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NGUYEN TRONG KHOA

THE SITUATION OF RATIONAL USE OF ANTIBIOTICS AND THE EFFECTIVENESS OF INTERVENTION AT SOME PROVINCIAL GENERAL HOSPITALS

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Scientific supervisors: 1. Assoc. Prof. Luong Ngoc Khue
2. Assoc. Prof. Phan Le Thanh Huong

Counter arguer 1: Assoc. Prof. Nguyen Thanh Huong
– Hanoi University of Public Health

Counter arguer 2: Assoc. Prof. Le Thi Minh Huong
– Vietnam National Children's Hospital

Counter arguer 3: Dr. Tran Thi Mai Oanh
– Health Strategy and Policy Institute

The doctoral thesis will be defended at the Dissertation Committee of Institutional level at:

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The doctoral thesis can be found at:

1. The National Library

2. The Library of National Institute of Hygiene and Epidemiology

A. THESIS INTRODUCTION

1. The urgency of the thesis

Antibiotic resistance is a condition in which microorganisms are resistant to antibiotics that were previously sensitive to them, leading to ineffective application of specific treatment methods and drugs. As a result, the infection is long-lasting (even fatal) and can be spread to others. Improper use of antibiotics leads to the risk of antibiotic resistance of bacteria due to increase of the selection risk of resistant bacteria. Therefore, rational use of antibiotics in treatment is one of the important measures to reduce the risk of antibiotic resistance.

Within the medical examination and treatment system of Vietnam, the provincial general hospital plays an important role. The rational use of antibiotics at provincial general hospitals showed the importance in the prevention and control of antibiotic resistance in the whole system. 7/16 provincial general hospitals were participated in the antibiotic resistance surveillance network in Vietnam for the period of 2016-2020.

Managing antibiotic use in the hospital is an important strategy of the antibiotic resistance prevention plan. The objective of this activity is to optimize the use of antibiotics in treatment, contribute to improving clinical efficiency, reducing unwanted consequences related to antibiotic use and reducing medical costs for patients, community, society while improving the quality of patient care. The interventions conducting by the Antibiotic Use Management Program to promote rational antibiotic include cross-functional activities such as establishing a multidisciplinary management team, establishing and updating treatment regimens and guidelines, monitoring the adherence to guidelines and responding to prescriptions.

In the situation of increasing antibiotic resistance and irrational use of antibiotics, the management of antibiotic use is very necessary and is one of the important key stages of health management. Good antibiotic management has been shown to be effective in limiting inappropriate antibiotic prescribing in several studies. However, there are no studies in Vietnam evaluating this issue at general hospitals of provincial level. Therefore, we conducted the study on «Situation of rational use of

antibiotics and the effectiness of intervention at some provincial general hospitals».

2. Objectives of the thesis

1. Describe the current situation of rational antibiotic use and some influenced factors at Thai Binh and Nam Dinh General Hospital in 2017.

2. Evaluation of the effectiveness of some prevention measures on antibiotic rational use at Thai Binh General Hospital in 2019.

3. New contributions of the thesis

To our knowledge, this is the first study on antibiotic use management at the hospitals of provincial level in Vietnam. This study conducted the assessment on current situation of antibiotic use management at two provincial general hospitals, then intervened through the antibiotic use management program at the hospital by a number of specific activities: establishment of a Management Committee on antibiotic use at the hospital with its members being the hospital leaders, head of pharmacy department, heads of some clinical departments, clinical microbiological department, informatic technology, quality management, finance and accounting; providing the training on drug use, clinical microbiology; development of treatment guidelines, monitoring the treatment compliance and providing information on drugs.

The study has shown the intervention effects of antibiotic management program: The average number of antibiotics used has been significantly reduced to 1.51 ± 0.6 in 2019 from 1.77± 1.0 drugs in 2017 ($p<0.05$). The rate of rational antibiotic use at Thai Binh provincial general hospital has been increased statistically significant from 41.1% in 2017 to 56.7% in 2019. The rate of rational antibiotic use after having suitable antibiogram results increased from 40.3% to 47.3%%. The average number of days of antibiotic therapy has reduced from 8.7 ± 3.5 days in 2017 to 8.3 ± 5.7 days in 2019. The average antibiotic cost for 1 patient has decreased significantly from 1.6 million VND in 2017 to 638,312 VND in 2019.

The factors that affecting the management of antibiotic use were training, updating information, clinical pharmacy and adequate supply of drugs.

4. Value of the thesis

The thesis has provided scientific evidence to support the policy makers

and managers in developing the intervention solutions and implementing the antibiotic use management program at provincial general hospitals.

5. The structure of thesis

Thesis consisted of 121 pages, including 3 pages of the Introduction; 33 pages of Literature overview (Chapter 1); 16 pages of Study subjects and methods (Chapter 2); 48 pages of Research Results (Chapter 3); 22 pages of Discussion (Chapter 4); 3 pages of Conclusion and Recommendation; 32 tables, 13 figures and 8 appendixies. The thesis has used 116 scientific articles and documents for references, including 14 articles in Vietnamese and 112 articles in English.

35 tables and 22 figures.

B. CONTAIN OF THE THESIS

Chapter 1. LITERATURE REVIEW

1.1. Antibiotics and antibiotic resistance

Antibiotic resistance is an important issue in the world today as well as in Vietnam. Since the discovery of the penicillin in 1930, no one could have predicted that after 10 years of use, the antibiotic would begin to decrease in effectiveness.

1.2. Rational use of antibiotics at the hospitals

For appropriate antibiotic therapy, correct diagnosis should combine administration of the right antibiotic by the most appropriate route, at the right dose, for the optimal duration, and at the appropriate time.

Basic principles of rational antibiotic use

- Identify indications for antibiotic use
- Collect and test appropriate specimens before starting treatment
- Identify potentially pathogenic microorganisms.
- Know the pharmacological properties of antibiotics
- Evaluate subjective factors
- Determine the indications for the use of antibiotics in combination.

Indications for a change in antibiotic therapy should be identified and response to treatment should be monitored.

1.3. Situation of antibiotic use

1.3.1. Situation of antibiotic prescribing

In the world

Studies showed that the rate of inappropriate antibiotic use is quite high, about 25-50% in developed countries such as the Netherlands and the United States [45]. The rate of inappropriate antibiotic use is reported to be higher in developing countries (88% in Nigeria, 79% in Indonesia) [20]. Inappropriate initiation of antibiotic therapy is reported in approximately one-third of patients with Gram-negative septic shock in a university hospital. Studies showed that inappropriate antibiotic use is one of the important causes of increased antibiotic resistance, increased mortality, prolonged hospital stay and increased treatment costs [3].

In Vietnam

According to a study conducted by the Medical service and Administration Department, Ministry of Health, in 2009 at Vietnamese hospitals, the average number of drugs given to an inpatient at district, provincial and central hospitals was 6.38, 7.95, 8.48, respectively; for outpatients, this rate was 3.64, 3.33, 3.76, respectively.

One study on antibiotic prescribing in Vietnam in 2009 showed that out of 2953 prescriptions (2083 in urban areas and 870 in rural areas), antibiotics were accounted for 24% and 18%, respectively, of total sales of pharmacies. Most antibiotics were sold without doctor's prescription (88% in urban and 91% in rural pharmacies). The most common cause of antibiotic purchase was cough in urban areas (32%) and fever in rural areas (22%). Consumers often requested antibiotics without a prescription (50% in urban areas and 28% in rural areas). Qualitative data showed low knowledge about antibiotics and antibiotic resistance among drug sellers and customers, especially in rural areas.

1.3.1. Antibiotic Management Program in the hospital

Antibiotic use management programs often include cross-functional activities such as establishing a multidisciplinary management team, monitoring, and responding to prescriptions. Improving the prescribing includes training on prescribing: choosing the right antibiotic, choosing the optimal dose and duration of antibiotic treatment to treat the infections, organizing specialist consultation before prescribing, improve prescribing, antibiotic rotation and use of software-based monitoring. There are many methods for implementing an antibiotic use management program.

The Infectious Diseases Society and the American Society of Epidemiology have released guidance on strengthening antibiotic use including:

- Organize a multidisciplinary antibiotic management group
- Active monitoring, direct feedback to each doctor
- Training combined with active intervention.
- Update antibiotic guidelines based on results of local antibiogram testing.
- Usage restrictions and require the Association to:

* strengthen the information system to support antibiotic prescription
* provide timely microbiological data.
* prepare a table of recommended antibiotics for each case.

1.4 The Factors affecting antibiotic use management program in hospitals

- Support activities of hospital leadership
- Pharmacy expertise: assign pharmacists responsible for activities to improve antibiotic use
- Develop activities to support antibiotic use management program
- Monitor prescribing and antibiotic resistance status
- Evaluate the results of the antibiotic use management program
- Report the effectiveness of the antibiotic use management program
- Training: organizing courses, developing programs, training information for doctors and related health workers to improve antibiotic prescribing

1.5 Characteristics of Thai Binh Provincial General Hospital and Nam Dinh Provincial General Hospital

The Thai Binh Provincial General Hospital and Nam Dinh Provincial General Hospital are two general hospitals located in the Red River Delta region. The two hospitals are similar in terms of economy, culture, society, customs and lifestyle. The two hospitals are also similar in number of beds, number of medical staff and disease patterns. Therefore, we selected these two hospitals for the research.

Chapter 2. STUDY SUBJECTS AND METHODS

2.1 Study subjects

- Patient's medical record that has used antibiotics to treat diseases: respiratory infections, urinary tract infections, skin soft tissue infections, abdominal infections.
- Member of the Management Board of antibiotic use at the hospital
- Doctors directly involved in treatment at clinical departments.
- Reasearch site: Thai Binh and Nam Dinh Provincial General Hospitals

- Time frame: From 7/7/2017 till 30/4/2020.

2.2 Research methods

2.2.1. Study design

For Objective 1: Cross-sectional study using data obtained from secondary data analysis (retrospective) and field survey. Analise the factors that influence the management.

For Objective 2: Semi-experimental intervention, using before/after and intervention/control comparison

The designs used in research

Objective		Study contains	Study design
Describe the current situation of rational antibiotic use and some influenced factors at Thai Binh and Nam Dinh general hospital in 2017	1.1	- Survey the current situation of antibiotic use at Thai Binh and Nam Dinh General Hospital in 2017	Retrospective description and analysis of secondary data
	1.2	Analysis of some factors affecting the management of antibiotic use at Thai Binh and Nam Dinh General Hospital in 2017	Qualitative research, in-depth interviews with individuals related to antibiotic use management at Thai Binh and Nam Dinh General Hospital in 2017
Evaluation of the effectiveness of some prevention measures on antibiotic rational use at Thai Binh General Hospital in 2019	2.1	Post-intervention evaluation on the impact of some intervention measures on rational use of antibiotics at Thai Binh General Hospital in 2019	Cross-sectional description of the current situation of antibiotic use at Thai Binh General Hospital in 2019 (after the intervention) according to the research criteria of the study 1.1.

			Evaluation of the program at the intervention/non-intervention sites for comparison the 2 study groups

2.2.2 Sample size and sampling method

2.2.2.1. *Study 1.1 Survey the current situation of antibiotic use at Thai Binh Provincial General Hospital and Nam Dinh Provincial General Hospital in 2017*

Sample size for study 1.1:

The following formula was used to calculate the estimated sample size for a ratio:

$$n = \frac{z^2_{1-\alpha/s} P(1-P)}{d^2}$$

Of which, n is minimal sample size;

A: Statistical significance level (choose $\alpha = 0.05$, corresponding to 95% confidence level, $Z(1-\alpha/2) = 1.96$; $p = 0.5$

(Because there has been no previous study on the same subject, the rational antibiotic use rate was chosen as 50%); d: acceptable error with $d = 0.08$. Substituting into the formula, the sample size (n) was 300 cases. In fact, 297 patient records were collected at Thai Binh General Hospital and 302 patient records were collected at Nam Dinh General Hospital.

Selection criteria:

At Thai Binh and Nam Dinh General Hospital:

- The medical record of adult patients (≥18 years old), of both sexes.
- Medical record of inpatient treatment for 3 days or more of the following diseases: respiratory infections, urinary tract infections, skin soft tissue infections, abdominal infections.

Exclusion criteria:

- The patient that did not have to take antibiotics.
- The patient that had a prognosis of death within 24 hours after admission.
- The medical record that was not accessible.

2.2.2.2. *Study 1.2 Analysis of some factors affecting the management of antibiotic use at Thai Binh and Nam Dinh General Hospitals in 2017*

Sample size for study 1.2:

- Members of the Management Board of antibiotic use at 2 hospitals

- All Doctors involved directly in treatment at clinical departments that agreed to participate the study

2.2.2.3. *Study 2.1: Evaluation of the impact of some intervention measures on rational use of antibiotics at Thai Binh Provincial General Hospital in 2019*

*Sample size before and after intervention**:***

*Sample size of medical records of patients treated with antibiotics

$$n = \frac{p2(1-p2) + p1(1-p1)}{(p2-p1)^2}(Z^{\alpha} + Z^{\beta})^2$$

Of which,

n: Sample size

Z: Normal distribution with 95% confidence

$Z^{\alpha} = 1.96$; $Z^{\beta} = 0.84$

Hypothesized that the reasonable rate of antibiotic use before the intervention is 50%, with an increase of at least 12% after the intervention, p2=0.5, p1=0.62. The number of study samples was calculated as of:

$$n = \frac{0.5*0.5 + 0.6*0.4}{(0.6-0.5)^2}(1.96 + 0.84)^2$$

➔ $n = n_1 = n_2 = 271$

The sample size of medical records of patients treated with antibiotic used for descriptive study was 271. In fact, 305 patient's medical records were collected at Thai Binh General Hospital and 302 patient records were collected at Nam Dinh General Hospital.

Selection criteria:

- The medical records of adult patients (≥18 years old), of both sexes.
- Medical record of inpatient treatment for 3 days or more of the following diseases: respiratory infections, urinary tract infections, skin soft tissue infections, abdominal infections.

Exclusion criteria:

- The patient that did not treated with antibiotics.
- The patient that had a prognosis of death within 24 hours after admission.
- The medical record that was not accessible.

2.2.1. Information collecting methods

- Direct interview using questionnaire
- Group discussion
- Quantitative study

2.2.2. Data processing

- Collected data were entered using EpiData 3.1 software and analyzed by SPSS 16.0 software. The in-depth interviews and group discussions were de-tape and analyzed by topic and presented the results based on qualitative study techniques.

- For qualitative research: encoded information were analyzed with identified common problems. Information from individual in-depth interviews and group discussions as well as of different activities was collated, supporting the results of data analysis and validity of the findings.

2.2.3 Research ethics

- The study was agreed and accepted to coordinate the research and to collect data from selected hospitals for investigation.
- The study design was approved by the Ethics Committee for Biomedical Research of the National Institute of Hygiene and Epidemiology on scientific and ethical aspects in the study.
- Subjects participating in the study were clearly and fully explained about the content and purpose of the study and have the right to agree or disagree to participate.
- The collected information is only used for research purposes and does not have any negative effects on the respondents and the surveyed units.

Chapter 3. RESULTS

3.1 Characters of study subjects

The total number of patients in the study sample was 1206 patients, of which 52% were female and 48% were male (Figure 3.1).

Regarding the patients at Thai Binh General Hospital in 2017 that participated in the study (Table 3.1), their mean age (± standard deviation - CI) was 57.7 ± 19.8 (from 18 to 95 years old) and 59.9 ± 17.7 in 2019; the number of patients over 60 years old was accounted for a high rate (from 47% to 50%), patients with accompanied disease were accounted for 33% to 35%. The average length of hospital stay in 2017 was 8.7 days, reduced to 8.3 days in 2019.

At Nam Dinh Provincial General Hospital, the proportion of patients over 60 years old was over 50%. The proportion of patients having accompanied disease was 38.1% in 2017 and 47.7% in 2019. The average length of hospital stay was 8.9 days in 2017 and 9.2 days in 2019. Patients without comorbidities involved in the study group were accounted for over 60%.

There were 602 patients records obtained at Thai Binh Province General Hospital and 604 patients records collected at Nam Dinh Province General Hospital, including 4 types of infection: respiratory, urinary, soft tissue skin and abdominal cavity. Each type of bacterial infection was accounted for 22% to 28% among the study group.

The rate of positive microbiological culture at Thai Binh Provincial General Hospital in 2017 was 31.6% and 38% in 2019. At Nam Dinh Provincial General Hospital, this rate was 27.1% in 2017 and 35.4% in 2019.

3.2 Current situation of rational antibiotic use and influenced factors at Thai Binh and Nam Dinh General Hospitals in 2017

3.2.1. Number of antibiotics use in 2017

The total number of antibiotics use in 2017 was 526 times at Thai Binh General Hospital and 469 times at Nam Dinh General Hospital.

The highest rate of antibiotic use (33.8%) was obtained for treatment of abdominal cavity infections, while the lowest rate (20.3%) was found in treatment for soft tissue skin infections at Thai Binh General Hospital in 2017.

3.2.2 Combination of antibiotics in 2017

At Thai Binh General Hospital, rate of using one antibiotic in treatment in 2017 was 48.2%, rate of using combination of two antibiotics was 36.7% and rate of combination of three antibiotics was 9.8%, the rate of using the combination of more than three antibiotics was 5.3%. At Nam Dinh Provincial General Hospital, this rate was 55.3%, 37.1%, 5% and 2.6%, respectively. The difference in using the combination of antibiotics among the two hospitals was not statistically significant.

At Thai Binh General Hospital, the average number of antibiotics used in 2017 was 1.77± 1.0 antibiotics; at the Nam Dinh General Hospital, the average number of antibiotics was 1.55 ± 0.7. The difference in the mean number of antibiotics of the two hospitals was not statistically significant.

3.2.3 Rate of proper initial antibiotic selection

Table 3.1 Rate of proper initial antibiotic selection

Infection	Total		Thai Binh General Hospital		Nam Dinh General Hospital		p
	n	%	n	%	n	%	
Respiratory	48	30.4	24	30.7	24	30.0	>0.05

Urinary tract	72	49.0	34	45.3	38	52.8	
Soft tissue skin	72	52.6	29	44.6	43	59.7	
Abdominal cavity	44	28.0	32	40.5	12	15.4	
Total	236	39.4	119	40.1	117	38.7	

The rate of proper initial antibiotic selection was found 40.1% at Thai Binh General Hospital and 38.7% at Nam Dinh General Hospital. This rate was the highest in the treatment of soft tissue skin infections at the both hospitals (44.6% and 59.7%, respectively). The rate of proper initial antibiotic selection for treatment respiratory infections at the two hospitals was about 30% and was only 15.4% in treatment of abdominal cavity infections at Nam Dinh Provincial General Hospital.

3.2.4. Rate of rational antibiotic use after having antibiogram results

Table 3.2 Rate of rational antibiotic use after obtaining antibiogram results

Infection	Total		Thai Binh General Hospital		Nam Dinh General Hospital		p
	n	%	n	%	n	%	
Respiratory infection	46	70.8	44	74.6	2	33.3	<0.05
Urinary tract infections	18	62.1	16	76.2	2	25.0	
Skin soft tissue infections	1	12.5	0	0	1	33.3	
Abdominal cavity infections	29	46.0	3	100	26	43.3	
Total	94	57.0	63	71.6	31	40.3	

The rate of proper antibiotic selection after having the results of antibiotic susceptibility test was 71.6% at Thai Binh General Hospital and 40.3% at Nam Dinh General Hospital. This difference is statistically significant ($p<0.05$).

Rate of rational antibiotic use

Table 3.3 Rate of rational antibiotic use

Infection	Total		Thai Binh General Hospital		Nam Dinh General Hospital		p
	n	%	n	%	n	%	

Respiratory	127	80.4	60	76.9	67	83.8	>0.05
Urinary tract	106	72.1	49	65.3	57	79.2	
Soft tissue skin	119	86.9	55	84.6	64	88.9	
Abdominal cavity	74	47.1	39	49.4	35	44.9	
Total	426	71.1	203	68.4	223	73.8	

The rate of rational antibiotic use of at two general hospitals in Thai Binh and Nam Dinh provinces was 68.4% and 73.8%, respectively. This difference is not statistically significant.

3.2.5. Some factors influenced to situation of antibiotic use managemnt at Thai Binh and Nam Dinh General Hospital in 2017

Thai Binh General Hospital: The Antibiotic Use Management Group was established, however, tasks have not yet been assigned to members of the management board; a number of guidelines for the treatment of infectious diseases has been developed to use at the hospital; antibiotic use in clinical departments has been monitored, the reports on antibiotics and drug resistance in the hospital has been performed regularly and results were notified to clinical departments, a number of training courses on antibiotics and microbiology has been organized.

Nam Dinh General Hospital: The Antibiotic Use Management Group was established, but guidelines for the treatment of infectious diseases at the hospital has not yet been developed, but applying the treatment guidelines of the Ministry of Health. The hospital has implemented clinical pharmacy activities, for the first step, consulting on antibiotic dose adjustment. Some supervisions on antibiotic use in clinical departments were conducted and a number of training courses on antibiotics and microbiology has been organized.

3.2.6 Knowledge, attitude on antibiotic use of the doctors at Thai Binh and Nam Dinh General Hospitals

3.2.6.1 Knowledge on antibiotic use of the doctors

The majority of doctors answered 4-5 questions correctly (56.3% for both hospitals). At Thai Binh General Hospital, 29.2% of doctors correctly answered 5 questions, 6.7% of doctors correctly answered 7/7 questions. At Nam Dinh General Hospital, 35.1% of doctors answered correctly 4 questions, 9.1% correctly answered 7/7 questions.

3.2.6.2 Attitude of the doctors on antibiotic use and antibiotic resistance

The level of confidence about the optimal use of antibiotics among the doctors: 56.3% of the subjects felt confident, 26.4% were very confident; however, there were 13% and 4.3% of subjects felt rather unconfident and unconfident when prescribing. All subjects said that

antibiotic knowledge is important for clinicians and resistance is an urgent issue.

3.2.6.3 Sources of information for reference

Concerning the source of reference information, clinicians often refer to get information about antibiotic use from the source such as the superiors, colleagues at the same level, the Internet, the Ministry of Health's antibiotic manual, diagnostic and treatment guidelines issued by the Ministry of Health. Most of the doctors consider these sources very useful to them, especially the guiding documents issued by the Ministry of Health.

3.3 Evaluation of the intervention effectiveness to strengthen the rational use of antibiotics at Thai Binh General Hospital

3.3.1 Evaluation the use of antibiotic combination

The rate of using antibiotic in treatment at Thai Binh General Hospital in 2017 was 48.2%, and increased to 53.4% in 2019. Of which, rate of using a combination of two antibiotics has been increased from 36.7% in 2017 to 43.3% in 2019. But rate of triple and more than three antibiotic - combination was found decreased statistic significantly. At Nam Dinh General Hospital, rate of using 1 antibiotic in 2019 decreased compared to that in 2017, while the rate of using the combination of three antibiotics and more than three antibiotics was found increased.

At Thai Binh General Hospital, the average number of antibiotics used in 2017 was 1.77± 1.0 antibiotics; in 2019 this reduced to 1.51 ± 0.6 with the difference statistically significant (<0.05). At Nam Dinh General Hospital, the average number of antibiotics used increased from 1.55 ± 0.7 in 2017 to 1.65 ± 0.8 in 2019.

3.3.2 Rate of appropriate use of initial antibiotics at Thai Binh General Hospital

Rate of appropriate initial antibiotic use in 2017 at Thai Binh Hospital was 41.1%, the highest rate (45.3%) was obtained in treatment of urinary tract infections, followed by this rate in treatment of skin and soft tissue infection (44.6%), of intra-abdominal infection (40.5%) and of respiratory infection (30.8%). In 2019, rate of appropriate initial antibiotic use was 56.7%, the highest rate (67.1%) was found in treatment of skin and soft tissue infections, followed by 57.5% in urinary tract infection treatment, 55.3% in intra-abdominal infections, and 47.1% in threatment of respiratory infections. The difference of these rates in two years is statistically significant.

3.3.3. Rate of appropriate selection of initial antibiotics at Nam Định General Hospital

Table 3.16 Rate of appropriate selection of initial antibiotics at Nam Định General Hospital

Infection	In 2017 (N=302)		In 2019 (N=302)		p
	Appropriate use	Inappropr. use	Appropriate use	Inappropr. use	
Respiratory	24 (30.0%	56 (70.0%)	42 (51.2%)	40 (48.8%)	>0.05
Urinary tract infections	38 (52.8%)	34 (47.2%)	36 (48.0%)	39 (52.0%)	
Soft tissue skin	43 (59.7%)	29 (40.3%)	24 (34.3%)	46 (65.7%)	
Abdominal cavity	40 (51.3%)	38 (48.7%)	61 (81.3%)	14 (18.7%)	
Total	**145 (48.0%)**	**157 (52.0%)**	**163 (54.0%)**	**139 (46.0%)**	

Rate of appropriate use of initial antibiotics in 2017 at Nam Dinh General Hospital was 48.0%, of which in treatment of soft tissue skin infections, the highest rate (59.7%) was obtained. This rate was 52.8% in treatment of urinary tract infections, 51.3% of abdominal infections and 30.0% of respiratory infection.

In 2019, the rate of appropriate initial antibiotic use was 54.0%, highest in intra-abdominal infection treatment (81.3%), followed by 51.2% in respiratory infection treatment, 48.0% in urinary tract infection and 34.3% in skin soft tissue infection treatment. The difference of these rates obtained in two years was not statistically significant.

3.3.4 Result of rational antibiotic selection after having antibiogram result at Thai Binh General Hospital

In 2017, 88 samples with positive results were obtained at Thai Binh General Hospital, of which 63 cases were treated with appropriete antibiotics selected after having antibiogram results, rated for 71.6%; the inappropriate selection of antibiotics was happed in treatment of 25 cases, accounting for 28.4%.

In 2019, the number of culture positive microbiological samples was 116 samples, in which, 93 cases were treated with appropriete antibiotics selected in accordance to antibiogram results, accounting for 80.2%. 19.8% of cases were treated with inappropriete selection of

antibiotics in term of antibiogram results. The difference of these rates obtained in two years was not statistically significant.

3.3.5 Rate of rational antibiotic selection after having antibiogram result at Nam Định General Hospital

In 2017, at Nam Định General Hospital, among 77 samples culture positive, 31 cases (40,3%) were treated by rational use of antibiotics based on antibiogram results with the highest rate obtained in the treatment of abdominal cavity infection; 46 cases were treated with inappropriate selection of antibiotics after having antibiogram results.

In 2019, among 91 saples positive in culture, 53 cases were treated with rational used of antibiotics, rated for 47,3%. The rests (58 cases) were treated with inappropriate selection of antibiotics after having antibiogram results. The difference of these rates obtained in two years was not statistically significant.

3.3.6 Analysis of antibiotic use by number of usages

Table 3.19 Rate of rational antibiotic use by number of antibiotic usages

Hospital	In 2017			In 2019			p
	Rational	Irrational	Total	Rational	Irrational	Total	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Thai Binh GH	372 (70.7%)	154 (29.3%)	526 (100%)	331 (71.8%)	130 (28.2%)	461 (100%)	0,709
Nam Dinh GH	347 (69.7%)	122 (30.3%)	469 (100%)	337 (67.7%)	161 (32.3%)	498 (100%)	0,031
p	0.251			0.165			

Rate of rational antibiotic use based on the number of antibiotic usages in 2017 at Thai Binh General Hospital was 70.7%. 29.3% of cases were treated by irrational antibiotic prescription. In 2019, this rate was not increased.

The rate of rational antibiotic use according to the number of antibiotic usages in 2017 at Nam Dinh General Hospital was 69.7%. In 2019, this rate decreased to 67.7%.

3.3.7 Reasons of irrational use of antibiotics

Table 3.20. Reasons of irrational use of antibiotics

Reason of irrational antibiotic use	Thai Binh General Hospital		Nam Dinh General Hospital	
	In 2017	In 2019	In 2017	In 2019

Administration rout	64 (41.6%)	53 (40.7%)	70 (57.4%)	63 (39.1%)
Volume of solvent	6 (3.9%)	33 (25.4%)	5 (4.1%)	6 (3.7%)
Infusion speed	84 (54.5%)	44 (33.9%)	47 (38.5%)	92 (57.2%)
Total	**154 (100%)**	**130 (100%)**	**122 (100%)**	**161 (100%)**

The reasons of inappropriate antibiotic use at Thai Binh General Hospital in 2017 and 2019 were: wrong infusion speed (54.5% and 33.9%, respectively), wrong route of administration (41.6% and 40,7%, respectively), solvent volume error (3.9% and 25.4%, respectively).

At Nam Dinh General Hospital, the causes of inappropriate use in 2017 and 2019 were: wrong infusion speed (38.5% and 57.2%, respectively), wrong route of administration (57.4% and 39.1%, respectively) and solvent volume error (4.1% and 3.7%, respectively).

3.3.8 Cases of inappropriate drug use

The reasons of irrational antibiotic use were concentrated on a few drugs at both hospitals. The most common cause of incorrect route of drug administration is intravenous administration of recommended antibiotics. The wrong infusion speed is also common with quinolones, vancomycin and metronidazole. Studies have shown that these drugs are often used at a faster infusion rate than recommended.

The wrong diluent volume resulted in difficult or unstable drug dissolution for some drugs.

3.3.9 Total antibiotic defined daily dose (DDD) at the two studied hospitals

The total number of antibiotic defined daily dose (DDD) used for the research patients at Thai Binh General Hospital in 2017 (Table 3.20) was 2563 doses, in 2019 it was 2503 doses. In 2017, the most used antibiotic group was the 3rd generation cephalosporin with a DDD number of 730, followed by Quinolone group (503 DDD); Nitro-Imipenem group and Amino Penicillin + beta lactamase inhibitor group were used with 374 DDD. In 2019, DDD number of 3rd generation cephalosporin antibiotics decreased to 369 and this number of 2nd and 4th generation cephalosporin has increased in comparison to that in 2017. In 2019, the amount of macrolide antibiotics increased more than 10 times compared to 2017.

At Nam Dinh General Hospital, total number of antibiotic DDD among the studied subjects in 2017 was 2024 doses, in 2019 this has

increased up to 2954 DDD, of which, DDD of 3rd generation cephalosporin was the highest (789 DDD), followed by 2nd generation cephalosporin (223 DDD) and quinolone group (229 DDD). In 2019, DDD of quinolone group has been increased from 229 to 894, of 2nd generation cephalosporin increased from 223 DDD to 674 DDD.

3.3.10 Days of antibiotic therapy

The average number of days spent for one antibiotic therapy at Thai Binh General Hospital in 2017 was 8.7 ± 3.5 days and was reduced to 8.3 ± 5.7 days in 2019; this difference in two years was statistically significant ($p<0.05$). The longest average treatment days was found for soft tissue skin infections (10.7 ± 5.1 days) and the shortest was seen in the treatment was obtained for abdominal infections (8.1 ± 3.1 days).

The number of days of antibiotic therapy at Nam Dinh General Hospital in 2017 was 8.9 ± 4.9 days, in 2019 it increased to 9.2 ± 5.3 days. The longest average treatment days was observed among the respiratory infections (11.0 ± 6.1 days) and the shortest was found in urinary tract infections (7.3 ± 2.1 days). The difference of these in two years was not statistically significant.

3.3.11 Length of antibiotic therapy

Table 3.24 Days of antibiotic therapy

	Nam Dinh General Hospital		**Thai Binh General Hospital**	
	In 2017	**In 2019**	**In 2017**	**In 2019**
DOT (median (min, max))	10.23 ± 6.18 9 (1; 38)	13.14 ± 9.83 11 (1; 80)	10.92 ± 5.22 10 (1; 30)	9.64 ± 4.66 9 (1; 26)
LOT (median (min, max))	8.34 ± 3.97 8 (1; 24)	9.23 ± 5.17 8 (1; 36)	8.09 ± 3.05 8 (1; 18)	7.19 ± 2.77 7 (1; 19)
DOT/LOT	1.20 ± 0.35	1.37 ± 0.42	1.35 ± 0.18	1.36 ± 0.43

Study results showed that the mean number of antibiotic treatment days at Nam Dinh General Hospital for all 4 types of studied infections in 2017 was 10.92 ± 5.22, of which the shortest was 3 days, the longest was 30 days. In 2019, the mean duration of treatment was 13.14 ± 9.83 days, of which the shortest was 3 days and the longest was 80 days.

At Thai Binh General Hospital, mean duration of antibiotic therapy was found 10.23 ± 6.18 in 2017, of which, the shortest was 3 days, the longest was 38 days. In 2019, mean duration of antibiotic therapy was of

9.64 ± 4.66, of which the shortest duration was 3 days and the longest was 26 days.

Regarding the length of treatment, at Nam Dinh General Hospital it's not change much in 2017 and 2019. However, at Thai Binh Provincial General Hospital, the LOT in 2019 was 7, decreased in comparison to that in 2017 (8).

The DOT/LOT ratio is the frequency of antibiotic combinations. The DOT/LOT ratio showed that in 2019, the antibiotic combination rate was higher than in 2017 in both hospitals.

Length of antibiotic therapy according to type of infection

Results showed that the DOT, LOT, DOT/LOT values of respiratory infections, urinary tract infections, and soft tissue skin infections at the two hospitals in 2017 were not different statistically significant ($p>0.05$), while the DOT, LOT, DOT/LOT values of intra-abdominal infections in 2017 were different significantly ($p<0.05$) between two hospitals.

The number of days of antibiotic treatment for respiratory, urinary, and soft tissue infections have ranged from 8 to 9 days, for abdominal infections it's more than 10 days at Nam Dinh General Hospital and more than 13 days at Thai Binh General Hospital.

The length of antibiotic treatment for infectious diseases ranges from 7 to 8 days. The DOT/LOT ratio of respiratory infections, urinary tract infections, and soft tissue skin infections was of 1-1.1. However, of intra-abdominal infections, this rate was 1.86 at Thai Binh General Hospital and 1.32 in Nam Dinh General Hospital.

3.3.12 Cost of antibiotic use

Average cost according to infection type at Thai Binh General Hospital

The average antibiotic cost for 1 patient at Thai Binh Provincial General Hospital in 2017 was 1.6 million VND, in 2019, this cost decreased to 638,312 VND, the difference of cost in two years was statistically significant.

The cost of antibiotics therapy for respiratory infections has decreased from 1.2 million to 0.9 million VND; this cost was decreased from 0.8 million to 0.5 million VND for urinary tract infections, from 0.7 million to 0.6 million for treat soft tissue skin infection and from 1.3 million to 0.6 million for treatment of intra-abdominal infections.

Average cost by type of infection at Nam Dinh Provincial General Hospital

The average cost of antibiotic therapy for 1 patient at Nam Dinh General Hospital in 2017 was 0.7 million VND and increased significantly in 2019 to 2.4 million VND.

The cost of antibiotic use to treat respiratory infections has increased from 0.8 million to 4.2 million, to treat urinary tract infections this increased from 0.8 million to 1.8 million, increased from 0.8 million to 1.6 million for treatment soft tissue skin infections and increased from 0.66 million to 1.9 million for treatment of intra-abdominal infections. The difference in costs between 2017 and 2019 is statistically significant.

Chapter 4. DISSCUSSION

4.1 Characteristics of study subjects

General characteristics of enrolled patients

Patients at Thai Binh General Hospital has the mean age (± standard deviation - CI) of 57.7 ± 19.8 (from 18 to 95 years old) in 2017 and 59.9 ± 17.7 in 2019. Patients over 60 years old were accounted for a high rate (from 47% to 50%); rate of patients with accompanied disease was about 33% to 35%. The average length of hospital stay in 2017 was 8.7 days and reduced to 8.3 days in 2019. At Nam Dinh General Hospital, the average age of patients enrolled in the study was also about 60 years old. The proportion of patients over 60 years old accounted for over 50%. The proportion of patients with comorbidities was 38.1% in 2017 and 47.7% in 2019. The average length of hospital stay was 8.9 days in 2017 and 9.2 days in 2019.

Characteristics of samples cultured for microbiology

Results of culture and isolation of bacteria showed similar characters as that obtained from the studies evaluating the microbiological situation and antibiotic resistance in hospitals in Vietnam. Among the isolated bacteria, the most frequently isolated strains were *A.baumannii*, *Klebsiella, E. coli*, *S.coagulase negative* and *S.aureus*. The number of microbiological cultures increased significantly after the program established, the number of isolated bacteria has also increased, this contributed to support the better antibiotic prescribing, reducing the use of antibiotics according to experience.

4.2 Current situation of rational antibiotic use and some influenced factors at Thai Binh and Nam Dinh General Hospitals in 2017

Combination of antibiotics in 2017

Rate of use 1 antibiotic in treatment of infection at Thai Binh General Hospital in 2017 was 48.2%. Rate of use two antibiotic in combination was 36.7%. At Nam Dinh Provincial General Hospital, rate of using one antibiotic was 55.3%, and rate of using two antibiotics was 37.1%. At Thai

Binh General Hospital, the average number of antibiotics used in 2017 was 1.77± 1.0; at the General Hospital of Nam Dinh province, this average number was 1.55 ± 0.7. Results showed that the rate of using single antibiotic in treatment is high in both hospitals, similar to the results obtained by Nguyen Viet Hung at Dien Bien Provincial General Hospital.

Rate of appropriete selection of initial antibiotics

Our results showed 40.1% of appropriete selection of initial antibiotics at Thai Binh General Hospital and 38.7% at Nam Dinh General Hospital. This result was lower than the results obtained at the hospital in Australia, in which, 24.3% of prescriptions did not comply with treatment guidelines, 23.0% were evaluated as inappropriate. This rate was higher at Cho Ray Hospital in 2017 and at Dien Bien Provincial General Hospital in 2019. Our obtained rate at Thai Binh General Hospital was similar to the results of a study in France with an appropriate antibiotic prescribing rate of 40%.

Rate of rational antibiotic use

The causes of irrational antibiotic use were concentrated on a few drugs at both hospitals. The most common cause of incorrect dosing was intravenous administration of the antibiotics that recommended for only intravenous administration. The cause of wrong infusion speed was also common in case of Quinolone, Vancomycin, and metronidazole groups. Studies have shown that these drugs were often used at a faster infusion rate than recommended. Some drugs were used with wrong volume of diluent, resulting in difficult or unstable drug dissolution. This result is similar to the results of a study done in Singapore hospital with the reasons of inappropriate prescribing including inappropriate choice (36.1%) and duration (31.3%).

4.2.1. Some factors influenced on situation of antibiotic use management at Thai Binh and Nam Dinh General Hospitals in 2017

Results of this study conducted at Thai Binh and Nam Dinh General Hospitals are similar to those obtaoned in Ho Chi Minh City in 2017.

Nam Dinh General Hospital has not yet implemented interventions to increase the efficiency of antibiotic use, so some research results showed that in 2019, the number of antibiotics used at Nam Dinh General Hospital was increased, the rate of appropriate selection of initial antibiotic or selection of appropriate antibiotics after having the antibiogram results has not changed compared to that in 2017. In addition to the difficulties due to the large number of patients, the lack of clinical data in hospitals is also one of the reasons leading to the loosen monitoring of drug use in general and monitoring antibiotic use in the hospitals.

At Thai Binh General Hospital, the full-time clinical pharmacist was not yet appointed, but only part-time. Newly implemented clinical pharmacy activities such as adverse drug reaction (ADR) monitoring, drug information, reporting on drug use, participation in the selection of the drugs list for bidding were implemented. At the General Hospital of Nam Dinh Province, the Faculty of Pharmacy has a dedicated clinical pharmasist. However, due to too the limited human resources, many activities have not been implemented.

Knowledge and attitudes of doctors about antibiotic use at Thai Binh and Nam Dinh General Hospitals

There are many causes of antibiotic resistance, one of which is the knowledge and attitude of the prescriber. Most of the doctors in the study were confident with the optimal use of antibiotics for treatment of their patients. According to all enrolled doctors, antibiotic knowledge is important for clinicians and antibiotic resistance is an urgent issue. It can be seen that the clinicians in this study were aware of the seriousness of the antibiotic resistance. This result is similar to the results obtained from previous study done by Le Thi Anh Thu with 67.2% of surgeons have the right attitude about antibiotic use and results of other researchs conducted in other countries. The fact that doctors have the right attitude on the issue of antibiotics and antibiotic resistance can help positively in improving the effectiveness of the Antibiotic Use Management Program of the Ministry of Health. In particular, with the frequency of antibiotic prescribing by doctors, as shown in Figure 1, one know that the knowledge and attitude of clinicians needs to be paid more attention. If the doctors do not master the knowledge and have wrong attitude towards the problem of antibiotic resistance, it will lead to the inappropriate use of antibiotics, increasing the resistance of bacteria to antibiotics.

4.3 The intervention effectiveness to strengthen the rational use of antibiotics at Thai Binh General Hospital

Average number of prescribed antibiotics

Our results showed that in 2017, the rate of using one type of antibiotic in treatment at Thai Binh General Hospital was 48.2%, in 2019 it increased to 53.4%. The rate of using a combination of two antibiotics also increased from 36.7% in 2017 to 43.3% in 2019 while rate of using a combination of triple and more antibiotics was decreased. The difference of these parameters in two years was statistically significant. The average number of antibiotics used in 2017 was 1.77± 1.0 and reduced to 1.51 ± 0.6 in 2019 with the difference statistically significant (<0.05).

At Nam Dinh General Hospital that served as control hospital, rate of using 1 antibiotic for treatment has decreased in 2019 compared to that in 2017. Rate rate of using the combination of three and more antibiotics showed to increase and the average number of used antibiotics increased from 1.55 ± 0. 7 in 2017 to 1.65 ± 0.8 in 2019.

Thai Binh General Hospital has carried out a number of interventions, results showed the improvement in antibiotic prescribing and reducing number of antibiotics in the prescriptions.

Rate of appropriate initial antibiotic use

Appropriate initial antibiotic use is important for the treatment of infectious diseases. This rate increased after the intervention, showing that the prescription of doctors has being more considered, the rate of adherence to the treatment regimen was also higher. But our obtained rate is lower than results of the intervention conducted at Cho Ray Hospital in 2017.

Rate of appropriate initial antibiotic use at Nam Dinh General Hospital was 48.0% in 2017 and 54% in 2019. However, the increased rate of rational antibiotic use was observed only in treatment of respiratory and intra-abdominal infections (from 30.0% to 51.2% and 51.3% to 81.3%, respectively). In the treatment of skin and soft tissue infections and urinary tract infections, this rate has decreased from 59.7% to 34.3% and from 52.8% to 48%, respectively.

One other study evaluating the impact of an intervention through training on antibiotic prescribing has found that antibiotics (176/332) were not appropriately used at the start of the program. The inappropriate prescribing rate consistently decreased to 26.4% (107/405) in the fourth trimester (RR = 0.38; 95% CI=0.23-0.43;$p<0.001$). Antibiotic consumption fell from 1,150 defined daily doses (DDDs) per 1000 inpatients in the first quarter to 852 DDDs in the fourth quarter, reflecting a 42% reduction in antibiotic spending.

Nam Dinh General Hospital has not yet implemented activities on the management antibiotic use, although the hospital has initially implemented clinical pharmacy activities, but due to the shortage in staff resource, has only one dedicated clinical pharmacist, so the prescription of antibiotics at clinical departments could not be well controled. Moreover, drug bidding is also one of the reasons for difficulty in treatment compliance because there was not defined treatment protocol for using at Nam Dinh General Hospital, hospital treatment guidelines were not yet available therefore

difficult in development of drug list used for hospital, resulting the difficulty in supplying enough drugs according to the treatment regimen.

About antibiotic use

The rate of rational antibiotic use analyzed according to the number of antibiotic usages at Thai Binh General Hospital was 70.7% in 2017, the rest 29.3% was of irrational use rate. In 2019, this rate has increased to 71.8%, almost unchanged after two years. This rate is higher than the results obtained from the research conducted at Cho Ray Hospital.

The Ministry of Health has issued a document on the use of antibiotics, including instructions for solving the infusion antibiotics. The Thai Binh General Hospital has developed guidelines for solving the infusion antibiotics at the hospital, but has not organized training on this content, so the use of the drug has not changed.

Another study evaluating the effectiveness of ASP through training in antibiotic prescribing found 53% of inappropriate antibiotic prescriptions (176/332) at the time the program was started and this decreased to 26.4% (107/405) in the fourth trimester ($p < 0.001$; RR = 0.38; 95% CI, 0.23-0.43) of the program implementation. Results showed that despite the development and issuance of documents, but without continuous training for health workers, the effectiveness of the intervention is not clear.

Amount of antibiotics used

Results showed that the reduction of antibiotic use in the post-program period indicating the effectiveness of the antibiotic management program. The antibiotic management program needs to be implemented continuously, because the appointment of antibiotics for patients depends heavily on the habits and experience of the doctor. A program that is implemented consistently with many new measures can change behaviors and improper prescribing habits. A study in Singapore also showed that the effectiveness of an antibiotic management program significantly reduced DDDs per 100 patient days by 55.6% compared to baseline 0.9-0.4 ($p = 0.013$). One study at a hospital in Spain showed that the effectiveness of an antibiotic management program intervention reduced antibiotic consumption from 1150 DDD/1000 patients in the first quarter to 852 DDDs in the fourth quarter, reflecting a 42% reduction in spending on antibiotics.

Days of antibiotic use

DOT (Day of Therapy) is the total number of days of antibiotic treatment of one patient and LOT (Length of Therapy) is the duration of antibiotic course, calculated as the number of days with antibiotic use. Our results showed that at Thai Binh General Hospital, the average number of

days of antibiotic treatment in 2017 was 10.23 ± 6.18, of which the shortest was 1 day, the longest was 38 days. In 2019, this number was 9.64 ± 4.66 days, of which the shortest was 1 day and the longest was 26 days. Study conducted at a hospital in Singapore showed that after intervention with ASP, the reduction in DOTs per 100 days of patients was 46.7% compared to the baseline level of 1.5-0.8 (p = 0.06).

Cost of antibiotic use

One of the criteria used to evaluate the effectiveness of the program of antibiotic use is to reduce the cost of antibiotic use. Our results showed that antibiotic costs by type of infection at Thai Binh General Hospital in 2017 range from 50 million to 100 million. The cost of antibiotic used in 2019 decreased in all disease groups.

CONCLUSION

1. Current situation of rational antibiotic use and some influenced factors at Thai Binh and Nam Dinh General Hospitals in 2017

- The rate of apropriete selection of initial antibiotic was 40.1% at Thai Binh General Hospital and 38.7% at Nam Dinh General Hospital. The highest rate in the two hospitals was found in treatment of soft tissue skin infections (44.6% and 59.7%, respectively). Appropriete antibiotic selection of about 30% was obtained in treatment of respiratory infections in both hospitals.
- Rate of antibiotic use in treatment at Thai Binh General Hospital in 2017 was 48.2%. Rate of using a combination of two antibiotics was 36.7%, of three antibiotics was 9.8% and of more than three antibiotics was 5.3%. At Nam Dinh General Hospital, these rates were 55.3%, 37.1%, 5% and 2.6%, respectively.
- The average number of antibiotics used in 2017 was 1.77± 1.0 antibiotics at Thai Binh General Hospital and 1.55 ± 0.7 at Nam Dinh General Hospital
- The rate of rational antibiotic use based on the number of used days in 2017 was 70.7% at Thai Binh General Hospital and 69.7% at Nam Dinh General Hospital.
- Some factors affected the rational use of antibiotics at Thai Binh and Nam Dinh General Hospital were the establishment of antibiotic use management boards, no clear assignement of tasks to members of the committee, organizion of a number of training courses on antibiotics and microbiology, certain level of knowledge about antibiotic use but not comprehensively among the clinicians, the continue need of knowledge supplement, updating and interven.

2. The intervention effectiveness on strengthen the rational use of antibiotics at Thai Binh General Hospital

The average number of antibiotics used in 2017 was 1.77± 1.0 drugs, reduced to 1.51 ± 0.6 in 2019; rate of use of reasonable initial antibiotics has increased from 41.1% in 2017 to 56.7% in 2019. The rate of rational antibiotic use after having antibiogram result has been increased from 40.3% to 47.3%. The average number of days of antibiotic therapy has reduced from 8.7 ± 3.5 in 2017 to 8.3 ± 5.7 days in 2019; the average cost of antibiotic therapy for 1 patient decreased from 1.6 million VND in 2017 to 638 312 VND in 2019.

RECOMMENDATION

The following recommendations resulting from our research results:

1. For the hospitals:

- It is necessary to develop an antibiotic management program in hospitals

- The antibiotic use management program should be implemented synchronously with many coordinated measures, and at the same time with the strengthening of infection control measures to achieve higher effectiveness.

- Strengthening the capacity of the microbiology department to perform bacterial cultures is important in the development of hospital antibiotic guidelines.

2. For the Ministry of Health and the Provincial Department of Health:

- The Department of Health should strengthen the implementation of the antibiotic use management program in the hospitals. Regularly organize training courses for medical staff and inspect, supervise the use of antibiotics at health facilities.

- The Ministry of Health should continue to direct the application of the Antibiotic Management Program in hospitals to improve the quality of treatment, increase the rational use of antibiotics, and reduce antibiotic costs.

LIST OF PUBLISHED SCIENTIFIC ARTICLES RELATED TO THE THESIS

1. Nguyen Trong Khoa, Luong Ngoc Khue, Phan Le Thanh Huong, Tran Khanh Thu, Hoang Ngoc Ha (2017). Knowledge, attitude on antibiotic use among the clinicians at Thai Binh General Hospital and Nam Dinh General Hospital in 2017", *Journal of Vietnam Preventive Medicine*, Vol. 27 (9): 98-103.
2. Nguyen Trong Khoa, Luong Ngoc Khue, Phan Le Thanh Huong (2020), "Current situation of rational use of antibiotics at Thai Binh and Nam Dinh provincial general hospitals in 2017", *Journal of Vietnam Preventive Medicine*, Vol. 30 (7): 173-178.
3. Nguyen Trong Khoa, Luong Ngoc Khue, Phan Le Thanh Huong (2020), "The effectiveness of some intervention measures to strengthen the rational antibiotic use at Thai Binh General Hospital from 2017 to 2019", *Journal of Vietnam Preventive Medicine*, Vol. 30, (7): 179-186.