Ongoing Initiatives in China to Enhance Prescribing Efficiency: Impact and Proposals for Improvement

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Abstract

Background: Pharmaceutical expenditure is currently rising by 16% per annum in China, greater in recent years. Initiatives to moderate this growth include drug pricing regulations, essential medicine lists and encouraging generic prescribing. These measures are principally concentrated in hospitals as they account for over 80% of total pharmaceutical expenditure. However, no monitoring of prescribing and perverse incentives enhances irrational prescribing.

Objective: Review the influence of recent measures on subsequent utilization and expenditure of high-volume classes in China to provide future guidance.

Methods: Principally a narrative review of published studies of the proton pump inhibitors (PPIs), statins, renin–angiotensin inhibitor drugs and traditional Chinese medicines (TCMs) between 2004 and 2013 in the largest teaching hospital group in Chongqing District.

Results: Applicable increase in drug utilisation including TCMs. Generics typically only 30% to 34% of total utilisation for the molecule for CV medicines, with decreasing trends in recent years. Greater utilisation of generic PPIs; however, this includes generic injectable preparations with considerably higher prices. Prices decreased over time, with appreciable reductions for some generics. Overall, considerable opportunities to save resources without compromising care. Restricting the formulary to just one statin, angiotensin receptor blocker or PPI based on the cheapest one would have saved 50-84% of total accumulated expenditures.

Conclusions: Encouraging to see high utilisation of generic PPIs and low prices for some oral generics. However, real progress will only be made by addressing current perverse financial incentives. Potential reforms could include limiting the number of available medicines in a class to enhance the quality and efficiency of prescribing.

Keywords: ARBs; China; Generics; Incentives; PPIs; Reforms; Statins

Background

As a developing and transitional country, China has seen considerable increases in pharmaceutical expenditure in recent years, growing at over 16% per annum during the past decade and over 35% per annum recently [1-4]. This growth has principally been driven by an increase in insurance coverage [4], although a change in the financing of hospitals has also contributed to this growth [5]. For example, the Chinese government introduced three different types of health insurance in recent years targeting different populations, with coverage reaching over 90% of the population by 2011 [3,6-8], although large disparities still exist [9]. The ultimate goal of the authorities in China is universal coverage by 2020 [6-8,10]. As a result of increased coverage, healthcare expenditure increased from 3.5% to 5% of GDP between 1995 and 2010, equating to a ten-fold increase in yearly per capita spending from US$21 to 220 [8]. This further increased to US$350 per year in 2011 [4]. Expenditure on pharmaceuticals was 42% of total healthcare expenditure in 2009 [3], amounting to CNY580 billion (US$92 billion) in 2012 and CNY695 billion in 2013 [4].

Consequently, the authorities in China have introduced a number of measures in recent years to help moderate this growth given the continual pressure on resources [1,2,8,9,11]. To date, these measures have principally concentrated on trying to control pharmaceutical prices and expenditure in hospitals since more than 80% of total expenditure is currently rising by 16% per annum in China, greater in recent years.
pharmaceutical consumption is currently dispensed in public hospitals in China [1,2,12].

Medicines in hospitals are subject to tenders in each province and municipality with each hospital pharmacy deciding on its own procurement list [5]. Studies suggesting these bidding processes reduced the prices of essential medicines by 16.9% between 2009 and 2011 [8]. However, there are no formal pricing policies for generics in China unlike the policies introduced across Europe, which have resulted in low prices in some countries [13-16]. This lack of policies is at least partially responsible for the fact that there are more than 5,000 pharmaceutical manufacturers in China producing mainly generics [1,4,12]. In addition, pharmaceutical expenditure in hospitals accounted for approximately 40% to 50% of their total income during the past decade [1,4,5,17-20]. This arose because the financial support from the Chinese government to public hospitals declined steadily from approximately 60% of hospital revenues in the 1980s to 8.2% by 2003 or lower [5,21]. As a consequence, hospitals in China must necessarily use the revenues from drug procurement and dispensing for their sustainability [3,5,8,17,22]. Even with the various measures to reduce procurement prices over time, the actual mark-up of medicines in hospitals in 2005 averaged approximately 42% [17]. There are also incentives for physicians to overprescribe drugs as well as prescribe drugs that produce the greatest profit for them and the hospital [1,3,5,23,24]. This has resulted in for instance the overuse of antibiotics, especially injectable antibiotics, as well as injections generally [5,20,22,25-27]. This situation is exacerbated by currently low salaries for physicians in China, with many physicians earning 5000 CNY (US$ 780) a month or less [28], and expected to earn up to 30% of their earnings through profit sharing with hospitals [4].

Demand-side measures to enhance the quality and efficiency of care include the development of an essential medicine list, clinical guidance and guidelines [2,4,8,19,29]. However, there are currently few initiatives among public insurers to monitor the quality of prescribing in China [20,23]. There were reforms specifying that prescriptions should be written by generic (INN) name but limited enforcement to date [1,17,21]. As a consequence, physicians tend to write prescriptions with the generic (INN) name and simultaneously indicate the brand or manufacturer’s name; alternatively, they simply choose medicines listed in hospitals’ information technology (IT) systems with the corresponding brand name or manufacturer [1,17,21]. This situation is not helped by similar patient co-payments for an originator or a generic as well as physicians and hospitals necessarily using the profits from medicine procurement for their sustainability [4,5,21,23].

The objective of this review article is to appraise the influence of the various measures and initiatives introduced in China during the past decade to improve prescribing efficiency among a number of high-volume classes on their subsequent utilization and expenditure. Following this, use the findings to give guidance on potential measures and initiatives that the authorities in China could consider as they strive for universal coverage by 2020. This will be based on measures successfully introduced in Europe, with Europe already attaining and maintaining universal coverage through a variety of initiatives and measures [15,30-33].

Methodology

The authors conducted a narrative review of multiple publications written by themselves and others regarding generics, injectables and Traditional Chinese Medicines (TCMs) in China and across Europe. These included the angiotensin receptor blockers (ARBs), cerebrovascular and cardiovascular (CV) medicines including TCMs, proton pump inhibitors (PPIs) and statins. The authors did not undertake an extensive systematic review of the literature regarding ongoing reforms to enhance the prescribing of low cost generics to give guidance to the authorities in China since such reviews have already been undertaken [30,34-43]. They employed a similar methodology in other review publications regarding generics that they have been involved with [16,30-32,35,44-47]. No attempt has been made to assess the quality of the referenced papers using for instance a modified Jadad scale as a number of the cited publications involved the coauthors.

The following definitions are used in this paper:

**Originator products:** These include products from multinational companies imported into China or manufactured by joint ventures in China founded by multinational pharmaceutical companies. Since these medicines have the original intellectual property and are considered by some to have better quality, they typically command premium prices versus generics.

**Generic products:** These are produced by enterprises with local investment, including state-owned and private enterprises. Their quality has improved in recent years with a number of different measures to enhance manufacturing standards, e.g. in 2009, all medicines on the Chinese essential medicine list were required to undergo quality sampling and testing at the provincial level at least annually and at the central level at least every three years [8]. Good Manufacturing (GMP) standards were also revised in 2011 to further improve the quality of generics manufactured in China [8].

**Traditional Chinese medicines (TCMs):** Usually prepared from herbs or other traditional sources, with some preparations including chemical substances. The main delivery route is via an injection. The characteristics of TCMs are multi target and multi utility, and they are believed to provide comprehensive treatment of patients with chronic cerebrovascular and cerebrovascular diseases enhanced by a high degree of acceptance among both physicians and patients. They are also believed for instance to improve blood circulation and remove blood stasis and activate collaterals [48,49].

Medicine utilisation in the principal studies was typically measured in defined daily doses (DDDs), with the latest DDDs used in line with international guidance [50,51]. The only exception were medicines to treat cerebrovascular and cardiovascular diseases. Here, the unit of utilisation employed were package units as there is currently no reliable source for DDDs for traditional Chinese medicines, most physicians use the package unit as the charging unit when calculating their patients’ expenditure and the specifications of the products typically did not change during the study period [49,52]. The Chinese currency Renminbi “yuan” (CNY) was used in these four studies to determine expenditure over time [21,49,53,54]. Expenditure was typically not converted to either US$ or Euros in the quoted studies as the authors did not want pricing data influenced by currency fluctuations especially during the recent financial crises in Europe and the US. Expenditure figures were also not adjusted for inflation or deflation as the authors wanted to compute actual changes over time as a result of tendering process [21,49,53,54].
Results

The findings for cardiovascular and cerebrovascular medicines including TCMs, ARBs, statins, and the PPIs process [21,49,53,54] will first be displayed in a consolidated table (Table 1) before describing the research findings in more detail. This will also consider potential savings if the authorities in China were to adopt measures that have been successfully introduced in Europe.

| Product Class | Number of products | Total utilisation | Total Expenditure | Price | Generics | Implication |
|---------------|--------------------|-------------------|-------------------|-------|----------|-------------|
| CV medicines (2006 to 2012) [49] | Medicines: 48 TCM: 52 | Total increase- 3.3 fold. TCMs higher at 4.41 fold | Increased overall 4.85 fold TCMs 7.78 fold | New products (typically injectables) with higher prices increased overall expenditure—higher than utilisation | Price reductions (combined): (i) Single generics: 44% reduction (ii) Single originators: 7% reduction (iii) Generic FDCs: 49% reduction (iv) Originator FDCs: 21% reduction | Generics utilisation was 29% to 31% of total utilisation for 12 identified CV medicines Steady growth in the utilisation of originator products despite generics being available at reduced prices (up to 64% to 82% lower prices, e.g. 16% to 35% of originator 2006 prices) Four models were subsequently identified to explain utilisation patterns |
| ARBs (2006-2012) [54] | Single ARBs: 5, FDCs : 3 | 12 fold increase | Rising 9.8 fold to 9.87million CNY in 2012 | Price reductions (combined): (i) Single generics: 44% reduction (ii) Single originators: 7% reduction (iii) Generic FDCs: 49% reduction (iv) Originator FDCs: 21% reduction | Variable use of generics led to their overall utilisation increasing from 24% of total single ARBs in 2006 to 31% in 2008 before falling to between 22% and 24% between 2010 and 2012 This was despite increasing availability of generic ARBs Overall limited utilisation of generics either single or as FDCs despite increasing availability. Utilisation driven by higher list prices |
| Statins (2004-2013) [53] | 6 statins available in two hospital groups | Increasing 32 fold in one hospital group and and 54 fold in the other | Increasing 24 fold in one hospital group and 39 fold in the other | 23% reduction in one hospital group for originator statins vs. 38% for generics (combined) Limited price reduction for generics (combined) in the other hospital group (3%) Greatest price reduction for generic simvastatin (91% and 74% reduction) | In one hospital group, generic utilisation increased from 18% to 28% in 2013 In the other, generic statins accounted for only 9% to 10 % of total statin utilisation Initiatives have resulted in low costs statins (simvastatin) Limited utilisation of generics have increased expenditure inappropriately |
| PPIs (2004-2013) [21] | 6 PPIs were available | Rising 10.4 fold Greatest increase (15.7 fold) for injectable PPIs | Rising10.1 fold, Greater for injectable than oral PPIs | Injectable lansoprazole at 13.4-18.0 fold higher than oral formulation between 2010 and 2013 Price for oral PPIs combined decreased by 34% vs. 19% for injectables | Generic oral PPIs reached 84% of total oral PPIs by 2013 Steady growth in generic injectable PPIs reaching 93% of total injectable utilisation in 2013 Utilisation of lansoprazole grew 28.4 fold especially after the launch of generic injectable lansoprazole in 2010 Utilisation of injectible PPIs is higher than the WHO guidelines for injections among developing countries This needs to be addressed to save resources |

NB: CV medicine = cerebrovascular and cardiovascular medicines; ARBs = angiotensin receptor blockers; FDCs = fixed dose combinations; PPIs = proton pump inhibitors; CNY = Renminbi “yuan”; TCM = Traditional Chinese Medicines

Table 1: Findings for cardiovascular and cerebrovascular medicines, ARBs, statins and PPIs among hospitals in the Chongqing District of China.

Medicines to treat cardiovascular and cerebrovascular diseases

Total utilisation increased 3.3 fold between 2006 and 2012, greatest for TCMs at 4.41 fold [49]. Total procured expenditure increased by 4.85 fold. This was greatest for TCMs at 7.78 fold, helped by a 1.77 fold increase in procured prices over time. This was facilitated by the launch of new products with higher prices, relatively limited competition, and typically administered via injection. As a result, the share of expenditure on TCMs on total CV medicines increased from 35% in 2006 to 57% in 2012.
There was also steady growth in the expenditure of originator products with procured values of more than one million CNY in 2012 (Table 2). Telmisartan is included in view of its rapid rise in recent years.

Table 2: Total procured expenditure of 12 originator cardiovascular and cerebrovascular medicines in CNY in the Chongqing District 2006 to 2012 [49].

|        | 2006     | 2007     | 2008     | 2009     | 2010     | 2011     | 2012     |
|--------|----------|----------|----------|----------|----------|----------|----------|
| Nifedipine | 408492   | 634433   | 1059304  | 850230   | 1316610  | 1161800  | 1731451  |
| Felodipine | 95357    | 230576   | 428861   | 671820   | 1008336  | 1182072  | 1731600  |
| Amlodipine | 303142   | 338616   | 353088   | 715638   | 952956   | 860417   | 1378092  |
| Benazepril | 307854   | 400865   | 528242   | 775505   | 826081   | 1114124  | 1348217  |
| Losartan  | 426804   | 796349   | 1369708  | 1661338  | 2660355  | 2395552  | 2738551  |
| Irbesartan | 226915   | 506012   | 698425   | 1124449  | 1721435  | 1812780  | 2349528  |
| Valsartan  | 77222    | 185410   | 618854   | 913311   | 1026720  | 1618663  | 2301978  |
| Telmisartan | 54881    | 122496   | 286660   | 304960   | 396140   | 507059   | 894730   |
| Atorvastatin | 162092   | 168840   | 357763   | 1393600  | 2106480  | 2204728  | 2631632  |
| Simvastatin | 365627   | 790921   | 1579420  | 1726296  | 1702398  | 1907784  | 1420866  |
| Metoprolol | 208246   | 256202   | 297993   | 357173   | 445450   | 823460   | 1416130  |
| Bisoprolol | 285392   | 433904   | 565653   | 544171   | 1062686  | 1121249  | 1242144  |

There was variable utilisation of generics over the years (Figure 1), with overall utilisation of generic CV medicines stabilising at 29% to 31% of total utilisation for the 12 cardiovascular products in recent years (Table 1 and Figure 1).

Concerns with irrationality in prescribing were further confirmed by the continued growth in the utilisation of originator medicines despite generics being available at lower prices (Table 1) [49].

Based on the findings, there appears to be four different models in operation for CV medicines in China. These are [49]:

**Model 1** – a substantial drop in prices adversely affects subsequent use (with higher prices translating into higher profitability for the hospitals). This is illustrated by some products no longer procured or with limited procurement after an appreciable price decline, e.g. limited utilisation of generic versus originator simvastatin with a 67% price reduction for generic simvastatin over the study period (originator price only decreased by 29%).

**Model 2** – a small decrease in procured prices, e.g.10%, does not appear to typically change utilisation trends (may also be an increase). One explanation for this could be that the whole supply chain,
including manufacturers and prescribing doctors, adjust their profitability mix accordingly. This is illustrated by generic benazepril and telmisartan as well as both originator and generic atorvastatin, with increased utilisation over time despite limited decreases in procured expenditure/unit.

**Model 3** - Some medicines maintain a relatively high price and their consumption substantially increases, e.g. originator bisoprolol, metoprolol and oxiracetam. Other products with relatively stable prices over time also increased their volume in line with market growth, e.g. amlodipine besylate.

**Model 4** - "CNY 20 phenomenon", i.e. when the procurement price per pack drops to near or below CNY 20, utilization rates usually decreases/stops increasing. Examples include generic nifedipine, generic enalapril and generic simvastatin (Figure 1).

### Angiotensin receptor blockers

As documented in Table 1, the prescribing of ARBs alone or as FDCs in the Chongqing hospital group increased 12 fold between 2006 and 2012 [54]. This greatest increase was seen with telmisartan and valsartan among the single ARBs and irbesartan among fixed dose combinations (FDCs) (Table 3). Total ARB expenditure (single and FDCs) increased appreciably from just over 1million in 2006 to 9.87million CNY in 2012 (Table 3).

| Utilisation (DDDs) | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 |
|--------------------|------|------|------|------|------|------|------|
| Candesartan        | 36960| 62580| 70560| 60480| 30880| 52400| 83190|
| Irbesartan         | 46550| 84700| 156602| 255240| 384850| 358200| 452400|
| Losartan           | 61740| 114597| 182700| 252210| 414400| 379400| 495740|
| Telmisartan        | 23912| 71218| 191968| 203420| 268800| 345072| 523250|
| Valsartan          | 18060| 38150| 103663| 154560| 179200| 290080| 424235|
| Irbesartan FDC     | 2800 | 27314| 71610| 116060| 178080| 216720| 301280|
| Losartan FDC       | 19306| 38850| 78400| 79100| 122990| 131600| 173250|
| Valsartan FDC      | 350  | 1960 |      |      |      |      |      |
| Expenditure (CNY)  |      |      |      |      |      |      |      |
| Candesartan        | 199459| 281139| 304114| 260669| 132613| 173592| 275783|
| Irbesartan         | 212367| 377438| 655902| 1068325| 1619697| 1450664| 1808932|
| Losartan           | 300385| 540814| 859548| 1146623| 1886528| 1677952| 2102293|
| Telmisartan        | 60594| 178430| 473949| 502192| 663812| 746167| 1126164|
| Valsartan          | 93891| 209218| 624353| 920495| 1056180| 1640615| 2329578|
| Irbesartan FDC     | 14548| 144646| 354734| 573381| 866556| 904673| 1241512|
| Losartan FDC       | 126419| 255535| 510160| 514715| 787467| 755792| 990422|
| Valsartan FDC      | 2437 | 13647|      |      |      |      |      |

Table 3: Utilisation (DDDs) and expenditure (CNY) of ARBs in the Chongqing hospital group 2006 to 2012 [54].

The lesser increase in total expenditure (9.8 fold) versus utilisation (12 fold) was helped by reduced expenditure/DDD for the various ARBs over the study period [54]. This was greatest for single generics (44% reduction over time vs. only 7% for single originator ARBs) resulting in an overall 17% price reduction for single ARBs combined over time. However, there was a greater procured price reduction for combined originator FDCs at 21% [54]. Expenditure/DDD for generic FDCs combined were lower by 49% in 2012 versus combined originator prices in 2006.

The variable use of generic ARBs led to their overall utilisation increasing from 24% of total single ARBs in 2006 to 31% in 2008 before falling to between 22% and 24% between 2010 and 2012. This was despite increasing availability of generic ARBs (there were over 250 generic ARBs in China in 2013). There was though increased utilisation of generic ARB FDCs, reaching 19% of total ARB FDCs in 2012 (54). Overall there were [54]:

- A 21.5 fold increase in ARB FDC utilisation between 2006 and 2012 (DDD based), greatest for irbesartan FDC (Table 3) leading to increased use of ARB FDCs as a % of total ARBs.
- Variable use of generic ARBs, i.e. a rapid increase in the utilisation of generic irbesartan peaking at 44% of total irbesartan in 2009 before declining to 33% by 2012 (DDD based). There was a similar pattern for telmisartan, with generics peaking at 40% of total telmisartan in 2011 before falling to 30% in 2012.
- There was also increased utilisation of generic candesartan in 2012 vs. 2006, although this varied by year, resulting in its share of total single ARBs falling from 20% in 2006 to between 2% to 4%
between 2010 and 2012. No originator candesartan was procured between 2006 and 2012.

- Considerable variation in procured price reductions for generics by the end of the study. This ranged from -22% for generic valsartan to -39% for candesartan and -54% for telmisartan. This resulted in variable differences in procured prices for generic versus originator single ARBs over time. This greatest for valsartan reaching -59% in 2012. This compares to a maximum of -32% for irbesartan in 2012, with the difference steadily growing over time.

**Statins**

There was an appreciable increase in the prescribing of statins, 32 fold from 2004 to 2013 in the Third Military Medical University (TMMU) hospitals and 54 fold among the Chongqing Medical University (CMU) hospitals (Table 1). There was a lower increase in total expenditure (24 fold in the TMMU hospital and 39 fold in the CMU hospital) compared with utilisation, helped by reducing expenditure/DDD for the various statins [53].

In the TMMU hospitals, there were lower price reductions (-23%) for originator statins combined in 2013 vs. 2004 versus a 38% decrease for generics (combined), which was greatest for generic simvastatin (-74%). This resulted in an overall 27% price reduction for combined statins between 2004 and 2013. In the CMU hospitals, there was also considerable variation in the price reductions for individual generic and originator statins over time. The greatest price decline was seen with generic simvastatin (-91%). As a result, generic simvastatin in TMMU hospitals in 2013 was 49% below 2013 originator prices and 86% below 2013 originator prices in CMU hospitals [53].

Overall, there was variable uses of generic statins in both hospital groups. In the TMMU hospitals, there was a rapid increase initially in generic utilisation, e.g. generic atorvastatin was 97% of total atorvastatin utilization in 2004 (DDD based) before declining to 22% in 2009 and subsequently increasing to between 45% and 55% in recent years. A similar pattern was seen with generic pravastatin once procured, peaking at 50% of total pravastatin in 2009 before falling to 24% in 2010 and subsequently increasing to between 41% and 57% in recent years. However, there was limited utilisation of either generic pitavastatin and rosuvastatin in recent years. This variable use of generic statins resulted in their overall utilisation increasing from 18% of total statins in 2004 to 28% in 2013 among TMMU hospitals [53] (Table 4).

### Table 4: Utilisation (DDDs) and expenditure (CNY) of PPIs in the Chongqing hospitals 2004 to 2013 [21].

| Year | Total PPIs | Total oral PPIs | Total injectable PPIs | Total Injectable Generics | Total Injectable Originators | Total Oral | Total Oral PPIs | Total Injectable | Total Injectable Generics | Total Injectable Originators |
|------|------------|----------------|----------------------|--------------------------|---------------------------|-----------|----------------|----------------|--------------------------|---------------------------|
| 2004 | 242113     | 195845         | 48268                | 125062                   | 70783                     | 21136     | 113075         | 210854         | 62673                    | 35518                     |
| 2005 | 346445     | 273527         | 72918                | 210854                   | 62673                     | 21136     | 113075         | 210854         | 62673                    | 35518                     |
| 2006 | 474146     | 361071         | 265059               | 48268                    | 72918                     | 21136     | 113075         | 210854         | 62673                    | 35518                     |
| 2007 | 824062     | 559003         | 481956               | 72918                    | 265059                    | 21136     | 113075         | 210854         | 62673                    | 35518                     |
| 2008 | 1151371    | 669415         | 589805               | 21136                    | 481956                    | 21136     | 113075         | 210854         | 62673                    | 35518                     |
| 2009 | 1390171    | 800366         | 728464               | 1390171                  | 589805                    | 21136     | 113075         | 210854         | 62673                    | 35518                     |
| 2010 | 1765443    | 1036879        | 727087               | 1765443                  | 728464                    | 21136     | 113075         | 210854         | 62673                    | 35518                     |
| 2011 | 2113162    | 1386099        | 656717               | 2113162                  | 727087                    | 21136     | 113075         | 210854         | 62673                    | 35518                     |
| 2012 | 2427049    | 1770332        | 725396               | 2427049                  | 656717                    | 21136     | 113075         | 210854         | 62673                    | 35518                     |
| 2013 | 2509195    | 1783799        | 723596               | 2509195                  | 725396                    | 21136     | 113075         | 210854         | 62673                    | 35518                     |

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In the CMU hospitals, decreasing utilisation of generic atorvastatin resulted in generic statins accounting for only 9% to 10% of total statin utilisation (DDD based) in 2012 and 2013 [53].

Proton pump inhibitors

PPI utilisation among the Chongqing hospitals increased 10.4 fold between 2004 and 2013, greatest for injectable PPIs at 15.7 fold (Table 1) [21]. At one stage (2008 and 2009), injectable PPIs accounted for 42% of total PPI utilisation before falling to below 30% in recent years (Table 4).

This utilisation of injectable PPIs is considerably higher than the WHO guidelines for injections among developing countries, and appreciably higher than the suggested limited use generally given the effectiveness of oral PPIs [27,55,56].

Total PPI expenditure increased steadily during the study period, rising 10.1 fold between 2004 and 2013 (Table 4).

The growth in expenditure was also greater for injectable than for oral PPIs, resulting in expenditure on injectable PPIs increasing from 57% of total PPI expenditure in 2004 to 71% to 74% between 2008 and 2013 (Tables 1 and 4) [21].

Utilisation of oral generic PPIs grew at a faster rate than for oral PPIs, resulting in utilisation on injectable PPIs increasing from 64% of total PPIs in 2004 (DDD basis) to between 82% and 87% between 2007 and 2013 (Table 4). There was also greater growth for generic versus originator injectable PPIs, enhanced by these typically being produced by domestic manufacturers. As a result, the utilisation of generic injectable PPIs grew from 46% of total injectables in 2004 to 93% between 2011 and 2013. Utilisation of lansoprazole grew 28.4 fold during the course of the study, especially after the launch of generic injectable lansoprazole in 2010, with the utilisation of pantoprazole declining from 2010 onwards due to falling utilisation of generic injectable pantoprazole [21].

Price reductions were seen for the various PPI formulations over time. These were greater for oral formulations combined (-34%) than injectable formulations combined (-19%) [21]. The greatest procured price reduction was seen with generic oral omeprazole. In 2010, prices were 87% below the 2004 originator price (expenditure/DDD). The price of generic injectable omeprazole in 2013 was 80% below the 2004 originator price (expenditure/DDD). However, this was accompanied by limited utilisation [21]. Injectable PPIs were typically 4.2 to 6.8 fold more expensive (CNY/DDD) than their equivalent oral formulations. The greatest difference was seen with injectable lansoprazole at 13.4 to 18.0 fold higher than the equivalent oral formulation between 2010 and 2013 [21].

Potential savings

Overall, there are considerable opportunities for savings within the Chongqing District as there was typically greater utilization of more expensive originator CV medicines versus generics as well as greater utilization of more expensive injectable than oral PPIs (Table 4).

Table 5 documents the potential savings based on experiences among European countries to obtain low prices for generics and enhance their utilisation versus originators and patented products in a class [13-16]. This also includes limiting the number of available products within a class based on the experiences of Stockholm County Concil [13,57,58].

| Class       | Potential savings                                                                                                                                                                                                 |
|-------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ARBs [54,59-63] | Restricting the formulary to just one ARB and one ARB FDC based on the cheapest ARB (telmisartan for single ARBs and irbesartan for FDCs) would have saved an accumulated 17 million CNY for this hospital group alone between 2006 and 2012 with limited differences between the ARBs at therapeutically equivalent doses. In addition, no concerns with reduced outcomes or persistence from generics versus originators Total expenditure on ARBs (alone and FDCs) was 9.87 million CNY in 2012 |
| Statins [15,53,58,64-67] | Restricting the formulary to just one statin based on the cheapest statin (simvastatin) with limited differences between the statins at therapeutically equivalent doses, and no concerns with patient outcomes with generics versus originators, would have saved an accumulated 27 million CNY for the TMMU hospital group alone between 2004 and 2013 (Total statin expenditure was 15.3 million CNY in 2013). Accumulated savings could increase to 49 million CNY with the attainment of generic prices similar to low prices achieved in some Western European countries Simvastatin is recommended in the ‘Wise List’ in Stockholm County Council. In addition, SIGN (Scottish Intercollegiate Guidelines Network) in Scotland advocate the use of only 40 mg simvastatin for the prevention of cardiovascular disease as well as for primary prevention of cardiovascular disease in patients with Type 1 diabetes. In addition, 40mg simvastatin or 10mg atorvastatin for the prevention of cardiovascular disease in patients with Type 2 diabetes irrespective of starting lipid levels |
| PPIs [21,57,58,68] | Restricting hospital procurement to just one oral PPI, i.e. generic omeprazole, following similar initiatives among European countries and regions, e.g. the ‘Wise List’ in Stockholm Metropolitan Healthcare Region and Germany placing all PPIs in a Jumbo class as no perceived clinical differences between them, and (i) assuming its procured price in 2010 continued to the end of the study and (ii) limiting the utilisation of injectable generic PPIs to just 5% of total PPIs – generic omeprazole (cheapest) - at its procured price each year, would have saved an accumulated estimated 249.65 million CNY for this hospital group during the study period This amounts to 84% of total accumulated PPI expenditure |

Table 5: Potential savings among the hospitals in the Chongqing district from greater use of generics.
Discussion

We believe there are a number of key points arising from the findings (Tables 1 to 5 and Figure 1) to provide future guidance to the authorities in China as they strive for universal coverage. Positive findings include the considerable price reductions for some generics over time, e.g. 87% to 91% price reductions for generic omeprazole and generic simvastatin respectively during the study period (Table 1) [21,53]. This is similar to the low prices for high volume generics seen among a number of European countries, e.g. Netherlands, Sweden and the UK [13,15,69], showing that competition among generic companies is working to lower prices. There was also appreciable utilization of generic oral PPIs at 82% to 87% of total oral PPI utilization, between 2007 and 2013 [21]. This is similar to the high utilization of generics versus originators among a number of European countries [14,15,36,37,44,45,59]. For instance in Scotland, generics accounted for between 98% to 99% of total utilization across a range of molecules, aided by high voluntary INN prescribing [15].

However, there were a number of areas of concern providing opportunities for the future. These include firstly typically greater utilization of more expensive originators versus generics among the cardiovascular medicines as well as still appreciable utilization of TCMs despite often limited evidence (Table 1). The latter is facilitated by the launch of new TCMs with higher prices, relatively limited competition, and the fact that they are typically administered by injection (Table 1) [21,49,53,54]. Secondly, there was high and unsupportable utilization of injectable versus oral PPIs (Table 1) [21].

Thirdly, the findings from the research into the utilization and expenditure on cardiovascular and cerebrovascular medicines in the Chongqing District resulted in the 4 postulated models which are a potential concern (Table 1) [49]. Models 1, 2 and 4 are a particular concern and need to be addressed to enhance universal coverage. However, we acknowledge that these postulated models need to be researched in more detail to be able to provide comprehensive and robust guidance to the Chongqing District in particular and China in general in future years, although we are already seeing a reduction in the utilization of TCMs [49]. This will be the subject of future research activities.

We believe the considerable differences in the utilization of oral generic PPIs versus originators, and compared to the findings with cardiovascular medicines including ARBs and statins (Figure 1 and Table 1), can be explained by a number of factors [21,49,53,54]. These include the fact that diseases of the cardiovascular system are seen as having greater importance in China compared with acid-related stomach disorders, and originator medicines are thought to have a more consistent effect in treating cardiovascular diseases than generics. Secondly, there are few TCMs to treat peptic ulcer diseases unlike cardiovascular and cerebrovascular diseases [49]; consequently, domestic generic oral manufacturers have less competition. Lastly, it is believed some physicians think that doubling the dose of oral generic PPIs could lead to the same effectiveness as the originators at the standard dose, and this is acceptable in this situation [21]. However, we cannot say this with certainty without further research in this area.

Potential measures that could be considered by the authorities in Chongqing District and elsewhere in China to enhance patient access to medicines without prohibitive increases in expenditure include firstly enhancing INN prescribing, building on earlier measures. This could become compulsory if needed [30,70]. Secondly, measures to enhance the rational use of medicines, building on the essential medicine list concept [8,58]. This includes encouraging the preferential prescribing of evidenced based low cost and equally effective generics versus more expensive originators [16,57,58]. Thirdly, introducing measures to restrict prescribing choices within a class. This was seen with the ARBs among European countries including Austria, Belgium, Croatia, Lithuania and Sweden [47,59,71-73].

Limiting physician choices enhances their familiarity with the medicines they prescribe, potentially reducing adverse drug reactions and drug: drug interactions. This was the philosophy behind the generation of the ‘Wise List’ in the Stockholm Metropolitan Healthcare Region, which contains approximately 200 drugs including first and second line choices covering most of the therapeutic needs in ambulatory care [57,58]. High adherence rates at 80 to 90% of all utilization in ambulatory care to the voluntary ‘Wise List’ are achieved by the involvement of prescribers in the selection process, robust methodologies for selecting the medicines based principally on published evidence of effectiveness and safety, a comprehensive communication programme as well as physician trust in the guidance and regular feedback [57,58,74]. Research findings have also shown that increased adherence to the ‘Wise List’ reduces costs without compromising care [13,58,75]. There are similar examples in Spain and Scotland [15,57,76]. Other initiatives include potentially introducing prescribing quality indicators, which are increasingly used in healthcare as a tool to achieve safe and quality clinical care and cost-effective therapy, as well as for professional learning, remuneration, and accreditation along with financial incentives [74,77-79]. Adoption of such measures will realise considerable savings in the Chongqing District without compromising care (Table 5).

However, real progress to enhance the rational use of medicines in China will only be made by addressing the current perverse financial incentives for both physicians and hospitals that have translated into high utilization of more expensive originators than generics as well as high and unjustified utilization of TCMs and injectable medicines when effective oral medicines are available (Table 1). This is starting to happen [3].

In conclusion, the authors believe that despite the limitations in their research including no formal systematic review for the reasons stated, the findings from the various disease areas and classes provide guidance to the authorities in China on potential ways forward to enhance the quality and efficiency of future prescribing. This has been achieved by reviewing a number of cases histories and comparing the findings with those from a number of different European countries. We are already seeing countries learning from each other especially in Europe, and this will grow.

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Conflicts of Interest

The authors declare that they have no conflicts of interest apart from those stated. No writing assistance was utilized in the production of this manuscript.
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