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Cross-sectional study of zero-medicine markup policy, prescribing trends and drug indicators using WHO/INRUD methodology in Chinese Jingzhou area

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Abstract: In order to get the baseline data of Chinese Zero-Medicine Markup Policy, before any administrative intervention we investigated the drug indicators, the prescribing trends and economic data. In accordance with the WHO/INRUD criteria and cross-sectional studies, the retrospective methods along with equal sample interval of systematic sampling were used. We sampled from daily prescriptions and calculated the means over a twelve day period. We sampled from 38,246 adult prescriptions, the sampling percent was 3.06%, and the drugs prescribed by generic name were 100.00%. During 2012-2014, the percentage of antibiotic cost in the total daily drug cost decreased from17.44% to 8.01%, the percentage of prescriptions with antibiotic prescribed decreased from 12.64% to 9.64%, the percentage of encounters with an injection prescribed decreased from 15.21% to 12.77%. The average drug cost per antibiotic prescription ranged from ¥169.33 to 186.66. By comparing the related data, Zero-Medicine Markup Policy had greatly affected prescribing indicators, some indicators had a decreasing trend and became more rational, Zero-Markup Medicine Policy decreased both the patient-level and hospital-level drug expenses, and the reformation of the Zero-Medicine Markup Policy was steadily advanced.

Keywords: Cross-sectional study, markup policy, pharmacoepidemiology, rational use of drugs, economic data, drug indicator, prescribing trend, antibiotic percent, injection percent.

INTRODUCTION

In September 2012, Beijing selected five tertiary hospitals (Zeng *et al*, 2019) as pilots to remove the previously allowed 15% fixed percent markup (Ni *et al*, 2021) for drug sales. The researcher extracted 2012-2015 individual-level data from the Beijing Urban Employee Basic Medical Insurance database to evaluate the short-term and long-term impacts of medical expenses. In 2016 the Chinese public hospitals in 200 pilot cities abolished the 15% drug price markup policy, the price of drugs decreased 15% after this reform. The Zero-Markup Medicine Policy (ZMMP) was heralded as the biggest reform (Shi *et al*, 2019) to China's modern health system. The *Report on the Work of the Government (2017)* (Li Keqiang, 2017) introduced Chinese overall reform in all public hospitals, the government canceled the 15% markup on drug prices and this reform made progress in the overall cost of health care pricing, medicine distribution and models of health insurance payments. After the reformations the public hospitals have two types of compensations, medical service fees and government subsidies.

Among the American 3,498 hospitals (Gani *et al.*, 2016), markup ratios ranged from 0.5-12.2, median markup ratio of 2.8 (interquartile range 2.7-3.9), 10% of these hospitals billing more than 7 times the Medicare-allowable costs (markup ratio ≥7.25). Extreme markup hospitals were more large (46.3% vs 33.8%, P<0.001), urban, nonteaching centers (57.0% vs 37.9%, P<0.001), which located in the Southern (46.4% vs 32.8%, P<0.001) or Western (27.8% vs 17.6%, P<0.001) regions of the United States. In American highly concentrated markets, private for-profit status was associated with an 80.8% higher markup compared to public/private not-for-profit status (95%CI: +69.5% - +96.9%; p<0.001) (Cerullo *et al*, 2018). In 1993 the World Health Organization (WHO) published *How to Investigate Drug Use in Health Facilities*, in 2014 the *WHO Handbook for Guideline Development* (WHO, 2014) and *Monitoring and Evaluation of the Global Action Plan on Antimicrobial Resistance: Framework and Recommended Indicators* (World Health Organization *et al.*, 2019) in 2019, these indicators can compare between different areas and different times. The European Surveillance of Antimicrobial Consumption (ESAC; http://www.esac.ua.ac.be) project (Adriaenssens *et al.*, 2014) proposed the 21 disease-specific antibiotic prescribing quality indicators (Ogrinc G Fau - Davies *et al.*, 2015) to assess antibiotic prescribing in primary care. *How to Investigate Antimicrobial Use in Hospitals* was published by the American Agency for International Development, 16 indicators were inpatient antimicrobial use in hospitals: 5 were hospital related, 9 were prescribing indicators, 2 were related to patient care and the 17th supplemental indicator was drug sensitivity tests. Compared with WHO indicators, the American and

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European (Adriaenssens *et al*, 2014) indicators were more complex which consumed more time and effort; so we chose to use the WHO/International Network for Rational Use of Drugs (INRUD) methodology. WHO/INRUD suggested a period of one year or longer and larger cases were preferred to minimize bias due to seasonal variations or interruptions in the drug supply cycle.

Before the ZMMP reform, the National Health Commission of the People's Republic of China (NHCPRC) (The National Health Commission of the People's Republic of China, 2016) promulgated the *Prescription Management Regulation* in 2007, *Management Practices of Hospital Prescription Comment* in 2010 and the National Antibiotic Special Rectification Activities in 2011. According to the WHO/INRUD criteria and cross-sectional studies, the effect of 15% markups on pharmaceuticals (Gani *et al.*, 2016) was investigated at the tertiary teaching hospital in Jingzhou, Hubei province, China. According to the Statistical Bulletin of National Economic and Social Development of Jingzhou (Jingzhou Municipal People's Government, 2019; Keqiang, 2019) in 2019, there were around 6,412,800 registered residents and 1,113,600 urban residents. There were around 3,204 medical institutions, with 31,342 beds and 42,145 medical professionals. The Jingzhou hospital affiliated to Tongji Medical College is the biggest general tertiary teaching hospital in Jiangzhou; which has 2,200 registered beds, 2,000 employees, the annual capacity of 1,300,000 outpatient clients and 700,000 inpatient clients. The aim of this study was to investigate the impact of the ZMMP on hospitalization drug indicators, prescribing trends and economic data, content of rational drug use, patient-level and hospital-level expenses.

MATERIALS AND METHODS

In order to get the impacts of the ZMMP and baseline data and, we sampled prescriptions in the second quarter of the year from 2012 to 2014 which was similar with our previous research of the year 2006 to 2009 (Jun *et al.*, 2011). We selected the First Monday of the second quarter (April, May and June) in 2012, the Tuesday of second week, the Wednesday of the third week, for a total of four days in every month and a total of twelve days in 2012; and repeated this again in 2013 and 2014. These twelve days included ten working days from Monday to Friday, two were on Saturday and Sunday. The daily prescriptions were summed to N, SQRT (N) which was used as daily prescription number and equal sample intervals. Original data file was available from the corresponding author.

Inclusion and exclusion criteria

We sampled from the daily prescriptions, computed the daily drug indicators, prescribing trends and economic data (Husereau *et al*, 2013; National Development and Reform Commission, 2019) and compared the means over the twelve days. In order to minimize bias (von Elm *et al*, 2014), only the adult ordinary prescriptions were included. The departments of pediatrics, emergency and Traditional Chinese Medicine (TCM) were excluded. Narcotics, poisonous substances and radio-pharmaceuticals prescriptions were also excluded. Antibiotics are defined as any agents included in the J01 group (WHO Collaborating Centre for Drug Statistics Methodology & Norwegian Institute of Public Health, 2020) of the Anatomical Therapeutic Chemical (ATC) classification system.

STATISTICAL ANALYSIS

SPSS17.0 for windows was used to make statistical analysis. The results were expressed as Mean ± Standard Deviation (M±SD). The Analysis of variance (ANOVA) was used to compare mean of measurement data, Kruskal-Wallis H was used to compare mean of numeration data. The Levene test was used to test homoscedasticity of measurement data. The Post Hoc Test was used for Multiple Comparisons. The P-value <0.05 was the statistical significance.

RESULTS

1,171 prescriptions were sampled from 38,246 cases. The descriptive results are shown in table 1. Because the hospital adapted the new Hospital Information System (HIS) in 2009, the prescriptions were prescribed by the computer system, so the percentage of drugs prescribed by generic name was 100.00%. The percentage of injection prescriptions in the sampled prescriptions was 14.43% and the percentage of antibiotic prescriptions in the sampled prescription was 25.36%. Total 2328 prescriptions of National Survey from Sri Lanka (Galappatthy *et al.*, 2021) were included in 80 pharmacies, representing all 25 districts of the country. A cross-sectional study was also conducted among 1200 prescription papers retrospectively and 60 patients prospectively at two health centers of Gondar town (Sema *et al.*, 2021), northwest Ethiopia.

CNY-Chinese Yuan

The average number of drugs per prescription in table 1 was 2.29, Average number of drugs per prescription which was different with the relevant domestic research findings of Inner Mongolia (2.7), Guangdong (2.36), Guangxi (1.95) and Beijing (2.0) (Jin *et al.*, 2019).

The economic data was shown in table 2. Average drug cost per prescription ranged from ¥191.32 to 363.32, average drug cost per antibiotic prescription ranged from ¥178.07 to 186.66, the percentage of antibiotic cost in the daily drug cost remarkably decreased from 17.44% to 8.01%. This improvement might be due to the increase in overall drug costs and administrative interventions.

The WHO uses 0/1 (no or yes) in the survey of antibiotics and injections. The number of the prescriptions with two or more antibiotics was 1 (yes), which might result in loss of information. So we decided to use actual numbers, instead of 0/1 (no or yes). The WHO recommends that the average number of medications per encounter for outpatients should be 1.6 to 1.8 in developing countries (Atif *et al.*, 2016; Yimenu *et al.*, 2019).

Prescribing core drug indicators of 2012-2014 is shown in table 4, according to the WHO recommendation (Atif *et al.*, 2016; Yimenu *et al.*, 2019), the proposed optimal range for an injection prescribed should be 13.4%-24.1%, and the optimal range for an antibiotic prescribed was 20.0%–26.8%. The percentage of prescriptions with an antibiotic prescribed shown in table 3 decreased from 12.64% to 9.64%, the percentage of encounters with an injection prescribed decreased from 15.21% to 12.77%, but the differences had no statistical significant. In Beijing the percentages of encounters with antibiotics or injections prescribed were 15.1 and 3.7% (Jin *et al.*, 2019).

The results of WHO/INRUD Indicator Studies in developed and developing countries (Sulis *et al.*, 2020) is shown in table 5, our results shown in tables 2, 3 and 4, any indicator were different with WHO optimal value and Africa standard. The government should also take action to control antimicrobial resistance (World Health Assembly, 2019a; World Health Organization *et al.*, 2019) according to WHO Global action plan on antimicrobial resistance (Regional Office for South-East Asia, 2016).

DISCUSSION

The majority of analytical observational (Kesmodel, 2018) studies between the exposure and outcome were cross-sectional studies, cohort or case-control studies. The advantages of cross-sectional studies (Kesmodel, 2018) were easy and quick to conduct and were less expensive. The information on attitudes, knowledge and regulation practice was available from cross-sectional studies, it was useful for planning health interventions. When time and resources didn't allow for continuous surveillance, the point-prevalence survey (von Elm *et al.*, 2014; Zarb & Goossens, 2011) was useful. The repeated point-prevalence surveys within the same institution could be used to monitor trends and effectiveness. The sampling method was very important for the comparability of data. The sample size was a compromise between statistical goals and feasibility.

Discussion of zero-medicine markup policy

Chinese medical insurance consists of commercial health insurance and social medical insurance (Sun *et al*, 2016). The latter consist of basic medical insurance system for urban and township employees and new rural cooperative medical system. According to the Statistical Bulletin of National Economic and Social Development of Jingzhou (Jingzhou Municipal People's Government, 2019; Keqiang, 2019) in 2019, basic medical insurance for urban and rural residents totaled 4.83 million patients. Our outpatient Economic Indicators of 2012-2014 are shown in table 2. Although average drug cost per prescription increased from ¥191.31 to 363.22, the percentage of antibiotic cost in the daily drug cost remarkably decreased from 17.44% to 8.01%. Because the increase in the inpatient expense reimbursement system and the outpatient expenses, some expensive drugs were not reimbursed by the social medical insurance, the average drug cost per prescription in 2014 increased, they were bought in the dispensary for inpatients; maybe this was one reason why the government abolished 15% drug price markups (Yi *et al.*, 2015). A total of 520,996 inpatients were extracted in Beijing's study (Zeng *et al.*, 2019). For patients in the pilot hospitals, the total expenditures per admission decreased from ¥17,140.3 in 2012 to ¥15,430.1 in 2013 and then increased to ¥16,789.8 in 2015. Expenditure on drugs reduced from ¥5811.7 in 2012 to ¥3903.4 in 2015. However, a significant substitution effect of medical consumables was first observed in the third quarter of 2014, which undermined the impact of the policy.

For the American 888 hospitals with extreme markup (greatest markup ratio quartile: markup ratio >3.9), the median markup ratio was 4.9 (interquartile range 4.3-6.0). Of the 639 investor-owned, for-profit hospitals, 401 hospitals (62.8%) had an extreme markup ratio compared with 19.3% (n = 452) and 6.8% (n = 35) of nonprofit and government hospitals, respectively. Perioperative morbidity (32.7% vs. 26.4%, P<0.001) was greater at extreme markup hospitals. In 2012 although the American hospitals charge for operations had broad financial implications, but American hospital pricing (Gani *et al.*, 2016) was not subject to regulation, American Hospitals with an extreme markup had greater perioperative morbidity. There was wide variation in hospital markup for cardiothoracic and gastrointestinal procedures, with approximately a quarter of hospital charges being 4 times greater than the actual cost of hospitalization. American overall median markup of adjusted costs for procedures was 85% (Cerullo *et al.*, 2018), private insurance was associated with 7.1% lower adjusted markup. American government and private not-for-profit hospitals employed lower markups in more concentrated markets, whereas private for-profit hospitals employed higher markups in more concentrated markets.

The *Health in the 2030 Agenda for Sustainable Development* (World Health Assembly, 2019b) pointed out that Sustainable Development Goals included much broader range of environmental, economic and social issues.

Table 1: Total prescribing indicators of 2012-2014 prescriptions

Indicators	2012-2014	WHO Value (Atif *et al.*, 2016; Yimenu *et al.*, 2019)	Africa Value (Amaha *et al.*, 2019; Ofori-Asenso *et al.*, 2016)
Total sampling percent=sampled prescription/Total ordinary prescription	3.06%	-	-
Percentage of drugs prescribed by generic name	100.00%	100	65.1
Average number of drugs per prescription	2.29	1.6-1.8	< 2
Average number of antibiotics per prescription	0.31	-	
Percentage of injection prescriptions in the sampled prescription	14.43%	13.4–24.1	45.9
Percentage of antibiotic prescriptions in the sampled prescription	25.36%	20.0–26.8	28.4
Percentage of antibiotic numbers in the drug number	13.62%	-	-
Average drug cost per prescription (CNY)	244	-	-
Average drug cost per antibiotic prescription (CNY)	175.71	-	-
The percentage of antibiotic cost in the total drug cost	12.53%	-	-
The percentage of antibiotic prescription cost in the total prescription cost	18.26%	-	-
Percentage of prescriptions with an antifungal prescribed	2.90%	-	-

Table 2: Outpatient Economic Indicators of 2012-2014

Indicators (N=12)	2012	2013	2014
Cost of antibiotic prescriptions(CNY)	1610.71±624.76	1222.26±540.92	1515.83±567.13
Daily antibiotic cost(CNY)	1079.10±497.97	945.54±356.18	959.05±498.21
Average drug cost per prescription(CNY)	191.32±41.89	179.37±26.70	363.22±76.54**
Average drug cost per antibiotic prescription(CNY)	178.07±65.36	169.33±49.38	186.66±65.65
The percentage of antibiotic cost in the daily drug cost (%) **	17.44±6.83	16.46±7.99	8.01±3.65**

*P<0.05, **P<0.01

Table 3: Outpatient Drug indicators and prescribing trends

Indicator s(N=12)	2012	2013	2014
Daily ordinary prescriptions	1014.42±303.32	1119.42±333.07	1053.33±274.48
Sampled ordinary prescriptions	31.67±4.85	33.58±5.37	32.33±4.46
Percentage of ordinary prescriptions in daily prescriptions (%)	3.32±0.75	3.18±0.73	3.19±0.53
Daily antibiotic prescriptions	9.25±2.77	7.33±1.78	8.17±2.25
Daily injection prescriptions	4.92±2.71	5.00±1.81	4.17±2.12
Number of antifungal prescriptions	0.92±0.90	1.25±1.36	0.67±0.65
Daily drug number**	63.92±11.67	62.92±10.77	97.00±10.22**
Daily antibiotic number**	12.17±3.81	9.00±2.32	9.33±2.93
Average number of drugs per prescription**	2.04±0.34	1.91±0.38	3.03±0.37**

Table 4: Prescribing Core Drug Indicators of 2012-2014

Indicators (N=12)	2012 (%)	2013 (%)	2014 (%)
Percentage of prescriptions with an antibiotic prescribed	12.64±3.65	10.30±3.79	9.64±2.83
Percentage of antibiotic prescriptions in the daily prescription	29.54±8.59	22.63±8.24	25.59±7.39
Percentage of encounters with an injection prescribed	15.21±6.89	14.68±4.36	12.77±6.22
Percentage of prescriptions with an antifungal prescribed	2.91±2.76	3.73±3.76	2.23±2.54
Percentage of drugs prescribed by generic name	100	100	100

Table 5: Results of WHO/INRUD Indicator Studies in Different Countries (Atif *et al.*, 2016; Yimenu *et al.*, 2019)

Performance Indicators	Study Reference (Atif *et al.*, 2016; Yimenu *et al.*, 2019)										Mean
	[A]	[B, C]	[D]	[E]	[F]	[G]	[H]	[I]	[J]	[K]	
Average number of medicines prescribed per patient encounter	2.2	2.4	2.3	2.5	2.3	3	2.2	2.2	2.4	3.1	2.5
Percent medicines prescribed by generic name	74	61.2	5.1	95.4	75.5	63.1	99	79.4	99.8	10.1	66.3
Percent encounters with an antibiotic prescribed	37	32.2	60.9	39.2	35.4	54.2	43	24.9	66	33	42.6
Percent encounters with an injection prescribed	11	2	1.2	9.9	19	38	18	10.6	2.4	2.4	11.4
Percent medicines prescribed from EML	78	99.2	93	95.4	87.1	75.6	98.8	90.3	99.7	65.2	88.2
Average consultation time (minutes)	5.8	7.3	3.9	7.1	3.6	6.1	3.7	6.2	4.4	2.3	5
Average dispensing time (seconds)	17	100	28.8	47.4	39.9	18.1	37	78	234	258	85.8
Percent medicines actually dispensed	66	99.6	81.8	95.9	91.6	99.1	84.5	83.4	100	81	88.3
Percent medicines adequately labeled	63	10	91.4	0	87.6	55.9	86.2	70.1	0	99.4	56.4
Percent patients with knowledge of correct doses	54	79.3	77.7	94	96.1	86.5	81.7	72.1	55	74.3	77.1
Availability of EML to practitioners	50	90	100	80	100	100	100	50	100	100	87
Percent key medicines available	55	59.2	80	78.3	100	91.7	86.5	65	86.6	84	78.6

EML Essential Medicines List; [A] Fortaleza of Brazil; [B, C] Saudi Arabia; [D] Jordan, [E] Alexandria of Egypt; [F] Dar Es Salaam of Tanzanian; [G] Africa; [H] Mozambique, [I] Ethiopia; [J] Kampong Thom of Cambodia; [K] Kolkata of India.

The longitudinal data of Shandong province in 2007-2017 (Jiang *et al.*, 2020) was investigated after the implementation of the ZMMP, the share of revenue from medicine sales reduced by 16.47 and 10.42%, the revenue from medicine sales reduced by 24.04 and 11.58%, in county general and TCM hospitals, respectively. The gross revenue reduced by 5.07% in county general hospitals. The number of annual outpatient visits reduced by 11.22% in county TCM hospitals. Government subsidies increased by 199.22% and 89.3% in county general and TCM hospitals, respectively. In terms of dynamic effects, the share of revenue from medicine sales, revenue from medicine sales, and gross revenue decreased by 20.20%, 32.58% and 6.08% respectively, and up to 28.53%, 63.89% and 17.94% after adoption, while government subsidies increased by around 170% to 200% in county general hospitals. The number of annual outpatient visits decreased by 9.70% and up to 18.84% in county TCM hospitals. Chinese Zhuhai's (Sun *et al.*, 2016) new expenditure per common disease outpatient and prescribing indicators were benefited from medical insurance and the expanded access to primary care, but it could led to a reduction in expensive specialist inpatient services. More explicit incentives and specific medication prescribing targets need to be incorporated into the insurance system.

Discussion of rational drug use

The WHO reported that a total of 241 South–South and triangular cooperation initiatives (World Health Assembly, 2019b), 47% covered health systems and universal health care, 30% covered promoting health through the life-course and 16% covered other issues. In addition, 74% included training and capacity-building, 76% of initiatives included technical support, 32% provided financial (World Health Assembly, 2016) and equipment support and 18% provide other services. The maternal mortality ratio has lowered from around 1500 cases per 100 000 births in 1949 to 17.8 cases per 100 000 births in 2019, and the infant mortality rate has lowered from around 200 cases per 1000 births in 1949 to 5.6 cases per 1000 births in 2019 (Qiao *et al.*, 2021), it have benefited from many factors, including the rapid change in socioeconomic determinants, political will, the building of the maternal and child health system and the maternal and child health information system, the reformation of social health insurances, the launching of national programs and poverty alleviation.

A questionnaire was designed to evaluate the knowledge levels of physicians (Wushouer *et al.*, 2020), a total of 334 physicians in 60 county and the data of 385,529 prescriptions was collected. There was still a popular belief in China that injections and antibiotics were more convenient and effective (Zhang *et al.*, 2019), it was very common that patients demand injections and antibiotics for quicker recovery. The knowledge gap among Chinese physicians was evident and those with a higher degree of knowledge always prescribe fewer antibiotics. The NHCPRC (The State Council Information Office of the People's Republic of China, 2019b) has made more effort to enhance healthcare education on the rational drug use and antimicrobial resistance (Regional Office for South-East Asia, 2016), to develop more targeted policies (The State Council Information Office of the People's Republic of China, 2019a) and programs for the prescription practices at medical facilities.

In order to change the drug misuse and un-reasonable pricing, the NHCPRC promulgated (The National Health Commission of the People’s Republic of China, 2016) Guidelines for Clinical Application of Antibacterial Drugs in 2015 and the National Action Plan to Contain Antimicrobial Resistance (2016-2020) in 2016. The Guidelines for Clinical Application of Antibacterial Drugs in 2015 required that percentage of inpatient prescriptions with an antibiotic prescribed should be less than 20%, the percentage of emergency prescriptions with an antibiotic prescribed should be less than 40%, the defined daily dose (DDD) should be less than 40.

The limitation of the study was that the sample came from Chinese Jingzhou area, which economic development and healthcare resource were below the national average. Our findings may not be generalizable to populations living in the developed regions of China. Because of continual changes in the team we only evaluated the ZMMP impact in a relatively short period, we were not able to get the later data of the hospital after administrative interventions, future research was needed to evaluate its long-term effects.

CONCLUSION

The baseline data of the Zero-Markup Medicine Policy, prescribing trends and drug indicators were compared, some indicators showed a decreasing trend and becoming more rational, Zero-Markup Medicine Policy decreased both the patient-level and hospital-level drug expenses, administrative interventions of medicine markup policy were steadily advanced.

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