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Effects of a feedback intervention on antibiotic prescription control in primary care institutions based on a Health Information System: a cluster randomized cross-over controlled trial

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ABSTRACT

Objectives: Overuse and misuse of antibiotics are major factors in the development of antibiotic resistance in primary care institutions of rural China. In this study, the effectiveness of a Health Information System-based, automatic, and confidential antibiotic feedback intervention was evaluated.

Methods: A randomized, cross-over, cluster-controlled trial was conducted in primary care institutions. All institutions were randomly divided into two groups and given either a three-month intervention followed by a three-month period without any intervention or vice versa. The intervention consisted of three feedback measures: a real-time pop-up warning message of inappropriate antibiotic prescriptions on the prescribing physician's computer screen, a 10-day antibiotic prescription summary, and distribution of educational manuals. The primary outcome was the 10-day inappropriate antibiotic prescription rate.

Results: There were no significant differences in inappropriate antibiotic prescription rates (69.1% vs. 72.0%) between two groups at baseline ($P = 0.072$). After three months (cross-over point), inappropriate antibiotic prescription rates decreased significantly faster in group A (12.3%, $P < 0.001$) compared to group B (4.4%, $P < 0.001$). At the end point, the inappropriate antibiotic prescription rates decreased in group B (15.1%, $P < 0.001$) while the rates increased in group A (7.2%, $P < 0.001$). The characteristics of physicians did not significantly affect the rate of antibiotic or inappropriate antibiotic prescription rates.

Conclusion: A Health Information System-based, real-time pop-up warnings, a 10-day prescription summary, and the distribution of educational manuals, can effectively reduce the rates of antibiotic and inappropriate antibiotic prescriptions.

1. Introduction

Antibiotic resistance is a real threat to human health [1,2]. In 2019, about 1.27 million deaths were related to antibiotic resistance [3]. Overuse and misuse of antibiotics are major factors in the development of antibiotic resistance [4]. The total consumption of antibiotics increased by 46% in 204 countries from 2000 to 2018 [5]. According to a World Health Organization (WHO) report the inappropriate use of antibiotics is on the rise and is more likely to be found in low- and middle-income countries [6]. In China, more than 50% of outpatient antibiotic prescriptions are inappropriate [7] and this phenomenon is more prominent in primary care institutions [8]. In our previous study, approximately 90% of patients received inappropriate antibiotic treatment in Guizhou Province [9]. The majority of inappropriate

Abbreviations: CDSS, Clinical Decision Support System; HIS, HealthInformation System; LWTC, Lianke Weixin Technology Co., LTD.; ICD-10, International Classification of Diseases 10th Edition.

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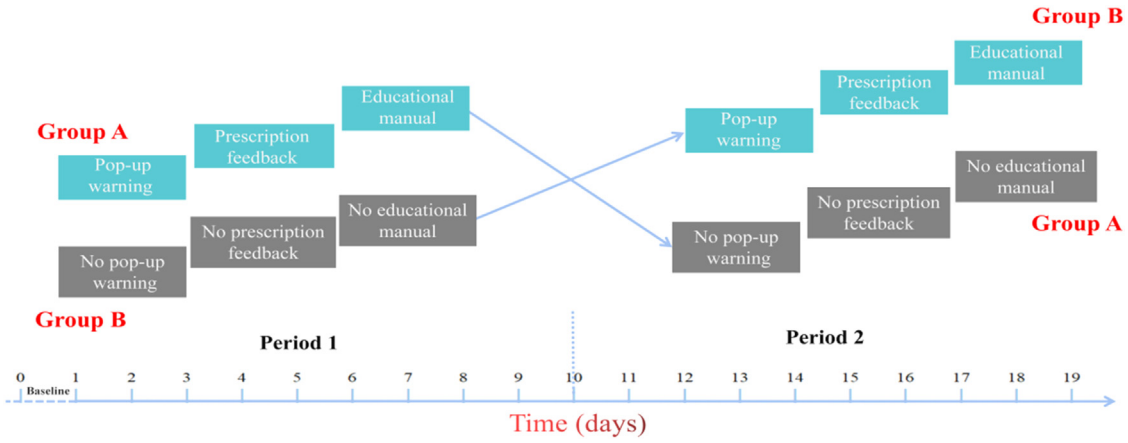

Fig. 1. Cross-over intervention diagram showing 10-day intervals.

prescriptions are related to physicians' individual prescribing behavior [10–14].

Previous researchers have developed a variety of interventions to control the misuse and overuse of antibiotic prescriptions, including information technology interventions, such as a Clinical Decision Support System (CDSS) or electronic health records, whereby electronic modules are sent to physicians to help them make the best clinical decisions [15–17]; educational interventions, such as distribution of educational manuals or training courses given to medical personnel or patients [18,19]; and antibiotic prescription audit and feedback interventions [20–22]. In 2019, we conducted a cluster randomized crossover-controlled trial based on a Health Information System (HIS) with 163 physicians in 31 primary care institutions in Guizhou Province. Significant results were achieved, with antibiotic prescription rates falling by 15% [23]. One limitation of the study, however, was that it did not measure the inappropriate antibiotic prescription rate.

Therefore, an automatic, confidential, and long-term feedback intervention warning system for inappropriate antibiotic prescription was developed. A real-time pop-up warning feature was added based on the previous feedback intervention study [23]. The objective of this study was to investigate whether the new feedback intervention could reduce the inappropriate antibiotic prescription rates and antibiotic prescription rates among primary care physicians.

2. Methods

2.1. Trial designs and setting

A randomized, cross-over, cluster-controlled trial was conducted from April 1st, 2021 to September 30th, 2021. A cross-over design is a repeated measurement method in which each unit receives different interventions at different times [24]. In this study, a primary health care institution was used as a cluster unit and physicians from the same institution were grouped together. As shown in Fig. 1, all primary care institutions included in the trial were randomly divided into two groups: group A and group B. The three-month intervention was performed in group A while group B acted as the control group (no intervention was given). As stated in the proposal [25], since this was a behavioral change intervention study, there was no washout period for this crossover design. Therefore, after three months, the two groups switched, with group A switching to be the control group and group B switching to receive the intervention for three months. The entire trial lasted for six months (April 1st, 2021 to September 30th, 2021) with the two groups entering the crossover point on June 30th.

Guizhou Province, the setting of the study, is located in southwest China and is one of the least developed provinces of the country. The study population involved 252 primary care institutions that use the same HIS in Guizhou Province. Township health centers and community health service centers are called primary care institutions, which mainly provide primary health care services for the local population [26]. The inclusion criteria were the same as in our previous study [23], and were also set out in the published protocol [25]: 1) institutions with at least three outpatient general physicians, 2) the physicians had worked in a primary care institution for at least one year, and 3) each physician saw at least 100 patients every 10 days [23]. The exclusion criteria for prescriptions included patients treated for tuberculosis, leprosy, and other diseases requiring combination drugs. Informed consent forms were signed by physicians before the trial commenced. One hundred thirty-two primary care institutions meeting the above criteria were included.

Antibiotic prescription records used in this trial were provided by Guizhou Lianke Weixin Technology Co., LTD. (LWTC). Guizhou Lianke Weixin Technology Co., LTD. is a technology service company that develops HIS. Authorized by the Information Center Guizhou Provincial Health Commission, an early warning intervention plug-in for antibiotic prescriptions was designed. The plug-in was used to provide a real-time warning and information feedback. Before the formal trial, the intervention plug-in had been successfully applied in two primary care institutions in Guizhou province for three months and the sensitivity and reliability of the plug-in have been scientifically verified. The protocol was published on January 7th, 2022 [25].

2.2. Randomization and masking

The 79 primary care institutions that met the criteria were randomly selected from the 132 using a random number table by LWTC information technology staff. In total, 335 qualified outpatient physicians were enrolled in the trial. Fig. 2 shows the flow chart of the trial. The 79 primary care institutions participating in the trial were randomly assigned to the two groups. All physicians involved in the study had a good sense of whether they were entering the intervention, so it was impossible to blind the participants and the researchers.

2.3. Intervention

Feedback interventions are the act of providing knowledge of the results of a behavior or performance to an individual [27,28].

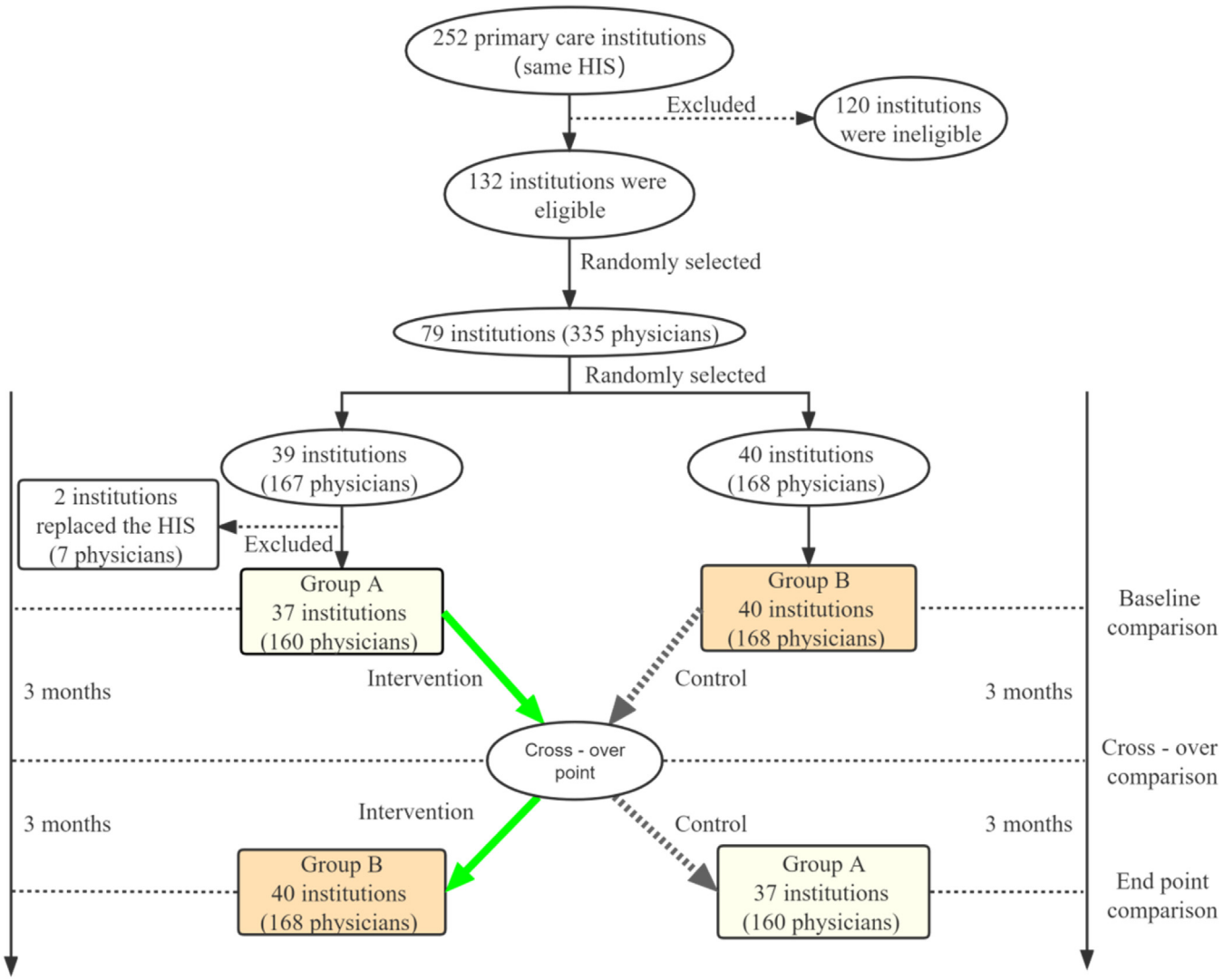

Fig. 2. Flow chart of the trial.

Feedback interventions can change behavior and improve performance and outcomes [16,29]. Physicians who entered the intervention group received three feedback measures, including a real-time pop-up warning message, a 10-day antibiotic prescription feedback summary, and distribution of educational manuals.

The first measure of the feedback consists of a real-time pop-up warning of inappropriate antibiotics based on the HIS. In previous studies, the Delphi method has been used to judge the rationality of big data prescriptions [30] and the influencing factors of rational use of antibiotics by both physicians and patients [9]. A self-designed recommendation table to evaluate the appropriate use of antibiotic prescriptions for common bacterial infectious diseases in primary care institutions (Appendix 1) was formed, and its judgment results and related contents were recorded into the HIS as algorithm rules. The steps are shown in Fig. 3 and are summarized as follows: 1) Determine whether the prescription included an antibiotic according to the drug name; 2) Query the specified disease according to the first three digits of the disease code; 3) If there was no disease code, use the disease name for matching; 4) Judge whether the antibiotic prescription was appropriate according to the self-designed recommendation table (Appendix 2, algorithm rules) input by disease and drug query. If the prescription was deemed inappropriate, then the reason would be displayed in a real-time pop-up window on the physician's computer screen.

Next, in the HIS, when a physician prescribed an inappropriate antibiotic, a small yellow window in Fig. 3 would immediately appear, reminding them of their inappropriate prescribing behavior. A brief explanation would also be displayed in the message. Our evaluation of antibiotic prescribing appropriateness was based on the following three criteria: 1) National Health Commission of China for Guiding Principle of Clinical Use of Antibiotics introduced in 2015 [31], 2) guidelines for the use of antibiotics issued by the United States Centers for Disease Control and Prevention [32], and 3) based on our previous research [9], we also added the opinions of 17 clinical and pharmaceutical experts familiar with the situation of primary care institutions in China. There are three criteria for inappropriate antibiotic prescribing: 1) unnecessary use, such as patients who were diagnosed with viral infections but received antibiotics; 2) incorrect antibiotic spectrum, such as aminoglycosides prescribed for Gram-positive bacteria; 3) combination of antibiotics without indication, referring to the use of more than one systemic antibiotic in a visit, such as amoxicillin and levofloxacin in combination. The feedback messages that the physicians received were shown in Chinese but have been translated into English, as shown in Fig. 3.

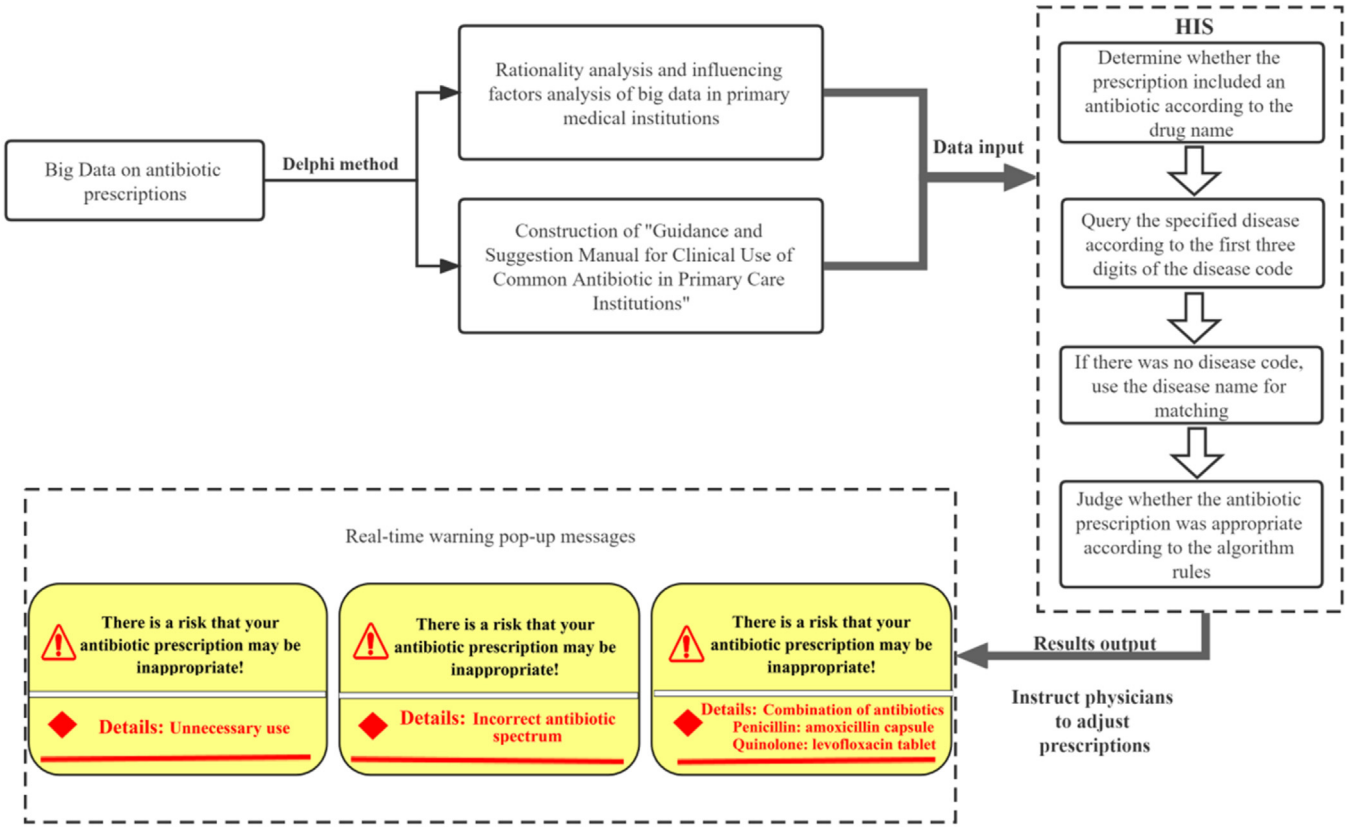

Fig. 3. Real-time warning process of inappropriate antibiotics prescription based on the Guizhou HIS.

The second measure of the feedback involves providing antibiotic prescription information to physicians every 10 days according to the HIS. The link to the prescription feedback information appears at the bottom of the physician's computer screen, which the physician can click at any time, and automatically updates every 10 days. As shown in Fig. 4, the 10-day antibiotic prescription feedback included five functional areas. An automatic pop-up message was used to remind physicians to click on the link to view the information. The message was confidential in that only the physician could see it. The physicians are free to pay attention to it or ignore it. The number of clicks per physician was also automatically recorded by the system.

The third part of the intervention is the educational manual: 'Guidance and Suggestion manual for Clinical Use of Common Antibiotics in Primary Care Institutions' (Appendix 2). The manual was derived from the previous Delphi study [30]. Appendix 1 contains the first part of the manual. The manual's cover, catalogue, and example of contents are shown in Appendix 2. The physicians could receive advice on antibiotic use and guidance on the diagnosis of common infections at the primary care level. The number in the disease diagnosis section represents the reference value; the higher the number, the higher the reference value.

2.4. Control

No intervention was provided for the physicians in the control group who were advised to continue to treat patients as usual. During this period, all prescribing information from the physicians was recorded, but was not reported back to the physicians.

2.5. Data collection and management

With the approval of the Information Center Guizhou Provincial Health Commission, a data port was opened by LWTC technicians. We collected the antibiotic prescriptions, total prescription data, and relevant patient information from primary care institutions participating in the intervention trial. Codes were used to correlate the names of the physicians and patients in their prescriptions. Demographic information on physicians was obtained from the personnel department of the primary care institutions. All researchers involved in data collection signed confidentiality agreements.

The International Classification of Diseases, 10th Edition (ICD-10) was used to classify the diseases of patients who were prescribed antibiotics. According to the list of essential medicines published by the World Health Organization, combined with the national guidelines for clinical application of antibiotics, the clinical application catalogue of antibiotics was summarized (Appendix 3) [31,33]. The antibiotics were categorized into seven classes: penicillins, cephalosporins, macrolides, quinolones, lincosamides, nitroimidazoles, and aminoglycosides. Only systemic antibiotics were considered in this study; patients given external antibiotics, such as erythromycin ointment and levofloxacin eye drops, were excluded.

2.6. Outcome variables

The primary outcome variable was the 10-day inappropriate antibiotic prescription rate, which was the number of inappropriate antibiotic prescriptions per 10 days divided by the total number of antibiotic prescriptions. The secondary outcome was the 10-day rate of antibiotic prescriptions, which was defined as the number of antibiotic prescriptions divided by the total number of prescriptions per 10-day period. The characteristics of the physicians (age, sex, title, education, working years) and information related to antibiotics were included in the analysis as covariates.

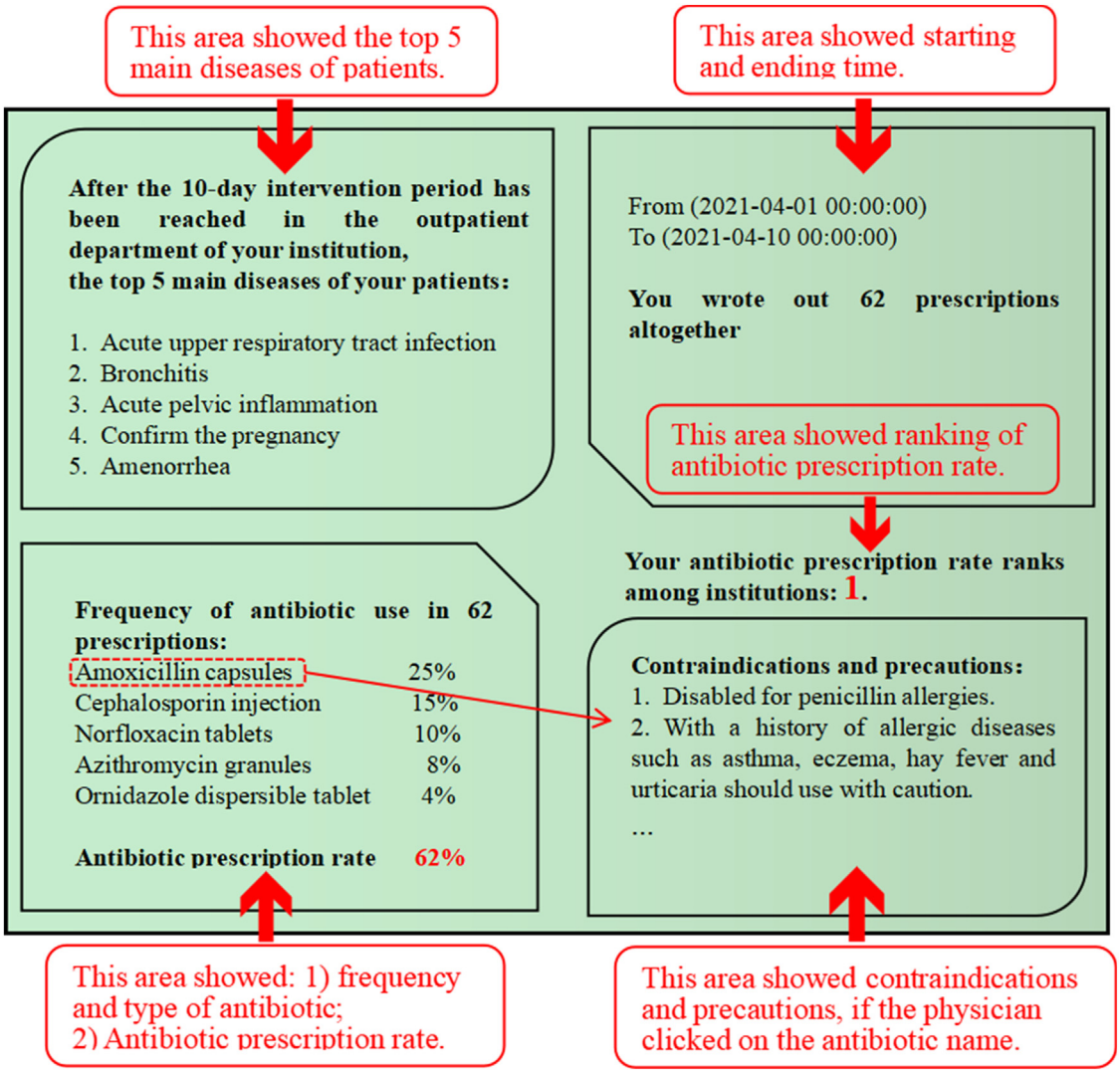

Fig. 4. Example of a 10-day antibiotic prescription feedback.

2.7. Sample size

The two independent means formula (two-tailed) was used to calculate the minimum number of physicians required for each group.

$$n = \frac{\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)\left[\delta_1^2 + \frac{\delta_2^2}{r}\right]}{\Delta^2}$$

$$r = \frac{n_2}{n_1}, \quad \Delta = \mu_1 - \mu_2$$

According to previous research experience [23], the average antibiotic prescription rates of the two groups were 35% and 30% and the variance was 15% for both. The type I error (α) was 0.05 and type II error (β) was 0.2. At least 142 physicians were needed in each group to observe the effects of the intervention. Considering a 10% attrition rate, at least 160 physicians were required in each group, for a total of 320.

2.8. Statistical analyses

Student's *t* tests and rank-sum tests were used to compare the 10-day inappropriate antibiotic prescription rate and the 10-day antibiotic prescription rate between the two groups and within the same group. The effect of the intervention was measured by comparing inappropriate antibiotic and antibiotic prescription rates at baseline, cross-over point, and end point. After the intervention, the inappropriate antibiotic prescription rate and antibiotic prescription rate of physicians may not change immediately, and the magnitude of the change in rates may be different over time. Consequently, two transition models were used to predict the effect of the intervention on the inappropriate antibiotic prescription rate and antibiotic prescription rate. These models can adjust for statistical differences of physicians' baseline characteristics before and after the cross-over point, and further explore the specific effect of the intervention on the antibiotic prescription rate. Spearman and Pearson correlation analyses were used to explore the relationship between inappropriate antibiotic prescription rates and antibiotic prescription rates during the intervention, as well as the relationship between physicians ranking and mouse-clicking frequency. Based on an intention-to-treat principle [34], data from outpatient physicians at all participating primary care institutions were included throughout the analysis (except for seven physicians at two primary care institutions where HIS was replaced). All data for this study was analysed using R version 4.0.4.

Table 1
Baseline characteristics of the physicians [Mean ± SD or n (%)].

Characteristic	group A (n = 160)	group B (n = 168)	Total (n = 328)
Sex			
Male	98 (61.2)	108 (64.3)	206 (62.8)
Female	62 (38.8)	60 (35.7)	122 (37.2)
Age group (years)			
21-31	58 (36.3)	61 (36.3)	119 (36.3)
32-41	44 (27.4)	59 (35.1)	103 (31.4)
42-65	58 (36.3)	48 (28.6)	106 (32.3)
Education			
Technical secondary school	23 (14.3)	27 (16.1)	50 (15.2)
Junior college	58 (36.3)	78 (46.4)	136 (41.5)
College	79 (49.4)	63 (37.5)	142 (43.3)
Title			
Resident physician	121 (75.6)	145 (86.3)	266 (81.1)
Attending physician	24(15.0)	14 (8.3)	38 (11.6)
Associate chief physician	15(9.4)	9 (5.4)	24 (7.3)
Working years	14.6 ± 10.7	13.2 ± 9.6	13.9 ± 10.3

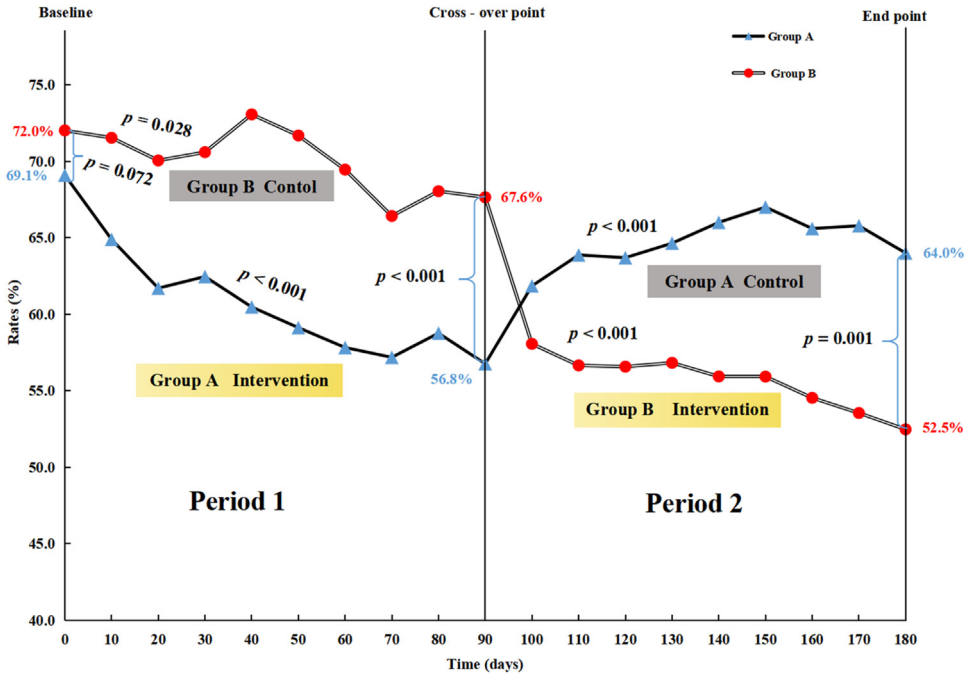

Fig. 5. Comparison of inappropriate antibiotic prescription rates over time between the two groups.

3. Results and discussion

A total of 79 primary care institutions consisting of 335 physicians were recruited. Thirty-nine primary care institutions containing 167 physicians were randomly assigned to group A (intervention followed by control) and 40 primary care institutions containing 168 physicians were randomly assigned to group B (control followed by intervention). However, in group A, two primary care institutions were excluded because they had changed their HIS, so we were unable to obtain their prescription data (Fig. 2). Overall, 313,165 antibiotic prescriptions were included in the analysis. Table 1 shows the baseline characteristics of the study physicians. The two groups were similar in terms of sex, age, education, title, and working years.

The trends of inappropriate antibiotic prescription rates over time in the two groups are shown in Fig. 5. 69.1% of antibiotic prescriptions were considered inappropriate in group A at baseline and 72.0% in group B ($P = 0.072$). In period 1, group A (intervention group) demonstrated a decrease by 12.3% ($P < 0.001$) while in group B (control group), the rate decreased by 4.4% ($P = 0.028$) during the same period. During period 2, group A (control group) demonstrated an increase by 7.2% ($P < 0.001$) while in group B (intervention group), a decrease of 15.1% was seen ($P < 0.001$).

Fig. 6 compares trends in antibiotic prescription rates between groups A and B. At baseline, the antibiotic prescription rate was 35.1% in group A and 35.6% in group B ($P = 0.085$). At the end of the first period (the cross-over point), a reduction of 11.9% ($P < 0.001$) in the antibiotic prescription rate was seen in group A, and a reduction of 4.5% ($P < 0.001$) was seen in group B during the same period. During period 2, group A demonstrated a decrease of 2.6% ($p = 0.045$) and a decrease by 11.7% ($p < 0.001$) in group B.

To predict changes in inappropriate antibiotic prescription rates and antibiotic prescription rates over time, two transition models were fit to the data with the results shown in Table 2. The coefficients represent changes in rates under the influence of explanatory variables. The intercept coefficients of inappropriate antibiotic rate and prescription rate were –0.04 ($P = 0.616$)/–0.05 ($P = 0.005$), indicating that when all variables were controlled for in the initial state, inappropriate antibiotic prescription rates and antibiotic prescription rates decreased by 4% and 5% every 10 days, respectively. The respective coefficients for the feedback intervention were –0.04 ($P < 0.001$) and –0.05 ($P = 0.046$), meaning that the interven-

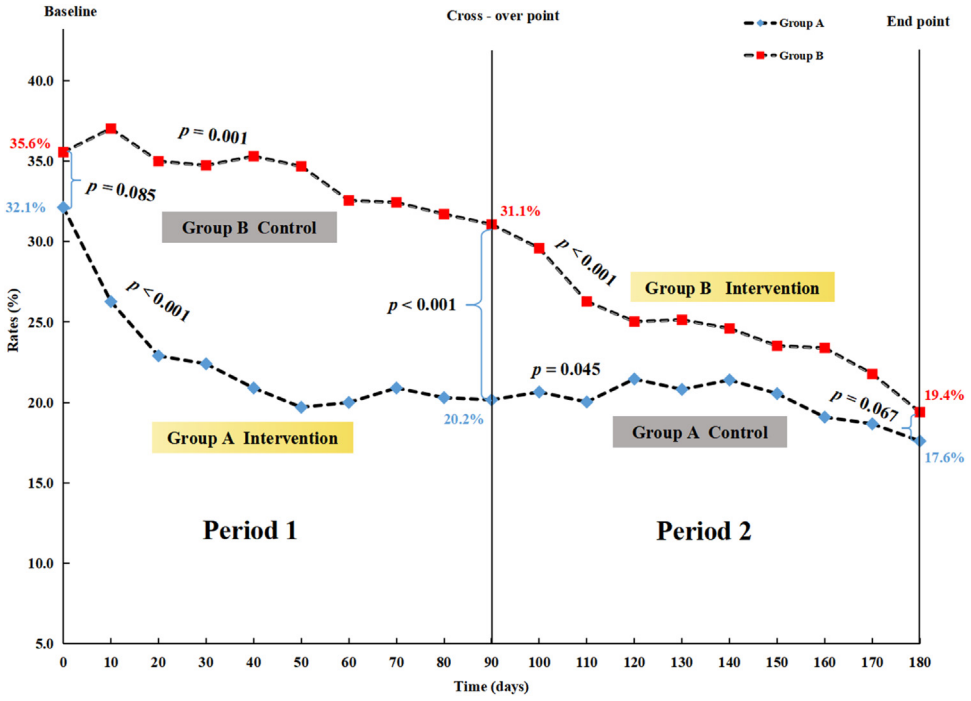

Fig. 6. Comparison of antibiotic prescription rates over time between the two groups.

Table 2
Transition model predicting the change in inappropriate antibiotic prescription rates and antibiotic prescription rates.

Characteristic	Coef. (#/*)	95% CI (#/*)	*P* (*t* test) (#/*)	*P* (F test) (#/*)
(Intercept)	−0.04 / −0.05		0.616 / 0.005	0.616 / 0.005
Feedback (intervention vs control)	−0.04 / −0.05	(−0.07, 0.00) / (−0.07, −0.03)	0.046 / < 0.001	0.046 / < 0.001
Time point (1–19)	0.007 / 0.01	(0.00, 0.01) / (0.00, 0.01)	0.037 / 0.009	0.037 / 0.009
Period (2 vs 1)	−0.05 / −0.04	(−0.13, 0.02) / (−0.08, 0.00)	0.145 / 0.041	0.145 / 0.041
Physicians' characteristic				
Sex: male vs female	0.00 / 0.00	(−0.04, 0.04) / (−0.02, 0.02)	0.917 / 0.872	0.917 / 0.872
Age: ref. = 22–31 years				0.999 / 0.992
32-41	0.00 / 0.00	(−0.05, 0.05) / (−0.03, 0.03)	0.991 / 0.908	
42-65	0.00 / 0.00	(−0.11, 0.11) / (−0.07, 0.06)	0.968 / 0.908	
Education: ref. = college				0.942 / 0.919
Junior college	0.00 / 0.00	(−0.04, 0.04) / (−0.03, 0.02)	0.95 / 0.687	
Technical secondary school	0.01 / 0.00	(−0.05, 0.07) / (−0.04, 0.03)	0.774 / 0.815	
Title: ref. = Associate chief physician				0.996 / 0.99
Attending physician	0.00 / 0.00	(−0.09, 0.09) / (−0.05, 0.06)	0.98 / 0.91	
Resident physician	0.00 / 0.00	(−0.08, 0.08) / (−0.04, 0.05)	0.972 / 0.886	
Working years	0.00 / 0.00	(−0.01, 0.00) / (0.00, 0.00)	0.877 / 0.947	0.877 / 0.947

IAPR: Inappropriate antibiotic prescription rate.
* APR: Antibiotic prescription rate.

tion resulted in a 4% and 5% reduction in 10-day inappropriate antibiotic prescription rates and antibiotic prescription rates, respectively. The coefficients for time point were 0.007 ($P = 0.037$) and 0.01 ($P = 0.009$), for inappropriate antibiotic prescriptions and antibiotic prescriptions, respectively; the coefficients for period were −0.05 ($P = 0.145$) and −0.04 ($P = 0.041$), indicating that both rates decreased gradually with the passage of time, and the decreasing rates in the second period were 5% and 4% lower than those of period 1. The correlation coefficients of physicians' demographic characteristics were not significant in both models. Period was also not significant for inappropriate antibiotic prescription rates.

Fig. 7 shows the correlation of antibiotic prescription rate and inappropriate antibiotic prescription rate between the two groups under the intervention state. The correlation coefficients were 0.954 ($P < 0.001$) and 0.947 ($P < 0.001$), respectively.

Fig. 8 shows the correlation of antibiotic prescription rate and number of mouse clicks under the intervention. There was a strong negative correlation between antibiotic prescription ranking and number of clicks on the pop-up during the intervention period ($r = 0.591$, $P < 0.001$). The lower the physicians' rankings (representing lower rates of antibiotic prescriptions), the higher the number of clicks.

The study was a prospectively designed randomized cross-over controlled trial based on HIS. Our previous study [23] implemented in 31 primary care facilities involved 82 physicians. In this study, we attempted to build on our previous study [23] with a more comprehensive and larger sample size feedback intervention in new primary care institutions (n = 77) and among outpatient physicians (n = 328). The intervention aimed to provide physicians with a summary of their antibiotic prescription history every 10 days, real-time warnings of inappropriate antibiotic prescriptions, and educational manuals. The latter two interventions were added from our previous study [23]. These interventions were significant and effective in reducing antibiotic prescription rates by outpatient

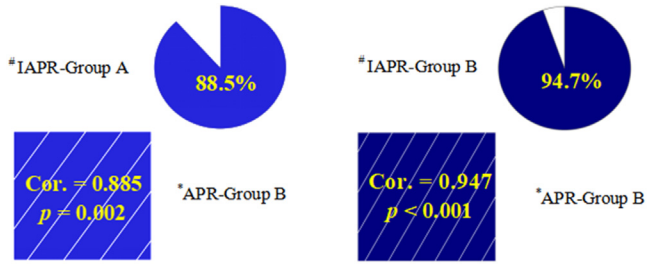

Fig. 7. Correlations between inappropriate antibiotic prescription rates and antibiotic prescription rates under intervention condition. Notes: the correlations between the antibiotic prescription rate and inappropriate antibiotic prescription rate are shown. The box in the lower left corner indicates the relevant direction; blue means positive. The top right pie chart shows the strength of the correlation. The larger the areas of the color portion of the pie chart, the stronger the correlation.

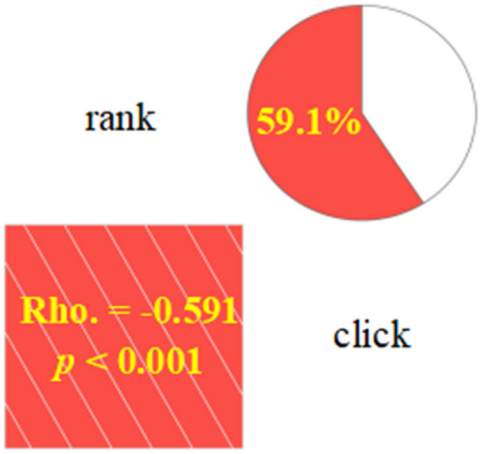

Fig. 8. Correlation between antibiotic prescription ranking and number of clicks under intervention conditions. Notes: the correlation between antibiotic prescription rate ranking and number of clicks during the intervention period are shown. The box in the lower left corner indicates the relevant direction; red means negative. The top right pie chart shows the strength of the correlation. The larger the areas of the color portion of the pie chart, the stronger the correlation.

physicians in primary care institutions. In terms of the inappropriate antibiotic prescription rate, the effect was evident in the first intervention period but had an upward trend in the second control period. None of the physician's characteristics were associated with antibiotic prescription or inappropriate prescription rates. Moreover, close electronic checks of the physicians' behaviors across intervention for antibiotic prescription. We collected the number of mouse clicks made by physicians looking at information about prescriptions. There was a negative correlation between the number of clicks and antibiotic prescription rate. This indicates that the physicians with high compliance were more likely to change their prescribing behavior.

A cross-over design study is commonly considered in randomized controlled trials because it is more effective than a parallel design. A cross-over design is suitable for palliative therapeutic interventions. If the patient has been cured after the first phase of the intervention, there is no point in carrying out a cross-over intervention. Therefore, the cross-over design is appropriate for behavioral interventions, especially feedback intervention [24,35]. Cross-over designs have been used extensively in the medical literature [36–38]. Therefore, our study used the cross-over design to observe the behavioral changes of primary care physicians after the intervention.

Large-scale designs can improve the reliability of the results. In 2014, Gulliford, et al. [39] published a cluster randomized trial that analyzed data from 603,409 patients. They found that using primary care electronic health records was effective in large samples in routine care settings. In 2015, Wei, et al. [18] conducted a cluster randomized controlled trial in 25 primary care institutions in China and the antibiotic prescription rate decreased by 29%. To further verify the extensibility of this study, they intend to expand the size of primary care facilities to 34 in a new protocol [40]. Therefore, our study also used a large sample size.

We observed a rebound in inappropriate antibiotic prescription rates after the transition from the intervention to control periods. This may be due to the generally low professional and technical level of physicians in primary care institutions in China [41,42]. Sixty percent of people in southwest China live in rural areas where there is a great demand for primary care physicians [43]. Most of the physicians there have not yet been trained at the university education level and are allowed to work as general physicians in primary care institutions due to personnel shortages. They can prescribe antibiotics in the national list [44]. Without the real-time pop-up warning message, physicians would not have been able to realize when they were prescribing inappropriate antibiotics. Because of the delayed effect of behavioral interventions [45], they might blindly reduce their rate of antibiotic prescription (even in the absence of an intervention) without effectively changing their inappropriate prescription behavior. This result may also reflect the high compliance of physicians to the real-time pop-up warning message. Therefore, long-term interventions and education are necessary in these primary care institutions. Overall, from our correlation test, there was a strong positive correlation between inappropriate antibiotic prescription rates and antibiotic prescription rates under the intervention conditions.

From baseline to endpoint, the antibiotic prescription rates of the two groups reduced by 14.5% (group A) and 16.2% (group B). This is like the reduction in antibiotic prescription rates seen in our previous study [23]. Recent studies have shown that interventions can reduce antibiotic prescription rates by 5.6% to 22% [15,46,47]. However, the limitation of our previous study [23] was that it only considered the reduction in antibiotic prescription rate; we didn't consider the rationality of antibiotic prescriptions. As a result, the primary care institutions and physicians focused only on reducing their antibiotic prescriptions, regardless of whether they were justified. Therefore, an effective intervention can only be achieved if both the overall prescribing rate and the inappropriate prescribing rate of antibiotics are reasonably reduced. In addition, we also collected secondary diagnostic information in this study. Therefore, the judgment of inappropriate antibiotic prescription rates was more reasonable.

The feedback intervention measures mainly reminded the outpatient physicians to pay attention to their prescribing behavior through real-time early warning feedback and information feedback once every 10 days. In our previous study [23], we found that three times a month is enough intensity without feeling too frequent for busy doctors. Real-time pop-up warning messages are used to intervene when the physicians are about to make an inappropriate prescribing behavior. This intervention makes them immediately aware that there might be a problem with their prescription. Physicians can choose to change prescriptions or ignore these warnings. The intervention was not mandatory, which may be why it was widely supported by physicians and primary care institution leaders. In addition, the confidentiality and noncoercive nature of the feedback made it more acceptable to physicians. Future researchers should devise interventions in which physicians voluntarily participate. In addition, the educational manuals distributed were introduced in our intervention protocol [25]. We developed the educational materials specifically for primary care physicians using the Delphi method [30]. The distribution of educational manuals is a common educational intervention

and does not fall within the scope of a feedback intervention [18,27]. In the preintervention period, the physicians were satisfied with this manual, which was provided free of charge. It was conducive to the further development of feedback intervention measures.

During the intervention period, the rates of antibiotic inappropriateness and antibiotic prescription in both groups showed a rapid decline followed by fluctuations. This phenomenon may be explained by the transtheoretical model [48], which interprets behavior change as a continuous, dynamic, and gradual process [49]. It is divided into five stages, including precontemplation, contemplation, preparation, action, and maintenance, and the transformation of each stage requires a process [50]. Real-time pop-up warning messages accelerate the first four stages of the process, enabling physicians to consider behavior changes and act in just a few minutes. The contamination effect and Hawthorne effect may also explain why the first four stages of the transtheoretical model were so rapid in our study. As a result, antibiotic prescription rates in the intervention group initially declined rapidly. However, because of obstacles such as physician prescribing habits, patient interference, and distrust by some physicians, not everyone can complete all five stages [51,52]. This is probably why there were two slight rises in the prescription rates during the intervention period. In the end, the intervention effect was consolidated again due to repeated reinforcement of prescription information reminders given once every 10 days and support from the educational manual; the overall change of physicians' prescribing behavior was finally realized.

To further explore the effects of the intervention, transition models were used to predict the effect of the rates of antibiotic inappropriateness and antibiotic prescription. As expected, the effect of the feedback intervention was significant and stable, which might be attributed to the real-time pop-up warning messages and educational manuals provided to the physicians. Further validation of the relationship of the inappropriate antibiotic prescription rates between the two periods may be required.

In conclusion, our intervention contributed to the long-term stewardship of antibiotics in primary care institutions. If the intervention is stopped, physicians may prescribe more inappropriate antibiotics. The combination of real-time pop-up warning messages, antibiotic prescription feedback, and educational manuals enabled primary care physicians to prescribe antibiotics appropriately and effectively reduce their antibiotic prescription rates. Our study plays an important role in reducing the risk of antibiotic resistance. This new intervention may be preferable to that of our previous study [23]. With the popularization of paperless offices, it is easier to realize a real-time, automated, low-cost, and high-compliance intervention of physicians' prescribing behavior. The intervention can be applied globally and has the advantage that it is not influenced by age, sex, education, and title of the physicians nor the local policy of the institution.

There are some limitations to the current study. First, our trial was only six months long, which may have created a seasonal bias. However, we used control group comparisons to reduce this potential bias. The study was also conducted during a period of low prevalence of infectious diseases, especially the most common respiratory diseases. Second, the study showed the effects of three interventions, but it is not possible to separately assess the contribution of each of the three bundles of interventions. Future studies could take a multigroup intervention approach to evaluate the effect of each intervention. Third, inappropriate use of antibiotics includes correct diagnosis and correct prescription. Since few laboratory test results are available in primary care institutions, this study covered only the latter. Fourth, we could not determine if the physicians' shift in the attitude of prescribing had a negative, positive, or neutral effect on the outcome of patients.

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Ethical approval

The trial was approved by the Human Trial Ethics Committee of Guizhou Medical University (Certificate No.: 2019 (148)) in Dec. 27, 2019).

Declaration of competing interest

None declared

CRediT authorship contribution statement

Junli Yang: Formal analysis, Investigation, Methodology, Software, Writing – original draft. **Zhezhe Cui:** Conceptualization, Visualization, Writing – review & editing. **Xingjiang Liao:** Supervision, Resources. **Xun He:** Supervision, Resources. **Lei Wang:** Data curation. **Du Wei:** Investigation. **Shengyan Wu:** Investigation. **Yue Chang:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Software, Visualization, Writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jgar.2023.02.006.

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