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Consequences for Accountability and Governance

Power of data in the governance of public hospitals: case of antibiotics control in Shanghai Municipality, China

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Power of data in the governance of public hospitals: case of antibiotics control in Shanghai Municipality, China

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ABSTRACT: The public sector dominates healthcare provision in many areas in China, including Shanghai Municipality, with a population of 24 million. The resources-wasting pattern of healthcare services provided by public hospitals is characterized by the mechanism of reimbursing hospitals by surplus from sales of drugs. As a result the average proportion from drug sales accounts for nearly half in the total revenue of each public hospital. The case of antibiotics control is about the efforts to contain antibiotic resistance which is of global importance, with the aim of surveillance systems of antibiotic use and resistance. **Methods :** We extracted data from Shanghai Municipal Medical Products Administration Agency, whose database covers 95% of total drug procurements of all public hospitals from 2009, and processed with a method from Europe and recommend by World Health Organization, to get comparable indicators for the level and patterns of antibiotic utilization. **Results :** The three-year (2011-2013) national campaign to contain unnecessary antibiotic prescriptions yielded a drop of 31% in the first half of 2011 and the level kept stable until the end of 2014. However the pattern of antibiotic use differentiate any reported areas or countries by preferences for cephalosporins, quinolones, macrolides and injections. **Conclusion :** The authoritarian centralized political system of China makes it rapid for new decisions and efficient to implement. Nevertheless the medical professionals' involvement is not sufficient to make policy and action sustainable. The governance of public hospitals could be optimized with more power from data accumulated in the healthcare infrastructure investment in China via evidence-informed decision making and researches.

Keywords : antibiotics, drug utilization research, sales records, public hospitals, health governance.

INTRODUCTION

The resources-wasting pattern of healthcare services provided at public hospitals of China, dominating heathcare provisions, has been criticized by both academia and decision-makers in the last decade.[1, 2] This pattern is characterized by the mechanism of reimbursing hospitals by surplus from sales of drugs. As a result, the average proportion from drug sales remain two fiftths in the total revenue of public hospitals, despite various efforts have been attempted to delink the connection.[3, 4] The pharmaceutical spending accounts for 40% of total health spendings or 2% of GDP in China, a substantial burden to the economy.[1, 5]

Among all categories of drugs, unnecessary and inappropriate antibiotic use causes the most extensive concerns. Antimicrobial resistance is of global importance,[6] and WHO has warned of the approaching of post-antibiotic era if urgent actions are delayed.[7] Epidemiological studies found that, the rates of resistance bacteria strains sampled from both humans and animals are alarmingly high in China, compared with neighbouring Hong Kong and Tai Wan.[8, 9]

The Chinese government lauched a three-year (2011-2013) national initiative to restrict antiboitic use at publich hospitals with educational and regulational interventions, echoing WHO's global actions to contain antimicrobial resistance. Evaluations on the impacts of these interventions and evidences to inform further decisions could be based on longitudinal

data from surveillance of antimicrobial consumptions and resistance, in accordance with the experience from European countries.[10] However difficulties from data collection detain the work in the rest of the world,[11, 12] while people of the emerging economies are found to be more likely exposed to overuse of antibiotics.[13]

In recent times the Chinese health system has evolved to empower us with real-world data to reshape researches, for instance from sales records of drugs, electronic healthcare records, and etc. This article strives to present how data could be applied in the governance of public hopitals with the case of antibiotics control in Shanghai Municipality.

MATERIALS AND METHODS

Settings

Shanghai municipality locates in east China, on the delta of Yangtze River to the sea, with a population of approximately 24 million. The per capita GDP of Shanghai has exceeded the high-income country level by the standard of the World Bank (12,616 USD) since 2012, and doubles the national per capita GDP of China.

Data collection

In order that the public hospitals could collectively bid for prescription drugs at reasonable prices, Shanghai piloted Municipal Medical Products Administration Agency (SMPA) in the early 2000s'. By 2010, this agency has been scaled up to every provincial administrative unit throughout

China.

We found that SMPA sales database has covered 95% of total drug procurements of all public hospitals since 2009, or equals to 97% of total drug expenditures from governmental financial reports. From 2013 more private healthcare providers were encouraged to be enclosed into SMPA bulk purchasing for safty reseasons, but they are small and account for less than 5% of the total healthcare volume.

It has been legislated by administration that antibiotics should be regulated as prescription-only drugs since 2003, and drug retailers were restricted to sale antibiotics. Nevertheless this legislation was poorly enforced at many provinces and cities, where upto 50%-60% of antibiotic sales was found to sold without presciptions through retailers.[14, 15] Shanghai is an exception. We estimated from a sample of 153 drug retailers from a total of 2378 (6%) provided by Intercontinental Marketing Services (IMS) Institute for Healthcare Informatics, that the volume of antibiotics via retailers accounts for less than 1% of total consumption in terms of DDDs, because of stricter implementation of the legislation in Shanghai.

Data analysis

We processed with a method from European Surveillance of Antimicrobial Consumption (ESAC),[16, 17] to get comparable indicators of the level and patterns of antibiotic utilization.[18] The volume of antibiotic consumption was measured by defined daily dose (DDD), which is the

maintaining dose for adults. DDDs were added up, and the total was divided by 1 000 inhabitants and days, to get the indicator of antibiotic consumption by population: DDDs/1000 inhabitants /day (DID). Different categories were classified by WHO's code of anatomic, therapeutic, and chemical classification (WHO/ATC), so that the patterns of use could be compared across places.

Sales records were labelled with managerial variables so as to evaluate the interventions. We employed a statistical model of interrupted time series (ITS),[19] and performed segmented regression analysis to present the trends before and after interventions, as well as variations within and across layers of healthcare providers.

This is an observational study per se, and the surveillance of antibiotic use has no connections with the interventions. In this paper we report the time series from 2009 to 2014.

RESULTS

Overall trends

Total spending on drugs increased from 21.6 billion RMB in 2009 to 35.0 billion in 2013, by an average annual growth rate of 12.8% in real value during the period in surveillance, meanwhile spending on antibiotics peaked at 4.1 billion, decreased and stabled at 3.7 billion thereafter. Antibiotics in total drug spending decreased from 17.7% in 2009 to 11.0% in 2014.

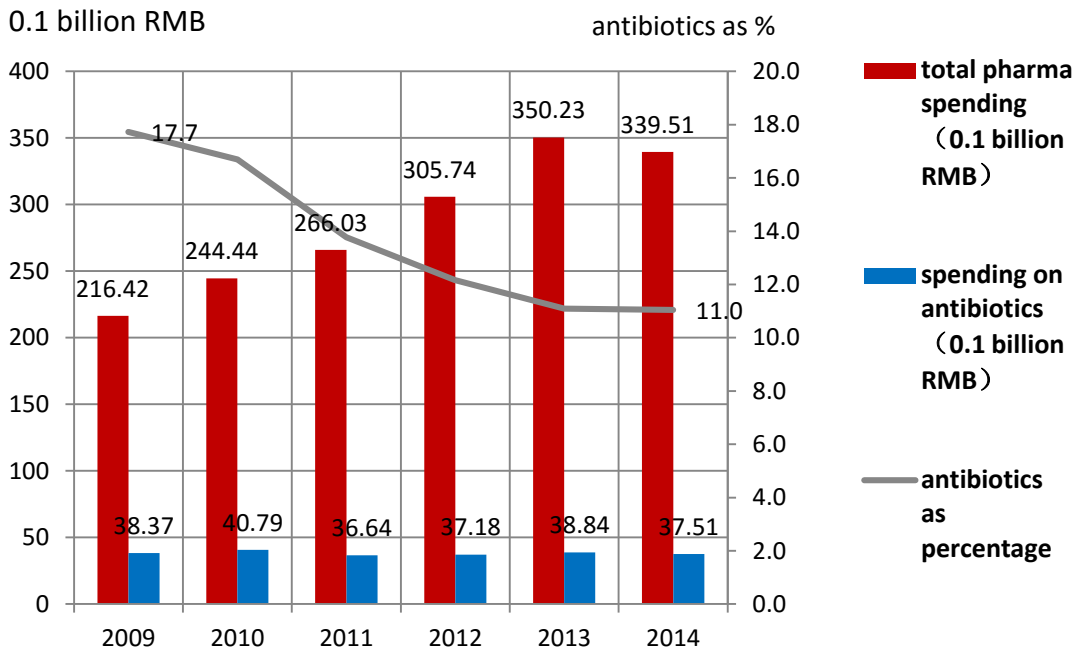

Figure 1 Antibiotics in total spending on pharma, Shanghai (2009-2014)

*Information system updated in 2014, and data is incomplete by 16%.

The antibiotic consumption peaked at at 25.9 DID in 2010, fell to 17.8 DID in 2012, dropped by 31% in the first quarter of 2011 and the level kept stable until the end of 2014.

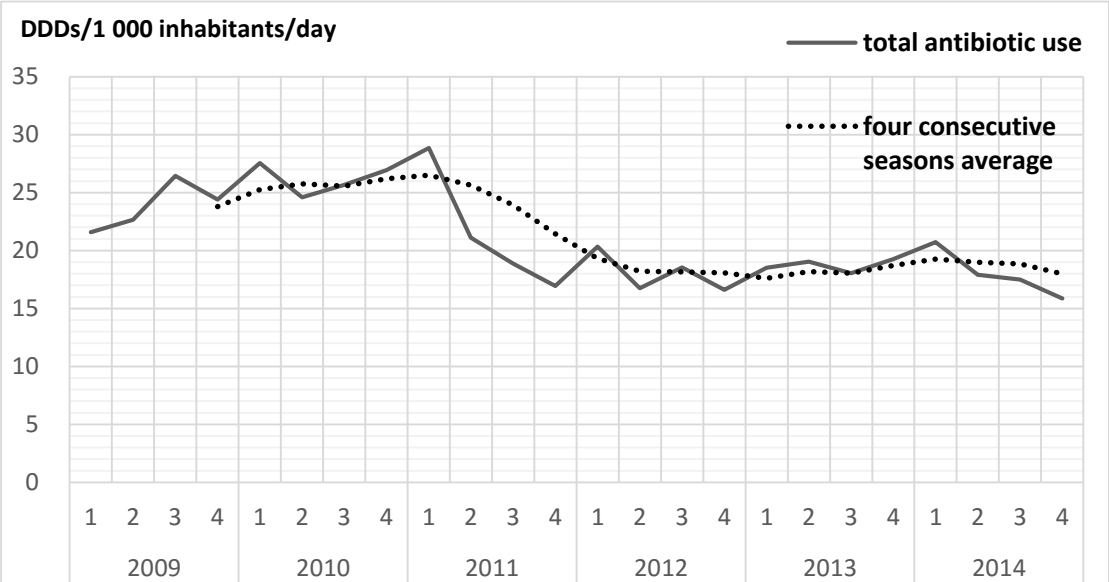

Figure 2 Consumption of antibiotics by seasons, Shanghai (2009-2014)

Patterns and quality of antibiotic consumption

Parenteral preparations accounted for 20.9% of the total antibiotic use in 2014, decrease from the highest point in 2010, 40.1%. Injection form of antibiotics constitute three fourths of total spending on antibiotics during the six-year period monitored, although the volume decreased.

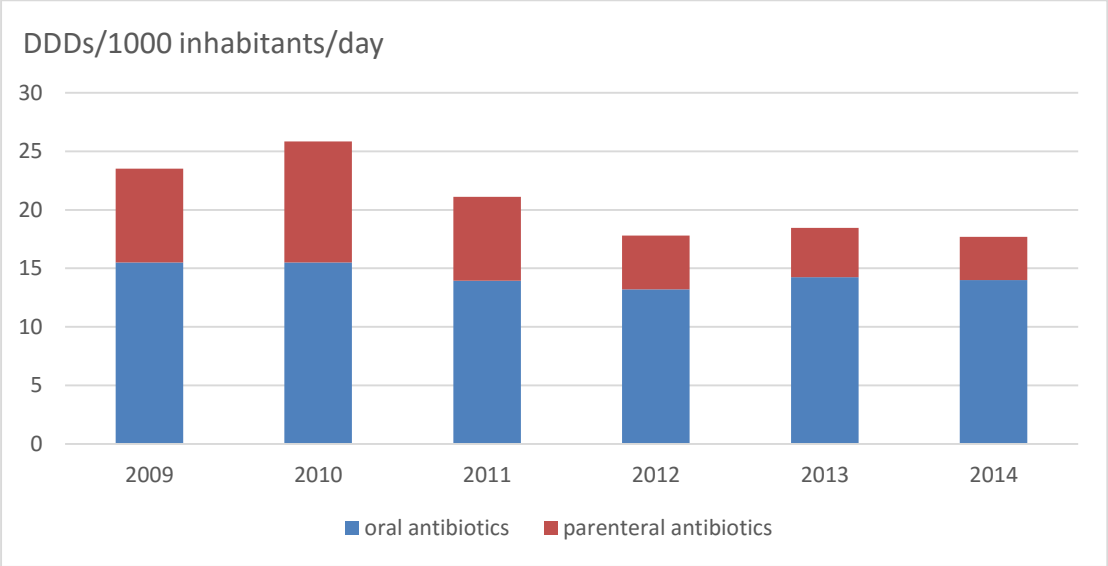

Figure 3 Consumption of oral and parenteral antibiotics in Shanghai (2009-2014)

European Surveillance of Antimicrobial Consumption (ESAC) developed twelve indicators to evaluate quality of antibiotic use, and we borrowed to assess the pattern of antibiotic use in Shanghai (See figure 4). The total use of antibiotics improved by turning light green, and below the median of Europe from 2012. Penicillins consumption, including the narrow-spectrum and those combined with enzyme inhibitors, are pretty low, while consumptions of cephosporins, macrolides, and quinolones are higher than all or most European countries. The proportion of third- and fourth-generation cephalosporins and fluruoquinolones in total antibiotic use are high. It is strongly proved by evidence that they cause more resistant ESBL-producing strains.[20]

Year	Consumption					Relative consumption				Broad/ Narrow	Seasonal variations	
	J01_ DID	J01C_ DID	J01D_ DID	J01F_ DID	J01M _DID	J01CE _%	J01CR _%	J01DD +DE_%	J01MA _%	J01_ B/N	J01_ SV	J01M_ SV
2009	23.52	3.79	10.16	4.44	3.31	1.56	5.93	5.30	14.07	3.54	3.38%	-0.78%
2010	25.86	3.09	13.47	4.38	3.23	1.56	2.91	7.53	12.48	4.14	39.51%	18.18%
2011	21.12	2.15	10.90	3.50	2.97	1.27	2.68	7.91	14.03	4.26	5.55%	10.43%
2012	17.81	1.54	8.74	3.18	2.88	1.27	3.08	8.43	16.12	4.62	-5.23%	-9.03%
2013	18.45	1.46	9.06	3.33	3.07	0.71	2.76	8.08	16.59	6.03	12.97%	8.40%
2014	17.71	1.30	8.89	3.22	2.83	0.62	2.43	8.43	15.88	6.62	N/A	N/A

Total antibiotic sales data, including those to hospitals and primary healthcare facilities.

With reference to the quartile distribution of outpatient antibiotic use in 32 European countries in 2009.

	J01_ DID	J01C_ DID	J01D_ DID	J01F_ DID	J01M_ DID	J01CE _%	J01CR _%	J01DD +DE_%	J01MA _%	J01_B/ N	J01_ SV	J01M_ SV
P0	10.19	4.23	0.03	0.63	0.48	32.21	0.00	0.00	2.86	0.17	11.73%	-6.94%
P25	15.15	6.88	0.55	1.88	0.88	6.61	10.30	0.04	5.71	3.85	18.04%	4.39%
P50	18.97	9.54	1.89	2.74	1.33	2.79	20.99	0.63	7.56	6.89	25.74%	7.64%
P75	23.10	11.86	2.90	3.87	2.01	0.48	28.39	2.04	10.12	28.11	33.43%	17.29%
P100	38.64	16.08	8.68	11.54	4.13	0.07	39.24	7.18	15.74	149.49	57.41%	31.52%

Figure 4. Quality indicators for antibiotic consumption in Shanghai, China (2009-2014).

Boxes were labeled using four colors, red in P75-p100, yellow in P50-p75, light green in p25-p50, and dark green in p0-p25.

The indicators mean the lower the better, except for J01CE_%.

J01_DID: consumption of antibacterials for systemic use (J01) expressed in DID;

J01C_DID: consumption of penicillins (J01C) expressed in DID;

J01D_DID: consumption of cephalosporins (J01D) expressed in DID;

J01F_DID: consumption of macrolides, lincosamides and streptogramins (J01F) expressed in DID;

J01M_DID: consumption of quinolones (J01M) expressed in DID;

J01CE_%: consumption of β-lactamase-sensitive penicillins (J01CE) expressed as a percentage;

J01CR_%: consumption of combinations of penicillins, including β-lactamase inhibitors (J01CR) expressed as a percentage;

J01DD+DE_%: consumption of third- and fourth-generation cephalosporins [J01(DD+DE)] expressed as a percentage;

J01MA_%: consumption of fluoroquinolones (J01MA) expressed as percentage;

J01_B/N: ratio of the consumption of broad-{J01[CR+DC+DD+(F-FA01)]}to the consumption of narrow-spectrum penicillins, cephalosporins and macrolides [J01(CE+DB+FA01);

J01_SV: Seasonal variation of the total antibiotic consumption (J01) of a 12-month period starting in July and ending the following June, expressed as percentage: [(DDD (winter quarters)/DDD (summer quarters)-1] x 100;

J01M_SV: Seasonal variation of quinolone consumption (J01M) of a 12-month period starting in July and ending the following June, expressed as percentage: [(DDD (winter quarters)/DDD (summer quarters)-1] x 100.

Variations within the same level of providers were found. The proportion of pencillins and quinolones in totoal prescribed antibiotics showed similar trends, but facilities varied cross-sectionally.

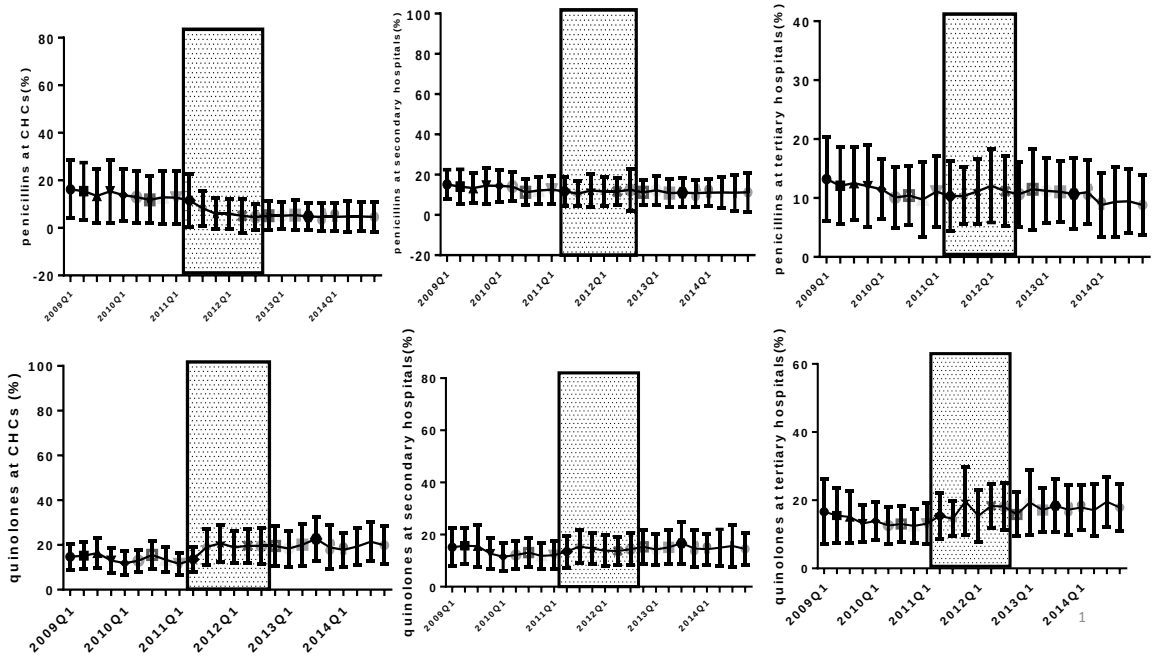

Figure 5 Penicillins and quinolones use in three layers of providers, Shanghai (2009-2014)

* Frames show the time of interventions.
Three layers of providers are Community health service centers (CHCs) for primary care, secondary hospitals, and tertiary hospitals. The two latter feature as regional and municipal healthcare centers.

Surveillance of the last resorts

Glycopeptides and carbapenems are the last resorts to multi-resistant bacterial pathogens. They are for Gram posititve and Gram negative bacterium respectively. The use of them correlates with the rate of resistant strains against themselves, and those infected patients have very

high mortality rates, for instance, Carbapenems resistant Enterobacteriaceae(CRE).

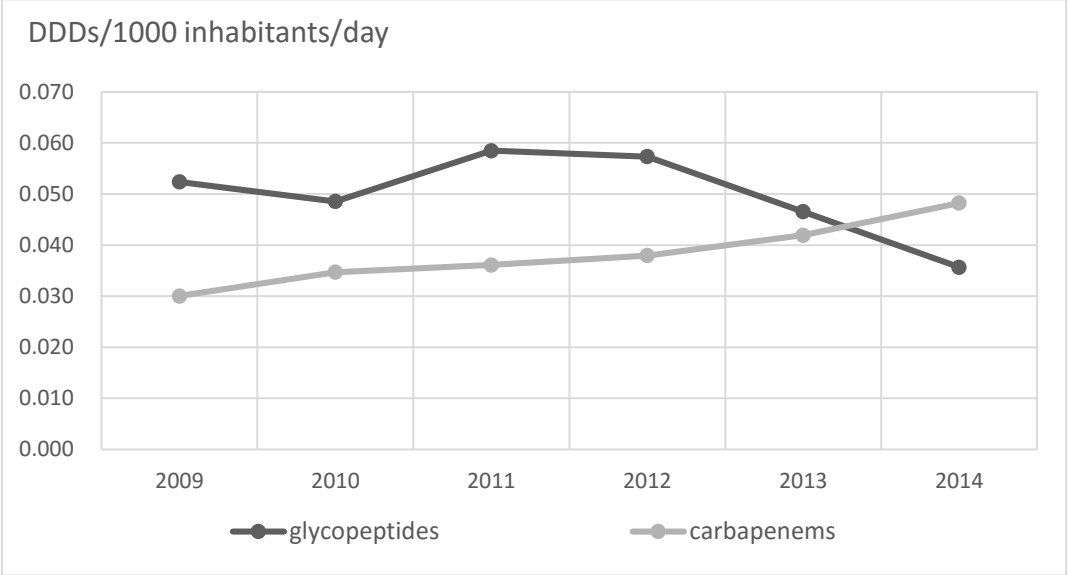

Figure 6 Glycopeptides and carbapenems use in Shanghai (2009-2014)

In the drug market in Shanghai, there are three glycopeptides, vancomycin, norvancomycin, teipcoplanin. Carbapenems are mainly meropenem, imipenem, biapenem, and panipenem.

The consumption of glycopeptides decreased since 2012, mirrors the trend of methicillin resistant *Staphylococcus Aureus* monitored. Carbapenems usage increased by 60% in 2014 compared with that in 2009.

DISCUSSIONS

We have successfully monitored the consumption of antibiotics with agregated sales data using internationally comparable indicators based on population, quality of antibiotic prescriptions was benchmarked against the

global best practice, and the variations were measured across providers. It is the first longitudinal study of this kind in China.

Although the proportion of antibiotics in total drugs decreased steadily from 17.7% to 11.0%, it is still a high proportion compared with OECD countries. According to the most recent data available, in 2013 most countries (92%, 22/24) spent less that 5% of the total drug expenditure on antibiotics. Korea (5.9%) and Turkey (11.3%) are the exceptions. There's a space in China for controlling the spending of antibiotics and make it for other categories such as drugs for cardiovascular diseases and cancers.

The level of antibiotics use decreased rapidly in the first half of 2011, and coincided with the time the three-year national campaign and national essential drugs reform took place. The decrease was substantial and sustained, compared with other reported interventions.

Table 1 Comparison of the impact of Antibiotic control programmes

country（programme）	Indicators	Time period	impact
Sweden（STRMA）	Outpatients DID	1993-1997, 5 years	16.3→13.0 DID（-22%）[21]
	Outpatients DID	1995-2004, 10 years	15.7→12.6DID（-20%）[22]
Slovenia	Outpatients DID	1999-2002, 4 years	20.8→17.7DID(-18.7%)[23]
France	Outpatients DID	2001-2003, 3 years	33.1→28.9DID(-9.6%)[16]
	prescriptions	2002-2007, 5 years	-26.5%[24]
USA（Smart）	Standard unit*	1999-2010, 12 years	-17%[25]
Korea（disclose RTI antibiotic use）	Population DID	2005-2007, 3 years	24.7→21.5DID(-13%) [26]
		2007-2009, 3 years	21.5→25.2DID(+17%)
Shanghai	Population DID	2010-2012, 3years	25.9→17.8DID(-31%)[27]

* Standard unit is a measurement of IMS, equaling one pill of medicine.

The authoritarian, centralized political system of China has strengths to pass pressure from the top to the managers of public hospitals and to individual precribing doctors. Numberous literatures describe the intervetions and conclude that stewardship strategies played a role, including implementing standard treatment guidelines, multidisciplinary committees, educational sessions, formulary restrictions, and prescription reviews. [28, 29]

The pattern of antibiotic use in Shanghai is unique by more injection preparations, and preference for cephalosporins, more macrolides and quinolones, and less penicillins. Any other reported pattern consumes mainly penicillins (nearly half), including Europe, USA, Iran, and Korea.[30,31] It could be explained by the obligatory skin tests before any penicillins use in the Chinese national guidelines, though skin tests itself is not accurate to predict allergy to penicillins.[32, 33] Physicians may have skipped the time consuming test and turned to other altherations, although penicillins are recommended as the first line choice on many occassions.

It was widely accepted that penicillins have the least impact to micro floras, in human respiratory tract and intestinals. [34-36] Quinolones and some cephalosporins intervene intestinal bacteria with more selective pressure, and correlate with higher ESBL-producing strains, thus have been explicitly controlled in Europe.[37, 38] The pattern of antibiotic consumption may explain the differenct of rate of ESBL between mainland

China, Hong Kong and Taiwan.[39]

The exposure to the Chinese population with less penicillins and more other β-lactams may have been for over ten years, estimated by the reported allergic shocks counts by literatures in Chinese.

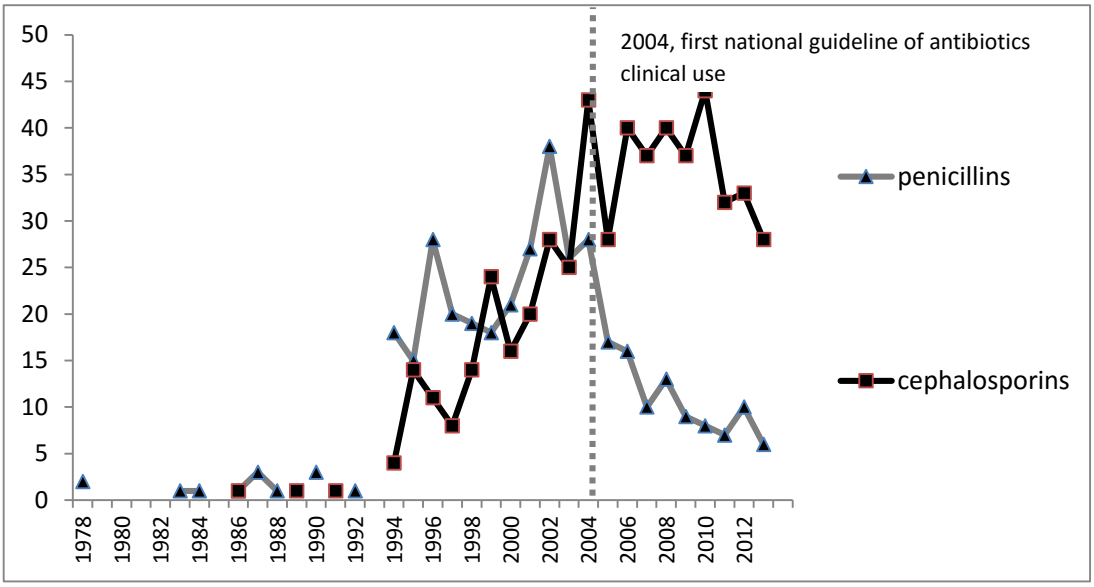

Figure 7 reported allgergic shocks after β-lactams use

Source: literatures in Chinese by SinoMed ,1978-2013

The variations between facilities with big data techniques were not sufficiently explained in this study. In all tertiary hospitals, Traditional Chinese Medicine (TCM) hospitals have the highest rate of penicillins use. Quinolone use is higher at CHCs in urban area than in rural areas. Interventions seemed raised the level of quinolone use at CHCs, but not in secondary and tertiary hospitals.

Carbapenems and glycopeptides, often required as last line treatment for multi-resistant bacteria, were used at very low levels in Shanghai, even

by EU standards.[40] This is likely because their use is highly restricted, and requires pre-authorization. Nevertheless, there was a 60% increase in carbapenem consumption, from 0.030 DID in 2009 to 0.048 DID in 2014; this may be in response to the rising prevalence of ESBL-producing bacteria, identified in surveillance studies.[41]

The most up-to-date data showed that in the end of 2016, the annual spending of antibiotic use bounced to a higher level by 0.7 billion RMB (17.5%) compared with the level of 2010, in which increased spending on carbapenems, quinolones, and third-generation cephalosporins constituted the majority.

CONCLUSION

The boundary between the information that should be disclosed and that could be kept within walls of public hospitals is still obscure. It challenges the governance of public hospitals and may risk losing the chance to improve in an era of big data. The case of antibiotics control is about the efforts to contain antibiotic resistance which is of global importance, with the aim of surveillance systems of antibiotic use and resistance.

The authoritarian centralized political system of China makes it rapid to do decisions and efficient to implement. Nevertheless the medical professionals' involvement is not sufficient to make policy and action sustainable. The governance of public hospitals could be optimized with

more power from data accumulated in the healthcare infrastructure investment in China, instead of resorting to enlarging the private sector in healthcare provision.

References:

1. Shi L, Yang HY, Cheng G et al. Time trends and determinants of pharmaceutical expenditure in China (1990-2009). *PHARMACOECONOMICS* 2014; **32**: 257-64.
2. Yip WC, Hsiao WC, Chen W et al. Early appraisal of China's huge and complex health-care reforms. *LANCET* 2012; **379**: 833-42.
3. Guan X, Qi L, Liu L. Controversy in public hospital reforms in China. *Lancet Glob Health* 2016; **4**: e240.
4. Xu S, Bian C, Wang H et al. Evaluation of the implementation outcomes of the Essential Medicines System in Anhui county-level public hospitals: a before-and-after study. *BMC HEALTH SERV RES* 2015; **15**: 403.
5. Lu Y, Hernandez P. The World Medicines Situation 2011 - Medicine Expenditures.: World Health Organization, 2011.
6. Laxminarayan R, Duse A, Wattal C et al. Antibiotic resistance-the need for global solutions. *LANCET INFECT DIS* 2013; **13**: 1057-98.
7. WHO. A global health guardian: climate change, air pollution, and antimicrobial resistance.
8. Hu FP, Guo Y, Zhu DM et al. Resistance trends among clinical isolates in China reported from CHINET surveillance of bacterial resistance, 2005-2014. *Clin Microbiol Infect* 2016; **22 Suppl 1**: S9-14.
9. Hu F, Zhu D, Wang F et al. Results from the Survey of Antibiotic Resistance (SOAR) 2009-11 and 2013-14 in China. *J Antimicrob Chemother* 2016; **71 Suppl 1**: i33-43.
10. Goossens H, Ferech M, Vander SR et al. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *LANCET* 2005; **365**: 579-87.
11. Chandy SJ, Thomas K, Mathai E et al. Patterns of antibiotic use in the community and challenges of antibiotic surveillance in a lower-middle-income country setting: a repeated cross-sectional study in Vellore, South India. *J Antimicrob Chemother* 2013; **68**: 229-36.
12. Wang J, Wang P, Wang X et al. Use and prescription of antibiotics in primary health care settings in china. *JAMA INTERN MED* 2014; **174**: 1914-20.
13. Van Boeckel TP, Gandra S, Ashok A et al. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. *LANCET INFECT DIS* 2014; **14**: 742-50.
14. Chang J, Ye D, Lv B et al. Sale of antibiotics without a prescription at community pharmacies in urban China: a multicentre cross-sectional survey. *J Antimicrob Chemother* 2017.
15. Dong L, Yan H, Wang D. Antibiotic prescribing patterns in village health clinics across 10 provinces of Western China. *J Antimicrob Chemother* 2008; **62**: 410-5.
16. Ferech M, Coenen S, Malhotra-Kumar S et al. European Surveillance of Antimicrobial Consumption (ESAC): outpatient antibiotic use in Europe. *J Antimicrob Chemother* 2006; **58**: 401-7.
17. Vander SR, Elseviers MM, Ferech M et al. European surveillance of antimicrobial consumption (ESAC): data collection performance and methodological approach. *Br J Clin Pharmacol* 2004; **58**: 419-

28.
18. Lin H, Dyar OJ, Rosales-Klintz S et al. Trends and patterns of antibiotic consumption in Shanghai municipality, China: a 6 year surveillance with sales records, 2009-14. *J Antimicrob Chemother* 2016; **71**: 1723-9.
19. Wagner AK, Soumerai SB, Zhang F et al. Segmented regression analysis of interrupted time series studies in medication use research. *J CLIN PHARM THER* 2002; **27**: 299-309.
20. Adriaenssens N, Coenen S, Versporten A et al. European Surveillance of Antimicrobial Consumption (ESAC): quality appraisal of antibiotic use in Europe. *J Antimicrob Chemother* 2011; **66 Suppl 6**: i71-7.
21. Molstad S, Cars O. Major change in the use of antibiotics following a national programme: Swedish Strategic Programme for the Rational Use of Antimicrobial Agents and Surveillance of Resistance (STRAMA). *SCAND J INFECT DIS* 1999; **31**: 191-5.
22. Molstad S, Erntell M, Hanberger H et al. Sustained reduction of antibiotic use and low bacterial resistance: 10-year follow-up of the Swedish Strama programme. *LANCET INFECT DIS* 2008; **8**: 125-32.
23. Cizman M, Srovin T, Pokorn M et al. Analysis of the causes and consequences of decreased antibiotic consumption over the last 5 years in Slovenia. *J Antimicrob Chemother* 2005; **55**: 758-63.
24. Sabuncu E, David J, Bernede-Bauduin C et al. Significant reduction of antibiotic use in the community after a nationwide campaign in France, 2002-2007. *PLOS MED* 2009; **6**: e1000084.
25. Center For Disease Dynamics EP. Antibiotic use and resistance at a glance: 1999 – 2010.
26. Lee YS, Kwon JW, Oh OH et al. Temporal decrease in overall antibiotic consumption accompanying antibiotic prescribing rate disclosure policy: evidence from analysis of national health insurance claims data in South Korea. *ARCH PHARM RES* 2014; **37**: 1295-300.
27. Lin H, Dyar OJ, Rosales-Klintz S et al. Trends and patterns of antibiotic consumption in Shanghai municipality, China: a 6 year surveillance with sales records, 2009-14. *J Antimicrob Chemother* 2016.
28. Song P, Li W, Zhou Q. An outpatient antibacterial stewardship intervention during the journey to JCI accreditation. *BMC Pharmacol Toxicol* 2014; **15**: 8.
29. Hou D, Wang Q, Jiang C et al. Evaluation of the short-term effects of antimicrobial stewardship in the intensive care unit at a tertiary hospital in China. *PLOS ONE* 2014; **9**: e101447.
30. Abdollahiasl A, Kebriaeezadeh A, Nikfar S et al. Patterns of antibiotic consumption in Iran during 2000-2009. *Int J Antimicrob Agents* 2011; **37**: 489-90.
31. Sohn HS, Oh OH, Kwon JW et al. Higher systemic antibiotic consumption in a population of South Korea (2008 - 2009). *Int J Clin Pharmacol Ther* 2013; **51**: 585-92.
32. Solensky R, Khan DA. Evaluation of antibiotic allergy: the role of skin tests and drug challenges. *Curr Allergy Asthma Rep* 2014; **14**: 459.
33. Fox S, Park MA. Penicillin skin testing in the evaluation and management of penicillin allergy. *Ann Allergy Asthma Immunol* 2011; **106**: 1-7.
34. Sullivan A, Edlund C, Nord CE. Effect of antimicrobial agents on the ecological balance of human microflora. *LANCET INFECT DIS* 2001; **1**: 101-14.
35. Rashid MU, Weintraub A, Nord CE. Effect of new antimicrobial agents on the ecological balance of human microflora. *ANAEROBE* 2012; **18**: 249-53.
36. Edlund C, Nord C. Ecological impact of antimicrobial agents on human intestinal microflora. *Alpe Adria Microbiology Journal* 1993; **2**: 137-64.
37. Zarb P, Amadeo B, Muller A et al. Identification of targets for quality improvement in antimicrobial

prescribing: the web-based ESAC Point Prevalence Survey 2009. *J Antimicrob Chemother* 2011; **66**: 443-9.

38. Adriaenssens N, Coenen S, Versporten A et al. European Surveillance of Antimicrobial Consumption (ESAC): quality appraisal of antibiotic use in Europe. *J Antimicrob Chemother* 2011; **66 Suppl 6**: i71-7.

39. Hirakata Y, Matsuda J, Miyazaki Y et al. Regional variation in the prevalence of extended-spectrum beta-lactamase-producing clinical isolates in the Asia-Pacific region (SENTRY 1998-2002). *Diagn Microbiol Infect Dis* 2005; **52**: 323-9.

40. Control ECFD. Surveillance of antimicrobial consumption in Europe 2012. Stockholm, 2014.

41. Xiao Y, Zhang J, Zheng B et al. Changes in Chinese policies to promote the rational use of antibiotics. *PLOS MED* 2013; **10**: e1001556.