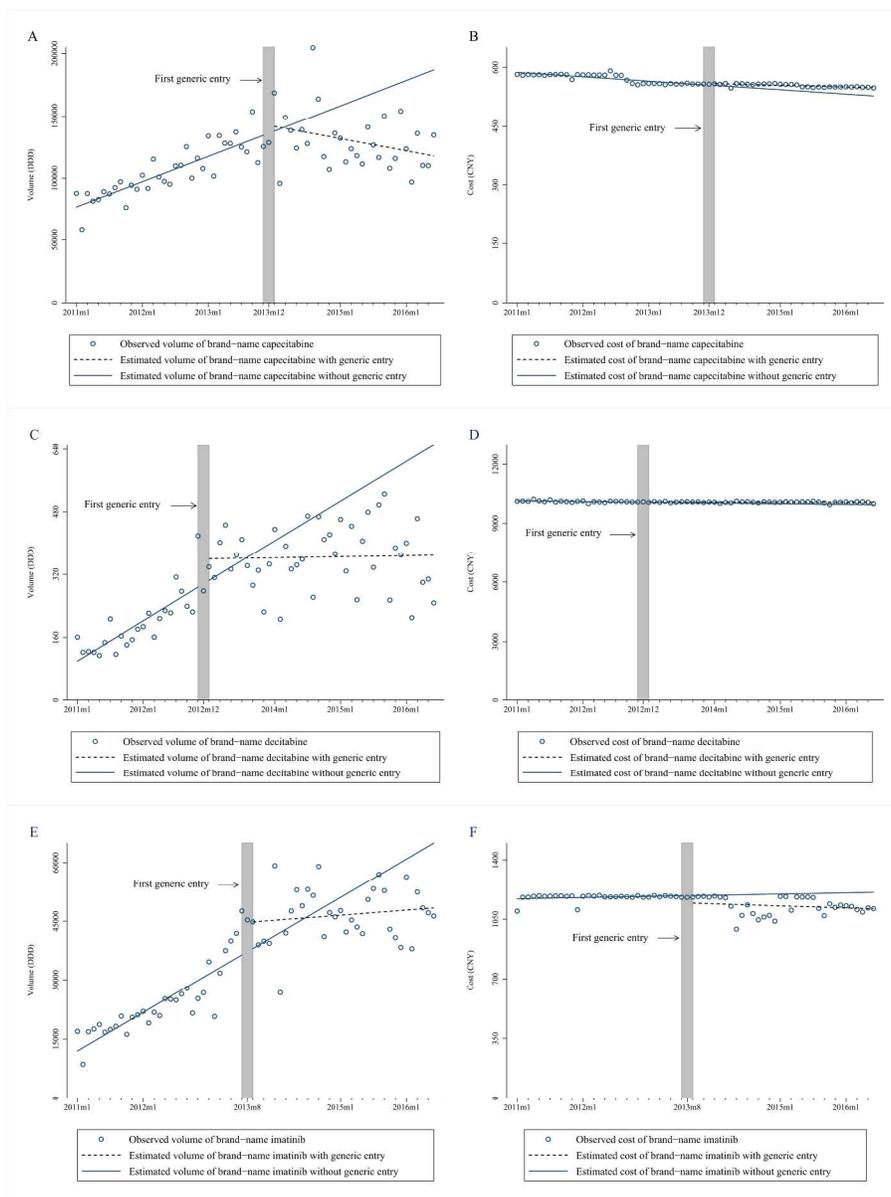
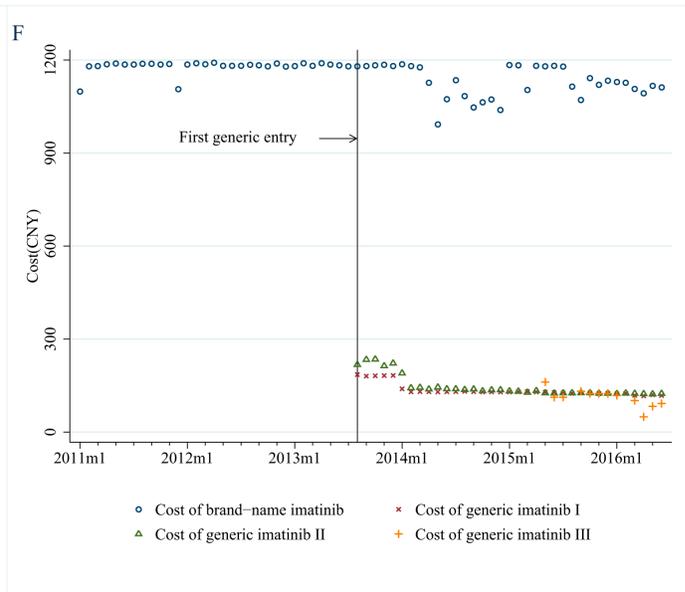
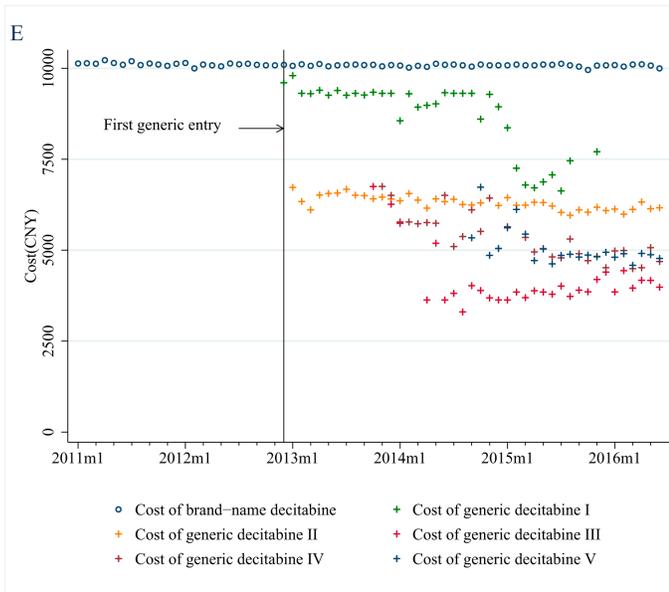
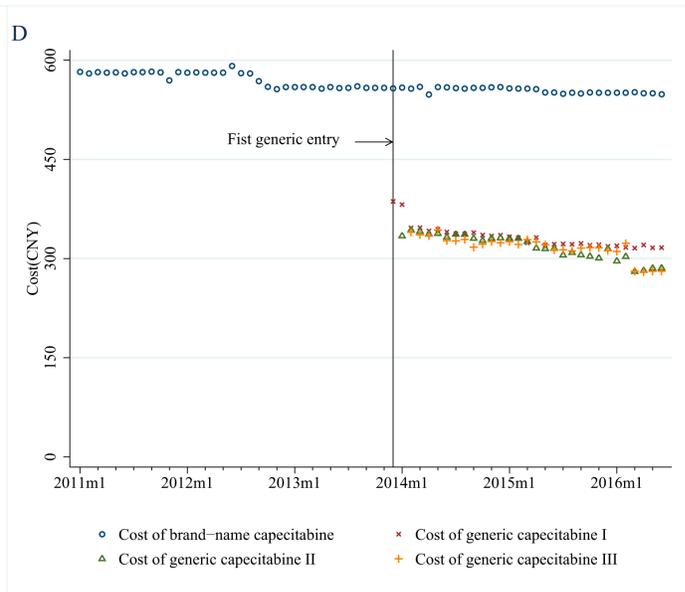
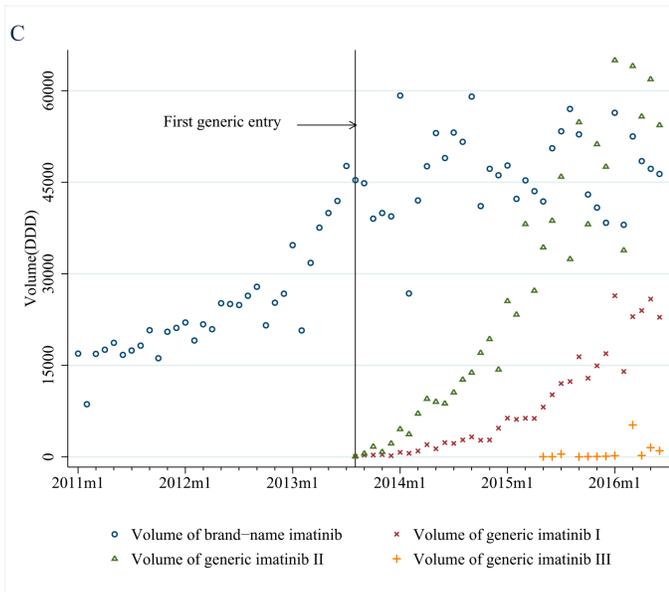
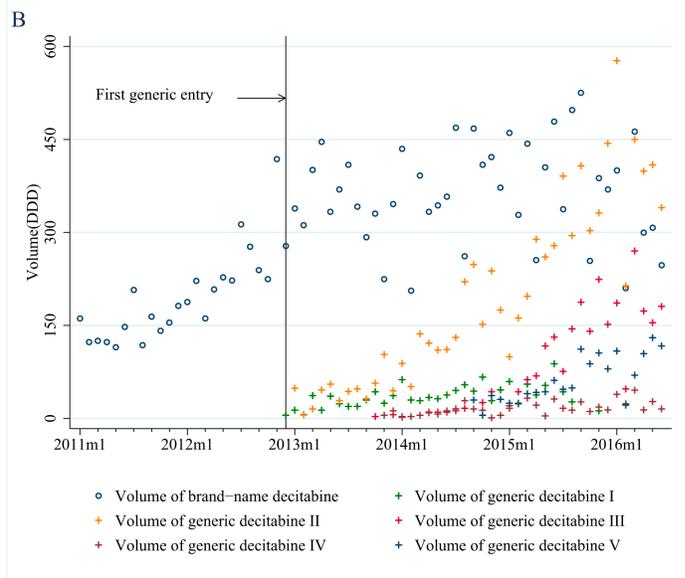
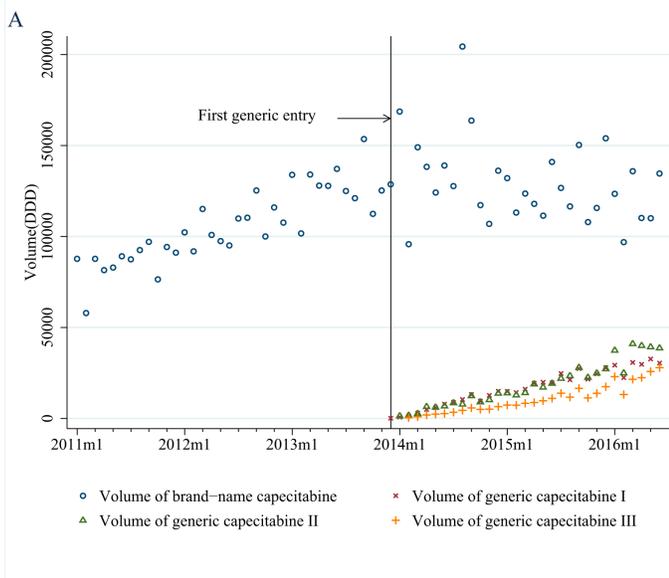


Figure 2 Change in volume and daily cost for three brand-name drugs before and after generic entry. (A) volume of brand-name capecitabine; (B) average cost of brand-name capecitabine; (C) total volume of brand-name decitabine; (D) average cost of brand-name decitabine; (E) total volume of brand-name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



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3 Supplement Figure 1 Volume and cost of three antineoplastic agents from January 2011 to June 2016. (A) volume
4 of brand-name capecitabine and three generic substitutions; (B) volume of brand-name decitabine and five generic
5 substitutions; (C) volume of brand-name imatinib and three generic substitutions; (D) cost of brand-name
6 capecitabine and three generic substitutions; (E) cost of brand-name decitabine and five generic substitutions; (F)
7 cost of brand-name imatinib and three generic substitutions
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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	<i>Single study-based estimates:</i> Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	NA



1		11b	<i>Synthesis-based estimates:</i> Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	_____
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3				
4	Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	_____
5				NA
6	Estimating resources and costs	13a	<i>Single study-based economic evaluation:</i> 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.	_____
7				
8		13b	<i>Model-based economic evaluation:</i> 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.	_____
9				NA
10	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.	_____
11				Page 8, line 45-50
12	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.	_____
13				Page 8, line 52-54
14	Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	_____
15				NA
16	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.	_____
17				Page 8, line 52-54 page 9, line 3-45
18	Results			
19	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.	_____
20				Page 9, line 52-54 page 10-12
21	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.	_____
22				NA
23	Characterising uncertainty	20a	<i>Single study-based economic evaluation:</i> Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	_____
24				

1		of methodological assumptions (such as discount rate, study perspective).	
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4		20b <i>Model-based economic evaluation</i> : Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	NA
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7	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
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13	Discussion		
14	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
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19	Other		
20	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
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24	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.	
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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>

The citation for the CHEERS Task Force Report is:

Husereau D, Drummond M, Petrou S, et al. 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. *Value Health* 2013;16:231-50.



BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-022328.R2
Article Type:	Research
Date Submitted by the Author:	05-Jun-2018
Complete List of Authors:	Guan, Xiaodong; Department of Pharmacy Administration and Clinical Pharmacy, School of Pharmaceutical Sciences, Peking University; International Research Center for Medicinal Administration, Peking University Tian, Ye; Department of Pharmacy Administration and Clinical Pharmacy, School of Pharmaceutical Sciences, Peking University Ross-Degnan, Dennis; Harvard Medical School and Harvard Pilgrim Health Care Institute, Department of Population Medicine Man, Chunxia; Department of Pharmacy Administration and Clinical Pharmacy, School of Pharmaceutical Sciences, Peking University Shi, Luwen; Department of Pharmacy Administration and Clinical Pharmacy, School of Pharmaceutical Sciences, Peking University; International Research Center for Medicinal Administration, Peking University
Primary Subject Heading:	Public health
Secondary Subject Heading:	Health policy
Keywords:	Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, HEALTH SERVICES ADMINISTRATION & MANAGEMENT, PUBLIC HEALTH

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Manuscripts

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3 **Interrupted Time Series Analysis of the Impact of Generic Market Entry of Antineoplastic**
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5 **Products in China**
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35 **Keywords:** generic entry; access; utilization; cost
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42 **Word count:** 2868
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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 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

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affordability of antineoplastic agents, which would benefit more patients.

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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

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3 obtain medicines from eligible suppliers through a centralized province-wide supply system at
4 agreed prices negotiated by the provincial government and suppliers.²⁴ A zero-markup policy
5 was introduced which prevents hospitals from marking up essential medicines in order to remove
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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

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

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

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49 We first created graphic displays of the monthly procurement volume and cost of each study
50 medication in order to observe and describe patterns over time. We then summed the monthly
51 volumes and procurement costs of each medication to determine total monthly volume and total
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3 cost; we calculated the average monthly cost as the total monthly volume divided by the total
4 monthly cost. The expense data were reported in both Chinese Yuan and US Dollars (1 Chinese
5 yuan (CNY) = 0.155 USD based on the 2011 exchange rate).³²
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10 We used interrupted time-series (ITS) analysis of each study medication to assess the change in
11 total volume and average cost associated with generic entry of substitute products. ITS is a
12 commonly used approach for evaluating changes in longitudinal series following a quasi-
13 experimental intervention occurring at a fixed point in time, such as the date of market entry of
14 generic alternatives. The date of first generic product entering the market (December 2013,
15 December 2012 and August 2013 for capecitabine, decitabine and imatinib, respectively, see
16 Supplement Table 1) was regarded as the intervention time point for ITS analyses. We used
17 segmented regression models that control for baseline trends to estimate changes in the levels
18 and trends of total volume and average cost after generic market entry.
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31 The following model was used for the analysis:

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

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33 Y_t is the independent outcome variable (total volume or average cost). β_0 estimates the level of
34 the outcome at the beginning of the observation period. β_1 estimates the linear trend during the
35 pre-intervention period where $time_t$ is an integer variable indicating the time in months at time t
36 from the beginning of the study period. β_2 which is coded as $time_t = 0$ is before generic entry and
37 $time_t = 1$ is after the entry estimates the change in the outcome immediately following the market
38 entry. β_3 estimates the change in trend in the outcome in the post-entry period compared to
39 baseline. ε_t is an estimate of the random error at time t . We set the time point immediately
40 following first market entry to missing in these models in order to allow time for market
41 adjustment and used the Durbin-Watson statistic to test for a serial autocorrelation of the error
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3 terms in the regression models. We performed the ITS analysis using STATA version 13.0.
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5 *Patient and public statement*
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7 Patients or public were not involved in this study, and ethical approval was not required
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9 according to the relevant requirements for conducting this type of survey in China.
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14 **Results**
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16 *Descriptive analysis of changes in volume and cost*
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19 The monthly sales of the all three antineoplastic agents increased over time following market
20 entry of generics, although increases in the volume of the brand-name medications tended to
21 attenuate (Supplement Figure 1A, 1B, 1C). For capecitabine, the brand medication remained the
22 dominant product throughout the study period exceeding the total volume of all generic
23 substitutes; for decitabine and imatinib, one of the generic alternatives increased to
24 approximately the same volume as the brand medicine, and total volume of generic alternatives
25 exceeded the brand product.
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35 The cost of all three brand-name antineoplastic drugs remained nearly constant or experienced
36 only a small decrease following market entry of generics, while the cost of most generic drugs
37 decreased over time (Supplement Figure 1D, 1E, 1F). The cost of all generic drugs were
38 consistently lower than the cost of brand-name drugs. By the end of the observation period, the
39 cost of all generic capecitabine were roughly half of the brand product, while all generic imatinib
40 were only 10%-20% of the brand. The cost of generic decitabine, though with high cost variance,
41 were 40% to 60% of the brand product by the end of the observation period.
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51 *ITS analysis of changes in total volume and average treatment cost*
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53 The entry of generic drugs triggered increases in the total volume of decitabine and imatinib, as
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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

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

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9 Our study showed that generic entry was associated with increases in the total volume of
10 antineoplastic agents for each of the three study medications, with decreases in volume of the
11 brand-name product. Rather than simply replacing the reductions of brand utilization with lower
12 priced generics, generic entry resulted in increases in the overall market volume. The increased
13 overall use of the three antineoplastic agents suggested that generic entry had a positive effect on
14 the availability, financial accessibility, and overall utilization of the agents. The growing number
15 of users for these important medications showed that generic entry improved patient access for
16 those who may have been unable to afford the more expensive brand-name drugs.^{3,33}
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19 Because generic prices tended to be much lower than the prices of brand-name drugs, the
20 average cost per treatment declined substantially after generic entry. This confirmed that generic
21 entry can increase the affordability of pharmaceuticals for patients. The entry of generic drugs
22 resulted in considerable savings and more efficient resource allocation for the Chinese healthcare
23 system, consistent with previous studies.^{34,35}
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26 Consistent with previous research, generic entry also had impact on use of brand-name drugs in
27 our study.^{19,20} The increasing volume of brand-name decitabine and imatinib experienced
28 attenuation following the entry of generic alternatives, while the volume of brand name
29 capecitabine began to decrease. The latter may have been because capecitabine was the only drug
30 of the three listed in National Reimbursement Drug List since 2009. Under the pressure of
31 increasing deficits in China's medical insurance system,²³ physicians are forced to prescribe
32 generic drugs. This might explain why uptake of generic capecitabine differs from the other two
33 drugs studied. Current studies have demonstrated that insurance coverage enhances medicine
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3 adherence and access.^{35,36} Although China has reached near-universal coverage after health
4 reform since 2009,³⁷ only twenty targeted antineoplastic agents were approved by CFDA before
5 2017 and none was listed in the National Reimbursement Drug List.^{38,39} Thus a strategy to
6 reduce the out-of-pocket cost for these high-cost medicines in China is urgently needed.
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10 We also found that daily treatment cost of the three brand-name drugs tended to remain stable
11 after the entry of generic alternatives, or to decrease only slightly. This illustrates that brand-
12 name manufacturers did not tend to decrease the prices of their products when facing generic
13 competition. Segmentation of the market might explain this phenomenon.³⁴ 'Loyal consumers'
14 continuing to use these products - in this case oncologists who prefer them - allowed brand-name
15 manufacturers to maintain their high price levels with relatively stable volumes. Information
16 asymmetry may be a contributing cause for this phenomenon; some oncologists may have been
17 more familiar with the brand product than the newer generic substitutes, or they may have been
18 motivated by economic incentives. Furthermore, physicians may have felt a responsibility to
19 ensure that patients received the best therapy. Local generics are not required to be bioequivalent
20 and may be of lower quality, so doctors prefer brand-name products in clinical use.^{26,40}
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22 Moreover, incentivized by a 15% mark-up rule, hospitals might seek to evade price ceilings by
23 switching to more expensive drugs during the study period.⁴¹ Patients' preferences for brand-
24 name drugs could also constitute a barrier to generic substitution, although this may be a less
25 likely explanation for antineoplastic medications.⁴²
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46 However, the results of this study should be interpreted in light of several limitations. First, we
47 were unable to assess drug utilization by individual patients, since only aggregate consumption
48 data were available. Drug consumption data presented in daily dose only provide an estimate of
49 the volume of medications consumed and do not present a precise picture of actual use. Second,
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3 we found only three antineoplastic drugs that had a generic enter the market in the observation
4 period, and these three examples may not represent all antineoplastic medications. In addition,
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6 we only focused on the antineoplastic market, so our conclusions may not generalize to other
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8 product classes, especially those that do not share the unique features of oncology treatment.
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10 Finally, we were unable to measure institutional factors that may have affected prescribing
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12 patterns and prices in the Chinese health system during the observation period.
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19 **Conclusions**

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21 This study demonstrated that the generic entry had substantial positive impacts on the
22 antineoplastic market in China. Generic entry improved the availability of antineoplastic therapy,
23 increased affordability, and generated cost-savings through reduced average treatment costs,
24 which will benefit more patients. However, this study also showed that generic entry had a
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26 negative impact on brand-name drugs sales, although the expected reduction in brand-name
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28 prices due to competition did not occur.
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38 **Acknowledgements** We acknowledge all the participants in the study. We are also grateful for
39 the support and cooperation of the staff from the Scientific Development Center of China
40
41 Pharmacy Association.
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44 **Contributors** Xiaodong Guan, Dennis Ross-Degnan and Luwen Shi conceptualised and
45 designed the study. Ye Tian screened and completed data extractions. Ye Tian and Chunxia Man
46
47 contributed to analysis of the data. Xiaodong Guan, Dennis Ross-Degnan and Ye Tian conducted
48
49 the final analysis and drafted the initial manuscript. All authors contributed to the critical
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51 revision of the paper and approved the final manuscript.
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3 **Funding** This research received no specific grant from any funding agency in the public,
4 commercial or not-for-profit sectors.
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8 **Competing interests** None declared.
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10 **Provenance and peer review** Not commissioned; externally peer reviewed.
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12 **Data sharing statement** No additional data are available.
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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

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3 total change by end 437.7 193.6 to 681.7 <0.001 -3266.4 -3459.9 to -3073.0 <0.001
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9 **All products of imatinib**

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11 baseline level 10903.9 5883.6 to 15924.2 <0.001 1185.7 1143.9 to 1227.5 <0.001
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14 baseline trend 817.8 544.7 to 1090.9 <0.001 -0.1 -2.3 to 2.1 0.90
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17 level change -6343.7 -13187.1 to 499.6 0.07 -43.1 -98.2 to 12.0 0.12
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20 trend change 2145.5 1784.1 to 2506.9 <0.001 -21.3 -24.2 to -18.4 <0.001
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23 total change by end 82559.3 61461.9 to 103656.9 <0.001 -986.1 -1055.8 to -916.3 <0.001
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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 10182.0	to <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	-283.8	-497.3 to -70.2	0.009	124.6	9.5 to 239.8	0.03
of observation						
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	-22227.6	-37807.7 to -6647.4	0.005	-109.7	-168.0 to -51.4	<0.001
of observation						

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5 Figure 1 Change in total volume and daily cost for three antineoplastic agents before and after generic
6 entry. (A) total volume of all products of capecitabine; (B) average cost of all products of capecitabine;
7 (C) total volume of all products of decitabine; (D) average cost of all products of decitabine; (E) total
8 volume of all products of imatinib; (F) average cost of all products of imatinib
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14 Figure 2 Change in volume and daily cost for three brand-name drugs before and after generic entry. (A)
15 volume of brand-name capecitabine; (B) average cost of brand-name capecitabine; (C) total volume of
16 brand-name decitabine; (D) average cost of brand-name decitabine; (E) total volume of brand-name
17 imatinib; (F) average cost of brand-name imatinib
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24 Supplement Figure 1 Volume and cost of three antineoplastic agents from January 2011 to June 2016. (A)
25 volume of brand-name capecitabine and three generic substitutions; (B) volume of brand-name decitabine
26 and five generic substitutions; (C) volume of brand-name imatinib and three generic substitutions; (D)
27 cost of brand-name capecitabine and three generic substitutions; (E) cost of brand-name decitabine and
28 five generic substitutions; (F) cost of brand-name imatinib and three generic substitutions
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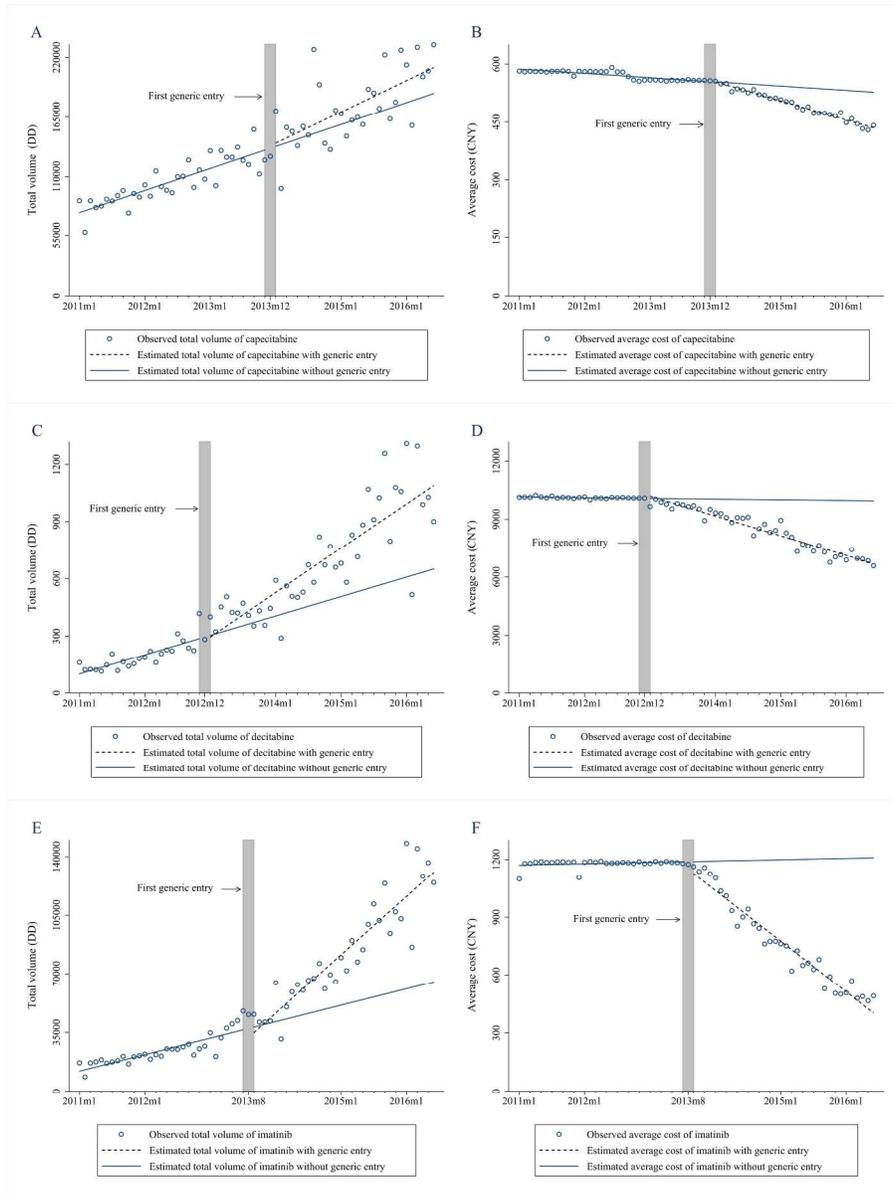


Figure 1 Change in total volume and daily cost for three antineoplastic agents before and after generic entry. (A) total volume of all products of capecitabine; (B) average cost of all products of capecitabine; (C) total volume of all products of decitabine; (D) average cost of all products of decitabine;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

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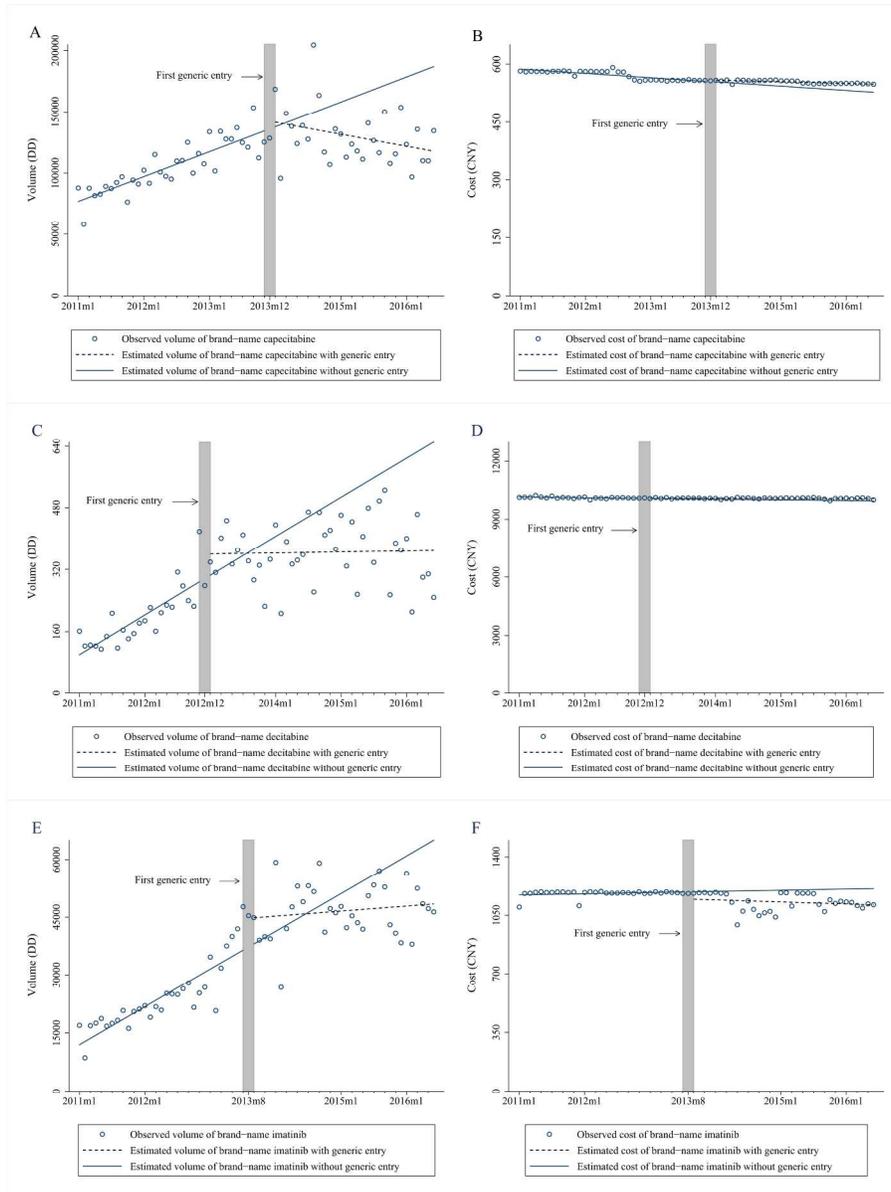
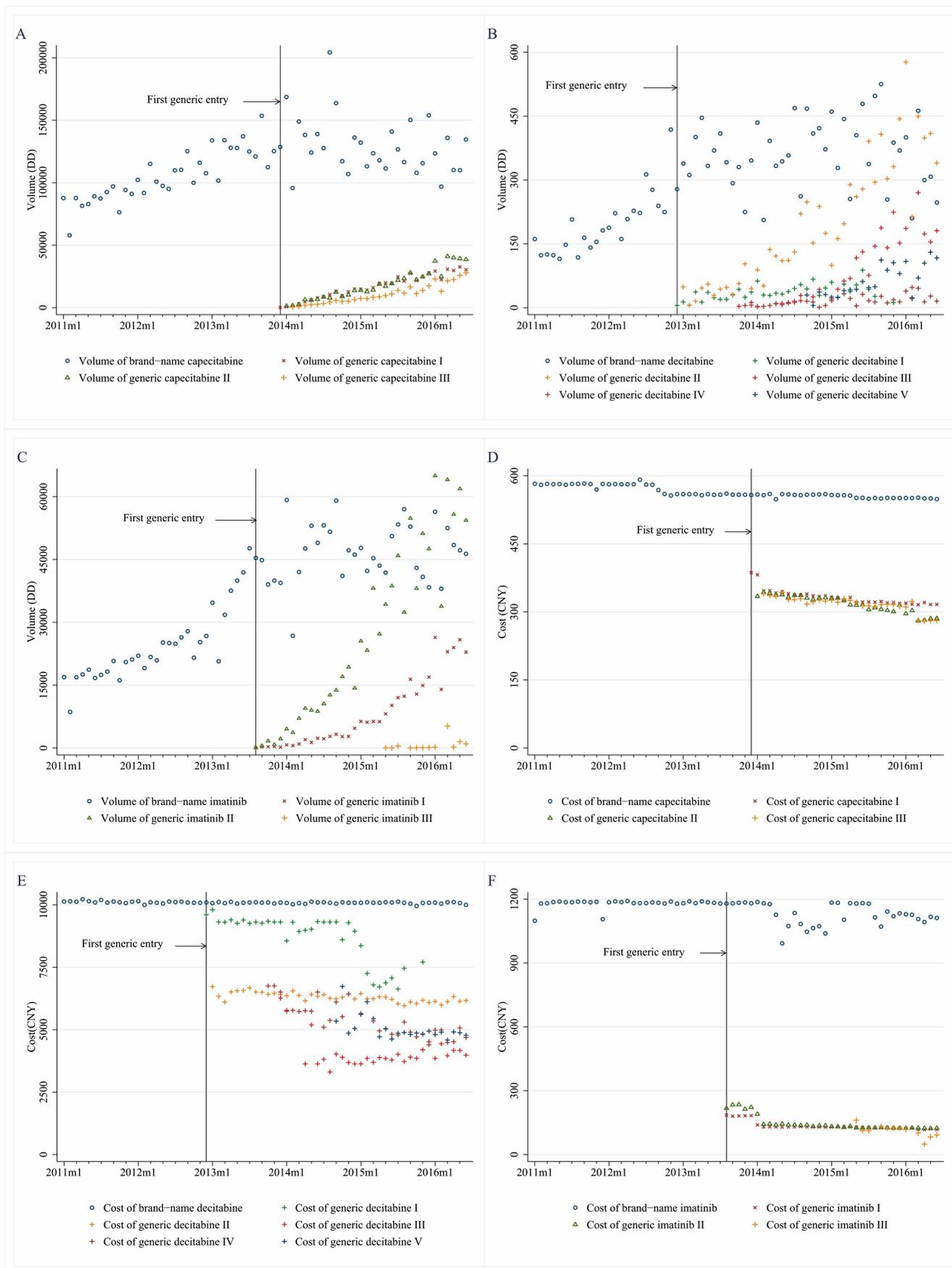


Figure 2 Change in volume and daily cost for three brand-name drugs before and after generic entry. (A) volume of brand-name capecitabine; (B) average cost of brand-name capecitabine; (C) total volume of brand-name decitabine; (D) average cost of brand-name decitabine; (E) total volume of brand-name 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	<i>Single study-based estimates:</i> Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	NA



1		11b	<i>Synthesis-based estimates:</i> Describe fully the methods used for	
2			identification of included studies and synthesis of clinical	
3			effectiveness data.	
4				
5	Measurement and	12	If applicable, describe the population and methods used to	
6	valuation of preference		elicit preferences for outcomes.	
7	based outcomes			NA
8	Estimating resources	13a	<i>Single study-based economic evaluation:</i> Describe approaches	
9	and costs		used to estimate resource use associated with the alternative	
10			interventions. Describe primary or secondary research methods	
11			for valuing each resource item in terms of its unit cost.	
12			Describe any adjustments made to approximate to opportunity	
13			costs.	
14				
15		13b	<i>Model-based economic evaluation:</i> Describe approaches and	
16			data sources used to estimate resource use associated with	
17			model health states. Describe primary or secondary research	
18			methods for valuing each resource item in terms of its unit	
19			cost. Describe any adjustments made to approximate to	
20			opportunity costs.	
21				NA
22	Currency, price date,	14	Report the dates of the estimated resource quantities and unit	
23	and conversion		costs. Describe methods for adjusting estimated unit costs to	
24			the year of reported costs if necessary. Describe methods for	
25			converting costs into a common currency base and the	
26			exchange rate.	Page 8, line 45-50
27				
28	Choice of model	15	Describe and give reasons for the specific type of decision-	
29			analytical model used. Providing a figure to show model	
30			structure is strongly recommended.	Page 8, line 52-54
31	Assumptions	16	Describe all structural or other assumptions underpinning the	
32			decision-analytical model.	NA
33	Analytical methods	17	Describe all analytical methods supporting the evaluation. This	
34			could include methods for dealing with skewed, missing, or	
35			censored data; extrapolation methods; methods for pooling	
36			data; approaches to validate or make adjustments (such as half	
37			cycle corrections) to a model; and methods for handling	
38			population heterogeneity and uncertainty.	Page 8, line 52-54
39				page 9, line 3-45
40				
41				
42	Results			
43	Study parameters	18	Report the values, ranges, references, and, if used, probability	
44			distributions for all parameters. Report reasons or sources for	
45			distributions used to represent uncertainty where appropriate.	
46			Providing a table to show the input values is strongly	
47			recommended.	Page 9, line 52-54
48				page 10-12
49	Incremental costs and	19	For each intervention, report mean values for the main	
50	outcomes		categories of estimated costs and outcomes of interest, as well	
51			as mean differences between the comparator groups. If	
52			applicable, report incremental cost-effectiveness ratios.	NA
53	Characterising	20a	<i>Single study-based economic evaluation:</i> Describe the effects	
54	uncertainty		of sampling uncertainty for the estimated incremental cost and	
55			incremental effectiveness parameters, together with the impact	
56				
57				
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1		of methodological assumptions (such as discount rate, study perspective).	
2			
3			
4		20b <i>Model-based economic evaluation</i> : Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	NA
5			
6			
7	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
8			
9			
10			
11			
12			
13	Discussion		
14	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
15			
16			
17			
18			
19	Other		
20	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
21			
22			
23			
24	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.	
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31 For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT
 32 statement checklist

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 34
 35 **The ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item
 36 CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the
 37 ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices
 38 webpage: <http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp>
 39

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 41 The citation for the CHEERS Task Force Report is:
 42 Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards
 43 (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication
 44 guidelines good reporting practices task force. *Value Health* 2013;16:231-50.
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