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Evaluation of rational drug use project, under the support of national health security office, on drug utilization and drug management in community care clinics in Bangkok

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EVALUATION OF RATIONAL DRUG USE PROJECT, UNDER THE SUPPORT OF NATIONAL HEALTH SECURITY OFFICE, ON DRUG UTILIZATION AND DRUG MANAGEMENT IN COMMUNITY CARE CLINICS IN BANGKOK

Miss Dararat Samretwit

A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Social and Administrative Pharmacy
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การประเมินโครงการส่งเสริมการใช้ยาอย่างสมเหตุผลภายใต้การสนับสนุนของสำนักงานหลักประกันสุขภาพแห่งชาติต่อการใช้ยาและการจัดการด้านยา ในกลุ่มคลินิกชุมชน เขตกรุงเทพมหานคร

น.ส.ดารารัตน์ สำเร็จวิทย์

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรดุษฎีบัณฑิต
สาขาวิชาเภสัชศาสตร์สังคมและบริหาร ภาควิชาเภสัชศาสตร์สังคมและบริหาร
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ดารารัตน์ สำเร็จวิทย์ : การประเมินโครงการส่งเสริมการใช้ยาอย่างสมเหตุผลภายใต้การสนับสนุนของสำนักงานหลักประกันสุขภาพแห่งชาติต่อการใช้ยาและการจัดการด้านยา ในกลุ่มคลินิกชุมชน เขตกรุงเทพมหานคร . (EVALUATION OF RATIONAL DRUG USE PROJECT, UNDER THE SUPPORT OF NATIONAL HEALTH SECURITY OFFICE, ON DRUG UTILIZATION AND DRUG MANAGEMENT IN COMMUNITY CARE CLINICS IN BANGKOK) อ.ที่ปรึกษาหลัก : ผศ. ภญ. ดร.ยุพดี ศิริสินสุข

โครงการเครือข่ายคลินิกส่งเสริมการใช้อย่างสมเหตุผล (Network of Rational Drug Use clinic) ได้ดำเนินการโดยสำนักงานหลักประกันสุขภาพแห่งชาติ เขตกรุงเทพมหานคร ในเดือนสิงหาคม พุทธศักราช 2558 โดยมีวัตถุประสงค์เพื่อส่งเสริมการใช้ยาอย่างสมุเหตุผลในกลุ่มคลินิกชุมชนอบอุ่นในเขตกรุงเทพมหานคร ซึ่งโครงการประกอบด้วยหลากหลายมาตรการ ได้แก่ การให้ความรู้ การบริหารจัดการ การข้อกำหนดบังคับในเชิงนโยบาย และการใช้กลไกทางการเงินเพื่อสร้างแรงจูงใจ การศึกษานี้ มีวัตถุประสงค์เพื่อประเมิน และตรวจสอบความสำเร็จของโครงการคลินิกส่งเสริมการใช้ยาอย่างสมเหตุผล โดยทำการประเมินคุณภาพของการใช้ยา โดยรูปแบบของการศึกษาแบบ Interuppted time-series intervention analysis ซึ่งเป็นรูปแบบของการศึกษากึ่งทดลอง เพื่อเปรียบเทียบผลของการให้ intervetion ที่มีต่อผลลัพธ์ ก่อน และ หลังการให้ intervention. โดยนำข้อมูลใบสั่งยารายสัปดาห์ที่ได้จากฐานข้อมูลการเบิกจ่ายของสำนักงานหลักประกันสุขภาพแห่งชาติ ระหว่างเดือน ตุลาคม พ.ศ. 2556 จนถึงเดือน กันยายน พ.ศ. 2562. โดยนำข้อมูลมาสร้างแบบจำลอง Autoregressive Intergrated Moving Average (ARIMA) เพื่อประมาณค่าแนวโน้มและระดับที่เปลี่ยนแปลงของผลลัพธ์ที่ทำการศึกษาในช่วงก่อนและหลัง intervention โดยได้ทำการคัดเลือกตัวชี้วัด 5 ตัว เพื่อใช้เป็นผลลัพธ์ของการศึกษา ได้แก่ 1) ปริมาณการใช้ยาปฏิชีวนะ 2) ร้อยละของใบสั่งยาที่มีการสั่งจ่ายยาปฏิชีวนะ 3) ร้อยละของใบสั่งยาที่เป็นไปตามแนวการรักษา 4) ค่าเฉลี่ยของราคาต่อใบสั่ง 5) ร้อยละของต้นทุนยาที่ใช้ในการสั่งจ่ายปฏิชีวนะ ผลการศึกษา พบว่า กลไกทางการเงิน มีผลต่อปริมาณการใช้ยาปฏิชีวนะอย่างมีนัยสำคัญทางสถิติ ($p < 0.05$, $p = 0.004$) การให้ความรู้มีผลต่อร้อยละของใบสั่งยาที่มีการสั่งจ่ายยาปฏิชีวนะอย่างมีนัยสำคัญทางสถิติ ($p < 0.05$, $p = 0.017$) ร้อยละของใบสั่งยาที่เป็นไปตามแนวการรักษาไม่ได้รับผลกระทบจาก intervention ค่าเฉลี่ยของราคาต่อใบสั่งไม่ได้รับผลกระทบจาก intervention และการให้ความรู้มีผลต่อร้อยละของต้นทุนยาที่ใช้ในการสั่งจ่ายปฏิชีวนะอย่างมีนัยสำคัญทางสถิติ การศึกษานี้ สรุปได้ว่า intervention จากโครงการเครือข่ายส่งเสริมการใช้ยาอย่างสมเหตุผล มีผลกระทบต่อคุณภาพการสั่งจ่ายเพียงบางส่วน ในด้านการใช้ยาปฏิชีวนะ ใบสั่งยา และค่าใช้จ่ายด้านยา ทั้งนี้ พบว่ากลไกทางการเงิน ถูกกำหนดขึ้นหลังจากการให้ความรู้เป็นเวลา 1 ปี ซึ่งผลของการกลไกทางการเงินที่มีต่อผลลัพธ์ที่ศึกษาอาจมีผลรวมของการให้การศึกษาร่วมด้วย

สาขาวิชา เภสัชศาสตร์สังคมและบริหาร ลายมือชื่อนิสิต

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ปีการศึกษา 2563 ลายมือชื่อ อ.ที่ปรึกษาหลัก

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5776551033 : MAJOR SOCIAL AND ADMINISTRATIVE PHARMACY
KEYWORD: Interrupted Time series analysis, ARIMA modelling, Rational Drug Use, community care clinic, NHSO

Dararat Samretwit : EVALUATION OF RATIONAL DRUG USE PROJECT, UNDER THE SUPPORT OF NATIONAL HEALTH SECURITY OFFICE, ON DRUG UTILIZATION AND DRUG MANAGEMENT IN COMMUNITY CARE CLINICS IN BANGKOK. Advisor: Asst. Prof. Yupadee Sirisinsuk, Ph.D.

Background: "The Network of Rational Drug Use Clinic (RDU Clinic)" campaign implemented in August 2015 to promote rational drug use in community caring clinic operated under National Health Security Office (NHSO) in Bangkok. The intervention composed of various measures such as education, managerial intervention, regulatory, and financial incentive. The purpose of the project is to evaluate and monitor the program effectiveness.

Objectives: The purpose of the study is to evaluate the impact of RDU project on the quality of drug use in community care clinics in Bangkok using an interrupted time-series intervention analysis

Methods: Quasi-experimental study using interrupted time series analysis was applied to compare the outcome variables before and after intervention. The aggregated weekly prescriptions data was extract from NHSO medical claim database between October 2013 to September 2019. Auto Regressive Integrated Moving Average (ARIMA) model was developed to estimate the level and trend in the pre-intervention data segment compare with the estimated changes in level and trend in post-intervention. : Five indicators are selected as outcome of interest for ARIMA model analysis; 1) antibiotics (ATBs) utilization, 2) percentage of encounters with antibiotics prescribed, 3) percentage of prescriptions of antibiotics in accordance with clinical guidelines, 4) average medicines cost per encounter, and 5) percentage of drug costs spent on antibiotics.

Results: ATBs utilization was significantly affected by financial intervention in Total ATBs, ($p < 0.05$, $p = 0.004$). Percentage encounter with ATBs, was significantly affect by education ($p < 0.05$, $p = 0.017$) The percentage of prescript adhere with guideline has an increasing trend but has no significant effect ($p > 0.05$). Average medicine cost per encounter is not significantly impacted by the interventions. The percentage of drug cost spent on ATBs has significant impacted

Field of Study:	Social and Administrative Pharmacy	Student's Signature .....
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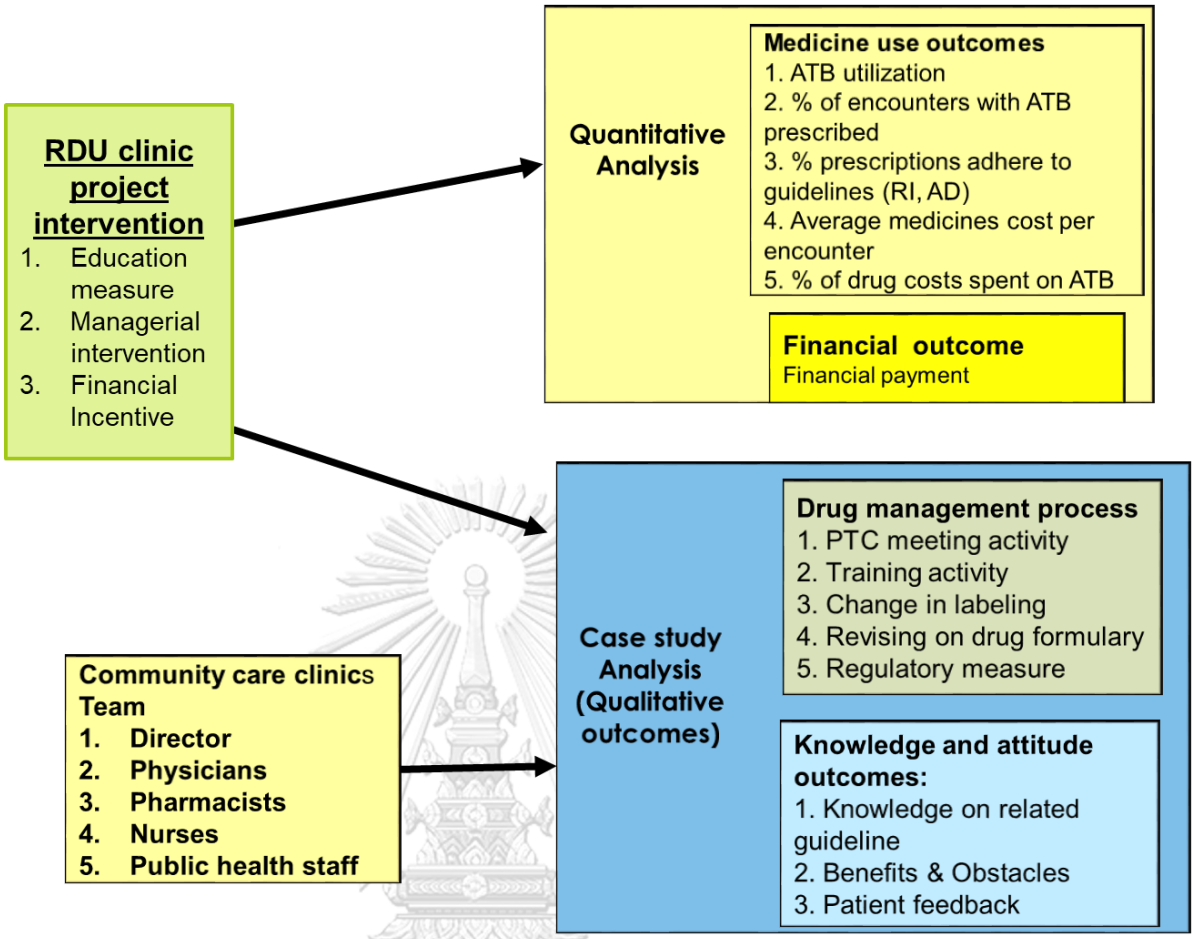

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CHAPTER I

Introduction

1.1 Background and rationale of the study

Rational Drug Use problem

Rational drug use is well recognized as an essential indicator that reflects the quality of health services. Rational use of drug require that patient receive medications appropriate to the clinical needs, in dose the meet patient's requirement, for the adequate period of time, at the lowest cost to the individual and community (1). This means the medicine should be used appropriately with regard to its proven benefit, the lesser risk to the patient. However, the irrational use of medicine persisted as a major problem worldwide. It was estimated that more than 50% of all medicines prescribed, dispensed, or sole inappropriately and around 50% of patient fail to take them correctly (2). Therefore, WHO had established guideline for promoting rational prescribing to improve quality and cost-effectiveness of healthcare through various interventions (3).

Drug Use Problems in Thailand

The prescribing survey data from regional advisor in Essential Drugs and Other Medicines from WHO revealed that there is a number of inappropriate outpatient was prescribed in Thailand, especially in common cold case, aches and pain, and hypertension (4). Inappropriate use of antibiotics in Thailand is common among both health professionals and public (5-8). Antibiotics was overprescribed, especially, in Upper Respiratory Tract Infections (URI) and diarrhea. (5, 6, 8). The study in a tertiary care hospital found that only 7.9% of URI cases were caused by bacterial infection (9). The increasing antibiotics consumption is correlated with the high rate of antimicrobial resistance. It has been recognized as a serious threat to public health and cause a huge burden on societies around the world (10). In Thailand, study in health and economic impact antimicrobial resistance in 2010 revealed that it cost at least 3.2 million extra hospitalization days and 38,481 deaths and up to 202.8 million

United State dollar (USD) losses in direct medical cost and more than 1333 million USD in indirect cost (the exchange rate at 30 Thai Bath (THB) per USD) (11).

Drug Policy intervention

In Thailand, national drug system development committee released national drug policy in 2011 which determined Rational Use of Medicine (RUM) as a key element for national drug system development strategy for year 2012-2016 (4) . The Network of Rational Drug Use Clinic (RDU clinic project) campaign had been implemented in August 2016 by National Health Security Office region 13 (NHSO-Bangkok) to promote rational drug use in community care clinic in Bangkok (12). The purpose the project is to create awareness of irrational drug use problems, develop drug management system and improve quality of healthcare services among participated clinics. The intervention is a continuous process that dynamic over the time. It composes of 3 interventions which were implemented simultaneously to drive the success of rational drug use. The detail of interventions is explained in chapter 2. RDU project primary outcomes are to assess the antibiotics prescriptions in Respiratory Infection (RI) and Acute Diarrhea (AD) treatment as the prescribing indicators in community care clinic. It was also become the one of Quality and Outcome Framework (QOF) in service plan.

The purpose of the study is to evaluate the impact of RDU project on drug utilization in community care clinics in Bangkok and investigate the selective community care clinics on the drug management and health personal's opinion after project implementation as a case study for further policy recommendation..

1.2 Research Question

Does RDU clinic project improve the rational drug use performance in community care clinics?

1.3 Research Objectives

1. To assess the effects of RDU clinic project on drug utilization in community care clinics in Bangkok.

2. To investigate the selective community care clinics on drug management process and health personnel's opinion after participating in the RDU clinic project as a case study for the further policy recommendations.

1.4 Scope of the study

This study was conducted in community care clinics in Bangkok which received capitation from NHSO-Bangkok. The study composes of 2 parts to evaluate RDU clinic project intervention on drug utilization, and to investigated on drug management process and health personnel's opinion after project participation as a case study for further policy recommendations.

Part I: To analyze drug utilization from NHSO's medical claimed database, selecting antibiotics as the study drugs. The effect of RDU project intervention on five medicines use outcomes were analyzed using quantitative interrupted time-series analysis. Prescribing and visiting data was collected from 162 community care clinics participating in the project since August 2015. The data collection was recovered from October 2013 to September 2019 to compare drug utilization from the community care clinic before and after intervention.

Part II: To describe the financial impact and investigate a selective community care clinics on drug management process, and health's personal knowledge and attitude toward the project intervention. The financial data derived from the NHSO's payment report was quantitatively analyzed by descriptive statistic. In-depth interviewing on health personal such as physicians, pharmacists, manager, nurse, or public health staff from the selected community care clinics were qualitatively analyzed to investigate the impact of intervention on drug management and health's personal knowledge and attitude outcome as a case study for the further policy recommendation

1.6 Conceptual framework

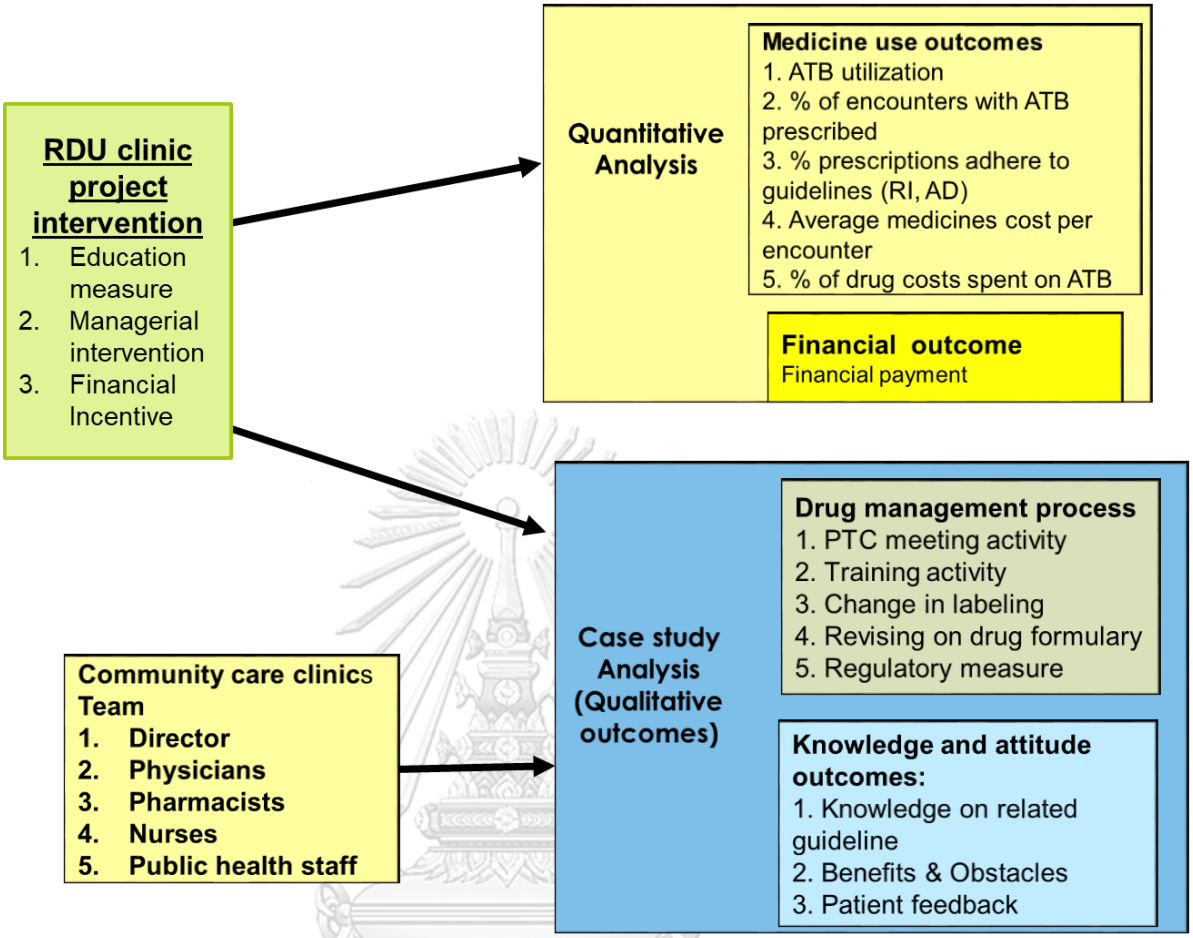

Figure 1 Conceptual Framework

The conceptual framework illustrated the RDU project, which composes of three categories of intervention that are: 1) Education measure; 2) Managerial intervention and 3) Financial incentive. There are four major outcomes of interested: medicine use outcomes, financial outcome, health personal's knowledge and attitude outcome, and drug management process. Five medicine use outcomes were quantitatively analyzed by comparing the change in drug use before and after interventions which are: 1) antibiotics utilization determined by DDD per 1000 patients, 2) Percentage of encounters with antibiotics prescribed, 3) Percentage of prescription adhere to guideline in two specific diseases: Respiratory Infection (RI) and Acute Diarrhea (AD), 4) Average medicines cost per encounter, and 5) Percentage of drug cost spent on Antibiotics. The financial outcome are the NHSO's payment to the clinic according to Key Performance Indicators (KPI) in

the Quality Outcome Framework (QOF). Drug management process outcome was qualitatively assessed on: 1) Pharmacy and Therapeutic Committee (PTC) activity, 2) Training activity, 3) Change in drug labelling, 4) Revising on drug formulary and 5) Regulatory measure (change in the criteria for drug prescription). The health personal's knowledge and attitude outcomes will be described on their knowledge on related guideline, identifying what are the benefits and the obstacles of the project and asking the patient feedback toward project in health personal's perspective.

Operation Definitiions

RDU clinics project : the campaign implemented by NHSO-Bangkok to promote Rational Drug Use in community care clinics in Bangkok compose of three major interventions; 1) Education measure; 2) Managerial intervention and 3) Financial incentive.

Community care clinic: the privately own clinic in Bangkok which received capitation from NHSO-Bangkok and signed agreement with NHSO-Bangkok participated in the the RDU clinic project.

NHSO-Bangkok: National Health Security Office which is responsible for capitation for universal health coverage scheme to all health service unit, both government and private, registered in Bangkok.

Medicine use outcomes: The outcome measurement analyzed in the study compose of 1) antibiotics utilization, 2) Percentage of encounters with antibiotics prescribed, 3) Percentage of prescription adhere to guideline 4) Average medicines cost per encounter, and 5) Percentage of drug cost spent on Antibiotics.

RI: Respiratory Infection disease determined by ICD10 code

AD: Acute Diarrhea disease determined by ICD10 code.

QOF: Quality and Outcome framework is the guideline for NHSO payment to health care service unit on quality of service performance.

KPI: Key performance Indicator is the criteria determined by NHSO-Bangkok for calculation on the QOF payment

CHAPTER II

Literature Review

2.1 The rational use of medicine concept

In order to explain Rational Use of Medicine concept, we need to understand the drug management cycle diagram.

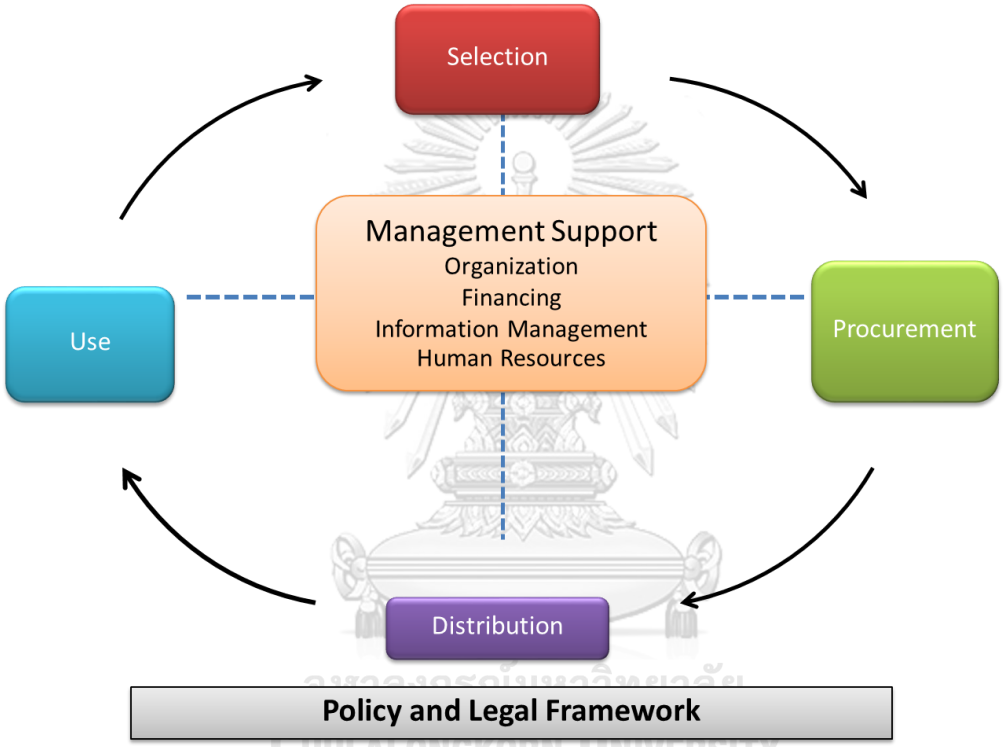

Figure 2 Drug Management Cycle
(Source: Managing Drug Supply: MSH/WHO, Kumantan 1997 (13).

The system composes of 4 phases and linked together within cycle, which means that it will continue to improvement over the time the 4 phases are explains as below

1) Drug Selection refers to the selection the drug into the system which start from National Essential List of Medicine (NLEM) to the hospital formulary listing. In the public hospital the Listing depend on PTC

2) Drug Procurement refers to the purchasing of medicine for using into the system. In case of public hospital, it relates with the PTC, inventory department and purchasing department. The

procurement also relates with the mode of purchasing whether production or importation or donation or other mode of purchase to have that available of drug for patient use when they needed

3) Drug Distribution refers to the transportation and logistics controlled to ensure that the medicine will supply to the hospital with the good quality require by Good Distribution Practice. This factor is important especially in susceptible drug such as vaccine which require cold chain management transportation.

4) Drug Utilization refers to the usage of the medicine by prescriber, pharmacist, patient and consumer.

WHO defines drug utilization research as "the marketing, distribution, prescription and the use of drugs in a society with special emphasis on the resulting medical, social and economic consequences". (WHO, 1977) (1). The related concept is pharmaco-epidemiology, which means the study of use and effects or side-effects of drugs in large number of people with the purpose of supporting the rational and cost-effective use of drugs in population, thereby improving health outcomes. Drug utilization research and pharmaco-epidemiology should provide the aspect of drug use and drug prescription (1).

The principle aim of drug utilization research is to facilitate the rational use of drugs in populations. It related to rational drug use in four aspects below (1):

1) Description of drug use patterns: means explaining how drug are being use. For example, the estimation of the number of patients exposed to drugs in a given time period, or the extent of drug use at a certain moment or in a certain area. The drug usage can be explained as: proper use, overuse, or underuse. The determination of pattern or profile of drug to compare which an alternative drug is being used to treat particular conditions. It can be used to compare the observed patterns of drug use to the standard treatment guidelines. Drug utilization (DU) data can be used as feedback to prescribers to improve pattern of drug use. The drug use problem can be explained as the number of case reports on the adverse drug effects regarding to the number of patients exposed to the drug to evaluate the magnitude of the problem.

2) Early signals of irrational drug use: Drug utilization may generate hypotheses for further drug use investigations. The research can be conducted by comparing drug utilization patterns and costs between different regions or time periods, or comparing the observed patterns of drug use to current recommendations from standard treatment guidelines. The type of irrational drug use are: the inappropriate prescription by doctors, poly-pharmacy, or the use of too many medicines prescribed per patient, inappropriate prescription of antimicrobials, such as the inadequate dosage for non-bacterial infections, over-prescription of injections where oral formulations would be more appropriate, failure to prescribe in accordance with clinical guidelines or the wrong choice of drugs, or inadequate dosages, or incorrect frequency of administration of drug, or improper duration of therapy, or failure to observe drug contra-indications, under-use of life extending drugs for illnesses such as hypertension, heart disease, asthma, and other chronic illnesses, choose more expensive drugs when the less expensive drugs would be equally or more effective, prescription of drugs with no indication for the purpose of their placebo effect, or for impressing the patient, or for vested interests in the prescribed drugs, and inadequate consulting time such as very short dispensing time and poor communication of information regarding of drugs to patient in verbal or written form which lead to an incorrect use by patients, inappropriate of patient self-medication especially the utilization of the prescription-only medicines.

The method to measure the type and degree of irrational medicine use had suggested by WHO (2003) drug use indicator. The indicator from WHO/DAP (1993) (14, 15), compose are 12 core medicine use indicators and 7 complementary medicine use indicators. The detail of each indicator are;

1. Core medicine-use indicators

1.1 Prescribing indicators

- Average number of drugs per encounter
- Percentage of drugs prescribed by generic name
- Percentage of encounters with an antibiotic prescribed
- Percentage of encounters with an injection prescribed
- Percentage of drugs prescribed from essential drugs list or formulary

1.2 Patient care indicator

- Average consultation time
- Average dispensing time
- Percentage of drugs actually dispensed
- Percentage of drugs adequately labelled
- Patients' knowledge of correct dosage

1.3 Facility indicators

- Availability of copy of essential drugs list or formulary
- Availability of key medicine

2. Complementary medicine-use indicators

- Percentage of patients treated without medicines
- Average medicines cost per encounter
- Percentage of drug costs spent on antibiotic
- Percentage of drug costs spent on injections
- Percentage prescriptions in accordance with clinical guidelines
- Percentage of patients satisfies with the care they received
- Percentage of health care facilities with access to impartial pharmaceutical information

The aggregate medicine consumption data should represent in Anatomical Therapeutic Classification (ATC)/Defined Daily Dose (DDD) in order to compare data between institution, regions and countries. ATC refer to WHO drug classification system, while the DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults.

ATC code are categorized into 5 levels.

Level 1: Anatomic System,

Level 2: Therapeutic Group,

Level 3: Therapeutic or Pharmacological sub-group

Level 4: Chemical, Therapeutic or Pharmacological subgroup

Level 5: Unique chemical substance

DDDs provide a fixed unit of measurement independent of price, currency, package size and strength enabling the researcher to assess trends in drug consumption and to perform comparisons between drugs and population groups. Drug utilization figures should ideally be presented as numbers of DDDs per 1000 inhabitants per day.

3) Intervention to improve drug use: is the process to monitor and evaluate the improvement measures of the information campaigns or the regulatory policies. The intervention could follow the impact of regulatory changes, or the changes in insurance, or the reimbursement systems. It could be done in form of assessing the promotional activities of pharmaceutical industry, or how the educational activities of the society impact pattern of drug use. Our research question is referred to this component on drug utilization research.

4) Quality control of drug use: this could portrait in term of Deming's quality control cycle: Plan, Do, Check, Act. (PDCA). The cycle which begin with Plan which the researcher and analyze the current situation to improve rational drug use. Then, Do is to implement the plan and Check to monitor the result of intervention. Finally, Act means assessment the result to improve the intervention in the larger scale. The cycle is the continuous development process for quality improvement of drug use.

Promoting a rational drug use concept (1-3)

The review of intervention research in rational drug use suggest the course of drug use problem categorize in three levels: community, health care and national level

1) *Community level*: referred to non-adherence problem result from various factors such as inadequate drug information, inadequate labelling, lack of money, and cultural perception on drug. Another community level problem is self-medication which influence by socio-cultural factors such as people's own perceptions and preference of certain pharmaceutical.

2) *Health care level*: the problem in this level relate with lack of knowledge and continuing education on drugs. Moreover, the conflict of interest occurs from the ownership of health facility

and practitioners. The socio-cultural factors such as patient's demand, prescriber attitude, previous experience and drug promotion also involve with drug use problem in health care level.

3) *National level*: lack of national drug policies leads to the drug use problem. The adequate monitoring, good distribution system and regular supervision and adequate storage facilities is required to improve drug use in national level.

Result from root cause of drug use problem, WHO (2002) also suggested the core strategies to promote rational use of medicines which compose of (1):

1) Establishing a mandated multi-disciplinary national body to coordinate medicine use policies. All stakeholder should involve government, health professional, academia, pharmaceutical industry.

2) Implementing procedures for developing, using, and revising standard clinical treatment guidelines (STGs).

3) Implementing procedures for developing and revising and essential medicines list (or hospital formulary) based on treatment of choice.

4) Establishing a drug and therapeutic committee (DTC) in districts and hospitals, with defined responsibilities for monitoring and promoting rational use of medicine. The DTC is a committee designated to ensure safe and effective use of medicines in the respective hospitals.

5) Using problem-based training in pharmacotherapy based on national STGs in undergraduate curricula.

6) Continuing in-service medical education as a licensure requirement and targeted educational programs by professional societies, universities, and the government.

7) Developing a strategic approach to improve prescribing in the private sector through regulation and collaborations with professional associations.

8) Monitoring, supervision, and using group processes to promote rational medicine use.

9) Training pharmacists and drug sellers to offer useful advice to consumers and supply independent medicine information.

10) Encouraging involvement of consumer organizations, and devoting government resources to public education about medicines.

11) Avoiding perverse financial incentive.

12) Ensuring sufficient government expenditure and enforced regulation.

2.2 Quality use of medicine concept (QUM)

The definition of QUM in our study referred to Australia's National Medicine policy 2002 (16). It means: selecting management options wisely, choosing suitable medicines if a medicine is considered necessary and using medicines safely and effectively to get the best possible results by: monitoring outcomes, minimizing misuse, over-use and under-use, and improving people's ability to solve problems related to medication, such as negative effects or managing multiple medications. Three major components that working together to achieve QUM objective as portraited in Figure 3. That are: 1) Quality, Safety and Efficacy, 2) Equity of accessed, and 3) Viable & responsible pharmaceutical industry.

The quality use of medicine means medicines meet the appropriate standards of quality, safety and efficacy. It is divided into 2 criteria: Adherence to standard treatment guideline (STGs) and Improve Patient's outcome in terms of efficacy and safety. Equity of accessed is timely access to the medicines that patients need, at a cost the individual and the community can afford. Viable & responsible pharmaceutical industry refered to maintaining a responsible and viable pharmaceutical industry. The study objective focus on adherence outcome which will be explain later in the research methodology.

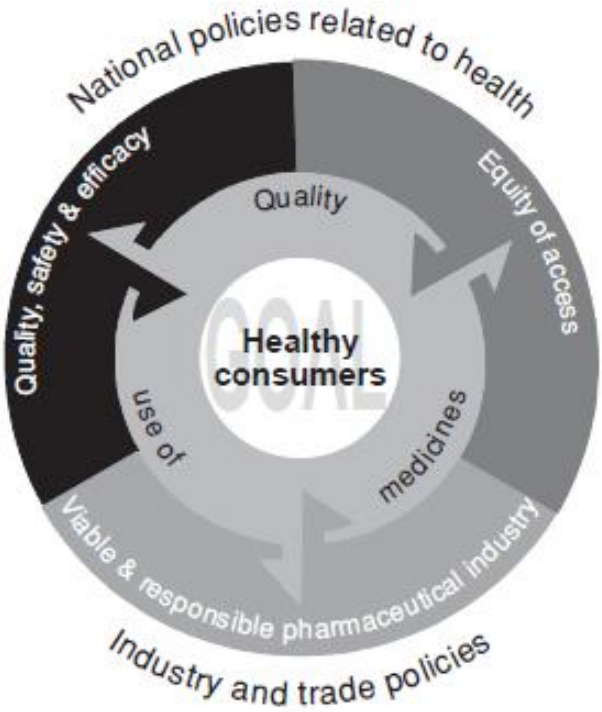

Figure 3 Australia's National Medicinie Policy

The conceptual framework of Australian's National Medicine Policy describes the approach for implementing strategies to achieve QUM. It uses principles derived from the education, behaviour change, community development, health promotion, public health and social advocacy literature. The framework required multi-level systems to take on various approach in individual, community development and public health to planning, implementing and evaluating initiatives to improve use of medicines.

2.3 Prior Research on Impact of Rational drug use campaign.

1) Research on Antibiotic Utilization

The study in a tertiary care hospital in Thailand revealed that the prevalence of bacterial infection in URI was only 7.9% and the clinic response were not different between those who received or did not receive antibiotics (9). The study followed the clinical practice guideline developed by the Centers for Disease Control and Prevention USA for principles of appropriate antibiotic use for treatment of acute upper respiratory tract infections in adults. The antibiotic should be given to the patients with pharyngitis/tonsillitis/ pharyngotonsillitis if at least 3 of the 4 clinical features (fever,

tonsillar exudates, tender anterior cervical lymphadenopathy, and no cough) were present or the patient with severe acute sinusitis/rhinosinusitis or patients with acute sinusitis/rhinosinusitis whose symptoms did not improve within 7 days. Another research in Pathumthani province measuring pharmacy sales of antibiotic without prescription suggest overestimate appropriate antibiotic use and shorter duration of antibiotic therapy in pharmacist interview method comparing with the mock-patient presentation method (8). The disease that commonly found the inappropriate use of antibiotics are acute viral pharyngitis, influenza, acute viral sinusitis, acute viral gastroenteritis and non-infected skin abrasion.

2) Intervention used in improving rational drug use

Numerous intervention researches have been conducted to evaluate the impact of RDU campaign. A systematic review in intervention research in irrational use of antibiotics summarized that are five types of interventions available as below (17): 1) *Educational intervention.* The purpose of intervention is to inform or persuade change in drug use via training, printed material and media-based approach. 2) *Managerial interventions*: The goal is to structure decision from two process;- Prescribing and dispensing such as treatment guideline, structured drug order forms, automatic stop orders, course-of-therapy packaging, effective labelling, audit plus "feedback" to providers, required consultations or justifications.- Standard diagnostic tools and laboratories 3) *Regulatory intervention*: Target on restrict decisions by market controls, banning previously registered drugs, controlling contents in drug advertisement, prescribing and dispensing controls, limitation of drug supply in public sector, required generic prescribing, restricting specific drugs to higher level of care, and allowing generic substitution. 4) *Economic or financing intervention* such as pricing of drugs according to health impact, patient cost-sharing and economic incentive. 5) *Education/managerial interventions*: the combination of education and managerial intervention in one study. 6) *Education/regulation*: the integration of education and regulation in one invention. 7) *Multifaceted interventions*: involve all of intervention above into one study design.

Other study of education intervention conducted in Long-Term Care facility in Chicago-area hospital in the United State using quasi-experimental before-after designed to assess the effects of

physician education and guideline implementation. The intervention compose of 4 teaching seesions over 18 months together with booklets detailing institutional guidelineson the optimal management of common LTC infection syndrome. The results show that there were and improved in quality of drug use in term of percentage therapy adhere with guideline recommendation and the quantity of antimicrobial use were reduced (18).

The study of the effect of financial interventions on the drug utilization was mentioned in a review by Le Grand (19). The common financial intervention was to initiate copayment method to reduce overconsumption of the drugs. However, there was also result in opposite outcomes when the prescriber prescribed more drug to increase revenue for the facility. The stugy in Nepal reveal that even cost-sharing strategies improved the appropriate prescription, it was also led to more policy pharmacy and overprescribing.

3) Type of outcomes used in the Intervention research related to RDU campaign.

The main purpose of the RDU intervention is to change on irrational drug use problem. The researchers assess the effectiveness of invention by monitoring changes of outcomes. These outcomes can be categorized into type of change as explain below:

3.1) Change in drug utilization pattern.

Drug utilization pattern is widely used as a primary outcome in many intervention studies. The research will determine an appropriate use of medicine before and after program implementation. These changes are classified in many groups of outcome

3.1.1) Outcome of change in quantity of drug use

This outcome was measure on the defined daily dose (DDD) and sale change. An intervention study in Singapore assessed the impact of a prospective audit and feedback antimicrobial stewardship program (ASP) on antibiotic prescription and resistance trend in a hematology-oncology unit in a university hospital using interrupted time-series study (20). The researcher used DDD per 100 inpatient-day of ASP-audited antibiotics as a primary outcome, while

DDD/100 inpatient-days of all evaluated antibiotics was used as a secondary outcome. The result of the study shows that there was a reducing trend in prescription in both audited and all evaluated antibiotic after intervention. Another study in Chinese teaching hospital also monitored antibacterial stewardship intervention to determine as correlation between antibacterial usage and resistance of bacterial isolated from inpatients (10). The researcher also uses DDD per 100 patients day as the main outcome of the study. Another study using antibiotic sale data as the proxy for drug utilization outcome was conducted in Belgium from year 2000 - 2002. They researcher monitored the effectiveness of 3-months public campaigns to reduce overuse or misuse antibiotics in the community. The intervention implemented were booklets, handouts, posters, prime-time television spots and Websites. The DDD was convert from sale data derive from Intercontinental Marketing Service (IMS-Health) which covered 80.1% of all community pharmacies and 76.1% of the population. The results shown that antibiotics sale decrease at 11.7 % in year 2000 – 2001 and 9.6% (in DDD) in year 2001 – 2002 after 3-month campaign period comparing with the same period in year 1999 – 2000. Overall, the yearly antibiotics sale decreased at 5.3% (in DDDs) between year 2000 and year 2002 (21).

3.1.2) Outcome of change in drug expenditure.

Not only has the researcher interested in how drug was prescribed in term of usage, but also in term of the drug expenditure. In Canada study present that the administrative restriction has effect on change of antibiotic prescription and expenditure (22). Time series analysis intervention study in the U.S. used quarterly expenditure data from Medicaid pharmacy claims database to monitor impact of various inventions on change in drug expenditure of six antidepressant agents(23).

3.1.3) Outcome of change in percentage of adherence to the guideline

The percentage of adherence to the guideline has been recommend by WHO as a complementary drug use indicator for irrational medicine use. The multi-level regression analysis in Sweden evaluated the effect of a decentralized drug budget on the lipid-lowering drug use summarized that the increase in the percentage of prescription of recommended statin (or adherence

to guideline) after implemented of interventions (24). A quasi-experimental study in Canada also us the proportion of appropriate prescription to assess the impact of a retrospective and concurrent Drug Utilization Review (DUR) program on cisapride prescriptions using interrupted time series analysis (25).

3.2) Change in clinical outcome and quality of life

These outcome measure regarding to antibacterial resistance, hospital stay, or the quality of life indicators. A study in Chinese teaching hospital monitored antibacterial stewardship intervention to determine as correlation between antibacterial usage and resistance of bacterial isolated from inpatients (10). The study revealed that the decrease use of antibacterial was associate with the improved on bacterial resistance without reduction in quality indicators. The education intervention study targeted on the internist who provided the medical care to long term care (LTC) show the impressive result on the improvement of quality of care that comply with guideline and reduction in antimicrobial usage (18). The researcher selected antimicrobial starts and antimicrobial day per 1000 patient-day as the main outcome of the study.

3.3) Change in drug management system

In term of drug management system, there are four perspective of drug management system cycle we should consider: selection, procurement, distribution and utilization. Studies on the utilization have been mentioned in the prior session. Therefore, this session will emphasize the studies on the rational drug use intervention toward change in selection, procurement and distribution. The qualitative survey study interview pharmacist who had works related to a Pharmacy and Therapeutics Committee (PTC) summarized that PTC's practical policies have been establish to promote RDU (26). Their role is related with drug selection and procurement which involved planning on cost-effective hospital formulary and inventory controls, developing drug system policies and clinical guidelines, and utilizing information of drug use evaluation (DUE), medication errors (ME) and adverse drug reactions (ADR) (26).

Regarding to studies concerned with change in distribution process, the internal study surveyed the opinion of healthcare workers who joined the training program to assess the successes of the RDU project. They response that there is a transition of labeling and intended label after participating program and also report high satisfaction level of toward program (27) . The cross-sectional descriptive study evaluates the outcome of pharmaceutical care service in rational drug use suggest that the clinical pharmacist was one tool to successes of rational drug use in patient care setting. Their role involved providing pharmaceutical care service, promoting effective use of drug utilization by audit and feedback inappropriate prescriptions, increasing patient safety by preventing adverse drug event, encouraging patient compliance and reduce drug cost from medication reconciliation process (28).

3.4) Change in Personnel's knowledge, attitude, and behaviors.

Regarding to the attitude and behavior outcome, most studies concern on the attitude of healthcare providers toward the intervention such as satisfaction level or knowledge improvement. The descriptive study that interviewed the pharmacist, doctors, and nurses responded that they were satisfied with the pharmaceutical care service provided by pharmacist (28). They also advised that the service is beneficial to the patients on rational use of drug perspective such as patients can use the drug properly, patient did not receive unnecessary drug or duplicate items, prevent antimicrobial resistance, and patients received quality and cost-effective drug. Another survey study interview five pharmacist who had works relate to PTC in public hospitals in lower northern part of Thailand revealed that three out of five pharmacists have satisfied with the PTCs while other two pharmacist feel that there are some obstacles which make the policies not be successfully adhere (26). The quasi-experimental pre-post study of antibiotics smart use project conducted in pilot hospitals and primary health care centers in Saraburi province reported the increase knowledge and attitude of prescribers (15). Moreover, the patients perceived health improvement and satisfied with the treatment outcome.

4) Methodology which are related with Time Series Analysis

Interrupted Time Series (ITS) is a quasi-experimental research design that is suitable for the assessment of the effectiveness of pharmacy interventions or policy interventions. It is common in the real-world situation when the data cannot be randomized into study and control group, for example, a nationwide mass media campaign to reduce prescribing of antibiotics for common cold cannot suitably be controlled (15). A review on intervention research in rational use of drugs suggested ITS study design to compare drug use in experimental group (post-intervention) with no intervention group (pre-intervention) (19). ITS study involves a longitudinal data which data were collected at equally space intervals of time (29). ARIMA models require a long time-series data, or at least 100 points, to be consider robustness of the analysis. The purpose of Time Series Analysis is to monitor the secular trend which was affected by the policy intervention. ITS is suitable to control for the maturation effect in the study. Due to outcome characteristics that are: non-stationary, auto-correlation and seasonality, it is not appropriate to measure the outcomes as in the cross-sectional study design (30). In addition, policy change requires gradually time for learning effect to observe the change in the outcome. ITS study result is useful for the policy-maker to launch the health policy that suitable for country's need. The systematic review of ITS suggest an appropriate two statistical methods to reduce bias on identifying invention effect: time series segmented regression techniques, or autoregressive integrated moving average (ARIMA) model building (31).

The study of U.S. Medicaid data in 2011 using interrupted time-series intervention analysis study identified how 5 categories of 29 interventions effect on expenditure of six antidepressants (23). The researcher using ARIMA modeling approach to compare as forecast from model with a holdout sample from of actual expenditure. Another study conducted in UK using segmented regression analysis to determine the effect of alert antibiotic intervention in three outcomes: change in level immediately after the intervention, difference between pre-intervention and post intervention slope, and the estimation of monthly average intervention effect after intervention (32). This study using segmented regression analysis to identify the effect size of changes in the outcome.

2.4 RDU hospital: PLEASE program

Thailand's national drug policy released in 2011 determined that Rational Use of Medicine (RUM) is a key element for national drug system development strategy from year 2012 to 2016. The program "Rational Drug Use (RDU) Hospital: PLEASE" had first launched in March 2015. The main purpose of the program is to promote and maintain the culture of RUM. The bureau of Drug Control, Food and Drug Administration (FDA), under the ministry of public health, is the main government body acting as the central administrator. Once the hospital joins the program, they will receive the RDU hospital operation manual to follow and required to submit the key performance indicators according to PLEASE. These compose of six operational keys which are the mechanism for the success of the rational use of medicine in RDU hospital (33, 34). These key indicators are: 1) Pharmacy and therapeutics Committee strengthening, 2) Labeling and leaflet for patient information, 3) Essential RDU tool, 4) Awareness for RDU principle among health personal and patients, 5) Special population care, 6) Ethics in prescription.

These keys are relevance with WHO's strategies to promote rational drug use (2002). The indicator in RDU tool are similar to WHO medicine indicator with some adjustment to specific objective in Thai medication use practice. The role and responsibility of the participated RDU hospital are as described below:

PLEASE key

There are six operational keys in PLEASE that participated RDU hospital has to follow:

1) Pharmacy and Therapeutics Committee (PTC) competency.
2) Labeling and leaflet for patient information
3) Essential RDU tool
4) Awareness for RDU principle among health personal and patients.
5) Special population care
6) Ethics in prescription.

2.5 RDU clinic project

The success of PLEASE hospital program lead National Health Security Office (NHSO) to expand the rational drug use campaign into the health service unit under controlling of NHSO. Regarding to health benefit schemed in Thailand, NHSO is responsible to manage Universal Health Coverage (UHC) for Thai citizen who are not insured by other government health insurance schemes such as the civil servants medical benefit scheme (CSMBS) for civil servants and their dependents, the Social Security Scheme (SSS) providing health care for employees of all private firms, or other state enterprise schemes or by the local government schemes in comparative to the CSMBS (35). In 2014, there are around 48.31 million of Thai citizens registered for UHC (35). All budgets for implementing the UHC in Thailand have been supplied by the government through the universal coverage scheme (UCS) (35). There are total of 13 branches of the NHSO regional offices nationwide. NHSO region 13 (NHSO-Bangkok) is the controlling office of budgeting to health service units in Bangkok. In September 2014, approximately 3.93 million citizens were register under NHSO-Bangkok (12). Health service facility under UCS received capitation rate around 2,895 Bath per head from NHSO in 2014 (35). The Network of Rational Drug Use Clinic (RDU Clinic) campaign implemented by NHSO-Bangkok since July 2015. NHSO-Bangkok is selected community caring clinics, which are the private clinic in Bangkok receiving funding from NHSO-Bangkok, as initial target group due to 3 reasons.

1) They contribute most of population of health service units (45.96%),

2) An uncomplicated organization structure contains small number of health personal (at least 1 doctor, 1 pharmacist and 2 nurse) which facilitate the co-operation and would be helping for program achievement.

3) The community care clinics are closely connected with local population in the area which suitable for aggressive operation for expanding to wider level.

The purpose of the project is to create awareness of irrational drug use problems, develop drug management system and improve quality of healthcare services among participated clinics.

The intervention composed of various measures such as education measure, managerial intervention, regulatory intervention, and financial incentive as explain below.

Table 1 List of interventions and content in each intervention

No	Intervention from NHSO toward Clinics	Content
1	**Education measure**	1) Training on "National Strategic plan on RDU"
		2) Training on "PTC strengthening & PTC election"
		3) Training on "ASU in URI, Acute diarrhea & wound"
		4) Training on "Labeling adjustment & Software management"
		5) Training on "RDU in NCD & Evidence base formulary in Primary care unit"
		6) Printed material: Manual, handout, poster
		7) Media based approach: DVD, social media
2	**Managerial intervention**	1) Standard Treatment Guideline
		2) Labelling adjustment
		3) Steering committee
		4) PTC establishment
		5) Reviewing drug listing
3	**Financial incentive**	Quality Outcome Framework (QOF) plan for payment from NHSO

1) Education measure

1.1) Training program. NHSO Bangkok organized five training programs to the 162 clinics during the course of the project. Each training covers the different topic concerning rational drug use in primary care clinic. The detail of each training is;

Training 1: conducted on 15 June 2015 covered the topic on the concept of rational drug use in clinic and determined the importance of rational drug use for national drug system development strategy for year 2012-2016. In this meeting, there were 100 attendees from community care clinic.

Training 2: conducted on 5 August 2015. There were 100 representatives from community care clinic attend at this meeting. This training focusing on the importance of PTC and there was an election of PTC which compose of 15 PTC committee. The PTC role is to monitor and promote rational use of medicine to ensure the safety and effective use of medicines. In this meeting, total of 162 clinics agree to participate in the project.

Training 3: was organized twice on 5 and 29 September 2015 on the topic on the concept of Antibiotics Smart Use. In these meeting, total of 211 attendee participated in the training.

Training 4: conducted on 19 November 2015 on the topic of the appropriated labeling and intended label in private institutions. The guideline for standard labeling in 13 drug group have been introduced. There were 210 participants in this meeting.

Training 5: was organized twice on 29 and 31 August 2016 on the topic of rational drug use in Non-communicable disease (NCD) and establish the list and de-list drug formulary for primary care unit. In these meeting, total of 470 attendees from 162 clinics participated in the training.

1.2 Printed Material

Printed materials, handouts and manuals had been distributed to attendee over during every training program relate with each topic. These materials compose of manual, poster, leaflet, and desk calendars which related with rational drug use, antibiotics smart use and steroid. The list as of manual that was distributed are:

1) Rational Drug Use Hospital Manual copyrights by Thai Food and Drug Administration.
2) Rational Drug Use in Primary Care printed by NHSO.

3) Recommendation on labeling and intended label in Rational Drug Use printed by NHSO

In addition, during the training the NHSO staff also present the roll-up (which was borrowed from Thai FDA) provide information on Rational Drug Use, Antibiotics Smart Use and to promote the rational drug use throughout the event. Moreover, there are an example of labeling and intended label have been provided to the attendee during the fourth training.

1.3 Media based approach.

DVD education media on Rational Drug Use and Antibiotics Smart Use had been distributed to the attendee in every training event. The NHSO training organizer also develop social media such as Facebook page and Line group and invited all participants to join in order to received updated information on Rational Drug Use concept. The page organizer also provides information about how to download free printed material from Thai FDA website.

2) Managerial Intervention.

2.1) Standard Treatment Guideline

According to the "Rational Drug Use in Primary Care" manual, NHSO had developed standard treatment guideline for 8 diseases (diabetes mellitus type II, hypertension, hyperlipidemia/dyslipidemia, Upper Respiratory Infection, Acute Bronchitis, Acute diarrhea/Acute Gastroenteritis/Food poisoning, Antibiotic prophylaxis in simple wound, antibiotic prophylaxis in vagina delivery, and common) cold. Moreover, the recommendation on 12 drug group have been advised in the manual which are: allopurinol, antihistamine, azithromycin & clarithromycin, cinnarizine & flunarizine, colchicine, domperidone, ketoconazole, nicergoline & ergot derivatives, NSAID & coxib, paracetamol, serratiopetidase enzyme and antibiotic component in sore throat lozenge.

2.2) Labelling adjustment

During the fourth training, the NHSO had provide the example of the appropriate label and intended label in pilot 13 drugs (paracetamol, parcetamol with orphenadrine, ibuprofen, cetirizine, amoxicillin, domperidone, enalapril, amlodipine, metformin, sulfonylurea, simvastatin, colcicine,

and allopurinol) and advised every clinic to adjust their labeling in clinic. The purpose of the labeling is to inform the patient the appropriate use of medicine. After the training, NHSO also summarized the health personal's option and feedback on the new labeling from all 162 clinic who participated the project.

2.3) Steering committee

The NHSO had establish steering committee for RDU clinic to 6 July 2015. The role of this committed is to develop an operational procedure, standard treatment guideline and drive rational drug use project and monitor the effectiveness of the project. This committee compose of 13 staffs representing the stakeholder involve with the project which are 1 chairman, 4 staff (owner or pharmacists) from community care clinic, 1 clinical pharmacist, 1 hospital pharmacist, 2 public representatives, and 4 NHSO personal.

2.4) PTC establishment

On the second training, there was an election of PTC for the project. The PTC is responsible for develop the drug formulary list for clinic based on rational drug use concept, monitoring efficacy and safety of drug use in clinics to ensure the quality of drug use in the community care clinic which participated in the project. There was 15 committee representing community care clinic health personal which compose of 7 doctors, 7 pharmacists and 1 nurse. The committee first meeting was on 7 October 2015. The result of this meeting is Evidence-based Clinic Formulary in the community care clinic which means enlisting or relisting from drug formulary. Also, the PTC have been released the standard label and intended label in pilot 13 drugs for the clinic to adjust for their own use.

2.5) Reviewing drug listing

According to the first PTC meeting, the Evidence-Base Clinic Formulary have been released as the guidance for each clinic to follow based on treatment of choice. The list of that of 12 non-essential drug group that should delete from clinic also explain in the Rational Drug Use in Primary Care. The example of 12 drug groups are; eperisone, tolperisone, ketoconazole, diclofenac,

nimesulide, piroxicam, etoricoxib, nicergoline, cinnarizine, flunarizine, Antibiotic lozenge (Neomycin sulfate + Bacitracin + Amylocaine). However, the decision to delete or include the drug items into their clinic formulary is voluntary in each clinic.

3) Financial incentive

NHSO have announce the new Quality and Outcome framework (QOF) which related with rational drug use concept in October 2016. The QOF is the guideline of NHSO reimbursement to health care unit on quality of service performance funding from Outpatient service and Health promotion service capitation in UCS. The evaluation for reimbursement was calculated from Key Performance Indicator (KPI). The QOF plan identify the reimbursement twice a year in January and July. There are six main KPI that NSHO will assess on health care unit which are: percentage of patient who have been screening on diabetes mellitus, percentage of patient who have been screening on hypertension, percentage of pregnancy women who have been access to clinic with the first trimester (12 weeks), percentage of women aged 30 - 60 who have been screening on cervical cancer, percentage of responsible use of antibiotic in Acute Diarrhea and Respiratory Infection and The reduction of hospitalized patient in diseases that should be treated at OPD level such as ACSC: (Ambulatory Care Sensitive Condition), Epilepsy, COPD, Asthma, Diabetes Mellitus and Hypertension.

2.6 Summary of Gap in the literature

Network of Rational Drug Use clinic is new intervention introduced to community care clinic in 2015. The purpose of intervention is to promote rational drug use in the doctors, healthcare personal and Thai population. The intervention is a continuous process that dynamic over the time. It composes of 3 interventions which work as a hold unit to drive the success of rational drug use. Since there is limitation of research assessing the success of RDU campaign using Interrupted Time Series analysis, the purpose of the study is to evaluate and monitor the program effectiveness from NHSO medical claim database and assess the change in drug management system and find the health personal's opinion on project for improvement of future project implementation.

CHAPTER III

Methodology

The research objectives were to assess the effects of "Rational Drug Use Clinic", or RDU clinic project, which was regarded as the intervention of the study, at the community care clinics level on two objectives 1) assessing the quality of medicine use outcome; and 2) assessing the change in drug management and describe health personnel's attitudes toward RDU clinic project. The study was divided into 2 parts for answering each objective.

Part I: Assessing the quality of medicine use outcomes by analyzing data from NHSO claimed database which compose of 162 clinics which joined the project since August 2015.

Part II: Assessing the change in drug management and describing health personnel's attitudes toward RDU clinic project by interviewing the health personal such as physicians, pharmacists, nurse or public health staff from the selected community care clinics to describe the change in drug management process and their opinion on the project intervention.

Table 2 Operational definitions

Evaluation construct	**Meaning**
RDU clinic project	"The Network of Rational Drug Use Clinic" campaign organized by NHSO region 13 which started in August 2015. It composed of three major interventions; 1) Educational measure 2) Managerial intervention 3) Financial incentive
Community care clinic	The privately own healthcare facility that is primarily focused on the care of outpatient within local community in Bangkok and receive budget from NHSO's UC scheme.

Evaluation construct	**Meaning**
Medicine use outcome	The quantitative measurement outcome on the improvement of medicines use. There are five outcomes of interest: 1) The amount of antibiotic utilization determines by DDD 2) Percentage of encounters with antibiotics prescribed. 3) Percentage of prescription that adhere to guideline in two specific diseases (upper respiratory infection and acute diarrhea). 4) Average medicines cost per encounter. 5) Percentage of drug cost spent on Antibiotics.
Financial outcome	NHSO's financial payment to the clinic according to Key Performance Indicators (KPI) in the Quality and Outcome Framework (QOF).
Health personal's knowledge and attitude	Descriptive qualitative outcomes on the health personal's opinion after the clinic participated in the project. Outcomes which will be described were: 1) Knowledge on related clinical practice guidelines 2) The benefits and the obstacles of the project. 3) The opinion of patient feedback toward project in health personal's perspectives
Drug management process	Descriptive qualitative outcomes of change in drug management process. The outcomes included: 1) Clinic Pharmacy and Therapeutic (PTC) activity. 2) Training activity 3) Changing in labeling 4) Revision on drug formulary 5) Regulatory measure

Part I study

Assessing the effect of the intervention on the quality of drug use.

Research Design

Quasi-experimental study using interrupted time series intervention analysis.

Research Hypotheses

Hypothesis 1: After the implementation of RDU clinic project, antibiotics utilization in the community care clinics would significantly decrease if the project was effective.

Hypothesis 2: After the implementation of RDU clinic project, the percentage of encounters with antibiotics prescribed in community care clinic would significantly decrease if the project was effective.

Hypothesis 3: There is a significant increase in the percentage of prescription that adhere to guideline in two specific diseases (Respiratory Infection and Acute Diarrhea) in the community care clinics after the implementation of RDU clinic project.

Hypothesis 4: There is a significant decrease in the average medicines cost per encounter in the community care clinics after the implementation of RDU clinic project.

Hypothesis 5: There is a significant decrease in the percentage of drug cost spent on antibiotics in the community care clinics after the implementation of RDU clinic project.

Setting:

The intervention was implemented in 162 community care clinics in Bangkok which received capitation from NHSO. NHSO-Bangkok manage Universal Health Coverage Scheme for health service facilities in Bangkok area. The community care clinics was selected by NHSO Bangkok as an initial target group for RDU clinic project due to 3 reasons: 1) They contribute to most of population of health service units (45.96%); 2) An uncomplicated organization structure containing small number of health personal (at least 1 doctor, 1 pharmacist and 2 nurse) which were convenient for the co-operation and would facilitate to the

program achievement; 3) The community care clinics were closely connected with local population in the area.

Data source:

OPBKK-Claim is the database maintained by NHSO-Bangkok for the purpose of reimbursement. Every medical service unit used HOS-OS software to submit outpatient visit data into the system on a daily basis. All of visiting data from the community care clinics has been input into the system since October 2013 until now.

Unit of analysis: the weekly aggregated prescription data from all participated RDU clinic project.

Population: Total prescriptions that was retrospective extracted from OPPBKK claim database during October 2013 to September 2019. This was equal to six government fiscal budgeting years since Thai government determine the beginning of fiscal budgeting year at October of each year.

Sample: All prescriptions from participated RDU clinics

Inclusion criteria:

1) The prescription from the community care clinic joining RDU project since the beginning of RDU project until the end of the study period.
2) In order to limit the data duplication, the prescription was extracted from only main diagnosis code (with or without co-diagnosis) to count for one prescription.

Exclusion criteria: The prescription data that was incomplete from database, such as error on drug coding, or cannot classified into drug group, or the Thai Medicinal Terminology (TMT) data were not available.

Sample size: Sample size was not calculated in the study due to all prescriptions data was collected from OPBKK-Claim database to analyze by interrupted time series analysis.

Intervention

There were three major interventions implemented by NHSO-Bangkok 1) Education intervention, 2) Managerial intervention, and 3) Financial Intervention. Table 3 provided the details of each intervention. Since there were data limitations to determine the intervention date of managerial interventions in each clinic, there were only two major interventions used as the intervention in the study: Education Intervention and Financing incentive.

For Education intervention, the education period started from August 2015 to September 2016 which was determined as Week 32 Year 2015 to Week 36 Year 2016. These composed of five trainings, disseminated printed material and educational media.. NHSO-Bangkok organized five training programs to the 162 clinics. Each training covered the different topics concerning rational drug use in primary care clinic. Since the education on Antibiotics Smart Use was implemented twice in September 5 and 29, 2015 (week 36, 39) to cover participants from all clinics. The researcher should allowed for a delay effect of intervention, so it was decided to use Week 41 Year 2015 as the index date of education intervention in the study.

For financial incentive, NHSO have announced the new Quality and Outcome framework (QOF) on rational drug use (RDU) concept in October 30, 2016 (on the fiscal budget year 2017). The concept of NHSO's QOF was derived from Britain's Pay for Performance (P4P) or Value Based Purchasing concept that the purchaser set payment criteria based on quality indicators as the incentive for healthcare service provider to provide quality and accountability services in primary healthcare (36). The QOF is the guideline for NHSO payment to health care unit on quality of service performance funding from out-patient service and health promotion service bugeteary part in UCS. The amount of incentives was calculated from the health care unit's performances according to Key Performance Indicator (KPI). NHSO set the criteria for QOF on the percentage of prescription with ATBs in Respiratory Infection (RI) and Acute Diarrhea (AD) treatment either in primary diagnosis or co-diagnosis as KPI for RDU (RDU-KPI). In fiscal budget

year 2017, the criteria for marking community caring clinics on RDU-KPI was evaluated from the percentage of prescription of antibiotics in RI and AD into 4 levels: (37)

1) If the percentage of prescription with ATBs was less than 20.00, clinic receive 5 marks
2) If the percentage of prescription with ATBs was between 20.01 – 30.00, clinic receive 3 marks
3) If the percentage of prescription with ATBs was between 30.01 – 40.00, clinic receive 1 marks
4) If the percentage of prescription with ATBs was is more than 40.01, clinic received 0 marks

NHSO-Bangkok identified disease in RI and AD by International Classification of Diseases 10 (ICD10) diagnosis of disease. The list of ICD10 codes in RI and AD used for calculation RDU-KPI were;

- RI (Respiratory Infection), means ICD10 code "B053, J00, J010, J011, J012, J013, J014, J018, J019, J020, J029, J030, J038, J039, J040, J041, J042, J050, J051, J060, J068, J069, J101, J111, J200, J201, J202, J203, J204, J205, J206, J207, J208, J209, J210, J218, J219, H650, H651, H659, H660, H664, H669, H670, H671, H678, H720, H721, H722, H728, H729".
- AD (Acute diarrhea), means ICD10 code "A000, A001, A009, A020, A030, A031, A032, A033, A038, A039, A040, A041, A042, A043, A044, A045, A046, A047, A048, A049, A050, A053, A054, A059, A080, A081, A082, A083, A084, A085, A09, A090, A099, K521, K528, K529".

NHSO-Bangkok calculated the payment amount based on each year QOF global budget, weighted KPI, mark and number of population each clinic received on capitation (36). The detail of payment was descriptive analyzed in Part II phase I. NHSO – Bangkok paid on QOF once yearly in each fiscal budget year. The first payment, utilized the budget from fiscal year 2018, was calculated based on 12-months period during April 2017 to

March 2018 (which covered 6 months from fiscal year 2017 to 6 months of fiscal year 2018). The actual first payment date occurred in August 2018 which was 21 months after the first criteria announcement in October 2016. The NHSO-Bangkok adjusted the marking criteria in fiscal budget year 2019. Table 4 illustrated the criteria for QOF payment in 2 fiscal budget years. Since the delay of payment and the change of criteria on the second year, we decided to identify the first date of criteria announcement at 30 October 2016, or Week 44 Year 2016, as the intervention date for financial incentive intervention analysis.

Table 3 List of interventions implemented by NHSO-Bangkok and contents in each intervention

Intervention	Contents	Date	Number of Participants
Education measure	1) Training 1 on "National Strategic plan on RDU"	15 June 2015	100
	2) Training 2 on "PTC strengthening & PTC election" Total of 162 clinics sign an agreement to participate in the project.	5 August 2015	100
	3) Training 3 on "Antibiotic Smart Use (ASU) in Urinary Tract Infection (URI), Acute diarrhea (AD) & wound"	5 and 29 September 2015	211
	4) Training 4 on "Labeling adjustment & Software management"	19 November 2015	210
	5) Training 5 on "RDU in NCD & Evidence base formulary in Primary care unit"	29 and 31 August 2016	470
	6) Printed material: Manual, handout, Poster (Manual list: Rational Drug Use Hospital Manual, Rational Drug Use in Primary Care, Recommendation on labeling and intended label in Rational Drug Use)	During the training	All attendees
	7) Media based approach: social media such as Facebook page and Line, Thai FDA website	Continuous updated	Voluntary participate

Intervention	Contents	Date	Number of Participants
Managerial intervention (not further analyzed)	1) Standard Treatment Guideline launch	7 October 2015	n/a
	2) Labelling adjustment	19 November 2015	n/a
	3) Steering committee establishment	6 July 2015	13
	4) PTC establishment	5 August 2015	15
	5) Reviewing drug listing	7 October 2015	n/a
Financial incentive	Quality Outcome Framework (QOF) plan for payment from NHSO	30 October 2016	All clinics

Table 4 NHSO's marking criteria for QOF payment of 2 fiscal years, 2018 - 2019

Fiscal Budget Year 2018		Fiscal Budget Year 2019	
Percentage of prescriptions with antibiotics in RI and AD	Mark	Percentage of prescriptions with antibiotics in RI and AD	Mark
=< 20	5	= < 20	5
20.01-30.00	3	> 20.0 - 22.5	4
		>22.5 - 25.0	3
		> 25.0 - 27.5	2
		>27.5 - 30.0	1
30.01 -40.00	1	>30.0	0
> = 40.01	0		

Selection of the drugs

Antibiotics utilization in RI and AD was selected as the target drug for evaluation due according to the criteria of RDU - KPI for payment in QOF from NHSO. The ATBs in the study was identified by WHO drug classification system for Anatomical Therapeutic Chemical (ATC) code level J01 (ATC-J01) version 2016 (38). ATC-J01 means antibacterials for systemic use.

Drug data cleaning

Drug data from the database were collected as TMT code. TMT code is the terminological system of drugs that are used in Thailand healthcare system. The terminology

standardizes drug information attributes with identifier and drug concepts relationships which are sufficient for uniquely identify drug (medicine) entity, necessary for clinical care and reimbursement use in Thailand healthcare services (39). ACT-J01 were matched with TMT code by data dictionary provided from "Thai Health Information Standards Development Center" (THIS). However, TMT code was implemented as a standard drug code for all community care clinics from October 2015 onward. Before this period, every clinic used the working drug code as drug coding data and this drug data cannot combined for the analysis purpose. Even some clinics (89 clinics) implemented TMT into their system before this period, there were nearly half of the clinics (70 clinics) that TMT drug code data was missing before October 2015. Using only TMT drug data for the analysis would result in missing substantial amount of drug data in the pre-intervention period. Therefore, ATBs without TMT code were semi-manually coded by drug name using Tableau® software data management program. This ATBs drug group were used for analysis of hypothesis 2 to 5, where the analysis for hypothesis 1 using TMT code as ATBs drug identification. Data was aggregated in weekly for analysis purpose. To analyse the seasonal variation of time series data, the seasonal data need to expressed as 52 weeks per year. The equally interval 52 observations was identify as one cycle. However, due to the data was extracted in weekly separate by year result in some obersevation dose not meet 7 days per week (for example number of days at the last week (Week 53) in year 2013 were 3 days and number of day at Week 1 Year 2014 were counted as 4 days). Therefore, we combined data in Week 1 in each with the data of Week 53 from the previous year and recode the data as Week 1 of that year. Except for the data in Week 53 Year 2016 that account as 7 days, the data in Week 1 Year 2017 was calculated from the average data of Week 53 Year 2016 with data from Week 1 Year 2017.

Outcomes

The quality of drug use outcome was measured according to WHO's drug use indicators regarding to prescribing indicator and complementary medicine use indicators (14). The selection of indicators based on two criterion; 1) The availability of data from the

database; 2) The indicators that related with utilization of antibiotics. Therefore, five outcome variables were analyzed including:

1) The amount of antibiotics (ATC code J01) utilization before and after intervention. Antibiotics consumption was expressed as Defined Daily Dose (DDD) per 1000 patient day (DDD/1000 Pts), regarding to WHO's ATC/DDD classification version 2016 (38). The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. Since the limitation of drug data code due to missing of TMT code before October 2015, only the group of 89 clinics that TMT data available were selected for the analysis. The period of analysis start from Week 10 Year 2015 onward. The data from the rest of 70 clinics was assumed to have a similar characteristics with these 89 clinics. The formula for calculation in each weekly aggregated data is;

$$\text{DDDs/1000 people/week} = \frac{\text{amount of drug (mg) prescribed in 1 week}}{\text{DDD (mg)} \; x \; \text{number of people} \; x \; \text{number of days}} \; x \; 1000$$

Where;

amount of drug (mg) = strength (mg) x quantity (tablets, capsule, bottle, or vials)

DDD (mg) = standard DDD from WHO's ATC/DDD classification version 2016

Number of people = population registered in each clinics at 1 October each year (the first date of fiscal budget year)

Number of days = 7 days

2) Percentage of encounters with Antibiotics (ATC code J01) prescribed. The formula for calculation in each weekly aggregated data is

$$= \frac{\text{Number of encounters during which an antibiotic}}{\text{Total number of encounters surveyed}} \; x \; 100$$

3. Percentage of antibiotics (ATC code J01) prescriptions adherence with guidelines in RI and AD disease. The adherence means the prescriptions that was diagnosed with RI and AD theat was not prescribed with Antibiotics. The formula for calculation in each weekly aggregated data is;

$$= \frac{\text{number of prescription in RI and AD} - \text{number of prescriptions with antibiotics in RI and AD}}{\text{number of prescription in RI and AD}} \; x\; 100$$

Where;

Number of prescription in RI and AD = Weekly aggregate amount of prescriptions in Respiratory Infection , and Acute Diarrhea, either primary diagnosis or co-diagnosis. The RI and AD was determine by ICD10 code as described in the intervention section for NHSO's RDU-KPI calculation

4. Average medicines cost per encounter. Total medicine cost data was calculated from total reimbursement price per prescription which is the actual cost of payer paid to each clinic. The formula for calculation in each weekly aggregated data is;

$$= \frac{\text{Total medicine cost precribed in one week}}{\text{Number of prescriptions in one week}}$$

5. Percentage of medicine costs spent on antibiotics (ATC code J01). Total medicine cost data was calculated from total reimbursement price per prescription which is the actual cost of payer paid to each clinic. The formula for calculation in each weekly aggregated data is;

$$= \frac{\text{Cost of antibiotics prescribed in one week}}{\text{Total medicine cost prescribed one week}} \text{ x } 100$$

During the period of study, there were 3 clinics resigned from the NHSO-Bangkok agreement in October 2017. Therefore, 159 Clinics were selected for the analysis of hypothesis 2 to 5. However, the analysis for hypothesis 1 required TMT code as drug identification for DDDs calculation and there was some clinics that TMT code data were not available befor October 2015. In order of limit missing drug data during pre-

intervention period, the researcher grouped the clinics which TMT data were available during Week 10 to Week 39 Year 2015 using Tableau® software data management program. There were 89 clinic that TMT code data were available Thererfore, the analysis for Hypothesis 1 were conducted in only 89 clinics and the period of study start from Week 10 Year 2015 onward

Total of 10 events were examined using intervention analysis. A list of the Intervention tested and the outcome variables analyzed shown in Table 5.

Table 5 Inventions tested in the study

Outcome variables	Number of Clinics	Event type	Dummy variable	Intervention date	Number of Observations
Antibiotics utilization	89	Education	Edu	Week 41, Year 2015	238
		Financing	Fin	Week 44, Year 2016	
Percentage of encounters with antibiotics	159	Education	Edu	Week 41, Year 2015	312
		Financing	Fin	Week 44, Year 2016	
Percentage of prescriptions of antibiotics adherence with guidelines in RI and AD	159	Education	Edu	Week 41, Year 2015	312
		Financing	Fin	Week 44, Year 2016	
Average medicines cost per encounter	159	Education	Edu	Week 41, Year 2015	312
		Financing	Fin	Week 44, Year 2016	
Percentage of drug costs spent on antibiotics	159	Education	Edu	Week 32, Year 2015	312
		Financing	Fin	Week 36, Year 2016	

We also conducted subgroup analysis to determine different effects of the intervention on the different performance clinic. The average ATBs utililiztion rates in RI and AD were calculated from 4 months pre-intervention period from Week 23 to Week 40, 2015. Using pre-intervention period performance for grouping the clinics as baseline performane, so it could determined wheter the intervention had a different effect in the different group of clinic. Rank 1 to Rank 3 were assigned to each clinic according to the percentages of prescription with ATBs. Table 6 explained the assigned rank for each clinics and the number of clinics included. The grouping critera were; Rank 1, 2, and 3 for

the clinic that had the prescriptions with ATBs in RI and AD less than 50% between 50.01 – 70.00%, and more than 70.01% respectively.

We also conducted subgroup analysis of the prescriptions in RI and AD to identify the different effects of interventions on different group of diseases. According to the outcomes of hypothesis 2 to 5, subgroup analysis in RI and AD by clinic rank was conducted to find the effect of intervention on different group of clinic.

Table 6 Grouping of the clinics according to their performance, the percentage of prescription with ATBs

Percentage of prescriptions with antibiotics in RI and AD during 4-month pre-intervention	Rank	Number of Clinic
< 50%	1	58
50.01-70.00 %	2	48
> 70.01%	3	53

Data collection:

The data was extracted by NHSO-Bangkok Information Technology (IT) staff.. The derived data included patient gender, age, type of health insurance, date and time of visit, prescriptions number, clinic code, number of population in each clinic, drug name, drug working code, Thai Medical Terminology (TMT) code, drug quantity, diagnosis code (ICD10), total drug price in Thai bath (THB), total reimbursement in THB. The personal medical record encrypted by NHSO-Bangkok IT staff.

Data validity

The data source used in the analysis was acquired from NHSO's OPBKK-Claim database. Every clinic had to download HOS-OS software to input daily visit and prescription data. The HOS-OS softwere created medical information and data exchange through web service system into OPBKK-Claim database. The clinic had to submit claim data within each fiscal budget year (from Octerber to September of the following yere) for reimbursement purpose. NHSO-Bangkok has implemented the internal audit system before reimbursement approval.

The incomplete data (such as no ICD10 data missing) would be rejected and the clinic need to re-submit complete data into the system by the end of fiscal year (40). Therefore, it was assumed that database had been validated by NHSO internal audit system. The Quality Assurance (QA) criteria Interuppted Time Series (ITS) analysis suggested by Donnelly stated that it is imperative to the validity of any givent ITS evaluation that the method of data collection for quantifying the outcome of interested has not changed as a consequence of the intervention (41). This imply that the data were valid for ITS analysis.

Data Analysis

The analysis method followed the non-randomized quasi-experimental before-after study with interrupted-time series analysis. Since we could not match an appropriate comparison group for the program intervention, the interrupt time series analysis was the suitable technique to assess the impact of intervention. In times series analysis, the data was collected at multiple time points at equal interval which pre-intervention act as their own control. We would evaluate the RDU project intervention effect in relation to the underlying of autocorrelation and secular trend. Then, we could estimate level and trend in the pre-intervention data segment compare with the estimated changes in level and trend post-intervention (1).

Data was extracted as text file from OPBKK-Claim database, then using Tableau® and Microsoft access® 2003 for database management and data was converted into SPSS datasheet in order to make it applicable to the analytical technique (SPSS software version 22.0, SPSS Co., Ltd, Bangkok, Thailand).

Statistical Analysis

The researcher used Autoregressive Integrated Moving Average (ARIMA) model to estimate coefficient for change in outcome trend and compared slope before and after the intervention in each outcome of interest. ARIMA models is a class of stochastic process model widely used in the social sciences. In 1980, Box and Jenkins introduce the basic model that a time series was a sequence of random shock that passes through a series of filter. ARIMA

structure determine the properties of the output series. (15, 23). There are three basic components to an ARIMA model: Autoregression (AR), diffrencing or intergration (I), and moving-average (MA). All three are based on the simple concept of randon disturbances or shock (42). Between two observations in a series, a disturbance occurs that somehow affects the level of the series. These disturbances can be mathematically described by ARIMA model (42). In its simplest form, an ARIMA model is typically expressed as

ARIMA(p,d,q)

Where;

p = the order of autoregression

d = the order of differncing

q = the order of moving-average involved

These component are used to explain significant correlation found in the autocorrelation (ACF) and partial autocorrelation (PACF) plots and to handle trends.

Autoregression (AR)

In an AR process, each value in a series is a linear fucion of the preceding value or values. The first-order autogressive means the single preceding value is used. An AR(1) or ARIMA (1,0,0) process has the below functional form;

$Value_t = Coefficient * Value_{t-1} + disturbance_t$

where;

$Value_t$ = the value of the series at time t.

Coefficient = a value that indicates how strongly each valule depends on the preceding value. The sign and magnitude of the coefficient are directly related to the sign and magnitude of the partial autocorrelation at lag 1.

$disturbance_t$ = the chance error associated with the series value at time t

Differencing (I)

Differencing make a series stationary. Time series oftern reflect the cumulative effect of some process that is responsible for changes in the level of the series but is not responsible for the level itself. A seires that measures the cumulative effect of something is call intergrated. The models that need to be difference is I(1) or ARIMA (0,1,1).

Moving-average (MA)

In MA process, each value is determined by the weighted average of the cureent disturbance and one more previous disturbances. The ordere of the moving-average process specific how many previous disturbances are averaged into the new value. An MA (1) or ARIMA (0,0,1) has the functional form;

$$Value_t = Coefficient * Value_{t-1} + disturbance_t$$

where;

$Value_t$ = the value of the series at time t.

Coefficient = a term that indicates how strongly each value depends on the preceding disturbance terms. The sign and magnitude of the coefficient are directly related to the sign and magnitude of the autocorrelation at lag 1.

$disturbance_t$ = the chance error associated with the series value at time t

Seasonal Orders

The full notation for an ARIMA model is ARIMA (p,d,q)(P,D,Q), where P, D, Q are the seasonal AR, I, and MA components. Seasonal components work just like their nonseasonal with the skip over the seasonal interval. Our study include seasonal order into the analysis considering 52 week (or 1 year) as one seasonal cycle. If the data had a seasonal order it have of difference by one cycle to have a stationary data.

Times-Series Intervention Analysis

Time series involves decomposition into a trend, seasonal, cyclical, and irregular component which modelling the data by taking into account the autocorrelation among nearby observation. This study utilized ARIMA model which require a long time-series data, or at least 100 points, to be consider robustness of the analysis. The ARIMA modeling compose of four steps (43)

General steps of intervention analysis (43)

1) Identification of ARIMA model for the entired series

Create a sequence of random shocks, representing the multitude of factors producing the variation in the series. These random shocks are assumed to be independent and have zero mean, constant variance and normal distribution. In this step ARIMA mode have been identification. The number of three parameters in the tentative ARIMA model is identified by using the plot of autocorrelation function (ACF) and partial autocorrelation function (PACF). It is required a stationary series for the identification of autoregressive and moving average components. Transformation of differencing, logarithm, or square-root may be used to obtain a stationary series. If the data have a seasonal cycle, it would be differenced by one seasonal order to make data stationary. The model develpement where compare with the theoritcial ACF and PACF functions for the most common AR and MA models (42) (44).

2) Creating a dummy intervention variables.

After identifying a tentative ARIMA model, the intervention period must be identified to assess the significant change of the series. The next step is to create dummy intervention variable. The pre-intervention period will be code as 0, while post-intervention will be coded as 1. There are four possible types of impact from intervention regarding to onset and duration including abrupt and permanent impact, gradual and permanent impact, abrupt and temporary impact and gradual and temporary impact. The dummy intervention variable can be created as a step function or impulse function depend on the impact pattern. Table 5 show the dummy variable for each interventions. Two dummy variables was generated. Variable Edu was

generate for Education intervention determined at Week 41 Year 2015, while Fin variable were generated for Financing intervention determined at Week 44 Year 2016,.

3) Estimation and model diagnosis

This step composes of parameter estimation and testing the significance of the model through the use of residual analysis. The goal is to select a stationary and parsimonious model that has significant coefficients. The diagnosis is to examine how well the model fits the data. The Box-Ljung Q statistic and ACF and PACF plots are commonly use in this stage to verify that residuals are random noise. The step is to continueign develop model until the parsimonious model where identify.

4) Interpreting the coefficient of the dummy intervention variable

This step is to interpret the coefficient of the intervention variable and assess the impact of the intervention. The positive effect means the intervention variable act to increase the level of time series, negative effect means the opposite direction. The significance of the coefficient means there are significance difference between pre- and post- intervention period. All reported *p*-values were two-sided, and *p*-value < 0.05 was considered statistically significant.

Part II study

To describe financial impact, drug management process, and health's personal knowledge and attitude toward the project intervention.

The study composes of 2 phases:

1) Analyze financial impact data derived from the NHSO's payment report and the descriptive statistic was used to describe the effect of intervention on financial outcome.

2) In-depth interview was employed among clinic's staff including physicians, pharmacists, managers, nurses or public health staff from the selected community care clinics to describe the changes in drug management and health personal's knowledge and attitude

toward the projection intervention. Thematic qualitative analysis was used in the qualitative data collected.

Phase I

Research Design: Descriptive study

Data collection: QOF payment data to all 159 clinics according to KPI was derived from NHSO-Bangkok in fiscal year 2018 and 2019.

Measurement Outcome: QOF payment was calculated according to NHSO's marking criteria. The payment amount was calculated based on yearly QOF global budget multiply with weighted KPI and mark and divided by number of population each clinic received on capitation (36, 45). NHSO – Bangkok paid on QOF once yearly for each fiscal budget year. Table 7 illustrated the criteria for QOF payment and weighted KPI in 2 fiscal budget years.

Table 7 NHSO's marking criteria for QOF payment in fiscal budget year 2018

Fiscal Budget Year 2018			Fiscal Budget Year 2019		
Percentage of prescriptions with antibiotics in RI and AD	Mark	Weighted KPI	Percentage of prescriptions with antibiotics in RI and AD	Mark	Weighted KPI
=< 20	5	RI = 5/86 AD = 5/86	=< 20	5	RI = 10/100 AD = 10/100
			>20.0 - 22.5	4	
			>22.5 - 25.0	3	
			> 25.0 - 27.5	2	
20.01-30.00	3		>27.5 - 30.0	1	
30.01 -40.00	1		>30.0	0	
> 40.01	0				

Data analysis: Descriptive statistic was described as the percentage data to compare on marking and amount of payment each clinic receive between fiscal year 2018 and 2019

Phase II

Research Design: Qualitative study design

Study site

The study was conducted in four target clinics which meet with the selection criteria:

1) The top two of clinics whose clinics received the highest mark from NHSO according to QOF mark of ATBs prescriptions in AD and RI.
2) The bottom two of clinics whose clinics received the lowest mark from NHSO according QOF mark of ATBs prescription in AD and RI.
3) The key informants agreed to participate in the study with an informed consent.
4) In case that the prior selected clinics were not willing to participate in the research, the researcher re-selected the next clinics until the number of four clinics were met.

Inclusion criteria

1) Healthcare personel who were working in community care clinic as the role of director, physician, and pharmacist

2) Agreed to participate in research with signed inform consent agreement

Exclusion criteria

Healthcare personal who were working in community care clinic less than 8 hours per week.

Sampling method:

Purposive sampling technique was adopted to select key informants from the target clinics according to the preset criteria. Key informants were selected from four target clinics who had different roles in clinic's operation which composed of:

1) Directors the one who make the decision on clinic management.
2) Physicians of the clinic who practicing at the clinic at least 8 hours per week.
3) Pharmacists or other healthcare personel who was responsible on drug management and dispensing in the clinic.

Since each clinic had the different management system, one of healthcare personel could have several roles within the clinic (for example, director was the same person as physician). In case of dual role person, we selected one more health personel who involved with drug management or the operation at the clinic as a key informant. Therefore, three key informants from each clinic were interviewed. In total, twelve key informants were selected in in the study. All the key informants was received the informed consent to join and described the objectives of the interviews by the researcher. Audio recorder was used according to the permission from each participant. When the recording was allowed the note used instead. The researcher asked for permission before accessing to any related documents. The confidential data was not disclosed.

Measurement Outcome:

The descriptive data within specific RDU clinics after project was implemented. The researcer assessed on two level of outcomes: Change in drug management process and health personel's opinion on the project.

1. Drug management process outcome.

We measured the management process on monitoring and promoting rational use of medicine within clinic. To explain the activity, we interviewed the key informants on the change in clinic management, requested to see the record, or reviewed document of related activity, by using semi-structured interview and data collection forms. The outcomes of interest were;

1.1 Pharmacy and Therapeutic (PTC) activity and performance. Change in PTC activity which resultsed in the improvement of PTC performance. The data collected were:

- Establishment of PTC within the clinic.
- The frequency of PTC meeting.
- Minute of meeting of Pharmacy and Therapeutic Committee and describe the content in the minute of meeting of how it related with improving on rational drug use in clinic.

1.2 In-house training: organizing in-house training to other clinic staff on the concept on rational drug use, request to see the use of material related with rational drug use campaign such as printed media, advertising, brochure, attaching poster in the examination room, and spread rational drug use awareness to the patients

1.3 Monitoring labelling adjustment: (on the 13 drug items.) from sampling medicine that was dispensed from pharmacy department

1.4 Revising on drug formulary: request to on the drug listing accordance to rational drug use guideline which means deleting the inappropriate drug from drug formulary or including the appropriate drug into the drug formulary.

1.5 Regulatory measure: ask whether there any changes in criteria on drug prescription especially in antibiotics use.

2. Health personal knowledge and attitude outcome

After clinic interventions have been implemented, the researcher interviewd the key informants to describe the health personel's opinion on the project in two areas;

1) Health personal's knowledge and opinion:
   - Knowledge on RDU concept project.
   - Attitude toward project whether they were satisfied on the project.
   - Identifying what were the benefits and the obstacles of the project such as the reduction in total healthcare cost, or what support the clinic needed to improve rational drug use from the policy maker. Comparing the feedback from difference group of key informants and explain what are the factors that result in improving prescription to adhere with the treatment guideline.
2) Feedback from patient toward project to health personal such as the cure rate and antibiotics resistance reduction.

The questions were derived as opened-ended type. All of the interview questions ๖๖ (**appendix 1**) tested for quality in term of content validity by three experts in academic field. Content validity was assessed using the Index of Item-Objective Congruence (IOC). The questionaire was modified or deleted when the IOC score were less than 0.5 since they lacked clarity. Reliability value or the internal consistency of questionnaire was not measured in this phase due to limited number of sample size.

Data collection

The process of data collection was conducted according to the follow step;

1) Select the target clinic from derived NHSO data. The reimbursement data and contact information also provided by NSHO. The reimbursement data derived from KPI for reimbursement in Acute Diarrhea and Respiratory Infection.
2) Schedule an appointment with key informants in each target clinic via telephone on their convenient date and time. The researcher contacted the clinics to get an

appointment for interviewing. In case that the prior listed clinic refuses to participate in the research, the next level of clinics was contacted further until the number of 4 clinics are reached

3) Visiting the study site to have a face to face interview with the key informant using semi-structured interview (**appendix 1**) and data collection form. The researcher took note and recorded an audiotape (under permission from the key informant) during the interview. The interview took no later than one hour per one interviewee. Audio recording tape was kept confidentially and was destroyed within one year after the completing of the study.

Data analysis

Descriptive data on the progression of the RDU project campaign was analyzed by thematic analysis. It is the independent qualitative descriptive approach described as a method for identifying, analysising and reporting pattern (themes) within data (46). All notes and transcript were review and coded.The procedure included data managing, reading and memo taking, interpreting and data coding, classify and describing the theme, and drawing conclusion.

Qualitative data on the health personal's opinion toward project was analyzed using thematic analysis. After finishing the interview, the data was extracted. All notes and transcript were reviewed and coded. Thematic analysis was done by two researchers independently. If theme was interpreted differently, additional researcher was involved for final conclusion.

Ethical consideration

Part I of the study:

The patient and clinic data were anonymous and kept completely confidential.. Informed consent was not required from individual patient. NHSO data provider provided encrypted data as coding number and the researcher was blinded on the subjected name and identification number. The analyzed data was presented as group summary report.

Part II of the study:

Phase I: The clinic data was anonymous and kept completely confidential. The analyzed data was presented as group summary report.

Phase II: The response data was anonymous and kept completely confidential. The audiotape was saved as coding number. The researcher encrypted the data which allow only researcher could access the data. The audio tape will be destroyed immediately after finishing analysis. The key informant could refuse any questions they considered as personal. Informed consent was explained before starting the interview.

The study was approved by Ethical Review Committee for Research Involving Human Research Subjects, Health Science Group, Chulalongkorn University, on 9th September 2019 with COA No. 223/2562.

CHAPTER IV
RESULTS

Part I study

Data Characteristics

General yearly data characteristics appear in Table 8. From 162 clinics enrolled in RDU clinic project in August 2015, the number of registered clinics in year 2013 was 146 and increase to 162 between year 2015 to 2017. In October 2017, there was three clinics withdraw from NHSO. Therefore, total number of clinics analyzed further in the study is 159 clinics. Due to government fiscal budget year start from October to September of the next year, the data in year 2013 was covered 3-months period, and the data in year 2019 was covered 9-months period. From year 2013 to 2018, the number of registered population with NHSO increase from 1,638,446 to 1,860,916 and the number decrease to 1,805,094 in 2019. These results are related with the increase number of visits from 1,853,130 to 2,529,172 between year 2014 to 2018. Also, the number of visiting patients is increasing from 441,116 to 512,131 in year 2014 to 2018. The average visit per patient range from 2.05 to 4.94 during year 2013 to 2019. From total visiting patients, the percentage of Female population range from 62.60% to 57.73% and the average age is 48.3 to 53.12 years between year 2013 to 2019. Considering 12-months period from 2014 to 2018, the number of drug prescriptions is increasing from 1,282,239 to 1,571,362 prescriptions. Between year 2013 to 2019, the percentage of prescription in RI is decreasing from 22.13% to 14.01%, while percentage of prescription in AD seems to be stable from 1.40% to 1.34%. Regarding to the right of treatment, majority of patients visiting are cover by Universal Coverage Schemed (patients with co-payment at 30 THB) and Welfare Scheme (patients are exempt from co-payment), while small amount of visiting patient are classified as blank rights or disability right.

Table 8 Data Characteristics

Year	2013* (%)	2014 (%)	2015 (%)	2016 (%)	2017 (%)	2018 (%)	2019[1] (%)
Number of registered clinics	149	155	162	162	162	159	159
Number of registered population^	1,638,446	1,693,622	1,772,706	1,778,954	1,840,809	1,860,916	1,805,094
Number of visits	402,393	1,853,130	1,982,665	2,226,368	2,370,140	2,529,172	1,804,743
Number of visiting patients	196,334	441,116	464,430	502,358	510,794	512,131	438,377
Average visit per patient	2.05	4.20	4.27	4.43	4.64	4.94	4.12
Female (patient)	123,146 (62.60)	263,991 (59.18)	271,569 (58.45)	295,432 (58.52)	297,209 (58.10)	295,923 (57.76)	253,228 (57.73)
Average age (year)	48.30	48.14	49.03	49.15	50.67	52.14	53.12
Number of drug prescriptions	282,496	1,282,239	1,301,357	1,395,825	1,483,510	1,571,362	1,101,175
Number of Prescriptions with ATBs	68,791 (24.35)	301,516 (23.51)	260,197 (19.99)	236,875 (16.97)	208,669 (14.07)	186,070 (11.84)	116,961 (10.62)
- Number of Prescriptions in Respiratory Infection (RI)	62,527 (22.13)	270,394 (21.09)	252,591 (19.41)	265,663 (19.03)	250,675 (16.90)	230,253 (14.65)	154,226 (14.01)
- Number of Prescriptions in Acute Diarrhea (AD)	3,961 (1.40)	18,046 (1.41)	18,739 (1.44)	21,860 (1.57)	23,187 (1.56)	29,447 (1.87)	14,777 (1.34)

^ Number of Population determined at 1 October of a year before according to government fiscal budget year.

* Data collected from October to December 2013 according to government fiscal budget year.

[1] Data collected from January to September 2019 according to government fiscal budget year.

Antibiotic Utilization

In order to analyze drug utilization in each drug name. The drug prescriptions was extract to describe amount of antibiotics that was prescribed during the period of study. Number of Antibiotics prescriptions from year 2013 to year 2019 was ranked by ATC level name as appear in Table 9. Amoxicillin oral had the highest number of prescriptions in total 6 years followed by dicloxacillin oral and roxithromycin oral respectively. However, counting on the number of prescriptions was to roughly estimate amount of drug prescribed but was not the present the real drug utilization, since it was not considering the drug quantity prescribed with dose adjustment.

Table 9 Number of Antibiotics prescriptions from year 2013 to year 2019 rank from the highest to the lowest total number of prescriptions.

No	ATC level name	Dosage Form	Total no. 6 Years	Percent in ATBs	Number of Prescriptions with ATBs						
					2013	2014	2015	2016	2017	2018	2019
1	amoxicillin	O	403,573	43.5038	63	3,511	72,329	108,709	91,732	77,171	50,058
2	dicloxacillin	O	103,533	11.1605	6	679	11,138	22,966	25,498	26,002	17,244
3	roxithromycin	O	88,288	9.5172	44	880	14,485	26,261	19,678	16,872	10,068
4	norfloxacin	O	61,529	6.6326	18	479	8,857	15,964	14,195	14,354	7,662
5	cloxacillin	O	37,768	4.0713	1	353	7,620	11,854	7,733	6,622	3,585
6	sulfamethoxazole and trimethoprim	O	34,932	3.7656	7	158	3,759	9,515	9,271	7,834	4,388
7	amoxicillin and beta-lactamase inhibitor	O	34,800	3.7513	8	122	3,653	7,679	8,562	8,681	6,095
8	ciprofloxacin	O	32,565	3.5104		155	4,228	7,994	7,428	7,682	5,078
9	doxycycline	O	15,259	1.6449	7	196	2,295	3,538	3,868	3,176	2,179
10	ofloxacin	O	14,853	1.6011	4	42	1,572	3,443	4,132	3,532	2,128
11	erythromycin	O	13,005	1.4019	18	77	2,706	4,473	2,507	2,137	1,087
12	clindamycin	O	9,467	1.0205		33	977	1,996	2,308	2,572	1,581
13	cefalexin	O	8,256	0.8900	13	55	923	2,273	2,089	1,832	1,071
14	azithromycin	O	1,365	0.1471		1	80	253	507	397	127
15	phenoxymethylpenicillin	O	1,090	0.1175		13	168	478	271	106	54
16	clarithromycin	O	1,034	0.1115		3	119	193	306	237	176

No	ATC level name	Dosage Form	Total no. 6 Years	Percent in ATBs	Number of Prescriptions with ATBs						
					2013	2014	2015	2016	2017	2018	2019
17	tetracycline	O	66	0.0071			2	58	4	1	1
18	ampicillin	O	59	0.0064			1	13	9	24	12
19	levofloxacin	O	30	0.0032				3	3	12	12
20	cefdinir	O	26	0.0028		4	1	12	5	4	
21	cefaclor	O	25	0.0027				2	1	17	5
22	ampicillin, combinations	O	12	0.0013			12				
23	sulfadiazine	O	11	0.0012			1		6	2	2
24	cefixime	O	2	0.0002			1		1		
25	lincomycin	P	31,801	3.4280	12	283	4,818	9,395	7,905	5,848	3,540
26	ceftriaxone	P	28,200	3.0399	2	89	2,880	6,148	7,875	7,061	4,145
27	ceftriaxone, combinations	P	3,670	0.3956		31	711	877	810	820	421
28	cefazolin	P	1,292	0.1393		6	129	364	328	323	142
29	amoxicillin and beta-lactamase inhibitor	P	287	0.0309	13	75	117	18	24	17	23
30	chloramphenicol	P	277	0.0299		11	60	87	62	31	26
31	gentamicin	P	233	0.0251		3	44	72	54	29	31
32	cloxacillin	P	114	0.0123		1	10	6	42	36	19
33	amikacin	P	53	0.0057				11	6	31	5
34	colistin	P	47	0.0051				19	26	2	

No	ATC level name	Dosage Form	Total no. 6 Years	Percent in ATBs	Number of Prescriptions with ATBs						
					2013	2014	2015	2016	2017	2018	2019
35	ceftazidime	P	44	0.0047			4	3	3	20	14
36	streptomycin	P	21	0.0023			7	5	6		3
37	meropenem	P	19	0.0020						4	15
38	benzathine benzylpenicillin	P	17	0.0018					4	7	6
39	cefotaxime	P	16	0.0017			2	4	6	4	
40	ampicillin and beta-lactamase inhibitor	P	12	0.0013					12		
41	ciprofloxacin	P	9	0.0010				2	2	2	3
42	clindamycin	P	8	0.0009				7		1	
43	combinations of penicillins	P	2	0.0002			2				
44	kanamycin	P	2	0.0002				2			
	Total Oral Preparations	**O**	**861,548**	**92.87**	**189**	**6,761**	**134,927**	**227,677**	**200,114**	**179,267**	**112,613**
	Total Parenteral Preparations	**P**	**66,124**	**7.13**	**27**	**499**	**8,784**	**17,020**	**17,165**	**14,236**	**8,393**
	Total oral and parenteral		**927,672**	**100.00**	**216**	**7,260**	**143,711**	**244,697**	**217,279**	**193,503**	**121,006**

Hypothesis 1

After the implementation of RDU clinic project, antibiotics utilization in the community care clinics would significantly decrease if the project was effective.

Antibiotics utilization by DDD per 1000 patients

To understand the overall trends of drug utilization, the sequence chart of DDDs per 1000 patient were created. Weekly aggregated drug utilization for each drug by ATC level name was calculated into DDD unit and combined into Total DDDs for each dosage form (oral and parenteral). The descriptive statistics were also used to compare drug utililization before and after implementation of interventions.

The trend of drug utilization in Total, oral and parenteral was illustrated in Figure 4. The oral ATBs contributed to the majority of Total ATB utilization (the presented data was the overlapped lines). Oral ATBs utilizaion is gradually decreasing after financial intervention in Week 44 Year 2016. In constrast, there was no apparent change parenteral ATBs utilization after the implementation of education intervention and financial intervention.

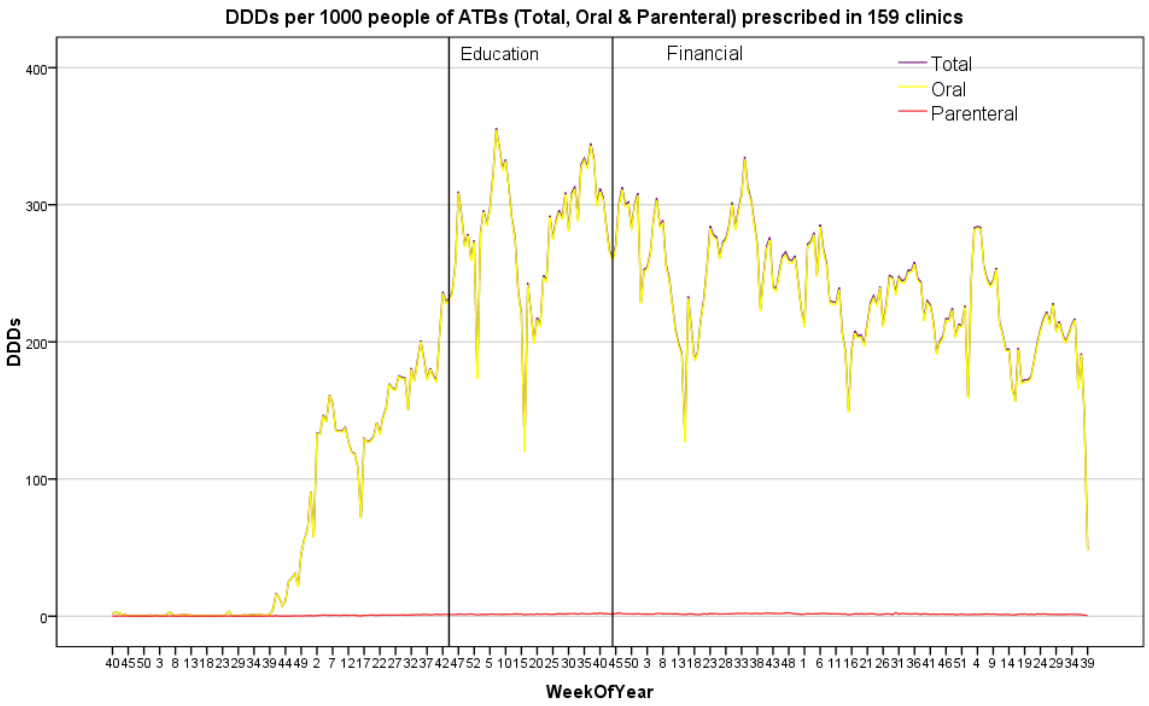

Figure 4 Sequence charts of weekly aggregated antibiotics utilization (Total, oral and parenteral) in 159 Clinics

The weekly aggregated drug utilization data prescribed in RI and AD disease for each drug by ATC level name was extracted and combined into DDD unit.. Figure 5 illustrated the trend of weekly aggregated ATBs utilization in subgroup RI and AD. The chart generally show that ATBs utilization in RI contributed to the majority of ATB utilization. However, the difference of DDDs between Total and RI indicated that there were a substantial amount of ATBs prescribed in other diagnosis rather than in RI or AD. The ATBs utilization in Total and RI prescriptions show a similar trend where they were slightly increase during the education intervention period from Week 41 Year 2015 and was gradually decrease after financial intervention in Week 44 Year 2016 until the end of study period in Week 39 Year 2019. The ATBs utilization in AD was stable throughout the period of the study, except for a sharply increase level during Week 49 Year 2017 to Week 8 Year 2018.

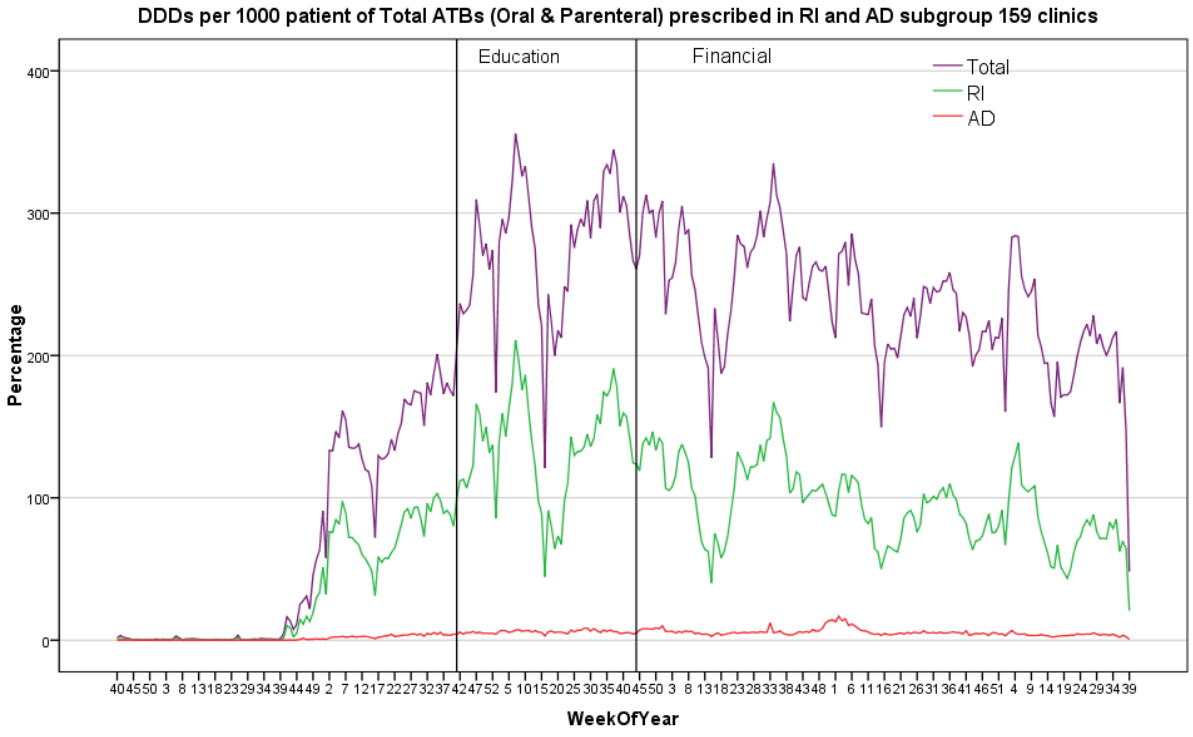

Figure 5 Sequence charts of weekly aggregate Total antibiotics utilization (Oral and Parenteral) in Respiratory Infection (RI) and Acute Diarrhea (AD) in 159 Clinics

Due to the incomplete TMT drug data in 70 clinics, the prescriptions data was extracted from 89 clinics where the TMTdrug code data was completed. Figure 6 presents the weekly trend of ATBs utilization in Total, Oral and Parenteral ATBs in 89 clinics. The trajectory of subgroup in RI and AD was also analyzed. ATBs utilization in 89 clinics had a similar trend with ATBs utilization in 159 clinics (Figure 4, 5) with a difference level of DDDs. This imply that the intervention analysis within 89 clinics is applicable.Total ATB s and oral ATBs had the overlapped lines suggested that oral ATBs contributed to the majority of ATBs utilization comparing with parenteral ATBs. ATBs utilization in RI subgroup were fairly stable during the period of education intervention and gradually decrease after financial intervention in Week 44 Year 2016. Meanwhile, ATBs utilization in AD and Total parenteral ATBs remained stable thoughout the period of study. ATB utilization in subgroup RI contribute to the majority of ATBs. However, the difference level between Total and RI implied that there was a considerable amount of ATBs prescribed in other disease rather than RI and AD. The data for further analyzed with ARIMA modeling was collected from Week 10 Year 2015 as indexed in the graph.

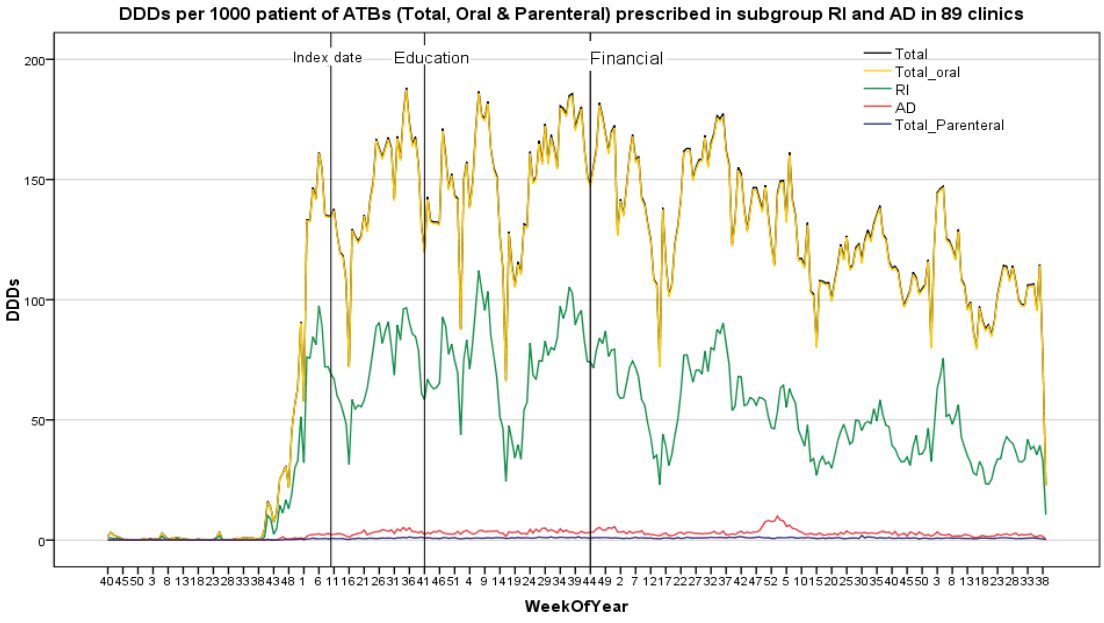

Figure 6 Sequence charge of weekly aggregate ATBs utilization (Oral & Parenteral) in Total, RI, and AD subgroup analysis in 89 clinics

Oral ATBs utilization

Figure 7 present oral ATBs utilization for each drug in 89 clinics. Amoxicillin had the highest DDDs followed by Roxithromycin, Dicloxacillin, Norfloxazin, Cloxacillin, Ciprofloxacin, Doxycycline, Sulfamethoxazole and Trimethroprim, Ofloxacin, Erythromycin, Clindamycin, Cefalexin, Clarithromycin, Azithromycin, Penicillin V, Levofloxacin.

Trend of Amoxicillin utilization was decreasing after education intervention in Week 41 Year 2016. Due to the limitation of data presentation unit, the trend in other drugs seem to be stable throughout the period of study. Amoxicillin , Roxithromycin, Dicloxacillin, Norfloxazin, Cloxacillin, Ciprofloxacin, Doxycycline, Sulfamethoxazole and Trimethroprim, and Ofloxacin were analyze further in ARIMA modelling method.

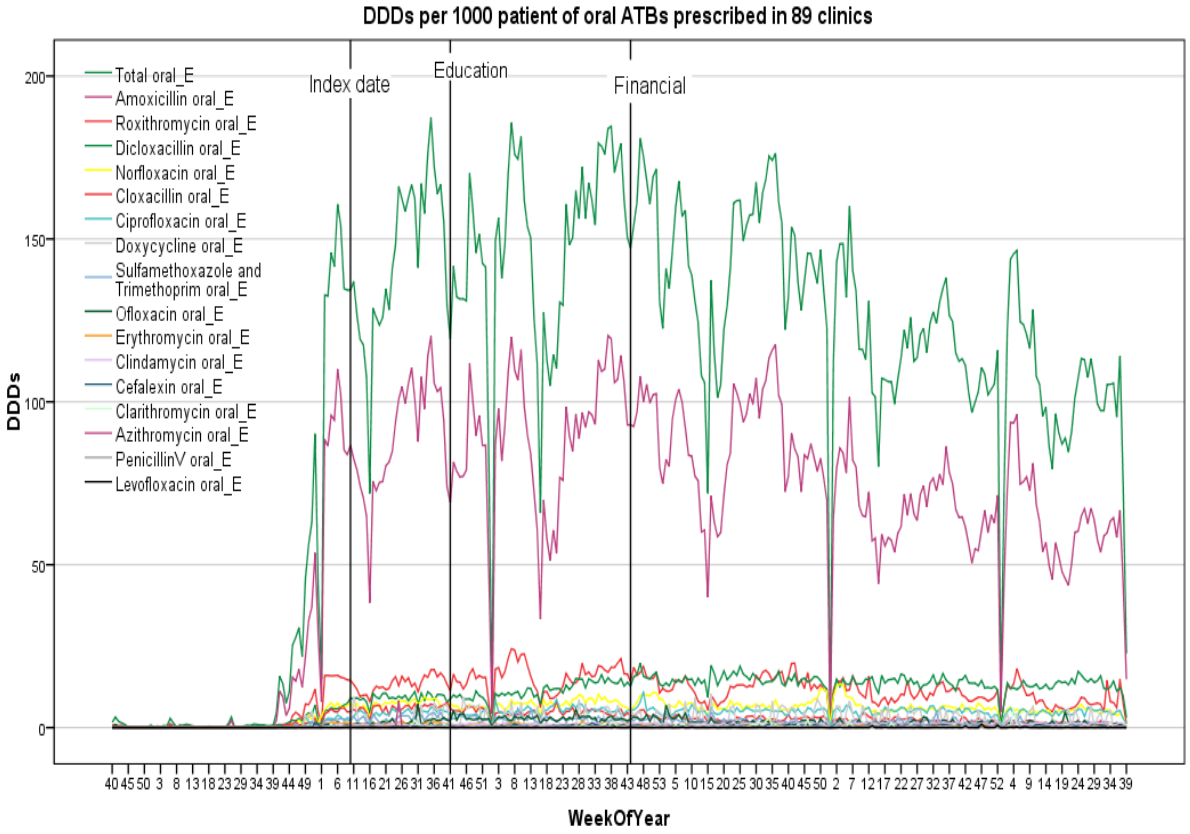

Figure 7 Sequence charge of weekly aggregate oral ATBs in 89 clinics

Parenteral ATBs utilization

Figure 8 portraited the parenteral ATBs utilization for each drug in 89 Clinic applied for education intervention analysis. Ceftriaxone had the highest DDDs followed by Lincomycin, Amoxicillin, Cefazolin, Gentamicin, Amikacin, Cloxacillin, Chorramphenicol. Ceftriaxone and Lincomicin utilization had a decreasing trend after education intervention in Week 36 Year 2016. Due to the limitation of data presentation, the trend in other drugs seem to be stable throughout the period of study Ceftriaxone and Linccomycin was analyzed furether in ARIMA modelling method.

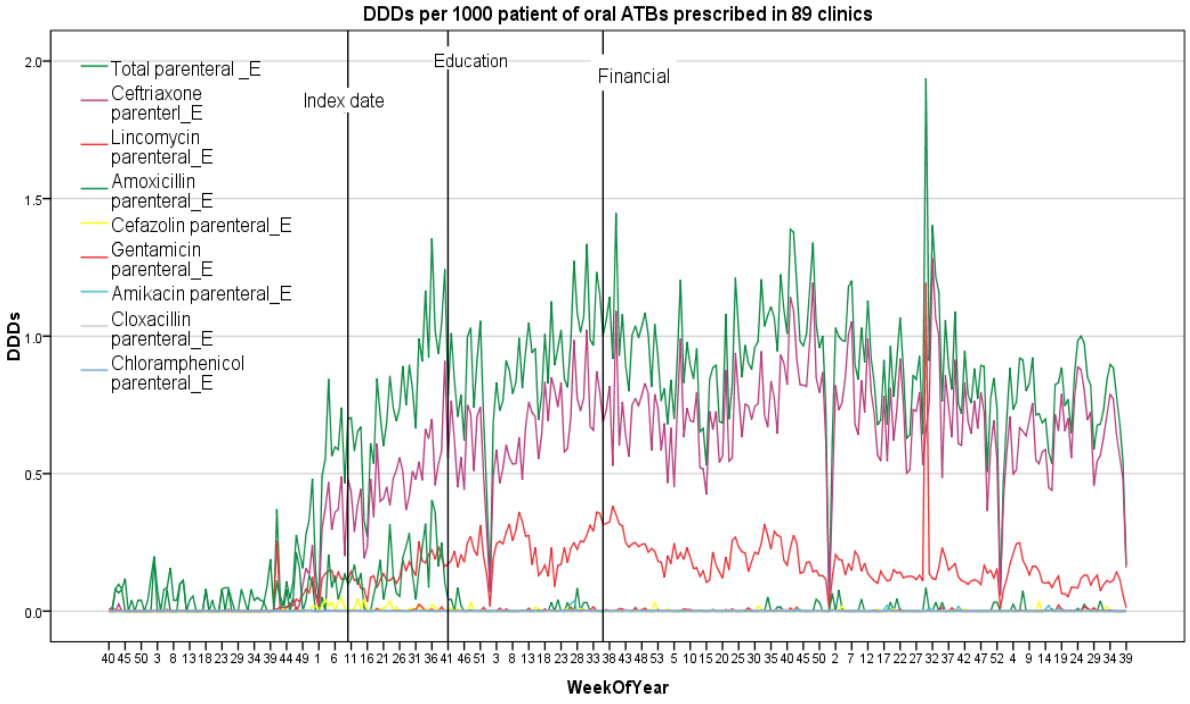

Figure 8 Sequence charge of weekly aggregate parenteral ATBs in 89 clinics

Therfore, we selected antibiotics which were prescribed at the high DDDs to run ARIMA model. Nine oral antibiotics (Amoxicillin, Roxithromycin, Dicloxacillin, Norfloxacin, Cloxacillin, Ciprofloxacin, Doxycline, Sulfamethoxazole and Trimethroprim, and Ofloxacin) and 2 Parenteral Antibiotics (Ceftriaxone and Lincomycin) were selected for ARIMA model analysis.

The final data that was analysis further in ARIMA modeling was shown in figure 10. The amount of amoxicillin was at the highest level comparing with other ATBs and the level were even higher than ATBs utilization in RI subgroup. This suggested that the change in amoxicillin should result in a significant change in the Total ATBs prescriptions. A particular ATBs utilization in subgroup disease was also analyzed to determine the effect of the intervention in the specifici disease group that we expected to have the high prescription rate. The ATBs that was analyze further in disease subgroup are Amoxicillin in RI, Roxithromycin in RI and Norfloxacin in AD.

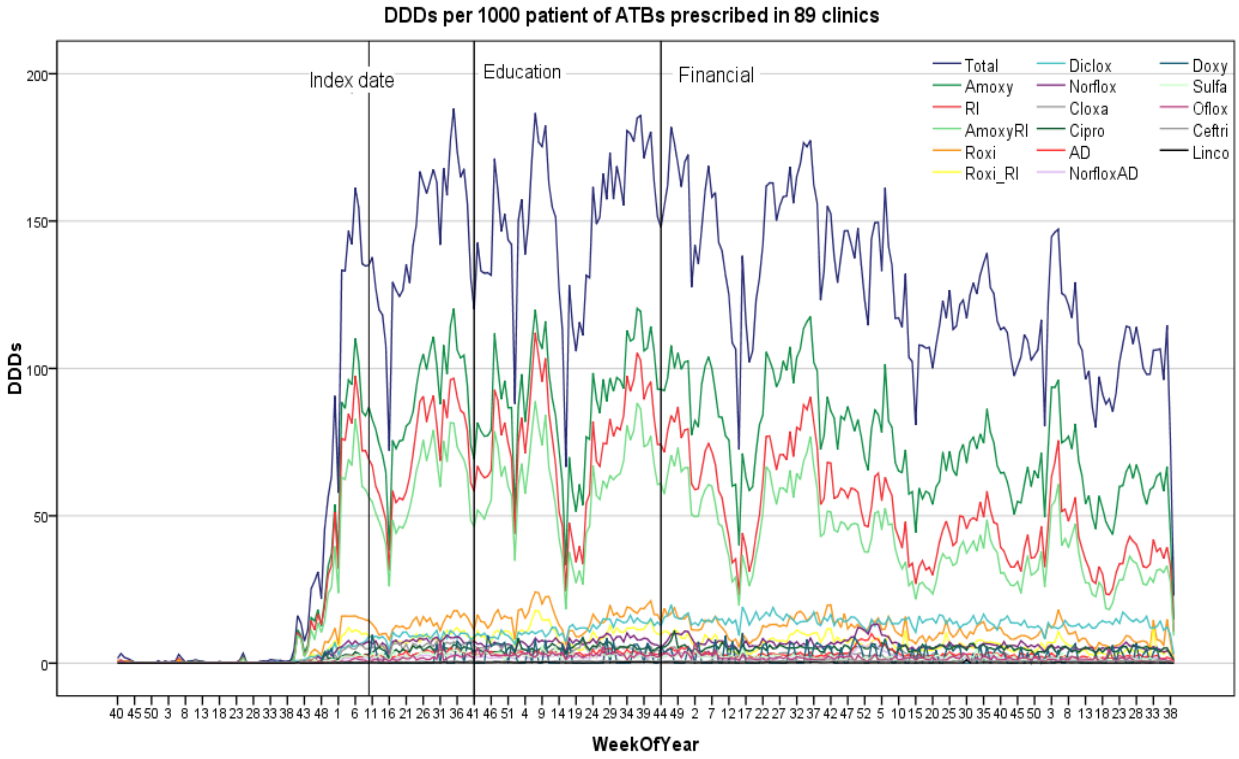

Figure 9 Sequence charge of weekly aggregate oral ATBs in 89 clinics

Before analyzing data using interrupted time series analysis, the descriptive statistics were present to asses how ATBs utilization changed during the entire period of the study. The average drug utililization (DDD per 1000 patients) before intervention (before Week 41 Year 2015), during education intervention (between week 41 Year 2015 to Week 43 Year 2016) and after financial intervention (after Week 44 Year 2016) in 89 Clinics by subgroup and drug item. The descriptive data are as show itn Table 10.

Total ATBs utilizations had an increase trend during the intervention period and change to decrease trend after financial invention. The percentage decrease was 12.91% between pre- and post- interventions. Total oral ATBs also had the similar trend which the percentage utilization was decrease by 13.05%. Total parenteral ATBs had an increase trend during the education intervention period and changed to a slightly decrease trend after financial invention. However, the overall percentage change was increase 12.52% between pre- and post- intervention.

The decreasing trend of oral ATBs were similar in RI and AD subgroup, where there were 30.07 % decrease in RI subgroup and 5.86% decrease in AD subgroup. When considering utilizations in each drug items, Cloxacillin had the greatest reduction at 59.99% followed by Sulfamethoxazole and Trimethoprim (39.37%), Roxithromycin (17.30%), Amoxicillin (16.70%), Norfloxacin (13.42.%), and Ofloxacin (5.86%), respectively. On the contrary to the hypothesis, Dicloxacillin, Cetriaxone, Doxycycline, Lincomycin and Ciprofloxacin utilization had an increasing trend at 52.50% , 48.42%, 29.60%, 14.72% and 2.80% accordingly.. Since parenteral preparation was contribute to small amont of utilization, we can assume that the percentage increase in parenteral prescription would not effect the overall Total ATBs utilization. Interestingly, Lincomycin had a decreasing trend when comparing between during education intervention to after financial intervention.

When considering utilizations in each drug item in subgroup of disease, both Amoxicillin and Roxithromycin utilization in RI subgroup had the higher decreasing trend comparing with the utilization of the drug in total prescription (-31.23% in Amoxicillin RI and -24.26% in Roxithromycin RI subsequently). This imply that most of Amoxicillin and

Roxythromycin was prescribed in RI. On the contrary, Norfloxacin in RI had the lower decreasing trend comparing with utilization of drug in total prescription. This suggested that Norfloxacin were most prescribed in other disease rather than AD disease

Table 10 Average drug utilization (DDDs per 1000 patients) before, during and after education intervention in 89 clinics

Drugs & Subgroup (Dosage Form)	**Before***	**During Education Intervention[1]**	**After Financial Intervention[2]**	**Difference (After - Before)**	**Percent difference**
Total ATBs	144.84	149.98	126.14	-18.71	-12.91
Total ATBs (oral)	144.05	149.05	125.25	-18.80	-13.05
Total ATBs (parenteral)	0.79	0.93	0.89	0.10	12.52
RI ATBs	72.19	74.41	50.48	-21.71	-30.07
AD ATBs	3.24	3.35	3.05	-0.19	-5.86
Amoxicillin (oral & parenteral)	89.40	89.48	74.47	-14.93	-16.70
Amoxicillin (oral & parenteral) in RI	59.95	60.12	41.23	-18.72	-31.23
Roxithromycin (oral)	13.47	15.81	11.14	-2.33	-17.30
Roxithromycin (oral) in RI	8.31	10.16	6.30	-2.02	-24.26
Dicloxacillin (oral)	9.21	11.54	14.05	4.84	52.50
Norfloxacin (oral)	7.43	7.27	6.43	-1.00	-13.42
Norfloxacin (oral) in AD	2.19	2.18	2.05	-0.14	-6.59
Cloxacillin (oral & parenteral)	6.00	4.86	2.40	-3.60	-59.99
Ciprofloxacin (oral & parenteral)	4.64	5.18	5.07	0.43	9.27
Doxycycline(oral)	1.91	2.37	2.47	0.56	29.60
Sulfamethoxazole and Trimethoprim (oral)	2.93	2.73	1.78	-1.15	-39.37
Ofloxacin(oral)	1.80	2.87	1.70	-0.11	-5.86
Ceftriaxone (parenteral)	0.14	0.24	0.17	0.02	14.72
Lincomycin (parenteral)	0.48	0.67	0.71	0.23	48.42

*Before = Week 10 Year 2015 to Week 40 Year 2015, [1]During = Week 41 Year 2015 to Week 43 Year 2016,
[2]After = Week 44 Year 2016 to Week 39 Year 2019

The example of ARIMA modelling development was shown in the **Appendix A**. Summary of the best fitted ARIMA model in each intervention, disease group, and each drug items appears in Table 11.. Total ATBs and Total oral ATBs was significantly affected by financial interventions ($p < 0.05$). Both education and financial intervention has a significant effect on the utilization of Total parenteral ATBs utilization ($p < 0.05$). Considering the financial intervention occur around 1 year after eduction intervention, the effect of financial intervention was the combined of education, this can concluded that education intervention alone might not be the effective to reduce ATBs utililization. However, both interventions had no significant effect in subgroup analysis in RI and AD diagnosis ($p > 0.05$). This can imply that most of ATBs was prescribed in other disease rather than RI and AD and interventions may not be effective to reduce ATBs utilization in particular disease diagnosis. However, there were negative coefficients of ATB utilization in RI and AD. This means that there was a decreasing trend of ATBs utilizations in RI and AD.

Regarding for each drug items, education intervention has a significantly effect on Dicloxacillin, Cloxacillin, Ciprofloxacin, Ofloxacin, Ceftriaxone, and Lincomycin utilization, while financial intervention has a significantly impact on Roxithromycin, Dicloxacillin, Cloxacillin, Sulfamethoxazole and Trimethoprim Ciprofloxacin, Ofloxacin, Ceftriaxone, and Lincomycin utilization ($p < 0.05$). This suggested that intervention is effective to reduce the ATBs utilization in particular ATBs, such as Roxithromycin, Cloxacillin, Ofloxacin, Sulfamethoxazole and Trimethoprim, Ceftriaxone and Lincomycin. This is in accordane with the guideline of Rational Drug Use in primary care where Roxithromycin had only an indication in the treatment acute bacterial rhinosinusitis and Group A Streptococcus (GAS) Pharyngitis when the patient are allergic to Penicillin. Also, Sulfamethoxazole and Trimethoprim had an indication only in the treatment for simple wound when the patients are allergic to Penicillin (47). However, the effect of education on Dicloxacillin were positive. This imply that the intervention is somehow enhance utilization in particular ATBs. The reduction on Cloxacillin utilization may relate with the increasing use of Dicloxacillin. It could deduce that since the guideline advised that, if the patient meet criteria for prescriptions, Dicloxacillin is the drug of choice for simple wound prophylasis

(47), while Cloxacillin have no indications in such disease. This could imply that the might be a switching on practice guideline from Cloxacillin to Dicloxaccillin in simple wound case. The guideline also suggest that target of ATBs prescriptions should less than 40% of total wound cases. This should note that simple wound prescriptions were not included in KPI target for QOF payment. Therefore, the financial intervention may not have a significant effect to reduce ATBs prescriptions in simple wound diagnosis.

Regarding to Ciprofloxacin, education intervention had a positive effect during education period and the the effect were negative financial intervention. This mean that there are a decreasing trend of Ciprofloxacin utilization. This is in accordance with the guideline that suggested to avoid prescriptions of Ciprofloxacin in Upper Respiratory Tract infection and Acute bronchitis and Ciprofloxacin only had indications in Acute Diarrhea, gastroenteritis and food poisoning only in high risk patients such as aging patient, patients with low immunity or patients with sepsis symptom. The target of ATBs prescriptions should less than 20% of total AD cases (47).

Considering Amoxycillin utilization, the guideline also suggested that Amoxicillin only have indications in the treatment acute bacterial rhinosinusitis and GAS Pharyngitis and the target of ATBs prescriptions should less than 20% of total RI cases (47). This can assume that prescriptions pattern of Amoxycillin were incordance with guideline at the pre-intervention period and the diagnosis cases were similar between pre- and post intervention. Therefore, both interventions did not have a significant impact on the Amoxicillin utilization. It can also deduce that the ATBs utilization in RI were not impacted by the interventions since Amoxicillin contribute to the majority of drug prescriptions in RI diagnosis (see Figure 7 and 9).

Regarding to parenteral ATBs utilization, both education and financing intervention have a significant effect on parenteral ATBs utilization ($p < 0.05$). However, the coefficient of education intervention in Total parenteral ATBs utilization is positive for education and negative for financial intervention. This mean that parenteral ATBs utilization has significantly increase during the education period and has decrease after financial

intervention. This imply that ATBs utilizations in parenteral preparation had a decreasing trend and interventions are effective to reduce ATBs utilization if the longer period of data were collected..

Considering on parenteral drug items, both intervention had a significant effect on Ceftriaxone and Lincomycin parenteral utilization ($p < 0.05$). The coefficient of financial intervention were positive in both Ceftriaxone and Lincomycin. Since the guideline suggested to avoid pareneteral ATBs prescriptions, such as Ceftriaxone and Lincomycin, in Pharyngitis of Acute tonsillitis (47). This imply that the intervention was effective to reduce utilization of Lincomycin and Ceftriaxone. Since Ceftriaxone contribute to majority of prescriptions of Total pareneteral ATBs (see figure 8), it can deduce that Ceftriaxone was the main parenteral ATBs that was prescribed.

Table 11 Summary of time series intervention analysis of Antibiotics utilization in 89 community care clinics in Bangkok, 2013 – 2019

Outcome (Dosage Form)	**ARIMA model**	**Parameter Estimate**		**S.E.**	**P-value**
Total ATBs	ARIMA (1,0,0)(0,1,1)	Education	6.923	7.096	.331
		Financial	-23.430	8.124	.004*
Total ATBs (oral)	ARIMA (1,0,0)(0,1,1)	Education	6.775	7.052	.338
		Financial	-23.234	8.073	.004*
Total ATBs (parenteral)	ARIMA (1,0,0)(1,1,0)	Education	.204	.052	.000*
		Financial	-.250	.058	.000*
RI ATBs	ARIMA (1,0,0)(0,1,1)	Education	-2.935	5.072	.564
		Financial	-9.430	5.802	.106
AD ATBs	ARIMA (2,0,0)(1,1,0)	Education	0.148	0.665	0.824
		Financial	-0.473	0.682	0.489
Amoxicillin (oral & parenteral)	ARIMA (2,0,0)(0,1,1)	Education	-.144	6.226	.982
		Financial	-10.542	7.022	.135
Amoxicillin (oral & parenteral) in RI	ARIMA (1,0,0)(0,1,1)	Education	-3.103	4.215	.463
		Financial	-6.933	4.821	.152
Roxithromycin (oral)	ARIMA (2,0,0)(0,0,0)	Education	.119	1.773	.946
		Financial	-3.406	1.427	.018*
Roxithromycin (oral) in RI	ARIMA (2,0,0)(0,0,0)	Education	.059	1.287	.964
		Financial	-2.474	1.051	.019*
Dicloxacillin (oral)	ARIMA (1,0,0)(0,1,1)	Education	3.680	.890	.000*

Outcome (Dosage Form)	ARIMA model	Parameter Estimate		S.E.	P-value
		Financial	-3.371	1.026	.001*
Norfloxacin (oral)	ARIMA (1,0,0)(1,1,0)	Education	-.298	.772	.700
		Financial	-.307	.851	.718
Norfloxacin (oral) in AD	ARIMA (1,0,0)(1,1,0)	Education	-.184	.436	.674
		Financial	.061	.470	.896
Cloxacillin (oral & parenteral)	ARIMA (2,0,0)(0,0,0)	Education	-1.303	.397	.001*
		Financial	-2.291	.290	.000*
Ciprofloxacin (oral & parenteral)	ARIMA (0,0,0)(1,1,0)	Education	.830	.221	.000*
		Financial	-1.018	.247	.000*
Doxycycline (oral)	ARIMA (0,1,1)(0,0,0)	Education	-.069	.054	.199
		Financial	.001	.019	.943
Sulfamethoxazole and Trimethoprim (oral)	ARIMA (1,0,0)(0,0,0)	Education	-.187	.242	.439
		Financial	-.949	.170	.000*
Ofloxacin (oral)	ARIMA (2,0,0)(0,0,1)	Education	1.038	.303	.001*
		Financial	-1.120	.216	.000*
Ceftriaxone (parenteral)	ARIMA (1,0,0)(1,1,0)	Education	.236	.048	.000*
		Financial	-.238	.053	.000*
Lincomycin (parenteral)	ARIMA (0,0,0)(1,1,0)	Education	.101	.017	.000*
		Financial	-.144	.019	.000*

* $p < 0.05$

Hypothesis 2

After the implementation of RDU clinic project, the percentage of encounters with antibiotics prescribed in community care clinic would significantly decrease if the project was effective.

Percentage encounter with ATBs

To understand the overall trends of antibiotics prescriptions, the sequence chart of percentage encounter with ATBs were created. Weekly aggregated percentageof ATBs prescription was calculated. Antibiotics was determined by grouping of drug name (not by TMT code) in order to include all of ATBs prescriptions before Week 40 Year 2015, as mentioned in Chapter III. The descriptive statistics were also used to compare percentage of encounter with ATBs before and after implementation of interventions.

Figure 11 illustrates trajectory of percentage encounter with ATBs during the research period in 159 clinics. The RI and AD subgroup was also analyzed. The percentage encounter with ATBs are gradually decrease throughout study period. Percentage encounter with ATBs in RI and AD subgroup were at the higher level comparing with Percentage in Total group.

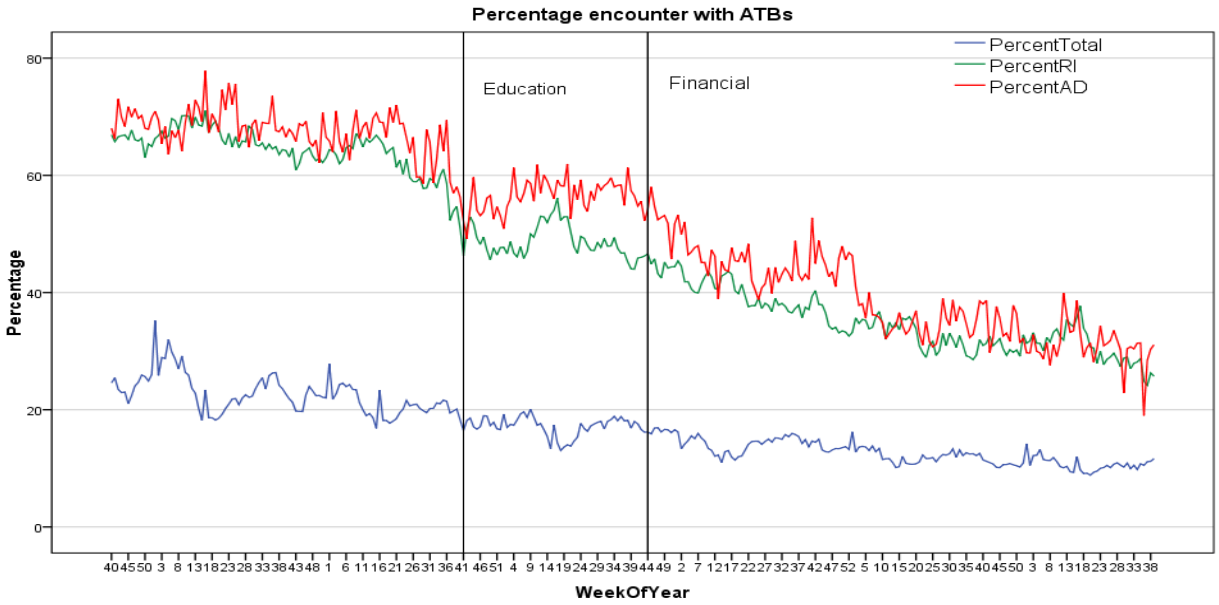

Figure 10 Sequence charts of weekly aggregate percentage encounter with ATBs in Total, RI and AD subgroup in 159 clinics.

Rank group

In order to determine whether the intervention had a significant impact on the clinics with different prescribing pattern, the data of antibiotics prescriptions was extracted by rank group.The assignment of clinic in each rank was described in Chapter III by calculating the average ATBs usage rate before intervention. The sequence chart of percentage encounter with ATBs were created separated by rank 1, 2 and 3, Weekly aggregated percentageof ATBs prescriptions in each rank group was calculated. Figure 12 illustrates trajectory of percentage encounter with ATBs during the research period in 159 clinics. As expected, rank 3 clinics had the highest percentage of ATBs prescriptions followed by rank 2, and 1 respectively. The percentage encounter with ATBs in three rank have the same trend which are gradually decrease overtime and remained at the lower level relative to the level in the pre-intervention period. However, ATBs prescriptions between rank 1 and 3 are too wide at the beginning of the series and were converged towards the end of the series.

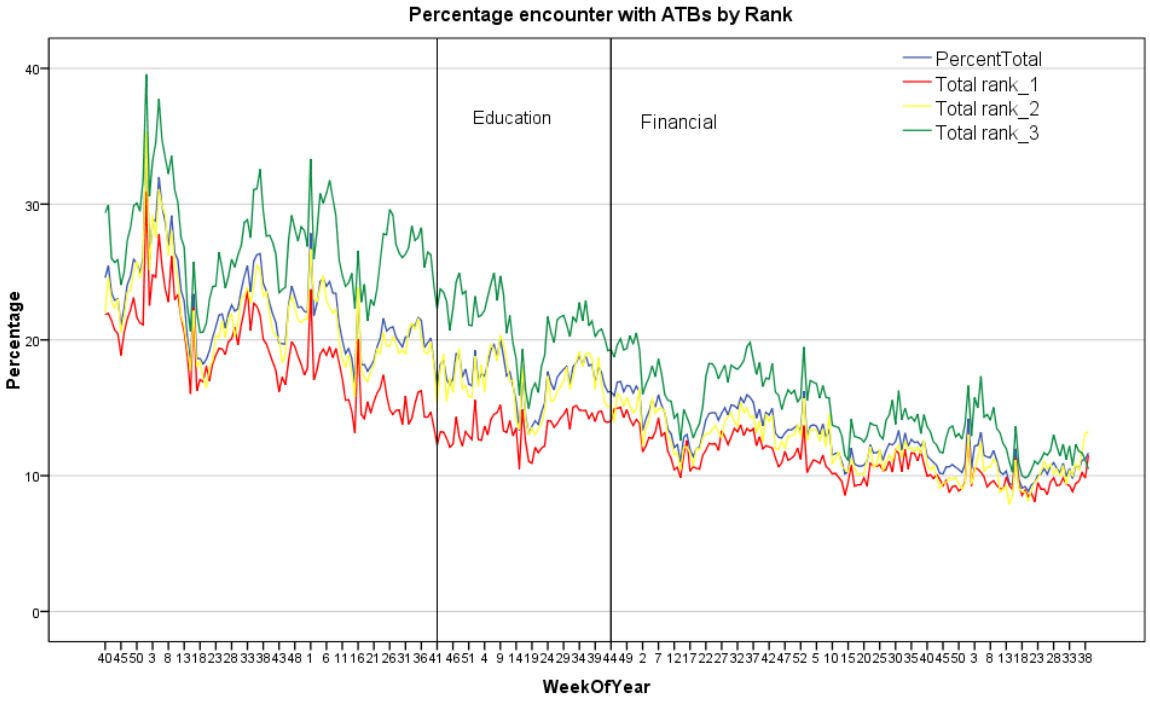

Figure 11 Sequence charts of weekly aggregate percentage encounter with ATBs separated into 3 ranks by the average ATBs usage rate before intervention in 159 clinics

RI subgroup

To analyze the trends of antibiotics prescriptions in RI subgroups, the sequence chart of percentage encounter with ATBs in RI were created separated by rank as 1, 2 and 3, as described in Chapter III. Weekly aggregated percentage of ATBs prescriptions in each rank group was calculated. Figure 13 illustrates trajectory of percentage encounter with ATBs during the research period in 159 clinics. As expected, rank 1 clinics had the highest percentage of ATBs prescriptions followed by rank 2, and 3 respectively. The percentage encounter with ATBs in rank 1,2 and 3 were sharply decrease during the education period, and gradually decline after financial intervention and remained at the lower level relative to the level in the pre-intervention period. However, ATBs prescriptions between rank 1 and 3 are too wide at the beginning of the series and were converged towards the end of the series.

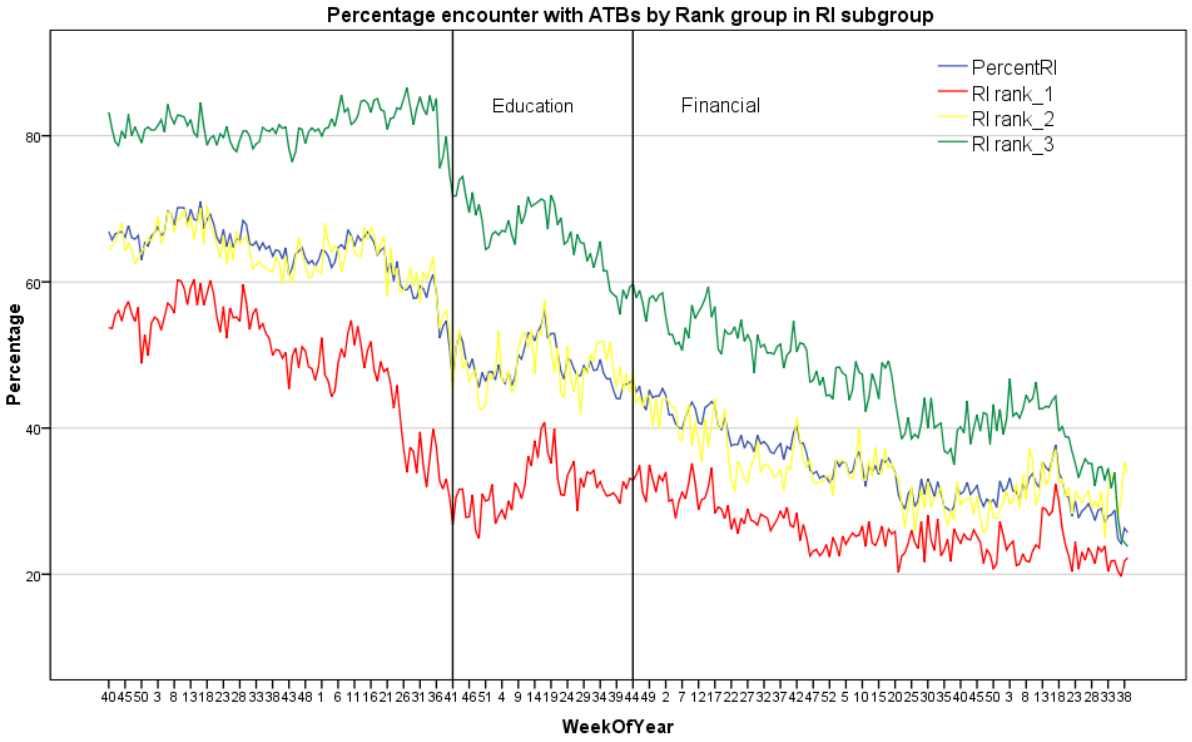

Figure 12 Sequence charts of weekly aggregate percentage encounter with ATBs in RI subgroup separated into 3 ranks by the average rate before intervention.

Subgroup AD

To analyze the trends of antibiotics prescriptions in AD subgroup, the sequence chart of percentage encounter with ATBs in AD were created separated by rank as 1, 2 and 3, as described in Chapter III. Weekly aggregated percentageof ATBs prescriptions in each rank group was calculated. Figure 14 illustrates trajectory of percentage encounter with ATBs during the research period in 159 clinics. As expected, rank 1 clinics had the highest percentage of ATBs prescriptions followed by rank 2, and 3 respectively. The percentage encounter with ATBs in rank 1,2 and 3 were sharply decrease during the education period, and gradually decline after financial intervention and remained at the lower level relative to the level in the pre-intervention period. However, ATBs prescriptions between rank 1 and 3 are too wide at the beginning of the series and were converged towards the end of the series.

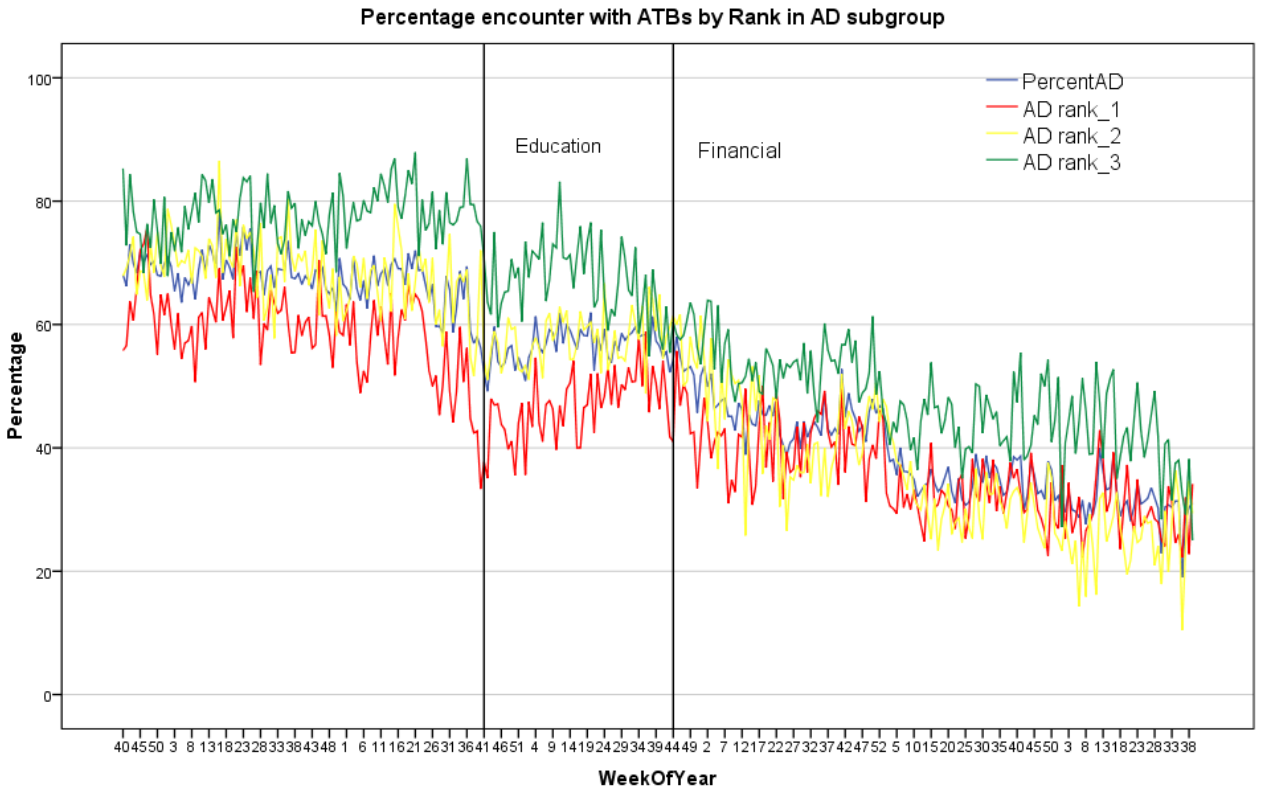

Figure 13 Sequence charts of weekly aggregate percentage encounter with ATBs in AD subgroup separated into 3 ranks by average rate before intervention (1, 2, 3)

Before analyzing data using interrupted time series analysis, the descriptive statistics were present to asses how percentage encounter with ATBs changed during the entire period of the study. The average percentage encounter with ATBs before, during education intervention and after financial intervention in 159 Clinics for each subgroup grade as show in Table 12. Regarding to education intervention, the percentage encounter with ATBs had a decrease trend in all outcomes of interested. Percentage encounter with ATBs in Total prescriptions was decreased from 22.54% before education intervention to 12.56% after financial the intervention. The percentage change was 44.30% reduction. Considering subgroup analysis between rank group, rank 3 had the higher percentage reduction at 45.82% follow by rank 2 (45.09%) and rank 3 (42.05%) respectively.

RI subgroup had a slightly higher percentage reduction at 45.96.% comparing with AD subgroup which had percentage reduction at 43..14%. As expected, rank 1 clinics in RI subgroups had the highest percentage reduction at 48.21%, follow by rank 2 (46.56%) and rank 3 (44.22%). Meanwhile, the highest reduction rate in AD group was rank 2 at 48.56% followed by rank 1 (40.37%) and rank 3 (38.75%). The percentage of encounter with ATBs after financial intervention in every rank group was more than 20% in both RI and and AD. This is not consistent with the target in guideline that the percentage of ATBs prescriptions should less than 20%. It should note that the percentage of ATBs in Total diagnosis was 22.54% at the beginning period of the study..This implied that the majority of prescriptions had not been diagnosed with RI or AD and ATBs were not prescribed.

Table 12 Average percentage encounter with Antibiotics before, during and after education intervention and before and after financial intervention in 159 clinics

Outcomes	**Before***	**During Education Intervention[1]**	**After Financial Intervention[2]**	**Difference (After - Before)**	**Percent difference**
Total	22.54	17.18	12.56	-9.99	-44.30
Total Rank 1	18.96	13.50	10.99	-7.97	-42.05
Total Rank 2	21.79	16.86	11.96	-9.82	-45.09
Total Rank 3	27.31	21.11	14.80	-12.51	-45.82
RI	64.39	48.71	34.80	-29.59	-45.96

Outcomes	Before*	During Education Intervention[1]	After Financial Intervention[2]	Difference (After - Before)	Percent difference
RI Rank 1	50.18	31.94	25.99	-24.20	-48.21
RI Rank 2	63.83	48.56	34.09	-29.74	-46.60
RI Rank 3	81.37	66.58	45.38	-35.98	-44.22
AD	67.66	56.56	38.47	-29.19	-43.15
AD Rank 1	59.11	46.85	35.25	-23.86	-40.37
AD Rank 2	68.62	57.59	35.27	-33.35	-48.60
AD Rank 3	77.83	67.28	47.67	-30.16	-38.75

*Before = Week 40 Year 2013 to Week 40 Year 2015, [1]During = Week 41 Year 2015 to Week 43 Year 2016,
[2]After = Week 44 Year 2016 to Week 39 Year 2019

The example of ARIMA modelling development was shown in the **Appendix A**. Summary of the best fitted ARIMA model in each intervention and subgroup shown in table 13. The coefficient of education intervention is -1.874 with significant effects ($p < 0.05$, $p = 0.017$). This indicates that percentage encounter with ATBs has significantly decrease during the education period for 1.874%. However, financial intervention did had a significant effect on the percentage encounter with ATBs. The imply that the percentage encounter with ATBs after education intervention was at the lower level and adding financial intervention did not significantly impact on the outcome further.The negative significant effect also found in AD subgroup (($p < 0.05$, $p = 0.001$). When considering subgroup analysis in each rank group, educattion intervention were significantly impacted rank 2 and rank 3 clinics ($p < 0.05$, $p = 0.000$, $p = 0.000$ respectively) and financial intervention was significantly impact rank 2. This imply that the percentage encounter with ATBs in rank 1 was at the lower level at the beginning period of the study and adding interventions did not significantly impact on the outcome further

Considering subgroup analysis in RI and AD subgroup, education intervention were significantly impacted only rank 2 clinics in RI ($p < 0.05$, $p = 0.002$, while it had a significant impact all three clinics clinics in AD subgroup ($p < 0.05$). Financial intervention also significantly impact AD rank 3 group. This imply that percentage encounter with ATBs in rank 2 clinics were sentitive to the interventions more than in other rank group of clnic.

Table 13 Time series intervention analysis of Percentage encounter with Antibiotics in community care clinics in Bangkok, 2013 – 2019

Outcome	ARIMA model	Parameter Estimates		S.E.	P-value
Total	ARIMA (2,0,0)(0,1,1)	Education	-1.874	.778	.017*
		Financial	-.020	.789	.980
Total Rank 1	ARIMA (0,1,1)(1,1,0)	Education	0.101	0.066	0.125
		Financial	-0.112	0.079	0.155
Total Rank 2	ARIMA (1,0,0)(0,1,1)	Education	-4.533	.278	.000*
		Financial	2.271	.335	.000*
Total Rank 3	ARIMA (2,0,0)(1,1,0)	Education	-3.701	.811	.000*
		Financial	.556	.926	.549
RI	ARIMA (1,0,1)(0,1,1)	Education	.980	1.176	.406
		Financial	-.611	1.044	.559
RI Rank 1	ARIMA (1,0,1)(0,1,1)	Education	.191	1.780	.915
		Financial	-.532	1.541	.730
RI Rank 2	ARIMA (2,0,0)(1,1,0)	Education	-6.784	2.126	.002*
		Financial	1.177	2.119	.579
RI Rank 3	ARIMA (2,0,0)(0,1,1)	Education	1.480	1.811	.415
		Financial	.412	1.667	.805
AD	ARIMA (1,0,1)(2,1,0)	Education	-6.418	1.997	.001*
		Financial	-2.262	2.104	.283
AD Rank 1	ARIMA (2,0,0)(0,1,1)	Education	-9.089	1.598	.000*
		Financial	2.458	2.089	.240
AD Rank 2	ARIMA (2,0,0)(0,1,1)	Education	-10.573	1.625	.000*
		Financial	-.168	2.121	.937
AD Rank 3	ARIMA (1,0,0)(0,1,1)	Education	-11.360	.822	.000*
		Financial	2.657	1.074	.014*

* $p < 0.05$

Hypothesis 3

There is a significant increase in the percentage of prescription that adhere to guideline in two specific diseases (Respiratory Infection and Acute Diarrhea) in the community care clinics after the implementation of RDU clinic project.

Percentage prescription adhere with guideline

To understand the overall trends of prescriptions adhere with guideline, the sequence chart of percentage ATBs adhere with guideline were created. Weekly aggregated data was calculated. Antibiotics was determined by grouping of drug name (not by TMT code) in order to include all of ATBs prescriptions before Week 40 Year 2015, as mentioned in Chapter III. The descriptive statistics were also used to compare the percentage adherence before and after implementation of interventions.

Figure 15 illustrates weekly percentage prescriptions adhere with guideline during the research period in 159 clinics. The RI and AD subgroup was also analyzed. The percentage prescriptions adhere with guideline are gradually increase throughout study period. Percentage adherence in both RI and AD subgroup has increasing trend along with Total group (RI and AD).

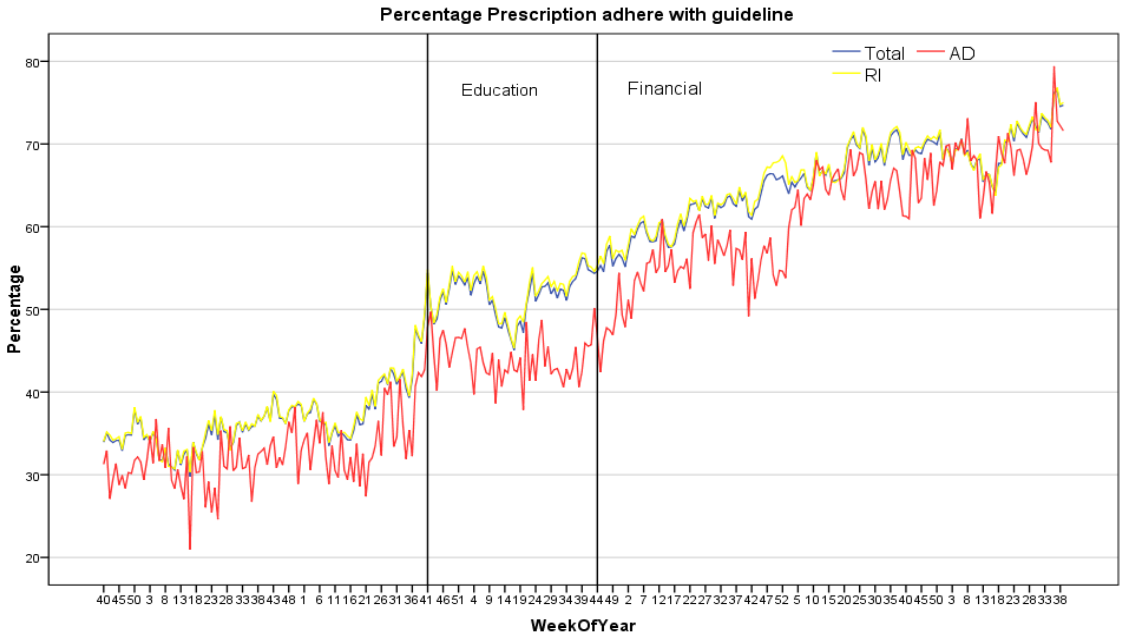

Figure 14 Sequence charts of weekly aggregate Percentage prescription adhere with guideline in Total, RI and AD subgroup

Rank group

In order to determine whether the intervention had a significant impact on the clinics with different prescribing pattern, the data of antibiotics prescriptions and diagnosis code was extracted by rank group.The assignment of clinic in each rank was described in Chapter III by calculating the average ATBs usage rate before intervention. The sequence chart of percentage prescription adhere with guideline were created separated by rank 1, 2 and 3, Weekly percentage prescription adherence in each rank group was calculated. Figure 16 illustrates trajectory of percentage prescription adherence during the research period in 159 clinics. As expected, rank 1 clinics had the highest percentage adherence followed by rank 2, and 3 respectively. The percentage adherence in three rank have the same trend which are gradually increase overtime and remained at the higher level relative to the level in the pre-intervention period. However, ATBs adherence between rank 1 and 3 are too wide at the beginning of the series and were converged towards the end of the series.

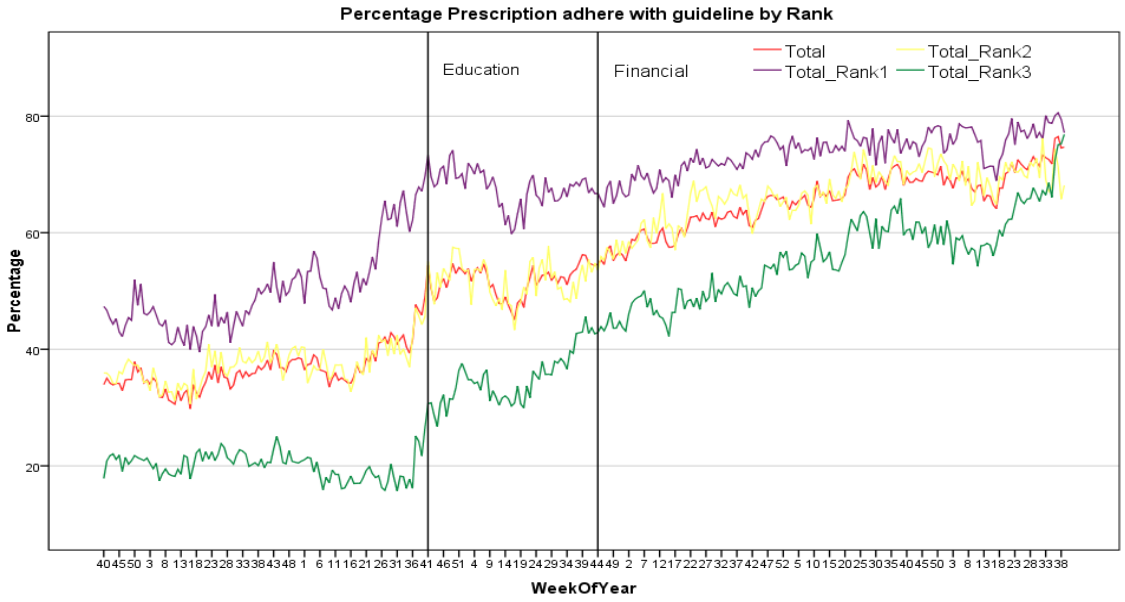

Figure 15 Sequence charts of weekly aggregate percentage encounter with ATBs separated into 3 ranks by the average ATBs usage rate before intervention in 159 clinics

Subgroup RI

To analyze the trends of percentage prescriptions adherence in RI subgroup, the sequence chart of percentage encounter with ATBs in RI were created separated by rank as 1, 2 and 3, as described in Chapter III. Weekly aggregated percentage adherence in each rank group was calculated. Figure 17 illustrates trajectory of percentage encounter with ATBs during the research period in 159 clinics. As expected, rank 1 clinics had the highest percentage adherence followed by rank 2, and 3 respectively. The percentage adherence in rank 1,2 and 3 were acceleratly rise during the education period, and are gradually increase after financial intervention and remained at the higher level relative to the level in the pre-intervention period However, ATBs prescriptions between rank 1 and 3 are too wide at the beginning of the series and were converged towards the end of the series.

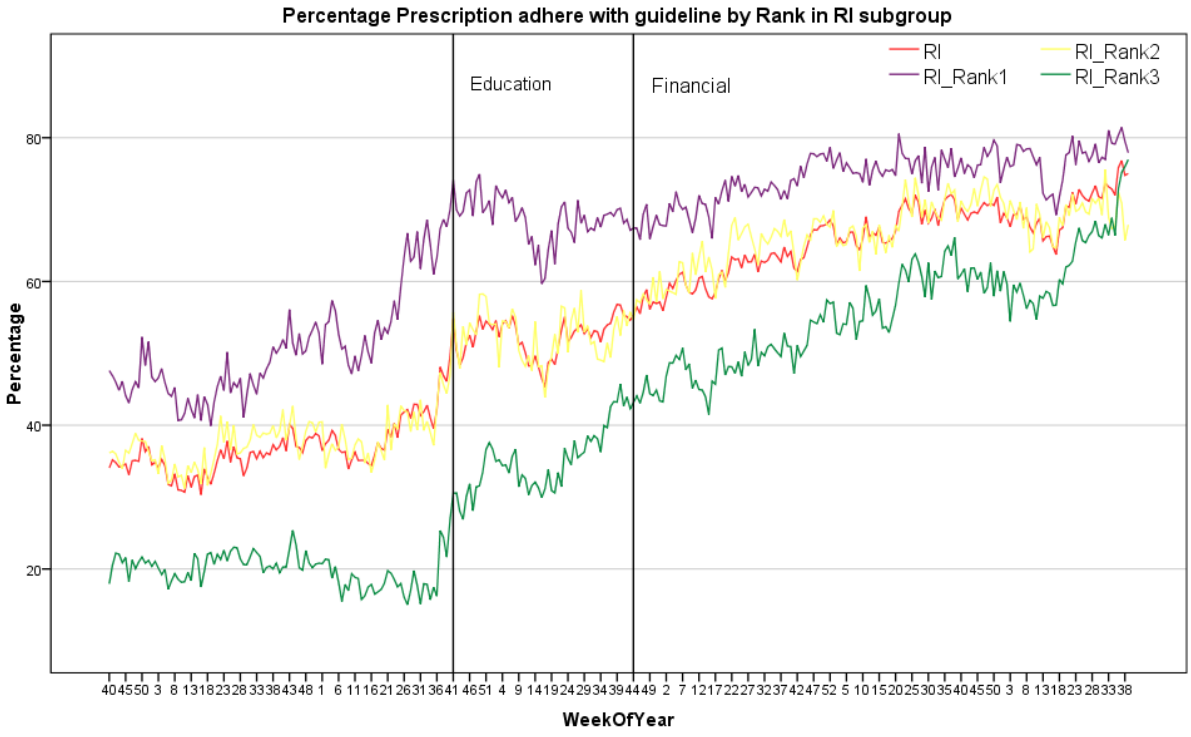

Figure 16 Sequence charts of weekly aggregate percentage prescription adhere with guideline in RI subgroup separated into 3 ranks by average rate before intervention (1, 2, 3)

Subgroup AD

To analyze the trends of percentage prescriptions adherence with guideline in AD subgroup, the sequence chart of percentage prescription adherence in AD were created separated by rank as 1, 2 and 3, as described in Chapter III. Weekly aggregated percentage adherence in each rank group was calculated. Figure 18 illustrates trajectory of percentage adherence during the research period in 159 clinics. As expected, rank 1 clinics had the highest percentage adrence followed by rank 2, and 3 respectively. The percentage adherence in rank 1,2 and 3 were sharply increase during the education period, and gradually increase after financial intervention and remained at the higher level relative to the level in the pre-intervention period. However, ATBs prescriptions between rank 1 and 3 are too wide at the beginning of the series and were converged towards the end of the series.

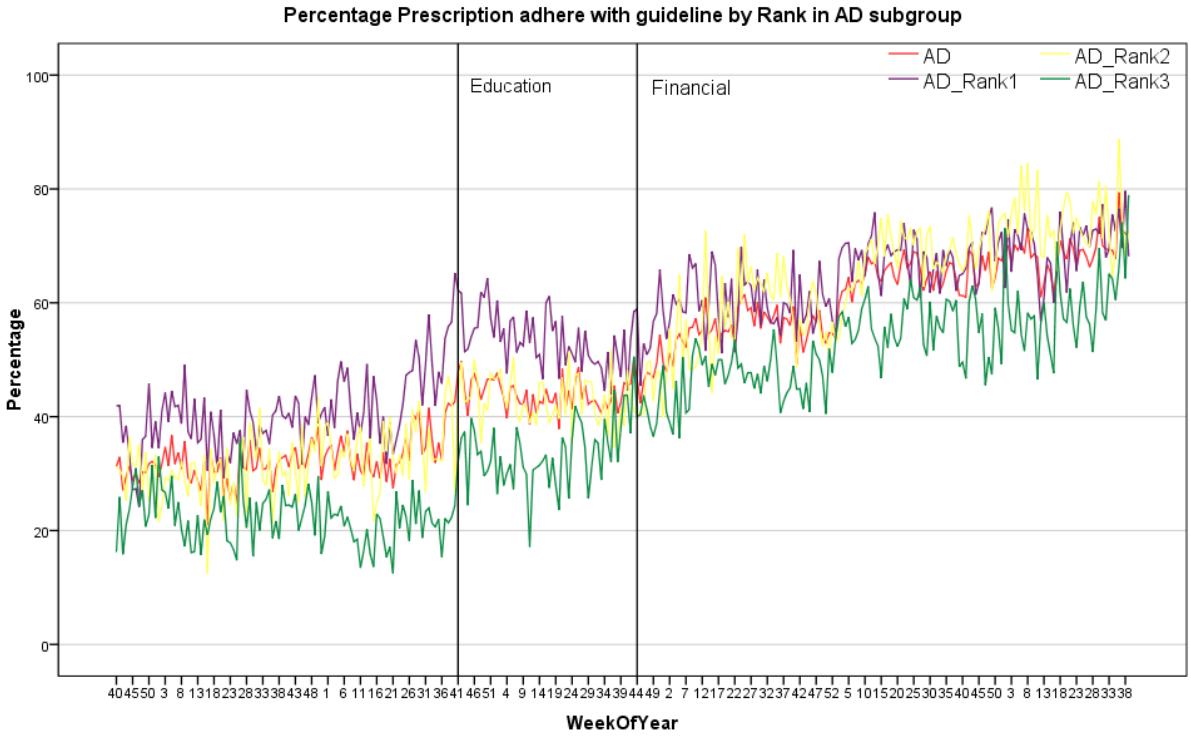

Figure 17 Sequence charts of weekly aggregate percentage prescription adhere with guideline in AD subgroup separated into 3 ranks by average rate before interventions (1, 2, 3)

Before analyzing data using interrupted time series analysis, the descriptive statistics were present to asses how percentage prescriptions adherence where changed during the entire period of the study. The average percentage prescriptions adherence before, during education intervention after financial intervention in 159 Clinics for each subgroup as show itn Table 14.

Regarding to education intervention, the percentage prescriptions adherence had an increase trend in all outcomes of interested. Percentage prescriptions adherence in Total prescriptions was increased from 36.51% before education intervention to 63.73% after the financial intervention. The percentage change was 80.06% raise. Considering subgroup analysis between rank group, rank 3 had the higher percentage reduction at 45.82% follow by rank 2 (45.09%) and rank 3 (42.05%) respectively.

AD subgroup had an higher percentage increasing at 90.56.% comparing with AD subgroup which had percentage increasing at 79.99%. Rank 3 clinics in RI subgroups had the highest percentage increaing at 177.74%, follow by rank 2 (78.45%) and rank 1 (47.22%). Meanwhile, the highest increasing rate in AD group was rank 3 at 138.36% followed by rank 2 (103.25%) and rank 1 (59.795%). The percentage adherence after financial intervention in every rank group was less than 20% in both RI and and AD. This is not consistent with the target in guideline that the percentage of ATBs prescriptions should less than 20%.(or the percentage of adherence are more than 80%)

Table 14 Average percentage prescriptions adhere with guideline before, during and after education intervention and before and after financial intervention in 159 clinics

Outcomes	Before*	During Education Intervention[1]	After Financial Interventio[2]	Difference (After - Before)	Percent difference
Total	36.51	51.81	65.73	29.23	80.06
Total_Rank1	50.11	67.76	73.77	23.66	47.22
Total_Rank2	37.32	51.80	66.60	29.28	78.45
Total_Rank3	20.04	34.95	55.66	35.62	177.74
RI	36.75	52.36	66.14	29.39	79.99

Outcomes	Before*	During Education Intervention[1]	After Financial Interventio[2]	Difference (After - Before)	Percent difference
RI_Rank1	50.77	68.80	74.68	23.91	47.10
RI_Rank2	37.70	52.50	66.80	29.10	77.19
RI_Rank3	19.89	35.03	55.86	35.97	180.80
AD	32.39	44.03	61.72	29.33	90.56
AD_Rank1	40.67	53.55	65.06	24.38	59.95
AD_Rank2	31.76	43.05	64.88	33.11	104.25
AD_Rank3	22.16	33.55	52.81	30.66	138.36

*Before = Week 40 Year 2013 to Week 40 Year 2015, [1]During = Week 41 Year 2015 to Week 43 Year 2016, [2]After = Week 44 Year 2016 to Week 39 Year 2019

The example of ARIMA modelling development was shown in the **Appendix A**. Summary of the best fitted ARIMA model in each intervention and subgroup shown in table 15. Regarding to education intervention, the intervention has a significant effect to percentage adhere with guideline in all Rank 2 subgroup in Total ($p < 0.05$, $p = 0.000$). The coefficient in Total rank 2 is 8.207. This means that percentage adherence with guideline has significantly increase during the education period for 8.207% in rank 2 subgroup. However, there was no significant effect after financial intervention. This imply that the education effect was temporary adding financial intervention did not have a sigficant effect on the outcom

Considering subgroup analysis in disease group, the intervention has a significant effect to percentage adhere with guideline in RI rank 2 and AD Rank 1, 2 and 3 ($p < 0.05$).

This imply that percentage adherence in rank 2 clinics were sentitive to the intervention more than other rank group of clnic. And AD were more sentitive to the intervention thant RI

Table 15 . Time series intervention analysis of Percentage prescription adhere with guideline in community care clinics in Bangkok, 2013 – 2019

Outcome	ARIMA model	Parameter Estimates		S.E.	P-value
Total	ARIMA (0,1,1)(0,1,1)	Education	-0.053	0.104	0.614
		Financial	0.063	0.137	0.643
Total Rank 1	ARIMA (2,0,0)(0,1,1)	Education	.473	1.798	.793
		Financial	.409	1.633	.803

Total Rank 2	ARIMA (2,0,0)(1,1,0)	Education	8.207	1.902	.000*
		Financial	-1.917	2.016	.343
Total Rank 3	ARIMA (2,0,0)(0,1,1)	Education	-1.249	1.711	.466
		Financial	.411	1.573	.794
RI	ARIMA (0,1,1)(0,1,1)	Education	-0.052	0.105	0.623
		Financial	0.061	0.138	0.662
RI Rank 1	ARIMA (2,0,0)(1,1,0)	Education	1.570	2.203	.477
		Financial	.833	2.108	.693
RI Rank 2	ARIMA (2,0,0)(1,1,0)	Education	7.113	2.011	.000*
		Financial	-1.334	2.049	.516
RI Rank 3	ARIMA (0,1,1)(0,1,1)	Education	0.045	0.167	0.787
		Financial	-0.003	0.219	0.988
AD	ARIMA (0,1,1)(0,1,1)	Education	-0.05	0.141	0.722
		Financial	0.09	0.182	0.62
AD Rank 1	ARIMA (2,0,0)(0,1,1)	Education	9.416	1.596	.000*
		Financial	-2.816	2.093	.180
AD Rank 2	ARIMA (2,0,0)(0,1,1)	Education	10.988	1.509	.000*
		Financial	-.553	1.973	.779
AD Rank 3	ARIMA (1,0,0)(0,1,1)	Education	10.988	1.509	.000*
		Financial	-.553	1.973	.779

* $p < 0.05$

Hypothesis 4

There is a significant decrease in the average medicines cost per encounter in the community care clinics after the implementation of RDU clinic project.

The average medicine cost per encounter

To understand the overall trends of medicine cost, the sequence chart of average medicince cost per encounter in Thai Bath (THB) were created. Weekly aggregated of average medicince cost was calculated. The descriptive statistics were also used to compare percentage of encounter with ATBs before and after implementation of interventions.

Figure 19 presents weekly average medicine cost per encounter during the research period in 159 clinics. The RI and AD subgroup was also analyzed. In Total prescriptions, the average medicine cost per encounter has not notably change after education and gradually decreasing after financial intervention. However, average medicine cost per encounter in both RI and AD subgroup has a decreasing trend.

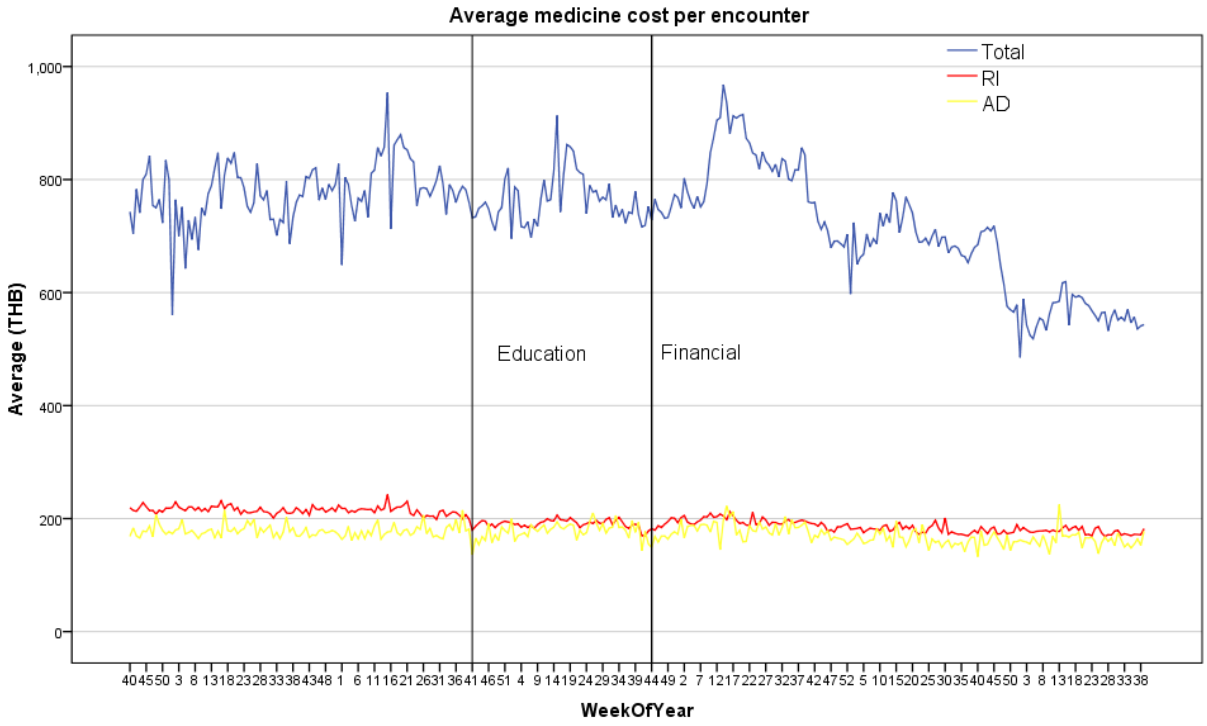

Figure 18 Sequence charts of weekly aggregate average medicine cost per encounter in Total, RI and AD subgroup

Rank group

In order to determine whether the intervention had a significant impact on the clinics with different prescribing pattern, the number of prescriptions and medicine cost was extracted by rank group.The assignment of clinic in each rank was described in Chapter III by calculating the average ATBs usage rate before intervention. The sequence chart of average medicinces cost were created separated by rank 1, 2 and 3, Weekly average medicinces cost in each rank group was calculated. Figure 20 illustrates trajectory of average medicinces cost during the research period in 159 clinics. The average medicinces cost in three rank have the same trend which are steady before and during interveniont gradually decreas aftere financial intervention. It should highlight there was a siginificant peak level of the average medicine cost in Week 14 Year 2017 at 968 THB per encounter which was the period before Songkron holiday in Thailand. This imply that there were drug stockpile by the patients before a long national holiday.However, since data in other year did not reach to this high level. It could deducted that there might be also another external factors such as, change in drug price, affect the medicince cost during that period of time.

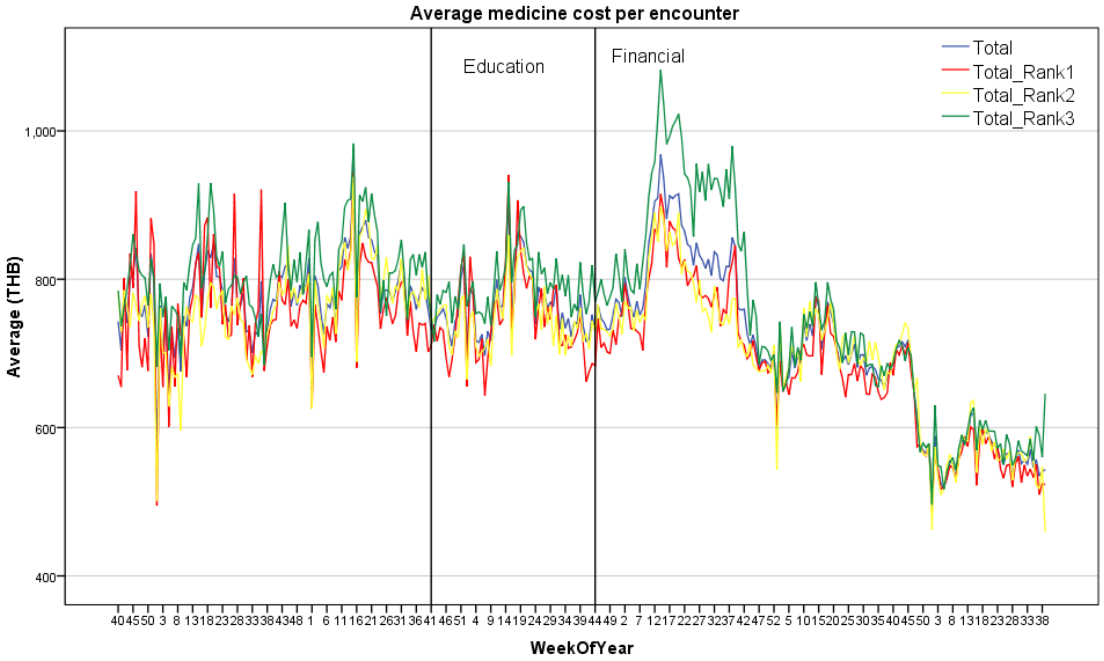

Figure 19 Sequence charts of weekly aggregate average medicine cost per encounter separated into 3 ranks by average rate before interventions (1, 2, 30

Subgroup RI

To analyze the trends of average medicinces cost in RI subgroup, the sequence chart of average medicinces cost per encounter in RI were created separated by rank as 1, 2 and 3, as described in Chapter III. Weekly aggregated average medicinces cost in each rank group was calculated. Figure 21 illustrates trajectory average medicinces cost during the research period in 159 clinics. At the beginning period of the study, rank 1 clinics had the highest average medicinces cost compare to rank 2, and 3. All of clinics rank had a similar decresing trend of average medicinces cost in RI prescriptions. The average medicinces cost per encounter are slowly decrease throughout the period of the study. However, The average medicinces cost per encounter between rank 1 and 3 are too wide at the beginning of the series and were converged towards the end of the series..

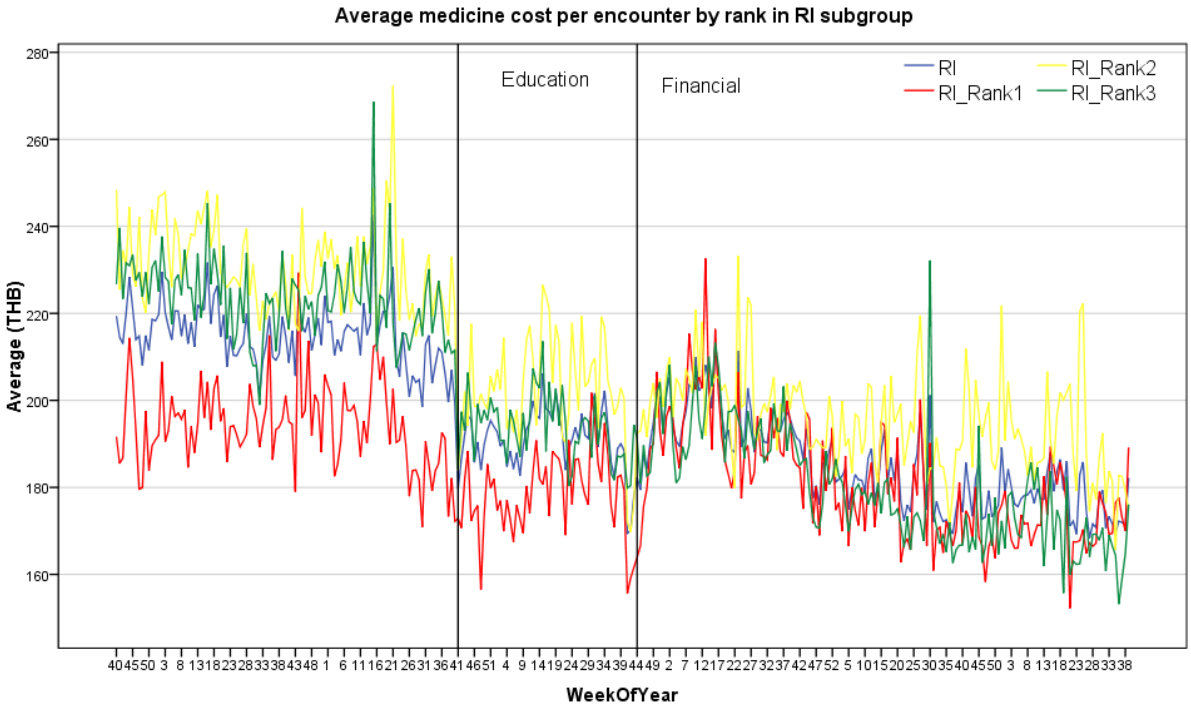

Figure 20 Sequence charts of weekly aggregate average medicine cost per encounter in RI subgroup separated into 3 ranks by average rate before interventions (1, 2, 3)

Subgroup AD

To analyze the trends of average medicinces cost in AD subgroup analysis, the sequence chart of average medicinces cost per encounter in AD were created separated separated by rank as 1, 2 and 3, as described in Chapter III. Weekly aggregated average medicinces cost in each grading group was calculated. Figure 22 illustrates trajectory average medicinces cost during the research period in 159 clinics. All of clinics rank had a similar stable trend of average medicinces cost in AD prescriptions. The average medicinces cost per encounter did not change much throughout the period of the study.

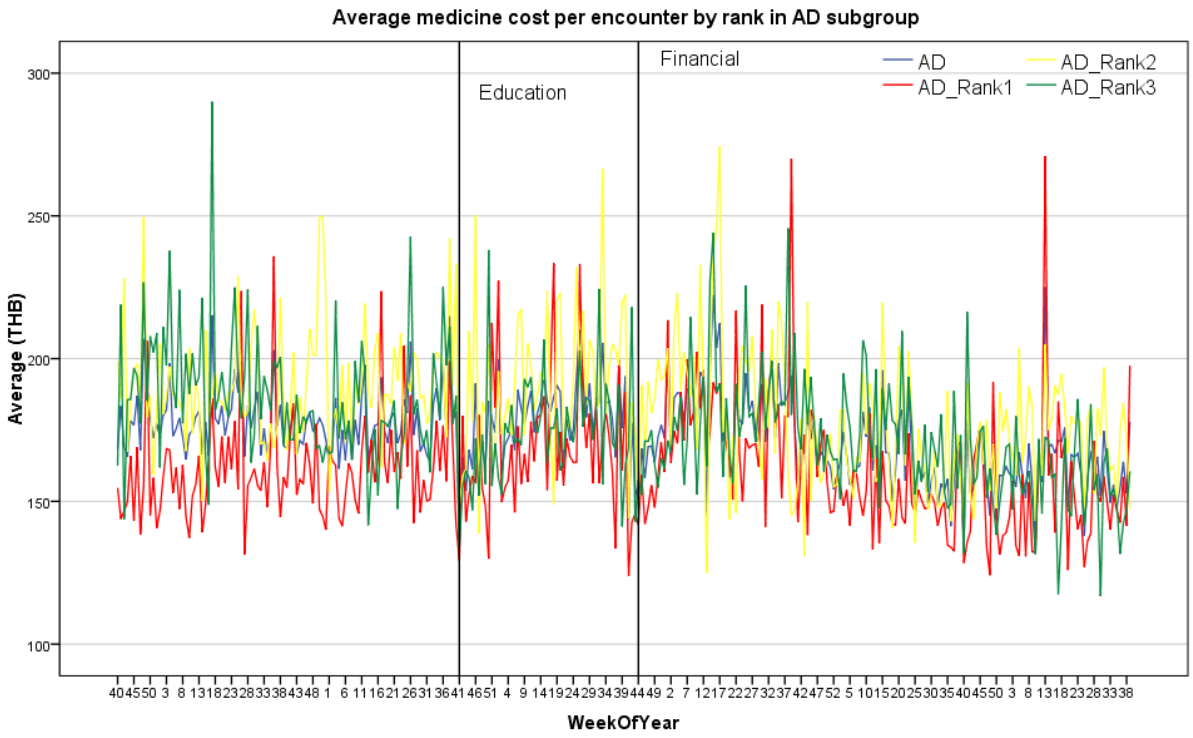

Figure 21 Sequence charts of weekly aggregate average medicine cost per encounter in AD subgroup separated into 3 ranks by average rate before interventions (1, 2, 3)

Before analyzing data using interrupted time series analysis, the descriptive statistics were present to asses how average medicine cost where changed during the entire period of the study. The average value of average medicince cost per encounter before, during education intervention and after financial intervention in 159 Clinics for each subgroup grade as show itn Table 16.

Regarding to the average of average medicince cost per encounter had a decrease trend in all outcomes of interested. The average cost in Total prescriptions was decrease from 771.33 THB before education intervention to 699.41 THB after the financial intervention. The percentage change was 10.02 % reduction. Rank 1 had a slightly decrease in average medicine cost comparing to rank 2 and rank 3.

Considering subgroup analysis disease group, there were a decrease trend in RI prescriptions that the average medicince cost per encounter reduce from the start of study period in Year 2013 at 214.90 THB to 185.00 THB in Year 2019. Whereas the average medicince cost per encounter in AD had not change much from the start of study period in Year 2013 at 178.30 THB to 168.81 THB in Year 2019. RI subgroup had a higher percentage decrease at 13.92%. compare to AD subgroup which had percentage decrese at 5.32%. The average medicince cost per encounter in RI subgroup were a little higher than the average medicince cost per encounter in AD subgroup. Contrary to the expectation, rank 3 clinics had the highest percentage reduction at 19..41% in RI prescriptions, while AD rank 3 had the highest percentage reduction at 5.32%. This imply that even rank 1 clinics were prescribe the lowest number of ATBs prescriptions, the medicine cost is not reduce accordingly. ATBs cost did not constribute to the majority of medicine cost.

It should also notice that the average medicine cost in Total prescriptions was about three to four times higher than the average medicine cost in RI and AD at the approximately 200 THB per prescription. This suggested that other diseases diagnosis, except RI and AD, was prescribed at the higher cost of medicines than the prescriptions diagnosis with RI or AD.

Table 16 Average of average medicine cost per encounter before, during and after education intervention and before and after financial intervention in 159 clinics

Outcomes	Before*	During Education Intervention[1]	After Financial Interventio[2]	Difference (After - Before)	Percent difference
Total	777.33	764.13	699.41	-77.92	-10.02
Total Rank 1	759.07	747.35	678.03	-81.04	-10.68
Total Rank 2	762.07	748.31	686.95	-75.12	-9.86
Total Rank 3	812.22	794.46	733.72	-78.50	-9.66
RI	214.90	191.05	185.00	-29.91	-13.92
RI Rank 1	194.23	178.61	180.75	-13.48	-6.94
RI Rank 2	230.91	202.46	195.02	-35.89	-15.54
RI Rank 3	223.56	193.70	180.16	-43.40	-19.41
AD	178.30	178.06	168.81	-9.49	-5.32
AD Rank 1	161.45	168.37	160.29	-1.16	-0.72
AD Rank 2	190.95	191.25	176.12	-14.83	-7.77
AD Rank 3	187.07	174.53	170.30	-16.77	-8.96

*Before = Week 40 Year 2013 to Week 40 Year 2015, [1]During = Week 41 Year 2015 to Week 43 Year 2016, [2]After = Week 44 Year 2016 to Week 39 Year 2019

The example of ARIMA modelling development was shown in the **Appendix A**. Summary of the best fitted ARIMA model in each intervention and subgroup appears in table 17. Both education intervention and financial intervention have no significant effect on the average medicine cost per encounter in Total, Total rank 1, 2 and 3. This could results from majority of prescriptions were prescribed in other diseases diagnosis, rather than RI and AD and ATBs did not contribute to majority of drug cost in each prescriptons. When considering subgroup analysis, education intervention has significantly impact in all RI subgroup (total, RI rank 1, 2 and 3), and AD rank 2. This imply that the ATBs cost contribute to majority cost of prescriptions in RI and AD diagnosis and the intervention were significantly impact to reduce the cost of ATBs which results in reduction of the total cost per prescription. Financial intervention had a significant effect in RI rank 2 and 3 subgroup ($p < 0.011$, $p = 0.001$, respectively). This imply that education intervention may be more effective to reduce drug cost than finantial intervention. However, medicine cost reduction may cause by other reasons rather than RDU intervention and ATBs was

not contribute to the major cost of drugs per prescription. It could also imply that Rank 2 clinics were more sentitive to the interventions than the other subgroup.

Table 17 Time series intervention analysis of Average Medicine cost per encounter in community care clinics in Bangkok, 2013 – 2019

Outcome	ARIMA model	Parameter Estimates		S.E.	P-value
Total	ARIMA (0,1,1)(0,0,0)	Education	-.506	3.024	.867
		Financial	-.954	2.849	.738
Total Rank 1	ARIMA (0,1,1)(0,0,0)	Education	-.561	3.004	.852
		Financial	-.711	2.828	.802
Total Rank 2	ARIMA (0,1,1)(0,0,0)	Education	-.842	2.861	.769
		Financial	-.763	2.695	.777
Total Rank 3	ARIMA (2,0,0)(0,0,0)	Education	-56.215	35.525	.115
		Financial	-31.151	35.151	.376
RI	ARIMA (2,0,0)(0,0,0)	Education	-24.599	3.417	.000*
		Financial	-4.126	3.286	.210
RI Rank 1	ARIMA (2,0,0)(0,0,0)	Education	-13.847	4.003	.001*
		Financial	1.319	3.800	.729
RI Rank 2	ARIMA (1,0,0)(0,0,0)	Education	-29.292	2.766	.000*
		Financial	-6.719	2.619	.011*
RI Rank 3	ARIMA (2,0,0)(0,0,0)	Education	-29.947	4.078	.000*
		Financial	-12.635	3.883	.001*
AD	ARIMA (2,0,0)(0,0,0)	Education	-2.310	3.972	.561
		Financial	-7.832	3.764	.038
AD Rank 1	ARIMA (2,0,0)(0,0,0)	Education	6.581	4.839	.175
		Financial	-7.621	4.582	.097
AD Rank 2	ARIMA (2,0,0)(0,1,1)	Education	-.047	4.195	.991
		Financial	-14.959	3.966	.000*
AD Rank 3	ARIMA (1,0,1)(0,0,0)	Education	-13.834	6.087	.024*
		Financial	-3.550	6.205	.568

* $p < 0.05$

Hypothesis 5

There is a significant decrease in the percentage of drug cost spent on antibiotics in the community care clinics after the implementation of RDU clinic project.

Percentage medicine cost spent on antibiotics

To understand the overall trends of Antibiotics cost, the sequence chart of percentage medicines cost on ATBs were created. Weekly aggregated percentage ATBs cost was calculated. Antibiotics was determined by grouping of drug name (not by TMT code) in order to include all of ATBs prescriptions before Week 40 Year 2015, as mentioned in Chapter III. The descriptive statistics were also used to compare percentage of encounter with ATBs before and after implementation of interventions.

Figure 23 illustrates weekly percentage medicine cost on ATBs during the research period in 159 clinics. The RI and AD subgroup was also analyzed. The percentage medicine cost on ATBs in Total prescriptions remain stable whereas the percentage in RI and AD subgroup are gradually decrease throughout study period. Percentage of ATBs cost in RI were a little higher than Percentage of ATBs cost in AD.

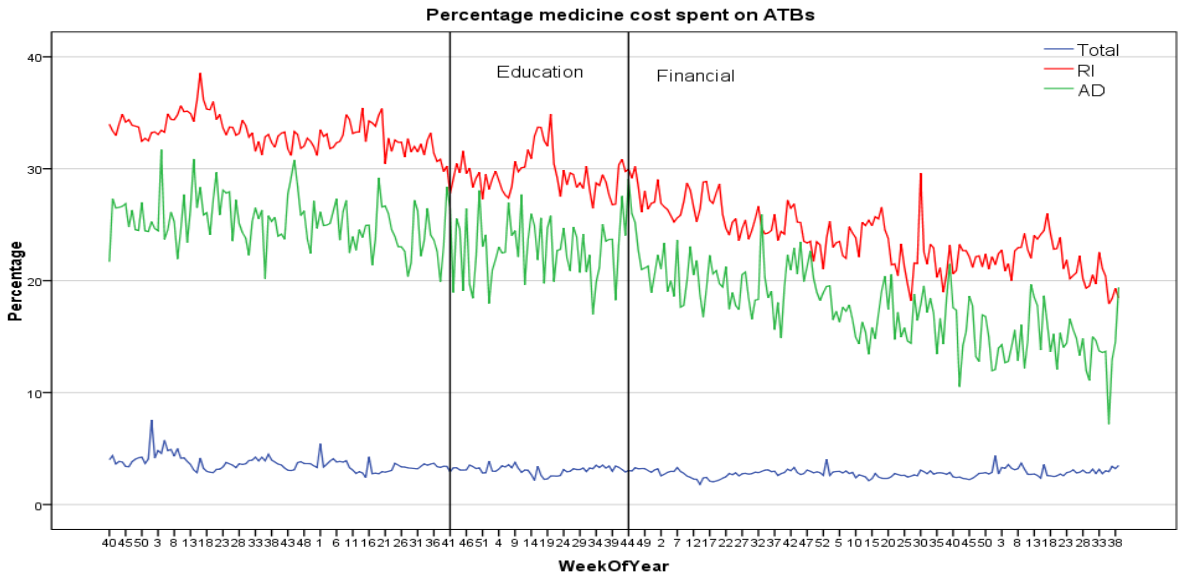

Figure 22 Sequence charts of weekly aggregate percentage medicine cost on ATBs in Total, RI and AD subgroup

Rank group

In order to determine whether the intervention had a significant impact on the clinics with different prescribing pattern, the drug prescription data and medicine cost was extracted by rank group.The assignment of clinic in each rank was described in Chapter III by calculating the average ATBs usage rate before intervention. The sequence chart of percentage ATBs cost were created separated by rank 1, 2 and 3, Weekly percentageof ATBs cost in each rank group was calculated. Figure 24 illustrates trajectory of percentage ATBs cost during the research period in 159 clinics. The average medicinces cost in three rank have the same trend which are steady throughout the period of study.

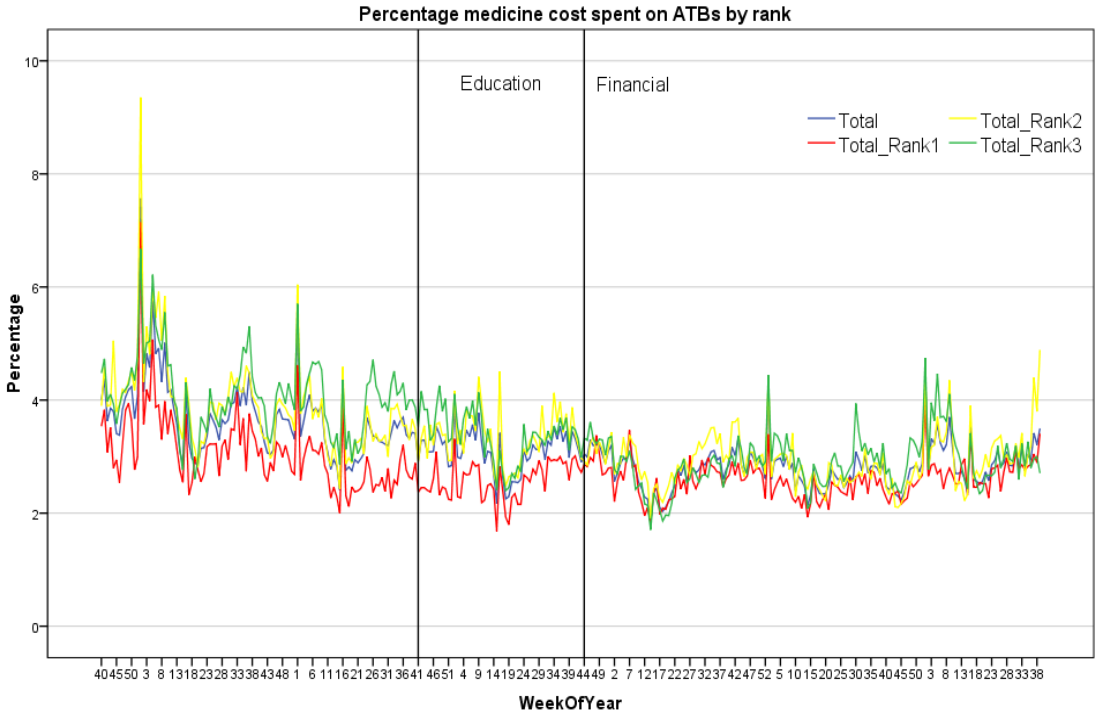

Figure 23 Sequence charts of weekly aggregate percentage medicine cost on ATBs separated into 3 ranks by average rate before interventions (1, 2, 3)

Subgroup RI

To analyze the trends of antibiotics cost in RI subgroup analysis, the sequence chart of percentage medicine cost spent on ATBs in RI were created separated by rank 1, 2 and 3, as described in Chapter III. Weekly aggregated percentageof ATBs cost in each rank group was calculated. Figure 25 illustrates trajectory of percentage medicine cost on ATBs during the research period in 159 clinics. As expected, rank 3 clinics had the highest percentage of ATBs cost followed by rank 2, and 1 respectively. The percentage ATBs cost in rank 1 are gradually decrease before the education period and remained at the steady level throughout the study period. Percentage ATBs cost in rank 2 and 3 clinics were gradually decrease overtime. However, Percentage ATBs cost between rank 1 and 3 are too wide at the beginning of the series and were converged towards the end of the series.

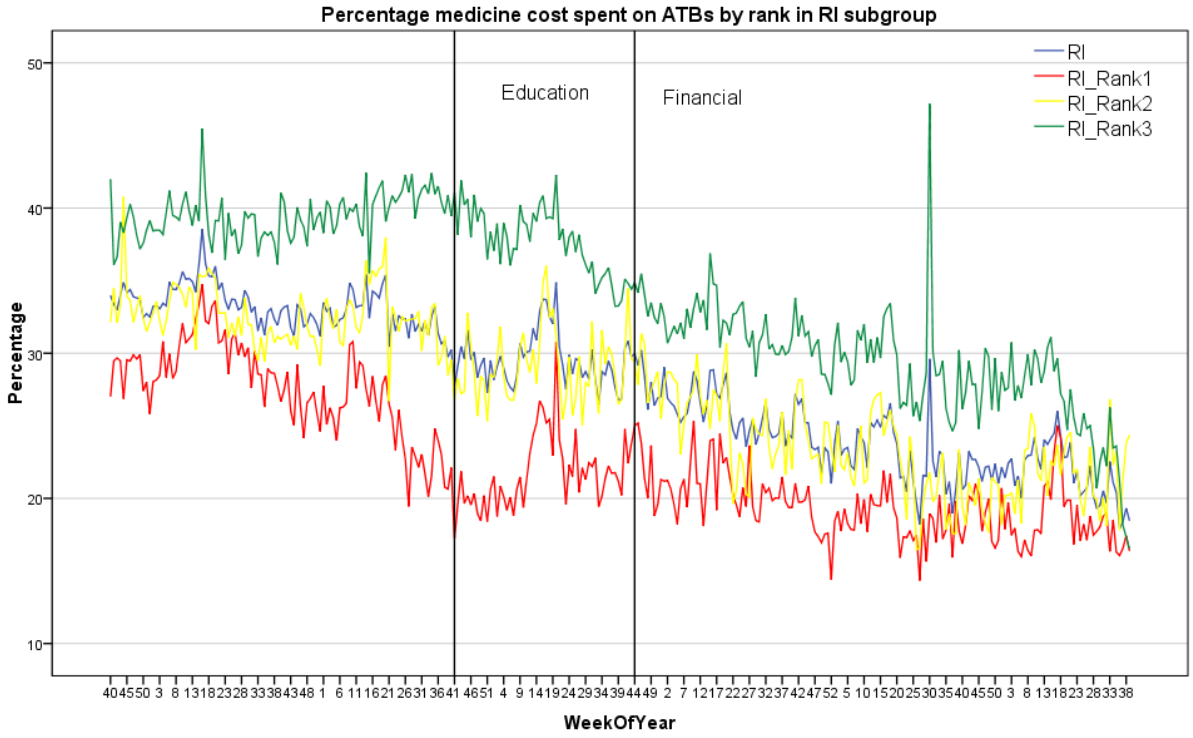

Figure 24 Sequence charts of weekly aggregate percentage medicine cost on ATBs in RI subgroup separated into 3 ranks by average rate before interventions (1, 2, 3)

Subgroup AD

To analyze the trends of antibiotics cost in AD subgroup analysis, the sequence chart of percentage medicine cost spent on ATBs in AD were created separated by rank 1, 2 and 3, as described in Chapter III. Weekly aggregated percentageof ATBs cost in each grading group was calculated. Figure 26 illustrates trajectory of percentage medicine cost on ATBs during the research period in 159 clinics. As expected, rank 3 clinics had the highest percentage of ATBs cost followed by rank 2 and rank 1 respectively. The percentage ATBs cost in all rank group were gradually decrease overtime..

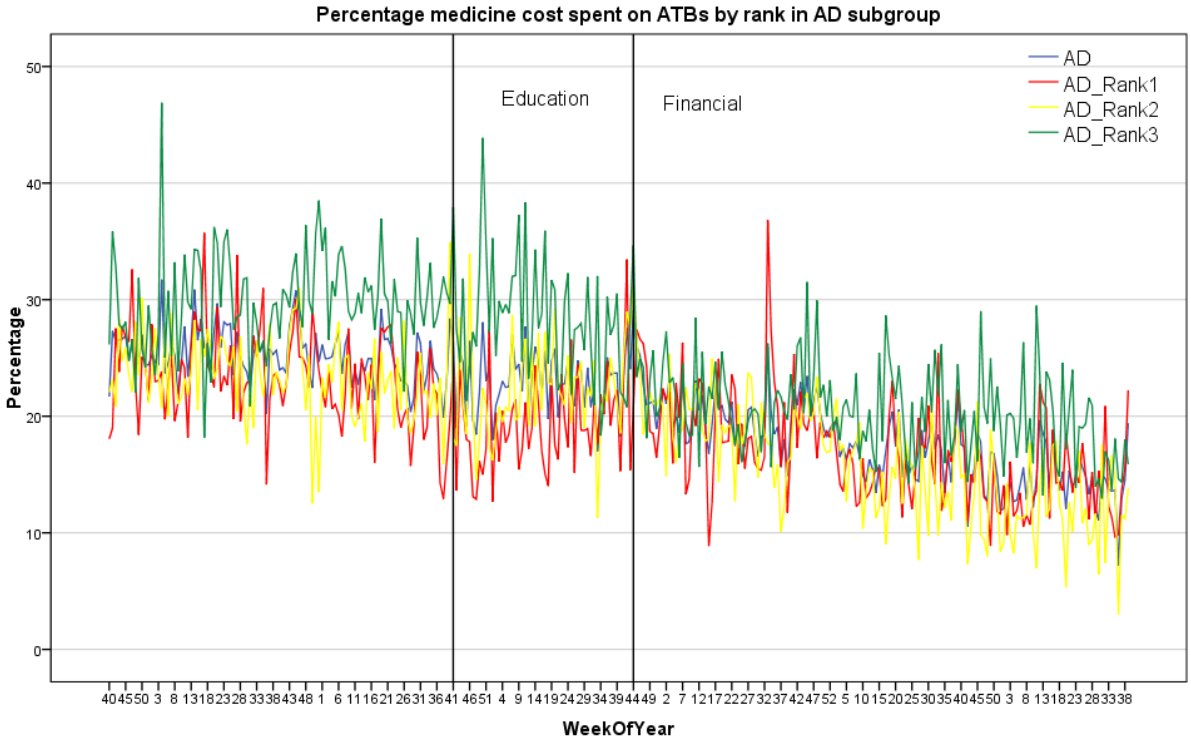

Figure 25 Sequence charts of weekly aggregate percentage medicine cost on ATBs in AD subgroup separated into 3 ranks by average rate before interventions (1, 2, 3)

Before analyzing data using interrupted time series analysis, the descriptive statistics were present to asses how percentage ATBs cost changed during the entire period of the study. The average percentage medicince cost spent on ATBs before, during education intervention and after financial intervention in 159 Clinics for each subgroup grade as show itn Table 18. Regarding to education intervention, the percentage ATBs cost had a decrease trend in all outcomes of interested. Percentage ATBs cost in Total prescriptions was decreased from 3.868% before education intervention to 2.80% after the intervention. The percentage change was 23.83% reduction. Total Rank 3 had the highest decrease in average medicine cost comparing to rank 2 and rank 3.

Considering subgroup analysis, the average percentage ATBs cost in RI after intervenition was at 23.74%, while average percentage ATBs cost in AD after intervention was at 17.51%. The percentage ATBs cost in RI were higher then the average percentage ATBs cost in AD. This implys that ATBs was prescribed in RI more than in AD, or ATBs that prescribed in RI were more expensive than in AD. Also, AD Subgroup had a higher percentage reduction at 30.99% comparing with RI subgroup which had percentage reduction at 28.51%..In RI subgroup, rank 1 clinics in had the highest percentage reduction at 30.13% in RI followed by rank 2 and rank 3 respectively.AD rank 2 had the highest reduction ATBs at 32.46.% followed by rank3 and rank 1.

Table 18 Average percentage medicine cost spent on antibiotics before, during and after education intervention and before and after financial intervention in 159 clinics

Outcomes	Before*	During Education Intervention[1]	After Financial Interventio[2]	Difference (After - Before)	Percent difference
Total	3.68	3.10	2.80	-0.88	-23.825
Total Rank 1	3.09	2.57	2.59	-0.50	-16.032
Total Rank 2	3.92	3.34	2.92	-1.00	-25.524
Total Rank 3	4.09	3.38	2.91	-1.18	-28.847
RI	33.21	29.55	23.74	-9.47	-28.507
RI Rank 1	27.61	21.68	19.29	-8.32	-30.13
RI Rank 2	32.57	29.05	23.22	-9.35	-28.713

Outcomes	Before*	During Education Intervention[1]	After Financial Interventio[2]	Difference (After - Before)	Percent difference
RI Rank 3	39.46	37.71	29.31	-10.15	-25.712
AD	25.27	22.90	17.51	-7.76	-30.724
AD Rank 1	23.34	19.32	17.00	-6.34	-27.154
AD Rank 2	23.39	22.07	15.80	-7.59	-32.456
AD Rank 3	29.81	28.39	20.57	-9.24	-30.992

*Before = Week 40 Year 2013 to Week 40 Year 2015, [1]During = Week 41 Year 2015 to Week 43 Year 2016, [2]After = Week 44 Year 2016 to Week 39 Year 2019

The example of ARIMA modelling development as shown in the **Appendix A**. Summary of the best fitted ARIMA model in each intervention and subgroup shown in table 19. The percentage medicine cost on ATBs had significantly affect by education intervention in Total, Total rank 1, 2, and 3. RI, RI rank 1, 2, and 3, and in AD, AD rank 2 and 3 ($p < 0.05$) When considering subgroup by disease, the significant impact was found in RI, RI rank 1, 2, and 3, and in AD, AD rank 2 and 3 ($p < 0.05$). However, financial intervention has a significant effect to the percentage medicine cost on ATBs in Total rank 3 and in AD rank 2 and 3 ($p < 0.05$, $p = 0.001$, $p = 0.000$ and $p = 0.000$) restively). This suggestion that education intervention had a significant effect to the medicine cost spent of ATBs, while financial intervention some had effect in some group of AD. This imply that education intervention may be more effective than financial intervention to reduce prescription of ATBs.

Table 19 Time series intervention analysis of Percentage medicine cost on Antibiotics in community care clinics in Bangkok, 2013 – 2019

Outcome	ARIMA model	Parameter Estimates		S.E.	P-value
Total	ARIMA (2,0,0)(0,0,0)	Education	-.587	.176	.001*
		Financial	-.260	.168	.123
Total Rank 1	ARIMA (0,1,1)(0,0,0)	Education	.013	.018	.473
		Financial	-.004	.017	.817
Total Rank 2	ARIMA (2,0,0)(0,0,0)	Education	-.593	.219	.007*
		Financial	-.373	.208	.074
Total Rank 3	ARIMA (2,0,0)(0,0,0)	Education	-.698	.208	.001*

		Financial	-.403	.199	.044*
RI	ARIMA (1,0,0)(0,1,1)	Education	-3.339	.318	.000*
		Financial	.493	.419	.240
RI Rank 1	ARIMA (2,0,0)(0,0,0)	Education	-5.862	1.100	.000*
		Financial	-1.475	1.042	.158
RI Rank 2	ARIMA (1,0,0)(0,1,1)	Education	-3.075	.474	.000*
		Financial	.166	.625	.790
RI Rank 3	ARIMA (2,0,0)(0,1,1)	Education	-1.932	.606	.002*
		Financial	-2.020	.789	.011*
AD	ARIMA (1,0,0)(0,1,1)	Education	-2.115	.403	.000*
		Financial	-.674	.529	.204
AD Rank 1	ARIMA (1,0,0)(0,0,0)	Education	8.181	4.179	.051
		Financial	6.881	4.336	.114
AD Rank 2	ARIMA (0,0,0)(0,1,1)	Education	-.912	.505	.072
		Financial	-2.462	.663	.000*
AD Rank 3	ARIMA (0,1,1)(0,0,0)	Education	-.162	.026	.000*
		Financial	.095	.022	.000*

* $p < 0.05$

Part II study

To describe the financial impact, drug management process, and health's personal knowledge and attitude toward the project intervention.

Phase I

The financial payment data in fiscal year 2018 and 2019 was derived from the NHSO's payment report. The descriptive data of Antibiotics prescription each disease (AD and URI) as show in Table 20 and 21.

.According to ATBs prescription in URI, the trend of the clinic that prescribed ATBs in accordance with guideline (ATBs prescriptions less than 20%) is increasing from 31% to 38% from year 2018 to 2019 (See table 20). However, the percentage of the clinics which did not meet guideline (ATBs prescription more than 40%) increasing from 32% to 42%. This can imply that the financial intervention affect the change in the group of clinics that tend to have good practice in RDU whereas the group of clinic that are not do a good practice seem to have no effect. The criteria adjustment in year 2019 seem to affect prescribing behavior in top clinic more than bottom clinic. The payment also increase from year 2018 to 2019 due to the weight calculation on KPIs is changed from 5/86 in year 2018 to 10/100 in year 2019. This change affect the middle group to increase a chance to received that higher payment in 2019 comparing with year 2018, while it give the punishment to the low grade group to not receiving the money if they keep the same level of drug prescription.

Table 20 Descriptive data of ATBs prescriptions in accordance with guideline in RI in 2018 – 2019 fiscal year

Criteria for URI in 2018 (Percentage ATBs prescriptions)	Mark	Number of clinics	Percent	Payment Amount (THB)	Criteria for URI in 2019 (Percentage ATBs prescription)	Mark	Number of clinics	Percent	Payment Amount (THB)
=< 20	5	50	31%	68,889.10	=< 20	5	61	38%	106,792.80
					>20.0 - 22.5	4	7	4%	85,434.24
>20.0 - 30.00	3	32	20%	41,333.46	>22.5 - 25.0	3	9	6%	64,075.68
					> 25.0 - 27.5	2	8	5%	42,717.12
					>27.5 - 30.0	1	7	4%	21,358.56
>30.0 - 40.00	1	26	16%	13,777.82	>30.0	0	67	42%	0
> 40.0	0	51	32%	0					
	Total	**159**				**Total**	**159**		

Table 21 Descriptive data of ATBs prescriptions in accordance with guideline in AD in 2018 - 2019 fiscal year

Criteria for AD in 2018 (Percentage ATBs prescriptions)	Mark	Number of clinics	Percent	Payment Amount (THB) Per Clinics	Criteria for AD in 2019 (Percentage ATBs prescription)	Mark	Number of clinics	Percent	Payment Amount (THB)
=< 20	5	42	26%	69,031.43	=<20	5	52	33%	105,210.69
					>20.0 - 22.5	4	10	6%	84,168.55
>20.0 -30.00	3	33	21%	41,418.86	>22.5 - 25.0	3	6	4%	63,126.41
					> 25.0 - 27.5	2	10	6%	42,084.27
					>27.5 - 30.0	1	12	8%	21,042.14
>30.0 - 40.00	1	26	16%	13,806.29	>30.0	0	69	43%	0
> 40.0	0	58	36%	0					
	Total	**159**				**Total**	**159**		

Table 20 present the trend of clinic that prescribed ATBs in accordance with guideline in AD (ATBs prescriptions less than 20%) is increasing from 26% to 33% from year 2018 to 2019. However, the percentage of the clinics which did not meet guideline (ATBs prescription more than 40%) is increasing from 36% to 43%. This can assume that the financial intervention affect the change in the group of clinics that tend to have good practice in RDU where the group of clinic that are not do a good practice seem to have no effect. The criteria adjustment in year 2019 seem to affect prescribing behavior in top clinic more than bottom clinic. The payment also increase from year 2018 to 2019 due to the weight calculation on KPIs is changed from 5/86 in year 2018 to 10/100 in year 2019. This change affect the middle group to increase a chance to received that higher payment in 2019 comparing with year 2018

Phase II

The researcher interviewed health personal from four selected community care clinics. Two top clinics received mark 5 on QOF in year 2018 (the first clinic prescribed 11.97% of ATBs in AD, and 5.78% of ATBs in RI, the second clinic prescribed 6.45% of ATBs in AD and 11.84% ATBs in RI). The pharmacist from the second clinics worked in the another clinic with the same owner. The clinic had a similar results of QOF marks to the second clincic (prescribed 7.2% of ATBs in AD and 7.96% of ATBs in RI). Two bottom clinics receive mark 0 on QOF 2018 (the third clinic prescribed 70.27% of ATBs in AD, and 84.95% of ATBs in RI, the fouth clinic prescribed 78.11% of ATBs in AD and 89.23% ATBs in RI) The key informants in each clinic are 1 physician, 1 pharmacist, and 1 manager. The manager from 3 clinics are nurse, while a manager in one clinic is public health officer. Total 12 informants was interviewed. Two physician was attending at least one of training program organized by NHSO-Bangkok, while two physician are new staff of the clinic and never participated in the training program. Four Pharmacists was attended at leaset one training program that organized by NSHO-Bangok. Characteristics of three informant group was shown in Table 23. The purspose to this phase of study was to describe the impact of intervention on drug management and health's personal knowledge and attitude outcome.

Table 22 Informant's characteristics

Characteristic	Frequency
% Female	7 (58.3%)
Average Age (mean ± SD)	42.58 ± 14.41
Role - Physician - Pharmacist - Nurse - Public health officer	 4 (2 attend the training, 2 not attend) 4 3 1

Characteristic	Frequency
Work status	
- Full time	10
- Part-time	2
Management position	
- Management	6
- Operation	6
Average work year (mean ± SD)	4.08 ± 2.81

Drug management process

The informant provide the information on the change of clinic management process after participating RDU clinic project campaign. However, the records, or review document of related activity was not present during the interviewing..

Pharmacy and Therapeutic (PTC) activity and performance.

Change in PTC activity which will results in the improvement of PTC performance. on RDU project. The activity that was implemented are

1. Establishment of PTC within the clinic. All key informants admitted that PTC activity was the main function for management which owner and the manager in each clinic will discuss about issues that was related to the internal management. The monthly meeting was organized informally within the clinic and the manager will communicate about policy or the change in the clinic to the operation staff. Many issues was addressed in the meeting, not only RDU clinic projects. In case of a vital news that need for an ergent resposes, the manager or the pharmacist will send the information in the Line (social media) group in which every staff within the group will know the information immedietatly. The minute of meeting was not present to the interviewer. The informant explained that most meeting are informal and the record was kept as an electronic file rather than paper copy. The content that related with RDU clinic project was addressed

during the meeting and the clinic representative who joined the education organized by NHSO – Bangkok will share new knowledged to the staff. The statement from many informants wear shown in the following example:

"...after attain the education event, the pharmacist will update the new drug guideline by sending information in Line group or circulating letter" (ID8)

"... the management team launch the new policy that require patients to bring the empty drug packaging everytime they visited, we will organized meeting to informed every staff about the new policy to tell patients. This policy will be beneficial to reduce duplicated drug dispensing items." (ID6)

2 Revising on drug formulary: The informant informed that some drugs was delisted from the clinics drug formulary due to there was no benefit evidence such as paracetmoal injection, serratiopeptidase, NSAIDs (piroxicam, nimesuline) in order to comply with guideline. However, all informant admitted that they keep some drug since they see some benefits such as Tolperisone hydrochloride, Flunarizine, Cinnarizine. As some physician state:

"...we still prescribed Norgesic since some patients received benefit in terms of psychological effect, for example, they feel revored if they received medicine. (ID2)"

"... Cinnarizine, flunarizine is non-ED drug so the patient have pay for the drug but it was not expensive and it becomes a revenue for the clinic" (ID3).

3. In-house training. The manager will decide who would be send to the training when there were new education event organized by NHSO or the training in the network referring hospital,. If the training topics was related with medicine or RDU, physician or pharmacist, was assigned to attend. After finished training, the attendee was responsible to training the health personal staff (nurse or public health officer) who did not participated the training program. The physician were informally trained the staff about the concept of RDU, when they have a freetime from practicing. The material receive from the training such as manual, poster, CD was used as the education media in this

stage. The poster was attaching in the examination room to create the rational drug use awareness to the patients. As pharmacist and nurse mentioned;

"...when I have freetime I will teach the staff about the concept of RDU to aware the important of RDU and know how to provide the good care to the patients. (ID8)"

"...we sent two staffs to attend the training each time, since the nures and public healt staff was not attend, the pharmacist will teach them what she learned" (ID11).

"... I used the manual received during the training as teaching material, It was really useful and easy to follow" (ID12).

4. Monitoring labelling adjustment: Key informants (pharmacist) informed that they used the standard drug labelling provided from the training in dispensing process. There were 13 drug items selected as the prototype for adjusting drug labelling to meet with RDU concept. However, there are some discrepenacy between top clinics and bottom clinic regarding to the application of drug labelling. Top two clinic informtd that they used new labelling as a prototype to adjust setting in the computor's label printing program to print new labeling for future use. As the informant state:

"...the HOS-OS program was designed to support label printing editting. You have to know how to do it" (ID8).

Whereas the bottom two clinics, admitted that they use used up provide labelling until and were not willing to produce new labeling further. As one informant mentions:

"...honestly I am the old people, the computer stuff is not comfortable to me. (ID5)"

Morever, some informants also comment that the information provided in the standard drug labelling was exaggerate and may frighten patient to concern about their drug safety. As one physian and one pharmacisted mentions;

"...the warning on leg edema from amlodipine may cause the patient afraid to taking drug and worried about there leg edema which was not actually cause by the drug" (ID7).

"...the patient can have swellow feet because he hit something by accident and this was not caused by the drug" (ID5).

5. Regulatory measure: From top two clinic, one physician from top two clinics agree that after attended the trainging, he had updated on new guideline and drug prescription, especially antibiotics was reduced.. As he state:

"...in case of pharyngitis, the patient have to meet 3 of 4 criteria, that are sore throat, fever, enlarge lymph node, and no cough, to meet with the indication for prescribing antibiotics. it was hardly to find patients who need antibiotics recently" (ID7".

Whereas another physician who did not attend the education, mention that his practice is in accordance with the guideline and meet with his prior knowledge he learned from medical school. So he did not change his prescribing practice. As he mentions:

"...I was new to this clinic and never attend RDU training, but my practice is the standard that I learned sicne medical school and from my experience as an intern in suburn area. This practice are the same as RDU guideline" (ID10).

However, the physicians from bottom two disagreed with some contents in the guideline and keep their own practice. They see that the guideline is not practical to their context. The example of their statement are:

"...the criteria establish by central department who do not see our real patients, I put the patients's benefits first and the criteria from the guideline is not applicable to my patients" and ",,, my antibiotics prescription meet with the disease diagnosis and I affirmed my practice." (ID4).

"...In practical, it was difficult not to prescribed antibiotics. I know very well that I the patients have no need form antibiotics, however, sometime when the patients insisted on receiving antibiotics and it waste my time and resource to explain to these stubborn patients. Antibiotics was prescribed as it improved the patient's emotional outcome" (ID2).

6. Financial Incentive: All informants answered that there is no financial incentive to physician, pharmacist or staff to reduce antibiotics prescription. From tops two clinics, one physicians aware that the clinic received the payment if their QOF meet with criteria, but this was not impact his practice since he did not receive any incentive. Another physician in tops two clinic also mention that he did not aware if the clinic will receive payment or not, but his practice is in accordance with standard guideline that most patients can recover without antibiotics. Regarding to physician from bottom two clinice, both physician agree that there was no incentive for not prescribing antibiotics and there is no pressure from the management team to meet with the RDU-KPI in QOF. The manager from bottom two clinic also mentioned that the physician had a full authority for their prescription practice and pharmacist intervention was almost impossible. The example of statement are:

"...I know the criteria of QOF, and our clinic performance meet with the criteria. But it did not affect my practice, since I did not earn any extra income regarding to ATBs prescribing reduction" (ID7).

"...I am not aware of KPIs criteria. What I practice is meet with the gulideline" (ID10).

"...the management team know the criteria, but they did not pay attention on RDU-KPIs, they put authority to the physician to decide on their practice" (ID1)

Health personal knowledge and attitude outcome

The informant provide their opinion about RDU clinice project in two aspects;

1. Health personal's knowledge and opinion:

1.1 Knowledge on RDU concept project.

The informants was requested to explain their knowledge on RDU on their own perception. All informant, who were pharmacist, have the similar opinion on Antibiotics Smart Use concept and their knowledde is consistant with the guideline. Whereas, the physician in top two clinics had a different opinion. Top two physian explain the concept of RDU in corresponse with the guideline, while physician from bottom two view the guideline on the different perspective and consider antibiotic prescribing was rely on the patients' context. The example of explainations from bottom two are:

"...the guideline should suggested what to prescribed rather than assume that all of infection did not required antibiotics" (ID4).

"...the guideline is OK, but in reality when you take care of Universal Coverage patient, they expected free drug when they visit doctor. They feel that the doctor prolong the disease for not prescribing any drug to them" (ID2).

1.2 Attitude toward RDU clinic project.

All informant are satisfied on the project implementation. Promote the RDU concept is a good deeds and the organizer do very well in terms of education course and material preparation. Attended the training to update new knowledge or new guideline that they never aware of. Even one physician who not agree with all content in the guideline admitted that some content in the training is applicable for their practice such as advers drug reaction or drug interaction. All of informant agreed that NHSO should support on continuation of the project. The example of key informant comment are;

"...The RDU project is beneficial. The content is OK. There should be a continuous support from NHSO" (ID11)

"...The project is good and should continue. The problem is lack of continuous reminder" (ID9).

1.3 Benefits and the obstacles of the project

All informant see the benefits of the project and support the project to continued

The benefits they see were not only for the reduction in total healthcare cost but also benefit to the society as reducing antibiotics utilization means reducing antibiotic resistance and improve drug use performance in total society.

However, the informants suggested that there are many obstracles for the success of the project.

1) lack of continuation support from the policy maker such as NHSO.

"...lack of continuation of the project, maybe th problems are related to policy maker to decied where the budget would flow into" (ID8).

2), the patient attitude toward antibiotics utilization still not improved. Some patients are stubborn and difficult to change.

"...the patient need to aware antibiotics smart use concept, so they will understand why they not need for antibiotics" (ID2).

Another patient's problem were they are not live around the registered clinic and they would like to received medicine for worth of their traveling cost

"...patient complained why they don't receive antibiotics since they travel so far" (ID3).

The NHSO should focusing on promotion RDU concept to society as a whole.

"...the promoting RDU should covered the whole society" (ID9) .

3) the personal management, since all clinics have only one physician, if physician attending the training, they need to find part-time staff. Also, there are limited budget to recruite full time pharmacist. So there are many workload to nurse on dispensing and patient communication..

2 Feedback from patient toward project to health personal

Key informants provided the patient feedback to physician on their satisfaction in term of cure rate. Some physicians admitted that the clinical outcome is difficult to monitor if the patients did not have follow up visit, they assume that the patients was recoverd so they did not return to the clinic. However, in case of rountine or chronic patient. The physician, pharmacist or healthcare staff are familiar with patient and the feedback from patient mostly

positive and the attitude of patients who did not receive antibiotic are very well. The example of statement are:

"...physician appoint patient for 1 week follow up, if they did not return, it simply means that they are recoved" (ID5)".

"...in case of chronic disease patients, they are return visit and happy with the recovery without antibiotics" (ID7).

CHAPTER V
DISCUSSIONS

Part I study

The purpose of Part I study is to determine the impacts of RDU clinic project on drug utilization. Finding from the study suggested that RDU clinics project is partially effective to improve quality of drug use in terms of ATBs utilization, number of ATBs prescribed and cost. For Total ATBs utilization (oral and parenteral), financial intervention has a significant effect on Total ATBs utilization and Total oral ATBs, while the education intervention shown no significant effect. This consistent with the suggestion from study on Antibiotics Smart Use (ASU) program suggested that adoption of ASU practice as a pay-for-performance (P4P) criterion was an important achievement that prompted nationwide expansion of ASU (11). Since the financial intervention occur around 1 year after eduction intervention, the effect of financial intervention was the combined effect of education, this can concluded that eduction intervention alone might not be effective for reducing ATBs utililization without the combined effect from financial intervention. This is consistant with a systematic review on the effect of intervention measure on irrational antibiotics/antibatrial drug use in developint countries (17), Bbosa suggested that the most significant improvement observe with multi-facet intervention measure that involved all intervention measure (education, managerial, diagnostic, regulatory and economi/financial measure) Also, both education and financial interventions had no significant effect in subgroup analysis in RI and AD diagnosis. This can imply that most of ATBs was prescribed in other disease rather than RI and AD and interventions may not be effective to reduce ATBs utilization in particular disease diagnosis. It could also result from a small number of observations at pre-intervention period The shorter the time-series, the more it will be subject to short-term changes in the target variable and the more likely the analysis is to miss long term patterns (29). Since the determination of drug name using TMT code start implementation in September 2016, this may result in an incomplete drug data in pre-intervention period.and all of ATBs prescribed were not be included for the analysis. Parenteral ATBs utilization was also significantly affected by both education and financial intervention.

ATBs items that were impacted from intervention are Dicloxacillin, Cloxacillin, Ciprofloxacin, Ofloxacin, Ceftriaxone, and Lincomycin. In could imply that the decreasing Cloxacillin utilization was related with the increasing utilization of Dicloxacillin. It suggested that there was a switching on prescribing practice from Cloxacillin to Dicloxacin. This is consistent with the guideline for prescribing in simple wound prophylasis (47), Dicloxacillin is the drug of choice, while Cloxacillin have no indications in such disease.

Considering Amoxycillin utilization, both interventions did not have a significant impact on the Amoxicillin utilization. Since the guideline suggested that Amoxicillin only have indications in the treatment acute bacterial rhinosinusitis and GAS Pharyngitis (47). This can assume that prescriptions pattern of Amoxycillin were incordance with guideline at the pre-intervention period and the diagnosis cases were similar between pre- and post intervention. Therefore,. It can also deduce that the ATBs utilization in RI were not impacted by the interventions since Amoxicillin contribute to the majority of drug prescriptions in RI diagnosis.

Considering Total prescriptions analysis, the education intervention had a measurable impact on the percentage encounter with ATBs, while the percentage adherence with guideline had not significantly impacted by either education or financial intervention. However, the previous study in individual-level summarized that the education intervention improved the quality and reduced the quantity of antimicrobial use long term care patients (18). We can concluded that education intervention improved the quality of drug use in general prescriptions, but not affect to a particular group of diagnosis of RI and AD. When analyzing data in subgroup, we found that education intervention had a significant effect on both the percentage encounter with ATBs and the percentage adherence with guideline in AD. The result is consistent with the study in Lao PDR using a cross sectional study to assess the effectiveness of the National Drug Policy revealed that the management of simple diarrhea in children was significantly more in accordane with standard treatment guidelines in pilot provined than a control province (48). This can also interpretation implies that even the lower number of prescriptions in AD comparing with RI, the number of ATBs prescriptions in AD are more likely affected by the interventions from NHSO-Bangkok. Whereas the prescription

ATBs in RI have a reducing trend without the intervention. Due to non-stationary of time series data that the mean and the variance of data series can change over time for reason other than the effect of the policy change (29).

Regarding to cost analysis, both education intervention and financial intervention have no significant effect on the average medicine cost per encounter in Total, Total rank 1, 2 and 3.. This could results from majority of prescriptions were prescribed in other diseases diagnosis, rather than RI and AD and ATBs did not contribute to majority of drug cost in each prescripton. It also suggest that the decreasing average medicine cost was the result of other drug cost reduction rather than ATBs. It could also result from difference pricing policy in the difference clinics. Meanwhile, the percentage medicine cost on ATBs had significantly affect by education intervention in Total, Total rank 1, 2, and 3. RI, RI rank 1, 2, and 3, and in AD, AD rank 2 and 3. We can assume that the education intervention incentive, is more effective than financial incentive to reduce ATB drug expenditure, but have no direct effect on total expenditure.. However, since financial intervention was implemented approximately one year after the beginning of the intervention, we can deduce that the effect of the education intervention was not sustain.

Our study has strength and limitations. The strength of the study is we can determine the association between intervention (RDU clinic project) and outcome (Quality of drug use). The interrupted time series analysis (ITS) is a powerful method for investigate medicine use and fit with data that are routinely collected in health system. It is common in the real-world situation when the data cannot be randomized into study and control group, for example, a nationwide mass media campaign to reduce prescribing of antibiotics for common cold cannot suitably be controlled (15). Due to outcome characteristics that are: non-stationary, auto-correlation and seasonality, it is not appropriate to measure the outcomes as in the cross-sectional study design (30). ARIMA modeling method have and can reveal dynamics of the intervention response in term of time to response and persistence of effect. ITS study result is useful for the policy-maker to launch the health policy that suitable for country's need. The study benefits will change the prescribing behavior, improve rational drug use, and reduce

antibiotics resistance in the public. The successes of the program will encourage more clinic to join the program and expand the rational drug use in the national level.

The study also has some limitations. First, selection of antibiotics as drug for analysis in the study may not represent rational drug use in the overall program performance. The content in the education intervention contain other issue of RDU such as prescription in hypertension or Diabetes Mellitus (47). Second, the problem of data collection from the database: such as incompleteness of the data or coding error, could result in miscalculation of outcome estimation. However, this error could consider insignificant comparing to the amount of big data analyze in the study. Third, threat to internal validity of the study design. Influence of the co-intervention, such as new clinical guideline, that occur during the study period and produce other explanation of the change rather than the intervention (43). Fourth, the limitation of interrupted time series analysis technique is that it provide a rough estimation of the relationship between the intervention and outcome and unable to determine the causal relationship (29). Fifth, the analysis focusing on two interventions; education and financing. This may not able to determine the effectiveness of program intervention. Multi-facet intervention show the most significant improvement in ATBs use (17). Finally, prescription database is not representing the actual drug use in the patients considering the non-adherence to treatment problem The qualitative analysis in Part II Phase II of the study should explain why the intervention in not effective to change the prescribing behavior by analysing the the heatlh personal attituge using In-depth interview method.

Part II study

The purpose of Part II study is to determine the impacts of RDU clinic project on drug management process and described health's personal opinion after participating the project. The analysis were devidd in two phases as discussed belows.

Phase I

Phase I Part II of the study is to describe the amount of payment NHSO –Bangkok had paid to community care clinic in 2 consecutive fiscal bugeting year. The result of data

suggested that financial incentive affect high grade clinic (good practice) more than low grade clinic. The qualitative analysis in Phase II study could explain why difference clinic had a differenct results ont percentage of antibiotics prescrtiption by In-depth interviewing the health personal regarding to their attitude and behavior.

Phase II

Phase II Part II of the study investigate the changed in participated clinic in term of internal management and analys health's personal knowledge and attitude toward RDU project. The outcome of health personal attitude indicated that the financial incentive is not the real motive for the precriber to change their prescribing practice. The management team in each clinic did not pay attention in this KPI as the source of their income. Whereas the education intervention seem to have an effect health person who have the positive attitude toword project than the health personal who have negative attitude. Even we did not analyzed the relationship between age and attitude.The health personal staff who have negative attitude seem to have the higher age that the health personal staff who have young age. The attitude of health personal is steady and is difficult to change, especially for the old age people. Another, barrier toward change in the attitude is the power status where the physician have full authority on their own practice which even pharmacist intervention is not effective. It is consistent with the study of power distance had a significant impact on prescribing behavior (49). This can explained by the Hofstede's model of cultural dimension (50) that country with hierarchical society are related with high power distance index (51). According to data from Hofstede insight (52), Thailand is the country where power distance index is high at 64. Therefore, we can predicted that Power distance had a major impact on physician prescribing behavior. In term of knowledge, there some different of knowledged and perception between 2 group doctors who have a completely opposite practice. The role of the patients attitude also influence the prescribing behavior in some extent. The patient attitude toward the right and free drug and service seem to encourage them demand more drug than the patient who have to pay for service. Another problem we also found from the study is there are many patients register their right at the clinics that are not close tho their area or their work place. This results in the higher cost of travelling expense and

the patient demand higher drug in each visit. The lack of continuous project the one of barrier for the project success. Behavior require more repetitive reminding and continouse training. Also, the barrier to the campaing also related with the monetary and budgeting. Limitted on the budget to hire enough pharmacisit emphasized on the importanct role of the pharmacist to improve in Rational Drug Use in the health care service and the society in the long run

The situation of drug management and health personal's opinion on RDU project in community care clinic, regarding to benefits and obstacles, will be learned and used for future project implementation.

CHAPTER VI
CONCLUSION

Finding from the study suggested that RDU clinics project is partially effective to improve quality of drug use in terms of ATBs utilization, number of ATBs prescribed and cost. The study reveal the benefit of using Interrupted Time Serie analysis to analyze the effect of policy intervention using the longtitudinal data where in the real-world situation the data cannot be randomized into study and control group. Analysis of the Rational Drug Use project intervention using ARIMA proved the robustness of the methodoly and suitable for analyzing data with seasonal and trend.

Irrational drug use especiall in Antibiotics prescript still are one of the common drug use problem in every level of drug utilization. Many interventions had inmplement in many setting to improve drug use and reduce cost of unnecessary drug that result in patient unsafety and bad outcomes. However, single intervention may not have a powerful effect to change the attitude in both prescriber and patient. Multti – facet intervention may required in further study to find the effective intervention that can improve proper drug use and reduce drug for patient and society.

REFERENCES

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1. WHO International Working Group For Drug Statistics Methodology, WHO Collaborating Centre For Drug Statistics Methodology. Introduction to drug utilization research: World Health Organization; 2003.
2. Organization WH. Promoting rational use of medicines: core components. 2002.
3. Chalker J. Promoting rational prescription. 2012. In: MDS-3: Managing Access to Medicines and HealthTechnologies [Internet]. Arlington, VA: Management Sciences for Health. Available from: https://www.msh.org/sites/msh.org/files/mds3-ch29-rationalprescribing-may2012.pdf.
4. Holloway KA. Thailand Drug Policy and Use of Pharmaceuticals in Health Care Delivery. Bangkok: World Health Organization, Regional Office for South East Asia, New Delhi; 2012.
5. Pagaiya N, Garner P. Primary care nurses using guidelines in Thailand: a randomized controlled trial. Tropical Medicine & International Health. 2005;10(5):471-7.
6. Suttajit S, Wagner AK, Tantipidoke R, Ross-Degnan D, Sitthi-amorn C. Patterns, appropriateness, and predictors of antimicrobial prescribing for adults with upper respiratory infections in urban slum communities of Bangkok. Southeast Asian journal of tropical medicine and public health. 2005;36(2):489.
7. Bhavnani D, Phatinawin L, Chantra S, Olsen SJ, Simmerman JM. The influence of rapid influenza diagnostic testing on antibiotic prescribing patterns in rural Thailand. International Journal of Infectious Diseases. 2007;11(4):355-9.
8. Apisarnthanarak A, Mundy LM. Comparison of Methods of Measuring Pharmacy Sales of Antibiotics without Prescriptions in Pratumthani, Thailand. Infection Control & Hospital Epidemiology. 2009;30(11):1130-2.
9. Treebupachatsakul P, Tiengrim S, Thamlikitkul V. Upper respiratory tract Infection in Thai adults: prevalence and prediction of bacterial causes, and effectiveness of using clinical practice guidelines. J Med Assoc Thai. 2006;89(8):1178-86.
10. Zou YM, Ma Y, Liu JH, Shi J, Fan T, Shan YY, et al. Trends and correlation of antibacterial usage and bacterial resistance: time series analysis for antibacterial stewardship in a Chinese teaching hospital (2009–2013). European Journal of Clinical Microbiology & Infectious Diseases. 2015;34(4):795-803.
11. Sumpradit N, Chongtrakul P, Anuwong K, Pumtong S, Kongsomboon K, Butdeemee P, et al. Antibiotics Smart Use: a workable model for promoting the rational use of medicines in Thailand. Bulletin of the World Health Organization. 2012;90(12):905-13.
12. สำนักงานหลักประกันสุขภาพแห่งชาติเขต13. โครงการเครือข่ายคลินิกส่งเสริมการใช้ยาอย่างสมเหตุผล (Network of Rational Drug Use Clinic). กรุงเทพ; 2559.
13. World Health Organization Regional Office for Africa. Management of Drugs at Health Centre Level: Training Manual. Brazzaville, The Republic of South Africa: WHO Regional Office for Africa; 2004. 84 p.
14. Shalini S, Ravichandran V, Mohanty B, Dhanaraj S, Saraswathi R. Drug utilization studies-An overview. Int J Pharm Sci Nanotechnol. 2010;3(1):803-10.

15. Matowe L. Investigating Medicine Use. 2012. In: Managing Drug Supply-3: MANAGING ACCESS TO MEDICINES AND HEALTH TECHNOLOGIES [Internet]. Arlington, VA: Management Sciences for Health. Available from: http://www.msh.org/sites/msh.org/files/mds3-ch28-investigatinguse-mar2012.pdf.
16. Council APA. The National Strategy for Quality Use of Medicines. Commonwealth of Australia: The Department of Communications, Information Technology and the Arts; 2002.
17. Bbosa GS, Wong G, Kyegombe DB, Ogwal-Okeng J. Effects of intervention measures on irrational antibiotics/antibacterial drug use in developing countries: A systematic review. Health. 2014;6(02):171.
18. Schwartz DN, Abiad H, DeMarais PL, Armeanu E, Trick WE, Wang Y, et al. An educational intervention to improve antimicrobial use in a hospital-based long-term care facility. Journal of the American Geriatrics Society. 2007;55(8):1236-42.
19. Le Grand A, Hogerzeil HV, Haaijer-Ruskamp FM. Intervention research in rational use of drugs: a review. Health policy and planning. 1999;14(2):89-102.
20. Yeo C-L, Chan DS-G, Earnest A, Wu T-S, Yeoh S-F, Lim R, et al. Prospective audit and feedback on antibiotic prescription in an adult hematology-oncology unit in Singapore. European Journal of Clinical Microbiology & Infectious Diseases. 2012;31(4):583-90.
21. Bauraind I, Lopez-Lozano J, Beyaert A, et al. Association between antibiotic sales and public campaigns for their appropriate use. JAMA. 2004;292(20):2465-70.
22. Marshall D, Gough J, Grootendorst P, Buitendyk M, Jaszewski B, Simonyi S, et al. Impact of administrative restrictions on antibiotic use and expenditure in Ontario: time series analysis. Journal of Health Services Research & Policy. 2006;11(1):13-20.
23. Ferrand Y, Kelton CM, Guo JJ, Levy MS, Yu Y. Using time-series intervention analysis to understand U.S. Medicaid expenditures on antidepressant agents. Research in social & administrative pharmacy : RSAP. 2011;7(1):64-80.
24. Ohlsson H, Merlo J. Understanding the effects of a decentralized budget on physicians' compliance with guidelines for statin prescription--a multilevel methodological approach. BMC health services research. 2007;7:68.
25. Gregoire JP, Moisan J, Potvin L, Chabot I, Verreault R, Milot A. Effect of drug utilization reviews on the quality of in-hospital prescribing: a quasi-experimental study. BMC health services research. 2006;6:33.
26. Sudchada P, Umnuaypornlert A, Kitikannakorn N. A Survey of Practical Policies to Promote Rational Drug Use (RDU) Of Pharmacy and Therapeutics Committee (PTC) in Thailand Srinagarind Med J. 2012;27(2):157-66.
27. 13กรุงเทพมหานคร ส. Using labeling and intended label in private institutions under the Network of Rational Drug Use Clinics, Bangkok 2559.
28. Sriviriyanupap W, Muenpa R. Outcomes of Pharmaceutical Care Services in Promoting rational Drug Use. Thai Journal of Pharmaceutical Sciences (TJPS). 2016;40(2).
29. Lagarde M. How to do (or not to do)… Assessing the impact of a policy change with routine longitudinal data. Health policy and planning [Internet]. 2011:[1-8 pp.].

30. Jandoc R, Burden AM, Mamdani M, Lévesque LE, Cadarette SM. Interrupted time series analysis in drug utilization research is increasing: systematic review and recommendations. Journal of Clinical Epidemiology. 2015;68(8):950-6.
31. Ramsey C, Matowe L, Grilli R, Grimshaw J, Thomas R. Interrupted time series designs in health technology assessment: lessons from two systematic reviews of behaviour change strategies. Int J Technol Assess Health Care. 2003;19(4):613-23.
32. Ansari F, Gray K, Nathwani D, Phillips G, Ogston S, Ramsay C, et al. Outcomes of an intervention to improve hospital antibiotic prescribing: interrupted time series with segmented regression analysis. Journal of Antimicrobial Chemotherapy. 2003;52(5):842-8.
33. Chongtrakul P. RDU hosptial: the pathway to Rational Drug Use. Thai J Pharmacol. 2015;37(1):48 - 62.
34. ชัยรัตน์ ฉายากุล, พิสนธิ์ จงตระกูล, วินัย วนานุกูล, พาขวัญ ปุณณปูรต, เพ็ญกาญจน์ กาญจนรัตน์, กิติยศ ยศสมบัติ, et al. คู่มือการดำเนินงานโครงการ โรงพยาบาลส่งเสริมการใช้ยาอย่างสมเหตุผล (Rational Drug Use Hospital Manual). กรุงเทพ: โรงพิมพ์ชุมนุมสหกรณ์การเกษตรแห่งประเทศไทย; 2558.
35. Srithamrongsawat S. JP, Suntorntham S. NHSO Annual Report 2014. Bangkok: National Health Security Office (NHSO); 2014.
36. กรุงเทพมหานคร สเ. แนวทางการประเมินตัวชี้วัดตามเกณฑ์คุณภาพและผลงานบริการควบคุม ป้องกัน และรักษาโรคเบาหวานและความดันโลหิตสูง ปีงบประมาณ 2561. กรุงเทพมหานคร2560.
37. สำนักงานหลักประกันสุขภาพแห่งชาติ. แนวทางการบริหารจัดการงบจ่ายตามเกณฑ์คุณภาพผลงานบริการ ปีงบประมาณ 2560. กรุงเทพ2559.
38. Guidelines for ATC classification and DDD assignment 2016 [Internet]. 2016.
39. Phuksaritanon R, Kijsanayotin B, Theeraroungchaisri A. A medicines terminology governance model for Thailand. Thai Journal of Pharmaceutical Sciences. 2017;41(2).
40. กรุงเทพมหานคร สเ. แนวทางการบริหารงบกองทุนหลักประกันสุขภาพแห่งชาติ เขตพื้นที่กรุงเทพมหานคร ปีงบประมาณ 2560. In: งานยุทธศาสตร์และการประเมินผล, editor. กรุงเทพมหานคร2560.
41. Donnelly NJ. The use of interrupted time series analysis to evaluate the impact of pharmaceutical benefits scheme policies on drug utilisation in Australia: University of New South Wales; 2005.
42. Inc. S. SPSS Trends™ 13.0. The United State.2004.
43. Khruakham S. Assessing the effectiveness of the 2001 drug policy and drug enforcement in Thailand: A Time-series analysis of police data [Dissertation]. United State: Sam Houston State University; 2011.
44. al Me. "Interrupted Time Series Analysis" Sage University Paper Series on Quantitative Applications in the Social Sciences. Lewis-Beck MS, editor. Newbury Park London New Delhi: SAGE publications. ; 1980.

45. สำนักงานหลักประกันสุขภาพแห่งชาติ เขต 13 กรุงเทพมหานคร. แนวทางการประเมินปีงบประมาณ 2562 - ตัวชี้วัดตามเกณฑ์คุณภาพและผลงานบริการ (QOF) - ตัวชี้วัดตามเกณฑ์คุณภาพควบคุมป้องกันระดับทุติยภูมิในผู้ป่วย DM/HT. กรุงเทพมหานคร2561.

46. Vaismoradi M, Turunen H, Bondas T. Content analysis and thematic analysis: Implications for conducting a qualitative descriptive study. Nursing & health sciences. 2013;15.

47. จงตระกูล พ. การใช้ยาอย่างสมเหตุผลใน primary care. กรุงเทพฯ: หจก. วนิดาการพิมพ์; 2559.

48. Paphassarang C, Wahlstrom R, Phoummalaysith B, Boupha B, Tomson G. Building the national drug policy on evidence-a cross sectional study on assessing implementation in Lao PDR. Southeast Asian journal of tropical medicine and public health. 2002;33(3):647-53.

49. Deschepper R, Grigoryan L, Lundborg CS, Hofstede G, Cohen J, Kelen GVD, et al. Are cultural dimensions relevant for explaining cross-national differences in antibiotic use in Europe? BMC health services research. 2008;8(1):123.

50. Hofstede G. Dimensionalizing cultures: The Hofstede model in context. Online readings in psychology and culture. 2011;2(1):2307-0919.1014.

51. Hulscher MEJL, Grol RPTM, van der Meer JWM. Antibiotic prescribing in hospitals: a social and behavioural scientific approach. The Lancet Infectious Diseases. 2010;10(3):167-75.

52. Borg MA, Camilleri L. Broad-spectrum antibiotic use in Europe: more evidence of cultural influences on prescribing behaviour. Journal of Antimicrobial Chemotherapy. 2019;74(11):3379-83.