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# Evaluation of a clinical pharmacist consultation service for patients with infectious diseases in China: a systematic review and meta-analysis

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## ABSTRACT

**Background** Since antibiotic resistance has become a global public health issue, a clinical pharmacist consultation service has been established in China.

**Objectives** To clarify the role of the clinical pharmacist consultation service in the management of infectious diseases (ID).

**Methods** Medline, Embase, Cochrane Library, Chinese National Knowledge Infrastructure, Chinese Biomedical Database, Vip Database and Wanfang Database were searched for studies meeting predefined inclusion criteria. The pooled acceptance rate of consultation (ARC) and effective rate of patients treated with the acceptance of pharmacists' suggestions (ERA) were then calculated.

**Results** Fifty studies (involving 8616 patients and 8828 consultations) from 17 different provinces in China were included. The pooled ARC and ERA were 93.13% (95% CI 90.62% to 95.00%) and 93.60% (95% CI 91.99% to 95.24%), respectively. Adopting pharmacists' suggestions can significantly improve the prognosis of patients with ID with a risk ratio of 2.08 (95% CI 1.41 to 3.06). Factors such as study time, characteristics of the research institution and patients have important influences on ARC.

**Conclusion** Prospective cohort studies with better methodology are needed, although a series of uncontrolled studies has shown that the service has excellent acceptance and improves the effectiveness of treatment for ID.

## INTRODUCTION

Clinical pharmacy<sup>1</sup> refers to the discipline in which the pharmacist provides patient care that optimises medication therapy and promotes health, wellness and disease prevention. Clinical pharmacists work closely with both clinicians and patients to ensure that the medications prescribed for patients contribute to the best possible health outcomes.

Nevertheless, the development of hospital clinical pharmacy in China is far behind that in developed countries. For medical institutions of the same scale (1000 beds), the number of pharmacists in the Johns Hopkins Hospital (0.04 per bed) is eight times that in a general tertiary hospital in China (0.005 per bed).<sup>2</sup> The shortage of human resources in China results in low accessibility to health-care from clinical pharmacists. The situation is, however, improving as a result of implementation of a clinical pharmacist consultation service, which generally consists of four steps: (1) clinicians send a consultation request to the Department of Clinical Pharmacy when treating patients with complicated

diseases; (2) the Department of Clinical Pharmacy assigns the pharmacists with specialist board certifications through 1 year residency training to deal with the consultation; (3) the designated pharmacists reply with treatment suggestions (eg, selection of antibiotics) based on the benefits and risks of medications; (4) the clinicians make the final decision on the therapeutic scheme.

The severity of infectious diseases (ID) in hospital is increasing due to an increase in drug-resistant bacteria and abuse of antibiotics.<sup>3–5</sup> Infections caused by resistant pathogens are difficult to treat and are associated with increased morbidity, mortality and costs.<sup>6,7</sup> The United States Centers for Diseases Control and Prevention estimates that antibiotic-resistant pathogens cause two million infections and 23 000 deaths each year in the USA.<sup>8</sup> In China, the resistance of clinical isolates is also widespread with a continuing upward tendency.<sup>9</sup> In response to the increasingly severe situation, the Ministry of Health of China launched the Antimicrobial Rectification Action<sup>10</sup> in 2011 and successively promulgated a series of antimicrobial stewardship regulations requiring pharmacists to participate in the management of antimicrobial drugs. Pharmacists are gradually being incorporated into the consortium for treatment of infectious patients via the consultation service, and there are accumulating studies focusing on the role of pharmacists in anti-infection consultation in China. However, these studies are case series reporting consultations in individual institutions and the results vary greatly. A study summarising the acceptance of the consultation service at a nationwide level is not available.

We conducted a systematic review to investigate the present status of the pharmacist consultation service in China and to evaluate the effectiveness of this service for patients with ID at a nationwide level.

## METHODS

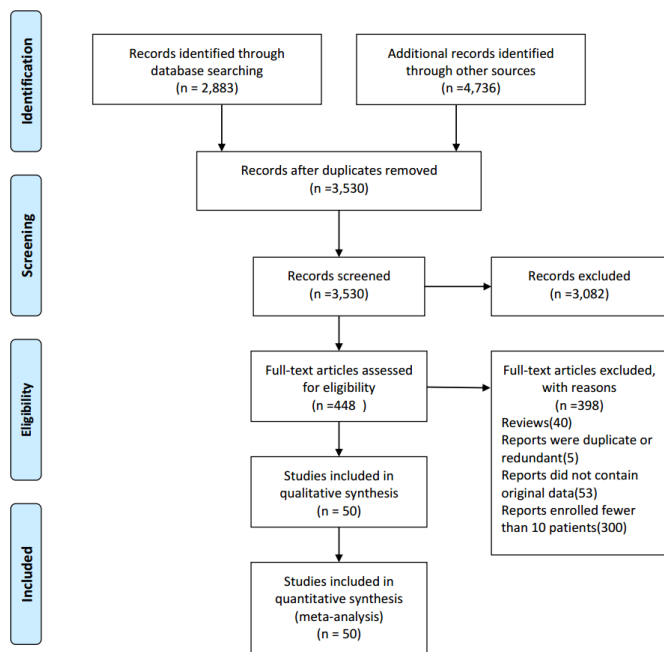
### Literature search

We searched PubMed, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL) published in the Cochrane Library using the search strategy detailed in online supplementary table S1; we also searched Chinese National Knowledge Infrastructure (CNKI), Chinese Biomedical Database (CBD), Vip Database (VD) and Wanfang Database (WD) for literature published in Chinese and the electronic databases of the Chinese Pharmaceutical Association (CPA). The references of all retrieved articles were checked for additional



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**Figure 1** Modified four-phase PRISMA 2009 flow diagram that maps out the number of records identified, included and excluded, and the reasons for exclusions.

relevant publications. We searched all databases from their earliest records to May 2018.

### Eligibility criteria

All included studies met the following criteria: (1) case series enrolling more than 10 patients; (2) inpatients (including both children and adults) with serious infections in a Chinese hospital and in need of pharmacist consultation; (3) intervention of pharmacist consultation; and (4) information on at least one of the following outcomes.

The primary outcome was the acceptance rate of consultation (ARC) measured by comparing the prescriptions of clinicians with the suggestions of pharmacists. Acceptance indicates that the clinicians completely or partially adopted the advice of pharmacists, and ARC was the proportion of consultation suggestions adopted by clinicians to the total consultation requests sent by clinicians.

The secondary outcome was effective rate (ER) evaluated according to the 'Guiding principles for clinical application of antibiotics' (2004).<sup>11</sup> Effective response is defined as healing, improvement, free of symptoms with bacterial colonisation or discharged after recovery. Healing means recovery of symptoms, signs, laboratory test results and pathogenic test results, while improvement represents obvious remission but with one of the above indicators not completely recovered. ER was the proportion of patients achieving an effective response.

### Study selection and data extraction

Two authors (JZ and XL) independently screened the titles and abstracts of all studies identified by the search strategy and assessed the studies for inclusion using predetermined inclusion criteria. The full texts of all potentially relevant articles were retrieved for detailed review. We resolved disagreements by discussion until consensus was achieved.

Two authors (JZ and XL) used a pre-designed data collection form to independently extract data from each included study. The following data were extracted: (1) patient characteristics

including number of patients meeting the inclusion criteria, number of consultation applications (multiple rounds of consultation for one patient), gender, age and the type of infectious bacteria; (2) study time and design; (3) information on the research institution including geographical location, rank graded by the Hospital Classification Management Standard and region according to economic level; (4) number of consultation suggestions adopted by clinicians, number of responsive patients whose treatment adopted pharmacists' suggestions or not, and total number of patients whose treatment adopted pharmacists' suggestions or not.

### Quality assessment

Quality assessment was based on the checklist for assessment of case series developed by the UK National Institute for Health and Care Excellence (NICE).<sup>12</sup> We answered eight questions in the checklist with yes, no, or unclear.

### Statistical analysis

Studies from the same institution conducted at different times were integrated into one study before analysis. We achieved exact binomial 95% CI of ARC and ER in each study. We estimated the between-study variance and determined pooled estimates of ARC and ER using the software R 3.3.1 with a random-effect model.<sup>13</sup> For dichotomous outcomes, if the primary studies reported the relative risks (RR), the pooled RR with 95% CI was calculated using RevMan 5.1 with a random-effect model. Heterogeneity among studies was assessed using the Cochran's Q-statistic and I<sup>2</sup> test. Significant heterogeneity was indicated if the corresponding p value of the Cochran's Q test was <0.01 or I<sup>2</sup> >50%. Considering possible confounders (eg, study time, characteristics of research institution and patients), subgroup analysis was also performed. Publication bias was assessed with the funnel Egger test in R 3.3.1, and p ≤ 0.05 suggested a significant publication bias.<sup>14</sup> Sensitivity analysis was performed using software R 3.3.1.

The kappa statistic ( $\kappa$ ) was calculated for measuring agreement between two authors on the decisions made in study selection.  $\kappa$  values of 0.40–0.59, 0.60–0.74 and >0.75 represent fair, good and excellent agreement, respectively.<sup>15</sup> The design and report of this review was checked with the PRISMA checklist.

### Data availability

All the data generated or analysed during this study were included in this article (and the online supplementary information files).

## RESULTS

### Study selection

A total of 3530 publications were identified from the literature search and 50<sup>16–65</sup> (8616 patients and 8828 consultations) were eligible and are included in this systematic review (figure 1). Agreement between the two reviewers for study selection was excellent ( $\kappa=0.80$ ). As shown in online supplementary table S2, all the included studies were case series published in Chinese and available as full text. The study time ranged from February 2005 to December 2014, with 12 studies before 2011.

### Institutions and patients

The institutions consisted of 36 tertiary hospitals and 14 secondary hospitals from 17 provinces in China. Most of them were in the eastern region (n=27) while 13 and 10 were in the central and western regions, respectively. The patient characteristics are described in online supplementary table S2. A total of

**Table 1** Results of meta-analysis of ARC

Subgroup	N	n	ARC (%)	95% CI	I <sup>2</sup> (%)	P value	Figure
Total	46	8828	93.13	90.62 to 95.00	92.8	<0.0001	
Location	Western region	12	92.80	88.14 to 95.72	82.6	<0.0001	
	Central region	12	87.32	81.93 to 91.28	85.8	<0.0001	
	Eastern region	22	95.78	92.25 to 97.74	95.7	<0.0001	
Rank	Secondary hospital	14	93.97	89.43 to 96.64	84.1	<0.0001	
	Tertiary hospital	32	92.74	89.46 to 95.06	94.3	<0.0001	
Risk	Non-resistant	36	92.63	89.63 to 94.81	93.5	<0.0001	
	Resistant	10	94.32	91.01 to 96.45	59.6	0.0081	
Age	A	43	92.79	90.07 to 94.81	93.0	<0.0001	
	C	4	95.91	91.46 to 98.09	44.9	0.1420	
Phase	Phase I	12	89.23	84.93 to 92.42	84.5	<0.0001	
	Phase II	34	94.63	91.60 to 96.60	93.9	<0.0001	

A, adults and children; ARC, acceptance rate of consultation; C, children; N, number of studies; n, number of consultations; non-resistant, non-resistant bacteria infection; resistant, resistant bacteria infection; phase I, study time before 2011; phase II, study time after 2011. I<sup>2</sup> and p value, results of heterogeneity test.

1698 patients (19.71%) had resistant bacteria infection, and four studies involved a total of 538 children.

### Quality assessment

As shown in online supplementary table S3, every study was conducted at a single centre and all described the hypothesis/objective and main findings clearly; however, only half of the studies defined the outcomes and patient inclusion criteria. Most studies did not provide information on data collecting; only one collected data prospectively and a further two enrolled patients consecutively. Five studies stratified patients according to the clinical characteristics.

### Acceptance rate of consultation (ARC)

ARC was reported in all studies. After merging seven studies<sup>28 36–38 53 54 62</sup> from three identical institutions, 46 studies were subjected to final analysis. The primary data were logit-transformed due to non-normal distribution before analysis. Online supplementary figure S1 shows that ARC ranged from 53% to 100% with a pooled rate of 93.13% (95% CI 90.62% to 95.00%). The heterogeneity among studies was statistically significant (I<sup>2</sup>=92.8%, p<0.0001).

To explore the cause of heterogeneity, subgroup analyses were performed according to geographical location, institution rank, risk, age and study time, respectively (table 1). The results

indicated that ARC was highly dependent on geographical location with a descending order of eastern (95.78%), western (92.80%) and central regions (87.32%). Interestingly, ARC in secondary hospitals was slightly higher than in tertiary hospitals (93.97% vs 92.74%). Higher ARC was also found in the context of resistant bacterial infection compared with non-resistant bacterial infection (94.32% vs 92.63%), and in children compared with the total population (95.91% vs 92.79%). ARC increased by around 5% after 2011 compared with before 2011 (94.63% vs 89.23%). These differences had no statistical significance, although the heterogeneity among studies decreased by subgroup analysis.

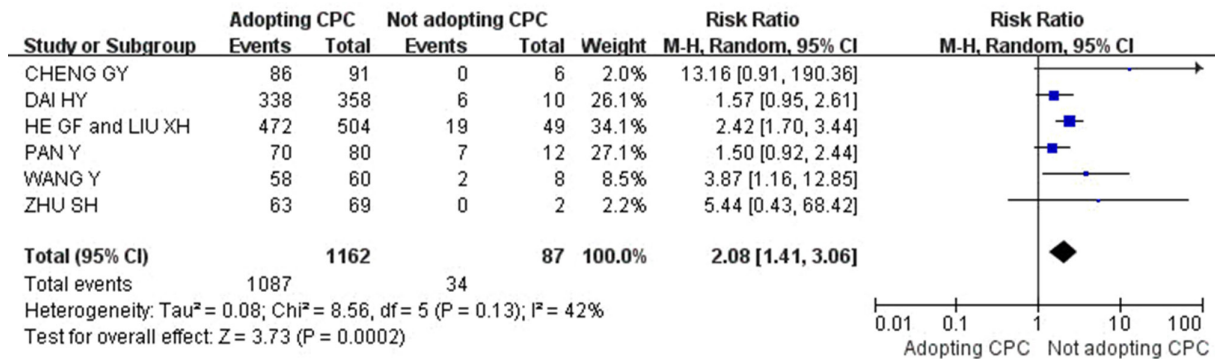
### Effective rate of patients treated after acceptance of pharmacists' suggestions (ERA)

After data screening,<sup>17 18 20 21 23 27 29 31 34 39 41 42 44 48 50 53–55 57–61 64 65</sup> 24 studies involving 2745 patients were finally included in the analysis. Online supplementary figure S2 shows that the ERA ranged from 69% to 100% and the pooled rate was 93.60% (95% CI 91.99% to 95.24%). Because of the significant heterogeneity among studies (I<sup>2</sup>=66.8%, p<0.0001), subgroup analyses were performed according to infection risk (table 2). ERA of resistant bacterial infection (94.43%) was higher than that of non-resistant bacterial infection (93.34%), but the difference was not statistically significant.

**Table 2** Results of meta-analysis of ERA

Subgroup	N	n	ERA (%)	95% CI	I <sup>2</sup> (%)	P value	Figure
Total	24	2745	93.60	91.99 to 95.24	66.8	<0.0001	
Non-resistant bacterial infection	19	2502	93.34	91.65 to 95.07	66.5	<0.0001	
Resistant bacterial infection	5	243	94.43	89.01 to 100.00	63.6	0.0266	

ERA, effective rate of patients whose treatment adopted pharmacists' suggestions; N, number of studies; n, number of patients; I<sup>2</sup> and p value, results of heterogeneity test.



**Figure 2** Meta-analysis forest plot of effective rate of patients in the two groups. CPC, clinical pharmacists' consultation opinion.

Among the 24 studies included, six studies<sup>34 48 53–55 57 58</sup> involving 1249 patients reported the ER of 1162 patients whose treatment followed pharmacists' suggestions and 87 whose treatment did not follow the pharmacists' suggestions. To compare the ER between the two groups, a meta-analysis using RR with 95% CI was conducted with a random-effect model. As shown in **figure 2**, the pooled RR was 2.08 (95% CI 1.41 to 3.06,  $p=0.0002$ ), meaning that adoption of pharmacists' suggestions could significantly improve the prognosis of patients with ID. The heterogeneity among studies was not statistically significant ( $I^2=42\%$ ,  $p=0.13$ ).

#### Publication bias

The funnel plot was graphed and the Egger test was conducted to investigate publication bias in the 46 studies reporting ARC and 24 studies reporting ERA in patients with ID. As shown in online supplementary figures S3 and S4, both the asymmetrical funnel plots and the results of the Egger test ( $p=0.003193$  and  $p=0.002872$ , respectively) demonstrated the presence of publication bias. Most studies reported a higher ARC, especially those with small sample size.

#### DISCUSSION

Fifty studies from 17 different provinces were included for analysis and we take these to be representative of the general status in China. According to the results of the meta-analysis, the consultation service for ID is well accepted by clinicians in China with a high ARC of 93.13%, and improves the effectiveness of treatment for ID with an excellent ERA of 93.60% (95% CI 91.99% to 95.24%) and RR of 2.08 (95% CI 1.41 to 3.06).

To fight against growing antimicrobial resistance, many countries have implemented an antimicrobial stewardship programme (ASP).<sup>66</sup> Pharmacists' contributions to ASP have been proved to be essential. The inclusion of pharmacists in the ASP has resulted in a significant improvement in the quality of antibiotic use in both developing<sup>67–70</sup> and developed<sup>71–78</sup> nations. In China, due to the insufficient number of clinical pharmacists and the regulation that the use of some special antibiotics (eg, vancomycin, carbapenem and tigecycline) needs to be reviewed and approved by clinical pharmacists (Measures for the Administration of Clinical Use of Antibacterials), a pharmacist-led consultation service became a major way for pharmacists to participate in the treatment of ID. During the process of consultation, clinical pharmacists participate in the treatment of ID through a variety of ways (eg, round with clinicians, discussion with patients, link with microbiologists and nurses, developing a therapeutic scheme, adjusting the dosage regimen according to pharmacokinetic-pharmacodynamic results and monitoring adverse events). The multiple contributions of

clinical pharmacists can help clinicians to optimise the treatment and improve patient outcome, which may explain the high scores of ARC and ERA.

According to the subgroup analysis, multiple factors (location, rank of research institution, study time, patient characteristics) have important effects on ARC. The increasing ARC after 2011 might result from implementation of the Antimicrobial Rectification Action which permits clinical pharmacists to participate more actively in the healthcare team. Higher ARC in the western region and in secondary hospital implies that clinicians from institutions of a lower economic and medical level are more prone to collaborate with the pharmacists. In addition, the clinicians incline to adopting the pharmacists' suggestions when treating patients with complicated conditions (eg, children or resistant bacterial infections). The limited sample size may result in the insignificant differences among subgroups.

There are some limitations to our analysis. First, the  $I^2$  value reported in the meta-analysis ( $I^2=92.8\%$ ) for ARC is very high. Although we conducted the meta-analysis using a random-effect model and then performed subgroup analyses to explore the cause of heterogeneity, most  $I^2$  values remain over 85%, which implies the presence of other confounders such as the professionalism of the clinical pharmacist, disease severity, and financial as well as psychological factors affecting the physician's decision. Unfortunately, none of the included studies provided this information so further analyses of heterogeneity were not conducted. However, sensitivity analyses by successively omitting studies (Figures S5 and S6) demonstrated a high level of robustness of the results from the meta-analyses. Furthermore, most of the studies eligible for ER analysis in this review failed to compare the effectiveness between adopting pharmacists' suggestions and not. Also, the obtained ER may be influenced by many confounders such as severity of infection, cause and development of ID. Studies on this topic with a better methodological design such as prospective cohort studies or controlled studies are urgently needed. Consecutive enrolling of patients can help to reduce selection bias in prospective multicentre case series studies; however, few studies provided information on this, which needs improvement in future studies. In addition, publication bias still exists, although we included those studies enrolling 10 or more patients to avoid extreme risk of reporting and selection bias from smaller studies. The results therefore need to be verified in large-sample studies with registered protocols.

Recently, increasing evidence has proved the positive impact of the clinical pharmacy service on disease treatment, especially for chronic diseases. Zhong *et al*<sup>79</sup> conducted a



systematic review including eight randomised controlled trials with 1327 patients and clarified the impact of pharmacist care for outpatients with chronic obstructive pulmonary disease. Although current evidence failed to illustrate a significant improvement in the health-related quality of life in intervention patients, pharmacist care improved medication compliance (RR 1.23, 95% CI 1.11 to 1.36) and reduced hospital admissions (RR 0.50, 95% CI 0.39 to 0.64) and health-related costs (standardised mean difference -0.37, 95% CI -0.59 to -0.15). For ID, pharmacists have to deal with every consultation request according to the requirement of the Antibiotic Clinical Research Guiding Principle. Considering the ethics and feasibility, it is impossible to perform trials to assess the effectiveness of the consultation service for ID so the studies included in our review are all observational. Peng *et al*<sup>80</sup> performed a literature analysis of 148 references (including a case report with a small sample (n<10)) on pharmacy consultation in China. In line with the findings in our study, they noted that the pharmacy consultation service in China was poor before 2010 but improved greatly due to the support and recognition of the management staff and clinicians. However, the study by Peng *et al*<sup>80</sup> is a qualitative description and lacks evaluation of research quality and quantitative analysis. In our study we assessed the quality of the included studies and also investigated the present research status of the pharmacist consultation service for ID by meta-analysis and subgroup analyses, calculated the pooled ARC and ERA and determined the important factors associated with the ARC.

## CONCLUSION

The consultation service has provided a significant breakthrough for clinical pharmacy in China and has achieved some success. Our study shows that the pharmacist-led consultation service may be an effective intervention for ID treatment, which can be shared with other developing countries where clinical pharmacists are not actively involved in patient healthcare. To the best of our knowledge, this is the first systematic review investigating the role of a pharmacist consultation service in ID, which is believed to shed light on this service in China. Because of the limitations of the included studies, our group is planning to establish a follow-up registry database and to conduct a prospective cohort study based on our clinical pharmacist consultation system in the western region of China to further evaluate the effectiveness of pharmacists' consultation for ID and investigate the important associated factors.

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**Contributors** JZ, XL and JX conceived and designed the experiments. JZ, XL and WZ performed the experiments. JZ, XL and WZ analysed the data. JZ, XL and JX contributed reagents/materials/analysis tools. JZ, XL, WZ and JX wrote the paper.

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