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**ASSESSING AND IMPROVING RATIONAL ANTIMICROBIAL USE IN URBAN  
AND RURAL HEALTH CARE FACILITIES IN VIETNAM**

by

DO THI THUY NGA

A thesis submitted to the Open University U.K

For the degree of Doctor of Philosophy in the field of Life Sciences

Oxford University Clinical Research Unit

Hanoi, Viet Nam

May, 2016

## **Abstract**

The global problem of antimicrobial resistance (AMR) is particularly pressing in developing countries including Vietnam, where the infectious disease burden is high and cost constrains the replacement of older antimicrobials with newer, more expensive ones. Along with surveillance and infection control, responsible use of antimicrobials is one of the main objectives of the Vietnam National Action Plan on combating AMR. This thesis aims to get a better understanding of how antimicrobials are used in the Vietnamese community and how its use can be improved, to tailor evidence-based interventions and inform policies in controlling AMR.

To assess the current situation of community access and use of antimicrobials and identify determinants associated with current practice, an observational study was conducted in 30 private pharmacies in northern Vietnam. This study was followed by a randomised controlled trial (RCT) to evaluate a point of care (POC) C-reactive protein (CRP, a biomarker of inflammation) test in reducing unnecessary antimicrobial prescribing for patients with non-severe acute respiratory infections (ARI) and analysis of the economic impact and acceptance of this intervention among users.

In private pharmacies, profit incentives coupled to poor knowledge about AMR are key drivers of over the counter dispensing of antimicrobials regardless the existence of regulations. Using a simple rapid blood test to identify customers who do not benefit from antimicrobial therapy would be a potential solution. Primary healthcare stations where over-prescription of antimicrobials for self-limiting infections are common, were chosen for the intervention. CRP POC testing reduced unnecessary AB use for ARI patients without compromising patient's recovery. This supports and extends findings from European trials by showing that such a stewardship approach is applicable even in resource constrained settings. However, there were several obstacles identified among users regarding test adherence associated with large between-site heterogeneity that need to be addressed to maximize the

intervention's effect in the future. More importantly, our cost analysis indicated that to encourage adoption at scale, proper funding mechanisms to balance the invested costs and achieve global impact on AMR is recommended.

In summary, antimicrobial use in Vietnam is largely uncontrolled both in the community and the healthcare system leading to overuse and over-prescription for non-severe ARI. Use of commercially available CRP tests can be an effective, scalable and economically viable approach, even in highly resource-constrained settings. For the future, we are looking at ways to optimise use of POC biomarker testing in primary healthcare and private pharmacy setting. The potential for biomarker based tests to be combined with rapid pathogen detection, enhancing test algorithm adherence, use of CRP tests with equal financial incentives as selling of antimicrobials and introducing pay for performance mechanisms may be crucial parts for optimisation.



### **Co-Authorship**

The work presented in this thesis was primarily completed by me, with close support from my supervisors and colleagues. For most of the works, I led day-to-day management and coordination of the studies implementation under supervision of my director of studies, Professor Heiman FL Wertheim. Pharmacy observation was done in collaboration with Hanoi Medical University, in particular under the supervision of Associate Professor Nguyen Thi Kim Chuc. All discussions with drug sellers and pharmacy owners were led by Dr. Nguyen Quynh Hoa, pharmacist, National Oncology hospital, who is one of my co-supervisors. The clinical trial was conducted in collaboration with ten regional polyclinics under the management of the Hanoi Health Bureau. For the statistical analysis, I worked with considerable support from Dr. Marcel Wolbers, statistician of Oxford University Clinical Unit (OUCRU) – Ho Chi Minh City, Vietnam. For health economics analysis, I was trained and supervised by Dr. Yoel Lubell, a health economist of Mahidol Oxford Research Unit (MORU) – Bangkok, Thailand. During my PhD programme, I was extensively trained by OUCRU faculties and closely supervised by my supervisors, either in persons, through telephone, Skype or via email.

## Publications

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Con cảm ơn bố mẹ và gia đình đã luôn bên con, luôn yêu thương và dành cho con những điều tốt đẹp nhất. Sẽ không có được thành quả của ngày hôm nay, nếu con không có gia đình bên cạnh. Thay ngàn lời muốn nói, con xin được dành tặng món quà này cho gia đình thân yêu!

## **Declaration**

Beyond the assistance indicated in the authorship and acknowledgment, I can confirm that the majority of work presented in this thesis is my own and was conducted under the supervision of Professor Heiman FL Wertheim at Oxford University Clinical Research Unit in Hanoi, Vietnam. The only work presented in Chapter 4 is not my own, which was majorly done by Dr. Yoel Lubell, of which I am a co-author. The work presented in Chapter 2 has been published in BMC Pharmacology & Toxicology in 2014, which has been updated with more recent available literature. This thesis has not been submitted for a degree or other qualification to any other universities.

## Abbreviations

&	And
ADDO	Accredited drug dispensing outlet
ADI	Active detection & isolation
ADR	Adverse drug reactions
AIDS	Acquired immunodeficiency syndrome
AM	Antimicrobial
AMR	Antimicrobial resistance
ANSORP	Asian Network for Surveillance of Resistant Pathogens
ARI	Acute respiratory infection
ATC	Anatomical Therapeutic Chemical
ATCC	American Type Culture Collection
AUC	Area under curve
BCG	Bacille Calmette–Guérin
BLNAR	Beta-lactamase negative ampicillin resistant
BSI	Bloodstream infection
CDC	Centre for Disease Control and Prevention
CDDEP	Centre for Disease Dynamics, Economics & Policy
CHC	Commune health centre
CIA	Centre intelligence agency
COPD	Chronic obstructive pulmonary disease
CRE	Carbapenem-resistant enterobacteriaceae
CRP	C-reactive protein
DALY	Disability adjusted life years
DDD	Defined daily dose

DNA	Deoxyribose nucleic acid
DPT	Diphtheria, Pertussis and Tetanus
DSS	Demographic surveillance sites
EARSS	European antibiotic resistance surveillance system
EPI	Expanded Program on Immunization
ESBL	Extended spectrum beta-lactamase
FGD	Focus group discussions
GARP	Global Antibiotic Resistance Partnership
GDP	Gross Domestic Product
GMP	Global Manufacturing Practice
GPP	Good Practice Pharmacy
GSK	Glaxo SmithKline
HAI	Hospital acquired infection
HCW	Healthcare worker
HI	Health insurance
Hib	<i>Haemophilus influenzae</i> type b
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICER	Incremental cost effectiveness ratio
ICPC	International Classification Primary Care
IDI	In-depth interviews
IMCI	Integrated Management for Childhood Illnesses
IPD	Invasive pneumococcal disease
IQR	Interquartile range
IRB	Institutional review board
ITT	Intention to treat

LMIC	Low and middle income countries
LPS	Lipopolysaccharide
MDR	Multi drug resistant
MOH	Ministry of Health
MORU	Mahidol Oxford Research Unit
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
MRSE	Methicillin-resistant <i>Staphylococcus epidermidis</i>
NA	Not available
NDM	New Delhi Metallo-beta-lactamases
NHTD	National Hospital for Tropical Diseases
NICE	National Institute for Health and Clinical Excellence
OR	Odd ratio
OUCRU	Oxford University Clinical Research Unit
PBP	Penicillin binding protein
POC	Point of care
PSA	Probabilistic sensitivity analyses
QALY	Quality-adjusted life-year
RCT	Randomised controlled trial
RNA	Ribonucleic
RR	Risk ratio
RSV	Respiratory syncytial virus
SD	Standard deviation
SOAR	Survey of antibiotic resistance
UK	United Kingdom
UN	United Nations
US	United States



USD	United States Dollar
VISA	Vancomycin intermediate resistant <i>Staphylococcus aureus</i>
VND	Vietnam dong
VRSA	Vancomycin resistant <i>Staphylococcus aureus</i>
WHO	World Health Organisation
WTP	Willingness to pay

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# Chapter 1

## Introduction

The term “antibiotics” was first used in 1942 by Selman Waksman to refer to substances naturally produced by microorganisms that selectively inhibit the growth of other microorganisms (1). By strict definition, antibiotics do not include substances that are synthetic (sulfonamides and quinolones), or semisynthetic (methicillin and amoxicillin), or those, which come from plants (quercetin and alkaloids) or animals (lysozyme). A broader term “antimicrobials”, which was derived from the Greek meaning “against (anti) little (mikros) life (bios)”, largely refers to all agents that act against microbial organisms including bacteria (antibacterials), viruses (antivirals), fungi (antifungals), and protozoa (antiprotozoals) as well as synthetic and semisynthetic agents.

Antimicrobial resistance (AMR) is the potential of a microbial organism to resist the effect of medicine previously used to treat them. This broader term also covers antibiotic resistance, which applies to bacteria and anti-bacterial drugs. Among antimicrobial classes, antibacterials are the largest and most widely studied group. Thus, the terms “antimicrobial” and AMR are often used interchangeable with the term “antibiotic” and “antibiotic resistance”. In my thesis, “antimicrobial” and AMR will be used to refer to medications with antibacterial spectrum only and the resistance against these substances among bacteria.

Since the introduction in clinical practice of penicillin and streptomycin in the 1940s, antimicrobials have revolutionised prevention, treatment and outcome of infectious diseases (2). However, these advances are being threatened increasingly by the development and spread of antimicrobial resistance. Infections which were previously treatable are becoming more difficult to cure, resulting in increasing costs, to both individual patients and the healthcare system, and higher mortality rates (3). Without proper and enforced policies to stop

the spread of AMR, the currently estimated annual 700,000 deaths would increase to 10 million per year in 2050 (4). The global problem of antimicrobial resistance is particularly pressing in developing countries, where the infectious disease burden is high, antimicrobials are available without prescription and costs constrain the replacement of older antimicrobials with newer, more expensive ones that also cover resistant organisms (5).

Antimicrobial pressure is a key factor promoting development of resistance in bacteria (6), but the drivers for antimicrobial use are multi-factorial. Although antimicrobial resistance is primarily a medical problem, the causes of resistance are ecological, epidemiological, socio-cultural and economic. Patients, physicians, veterinarians, clinics and hospitals, and retailers - from large pharmacies to local drug sellers - have little motivation to weigh the negative impact of their use of antimicrobials on others, especially those in the future (7). In order to improve the current situation, solutions must alter incentives for these stakeholders to act in society's best interests (8).

In this introductory chapter, I discuss the following topics: (1) Overview of antimicrobials, (2) Situation of global antimicrobial use (AMU) and resistance, (3) Potential control measures to tackle AMR, (4) local (Vietnamese) context, (5) Biomarker guided AMU – a potential control measure and (6) Objectives of my thesis. This introduction gives insight where interventions can be targeted to improve the current situation of antimicrobial use in Vietnam - which in turn may help to control AMR.

## **1.1 Overview of antimicrobials**

### **1.1.1 Definitions**

Antimicrobials for human or animal use comprise a variety of natural, semisynthetic or synthetic substances used to treat infections by inhibiting the growth of or kill

microorganisms without significant toxicity to the human or animal host. Antimicrobials with an antibacterial spectrum are used both in the treatment and prevention of bacterial infections.

Bacteria are generally classified by their membrane's structural differences that can be visualised using the Gram stain, named after the Danish microbiologist, Hans Christian Gram, who developed this staining method in 1884 (9, 10). A thick layer of peptidoglycan in the membrane of Gram-positive bacteria retains the crystal violet dye during the decolourisation in the staining procedure. The thin peptidoglycan layer of Gram-negative bacteria is decolourised in this step and subsequently stained by a counter stain (safranin or fuchsin). Among other structural differences, Gram-negative bacteria have two membranes with a selectively permeable outer membrane that inhibits certain drugs and antimicrobials to penetrate the cell. Thus, Gram-negative bacteria in general are more resistant to antimicrobials than Gram-positive bacteria.

### **1.1.2 Development of antimicrobial resistance**

Antimicrobials, together with vaccines, are the two most crucial discoveries in the history of medicine and have shaped the recent evolution of mankind. The modern "antimicrobial era" was initiated by Paul Ehrlich and Alexander Fleming. In 1910, a "magic bullet" (an organoarsenic compound called arsphenamine sulphonamide marketed as Salvarsan) was discovered by Ehrlich and Sahachiro Hata, showing significant effect in the treatment of syphilis, a then endemic and incurable disease (11). Despite its high toxicity, this agent was the most commonly prescribed drug for this venereal disease until it was replaced by penicillin in the 1940s (12). Penicillin was discovered in 1928 by a Scottish biologist: Alexander Fleming. After being introduced for clinical treatment in the 1940s, penicillin helped to save thousands of lives from wound infections and sepsis during World War II (13). Soon after penicillin's introduction, more antimicrobial compounds were discovered between the 1940s and 60s; a period known as the golden period of antimicrobial development, with

introduction of many new classes of antimicrobials, including: streptomycin (Selman Waksman, 1944), chloramphenicol, tetracyclines, macrolides and glycopeptides (1950s). The first quinolone antimicrobial, nalidixic acid, was introduced in 1962. A range of cephalosporins was developed during the 1970s to 80s. In the 1980s, finally, the carbapenems and fluoroquinolone antimicrobials were introduced (14, 15).

The major concern with antimicrobial development is that after introduction of any new antimicrobial, resistance to it will ultimately emerge (figure 1-1) (16). Among Gram-positive pathogens, penicillin resistant *Streptococcus pneumoniae*, methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecium* (VRE) and fluoroquinolone resistant *Neisseria gonorrhoeae* are of particular concern (17). Among Gram-negative bacteria, resistance to 3<sup>rd</sup> generation cephalosporins followed by fluoroquinolones, carbapenems and now colistin among Enterobacteriaceae pose a serious, worldwide threat that have changed therapeutic and infection control guidelines and resulted in a steep increase in mortality and treatment costs (18-21).

From 1970s to 1990s, a dramatic increase in penicillin resistance among *S. pneumoniae* and *S. aureus* has been attributed to excessive global usage of penicillins (3, 22, 23). In *S. pneumoniae* resistance is mediated by accumulation of chromosomal mutations in the genes coding for the penicillin-binding proteins (PBPs), essential components of the bacterial cell wall (24, 25). Resistance mechanism among *S. aureus* relate to production of penicillinases which inactivate antimicrobial agents in the penicillin class, and all other beta-lactams (see below) (26, 27). The discovery and introduction of methicillin in 1959 was considered a certain and definite defense against the penicillinases, but the rapid subsequent emergence of MRSA in 1962, mediated by *mecA*, which encodes for a novel penicillin-binding protein, PBP-2a, proved this to be an illusion (28, 29). Posing resistance to most then available antimicrobials, MRSA was one of the first multi-drug resistant (MDR) pathogens in

the hospital. Recent spread outside the hospital, MRSA has now also become a major community-acquired (CA) pathogen (30).

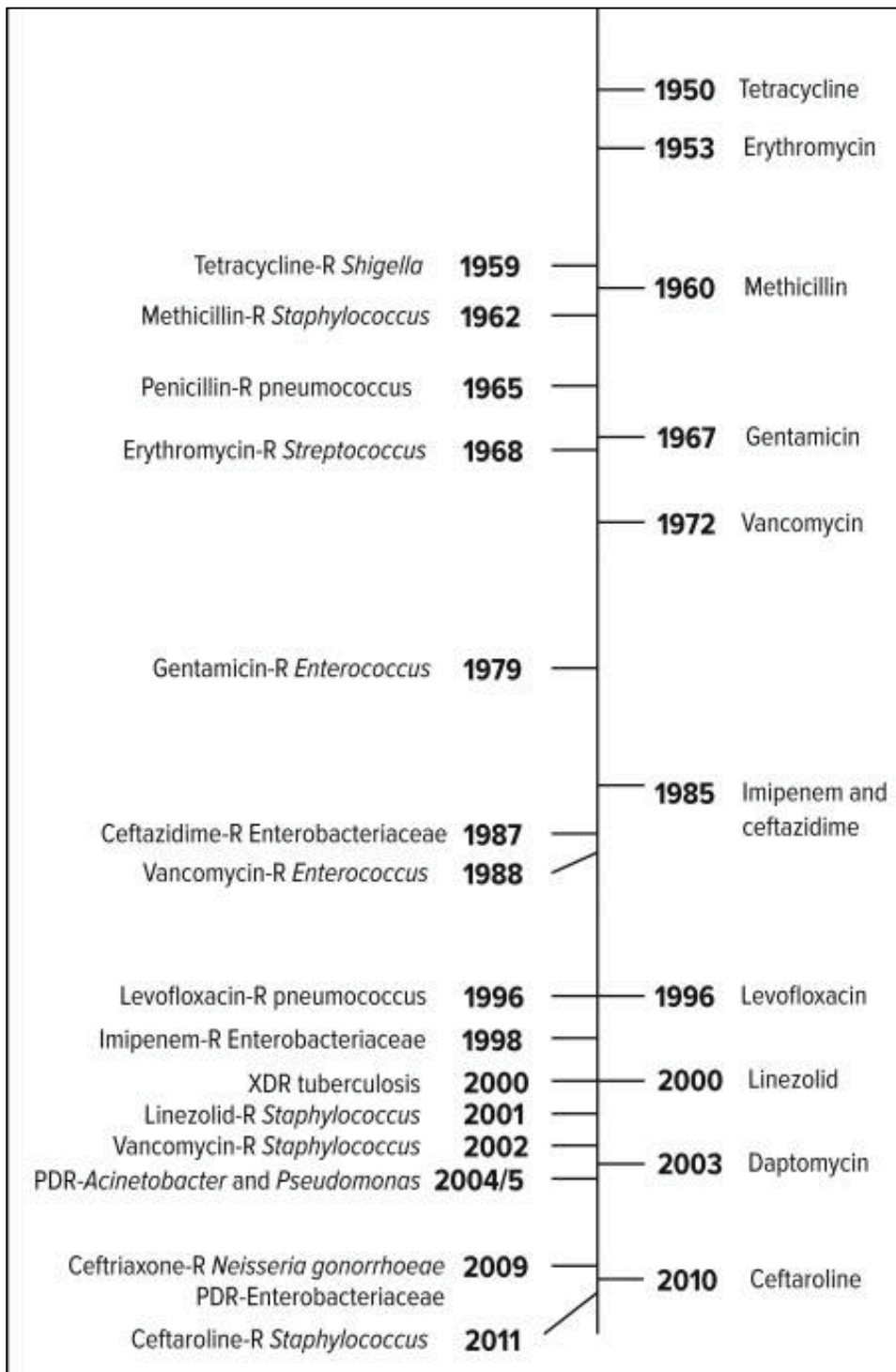
After widespread usage of broad-spectrum cephalosporins in the 1980s, a decade later, resistant Enterobacteriaceae started to be isolated in hospitals, caused by plasmid mediated production of extended-spectrum beta-lactamases (ESBLs), which have now become endemic in hospitals and communities worldwide (31, 32). Resistance evolution was largely attributed to the global spread of CTX-M type extended-spectrum  $\beta$ -lactamases (ESBLs) which are predominant among *Escherichia coli* and SHV type, which is dominant among *Klebsiella pneumoniae* (33). These genes and their derivatives including TEM-1, TEM-2, or SHV-1 are carried on plasmids, which facilitates the transfer of these genes among bacteria species (34, 35). ESBLs mediate resistance to all penicillins and third and fourth generation cephalosporins, limiting making treatment options for ESBL-producing gram-negative pathogens caused infections.

Carbapenems, retained as one of the limited treatment options for serious infections caused by ESBL-producing organisms, thus started to be used more widely, eventually resulting in the global emergence of carbapenem-resistant *Enterobacteriaceae* (CRE) (28). The emergence of CRE is attributed to bacterial acquisition of carbapenemases, enzymes that inactivate these agents. *K pneumoniae* carbapenemase (KPC-1) was first found in 1996 in the carbapenem-resistant *K pneumoniae* (36). The genes encoding carbapenemases are usually located on plasmids or other transferable elements, allowing bacteria to acquire genes conferring resistance to other classes of antimicrobials, such as aminoglycoside-modifying enzymes, fluoroquinolone-resistance factors, and beta-lactamases to become pan-drug-resistant (PDR) pathogens (37-39).

Polymyxins, including colistin, an old family of antimicrobials that had become redundant due to dosing difficulties and toxicity, were now recovered as the last resort

antimicrobials to treat serious infections caused by these CREs including those caused by New Delhi Metallo-beta-lactamase (NDM) producing strains (40). Recently detected, NDM-1 resistance gene confers resistance to most antimicrobials except polymyxins. Unfortunately, plasmid mediated resistance to this last resort drug has recently emerged in China, south Asia, Europe, Africa and South America, attributed to the *mcr-1* plasmid (41-46).

Though the impact of antimicrobial resistance in the community is less severe than in hospitals, these findings have raised major concerns that the emergence and persistence of multidrug-resistant pathogens may bring back the pre-antimicrobial era, where patients hospitalised for something trivial (like appendicitis) may die from a progressive infection as antimicrobials have become ineffective. Currently, antimicrobial research and development mainly concerns derivatives of older classes of antimicrobials and only few are potentially novel compounds. As per 2014, 37 antimicrobial derivatives are under development in the US, of which 22 are potentially effective against Gram-negative pathogens (47). Among these, 33 are derivatives and 4 are new compounds of a novel beta-lactamases inhibitor and an existing beta-lactam). In 2015, a new antimicrobial compound against Gram-positive pathogens was discovered in an uncultivable soil bacterium, named teixobactin. Mutants of *S. aureus* or *Mycobacterium tuberculosis* resistant to teixobactin were not found *in vitro* indicating that this finding may open a new path in modern antimicrobial research and development with the potential to avoid or delay the development of resistance (48).



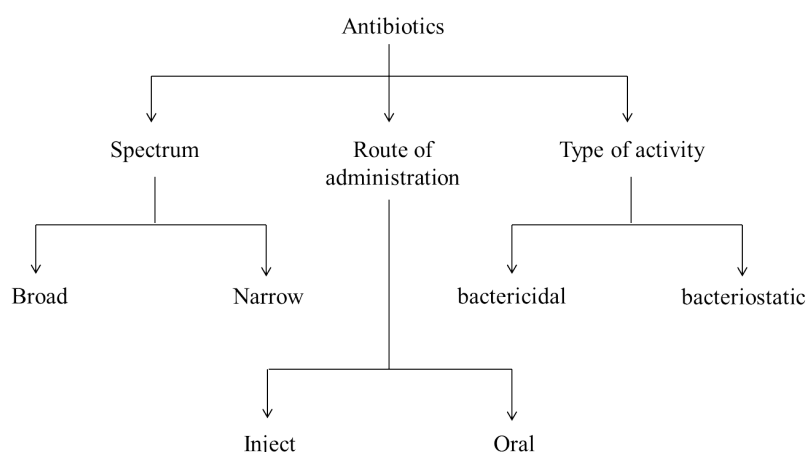
**Figure 1-1 Development of antimicrobial resistance: A timeline of key events (16)**

*PDR = pan-drug-resistant; R = resistant; XDR = extensively drug-resistant*

### 1.1.3 Antimicrobial classifications, mechanism of action and resistance

#### 1.1.3.1 Classification

There are several ways to classify antimicrobials, including: spectrum, route of administration, type of activity, chemical structure or mechanism of action. Broad spectrum antimicrobials are effective against a broad range of microorganisms in contrast to narrow spectrum antimicrobials. Bactericidal antimicrobials can kill the bacteria while bacteriostatic antimicrobials inhibit the growth of bacteria (figure 1-2).



**Figure 1-2 Basic antimicrobial classification**

(Source: <https://explorable.com/history-of-antimicrobials>)

Practically, the most useful classification system is the WHO Anatomical Therapeutic Chemical (ATC) classification, which is used for the classification of active ingredients of drugs according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties (table 1-1). The ATC system is a valuable tool for measuring drug consumption and adverse drug reaction monitoring as products with various dosage forms and strengths of a substance will mostly have the same ATC code.



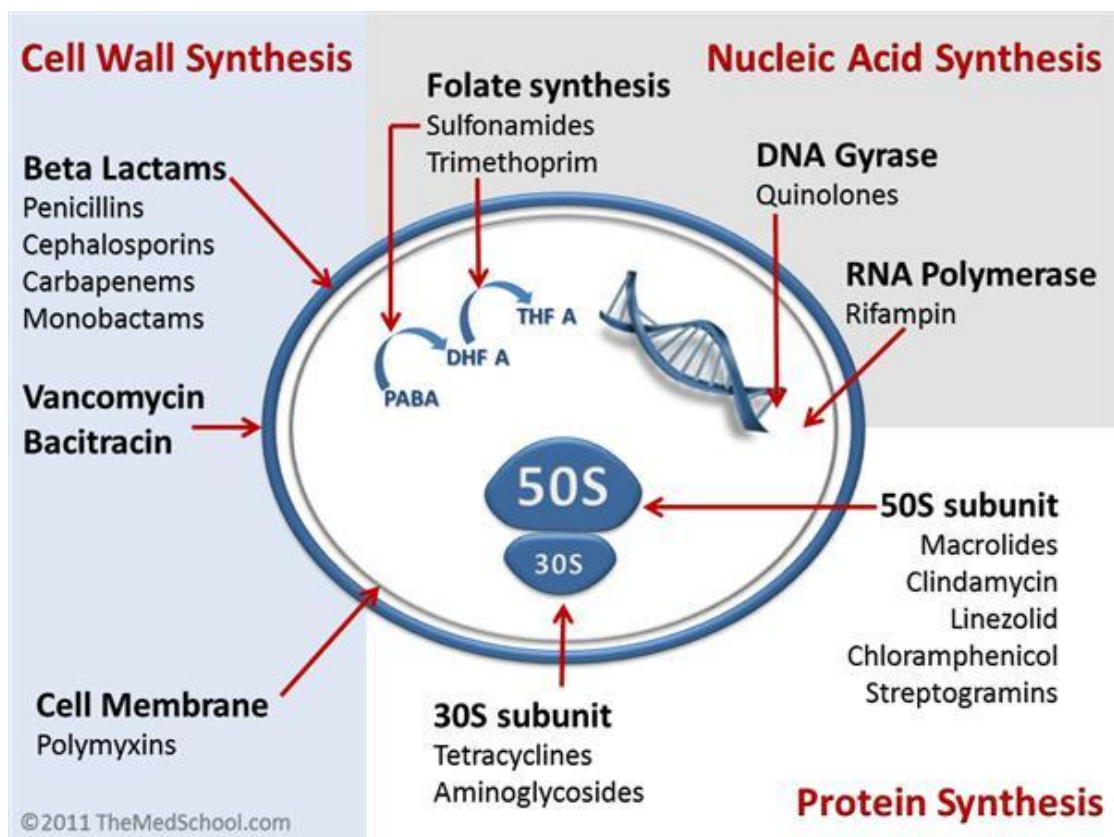
**Table 1-1 Anatomical Therapeutic Chemical Classification System of Antimicrobials**

<b>ATC-code</b>	<b>Antimicrobial group</b>
J01	Antibacterials for Systemic Use
J01A	TETRACYCLINES
J01AA	Tetracyclines
J01B	AMPHENICOLS
J01BA	Amphenicols
J01C	BETA-LACTAM ANTIBACTERIALS, PENICILLINS
J01CA	Penicillins with extended spectrum
J01CE	Beta-lactamase sensitive penicillins
J01CF	Beta-lactamase resistant penicillins
J01CG	Beta-lactam inhibitors
J01CR	Combination of penicillins, incl. beta-lactamase inhibitors
J01D	OTHER BETA-LACTAM ANTIBACTERIALS
J01DB	1st generation cephalosporins
J01DC	2nd generation cephalosporins
J01DD	3rd generation cephalosporins
J01DE	4th generation cephalosporins
J01DF	Monobactams
J01DH	Carbapenems
J01DI	Other cephalosporins and penems
J01E	SULFONAMIDES AND TRIMETHOPRIM
J01EA	Trimethoprim and derivatives
J01EB	Short-acting sulfonamides
J01EC	Intermediate-acting sulfonamides
J01ED	Long-acting sulfonamides
J01EE	Combinations of sulfonamides and trimethoprim, incl. derivatives
J01F	MACROLIDES, LINCOSAMIDES AND STREPTOGRAMINS
J01FA	Macrolides
J01FF	Lincosamides
J01FG	Streptogramins
J01G	AMINOGLYCOSIDE ANTIBACTERIALS
J01GA	Streptomycins
J01GB	Other aminoglycosides
J01M	QUINOLONE ANTIBACTERIALS
J01MA	Fluoroquinolones
J01MB	Other quinolones
J01R	COMBINATIONS OF ANTIBACTERIALS
J01RA	Combinations of antibacterials
J01X	OTHER ANTIBACTERIALS
J01XA	Glycopeptide antibacterials
J01XB	Polymyxins
J01XC	Steroid antibacterials
J01XD	Imidazole derivatives
J01XE	Nitrofurans derivatives
J01XX	Other antibacterials

(Source: [https://www.whocc.no/atc\\_ddd\\_index/](https://www.whocc.no/atc_ddd_index/))

### 1.1.3.2 Mechanism of action

There are five fundamental mechanisms of action for antimicrobials (figure 1-3): (1) inhibition of bacterial cell wall synthesis by inhibiting the synthesis of peptidoglycans – a crucial cell wall constituent of both Gram-positive and Gram-negative bacteria (beta-lactams, glycopeptides) (49, 50); (2) inhibition of transcription (rifamycins) or translation (30S ribosome site: tetracyclines, aminoglycosides; 50S ribosome site: macrolides, lincosamides, amphenicols, tetracyclines and streptogramins) (51-55); (3) inhibition of nucleic acid synthesis (imidazole derivatives) or supercoiling (quinolones); (4) alter cell membrane (polymyxins); (5) antimetabolite activity (sulfonamides, trimethoprim) (56).

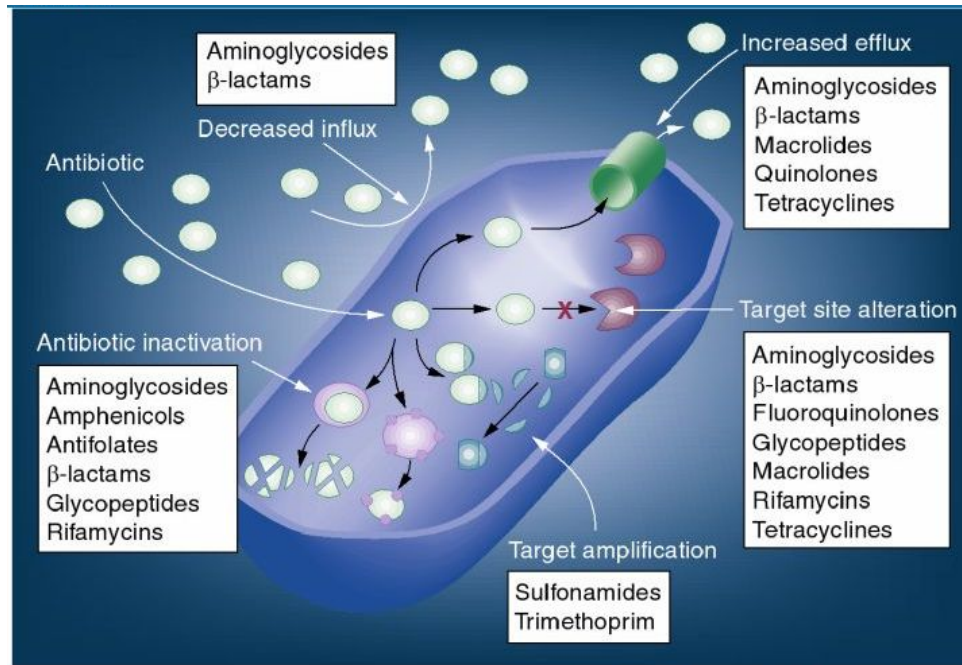


**Figure 1-3 Antimicrobial classes and mechanism of action**

(Source: <http://www.upinhealth.com/antimicrobial-classes-and-mechanisms-of-action/>)

### 1.1.3.3 Mechanism of antimicrobial resistance

Antimicrobial resistance is a natural phenomenon as bacteria produce and use antimicrobials (antibiotics) against other bacteria leading to low-level of natural selection for resistance (57). Resistance (figure 1-4) (58) may be caused by (1) enzymatic inactivation of the antimicrobial compound, (2) modification of antimicrobial targets including over-amplification of target and (3) alteration of the permeability of the cell membrane by either decreased influx (porin loss) or increased efflux (efflux pumps). Antimicrobial resistance genes encoding these resistance mechanisms can be located either in the chromosomal DNA or on transferable elements that may be integrated in the chromosome (integrons, transposons) or separate as plasmids (59). Plasmids, other transferable elements and genes encoding resistance mechanisms in general can be transmitted to other bacteria, known as horizontal gene transfer. This may occur through three main mechanisms: conjugation, transduction and transformation.



**Figure 1-4 Mechanism of bacterial resistance to antimicrobial (58)**

*The classes of antimicrobials affected by each of the mechanisms are listed in the boxes*

## **1.2 Situation of global antimicrobial use and resistance**

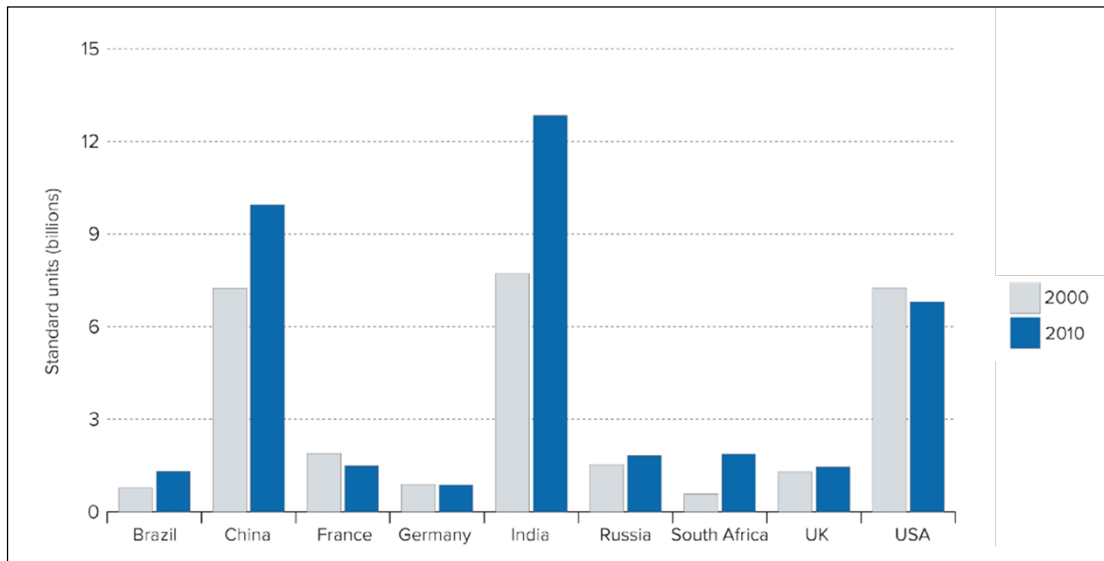
### **1.2.1 Global human antimicrobial consumption**

Antimicrobial pressure is the single most important factor promoting development of drug resistance in bacteria. Inappropriate antimicrobial use (e.g. too broad, without clinical indication, too low dose, too short duration) represents an avoidable additional pressure (60). To slow down the development of antimicrobial resistance, a control strategy to reduce the inappropriate use of antimicrobials in both community and health care facilities is required (61). Assessing variations in volumes and patterns of antimicrobial consumptions across countries is therefore crucial to develop rational-use policies to combat antimicrobial resistance.

IMS Health MIDAS (IMS Health, Danbury, CT, USA) is an American commercial organisation that tracks sales of the global pharmaceutical market through two main channels: retail pharmacies and hospital pharmacies (62). In each sector, the volume of antimicrobials sold are collected to quantify antimicrobial consumption either directly from manufacturers or indirectly from wholesalers. Annual reports are available in 71 countries for 16 classes of antimicrobials with volume of consumption estimated in standard units sold, which is defined as a single dosage unit such as a pill, capsule or ampule. The methodology applied varies by nations depending on their health systems (63). In high-income countries, IMS data is collected from both public and private channels while in low and middle income countries where IMS has no access to public channel, data is largely based on private sector. Consumption in some countries may be underestimated because the survey does not cover the entire market. Thus, interpreting and comparing consumption data should be performed with review the covered sectors and distribution channels. Nevertheless, IMS data are useful in looking at trends in consumption over time, benchmarking, and relative use of the different antibiotic classes.

Between 2000 and 2010, total global antimicrobial consumption in humans increased by 36% (compared to 19% 1990-2000) and reached 73 billion standard units of the smallest identifiable dose in 2010, in which penicillins and cephalosporins accounted for the majority of 60% (62). From 2000-2010, antimicrobial consumption was stable or declined in most high-income countries. The growth in BRICS countries (Brazil, Russia, India, China and South Africa), however, accounted for three-quarters of the total increase in global consumption against one-third of overall global population increase in this 10-year period (figure 1-5). In the hospital sector, up to 57% of the overall increase was attributable to China while 23% of the retail sales increase was attributable to India.

In 2010, the overall national antimicrobial consumption was highest in India with 12.9 billion units (10.7 units per person), followed by China with 10 billion units (7.5 units per person) and the US with 6.8 billion units (22.0 units per person). Australia and New Zealand were two exceptional high-income countries reporting a substantial increase in antimicrobial consumption per capita between 2000 and 2010 with corresponding rise from 25 to 87 units and 26 to 70 units per person. The reason for this significantly higher consumptions compared with European countries is not known. Additionally, there was a significant difference in consumption per person across high-income countries with similar economic status. For instance, 7.9 units per person in Netherland compared to 23.1 units per person in France. In Asia, the high-income countries including Hong Kong, Malaysia, Singapore, and South Korea ranked within the top eight nations of antimicrobial consumption per capita.

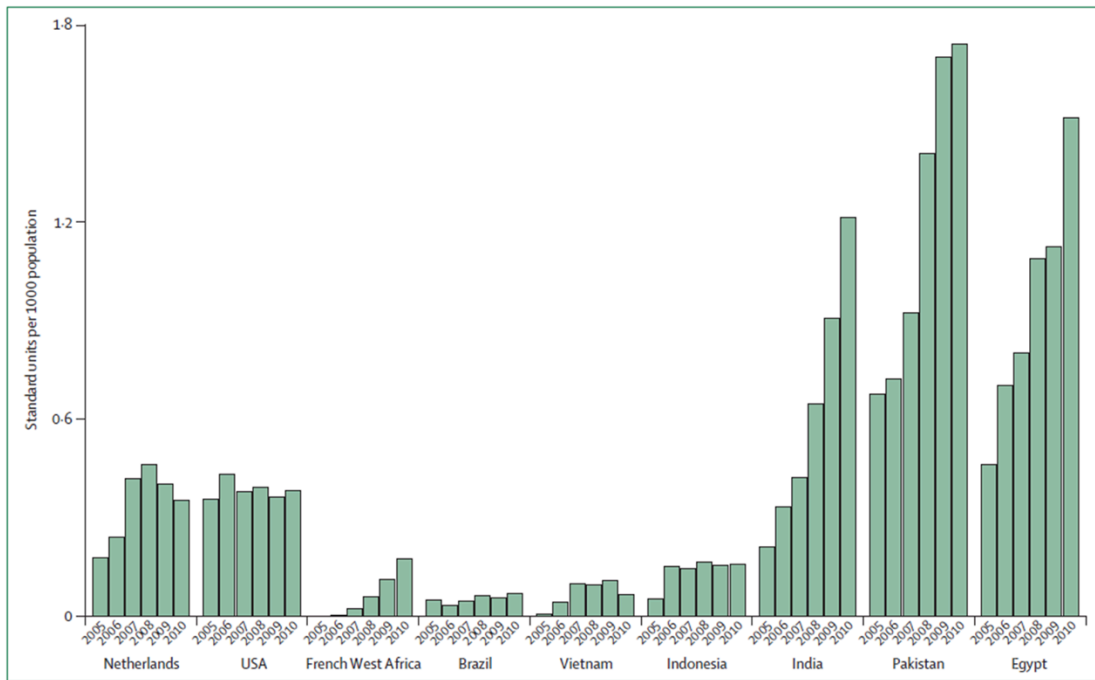


**Figure 1-5 Total antimicrobial consumption in selected countries, 2000-2010**

*The trend of antimicrobial consumption among nine selected countries between 2000 (grey) and 2010 (blue). Total consumption is expressed in standard units.*

*(Source: IMS Health MIDAS database)*

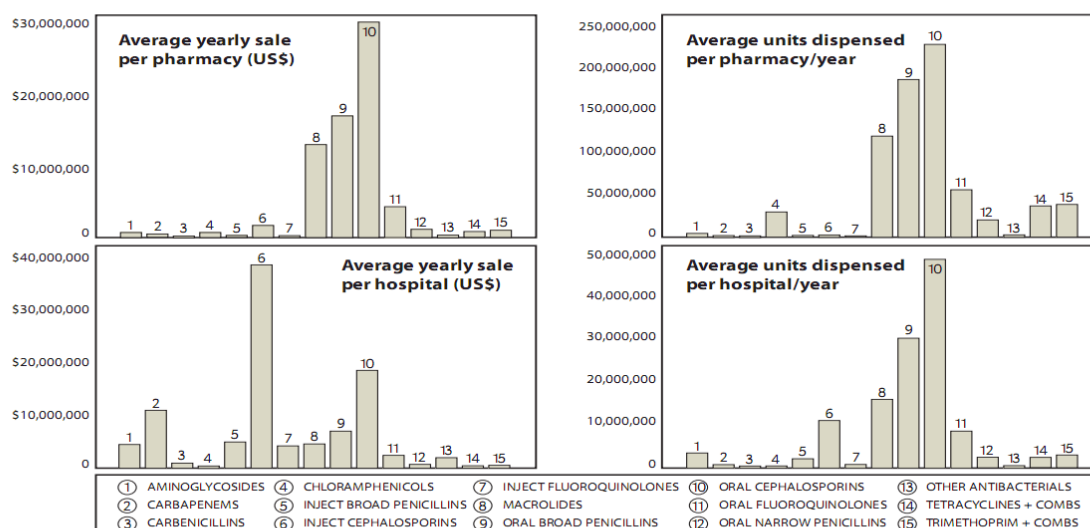
Worldwide, there is a significant increase in the global consumption of carbapenems (40%) and polymyxins (13%), which are considered “last-resort drugs” for treatment of multidrug resistant infections such as carbapenem-resistant Enterobacteriaceae (CRE). In the five years from 2005-2010, the highest increase in retail carbapenems sales was observed in India, Pakistan and Egypt. Despite the relatively low consumption of carbapenems per 1,000 inhabitants, Vietnam was also among countries with an increasing trend in the sales of this group (figure 1-6) (64). Global consumption of glycopeptides doubled in 2010 compared to 2000 and has also increased rapidly in European countries for treating MRSA infection (47).



**Figure 1-6 Carbapenem retail sales in selected countries in standard units per 1000 population, 2005-2010 (62)**

In Vietnam, available IMS data for the period of the 4<sup>th</sup> quarter of 2008 to the 3<sup>rd</sup> quarter of 2009 was collected from 439 retail pharmacies and 62 hospitals in 5 major cities across the country including Ha Noi, Ho Chi Minh City, Hai Phong, Da Nang and Can Tho (65). Considering the number of units sold, the most commonly sold antimicrobials are similar in retail pharmacies and hospital pharmacies. Oral cephalosporins (J01D01) are the most commonly sold antimicrobials at both pharmacy types, followed by oral broad spectrum penicillins (J01C01), macrolides and fluoroquinolones. Important differences between pharmacies and hospitals are that the bulk of injectable antimicrobials are sold in hospitals and rarely in retail pharmacies. Therefore, the intravenous antimicrobials aminoglycosides and carbapenems are dispensed mainly in hospitals and rarely in retail pharmacies. Older antimicrobials like chloramphenicol are mostly sold in the retail pharmacy and little in the hospital. The sales of polymyxins (e.g. colistin) are negligible, as these drugs are not yet

registered in Vietnam for systemic use in drug-resistant infections, even though it is listed on the common used drugs list. In term of the value in USD of the sales data, injectable drugs are more costly and have a big impact on the treatment budget. Injectable cephalosporins have the highest sales value in the hospitals, followed by carbapenems. Also in the retail pharmacy injectable cephalosporins become more important when considering the value (figure 1-7). These IMS data show a significant increase of global consumption of antimicrobials including consumption of carbapenems and polymyxins, especially in low and middle-income countries.



**Figure 1-7 Sales data of antimicrobials in Vietnam (65)**

*Left two panels: Average sales of antimicrobial per year in USD in retail pharmacy (top) and hospital (bottom). Right two panels: Average sold units of antimicrobials in retail pharmacy (top) and hospital (bottom).*

### 1.2.2 Global antimicrobial resistance

In 2014, the World Health Organisation issued the global report on surveillance of antimicrobial resistance (3). With data obtained from 129 member countries for nine bacteria-



antimicrobial combinations of public health importance, this report provides a broad picture of global situation of antimicrobial resistance. Among 129 reported countries, 114 provided data for at least one of the nine selected combinations. Data for all these combinations were available in 22 countries. Most data were based on healthcare associated infections. In most developing countries where a national surveillance system does not exist, resistance data come from individual studies rather than national reports and is therefore incomplete. Due to the non-representativeness of surveillance data, results interpretation and comparison should be performed with caution. In the report, it is shown that *E. coli*, *K. pneumoniae*, and *S. aureus*, which commonly cause community and hospital acquired infections, are the pathogens with the largest resistance threat proportions of resistance organisms (3). In five of six WHO regions, countries reported *E. coli* resistance of more than 50% to fluoroquinolones and third-generation cephalosporins. In 2013, carbapenem-resistant *E. coli* was reported in 26 countries, among them the highest rate was documented in India with 11%, followed by Vietnam with 9%. Third generation cephalosporins resistance in *K. pneumoniae* was more than 30% in most WHO member countries and exceeded 60% in some regions (87% in Bolivia). The rate of MRSA exceeded 20% in all WHO regions and was even above 80% in some regions (47). Other pathogens associated with community acquired infections of high global concern included *S. pneumoniae*, nontyphoidal *Salmonella*, *Shigella* spp., and *N. gonorrhoeae*. Resistance rates of 25% or more to penicillin among *S. pneumoniae* was reported in all six WHO regions, and exceeded 40%-50% in some countries.

To enable comprehensive monitoring and analysis of the occurrence and trends of AMR globally using standardised methodology, in 2015 the WHO has issued the Global Antimicrobial Resistance Surveillance System (GLASS) manual to support the Global Action Plan on Antimicrobial Resistance (66). This manual describes the GLASS standards for collection and analysis of resistance data of a list of important (sentinel) bacterial pathogens

in humans to enable data aggregation and sharing at national and international level. Pathogens presented above are prioritised for monitoring in this GLASS manual.

#### *1.2.2.1 Antimicrobial resistance in South East Asia*

National surveillance systems to collect data on antimicrobial resistance have not yet been established in most South-East Asian countries (3). Among 11 countries, 6 (Bhutan, Korea, India, Myanmar, Nepal and Thailand) have national surveillance systems in place (67). However, for selected bacterial pathogens, the available resistance data from these systems is insufficient. For instance, data on *Shigella* species resistant to fluoroquinolones are available in only three countries (Vietnam, Nepal and India); MRSA data are available from four countries (India, Nepal, Myanmar and Thailand). Other pathogen/antimicrobial (“bug/drug”) combinations such as *E. coli*/3<sup>rd</sup> generation cephalosporin, *E. coli*/fluoroquinolones; *K. pneumoniae*/3<sup>rd</sup> generation cephalosporin; *K. pneumoniae*/carbapenems are available in five out of six reporting countries. These limited available resistance data reveal that AMR is a growing challenge in this region. Among 5 (India, Nepal, Myanmar, Thailand and Indonesia) reporting countries, resistance to third generation cephalosporins among *E. coli* isolates ranged from 16-68%. Corresponding figures for fluoroquinolones were 32-64%. Among *K. pneumoniae* isolates in 4 (Thailand, Myanmar, Malaysia and Philippines) reporting countries, resistance to third-generation cephalosporins ranged from 34%-81% while resistance to carbapenems ranged from 0-8%.

Based on country’s priorities and resources, participating nations are recommended to decide the organisms included on a list of pathogens of global concern to be covered with good quality and representative of the population monitored. In the countries where national surveillance systems do not exist, GLASS provides guidance in compiling harmonised, standardised AMR data for the infections and pathogens of global priority from surveillance sites, and in sharing these data to form a global picture.

### 1.2.2.2 Situation of antimicrobial resistance in Vietnam

Vietnam, having a relatively high burden of infectious diseases, including a large portion of bacterial diseases considered treatable with antimicrobials, already experiences high levels of antimicrobial resistance (65). Among top ten causes of death, lower respiratory infections was the 4<sup>th</sup> leading cause, killing 25 thousand (4.8%) people in 2012 (68). Despite the absence of a nationwide surveillance program, the following presented figures indicate the seriousness of the antimicrobial resistance situation in Vietnam.

- Vietnam was among three countries having the highest prevalence of erythromycin-resistant (80.7%) *S. pneumoniae*, the most common cause of bacterial respiratory infections, among the 11 countries in the Asian Network for Surveillance of Resistant Pathogens (ANSORP) in 2008-2009 (69).
- Among 289 *S. pneumoniae* and 195 *Haemophilus influenzae* isolates obtained from adults and children with community acquired respiratory infections in 11 hospitals from a survey of antimicrobial resistance (SOAR 2009-2011), the susceptibility rate of *S. pneumoniae* to amoxicillin/clavulanic acid, cefuroxime, cefaclor and azithromycin was 96.9%, 18.7%, 8% and 4.2%, respectively. 40.5% of *H. influenzae* isolates produced beta-lactamase and 13.8% were beta-lactamase negative ampicillin resistant (BLNAR) (70).
- In 2013, carbapenem resistance was also reported in 9% and 22% in all isolates *E. coli* and *K. pneumoniae* collected from 16 hospitals, posing Vietnam among countries with alarming carbapenem resistance rates (47).
- In 2012-2013, the hospital acquired infections prevalence reported from 16 hospitals nationwide accounted for 29.5% (965/3266 patients), among them pneumonia was predominant with 79.4% (804/1012). The most commonly detected HAI pathogens were *Acinetobacter baumannii* (24.4%), *Pseudomonas aeruginosa* (13.8%), and *K.*

*pneumoniae* (11.6%), with carbapenem resistance rates of 89.2%, 55.7%, and 14.9% respectively (71).

### **1.3 Potential control measure to tackle antimicrobial resistance**

#### **1.3.1 Why tackling antimicrobial resistance is essential**

Currently, it's estimated that antimicrobial resistance attributable deaths are about 700,000 per year, which is lower than other major causes of deaths such as cancer (8.2 million), diabetes (1.5 million) and road traffic accidents (1.2 million). However, with an ongoing escalation in resistance, by 2050, it is estimated to lead to up to 10 million deaths per year, 2% to 3.5% loss in gross domestic product (GDP) and global social costs of up to 100 trillion USD [102]. Antimicrobial resistance poses an increasing threat to global health and has serious medical and economic impacts in all parts of the world however Asia and Africa will be continents with the highest estimated burden of AMR with 4,730,000 and 4,150,000 deaths per year by 2050, respectively (72).

Because of resistance, treatment of serious nosocomial and community-acquired infections is becoming more challenging. If the current situation is not controlled, we might return to the pre-antimicrobial era. Also, as a consequence, several high-risk treatments that include serious compromise of the immune system like cancer treatments or organ transplantation require antimicrobial prophylaxis and may become more challenging. For instance, among 416 Spanish patients undergoing kidney transplantations, 58 were infected with multi drug resistant (MDR) bacteria, predominantly Gram-negative. Death or graft failure was significantly higher among patients infected by MDR bacteria (19% vs. 8 %) (73). In India, over 50,000 neonatal sepsis deaths (30% of sepsis mortality) are caused by antimicrobial resistance (74). In Tanzania, the mortality rate from resistant Gram-negative BSI (43.5%) was more than double that of malaria (20.2%) (75). Antimicrobial-resistance also poses a financial burden to the healthcare systems. In the US, it is estimated that

healthcare expenditures and productivity losses including both direct and indirect costs due to AMR amounts to about USD\$ 20 – USD\$ 35 billion annually (76). In the United Kingdom (UK), 0.4% to 1.6% of real GDP lost attributed to AMR (77). Despite the lack of global data on antimicrobial resistance burden, especially for developing countries without a sufficient surveillance system, these data indicate that all continents have to deal with this global issue (47, 78).

### **1.3.2 Global action plan on antimicrobial resistance**

In 2015, a global action plan on antimicrobial resistance was issued by WHO that emphasises the need for more evidence to develop effective policy interventions in the struggle against the global problem of antimicrobial resistance, especially in LMICs (79). The plan outlines five strategic objectives including: (1) to improve awareness and understanding of antimicrobial resistance through effective communication, education and training; (2) to strengthen the knowledge and evidence base through surveillance and research; (3) to reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures; (4) to optimise the use of antimicrobial medicines in human and animal health; (5) to develop the economic case for sustainable investment that takes account of the needs of all countries and to increase investment in new medicines, diagnostic tools, vaccines and other interventions. Along with surveillance and infection control, responsible use of antimicrobials is considered the most effective policy area within and between nations with different income levels. To optimise antimicrobial use in both human and animal medicine, an improvement in the diagnostic technology with effective, rapid and low-cost diagnostic tools which are easily integrated into clinical, pharmacy and veterinary practice is required.

### **1.3.3 Vietnamese National Action Plan (2013)**

As bacterial infectious diseases remain common in Vietnam, access to effective antimicrobials is crucial. The increasing resistance rates in Vietnam are now jeopardising this access, as many antimicrobial regimens advised in current treatment guidelines are unlikely to be effective. However, the available information is not well collated and communicated, and a ‘strong voice’ advocating for action against inappropriate antimicrobial use is needed.

In 2013, Vietnam became the first country in WHO’s Western Pacific Region to approve a national action plan to combat antimicrobial resistance. The plan was developed in response to the call from the World Health Organisation to have a timely plan to deal with antimicrobial resistance before spring 2017 and largely based on data from GARP situation analysis (Appendix D), the National Action Plan outlines steps for implementing actions to reach six objectives: (1) Raise awareness of community and health workers on drug resistance; (2) Strengthen, improve national surveillance system on the use of antimicrobials and drug resistance; (3) Ensure adequate supply of quality medicines to meet the needs of people; (4) Promote proper safe use of drugs; (5) Promote infection control; (6) Promote proper safe antimicrobial use in livestock, poultry, aquaculture and cultivation. To date, several key activities have been conducted, including (1) Setting up national surveillance network on AMU and AMR with adequate reporting system based on existing surveillance network of 16 hospitals nationwide; (2) Developing quality standards (Qs) on appropriate use of antimicrobials for certain conditions including community acquired pneumonia (CAP) and exacerbation of chronic obstructive pulmonary disease (COPD) in Vietnamese hospitals (80); (3) Organising a number of One-Health AMR meetings, workshops with multi-stakeholders and advocacy campaign/events such as AMR awareness week to raise public awareness on AMR.

The expected outcomes by 2020 include an active national surveillance system; strengthened infection control and responsible use of antimicrobials in both humans and

animals. Progress towards achieving these outcomes will be led by the Ministry of Health. However, sustained, coordinated and complementary efforts of other ministries including Ministry of Rural and Agriculture Development, Ministry of Industry and Trade, Ministry of Natural Resource and Environment and international development partners are crucial to implement the activities and achieve objectives in the National Action Plan. Since a “One Health” approach is emphasised as a main mechanism to control AMR, a government-led multi-stakeholder and multisectoral engagement and action is required.

Two years after, four Vietnamese government ministries and foreign development partners (including OUCRU) in Vietnam signed an aide-memoire for multisectoral action to combat antimicrobial resistance in Vietnam. This engagement takes Vietnam’s AMR response forward and commits to coordinate and jointly implement the national action plan across different sectors. An antimicrobial awareness week was launched nationwide for the first time in 2015 and again in 2016 in an effort to raise awareness among the general public, prevent antimicrobial resistance and promote reasonable use of the drug. These efforts indicate that the need for policies and interventions to control the use of antimicrobials is recognised by the political, medical and pharmaceutical leadership of Vietnam.

Effective recommendations to alter antimicrobial use must consider the incentives for all related stakeholders including manufacturers, providers and purchasers. Mapping and addressing of the incentive structures is difficult and requires long-term cooperation between local stakeholders and policy makers. Regular review of any intervention is necessary to assess whether it has been successful in modifying these incentives and changing behaviour.

## **1.4 Vietnam context**

### **1.4.1 Basic indicators**

The Socialist Republic of Vietnam is situated in Southeast Asia with China, Laos, and Cambodia as bordering countries (figure 1-8), Vietnam is approximately 331,000 km<sup>2</sup> in area,

of which three-quarters are mountainous and hilly. The majority of the population (72%) lives in rural areas and the remaining 28% lives in urban areas, with an annual urbanisation rate of 3.03% per year. With a population over 93 million in 2014, Vietnam is the 13th most populous country in the world (table 1-2).



**Figure 1-8 Map of Vietnam**

(Source: <http://www.naturalearthdata.com/>, made by OUCRU Mapping team)

In the past decade Vietnam has been one of the countries with highest growth. Since the initiation of the *doi moi* reforms in 1986, Vietnam has transformed from one of the poorest in the world, with a per capita income of around 100 USD to 2100 USD in the end of 2015, making Vietnam a lower middle income country (81). Vietnamese children have good access to education, resulting in a literacy rate of 93.4% in 2014 compared to 90% in 5 years ago. Life expectancy is high compared to other developing nations, with current estimates at 70.4 years for males and 75.6 years for females.



In 2000, 189 UN Member States have agreed to try to achieve 8 Millennium Development Goals, which combat poverty, hunger, disease, illiteracy, environmental degradation, and discrimination against women, to be achieved by 2015 (82). The Millennium Development Goals are now transitioning into 17 Sustainable Development Goals including new areas such as climate change, economic inequality, innovation, sustainable consumption, peace and justice, among other priorities, to be completed by 2030 (83). Vietnam has made good progress towards achieving the Millennium Development Goals (MDGs) with almost all the health-related MDGs have already been achieved (84). Overall morbidity and mortality have decreased among vulnerable groups like women and young children. Infant mortality rate per 1000 live births reduced from 21.6 in 2010 to 19 in 2014 (85). Maternal mortality is relatively low at 54/100,000 births in 2015, when compared to some neighbouring countries, such as Cambodia where maternal mortality remains high at 161/100,000 or at 197/100,000 in Laos (23) (table 1-2). Health spending in Vietnam has increased rapidly and the total expenditure as a share of GDP rose from 5.2% in 1995 to 6.9% in 2012 (86).

The Vietnamese government funds 88% of the Expanded Program on Immunisation (EPI) recommended vaccines. As a result, over 90% of Vietnamese children receive the recommended vaccinations, including Bacillus Calmette–Guérin (BCG), Diphtheria, Pertussis and Tetanus (DPT), Hepatitis B (Hep B), polio, and measles. Vaccination against *H. influenzae* type b (Hib) and rubella have been introduced in EPI since in 2009. Vaccination coverage is lower in poorer and remote areas (87, 88). Others such as the pneumococcal and influenza vaccine are not scheduled to be introduced through EPI and are currently only available commercially in Vietnam.

There is a deficiency in human resources in health care, with a low ratio of nurses to doctors, a lack of specialists and trained managers (89). These shortages in healthcare workers are particularly acute in remote areas. For instance, in remote areas, the rate of health care

staff with a university degree (doctors-pharmacist) is 4.3 doctors/10,000 inhabitants and 0.2 pharmacist/10,000 inhabitants. In contrast, in the big cities, this number is significantly higher: 9 doctors/10,000 inhabitants and 4.5 pharmacists/10,000 inhabitants (65). While only 30% of the population living in the urban areas, qualified health workers are mostly concentrated here including 82% of total university pharmacists, 59% of doctors and 55% of nurses (90).

**Table 1-2 Key health and development indicators in Vietnam**

<b>Indicator</b>	<b>Year</b>	<b>Number</b>
Population (millions)	2014	93,4
Population growth rate (%)	2014	1.03
Life expectancy (male/female)	2014	70.4/75.6
Income per capita (USD)	2015	2,100
Infant mortality rate (per 1000)	2010-15	18.3
Maternal mortality ratio (per 100,000 live births)	2014	59
Adult literacy rate (%)	2014	93.4
Health expenditure (% of GDP)	2012	6.9
Hospital beds/10,000 people	2014	23
Doctors/10,000 people	2014	7.8
Pharmacists/10,000 people	2014	1.96

*Sources: World Health Organisation, World Bank, United Nations, CIA World Factbook (23, 41, 43)*

## **1.4.2 Structure of the healthcare system**

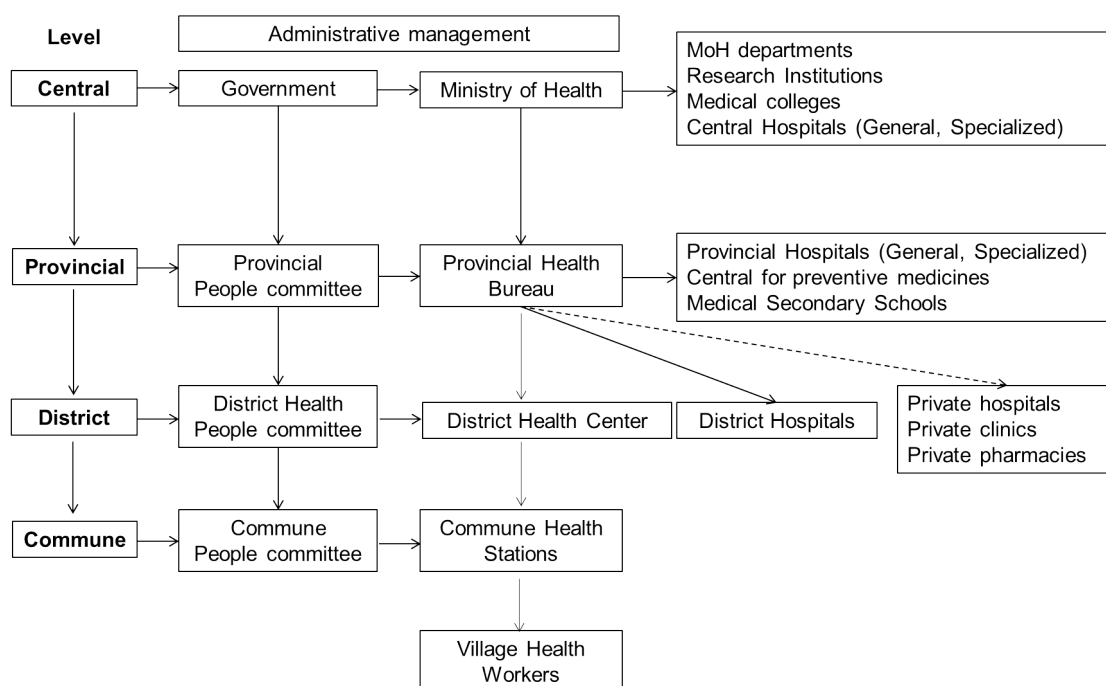
Twenty-five years ago, Vietnam's health care system was solely supported by the central government and the public sector was the only provider of healthcare services. At that time, drugs were scarce. To make health care more accessible, the government implemented several measures, including: the introduction of user fees at public hospitals, health insurance schemes, the legalisation of the pharmaceutical industry, and the deregulation of the retail trade in drugs (91). This has transformed the structure of Vietnam's health care into a mixed public-private system, where most drugs are now available at relatively low cost.

### *1.4.2.1 The public sector*

The public healthcare system is divided into four levels from central to commune (figure 1-9). Each level comprises several units that are responsible for different aspects of healthcare services including: (1) medical examination & treatment, (2) primary health care, preventive medicine (including vaccination) & National Health targeted Programs (NHPs) and (3) population and family planning. At the central level, the Ministry of Health (MoH) is responsible for national management of the whole health care system including research institutions, medical colleges and 44 national hospitals. At provincial level, there are 63 health bureaus corresponding to 63 provinces nationwide. Generally, in each province, there is a general hospital and a number of specialised institutions. At the lower level, there are 615 district hospitals, 686 regional polyclinics and 10,926 community health centres in communes (90). Commune health centres and regional polyclinics are responsible for primary health care delivery and, except for emergencies, are the first point of contact with the public health care system. These primary care facilities provide preventive and curative services and refer patients to larger centres for more advanced diagnostic and therapeutic services. The commune health stations are managed by the District Health Centres (90). In spite of attempts to provide care for common conditions at lower levels of the health system, provincial and

national hospitals still are preferred sources for accessing inpatient services resulting in the overcrowding in these facilities.

According to social insurance statistics, in 2017, 81.7% of the total population was covered by health insurance (92). With the policy that ensures everyone is automatically covered from birth, this rate would be expected to reach 100% in 2020. To get health insurance reimbursement, patients have to visit their local primary care facilities where they are registered (89). Otherwise, they need permission for transferring to higher levels except emergencies. Without this permission, health insurance will only cover 40% (at central level) to 60% (at provincial level) of total hospital cost. For out-patient health care cost, patients have to share 20% co-payment if the cost exceed 200,000 VND.



**Figure 1-9 The structure of health care system in Vietnam**

*(Source: A health financing review of Vietnam, WHO, 2011(93))*

#### *1.4.2.2 The private sector*

Since the market reforms in 1986, more than 100 private hospitals, 30,000 private clinics, and 21,600 private pharmacies and distributors have been established (94). These private practices play an increasingly important role in providing medical services, especially for outpatient care. The positive contributions of the private sector to the health system include providing more convenient conditions for patients and alleviating the overcrowding in the public healthcare facilities. The private sector has been scrutinised due to their insufficient quality of service. As profit-oriented facilities, overuse of high technologies and expensive medicine has been observed in many instances (95). As the low-cost alternative for the poor citizens, there are a number of unlicensed private providers, especially in rural areas, which are often out of control of the local authorities (96). With service provided by inexperienced practitioners, inappropriate treatment has commonly been reported in several studies (95, 97).

#### *1.4.2.3 Commune healthcare based system*

The main function of commune healthcare based system is to deliver most primary care services and NHPs to the population, especially in rural and mountainous areas. NHPs include hygiene, vaccinations, antenatal care, safe delivery and health education. This also provides screening examination, treatment and referrals for outpatients (90).

Strengthening the commune healthcare based system is a priority in Vietnam's health system development towards universal health coverage (98). With 460 out of 693 districts having separate district hospitals for curative care and health centers for preventive medicine service delivery and management of commune health stations (CHSs) and 233 district health centers perform both preventive and curative care functions, this network covers primary care for the whole population (90).

Nationwide, 99% of communes have a CHS with 78% employing a doctor; 98% of CHSs have midwives or obstetric/pediatric assistant doctors; 78% of villages and urban

neighborhoods are served by village health workers, in rural and mountainous areas this reaches 95%. Along with the increase in the number, the quality of health workers has also improved. The proportion of staff with university or higher education in districts and communes has increased from 17% in 2000 to 21.3% in 2013. Nevertheless, there is still a shortage of health workforce and inadequate training to meet current needs with disproportionate distribution of health workers between urban and rural areas (99). Accounting for only 28% of the total population, 59% of doctors and 82% of pharmacists serve urban facilities.

The quality of treatment services is poor and unmanaged at the commune level. Apart from the inadequate facilities, equipment and medicines, the limited expertise of health workers at CHSs is considered a critical factor for CHS service quality (100) This is one of the factors that leads to hospital overcrowding at higher levels. Among patients coming to central hospitals, 54 – 65% have diseases and health conditions that are diagnosable and treatable at the lower levels.

#### **1.4.3 Access to healthcare**

Access to healthcare through high granularity is one of the strengths of the Vietnamese healthcare system (90). With above limitations of the commune healthcare based system, the poor and those with health insurance use the commune health centres more regularly than the more wealthy citizens (91). Still, the richer households account for a larger share of the health services provided than poorer households. Since free health care was abandoned, health seeking behaviour has changed extensively: private healthcare facilities provide the rich with greater access to more and better health services while the poor often access to medicines via self-medication or private pharmacies. Self-medication is cheaper and less time consuming than visiting a health care provider. A study showed that the average household expenditure per episode of illness for self-treatment is 19,616 VND, for private providers 35,206 VND,

and for public providers 95,795 VND (91). There is still 18.3% of the total population that are not been covered by health insurance (92). This explains the preference for self-medication, but results in high numbers of inappropriate drug use.

#### **1.4.4 Legal framework of antimicrobial dispensing**

The most important law regarding antimicrobial use is the Drug Law of 2005 (101). The goal of this law was to improve appropriate antimicrobial use by permitting antimicrobials to be dispensed only with a prescription. This law also requires the patient to comply with the prescription strictly, to provide feedback to prescribers, and to report any side effects. Furthermore, this law prohibits advertisements for prescription-only drugs, like antimicrobials. For the outpatient setting a specific law has been developed in 2007 (Regulation No 04/2008/QD-BYT), and adjusted in 2016 (Circular No 05/2016/TT-BYT) regulating prescription for outpatients. Only doctors working in legal health care centres and as an exception, assistant doctors in remote areas, can be delegated to prescribe. The prescribers are allowed to prescribe after a medical examination and are responsible for their prescription. Interestingly, this law also states that the prescriber should ‘not prescribe to satisfy the irrational requirement of the patient’. A prescription is valid for five days after it is signed by the prescriber. Despite these laws and regulations, most drug sellers continue to sell antimicrobials freely, without a prescription. Currently, there is no sanction for not complying with regulations regarding selling prescription-only drugs without a prescription. This may explain why to this moment no pharmacy has been penalised for antimicrobial dispensing without prescription.

In 2007, a regulation to improve the quality of pharmacies was issued and re-stated in the Circular 46 in 2011 on implementing Good Pharmacy Practice (GPP). GPP requires the pharmacy to have proper facilities (area, drug storage), to supply of high quality healthcare products, record drug consumption, and not to sell prescription drugs without a prescription.

Furthermore, the responsible pharmacist should have a presence at their drugstore, in case patients need a consultation. Pharmacists will become part of providing health information to their clients, besides a quality drug provider. As a requirement of Ministry of Health, attaining GPP status is compulsory for all pharmacies that want to dispense prescription-only drugs. Pharmacies without GPP certificate are allowed to dispense over-the-counter drugs only.

As of 2013, all of Vietnamese pharmacies are supposed to have implemented measures to attain GPP certificated. In the big cities like Hanoi, all pharmacies are GPP certificated (3644 GPP pharmacies) and 98% pharmacies in Ho Chi Minh city (2286/4550) while the rate is much lower than 50% in remote areas (102). However, GPP only bring improvement in facilities (area, drug storage), but not in dispensing practice including compliance with the prescription regulation.

#### **1.4.5 The reasons for inappropriate antimicrobial usage**

Causes of inappropriate antimicrobial prescription are the same as in other countries including perceived expectations of patients, time constraints, lack of knowledge, lack of diagnostic capability, and financial benefits for the prescriber. Limited knowledge amongst consumers, drug sellers and pharmacists about the value and risks of antimicrobials is part of the problem but there are also financial incentives to sell antimicrobials and immediate personal benefits in taking antimicrobials that outweigh the future societal risks. Even within the health care sector, limited knowledge regarding appropriate indications for antimicrobial treatment, limited capacity for laboratory confirmation of a bacterial cause of infection, and incentives to prescribe have led to the widespread inappropriate prescribing of antimicrobials. A major challenge is to identify and modify the incentives for inappropriate prescribing. Furthermore, the high out-of-pocket expenditure in Vietnam forces patients to seek health care in the cheapest way. Therefore, both health care workers and the public in Vietnam need



to be targeted with appropriate interventions to enable changes in their behaviour and incentives (103).

## **1.5 Biomarker guided antimicrobial use – a potential control measure**

### **1.5.1 Biomarkers in acute infections**

There are a number of biomarkers, proteins or components of the immune system, that act as an acute reactant to infection/inflammation (104-107). These have been studied as potential substances to facilitate rapid diagnosis and guide therapeutic decisions (*e.g.* antimicrobial prescription) in acute infections (108). Currently, several tests have been developed that allow to diagnose infections by testing for the presence of several biomarkers (109). In the correct clinical context these tests could have an additional diagnostic value to assist prescribers in identifying patients with infections that are more likely to respond to antimicrobial treatment and therefore, reduce unnecessary use of antimicrobials.

### **1.5.2 C-reactive protein (CRP)**

C-reactive protein (CRP), a 24kDa protein, is an acute phase reactant produced by hepatocytes. It was first detected in serum of patients with pneumonia (110). Its name is derived from the reaction with C-polysaccharide in pneumococcal cell walls. CRP can also bind to chromatin in nuclear DNA-histone complexes. Once bound, it is able to activate the classical complement pathway. Acting as an opsonin, CRP flags up pathogens and damaged host cells for phagocytosis by binding to ligands on their cell surfaces (111). Increased production of this protein is triggered by pro-inflammatory cytokines released by infection or tissue damage such as tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-1 and IL-6 which are involved in protecting against bacteria (112). These cytokines are produced in the initial phases of the bacterial infection, stimulating neutrophils and macrophages to destroy bacteria. In the initial phase of viral infections, however, controlling the infection is done by type I

interferons (IFN-alpha and beta), macrophages and natural killer (NK) cells (113). CRP levels thus increase in bacterial infections and generally elevates much less or not at all in response to viral infections due to the virus-stimulated synthesis of  $\alpha$ -interferon by macrophages, which, in turn, inhibits TNF synthesis. Therefore, it may be used to distinguish bacterial infections from viral infections.

### **1.5.3 Mechanism of changes in CRP levels and clinical applications**

Normally, CRP is present at very low serum concentrations of less than 3 mg/L. In the presence of infection, transcription of CRP is rapidly induced by pro-inflammatory cytokines and serum concentration can rise 1000-fold (up to 500 mg/L) within 24-48 hours in cases of severe infection (114, 115). Transcription is also rapidly switched off after the acute phase response has subsided. Posing moderate specificity (70%) and high sensitivity (86%), an elevated CRP value provides a valuable addition to careful clinical and laboratory assessment in differentiating viral or self-limiting from bacterial infections and making a decision whether a patient requires antibiotic treatment (116). Except deranged liver function, very few factors interfere with CRP production. CRP concentrations are unaffected by anaemia, immunoglobulin levels, age or sex. During pregnancy, CRP levels will be higher in the second and third trimester (117-119). These characteristics make it a suitable biomarker for the presence of an inflammatory / infectious process – a process that may benefit from antimicrobial intervention. Other clinical applications of CRP include screening for early onset of sepsis in neonates (120) and monitoring response to (long-term) antimicrobial treatment (121, 122).

### **1.5.4 Alternative biomarker – Procalcitonin**

Among other alternative biomarkers, PCT has been the most studied and found to be a promising biomarker (107, 123). PCT has been shown to have higher diagnostic accuracy compared to CRP with higher sensitivity (88% vs 75%) and specificity (81% vs 67%) in

differentiating bacterial from noninfective causes of inflammation among patients hospitalised for suspected bacterial infections (116). This result has been supported in a recent prospective study investigating the diagnostic value of PCT, CRP, IL-6 and SAA for bacterial infection in 326 febrile adult patients. At the cut-off value of 0.26 ng/ml, PCT was shown to be superior to CRP, IL-6 and SAA in early diagnosis of bacterial infection with areas under the curve (AUC) of 0.804, 0.693, 0.658 and 0.687, respectively (124). However, other prospective studies conducted in Cambodia, Laos and Thailand in febrile patients yielded conflicting result by showing that CRP had higher AUC in discriminating between bacterial and viral infections than procalcitonin (AUC 0.83 (0.81–0.86) compared with AUC 0.74 (0.71–0.77),  $p < 0.0001$ ). At a threshold of 10 mg/L, CRP had a higher sensitivity (95% versus 90%) and specificity (49% vs 39%) in detecting bacterial infections compared to PCT at a low threshold of 0.1ng/ml. At a threshold of 20 mg/L sensitivity and specificity of CRP was 86 % and 67 %, respectively compared to 60% and 76% of PCT cut-off 0.5 ng/ml (125).

### **1.5.5 Biomarkers for optimising antimicrobial therapy for in-patients**

Among a number of biomarkers which have been studied in acute infections, only CRP and PCT have been evaluated well enough to use in daily practice for optimising antimicrobial therapy (126-128). Other biomarkers are not suitable (yet) because of a poor performance, limitations in result interpretation, studied in too small population (<50 patients) or too few studies (108, 129).

CRP has been tested in various conditions such as sepsis, CAP or COPD, but only few focused on optimising antimicrobial therapy (127, 130, 131). An individual, prospective, randomised, controlled trial was conducted in 176 newborns with sepsis (131). Findings showed that the mean treatment duration was significantly lower in the CRP-guided group with 3.7 (median, 4; range 3 to 6) days versus 5.5 (median, 5; range, 5 to 7) days in control group ( $p < 0.05$ ). It was concluded that CRP could be a key indicator to shorten the duration of

antimicrobial therapy in a subgroup of newborns with suspected bacterial infection. In another study, in 22/50 (44%) consecutive neonates with suspected septicemia antimicrobial therapy was stopped on 3<sup>rd</sup> day as CRP was normal ( $\leq 10$  mg/L) (130). In 4/50 (8%) patients, antimicrobials could be stopped within 5-7 days as CRP values returned to normal and in 24/50 (48%) duration of antimicrobial treatment was extended beyond 7th day, as CRP values were high or rising persistently. The correlation between CRP, raised micro ESR and positive blood culture was significant ( $p < 0.005$ ). Among 100 infants with suspected sepsis, 99 were correctly identified by the repeat CRP estimation as not requiring further antimicrobial treatment (negative predictive value, 99%; 95% confidence intervals, 95.6 to 99.97%) (127). A recent validation study showed the diagnostic value of a host-protein based assay combining CRP and two other biomarkers (tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) and interferon gamma induced protein-10 (IP-10)) in differentiating bacterial and viral infections among hospitalised children under five years-old with LRTIs (132). The assay showed higher sensitivity of 86.7% (95% CI 75.8–93.1) and specificity of 91.1% (87.9–93.6) than CRP in distinguishing bacterial from viral infections among 577 patients aged 2-60 months with lower respiratory infections or fever. However, incorporation bias could not be excluded as the assessed assay is included in the reference standard resulting in overestimation of the outcome. Additionally, the test was not superior to CRP in bacterial infections diagnosis ( $p=0.321$ ) indicating that two additional substances did not significantly improve diagnostic accuracy compared with CRP. Despite the few available studies confirming its usefulness, this approach has the potential to optimise antimicrobial therapy.

Compared to CRP, PCT has been more widely tested for optimising antimicrobial therapy in both children and adults. To date, 12 randomised, controlled studies using a similar approach have been published and provide consistent results (133-144). All these studies have used a similar algorithm to help decide on the initiation and continuation of antimicrobial

therapy, with a lower PCT threshold of <0.25 ng/mL to encourage physicians to withhold antimicrobial prescription (145). The absolute risk reduction of antimicrobial administration varies between 11% and 72% across these studies compared with “usual care” based on local recommendations and physicians’ judgment and preferences. In view of currently available data, PCT is superior to CRP in optimising antimicrobial therapy. Nevertheless, as of now PCT is an expensive test (10\$) as compared to CRP test (below 3\$) and a rapid diagnostic test at the point of care is not available, restricting its wider use in developing countries (107, 116). Efforts are being put in the development of point-of-care testing which allow rapid diagnosis at the bedside and the development of new methods, such as the analysis of gene expression (genomics) or of ribonucleic acid (RNA) which allow to identify new markers for better diagnosis, stratification of prognosis, and targeting antimicrobial therapy (146).

#### **1.5.6 CRP rapid diagnosis test in primary care in high-income settings for out-patients**

To date, there are three individual randomised controlled trials (RCT) and three cluster-RCT (3284 patients including 139 children) evaluating use of point-of-care C-reactive protein test in guiding antimicrobial prescription versus standard care in primary care patients with acute respiratory infections (ARIs) in high-income countries (147). Four trials have used a similar algorithm with a CRP cut-off of <20 mg/L to encourage physicians to withhold antimicrobial prescription (148-151). A lower CRP threshold of <10 mg/L has been used in one study to delay antimicrobial prescription (152). The remaining study used a higher CRP cut-off of <50 mg/L to adjust the treatment decision (153). An overall reduction in antimicrobial prescription was found in the the C-reactive protein guided groups compared to standard of care with a pooled effect estimate risk ratio (RR) of 0.78 (95% confidence interval (CI) 0.66 to 0.92). However, a high level of heterogeneity ( $I^2$  statistic = 68%) was found due to difference in study design. Separately, cluster-RCTs have yielded higher effects with RRs of 0.68, 95% CI 0.61 to 0.75;  $I^2$  statistic = 0% compared to RRs of 0.90, 95% CI 0.80 to 1.02;

$I^2$  statistic = 5% for individual RCTs. A difference in clinical recovery was not found though an increased risk of hospitalisations in the C-reactive protein guided group could not be excluded. Findings from these trials showed that point-of-care CRP testing significantly reduced antimicrobial use without affecting patient-reported outcomes although the degree of reduction remains uncertain (147).

Currently, point-of-care CRP tests are used as standard practice in primary care in some Scandinavian countries in patients with respiratory symptoms and have reduced the use of antimicrobials safely and cost-effectively (154, 155). Extending this strategy to other settings could reduce the unnecessary use of antimicrobials and curtail the spread of drug resistance. In low and middle income countries this is particularly important as second line antimicrobials can be unaffordable. Before implementation in resource constrained settings, a more precise effect estimate is needed to assess the costs of the intervention and compare the use of a point-of-care biomarker to other antimicrobial-saving strategies.

## **1.6 Objectives of this thesis**

To develop community-based interventions that may be used to improve antimicrobial consumption in Vietnam, which in turn will slow down the development of antimicrobial resistance, understanding the current situation of community level antimicrobial access and use and assessing potential control measure is of the essence. Therefore, I propose the following research questions:

1. What are the financial and behavioural incentives driving antimicrobial dispensing in the community?

Since the market reforms in Vietnam, many private pharmacies now exist, with easy public access to medicines as a result despite legislation preventing this being in place. The knowledge of the drug sellers is poor and drug dispensing is generally inappropriate.

Appropriate antimicrobial selling will reduce antimicrobial sales and therefore have an impact on pharmacy profits. To enable to develop effective strategies it is important to understand the magnitude of the profitability of antimicrobial sales in rural and urban pharmacies as well as other main drivers supporting current community antimicrobial practices from two aspects: supply and demand.

2. Can a Point-of-Care diagnostic, C-reactive protein (CRP) test, reduce antimicrobial prescribing for acute respiratory infections (ARI) safely in the primary care setting, and to what extent?

Effectiveness and safety of point of care (POC) C-reactive protein (CRP) in reducing unnecessary antimicrobial use have been proven in high-income countries (147, 155). However, no similar trials have been investigated in LMICs where inappropriate access and antimicrobial resistance is among the highest. Different social, clinical and environmental factors may affect its impact and impact may thus be different in LMICs. Therefore, in order to reduce inappropriate community antimicrobial prescribing safely in these settings, it is necessary to confirm its effectiveness and safety in resource constrained settings. Findings from this study will be the basis for further extension to the dispensing channel in settings where antimicrobials are commonly dispensed over the counter.

3. What is the economic impact of POC CRP test to reduce antimicrobials use in a lower middle income country (LMIC) setting of Vietnam?

In poor countries with low health system capacity, it is important to select interventions that require relatively little resources. Therefore, diagnostic interventions aimed at improving antimicrobial stewardship should meet acceptance in the healthcare system regarding their cost-effectiveness. Current evidence that POC CRP is cost-effective is limited (155-157). More accurate estimates of the economic impacts of POC CRP strategy compared with standard of care from a health care perspective is crucial to guide future investment,

especially in LMICs.

4. What is the acceptance of using a CRP test among patients and health care workers in the community setting?

Uptake of new technology in clinical practice is challenging and dependent on opinions of healthcare workers and patients about importance and feasibility of the proposed interventions (158). Previous qualitative studies assessing the acceptance of POC CRP test conducted in European countries only included healthcare providers. An understanding of both patients and healthcare providers' views and experiences of using proposed intervention in practice is helpful to assess the feasibility and acceptability of the intervention, which inform implementation in a wider scale.

To address the research questions above, I conducted four studies to achieve four specific objectives as follow:

1. An observational study to assess antimicrobial sales in private pharmacies to identify the economic and behavioural incentives for antimicrobial dispensing in urban and rural pharmacies in northern Vietnam (Chapter 2)
2. An open-label randomised controlled trial to evaluate the efficacy and safety of the point-of-care C-reactive protein test in reducing unnecessary antimicrobial prescribing for acute respiratory infections in ten primary healthcare centres (Chapter 3)
3. A health economics analysis to evaluate the economic implications of C-Reactive Protein point of care testing in the management of acute respiratory infections in the Vietnamese primary health care setting (Chapter 4)
4. A qualitative study to assess the acceptance of C-reactive protein POC testing among patients and health care providers in the same community settings (Chapter 5).



## Chapter 2

### Antimicrobial sales in rural and urban private pharmacies in northern Vietnam: an observational study

#### 2.1 Background

Pharmaceutical products are indispensable for the treatment and prevention of diseases. In developing countries the demand for health care has increased. In Vietnam, health expenditure accounted for 7.1% of GDP in 2014, compared to 6.2% in 2011 (85). Household direct out-of-pocket health expenditure as a share of the total health expenditure ranged from 50% to 70% (159). Pharmaceutical spending shared a large proportion of total health expenditure with 50.9% compared to 8.8% in Malaysia (160). The per capita annual expenditure on pharmaceutical products in Vietnam in 2010 was \$104 compared to \$148 in China and \$51 in India (161). The majority of the drug costs are incurred at drug retailers. Since the market reforms in 1986 in Vietnam, 21,600 private pharmacies now exist, with easy access to medicines as a result. The private pharmacies also provide consulting for customers about drug use but the knowledge of the drug sellers is poor and drug dispensing is generally inappropriate (162). In 2011, the Ministry of Health has issued a circular on the ‘principles and criteria of implementing good pharmacy practice (GPP)’ to enhance the service quality of pharmacies (163). However, the impact of GPP in dispensing practice remains largely unknown.

Since their introduction in 1940s, antimicrobials have revolutionised modern healthcare and together with vaccines have had the highest impact on human health of all drugs. However, their effectiveness has been threatened by the development of antimicrobial resistance. Both appropriate and inappropriate use of antimicrobials is a key driver of antimicrobial resistance development. However, overuse or misuse of antimicrobials (e.g. low

dose, too short duration, or treatment of self-limiting infections) provides an avoidable additional pressure leading to more antimicrobial resistance (164). In many countries inappropriate use of antimicrobials is common practice in the community setting, where antimicrobials are readily dispensed for self-limiting upper respiratory tract infections without a prescription (165-168). To slow down the development of antimicrobial resistance, an important control strategy is to reduce the inappropriate use of antimicrobials in both community and hospital settings. The incentives behind inappropriate antimicrobial dispensing need to be fully understood, so intervention strategies can be developed based on that knowledge.

In Vietnam, health seeking behaviour has changed since market reforms that were initiated since 1980s. User fees at public hospitals, health insurance schemes, the commercialisation of the pharmaceutical industry, and the deregulation of the retail trade in drugs have led to significant but also uncontrolled improvements in the quality and accessibility of health care. However, they have also increased out-of-pocket health expenditures as a proportion of total health expenditure. The high out-of-pocket expenditures encourage people to bypass the health care system, and obtain medicines – including antimicrobials – directly via self-medication or private pharmacies without proper diagnosis (91, 169). According to one study in 2002, the average household expenditure per episode of illness is 1.1 USD for self-treatment, 1.9 USD for private providers, and 5.2 USD for public providers. The relative higher costs of the health care system explains the preference for self-medication, which results in many cases of inappropriate drug use (91).

Even though prescriptions are legally required, antimicrobials (and a wide range of other drugs) can be purchased directly by consumers at pharmacies or drug outlets (170). Self-diagnosis is not accurate, but self-treatment is common. Previous studies have shown that most antimicrobials are sold without prescription. According to a community-based study

undertaken in 1999, 78 percent of antimicrobials were purchased in private pharmacies without a prescription. 67 percent of the participants consulted the pharmacist while 11 percent decided themselves about antimicrobial use (171). Only 27 percent of the pharmacy staff had correct knowledge about antimicrobial use and resistance (162). Reportedly, prevalence of self-medication with antimicrobials through private pharmacies in rural Vietnam is 80%, and is even higher in children with 88% of the children receiving self-medication before hospital visit (172). These results raised concerns about drugs being sold without prescriptions and the common practice of self-medication. Judicious use of antimicrobials can decrease unnecessary adverse effects of antimicrobials as well as out-of-pocket costs to the patient. But more importantly, decreased antimicrobial usage will help delay the rise of drug resistant bacteria, which is now a growing world-wide public health problem (173).

As other countries in the region, the development and spread of antimicrobial resistance is increasing in Vietnam. In order to improve this situation, one of the most important policies is to raise awareness by providing information training about appropriate antimicrobial use, especially those who sell drugs, "who directly deliver drugs to patients". Appropriate antimicrobial selling will reduce antimicrobial sales and therefore have an impact on pharmacy profits. To enable to develop effective strategies it is important to understand the magnitude of the profitability of antimicrobial sales in rural and urban pharmacies.

The present study aims to understand the economic and behavioural incentives that support inappropriate dispensing of antimicrobials at private pharmacies in urban and rural settings in Vietnam. This is crucial for designing effective interventions to reduce the inappropriate antimicrobial use in the community.

## **2.2 Materials and Methods**

The WHO Operational package (174) provides a range of indicators, which can be

studied at the national level of countries to evaluate three dimensions of pharmaceutical services: access, quality and rational use. We adhered to the recommended indicators as much as possible and adjusted when needed for geographical areas and pharmacies selection, observation time and supervision of data collection.

### **2.2.1 Study sites and selection of pharmacies**

The study was conducted at two well-established demographic surveillance sites (DSS) in the Hanoi region in 2010 (figure 2-1). As the study aims to understand the situation of antimicrobial dispensing at private pharmacies in both urban and rural settings in Vietnam, one urban (Dong Da) and one rural (Bavi) district were selected. Bavi is a rural community situated 60 km west of Hanoi. The district covers an area of 410 km<sup>2</sup> and has 262,000 inhabitants. Agriculture is the main source of income. Bavi district is heterogeneous in terms of geographical characteristics and representative for rural settings in and around Hanoi. The basic health care system includes a district hospital with 150 beds, 3 regional polyclinics, 32 commune health stations, and 90 licensed private health facilities including private clinics, pharmacies, drug stores and drug outlets (175). Dong Da is the biggest urban district of Hanoi that covers an area of 10 km<sup>2</sup> and has 352,000 inhabitants, with a public health care system including a district hospital with 300 beds, 3 regional polyclinics, 1 antenatal clinic, 21 commune health stations and 278 private pharmacies located in this district (176). With these characteristics, Dong Da district is considered a typical urban district in Hanoi.

There are two demographic surveillance sites (DSS) in these districts (FilaBavi and Dodalab) with well-established relationships between the healthcare system and the study teams. These features made it possible for invited pharmacies to participate in the study and to respond to sensitive issues such as the financial mechanism, including profits and drug management.



**Figure 2-1 Location of study sites**

*Observed pharmacies located in Ba vi district (red) and Dong Da district (blue)*

Private pharmacies in each site were randomly selected from a government pharmacy registry, using the Excel random number function for the rural and urban settings. To assess the situation of self-medication in the community, outlets directly surrounding hospitals were excluded in this selection. The randomly selected pharmacies were approached sequentially based on ascending random number allocation to get permission to participate until 15 shops in each site were reached. Two urban pharmacies refused to participate, no refusals occurred in the rural setting. All pharmacies that agreed to participate in the study allowed observers in their pharmacy during three days to observe and record drug sales and prices.

### **2.2.2 Sample size**

One of the major areas of focus in this cross-sectional study was the selling of antimicrobials without a prescription and the revenue of antimicrobial sales as compared to all sales. Based on previous work we expected 80% of customers to buy antimicrobials without a

prescription (177). With  $\alpha=0.05$ ,  $Z_{1-\alpha} = 1.96$  and a precision of  $d=5\%$ , we calculated that at least 246 drug transactions needed to be observed. In a pilot study, we observed that there were approximately six antimicrobial transactions per pharmacy per day in a rural pharmacy. Due to the limited number of observers, we selected 15 stores in each setting to be observed. To capture the estimated number of expected antimicrobial transactions, it's needed to observe each drug store in 3 consecutive days (3 days x 15 stores x 6 transaction/day = 270 transactions). We selected an equal number of urban and rural pharmacies to facilitate comparison although urban sales are expected to be considerably higher.

### **2.2.3 In-pharmacy observation**

During three consecutive days from 9AM to 5PM during opening time of the pharmacy, investigators observed and recorded all information related to pharmacy and drug selling practices onto data capture forms. The forms captured the following basic pharmacy data: facilities, number of staff and education level, presence of Good Pharmacy Practice (GPP) certificates, and presence of pharmaceutical guidelines. Pharmacies that have a GPP certificate are required to ensure a supply of high quality healthcare products and deliver sufficient information and advice to the consumer. The GPP policy also requires pharmacies to have proper facilities (area, drug storage), and comply with prescription regulation.

For the observation of drug transactions, we captured the following information: gender, estimated age of customer, indication for buying drugs (coded according to the International Classification Primary Care – ICPC edition 2), presence of a prescription, compliance to prescription, and any advice provided by drug seller. In cases in which a prescription was provided we checked whether the drug on the prescription was substituted by another drug with a different generic name or a different content/concentration than on the prescription was dispensed or a different dosage/duration than on the prescription was

dispensed. In case any of the above was done, we then determined that there was non-compliance with the prescription.

A “drug transaction” in this study included the purchase of any drug or other items present in the pharmacy (e.g. herbal medicine, cotton wools, band aid, etc.). Purchased drugs were recorded according to brand name, which was subsequently recoded into the corresponding generic name and Anatomical Therapeutic Chemical (ATC) Classification System (178). For each drug we also recorded the origin, unit, dosage, and selling price.

The observers included pharmacists who recently graduated from Hanoi Pharmacy University, master pharmacy students, and trained field workers. They were trained in observation skills, interview skills and how to complete the capture forms by senior and experienced investigators. The training included presentation and explanation of the study, discussion, interaction and case practice by acting as drug sellers/owners and interviewers. Furthermore we performed a pilot in two pharmacies (one in urban, one in rural) to test the questionnaire and revise if needed. The pilot pharmacies were not selected for the real observation.

The pharmacist/seller was informed that the observation would be for all drug sales, and thus not antimicrobials specifically, to reduce any potential biases by the observation. The observations were supervised and randomly checked by supervisors. At the end of each observing day, supervisors collected the forms and were checked for completeness. Bigger pharmacies had two observers present. Pharmacy customers were not interviewed by the study staff. All data capture forms and questionnaires were designed in the English language and send for peer review to experts in the field. The revised version was then translated into Vietnamese and piloted in a rural and urban pharmacy.

#### **2.2.4 Post-observation questionnaire**

After the observation, one drug-seller and one pharmacy owner per pharmacy were asked to complete a semi-structured questionnaire that focused on antimicrobial sales and their opinions about important causes for irrational antimicrobials dispensing in their region. Answers were provided on a 5-point rating scale which is named “likert scale” after its inventor, psychologist Rensis Likert: “1=strongly disagree” to “5=strongly agree” (179). There are three general indicators to estimate reliability (180) including: (1) stability or test-retest reliability which is the consistency of a measure evaluated over time, (2) internal consistency reliability which is the consistency of results across items or set of scale, often measured with Cronbach’s alpha, (3) interrater reliability (also called inter-observer agreement) is the degree to which different observers give consistent answers or estimates. In my analysis, to assess the reliability of survey responses, Cronbach’s alpha was analysed with respondents’ scores for all questionnaire items by SPSS. It is a measure of the internal consistency of a set of scale or test items, expressed as a number between 0 and 1 with values above 0.7 being acceptably consistent (181). All forms were anonymous to encourage interviewees to frankly share information. In total, 43 informants attended this survey including 26 respondents in urban pharmacies and 17 in rural site. Among them, 4 respondents in urban and 13 in rural were both pharmacy owners and sellers.

## **2.2.5 Qualitative assessment**

### *2.2.5.1 Rationale for choosing qualitative research*

Qualitative research methods have become more common in health services related research (182). While quantitative research aims to analyse phenomena in terms of trends and frequencies, qualitative research seeks to determine the meaning of a phenomenon through description and thus enables to answer questions that may not be easily answered by quantitative data (183). The advantage of qualitative research is that it is able to provide a comprehensive description of an issue relating to personal behaviors, beliefs, opinions,



emotions, and relationships of individuals. Qualitative research seeks answers about: (1) why people behave the way they do; (2) how opinions and attitudes are formed; (3) how people are affected by the contextual factors; (4) what are the differences between studied populations. In combination with quantitative methods, qualitative research can aid to interpret and deepen insight into the studied phenomenon (184). Therefore, to investigate behavioural incentives, qualitative methods including focus group discussions (FGD) and semi-structured in-depth interviews were used to better explore experiences and opinions of the drug sellers and pharmacists, as well as their perceptions of the factors that impact on inappropriate antimicrobial dispensing.

#### *2.2.5.2 Methods of collecting qualitative data*

Data collection methods in qualitative research aim to systematically collect information about study objects including people or phenomena and about the settings in which they occur. There are three main approaches to collect qualitative data including: (1) observations, (2) textual and visual materials review and (3) interviews (individual and group) (185). Among these methods, individual interviews and focus group discussions are the most commonly used in qualitative healthcare research to assess a set of personal beliefs, habits, opinions of those participating in the discussion as well as perceptions in the studied population that they represent (186).

##### *a. Individual interviews*

This method consists of three fundamental types: structured, semi-structured and unstructured interviews (186, 187). In structured interviews, the interviewer follows a structured questionnaire, which includes a list of predetermined questions to be asked. Structured interviews are therefore relatively quick and easy to conduct. However, its limitation is that there is little or no chance for follow-up questions to be further investigated.

Consequently, it does not allow the evaluator to assess the “depth” of an issue. Conversely, unstructured interviews, in which a formal interview schedule or question order is not provided encourage the interviewers to seek for free and open responses (188). It allows the interviewer to be flexible in conducting the interview to particular respondents or situations. Respondents are also encouraged to express perceptions in their own words which allow to capture the meaningfulness of their experience and warrant in-depth exploration. Disadvantages of this method are that it is relatively resource and time consuming, difficult to manage and it requires well-trained interviewers. Inconsistencies can be induced due to allowed flexibility resulting in interpreting bias. It is generally used when significant “depth” is required or nothing is known about the explored subject. Semi-structured interviews with a set of key questions help to define the aspects to be investigated (189). This format provides useful guidance to respondents on what they should talk about. Unlike structured interviews, this format also allows further discovery with follow-up questions to warrant “depth” of information. Therefore, it is most commonly used in healthcare related research. In my thesis, I chose the semi-structured interview format to facilitate individual interviews.

*b. Focus group discussion*

With similar features to less structured interviews such as depth and insight, this technique is used to generate information on collective opinions (190). Compared to individual interviews, its advantage is that a broader scope would be quickly obtained about the topic in focus and providing a good chance for debate and discussion between participants (191, 192). In this techniques, a monitor or facilitator who guides the discussion plays a crucial role (193). The moderator should be able to ensure that all respondents have an equal chance to contribute and avoid bias the situation by personal opinions. Participants are encouraged to share their own experience and knowledge on a few predetermined themes allowing differences of opinions to be discussed. However, transcription of FGDs is more

complex and time consuming than individual interviews. FGDs should be avoided if participants are uncomfortable to openly exchange their views with each other as interaction is key to a successful discussion. Group composition is an important feature in FGDs because this affects the quality of discussion and outcomes (194). There is no “best” formula to group mix by ages, gender, socioeconomic and professional status. The impact of group mix should be considered by the researcher before conducting discussions. Having six to eight participants in a FGD is an optimal size (195). Large groups might be hard to manage and participants would have insufficient opportunities to share their own views. Conversely, small groups will risk limited discussion and achieving poor data.

#### *2.2.5.3 Sampling in qualitative assessment*

Contrasting quantitative research, statistical representativeness is not considered a requirement in sampling in qualitative research (182). Qualitative data collection is normally more expensive and time consuming, thus using of a probability sample is unsuitable (196). To enhance the value of exploration in the “human” side of an issue, sampling in qualitative research tends to identify specific groups of people who hold relevant features to the studied phenomena. Therefore, sampling strategies in qualitative studies largely depend on the purpose of the study, given the time and resources available (197).

In our investigation, one FGD was held in the rural area and a total of six individual in-depth interviews were performed in both sites due to difficulties in finding participants for the FGD, especially in urban area. The FGD included the following participants: two pharmacy owners, one drug seller and three commune health centre workers. All of them had a primary degree in pharmacy and those working in commune health centres (CHCs) were also assistant doctors. The in-depth interviews were done with three rural (two pharmacy owners and one CHC staff) and three urban participants (two participants were both pharmacy owner and drug seller and one drug seller. One owner is a pharmacist and the two other participants had a

secondary degree in pharmacy). English guidelines were developed to cover general and specific issues for asking participants to discuss their own experiences and opinions. Both discussion and in-depth interviews included the following themes: (1) financial incentives, (2) knowledge of government regulations and (3) potential solutions for controlling inappropriate antimicrobial dispensing practices (table 2-1).

All discussions in both sites were led by a female senior pharmacist who had relevant training and experience. If needed, findings of the observation and questionnaire were presented during FGD and interviews to support the discussion. All contents of conversations were recorded and transcripts were made and translated into English. All reported qualitative characteristics including moderator, study design, analysis and findings meet consolidated criteria for reporting qualitative research (COREQ), which includes a 32-item checklist for interviews and focus groups.

**Table 2-1 Discussion topics for FGD and in-depth interview**

<p><b>1) Financial incentives</b></p> <p>1.1 What is the importance of antimicrobial sales compared to other drugs in your pharmacy?</p> <p>1.2 What factors affect the sales of antimicrobials? Can we change these factors or not?</p> <p>1.3 Why are antimicrobials still sold when there is no prescription?</p> <p>1.4 What is role of distributors /prescribers /patients?</p> <p>1.5 What type of patients demand antimicrobial without prescription and is this common?</p> <p>1.6 If a customer requests antimicrobials when not needed, would you sell or not?</p>
<p><b>2) Knowledge of government regulation</b></p> <p>2.1 What do you know about antimicrobial resistance and the role of inappropriate antimicrobial use? How did you acquire this knowledge?</p> <p>2.2 Are current government regulations sufficient to control inappropriate antimicrobial use?</p> <p>2.3 Will Good Pharmacy Practices help to improve control of inappropriate antimicrobial use?</p>
<p><b>3) Solutions</b></p> <p>3.1 What would happen if antimicrobial sales decline due to compliance with current regulations on dispensing antimicrobials?</p> <p>3.2 In your opinion, what do we need to do to improve the situation of antimicrobial use and resistance in Vietnam?</p> <p>3.3 What are the roles and responsibilities of other stakeholders like industry &amp; government?</p>

## **2.2.6 Ethical considerations**

The Ethical Review Board of Hanoi Medical University approved the study (Decision No: 78/HDDD-YHN). Permission was obtained from the local health bureau for the study and verbal consent was obtained from the owner of each participating pharmacy. All pharmacy data was anonymised.

## **2.2.7 Data analysis**

### *2.2.7.1 Quantitative data analysis*

Collected data were cleaned and entered into a Microsoft Access database, designed and maintained by a statistician (Dr. Tran Thanh Do) in Hanoi Medical University. Antimicrobial sales data was summarised using median and interquartile range (IQR) for skewed distributed data. Potential differences between urban versus rural pharmacies were compared by Mann-Whitney test for non-normal continuous data, Wilcoxon sign rank test for paired non-normal data and Chi-square test for categorical variables. P-values less than 0.05 were considered significant (2 tailed).

In terms of revenue, the contribution of antimicrobial sales to the total drug sales for each pharmacy was calculated. In addition, we calculated the retail mark-ups of the twenty most sold antimicrobials. The mark up is the difference between the cost and selling price of a particular product. Here, we used the percentage mark up to assess the profit of antimicrobials that was calculated as  $(\text{selling price} - \text{purchasing price}) / \text{purchasing price} \times 100\%$ . The purchase prices were obtained from major wholesalers and distributors in northern Vietnam. Data was analysed by SPSS software, version 16 (SPSS Inc., Chicago (IL), USA). The currency exchange rate of Vietnam Dong (VND) to US dollar (USD) at the time of study was: 1 USD = 18,500 VND.

### *2.2.7.2 Qualitative data analysis*

Qualitative data collected from in-depth interviews and focus group discussions were analysed by content analysis which is widely used and accepted in qualitative research to analyse text data from FGDs and IDIs (198). The goal of content analysis is to provide knowledge and understanding of the phenomenon by focusing on the characteristics of language as communication with attention to the content or contextual meaning of the text (199). There are three different approaches to interpret meaning from the content of text data including: conventional (text data is the direct origin of coding categories), directed (initial codes are indirectly derived from a theory or relevant research findings) and summative (involves counting and comparisons of keyword or content) (200). In this study, the summative approach that blends qualitative and quantitative analyses, while preserving the essential features of each, was chosen to improve the robustness of qualitative content analysis (201). Data from transcripts were analysed by listening to the tapes and reading and re-reading the transcripts to become familiar with the data and to categorise information. We used both the Vietnamese transcripts and the English translated version to identify common themes. Connections within and between themes were identified. The main themes and connections were used to identify important causes of inappropriate antimicrobial dispensing in urban and rural pharmacies (202).

## **2.3 Results**

### **2.3.1 Pharmacy characteristics**

Among thirty randomly selected pharmacies (15 urban and 15 rural), six urban pharmacies had a Good Pharmacy Practice (GPP) certificate, whilst none of the rural pharmacies had a GPP certificate.

None of the private pharmacy owners in the rural area were pharmacists, whereas 5 owners of urban pharmacies were pharmacists. Most (10) urban pharmacies had more than

one drug seller working in each store while rural pharmacies usually (11) had one seller per outlet. Drug sellers in the urban pharmacies had a higher level of education: 3/28 had a university degree on pharmacy, 21/28 were assistant pharmacists, and 4/28 had an elementary degree on pharmacy. In the rural pharmacies none were pharmacist, 9/17 were assistant pharmacists, 4 were elementary pharmacists and 4 were doctor assistants. Three urban pharmacies had a pharmacist on site in charge of managing and dispensing drugs. Only one pharmacy had up-to-date reference books available in the pharmacy and frequently used for consultation, the remaining did not (table 2-2).

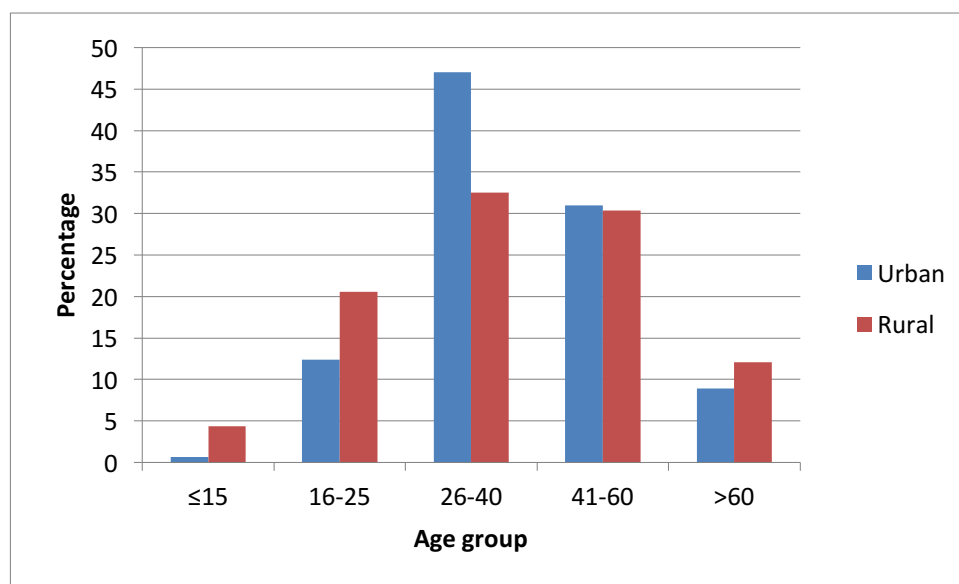
**Table 2-2 Pharmacy baseline information**

<b>Characteristics outcomes</b>	<b>Urban n (%)</b>	<b>Rural n (%)</b>
<i>Pharmacy is GPP licensed</i>	6 (40)	0 (0)
<i>Pharmacy owner's degree</i>		
Pharmacist	5 (33)	0 (0)
Licensed renter	10 (67)	15 (100)
Assistant Pharmacist	9 (60)	10 (67)
Elementary Pharmacist	1 (7)	1 (6)
Assistant Doctor	0 (0)	4 (27)
<i>Number of drug sellers in pharmacy</i>		
1 seller	5 (33)	11 (73)
2 sellers	7 (47)	4 (27)
3 sellers	3 (20)	0 (0)
<i>Drug seller's degree</i>		
Pharmacist	3 (11)	0 (0)
Assistant Pharmacist	21 (75)	9 (54)
Elementary Pharmacist	4 (14)	4 (23)
Assistant Doctor	0	4 (23)
<i>Drug seller uses references / guidelines</i>		
Frequent	1 (7)	0 (0)
Sometimes	4 (27)	6 (40)
Rare	2 (13)	3 (20)
Never	8 (53)	6 (40)



### 2.3.2 Client information

In total, 2083 clients visited urban pharmacies and 870 rural pharmacies during the observation over three days. At both sites, most clients were female: 61.8% and 69.8% in urban and rural pharmacies, respectively. Age of clients was estimated by the observer according to four age categories: under 15 years-old, 16-25 ys, 26-40 ys, 41-60 ys and above 60 ys. Therefore, prescriptions for children were not captured in sufficient detail. The most common age category visiting the pharmacy was 26 to 40 years-old with 53.5% in urban and 31.7% in rural area. Customers under 15 year-old accounted for 1.2% and 4.9% in urban and rural area, respectively (figure 2-2).



**Figure 2-2 Client profile**

*Estimated age group of clients in urban (blue) and rural (red).*

### 2.3.3 Observation of drug sales

In total 2953 drug sale transactions (2083 urban and 870 rural) were observed between the 30 pharmacies (table 2-3). The proportion of transactions that included antimicrobials was high: 24% (499/2083) in the urban sites and 30% (257/870) in the rural sites ( $p=0.002$ ). Most

antimicrobials were sold without a prescription: 88% (439/499) in urban and 91% (234/257) in rural area ( $p=0.2$ ). Compliance to regulations was better in the pharmacies that had a pharmacist on site with 19% (21/112) of total antimicrobials transactions having prescription versus only 10% (62/644) in the shops without pharmacist ( $p=0.004$ ).

**Table 2-3 Antimicrobials dispensing practices according to prescription regulation**

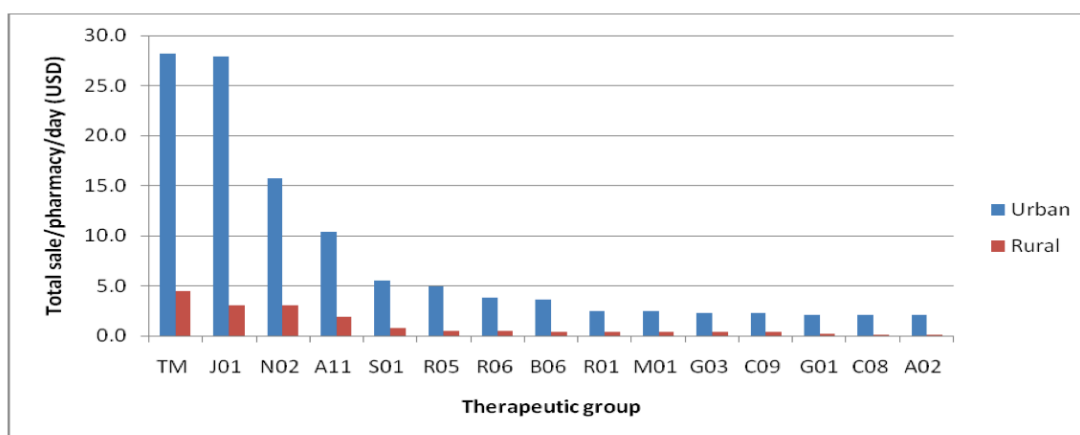
<b>Outcomes</b>	<b>Urban (n=2083)</b>	<b>Rural (n=870)</b>
Transaction with antimicrobials	499 (24%)*	257 (30%)*
<i>With prescription</i>	60 (12%)	23 (9%)
Comply with prescription	49 (82%)	18 (78%)
Not comply with prescription	11 (18%)	5 (22%)
<i>Without prescription</i>	439 (88%)	234 (91%)
Client made decision	221 (50%)*	66 (28%)*
Drug seller made decision	218 (50%)	168 (72%)

\* Significant different between urban and rural group using chi-square test ( $p<0.05$ )

*There was no significant difference between GPP versus non-GPP pharmacies regarding antimicrobials dispensing practices. Pharmacies with a GPP certificate sold antimicrobials without prescription in 88% (196/224) of cases, similar to 90% (477/532) ( $p=0.38$ ) rate in pharmacies without such a certificate. In term of self-medication, 50% (221/439) of the urban pharmacy customers decided by themselves which antimicrobials to buy, whereas the rural clients more often asked for advice from drug sellers, with only 28% self-prescribed ( $p < 0.0001$ ).*

It was observed that antimicrobials were the most common drug sold at the pharmacies in both areas (17% in urban and 18% in rural,  $p=0.15$ ), followed by herbal medicines (15% in

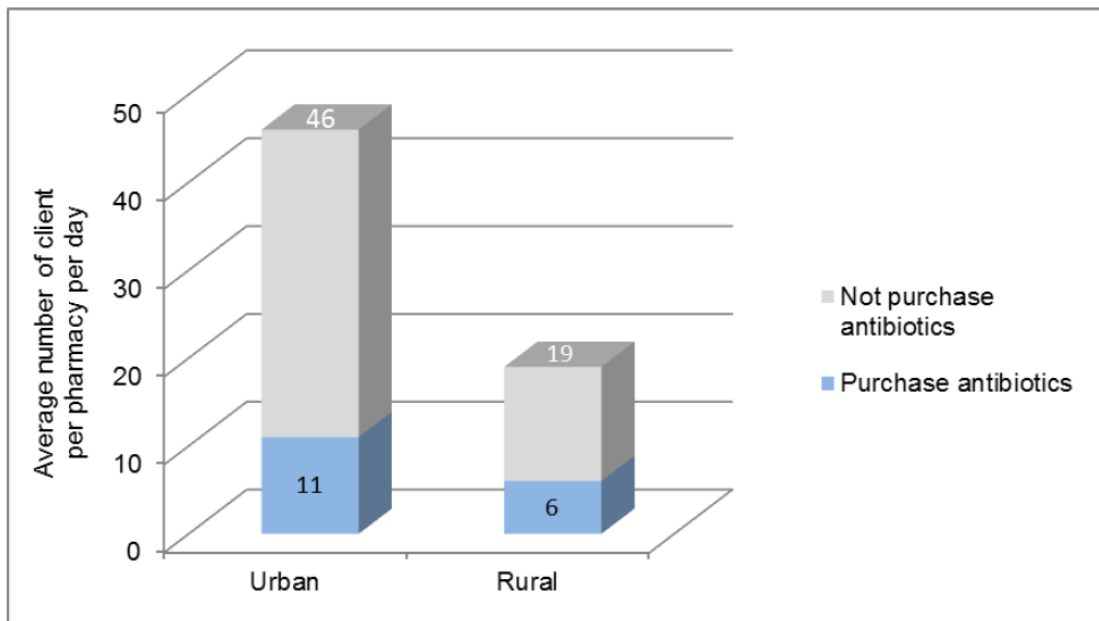
urban and 11% in rural,  $p < 0.0001$ ). However, in terms of monetary value, herbal medicines was the most important group which contributed to total sales of both urban and rural pharmacies with 24% in urban and 27% in rural, followed by antimicrobials (24% in urban versus 18% in rural), analgesics group and vitamins (figure 2-3).



**Figure 2-3 Average sales in USD per pharmacy per day by therapeutic groups in urban versus rural (in USD)**

*TM: Herbal medicines, J01: Antimicrobials, N02: Analgesic, A11: Vitamins, S01: Ophthalmological, R05: Cough and cold preparation, B06: Haematological agent, R06: Antihistamine, R01: Nasal preparations, M01: Anti-inflammatory and anti-rheumatic products, G03: genital system, C09: rennin-angiotensin, G01: Gynaecological, C08: Calcium channel blocker, A02: Acid related disorders.*

Average number of customers per pharmacy per day was 46 in the urban and 19 in the rural area. Among them, 11 clients in the urban area had transactions with antimicrobials and 6 clients in the rural area (figure 2-4).



**Figure 2-4 Average number of observed clients per pharmacy per day**

*Average number of encounters per pharmacy per day in urban pharmacies (left column) and in rural pharmacies (right column). Antimicrobials encounters per pharmacy per day (blue) and encounters without antimicrobials (grey).*

Other therapeutic groups, such as cardiovascular system, nervous system, or corticosteroid medications, were rarely dispensed in all observed pharmacies. Three most common sold antimicrobials in the urban area were: amoxicillin (13%), azithromycin (12%), cephalexin (9%) while in rural pharmacies these were amoxicillin (27%,  $p < 0.0001$ ), cephalexin (20%,  $p < 0.0001$ ) and ampicillin (12% versus 4% in urban setting,  $p < 0.0001$ ). The main difference between the urban and rural pharmacies was that older antimicrobials, such as chloramphenicol, and co-trimoxazole, were more commonly dispensed in the rural area. In the urban area more new and expensive drugs such as amoxicillin-clavulanic acid, 2<sup>nd</sup> and 3<sup>rd</sup> generation cephalosporins (cefuroxime, cefixime), and azithromycin were sold.

### 2.3.4 Reasons for antimicrobials purchasing

The most common reasons for buying antimicrobials in the urban sites were cough (32%) followed by throat symptoms/complaints (18%), fever (10%). Meanwhile, in the rural sites these were fever (22%), abdominal pain (13.5%), cough (12.2%), diarrhoea (11.5%) and throat symptoms (4.9%) (table 2-4). Antimicrobials were often sold in combination with other drugs: analgesics 17% (189/1122), cough and cold preparations 16% (182/1122), vitamins 9% (99/1122), corticosteroids 9% (98/1122), and herbal medicines 5% (54/1122).

**Table 2-4 Top ten common reasons for antimicrobial purchasing**

Urban			Rural		
Code	Symptom	%	Code	Symptom	%
R05	Cough	31.6	A03	Fever	21.7
R21	Throat symptom/complaint	17.8	D01	Abdominal pain/cramps general	13.5
A03	Fever	9.7	R05	Cough	12.2
D82	Limited function/disability	7.4	D11	Diarrhoea	11.5
F01	Eye pain	5.2	R21	Throat symptom/complaint	4.9
R74	Upper ARI	5.2	D82	Teeth/gum disease	4.6
S02	Pruritus	3.3	S02	Pruritus	3.9
D11	Diarrhoea	2.6	F01	Eye pain	3.6
F73	Eye infection/inflammation	1.9	N01	Headache	3.6
A80	Trauma/injury NOS	1.5	H01	Ear pain/earache	2.6

### 2.3.5 Economic indicators of antimicrobial sales

Antimicrobials represented a considerable proportion of total revenues per day: 24% (27.9USD/115.8USD) in urban and 18% (3 USD/16.5 USD) in rural area ( $p=0.59$ ) (figure 2-3). Urban pharmacies showed higher sales of imported antimicrobials with median sales of 11.5 USD per pharmacy per day (IQR = 5.3 – 41.7) compared to domestic antimicrobials (median=5.1 USD, IQR= 4.2-6.6, P-value 0.003). The opposite was observed in the rural area where very little imported products were sold with median sales of 0 USD per pharmacy per day compared to domestic products in term of total antimicrobials monetary sales with median sale of 1.6 USD (IQR=1.4-3.1),  $p$  value < 0.001). In the rural sites, available imported brands such as amoxicillin or cephalexin were mostly from India, with relatively low prices as compared to other brands. Meanwhile, more expensive imported brands were sold in urban pharmacies.

Retail mark-ups of twenty most common sold antimicrobial generics across all pharmacies in each setting varied considerably. In the urban area, mark-ups ranged from 17-243% (median=54%, IQR=30-79%) and in the rural area from 21-186% (median=58.5%, IQR=39-67%). There was no significant difference between the mark ups between the two regions ( $p=0.76$ ). Several imported brands that were only dispensed in urban pharmacies showed relatively high mark-ups such as: augmentin (amoxicillin – clavulanic acid), zinnat (cefuroxime), zithromax (azithromycin) as compared to domestic products (table 2-5).

**Table 2-5 Mark-ups of 20 most common sold generic antimicrobials**

Generic name	Origin	ATC	Unit/Content	Unit	% Mark-up <sup>s</sup>	
				Price*	Urban	Rural
Amoxicillin	Vietnam	J01CA	Tablet/500mg	0.02	78	67
Amoxicillin	India	J01CA	Tablet/500mg	0.04	54	54
Amoxicillin	Austria	J01CA	Tablet/500mg	0.04	88	NA
Cephalexin	Vietnam	J01DA	Tablet/500mg	0.04	67	67
Cephalexin	India	J01DA	Tablet/500mg	0.05	58	58
Cephalexin	France	J01DA	Tablet/500mg	0.07	25	NA
Ampicillin	Vietnam	J01CA	Tablet/500mg	0.02	122	43
Ampicillin	India	J01CA	Tablet/500mg	0.03	100	40
Chloramphenicol	Vietnam	J01BA	Tablet/250mg	0.03	17	59
Cotrimoxazole	Vietnam	J01EC	Tablet/480mg	0.01	33	67
Metronidazole	Vietnam	J01XD	Tablet/250mg	0.01	82	150
Lincomycin	Vietnam	J01FF	Tablet/500mg	0.03	41	25
Penicillin	Vietnam	J01RA	Tablet/1MIU	0.02	60	50
Spiramycin	Vietnam	J01FA	Tablet/0.75 MIU	0.04	43	29
Spiramycin	France	J01FA	Tablet/0.75 MIU	0.14	68	21
Ciprofloxacin	Vietnam	J01M	Tablet/500mg	0.02	233	186
Ciprofloxacin	German	J01M	Tablet/200mg	0.65	33	NA
Erythromycin	Vietnam	J01FA	Pack/250mg	0.08	103	69
Erythromycin	France	J01FA	Pack/250mg	0.23	31	67
Azithromycin	German	J01FA	Bottle/200mg/5ml	5.19	19	NA
Cefuroxime	UK	J01DA	Tablet/500mg	1.06	27	NA
Cefixime	Banglades	J01DA	Pack/200mg	0.20	49	NA
Amoxicillin+						
Clavulanic acid	GSK	J01CR	Pack/250mg	0.37	62	NA
Roxythromycin	India	J01FA	Tablet/150mg	0.06	81	NA
Klarithromycin	USA	J01FA	Tablet/250mg	0.43	31	NA
Tobramycin	Belgium	J01GB	Vial/0.3%	2.05	18	NA
Cefpodoxim	India	J01DA	Tablet/100mg	0.04	19	NA
Clindamycin	India	J01FF	Tablet/300mg	0.05	117	NA

<sup>s</sup> Difference between the cost and selling price of a particular product. \*Unit price is for smallest unit such as: tablet, vial, bottle or pack

The semi structured questionnaire on antimicrobial dispensing practices with drug sellers and drug store owners by semi-structured questionnaire, 41% (7/17) of rural respondents and 27% (7/26) of urban informants conceded that 20% to 40% of their total

profit was due to antimicrobial sales ( $p=0.33$ ). Meanwhile 53% (9/17) in rural and 23% (6/26) in urban site thought that profit from antimicrobials accounted for less than 20% ( $p=0.04$ ). Only 6% (1/17) of rural respondents and 4% (1/26) in urban considered that profits from antimicrobials accounted for 40-60% of their total profit.

### **2.3.6 Causes for inappropriate antimicrobial selling**

All rural pharmacy respondents thought that the fear of losing a customer leads to dispensing of antimicrobials without prescription. This opinion was shared with 69% (18/26) of urban respondents. Pressure from patients that demand antimicrobials was considered a significant driver of irrational dispensing practices in rural pharmacies according to 77% (13/17) of respondents, and 39% of urban respondents ( $p=0.01$ ). Only 27% (7/26) of the respondents in urban and 24% (4/17,  $p=0.8$ ) in rural area considered that knowledge of drug sellers was insufficient to dispense antimicrobials appropriately. The majority of urban respondents (69%) thought that inappropriate prescription of doctors contributed to irrational antimicrobial selling, whereas trust in doctors appeared stronger among respondents in rural setting (29%,  $p=0.01$ ). 31% in urban and 35% in rural sites conceded that inappropriate dispensing of antimicrobials to be due to high profitability of antimicrobial sales ( $p=0.75$ ). 71% (12/17) rural participants blamed inappropriate dispensing on other causes like quality of diagnostics and access to medical services versus 46% (12/26) in urban site ( $p=0.12$ ) (table 2-6). Only a minority 8% of urban and 18% of rural respondents thought that the current situation of antimicrobials dispensing was appropriate and does not need to be improved ( $p=0.32$ ).



**Table 2-6 Mentioned reasons for irrational antimicrobials dispensing**

Reasons	Percentage of respondents within area	
	Urban	Rural
Fear of losing customers	18 (69%)	17 (100%)
Pressure from patient's demand	10 (38%)*	13 (76%)*
Insufficient knowledge of dispensers	7 (27%)	4 (23%)
Inappropriate prescribing of doctors	18 (69%)*	5 (29%)*
High profitability of antimicrobials	8 (31%)	6 (35%)
Other (quality of diagnosis or health services)	12 (71%)	12 (46%)

\* Significant different between groups using Chi-square test ( $p$  value  $<0.05$ )

### **2.3.7 Qualitative study**

#### *2.3.7.1 Incentives structure*

Most interviewees in both the urban and rural setting did not think that profits from antimicrobial sales predominated in comparison with other drugs. According to their opinion, vitamins, tonic drugs or functional foods are more profitable than the antimicrobial group, which, however, is not confirmed by our quantitative data. *“Antimicrobials are commonly used items and customers know well their prices. That is why it not as profitable as less popular drugs like vitamins, tonics or functional foods”* was the response of one rural seller. Nevertheless, they conceded that pharmacy's income would be affected if they comply with prescription regulation. *“Not only antimicrobials but also thirty other groups have to be dispensed with a prescription. If we wait for a prescription, we sell hardly anything and total sales would be definitely influenced”* according to one urban seller.

All rural interviewees stated that patients' demand is a common factor affecting the sale of antimicrobials. An example of this is described as: *“I need to satisfy clients' demand.*

*That's in the interest of our business!"* According to their opinion, this factor can be changed if patients' awareness is improved and when the knowledge of sellers is strong enough to give professional advice. Meanwhile, fear of losing customers is common among urban sellers. *"If I refuse to sell antimicrobials without prescription, I will lose that customer for another pharmacy as they can easily buy anywhere"*.

Both urban and rural respondents reported that patients often avoided visiting doctors due to the inconvenience, and would rather go directly to a private pharmacy as the first choice for mild disease. *"It's very annoying and time-consuming to be examined in a hospital. And private clinic are very costly, as they do many kinds of test. Our customers only go to see doctors in case of severe disease"*.

#### 2.3.7.2 Knowledge on antimicrobials/resistance and regulations

All urban and rural participants expressed that they will give antimicrobials in case of suspected infection such as upper respiratory infections with fever, cough and sputum or even an injury to prevent infection. In addition, some rural interviewees noted that customers consider antimicrobials to be a 'miracle drug' that can treat many kinds of diseases and sometimes they demand it simply for maintaining a private stock for self-medication. Meanwhile, all urban interviewees believed that misconceptions about antimicrobial use changed among the urban population where there are better economic conditions and higher educational levels. *"Recently, public awareness of drugs' side effects has been improved, so there is less abuse of antimicrobials than before"* according to an urban seller.

All interviewees stated that they had heard about antimicrobial resistance. However, qualitative data also revealed insufficient knowledge of antimicrobial resistance among drug sellers and pharmacy owners, especially in the rural area. Most urban drug sellers demonstrated reasonable knowledge regarding the possible effects of resistance on all

populations, whereas some rural sellers did not. *“Antimicrobial resistance occurs in those overusing it. I do not abuse, so for me there is no need to worry”* (Rural seller).

Most respondents believed that patient-related factors such as self-medication and poor adherence to antimicrobial regimens contribute to the problems of antimicrobial resistance. It has been reported in the rural setting that patients often buy antimicrobials for an inappropriate duration. *“I advised the customer to take antimicrobials for at least 5 days, but they do not have enough money so they usually buy for just 2.5 days (10 tablets). When they recover, they will stop taking drugs, otherwise they would have bought more”* (Rural seller).

Regarding the knowledge of government regulations, most rural respondents did not know about GPP. *“This is the first time I heard about GPP”* said a rural seller. They also revealed misconception about prescription regulation by stating that: *“Some kind of weak antimicrobials such as amoxicillin or ampicillin can be sold without prescription”* (Rural seller). In contrast, all urban interviewee showed their understanding about GPP, but they conceded that there is little enforcement in dispensing practice. *“There is no difference between GPP and non-GPP pharmacy in terms of regulation compliance. Over the counter dispensing of prescription-only drugs is common in every pharmacy”*. (Urban seller)

#### 2.3.7.3 Proposed solutions

Rural respondents did not think that GPP could be deployed broadly in the rural setting due to the poor conditions of the facilities and education level of the work force. However, if regulations are enforced they will shift their business to dispense over the counter drugs like vitamins, cough and cold preparation; tonics that are allowed by the law to compensate pharmacies for financial losses. The urban respondents believe that GPP brings improvement to infrastructure but not to dispensing practices. *“To get a GPP certificate, we need to invest more in improving our infrastructure; as a result, the pharmacy looks more spacious. However, quality of service and dispensing practices has not been much improved”*.

Pharmacy workers have the understanding that the GPP policy objective is to improve the quality of pharmacy services in terms of infrastructure and quality drug supply. However, the awareness about their own professional contribution in promoting rational medicine use and its role in public health is very limited.

Both urban and rural respondents considered that training for drug sellers and the general population was needed to improve their knowledge and awareness about antimicrobials and resistance and thought that this would likely have a significant impact on controlling inappropriate antimicrobial use in the community. *“There will be less pressure to give customers antimicrobials if their awareness is improved”*.

Using a rapid blood test to determine which customers may need antimicrobials was considered to be a solution in improving rational antimicrobial use. However, several dispensers expressed concerns about losing time and income when the test result recommends to not prescribing antimicrobial. They recommended that, this approach should be applied in health establishments rather than in drug outlets. *“It’s impossible to implement it in pharmacy. We need to consider its price, not mentioned to implementation will take a lot of time and how to sell medicines along with the test and patient’s preference. Furthermore, kind of infection yet remains to be identified”*. (Urban owner) *“It’s more feasible to be applied in health care facilities than in dispensing channel”*. (Rural seller)

## **2.4 Discussion**

The results of this study illustrate the widespread inappropriate antimicrobial dispensing at private pharmacies in the Hanoi region. With only about 10% complying with prescription regulations, the situation in Vietnam is worse than has been reported in Saudi Arabia where the proportion was 51% (203) and Jordan with 74% (204). In a cross-sectional client simulation study in Syria, 87% of the pharmacies sold antimicrobials without a prescription. This proportion increased up to 97% when the client simulators insisted on

buying antimicrobials (205). Similar studies in India and Uganda had comparable results: 95% and 93.5% of visited pharmacies dispensed over the counter antimicrobials (206, 207). The most frequent reason for buying antimicrobials was acute upper respiratory tract infections, which are generally self-limiting (207, 208).

There are several successful interventions in other countries that brought important reduction in antimicrobial use. As reported in Tanzania, the accredited drug dispensing outlet (ADDO) program which combined extensive training, business incentives, authorisation to dispense a limited list of medicines to treat common conditions, regulatory enforcement of practice standards, and efforts to affect customer demand, has brought improvements in the use of antimicrobials. Before the introduction of ADDO program, antimicrobials were sold illegally by retail outlets which allowed dispensing over the counter medicines only. After 10 years of implementation, 63% of antimicrobial were sold with a prescription in ADDO. Among 85% client simulators presenting a mild ARI requesting an antimicrobial, only 34% of them were sold. For customers describing symptoms of pneumonia, 54 % were sold an antimicrobial and 90 % were referred (209). Similarly, unnecessary antimicrobial prescriptions remarkably declined as in England by sending social norm feedback to high prescribers of antimicrobials in general practice (210). In Vietnam, prescription-only regulation is embedded in the Drug Law that was issued in 2005 and re-stated in the Circular 46 in 2011 about implementing Good Pharmacy Practice (101, 163). In spite of these regulations, there is no sanction for non-compliance. This may explain why, to this moment, no pharmacy has been penalised for antimicrobial dispensing without a prescription. As there is a lack of enforcement of the regulations, self-medication is possible and is viewed as more economical and convenient than consulting a health professional (211, 212). Even if a pharmacy has a Good Pharmacy Practice registration, the results of this study revealed that the awareness of the concept of GPP among drug sellers was poor and they dispensed

antimicrobials without a prescription similar to pharmacies without a GPP standard. We also observed that more than 80% of the pharmacies rented pharmacist's licenses. According to Vietnamese regulations (Decree 79/2006/NĐ-CP), only pharmacists with at least 5 year experience can own a pharmacy(213). However, pharmacists often rent out their license and work elsewhere, making it easier for non-pharmacists to own a pharmacy. Despite the limited number of pharmacies in our study, we did observe better practices in sites that had a pharmacist present. As health promoter in the situation of being the “front-line health worker”, pharmacist should promote non-drug solutions for any health problems. Strengthening this role of pharmacist in distributing channel might have impact on reducing irrational antimicrobials in community. Furthermore, post qualification education of drug sellers should also be part of future quality improvement strategies.

Antimicrobials represented a considerable proportion of total revenues (24% in urban and 18% in rural pharmacies), illustrating that antimicrobials sales contribute an important part of total sales of pharmacies. Imported brands were sold more in urban pharmacies, whereas rural pharmacies generally mostly sold domestically produced antimicrobials. The study also found that in the urban area, patients' demands are a common factor affecting the sales of antimicrobials, with half (50%) of urban clients self-prescribing. In contrast, clients in the rural sites more often asked for advice from drug sellers. However, lack of knowledge of drug dispensers is common and will not lead to better antimicrobial dispensing practices. The qualitative study also disclosed that the government push to have all pharmacies comply with GPP standards is likely not a solution due to lack of enforcement and the shortage of a well-educated workforce (65). According to the Vietnamese General Statistics Office, in 2012, there were only 1.4 pharmacists/10,000 inhabitants, and for assistant and elementary pharmacists this was about 2 and 0.6 per 10,000 inhabitants. Pharmacy staffs with a university

degree mostly work in the big cities with 4.5 pharmacists/1000 inhabitants, despite a serious deficiency in remote areas with only 0.2 pharmacists/10,000 inhabitants (65).

Overuse of antimicrobials in the community is caused by people buying antimicrobials after self-diagnosis or diagnosis by, often poorly trained, health-care providers. The reasons for irrational antimicrobial prescribing in Vietnam are the same as in other countries including perceived expectations of patients, time constraints, lack of knowledge, lack of diagnosis capability and financial benefits for the prescriber (65). Identifying and modifying the incentives for inappropriate prescribing remains a major challenge.

In terms of impact of implementing pricing policies, high prices of antimicrobials and a tendency to sell branded drugs rather than cheaper generics is one of the important factors affecting irrational use and inadequate treatment as people often cannot afford to buy a full treatment course. The current mechanism of drug price control is not able to achieve the desired objectives as the drug prices in Vietnam are higher as compared to international comparators (214). The government has no leverage to negotiate on the wholesale prices even if those prices are higher than CIF prices (cost, insurance and freight). Retail prices are determined by the market, but there is a tendency to sell branded drugs rather than cheaper generics in urban areas. According to WHO's studies in the private sector, there was a large variation in mark-ups along the Vietnam medicines supply chain (215). Suppliers can easily increase prices and the government cannot control this. It is important to have a more structured and enforced price control mechanism, with strong generic policies, good procurement systems and single system leverage (such as health insurance and bulk procurements) to reduce drug prices.

As the symptoms of acute respiratory infections were among the most common reasons of antimicrobials purchasing, scale-up of a rapid diagnostic test in pharmacies and drug stores could be a solution to reduce antimicrobial consumption in the community (see Chapter 3).

Such point of care C reactive protein (biomarker of infection/inflammation) testing has previously been evaluated in reducing antimicrobial prescription in the primary care settings in Vietnam (216). Further work investigating the potential for POC CRP testing in this dispensing channel is needed.

Lastly, it was revealed in both the quantitative and qualitative study that there is poor awareness of consumers. As shared experiences from several developed countries in Europe (217), education campaigns targeting on providers and consumers through mass media contributed to reduction of antimicrobial overuse suggesting that public education campaigns can be effective.

There are some limitations to our study that need to be discussed. Our study was conducted only in the Hanoi region, with a relative small sample size and can therefore not be generalised to the whole country. However, discussions with doctors and pharmacists from other regions, do confirm that the issues are similar elsewhere. In larger pharmacies, some transactions may have been missed when large numbers of customers come to shops simultaneously. However, we believe this was limited as in larger pharmacies, as two observers were present. Awareness of being observed might have influenced antimicrobial dispensing practices (Hawthorne effect). To minimise this bias the sellers were unaware during the observation that the objective was to assess antimicrobial sales. Questionnaires focusing on antimicrobials were done after the observation. Some respondents were both drug seller and pharmacy shop owner, which may have affected the results as the owner may mostly be interested in profit and their opinion about incentives driving irrational antimicrobial dispensing may be different from a drug seller. There was limited participation for participants in the urban area to join focus group discussions, which may account for the relative paucity of solutions. Only one focus group discussion could be performed in the rural setting and in the urban area we conducted in-depth interviews. With relatively few



participants in the interview, we were not able to estimate where the saturation was reached. However, at the end of the discussion and interviews, little new ideas were recorded, so we do think we were close to saturation with our limited number of interviews. Furthermore, the study used wholesale prices to assess mark-ups of sold antimicrobials as we were unable to obtain purchasing prices from the pharmacies. In this observational study, antimicrobial encounters were not interviewed, as it was thought to interfere with normal routine. This may have affected the study findings on poor awareness among patients as reported by the dispensers. Finally, the limited observation time of three days in each pharmacy will not reflect the sales of antimicrobials and dispensing practices fully as these may be subject to change due to diseases with seasonality (e.g. influenza season). Furthermore, observation conducted only in workday time (9AM-5PM) may not cover the peak times of facilities in early morning and late afternoon with sufficient number of clients. Despite these limitations, the observations reveal the magnitude of antimicrobial dispensing without prescription.

## **2.5 Conclusion**

The revenues from antimicrobial sales are considerable for private pharmacies in both rural and urban northern Vietnam. Complying with drug regulations, to dispense antimicrobials only with a prescription, would therefore lead to economic loss for pharmacies. This would make acceptance and compliance with regulations challenging. Increasing the requirement for pharmacies to be GPP certified may only help in case the regulation that a pharmacist should be on site is enforced. For non-GPP pharmacies, substituting antimicrobial sales with sales of symptom relieving drugs or vitamins may be a strategy to compensate pharmacies for financial losses and to motivate them to comply with government regulations. Confronted with the situation of not enforcing regulations, continuing professional training for drug sellers will be helpful to increase their understanding of antimicrobials, resistance and how to dispense it appropriately. As the consumers often demand antimicrobials without

a prescription, public awareness campaigns should also be a central component of future control strategies. As promoting proper and safe use of antimicrobials is among the objectives of the national action plan on combating AMR, findings from this study may serve as targets for development of tailored interventions to improve rational antimicrobial use in the Vietnamese community.

## Chapter 3

### **Point-of-care C-reactive protein testing to reduce inappropriate use of antimicrobials for non-severe acute respiratory infections in adults and children in the Vietnamese primary health care setting: a multi-centre randomised controlled trial**

#### **3.1 Introduction**

Worldwide, bacterial pathogens are becoming increasingly resistant to antimicrobials. This problem is particularly pressing in developing countries, where the burden of infectious disease is high and resources for newer, more expensive antimicrobials scarce (218). Vietnam already experiences high levels of antimicrobial resistance. Prevalence of penicillin- (71%) and erythromycin-resistance (92%) in *Streptococcus pneumoniae* in Vietnam is the highest among Asian countries (219). Carbapenem-resistance rates are high in *Pseudomonas aeruginosa* (25%) and *Acinetobacter baumannii* (40%) hospital-acquired infections (HAIs) (103). Development of resistance is multi-factorial but a major driver is likely to be the frequent and often injudicious use of antimicrobials in humans and widespread use in agriculture and aquaculture (60).

Findings from my pharmacy study described in chapter 2 showed the proportion of antimicrobials dispensed over the counter in the community (88% in urban and 91% in rural settings) (220). Reasons for purchasing antimicrobials were predominantly ARIs (54.6%) which are largely self-limiting and complications are likely to be rare if antimicrobials are withheld (221, 222). The National Institute for Health and Clinical Excellence (NICE) clinical guideline 69 reviews the evidence of antimicrobials treatment for upper respiratory tract infections (URTI) and a syndromic risk based approach is recommended (223).

In the context of poor adherence to regulations, GPP was reportedly unsuitable to improve rational antimicrobial dispensing (220). Rapid blood tests to identify clients who are unlikely to benefit from antimicrobial treatment is a potential solution to reduce unnecessary

dispensing. However, discussions with drug sellers (Chapter 2) indicated that, it is impossible to implement such an intervention in drug stores. Of particular concern is losing income if the test shows a negative result and antimicrobials are not sold. Additionally, with the current available version of the test, it's inconvenient to perform this in drug stores. Thus, we decided to conduct this intervention study in primary health centres where similar overprescription of antimicrobials for ARIs has also been previously reported (97, 224).

Despite the evidence from randomised placebo-controlled trials (RCTs) showing that antimicrobials have limited efficacy in treating a large proportion of ARIs in adults and children, concerns of missing a serious infection can precipitate antimicrobial prescription. In lower-income settings, where health infrastructure is less developed, physicians may also be concerned about patients' perceived or actual inability to access healthcare if they deteriorate. These factors may motivate overuse of antimicrobials. The inappropriate prescribing of antimicrobials has the potential to cause drug-related adverse events, increase the prevalence of antimicrobial-resistant organisms in the community and increase primary care consultation rates for minor illness. Implementation of a rapid, affordable point-of-care test (POC) to aid diagnosis and management, and reduce antimicrobial use safely is therefore an attractive prospect in improving community consumption of antimicrobials. Findings from the intervention study will provide evidence to plan generalisation of this strategy.

C-reactive protein (CRP) is a biomarker for the presence of an inflammatory process (116, 125). Several studies in high-income countries have shown that primary health care providers who used a point-of-care (POC) CRP test prescribed fewer antimicrobials in patients with cough, without adversely affecting patient recovery (151, 225). Findings of usefulness of POC CRP testing in reducing antimicrobial prescription for ARIs in the primary care setting have been summarised in Chapter 1. The Genomics to combat Resistance against Antimicrobials in Community-acquired LRTI in Europe (GRACE) cluster randomised

controlled trial conducted in six European countries showed that guiding antimicrobial decisions in primary care with a combination of point-of-care measurement of CRP and enhanced communication was associated with the largest reduction in prescribing rates (CRP risk ratio 0.53, 95% CI 0.36–0.74,  $p < 0.0001$ ; enhanced communication 0.68, 0.50–0.89,  $p = 0.003$ ; combined 0.38, 0.25–0.55,  $p < 0.0001$ ).

No such trials have been performed in the primary health care setting of low and middle-income countries (LMICs) where unrestricted antimicrobial access and antimicrobial resistance is highest, and different social and clinical factors might affect its impact. Given the large number of self-limiting ARI that present to primary care in Vietnam, even modest reductions would greatly decrease the absolute number of antimicrobial prescriptions and thus one of the major drivers for bacterial resistance. Children in particular are frequently prescribed inappropriate antimicrobials for ARI, and any study should also address this important group (224). This study sets out to assess the efficacy of CRP POC testing for both children and adults presenting with non-severe ARI at primary healthcare centres in Vietnam in reducing inappropriate antimicrobial use safely. Findings can potentially be used in other resource constrained settings struggling with overuse of antimicrobials in ARIs.

## **3.2 Methods**

### **3.2.1 Study design**

An open-label randomised controlled trial was conducted in ten selected primary healthcare centres in northern Vietnam. Patients presenting with non-severe ARI were randomised to either CRP POC testing (intervention) or routine care (control). Randomised allocation was concealed from prescribers and patients but not masked as the test result was used to assist treatment decisions.

### **3.2.2 Study sites**

Public health services in Vietnam are decentralised from nation to province, district and commune level. Primary health care (district and commune level) provides routine and urgent health care and hospital referral to the population. Ten primary healthcare centres with a sufficient caseload of at least 5 ARI cases per day were selected within a 60 km radius from Hanoi. In urban Hanoi, we invited all twenty existing regional polyclinics to participate; three did not respond, two refused to participate, and six did not meet the caseload criteria. Thus, the remaining nine urban sites were selected to implement the trial. In rural Hanoi we selected the outpatient clinics of one district general hospital (Ba Vi hospital), which is situated 60 km west of Hanoi. Caseloads of other non-hospital clinics in rural Hanoi were too low.

### **3.2.3 Patients**

Patients, aged 1 to 65 years visiting one of these primary healthcare centres, suspected to have non-severe ARI with at least one focal and one systemic ARI sign/symptom by treating physician were eligible for this study. Focal ARI signs/symptoms include: (1) cough, (2) rhinitis, (3) pharyngitis, (4) shortness of breath, (5) wheezing, (6) chest pain, or (7) auscultation abnormalities. Systemic ARI signs/symptoms include: (1) fever, (2) perspiring, (3) headache, (4) myalgia, and (5) feeling generally unwell.

#### Exclusion criteria include:

- Severe respiratory disease as determined by treating doctor
- Any disease or symptom requiring hospital referral as determined by treating doctor
- Immunosuppressed patients (e.g. HIV, long term steroid use)
- Suspicion of tuberculosis
- Evidence of acute or chronic liver disease (e.g. hepatitis or cirrhosis due to any cause)
- Past medical history of: neoplastic disease, congestive cardiac failure, chronic obstructive pulmonary disease, insulin-dependent diabetes or renal disease
- Pregnancy

- No access to telephone
- Not able to come for follow up visit on day 4 ( $\pm 1$ ).
- Already taking antimicrobials at the time of presentation
- Symptoms present for more than 2 weeks

Children were defined as subjects aged 1 to 15 years old. Patients with signs of severe ARI were excluded. Other additional specific inclusion and exclusion criteria for age categories listed in table 3-1.

**Table 3-1 Additional inclusion and exclusion criteria for age categories**

1-5 years old	6-15 years old	>15 years old
<b>Inclusion</b>		
• Fever duration $\geq 24$ hours (226)	• No additional criteria	No additional criteria
<b>Exclusion</b>		
Any of: <ul style="list-style-type: none"> <li>• Respiratory rate <math>\geq 40</math> breaths/min</li> <li>• Unable to feed/drink</li> <li>• Hypothermia</li> <li>• Vomiting</li> </ul>	Any of: <ul style="list-style-type: none"> <li>• Respiratory rate <math>\geq 30</math> breaths/min</li> <li>• Temperature <math>\leq 35</math> °C or <math>\geq 40</math>°C</li> <li>• Pulse of <math>\geq 125</math>/min</li> </ul>	Any of <ul style="list-style-type: none"> <li>• Respiratory rate <math>\geq 30</math> breaths/min</li> <li>• Systolic blood pressure <math>&lt; 90</math> mmHg</li> <li>• Diastolic blood pressure <math>&lt; 60</math> mmHg</li> <li>• Temperature <math>\leq 35</math> °C or <math>\geq 40</math>°C</li> <li>• Pulse of <math>\geq 125</math>/min</li> </ul>

### 3.2.4 Enrolment and randomisation

All patients received a routine medical history and examination, consisting of medical history, mental status (Glasgow coma score), vital signs (blood pressure, pulse, respiratory rate) and temperature. Further examinations were performed at the discretion of the treating physician.

Eligible patients were randomised 1:1 to CRP POC testing or control (routine care) using an individual randomisation method, stratified by health station and age category (child versus adult). The randomisation list was computer-generated using variable block lengths of four (with probability 0.75) and six (with probability 0.25). Allocation was concealed by opaque sealed envelopes (227), opened at randomisation in strict chronological sequence. To protect the patient's identity, each participant was allocated a study identification number, which was used for all study material.

### **3.2.5 Assessments**

For patients in the CRP arm, a finger prick to collect capillary blood was performed and analysed using the quantitative NycoCard analyser (CRP single test kit used with the NycoCard II Reader, Alere Technologies, Norway) on enrolment (day 0) and retested on day 4 ( $\pm 1$  day) (figure 3-1). Patients in the control arm were treated according to routine practice and local treatment guidelines on enrolment and the second visit. All patients were followed-up at two weeks after the initial health clinic visit by a structured telephone interview.

Physicians were trained to use specific CRP cut-offs, which were based on previous studies and adapted for use in children (149-151, 226). For patients aged 6 to 65 years old, when the CRP was  $\leq 20$  mg/L, it was recommended that antimicrobials not be prescribed. For patients aged 1 to less than 6 years old, a CRP  $\leq 10$  mg/L was used to recommend that antimicrobials not be prescribed. Doctors were trained that adults with CRP  $\geq 100$  mg/L and children with a CRP  $\geq 50$  mg/L should generally receive antimicrobials and hospital referral should be considered for these cases. Between these thresholds no specific recommendation was given and clinicians were advised to use their clinical discretion.

After 2 weeks, enrolled patients were interviewed via telephone, blinded to the intervention, to assess whether: they have been to any health clinic; taken any medication for the same ARI; source of medication; serious adverse events (e.g. admission to hospital); time



to resolution of ARI symptoms and their satisfaction with the care provided. The patients were given a symptom diary as a memory aid.



**Figure 3-1 C-reactive protein point of care testing**

*The CRP value is obtained out of one drop of capillary blood by finger prick. Result is then available within few minutes by CRP POC Nycocard Reader.*

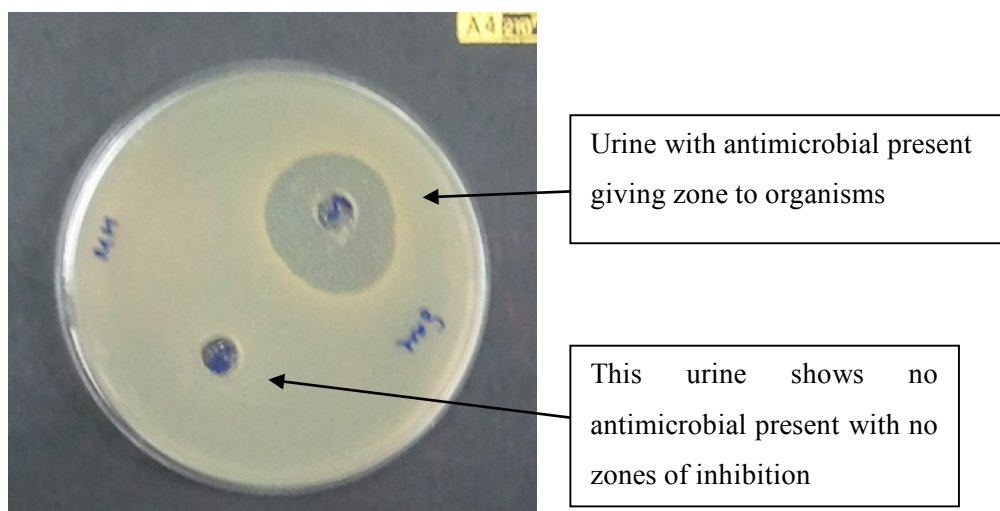
*(Source: Medilab product information: Nycocard® Reader II System)*

### **3.2.6 Urine antimicrobial activity testing**

Urine samples from enrolled patients (except those lost to follow up, toddlers who could not urinate on command at the visit, and women when menstruating) were collected on the second visit (day 4±1) for testing for the presence of antimicrobials. In urban sites, samples were collected and transferred to the laboratory to be processed and frozen on the same day to be assayed in the next weeks. In rural sites, a refrigerator was provided to temporarily store samples at 4 °C to be transferred to the laboratory twice a week. These samples were then assayed on the same or the next day on arrival in the laboratory.

The pansensitive ATCC 25923 *S. aureus* and ATCC 25922 *E. coli* were cultured on Müller Hinton agar (Oxoid) in the presence of participant's urine (228, 229). We used a positive control from a patient who was on antimicrobial treatment at time of urine collection. Negative control urines were from healthy people who had not taken any drug for at least 3 days before urine collection. A positive result was a zone of clearing >10 mm in either or both

agar plates with the two ATCC bacterial strains (figure 3-2). The sensitivity and specificity of this test are reportedly 97.4% and 98.9%, respectively (229).



**Figure 3-2 Urine test for detecting antimicrobial activity**

### 3.2.7 Endpoints

The primary endpoint was the proportion of patients receiving any antimicrobial within 2 weeks of enrolment. Antimicrobial use was defined as at least one of the following:

- 1) Antimicrobial prescription at enrolment (day 0);
- 2) Antimicrobial use reported at follow-up visit (day 4±1);
- 3) Antimicrobial prescription at second visit (day 4±1);
- 4) Antimicrobial activity in urine;
- 5) Antimicrobial use reported at follow-up interview (day 14).

Subjects were classified as positive for antimicrobial use if at least one of these conditions were met, negative if all five criteria were documented as negative, and missing if all reported criteria were negative but data were missing for at least one criterion.

Secondary endpoints included antimicrobial activity in urine (day 4±1), the proportion of patient with immediate antimicrobial prescription at enrolment, any antimicrobial usage in subjects without immediate prescription (subsequent antimicrobial use or ‘intervention failure’), prescriptions on the second visits in subjects without an immediate antimicrobial prescription (clinical management changed based on follow-up evaluation). Additional secondary endpoints were the source of any antimicrobial taken but not prescribed at enrolment or day 4 (self-medication/drug seller/doctor/other), the frequency of re-consultations, serious adverse events (hospitalisation or death), time to resolution of symptoms, and reported patient satisfaction with participating in the trial on day 14 (measured on a scale from 0 to 10). Patients with satisfaction score  $\geq 5$  were considered satisfied.

### **3.2.8 Sample size**

We expected CRP-guidance to reduce antimicrobial prescription for ARI by at least 20%: from 80% (224) to 60%. However, increased awareness of the issue through the study could itself bring antimicrobial prescription down, reducing the effect of CRP testing. Therefore, the trial was powered to detect a reduction of the antimicrobial prescription rate from 70% to 60%. To detect such a difference with 90% power and two-sided 5% significance level, a total of 477 patients are required per arm. In order to analyse adults and children separately, the target sample size was set at 2000 patients (two strata: 50% children and 50% adults).

### **3.2.9 Statistical analysis**

Statistical analyses were pre-defined in the protocol and the statistical analysis plan. The main population for all analyses was the intention to treat population including all randomised patients except for those who withdrew immediately and analysis was according to the randomised treatment arm. Patients with missing outcomes were excluded from the

analysis but for the primary outcome, we also performed an alternative analysis based on multiple imputation of outcomes for those patients. Moreover, the analysis of the primary endpoint was repeated in the per protocol population which included only subjects for whom all components of the primary endpoint as mentioned above were non-missing. For the formal comparison of the composite primary endpoint and its components between the two treatment groups, we used a logistic regression model of the outcome depending on the treatment group and the age stratum (children versus adults) as fixed effects and the healthcare centre as a random effect thereby taking clustering within centres into account. As we observed considerable heterogeneity in the primary endpoint between healthcare centres, we decided post-hoc to also visualise results by site using forest plots and to perform a standard random effects meta-analysis. Time to resolution of symptoms was visualised using Kaplan-Meier curves and formal comparisons between the two treatment arms were based on the Cox proportional hazards model with the treatment assignment and the age stratum as fixed effects and the healthcare centre as a Gaussian random effect (frailty). All data derivations were performed with SAS version 9.2 (SAS Institute Inc., Cary, USA) and statistical analyses were done with the statistical software R version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

### **3.2.10 Training of participating sites**

An initial training workshop was centrally conducted, followed by further training during on-site implementation visits at the 10 health centres by the study team. Training followed a model developed for a similar study in Maastricht, contextualised to the Vietnamese setting and carried out in Vietnamese (149, 230). Training materials were both verbal and written, consisting of oral presentations and written information leaflets for the doctors and health centres to keep for future reference. The health centres and doctors were given a telephone number to contact should any queries arise during the study. Laminated

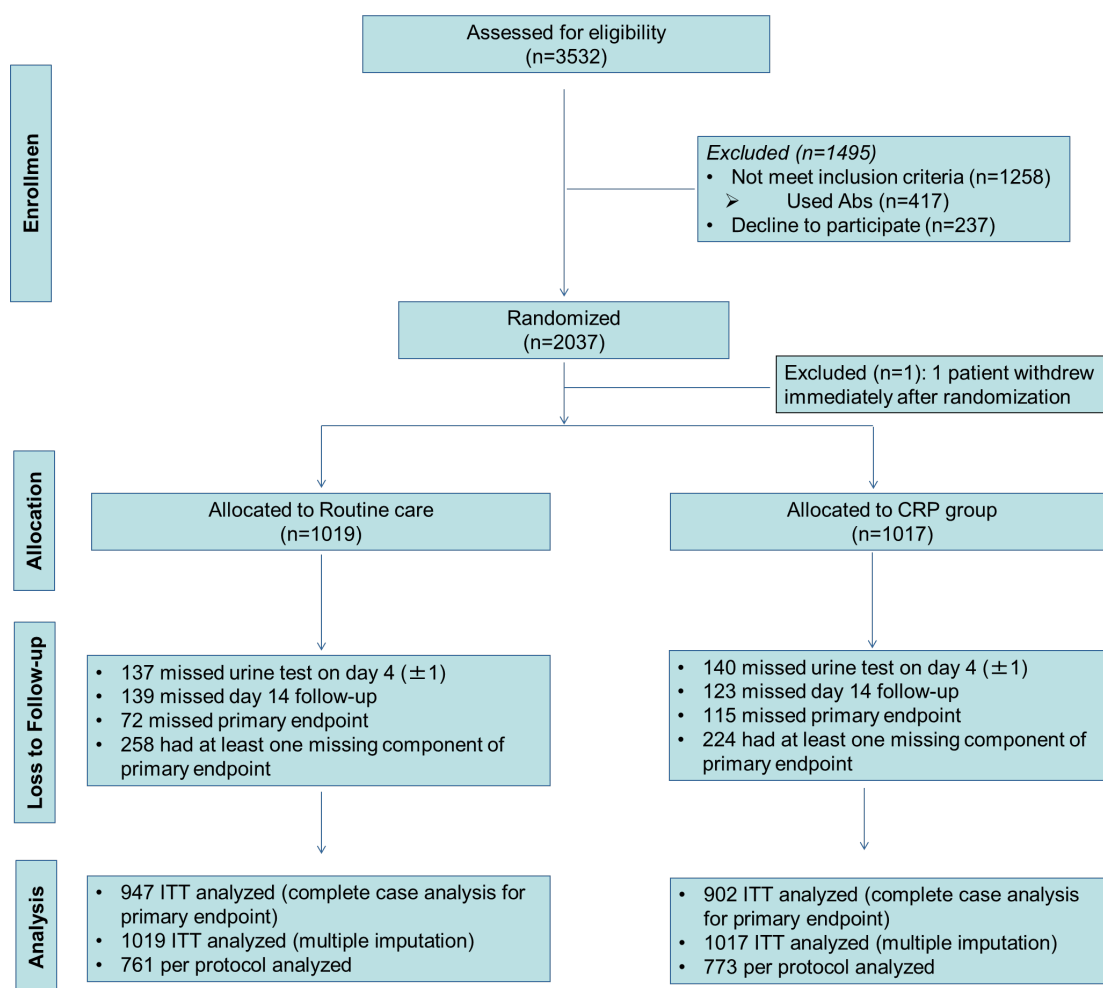
posters and desk reminders with recommended cut-off values for the specific age groups were provided.

### **3.2.11 Ethical considerations**

The trial was approved by the ethical committees of the National Hospital for Tropical Diseases in Hanoi (39/IRB-NHTD) and the Oxford University Tropical Research Ethics Committee (OxTREC Reference: 176-12). Permission for this study was also obtained from local authorities. A study doctor or study nurse explained to patients/legal guardian about the trial including risks and benefits. After verbal agreement, written informed consent was obtained. Patients were reimbursed for their travel expenses for the requested second visit on day 4±1. Once consent was obtained a case report form was completed for each patient containing all the information related to the study variables. This trial is registered at ClinicalTrials.gov under number NCT01918579.

### **3.3 Results**

Patients were enrolled from March 2014 to July 2015. Of 3532 patients screened, 1258 did not fulfill inclusion criteria, including 417 patients (33%) had already taken antimicrobials at presentation, and 237 declined to participate. A total of 2037 patients from 10 centres (range: 153-271 patients/site) were enrolled and randomised. One patient immediately withdrew after randomisation. 1017 [510 children, 507 adult] were allocated to the CRP group and 1019 [518 children, 501 adult] to the control group. The proportion missing primary outcome was 11% (115/1017) in the CRP group and 7% (72/1019) in the control group. The per protocol analysis contained 773 and 761 subjects in the CRP and control group, respectively (figure 3-3).



**Figure 3-3 Trial flow diagram**

*Excluded patients: age < 1 or > 65 years old: 244; severe respiratory infections: 16; hospital referral: 1; suspicion of tuberculosis: 3; liver disease: 6; medical history of neoplastic disease, congestive cardiac failure, COPD, insulin-dependent diabetes or renal disease: 110; pregnancy: 46; no access to telephone: 9; already taken antimicrobials: 417; symptoms present for more than two weeks: 65; not able to come for follow-up visit: 169; decline to participate: 237; uncoded: 172.*

Characteristics of participants at enrolment were similar between both arms regarding age, duration of illness, vital signs and clinical symptoms at presentation. Female patients

accounted for 60% (1224/2036). Symptoms at presentation were: cough (88%), sore throat (82%), coryza (62%), fever (35%), dyspnoea (3%) and earache (3%) (table 3-2).

**Table 3-2 Baseline characteristics by randomised treatment arm at enrolment**

General characteristics	Control (n=1019)	CRP (n=1017)
Gender – female (n, %)	591 (58%)	633 (62%)
Age (median, IQR) (years)	15 (8-41)	16 (8-39)
<6	146 (14%)	141 (14%)
6-15	372 (37%)	369 (36%)
>15	501 (49%)	507 (50%)
Duration of illness (median, IQR) (days)	2 (2-3)	3 (2-3)
Vital signs		
Heart rate (median, IQR) (time/min)	80 (75-86)	80 (75-86)
Resp. rate (median, IQR) (time/min)	20 (19-23)	20 (19-23)
SBP* (median, IQR) (mm Hg)	110 (100-120)	110 (100-120)
DBP* (median, IQR) (mm Hg)	70 (70-80)	70 (60-80)
Clinical symptoms		
Cough	905 (89%)	891 (88%)
Sore throat	833 (82%)	830 (82%)
Sputum	638 (63%)	653 (64%)
Coryza	619 (61%)	632 (62%)
Fever	347 (34%)	364 (36%)
Earache	40 (4%)	48 (5%)
Dyspnoea	32 (3%)	23 (2%)
Wheeze	22 (2%)	40 (4%)

*Data are median (quartiles) or numbers (%). Quartiles refer to the lower and upper quartiles of the distribution, i.e. the 25% and 75% quartiles. \*Blood pressure is reported for adults only. Age, gender, and heart rate were available for all subjects and blood pressure was measured in all adults. Respiratory rate was missing for 4 (0.2%) subjects, and clinical symptoms were missing for at most 13 (0.6%) of subjects.*

### **3.3.1 Primary endpoint: Any evidence of antimicrobial use within 14 days of follow-up**

In the intention to treat (ITT) analysis, 738/947 routine care patients (77.9%) used an antimicrobial within 14 days of follow-up compared to 581/902 (64.4%) in the CRP-guided group (OR: 0.49; 95%CI 0.40-0.61;  $p < 0.0001$ ). The corresponding effect sizes for the ITT analysis based on multiple imputation (OR: 0.50; 95% CI 0.41-0.61;  $p < 0.0001$ ) and the per-

protocol analysis (OR 0.51; 95%CI 0.41-0.63; p<0.0001) were similar and significant reductions were observed across all age groups (table 3-3).

In the ITT analysis for children, 374/487 (77%) routine care children had an antimicrobial treatment within 14 days compared to 295/448 (65.8%) in the CRP-guided group (OR: 0.55; 95%CI 0.41-0.61; p=0.0001). The corresponding figures for adults were 364/460 (79%) compared to 286/454 (63%) (OR: 0.41; 95%CI 0.3-0.56; p<0.0001) (table 3-3).

**Table 3-3 Proportion of patients receiving any antimicrobials within 14 days of follow-up**

Subgroup	Control (n=1019)	CRP (n=1017)	Comparison	
	events/n (%)	events/n (%)	OR (95%CI)	p value
ITT – complete case analysis <sup>‡</sup>	738/947 (77.9%)	581/902 (64.4%)	0.49(0.40-0.61)	p<0.0001
ITT – multiple imputation analysis <sup>§</sup>	747/1019 (73.3%)	598/1017 (58.8%)	0.50(0.41-0.61)	p<0.0001
Per protocol	552/761 (72.5%)	452/773 (58.5%)	0.51(0.41-0.63)	p<0.0001
Children (1-15 years)	374/487 (76.8%)	295/448 (65.8%)	0.55(0.41-0.75)	p=0.0001
Adult (>15 years)	364/460 (79.1%)	286/454 (63.0%)	0.41(0.30-0.56)	p<0.0001

OR: odds ratio from logistic regression model adjusted for age group and random site effect.

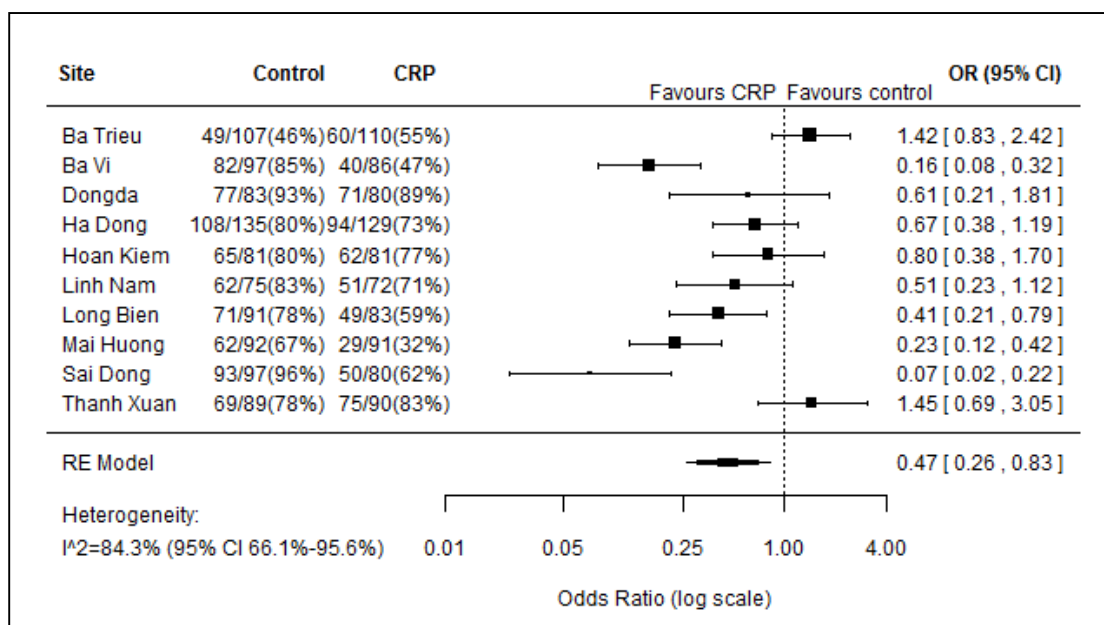
<sup>‡</sup>Variance of random site effect was estimated as 0.41 implying a intra-class correlation of  $0.41/(0.41+\pi^2)=0.11$ .

<sup>§</sup>An additive binomial regression model for the primary outcome (adjusted for age group and site effect) gives an adjusted absolute risk difference of -12.5% (95% CI -16.6% to -8.6%), p<0.0001

<sup>§</sup>Based on 20 imputed datasets. Reported event numbers and proportions refer to averages across all imputed datasets.



There was substantial heterogeneity between the health centres:  $I^2$  statistic = 84% (95%CI 66-96%) and the pooled median treatment effect estimate (OR: 0.47) from the random treatment effects model showed therefore a considerably wider 95% CI of 0.26-0.83 (figure 3-4).



**Figure 3-4 Impact of CRP testing on evidence of antimicrobial use during 14 days of follow-up (primary endpoint) – random effects meta-analysis by site**

*The mid-point of the box represents the median effect estimate for each site. The size of the box represents the weight given to each site. Length of the line represents the confidence interval (CI) for effect estimate for each site. The diamond below the studies represents the pooled median effect estimate. Width of the diamond represents the confidence interval for the pooled effect estimate.*

### **3.3.2 Secondary endpoint: Immediate versus subsequent antimicrobial use**

#### **(“intervention failure”)**

CRP guided immediate antimicrobial prescription at presentation was reduced by 20% from 647/1019 (63%) in the routine group to 441/1017 (43%) in the CRP arm (OR: 0·41; 95%CI 0·34-0·49;  $p < 0·0001$ ) in the intention to treat (ITT) analysis. This reduction remained significant in per protocol analysis (OR: 0·46; 95% CI 0·37-0·57;  $p < 0·0001$ ). The significant reductions were observed across all age groups with 19·8% decline in children (OR: 0·39; 95% CI 0·30-0·52;  $p < 0·0001$ ) and 20·5% in adults (OR: 0·40; 95% CI 0·30-0·52;  $p < 0·0001$ ) (table 3-4).

**Table 3-4 Summary of secondary endpoints**

Endpoint	Control (n=1019)	CRP (n=1017)	Comparison*	
			Estimate (95%CI)	p value
<b>Immediate Abs prescription - events/n (%)</b>				
All patients	647/1019 (63.5%)	441/1017 (43.4%)	OR=0.41 (0.34-0.49)	p<.0001
Children	333/518 (64.3%)	227/510 (44.5%)	OR=0.39 (0.30-0.52)	p<.0001
Adults	314/501 (62.7%)	214/507 (42.2%)	OR=0.40 (0.30-0.52)	p<.0001
<b>Subsequent Abs use - events/n (%)<sup>s</sup></b>				
All patients	91/300 (30.3%)	140/461 (30.4%)	OR=0.97 (0.70-1.35)	p=0.85
Children	41/154 (26.6%)	68/221 (30.8%)	OR=1.22 (0.78-1.94)	p=0.38
Adults	50/146 (34.2%)	72/240 (30.0%)	OR=0.73 (0.45-1.17)	p=0.19
<b>Abs management change -events/n (%)<sup>s</sup></b>				
All patients	12/345 (3.5%)	30/510 (5.9%)	OR=1.70 (0.85-3.41)	p=0.13
Children	4/170 (2.4%)	8/255 (3.1%)	OR=1.09 (0.31-3.85)	p=0.89
Adults	8/175 (4.6%)	22/255 (8.6%)	OR=1.99 (0.86-4.64)	p=0.11
<b>Presence of Abs in urine - events/n (%)</b>				
All patients	314/882 (35.6%)	267/877 (30.4%)	OR=0.78 (0.63-0.95)	p=0.015
Children	159/448 (35.5%)	132/439 (30.1%)	OR=0.76 (0.56-1.01)	p=0.06
Adults	155/434 (35.7%)	135/438 (30.8%)	OR=0.79 (0.59-1.06)	p=0.12
<b>Time to resolution of symptoms –median (IQR) days</b>				
All patients	5 (4-7) (n=758)	5 (4-7) (n=805)	HR=0.92 (0.84-1.02)	p=0.12
Children	5 (4-7)	5 (3-7)	HR=0.97 (0.84-1.11)	p=0.64
Adults	5 (4-8)	6 (4-10)	HR=0.89 (0.77-1.03)	p=0.10
Hospitalisation - events/n (%)	8/874 (1%)	6/901 (1%)	-	p=0.60
Re-consultation -events/n (%)	3/1019 (0.3%)	5/1017 (0.5%)	-	p=0.51
Satisfaction score <sup>s</sup> - median (IQR)	9.00 (8.00,10.00) [n=542]	9.00 (8.00,10.00) [n= 549]	-	p=0.75
Number of patients satisfied (satisfaction score≥5)	541/542 (99.8%)	545/549 (99.3%)		p=0.50

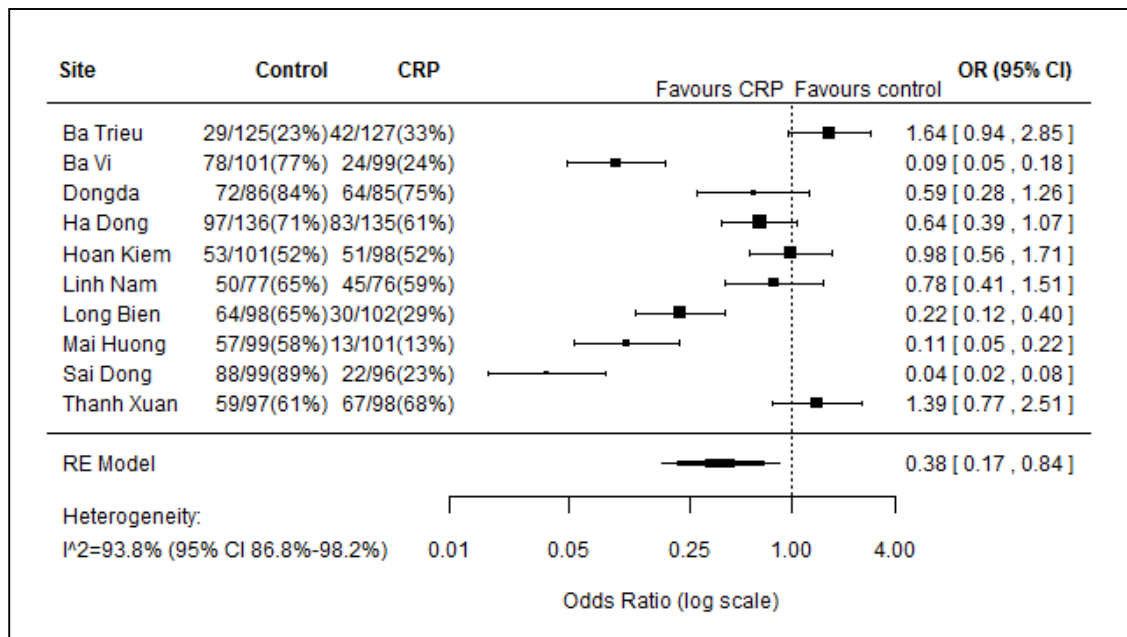
OR: odds ratio from logistic regression model adjusted for age group and random site effect.

HR: hazards ratio from Cox regression model adjusted for age group and random site effect.

IQR: inter-quartile range. Comparisons based on logistic regression, Cox regression,

Fisher's exact test (hospitalisation, re-consultation and number of patients satisfied), or Wilcoxon rank sum test (satisfaction score). *n* refers to the number of subjects with an evaluable outcome. <sup>§</sup>Subsequent Abs and Abs management change are reported in patients without immediate Abs prescription only, i.e. they refer to non-randomised comparisons because the denominator population depends on the randomised treatment arm. <sup>§</sup>Satisfaction score was measured on a scale from 0 to 10 and not available in all patients.

Substantial heterogeneity in immediate antimicrobial use between the health centres was detected:  $I^2$  statistic = 94% (95%CI 87-98%) (figure 3-5).



**Figure 3-5 Impact of CRP testing on immediate AB prescriptions on day 0 – Random effects meta-analysis by site.**

For each site: the mid-point of the box represents the median effect estimate; the size of the box represents the given weight; length of the line represents the confidence interval (CI) for

*effect estimate. The diamond below the studies represents the pooled median effect estimate.*

*Width of the diamond represents the CI for the pooled effect estimate.*

Subsequent antimicrobial use without immediate prescription (“intervention failure”) within 14 days of follow-up was recorded in a larger *absolute* number of patients in the CRP guided group but the *relative* proportion of intervention failures amongst patients without an immediate prescription was similar between the two groups with 140/461 (30.4%) patients in the CRP group compared to 91/300 (30.3%) patients in the routine care arm (OR 0.97; 95% CI 0.7-1.35;  $p=0.85$ ). The corresponding effect size was similar across all age groups (table 3-4). Among 165 patients (72 in the routine care group, 93 in the CRP group) who recorded antimicrobials without prescription at enrolment or the second visit, the source of antimicrobials was recorded in 133 cases and the most frequent source was drug seller guided antimicrobial use (66) followed by doctor’s prescription (39) and self-medication (27), or other sources (1).

### **3.3.3 Urinary antimicrobial activity presence**

Antimicrobial activity in the urine sample on day  $4\pm 1$  was significantly lower in the CRP group compared to the routine group. In ITT, this was 30.4% (267/877) in CRP group versus 35.6% (314/882) in the routine arm (OR 0.78; 95%CI 0.63-0.95;  $p=0.015$ ) (table 3-4). 581/1759 patients were positive for urinary antimicrobial activity. Antimicrobial activity was detected in 444/953 patients receiving immediate antimicrobials. The agreement between recorded prior antimicrobial use and detection of antimicrobial activity in the urine sample was moderate with  $\kappa=0.43$  (95%CI 0.39-0.47). Amongst those without recorded prior antimicrobials use, 46/487 (9%) in the CRP arm and 26/319 (8%) in the control arm had a positive urine test. Similarly, the rate of positive urine test amongst patients with recorded prior antimicrobials use was 221/390 (57%) in the CRP arm and 288/563 (51%) in the routine

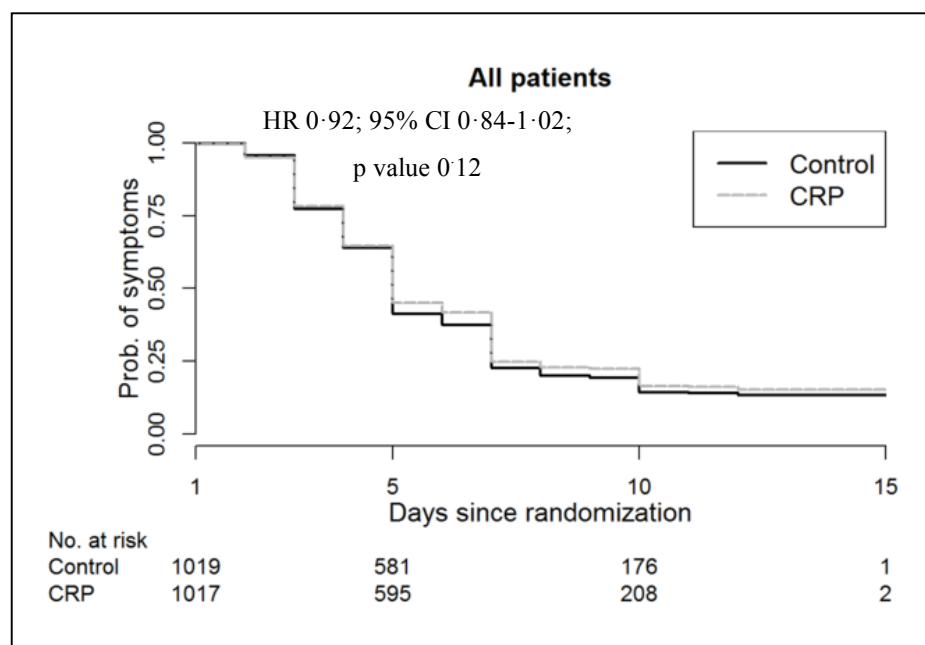
care group. This latter proportion was lowest in the control arm of the rural Ba Vi site with 23/71 (32%) positive urine tests in patients with recorded prior antimicrobials use.

### 3.3.4 Change in antimicrobial management

Amongst subjects without immediate antimicrobials prescriptions, the proportion of subjects with a prescription of an antimicrobial on day 4 ( $\pm 1$ ) was 30/510 patients (6%) in the CRP group compared to 12/345 patients (3%) in the routine arm in ITT analysis (OR: 1.70; 95%CI 0.85-3.41;  $p=0.13$ ) (table 3-4).

### 3.3.5 Time to resolution of symptoms and serious adverse events

Time to resolution of symptoms was similar across both arms (figure 3-6) with a median duration of 5 days (IQR 4-7) in both arms (HR 0.92; 95% CI 0.84-1.02) (table 3-4).



**Figure 3-6 Kaplan Meier curve of time to resolution of symptoms after enrolment by treatment arm (for all patients)**

*Time to resolution of symptoms in control (dark) and CRP group (grey)*

Adverse events, defined as hospitalisation or death between enrolment and day 14, were rare with zero deaths and 14 hospitalisations: 8 in routine arm and 6 in CRP arm. 3/1019 patients in the routine group and 5/1017 patients in CRP group needed re-consultation (table 3-4).

### **3.3.6 Patient satisfaction**

We detected no differences in patient's satisfaction between randomised arms (table 3-4).

### **3.3.7 CRP levels and immediate antimicrobial prescription**

Of all CRP measurements in this population 75% (758/1017) were below 10 mg/L, 13% (133/1017) between 11-20mg/L, 10% (101/1017) were 21-50mg/L and only 2% (25/1017) had a CRP >50mg/L. For children under 6 years old, 35% (28/81 patients) received immediate antimicrobial prescription when the CRP value at enrolment was  $\leq 10$ mg/L. The corresponding figure for adults with a CRP value at day 0 of  $\leq 20$ mg/L was 37% (171/459) (table 3-5). Adherence to the intervention algorithm was highly variable across sites. For patients aged 6-65 years-old with a CRP value at day 0 of  $\leq 20$ mg/L, the immediate antimicrobial prescription rate ranged from 4% (3/75) (in Sai Dong station) to 71% (49/69) (in Dong Da station).

**Table 3-5 CRP levels at enrolment versus immediate antimicrobial prescription**

	All patients (n=1017)	<6 years old (n=141)	6-15 years-old (n=369)	Adults (n=507)
CRP day 0	events/n (%)	events/n (%)	events/n (%)	events/n (%)
≤10 mg/L	257/758(33.9%)	28/81(34.6%)	83/268(31.0%)	146/409(35.7%)
11-20 mg/L	68/133(51.1%)	14/26(53.8%)	29/57(50.9%)	25/50(50.0%)
21-50 mg/L	91/101(90.1%)	25/28(89.3%)	29/31(93.5%)	37/42(88.1%)
>50 mg/L	25/25(100.0%)	6/6(100.0%)	13/13(100.0%)	6/6(100.0%)

### 3.4 Discussion

This study shows that access to C-reactive protein (CRP) point-of-care (POC) testing reduces unnecessary antimicrobial use for non-severe acute respiratory infections in adults and children in primary healthcare in Vietnam, without compromising clinical recovery or serious adverse events. Our findings were consistent across all outcome measures we used: dispensing and prescribing data, patient self-report and microbiologically confirmed antimicrobial presence in urine. This trial is the first study investigating the effects of CRP POC testing in a resource constrained setting and the impact of CRP testing on antimicrobial use in children has never been assessed before in a randomised controlled trial (RCT).

With an overall absolute reduction of 13.5% (77.9% versus 64.4%) in antimicrobial use, the effect of CRP testing in our trial is similar to that reported in the Netherlands, where the reduction was 12.4% (65.1% versus 52.7%; risk ratio [RR] 0.81) (148) and higher than in Norway, where a non-significant reduction was found (RR 0.95; 95%CI 0.76-1.18) (153). Cluster-randomised controlled trials in the Netherlands and Russia showed statistically significant reductions of 18.3% (149) and 15.3% (150) respectively. The decline in



immediate prescription rate was also larger in our study as compared with previous individual RCTs (152, 153, 230) but lower than in cluster-RCTs (149-151).

There was large heterogeneity in the effect of CRP POC testing across sites. Likely, several sites did not adhere to the intervention algorithm. The final decision to prescribe antibiotics were at the discretion of the physician making the adherence to algorithm so variable and is a fact of how healthcare works. More familiarity and presenting data it is safe to follow CRP cut-offs in low resource settings will enhance compliance. Of note the results of a previous study in European countries suggests that an intervention combining CRP testing and education had the highest impact on prescribing (151).

Similar to results from previous trials, no differences regarding recovery, serious adverse events and patient's satisfaction were found after the introduction of CRP testing, though given the benign clinical syndrome addressed it was unlikely to be powered to detect differences in outcome. One trial has previously documented an increase in hospital admissions associated with CRP guided treatment. However, this adverse event was rare (22 versus 8 among 4264 patients) and concerns regarding this risk must be balanced against benefits of reducing inappropriate antimicrobial use on a large scale (151). Such adverse events were also exceedingly rare in our study with no apparent difference between the groups. According to the National Institute for Health and Clinical Excellence (NICE) clinical guidelines 69, the usual average total length of the illness ranges from 4 days to 3 weeks depending on type of illness (223). In our trial, median duration of symptoms was about one week. Only 19% of patients had median length of the illness more than 10 days (Figure 3-6). It might be explained as all recruited patients had non-severe ARI and Vietnamese population is also different from UK population with lower healthcare seeking threshold.

While most previous large trials only looked at prescribing data or self-reporting on antimicrobial usage, testing urinary antimicrobial activity provided additional information in

this study. In comparison to levels of immediate antimicrobial prescription, detection of urine antimicrobial activity was substantially lower across both arms: 36% versus 30% in the routine group. The agreement between recorded antimicrobial use and detection of antimicrobial activity in urine was only moderate ( $\kappa=0.43$ ) (231) and detection rates in urine as a fraction of recorded use were lower in the control arm and lowest in the control arm of the rural Ba Vi site. This may be explained if patients stop their antimicrobial treatment before the second visit on day  $4\pm 1$  as suggested by a previous study among children in rural Vietnam that reported that 42% (341/818) of patients used antimicrobials for only one or two days (232). A further explanation could be the variability in days urines were collected, the urines not collected and biliary excretion of several popular antimicrobials such as azithromycin or spiramycin.

Procalcitonin may be an alternative biomarker to CRP. Procalcitonin was shown to be an effective biomarker in reducing antimicrobial use for ARIs in primary care setting in European countries (136, 139, 233). However, a well-validated point of care test for procalcitonin that is feasible for use in these settings is not yet commercially available as far as we are aware. Furthermore, a recent study assessed the diagnostic accuracy of procalcitonin and C-reactive protein (CRP) in distinguishing common viral and bacterial infections in malaria endemic settings of three Southern Asian countries. This study indicated that applied to samples from febrile patients with mono-infections, CRP was a highly sensitive and moderately specific biomarker for discriminating between viral and two bacterial aetiological groups (*Rickettsia/Leptospira*), as well as from the bacteraemia group and malaria (125). CRP had a higher sensitivity and specificity in discriminating viral and bacterial infections compared to procalcitonin in this study.

With the large sample size, our trial was robust to assess the intervention effect in different age subgroups in a real life situation. This provides us with relevant data on what

obstacles need to be overcome to make the intervention even more effective. Our findings suggest that CRP testing could be an important component of non-antimicrobial ARI management strategies in primary care settings in low and middle income countries. The intervention has the potential of being scaled up as several commercially affordable CRP rapid POC tests have been evaluated and found to be reliable (234). Before widely introducing CRP POC tests as routine care, a cost-effectiveness analysis should be performed to assess other additional requirements, including test cost, training and consultation time, compared to the reduction in antimicrobial prescription and subsequent burden of resistance. To achieve maximal impact on antimicrobial consumption in settings, such as Vietnam, where antimicrobial use is commonly off-prescription further work investigating the potential for POC CRP testing in pharmacies and drug stores will be needed. This trial provides important data necessary for planning such studies. There may be lessons to be learnt from the roll out of rapid diagnostic tests in community settings (235).

There are several limitations of our study. Due to the study design (individual randomisation) over time clinicians may have become familiar with the clinical picture associated with low CRP, resulting in reduced antimicrobial prescriptions even in individuals randomised to the control arm. A cluster RCT design may have prevented this contamination effect but would be more costly. However, this limitation would have led to a reduction in the observed effect rather than an overestimation. We may have not captured all antimicrobial use by the 2nd visit, the diary, urine test and the day 14 interview. Patients may have not reported antimicrobial use due to poor recall or self-perceived misuse of antimicrobials or were unaware pills they were given were antimicrobials. However, this bias should be equally distributed across both arms. Lastly the heterogeneity of the effect is far from ideal, but is likely to represent differences in context that will be explored further in qualitative analyses and must be addressed for successful implementation of this strategy.

## Chapter 4

### **Economic Implications of C-Reactive Protein Point of Care Testing in the Management of Acute Respiratory Infections in the Vietnamese Primary Health Care Setting**

#### **4.1 Background**

Acute respiratory infections (ARI) is the syndrome that accounts for the largest proportion of human antimicrobial consumption (236, 237). Antimicrobial use for ARI is very common in Vietnam, both in- and outside primary health care settings (97), despite a predominantly viral aetiology and minimal benefit of antimicrobials in uncomplicated cases (238). Treatment decisions are based solely on clinical examination, which in both low and high income settings is known to be of poor accuracy in identifying where antimicrobials are and are not required. It has been estimated that roughly 70% of examined patients in primary care in Vietnam receive an antimicrobial prescription and ARIs are the reason for 51% of these prescriptions. Furthermore, 71% of antimicrobials were given in an inadequate dose and duration (i.e. the drugs were either given for less than five days or fewer times per day than prescribed) (239).

Antimicrobial resistance (AMR) is an inevitable consequence of their consumption, and while this interaction can be complex it is widely accepted that safe reductions in antimicrobial consumption will have the desirable effect of mitigating the burden of AMR. The association between prescribing antimicrobial agents and antimicrobial resistance of *Streptococcus pneumoniae* among children under five years-old with acute otitis media (AOM) was reported in southern Israel, during 1999-2003. Rapid decrease in prescription rates was associated with lower observed resistance rates during the warm versus the cold months ( $p < .001$  for each antimicrobial). Each monthly increase in 10 prescriptions/1000 children was associated with a 1.05-fold increase in the odds of penicillin resistance during

that month (95% CI, 1.03–1.07;  $p < .001$ ). The corresponding OR for erythromycin resistance was 1.04 (95% CI, 1.02–1.05;  $p < .001$ ), for multidrug resistance, it was 1.04 (95% CI, 1.02–1.06;  $p < .001$ ) (240).

Several biomarkers in blood have been evaluated to guide the use of antimicrobials for ARIs in primary care, including C-reactive protein (CRP), procalcitonin and blood leukocyte. Recent evidence from diagnostic studies have shown CRP to have high discriminatory power in distinguishing between viral and bacterial infections (125, 241) and a meta-analysis of randomised control trials found it to significantly and safely reduce antimicrobial prescribing (225). Point-of-care (POC) tests for CRP are available and can be performed in general practice using a capillary blood sample, with results available within a few minutes (154, 242, 243). Such an approach is already widely used in a number of high income countries such as Norway and Sweden, (149, 244) and is being recommended in the UK by the NICE and Public Health England (245). Economic evaluations have concluded that despite a higher cost per patient, CRP testing can be cost-effective in the European context due to either direct health benefits to patients or the safe reduction in antimicrobial consumption (156, 246, 247).

How transferable the limited evidence from high income settings to other contexts is not clear. The aim of this study is to describe the economic implications of CRP testing for ARI patients and health providers in a lower middle income country (LMIC) setting. The study draws on a recent randomised control trial in Vietnam where CRP POC testing was compared against current practice in the management of ARIs in primary care, demonstrating a significant reduction in antimicrobial consumption with the use of CRP tests, without compromising patient recovery and satisfaction (216). Here we explore the direct medical costs for patients and providers, and the cost-effectiveness in terms of the cost per antimicrobial prescription averted. We also explore the budget-impact of CRP testing should such a policy be adopted at a national scale.

## **4.2 Methods**

An open-label randomised controlled trial was conducted in 10 primary healthcare centres in northern Vietnam to assess the effectiveness of CRP POC testing in reducing inappropriate antimicrobial use for patients, aged 1 to 65 years with symptoms of non-severe ARI; details of the study are described in Chapter 3. In brief, 2,036 patients (1028 children, 1008 adults) were enrolled. Among them, 1017 [518 children, 501 adult] were allocated to the CRP group and 1019 [510 children, 507 adult] to the routine care (control) group. All patients received routine clinical examination at enrolment and follow-up visit on day 4 ( $\pm 1$ ). Patients in the CRP group received additional evaluation by CRP POC testing at day 0 and at the second visit. Patients randomised to the control arm were treated according to routine practice and local treatment guidelines. Treatment for CRP patients was based on both clinical examination and CRP testing results. Different CRP cut-off values were given for different age categories to recommend withholding an antimicrobial prescription. All patients were required to provide a urine sample in the follow-up visit for testing the presence of antimicrobial activity. A telephone interview was done after two weeks of follow-up for all patients. The primary outcome was antimicrobial use within 14 days follow-up. Secondary outcomes included presence of antimicrobials in urine on day 4 $\pm 1$ , immediate versus subsequent prescription within 2 weeks, the source of any antimicrobial taken but not prescribed at enrolment or day 4 (self-medication/drug seller/doctor/other), the frequency of re-consultations, serious adverse events (hospitalisation or death), the duration of symptoms, and the reported patient satisfaction.

### **4.2.1 Cost survey forms**

A survey was carried out to collect medical and non-medical costs related to the management of the illness on the day of enrolment. Medical costs consist of those for

examination, routine diagnostic tests (other than CRP testing) and medications. Medical costs in Vietnam are partially covered by health insurance and the remainder by patients' out-of-pocket; both costs were recorded separately in the forms. The trial recruited outpatients only, therefore non-medical direct costs included those for transportation alone. At day 14 a similar form was used to collect any subsequent costs during the two-week follow-up period.

#### **4.2.2 Data analysis**

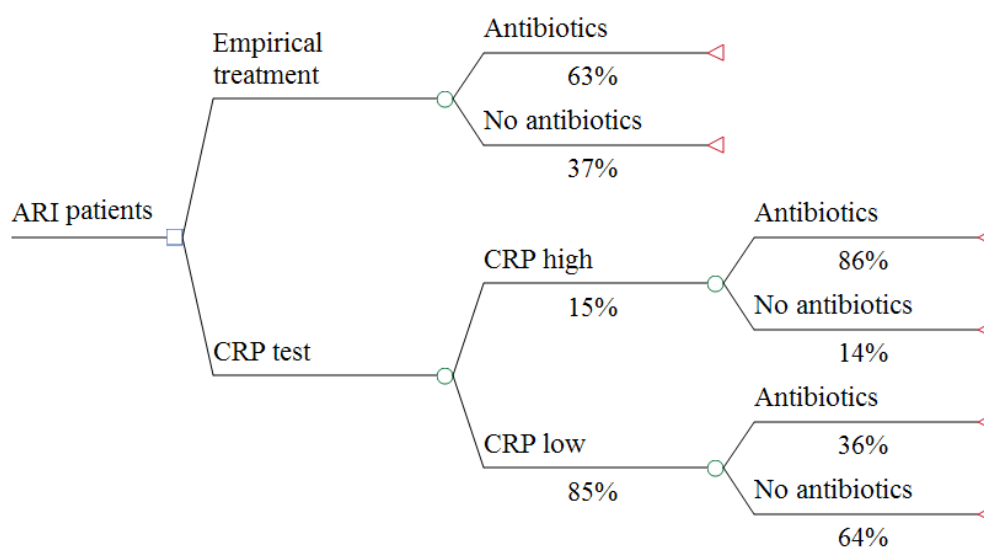
The data were cleaned and double entered into an electronic database and checked for quality by an independent data analyst. Medical and non-medical cost data were summarised using mean and standard deviation (SD) regardless of skewed distributed data (248). Potential differences between the CRP guided treatment group and the routine care group were compared by t-test and Mann–Whitney U (Wilcoxon rank sum) test for non-normal continuous data (248). P-values less than 0.05 were considered significant (2 tailed). All costs are reported in US Dollars (\$) using the 2015 currency exchange rate from Vietnam Dong (VND) of \$1 = 22,500 VND.

#### **4.2.3 Cost-effectiveness analysis**

The cost-effectiveness analysis estimates the cost per antimicrobial prescription averted on the day of attendance at the primary health facility (156). This reflects the demonstrated benefit of CRP testing in safely reducing antimicrobial consumption for ARI patients while maintaining non-inferior health outcomes, as hypothesised in chapter 3. The cost-effectiveness analysis is conducted from the health provider perspective and includes the costs for antimicrobials, CRP testing and other medical expenditure. The cost-effectiveness analysis is followed by a budget impact analysis to estimate the cost implications of introducing CRP testing across district level facilities.

#### **4.2.4 Model structure**

We use a simple decision tree to estimate the cost per antimicrobial prescription averted with the use of CRP testing as compared with current practice. In the current practice arm the trial data are used for the proportion of patients that received treatment in the control group on the first day of attendance. In the CRP arm of the model patients are subdivided into two groups. The first comprises those with CRP levels at which health workers were recommended not to prescribe an antimicrobial (up to a threshold of 10mg/L in children or 20mg/L in adults). The second group is comprised of patients with either intermediate CRP levels in whom health workers were advised to use local guidelines and clinical judgment (10-50mg/L) in children or 20mg/L-100mg/L in adults) or those with high CRP values for whom an antimicrobial was recommended (>50mg/L in children and >100mg/L in adults), as shown in figure 4-1.



**Figure 4-1 Decision tree outline for the cost-effectiveness model**

In the subgroup with low CRP levels, we used the proportion of patients that were not prescribed an antimicrobial to define the degree of adherence to low CRP test results, which in the trial averaged 64%. This value was varied from 50% to 100% to model the implication



of varying degrees of adherence to the test. For patients with intermediate or high CRP values we assigned the same antimicrobial prescription rate as in the trial (86%), and conservatively assumed no advantage in better identification of patients that genuinely required antimicrobials (as indicated by high CRP values). In summary, therefore, there was no assumed direct health benefit to patients in CRP testing due to better identification of patients requiring antimicrobial treatment, or the avoidance of side-effects and allergic reaction in patients receiving antimicrobials unnecessarily, only a potential reduction in the prescription rate in those with low levels of CRP.

The average provider costs for patients in each arm were comprised of a fixed and equal cost of medication and diagnostics other than the CRP tests and antimicrobials (which did not differ significantly in the trial between the trial arms) and the cost of antimicrobials, using a mean unit cost of \$1.5, as documented in the trial. The CRP reader and reagents in the trial were provided free of charge by the manufacturer; if purchased commercially the reagents would cost approximately \$3 per test. There are, however, commercially available accurate qualitative test such as DTS233 (Creative Diagnostics, USA) and semi-quantitative version such as WD-23 (Assure Tech, China) and bioNexia CRPplus (bioMérieux S.A., France) (243). The lowest cost test is the WD-23, which costs approximately \$0.6/test, the quote for the DTS233 is approximately \$2.5/test and the bioMérieux test is about \$2.2, but no longer in production. While these rapid tests require further validation, we used a baseline estimate of \$1 for the unit cost of the test with a range of \$0.5-\$3 in the sensitivity analysis. The model was then used to estimate the cost per antimicrobial prescription averted across a range of estimates for the cost of the CRP test, and for the adherence to the CRP test (in avoiding prescription of antimicrobials to patients with low CRP values); other model parameters were also included in the probabilistic sensitivity analyses (PSA) as described in table 4-1.

**Table 4-1 Parameter estimates used in the model**

Parameters	Point estimate	Range/distribution for sensitivity analysis	Source
Antimicrobial prescription rate in current practice	63%	Beta ( $\alpha=647, \beta=370$ )	Primary data from trial
Percentage of patients with low levels of CRP indicating that antimicrobials are not required	85%	Beta ( $\alpha=860, \beta=150$ )	Primary data from trial
Antimicrobial prescription in patients with high CRP values	86%	Beta ( $\alpha=130, \beta=22$ )	Primary data from trial
Adherence to test result when antimicrobials not indicated	64%	Range of 50%-100% in two way sensitivity analysis. Beta ( $\alpha=554, \beta=311$ ) for PSA	Primary data from trial
Unit cost per CRP test (USD)	\$1	\$0.5 - \$3 in two way sensitivity analysis; Gamma (shape=0.2, scale=6) for PSA	(243)
Unit cost per course of antimicrobials	\$1.5	Gamma (shape=0.25, scale=6)	Primary costing data from trial

#### 4.2.5 Willingness to pay threshold for safe reductions in antimicrobials

Despite the intuitive value of safe reductions in antimicrobial consumption, there are no established methods to quantify the health or economic benefits of doing so to determine what would be considered a cost-effective intervention with this aim. The societal willingness to pay for these gains should equate to the discounted future costs associated with the implications of AMR that could be explained by the consumption of antimicrobials. To our knowledge only one study has directly quantified the economic costs of antimicrobial resistance per antimicrobial consumed (249). The study was carried out in a very different context of hospitals in Germany, and the findings were that each defined daily dose (DDD) of

a 2<sup>nd</sup> generation cephalosporin was associated with a cost of €5 due to antimicrobial resistance; for other classes of antimicrobials the costs were higher (€11 for fluoroquinolones and €15 for 3<sup>rd</sup> generation cephalosporins).

Acknowledging the limitations of generalising these findings, in the absence of more relevant data we use these values, having adjusted them by the ratio of GDP/capita (measured in PPP) of Vietnam over that of Germany (0.12). We then applied the adjusted estimate of the cost of AMR for a DDD of 2<sup>nd</sup> generation cephalosporin for a five-day treatment course, implying that each full course of antimicrobials is estimated with a subsequent cost of \$3 due to AMR. This should also imply that policy makers are willing to pay (WTP) up to this value to avoid the unnecessary use of an antimicrobial. Given the extensive uncertainty surrounding this value, we use a range of \$0 to \$10 for this WTP threshold. These are provisional and admittedly poor estimates for the value of avoiding unnecessary antimicrobial consumption; we return to this point in the discussion.

#### **4.2.6 Budget impact analysis**

The model was then used to estimate the total cost for managing non-severe ARI patients in district hospitals and community health centres in Vietnam, the target settings for the intervention. Alongside the budget implications we also estimate the total quantities of antimicrobials avoided. The total number of community health centres and district hospitals were estimated at 600 each (90). The baseline surveys conducted prior to the trial estimated approximately 2000 ARI patients per year per community health centre and 20,000 outpatients at the district hospitals, of whom approximately 50% meet the trial inclusion criteria in terms of age and severity, and are therefore included in the budget impact analysis as the target population. We again used a range of estimates for the cost of the test and for adherence to the test result. The data were analysed and the models written in R version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

#### **4.2.7 Ethical considerations**

The trial was approved by the ethical committees of the National Hospital for Tropical Diseases in Hanoi (39/IRB-NHTD) and the Oxford University Tropical Research Ethics Committee (OxTREC Reference: 176-12). Permission for this study also was obtained from local authorities. Patients who fulfilled the inclusion criteria were asked to participate by signing the consent form. The cost surveys were included in these approvals and consent procedures. The trial is registered at ClinicalTrials.gov under number NCT01918579.

#### **4.3 Results**

Of the 2036 patients that were enrolled in the trial, cost data were available for 100% of patients on day 0 and for 90% (1828/2036) on the day 14 follow up visit.

##### **4.3.1 Patient and provider costs in the control and intervention arms on first attendance**

Patients travelled a mean distance of 3.6 km to attend the facility; most patients used their own means of transport and travel costs were low (mean < \$0.2). At the day of first attendance, the cost for antimicrobials were significantly lower in the CRP guided treatment group (mean difference = -\$0.18; 95% CI -\$0.28 to -\$0.08). This was slightly offset by a smaller increase in costs for other medication in the intervention arm (mean difference \$0.06; 95%CI \$0.01 to \$0.12). All other costs were similar between arms ( $p > 0.05$ ) (table 4-2). In both groups approximately 90% of the total costs were covered by health insurance and the remaining were co-paid by patients.

**Table 4-2 Summary cost by treatment arm at enrolment (in USD)**

	<b>CRP (n=1017) Mean (SD)</b>	<b>Control (n=1019) Mean (SD)</b>	<b>Difference mean (95%CI)</b>	<b>p value<sup>s</sup></b>
Total cost (USD)	1.24 (1.53)	1.31 (1.52)	-0.07 (-0.21 to 0.06)	p=0.28
Examination cost				
Total	0.35 (0.62)	0.34 (0.34)	0.01 (-0.04 to 0.05)	p=0.84
HI cover	0.22 (0.60)	0.20 (0.28)	0.02 (-0.02 to 0.06)	p=0.24
Self-paid	0.12 (0.29)	0.14 (0.31)	0.02 (-0.05 to 0.006)	p=0.14
Diagnostic test cost				
Total	0.18 (1.30)	0.12 (0.85)	0.06 (-0.04 to 0.15)	p=0.23
HI cover	0.15 (1.04)	0.11 (0.73)	0.04 (-0.04 to 0.12)	p=0.33
Self-paid	0.04 (0.54)	0.02 (0.16)	0.02 (-0.01 to 0.05)	p=0.26
Self-paid	0.18 (1.20)	0.07 (0.86)	0.11 (-0.02 to 0.24)	p=0.11
Antimicrobial cost				
Total	0.51 (1.04)	0.69 (1.23)	-0.18 (-0.28 to -0.08)	p=0.0004
HI cover	0.48 (0.94)	0.63 (1.04)	0.15 (-0.24 to -0.07)	p=0.0003
Self-paid	0.03 (0.17)	0.05 (0.49)	-0.02 (-0.05 to 0.01)	p=0.22
Other medications				
Total	0.39 (0.63)	0.33 (0.58)	0.06 (0.01 to 0.12)	p=0.02
HI cover	0.37 (0.60)	0.32 (0.56)	0.05 (0.01 to 0.11)	p=0.03
Self-paid	0.02 (0.09)	0.01 (0.09)	0.01 (-0.002 to 0.01)	p=0.13

<sup>s</sup>All comparisons were based on t-test.

#### **4.3.2 Patient and provider costs during the two weeks of follow-up**

In the two weeks following first attendance, total medical and non-medical costs were similar across treatment arms ( $p > 0.05$ ) (Table 4-3), despite a small increase of \$0.06 in treatment costs in the CRP arm ( $p = 0.02$ ). Self-reported duration of antimicrobial treatment was similar in both arms with median of five days ( $p = 0.44$ ).

**Table 4-3 Subsequent cost by treatment arm during 14 days (in USD)**

	<b>CRP (n=1017)</b>	<b>Control (n=1018)</b>	<b>Difference mean</b>
	<b>Mean (SD)</b>	<b>Mean (SD)</b>	<b>(95%CI)<sup>§</sup></b>
Total cost	1.18 (1.37)	1.28 (1.42)	-0.1 (-0.22 to 0.02)
Treatment cost	0.39 (0.63)	0.33 (0.58)	0.06 (0.01 to 0.12)
Antimicrobial cost	0.18 (1.46)	0.14 (1.14)	-0.04 (-0.07 to 0.16)
Other medications cost	0.07 (0.53)	0.09 (1.12)	-0.02 (-0.09 to 0.06)

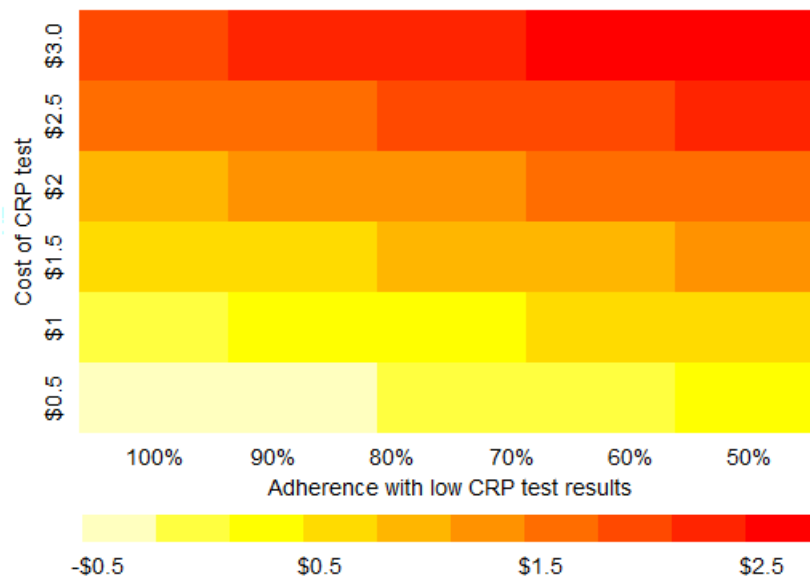
<sup>§</sup>All comparisons were based on *t*-test except duration of antimicrobial treatment (Wilcoxon rank sum test). All *p*-value > 0.05 except for comparison of treatment cost.

In summary, there was no significant difference in household and provider costs for patients in each of the trial arms, with a mean total cost from first attendance and during two weeks of follow-up in the intervention arm of \$2.42, lower but not significantly so than the mean cost of \$2.59 in the control arm (*p*=0.18).

#### **4.3.3 Cost-effectiveness analysis**

The costs reported above were based on primary data collected during the trial, and excluded the cost for the CRP tests that were provided free of charge. In the model, with the use of a CRP test with a unit cost of \$1, the incremental cost per patient managed with the aid of a CRP test would be \$0.71. Two parameters are key drivers for this incremental cost – the unit cost of the test and the probability that health workers adhere to the results in avoiding prescription of antimicrobials to patients with CRP levels below the age-specific threshold. When varying these two parameters between a range of \$0.5 to \$3 for the cost of the test and 100% to 50% adherence to the test results, as shown in figure 4-2 the difference in costs per

patient range from a cost saving of \$0.3 (low cost, high adherence) to an incremental cost of \$2.7 (high unit cost, low adherence).

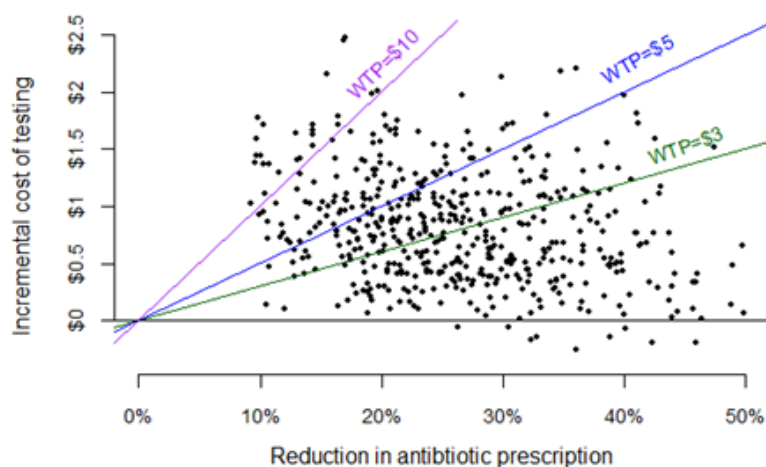


**Figure 4-2 Difference in mean cost per patient between CRP testing and current practice.**

*Given a range of unit costs for the test and varying the level of adherence to test results. For the CRP test to be cost saving at the lowest estimate of \$0.5, adherence would have to exceed 80%.*

The effect of CRP testing is a 20% (absolute) reduction in the antimicrobial prescription rate, using the trial data for immediate antimicrobial prescription rates, including 36% of patients with low levels of CRP being prescribed an antimicrobial. If adherence to low CRP test results was complete this would result in an absolute reduction of 51%, so that only 12% of patients would be prescribed an antimicrobial as compared with current practice of 63%. Increasing compliance would require additional costs for training health care workers, not accounted for in our study.

Using the point estimates of \$0.71 in incremental costs and an effect of 20% reduction in antimicrobial prescription results in an incremental cost of \$3.7 per antimicrobials prescription averted. In the two-way sensitivity analyses this implies a range from the aforementioned cost saving and very high reduction in antimicrobial prescription rates for the low cost test with 100% adherence, up to a cost of \$36 per antimicrobials prescription averted for a test costing \$3 if adherence in patients with low levels of CRP is only 50%. A probabilistic sensitivity analyses was also performed varying all model parameters; a cost-effectiveness plane with the results of 200 Monte-Carlo simulations in figure 4-3 illustrates the incremental costs and effects accounting for all parameter uncertainties.



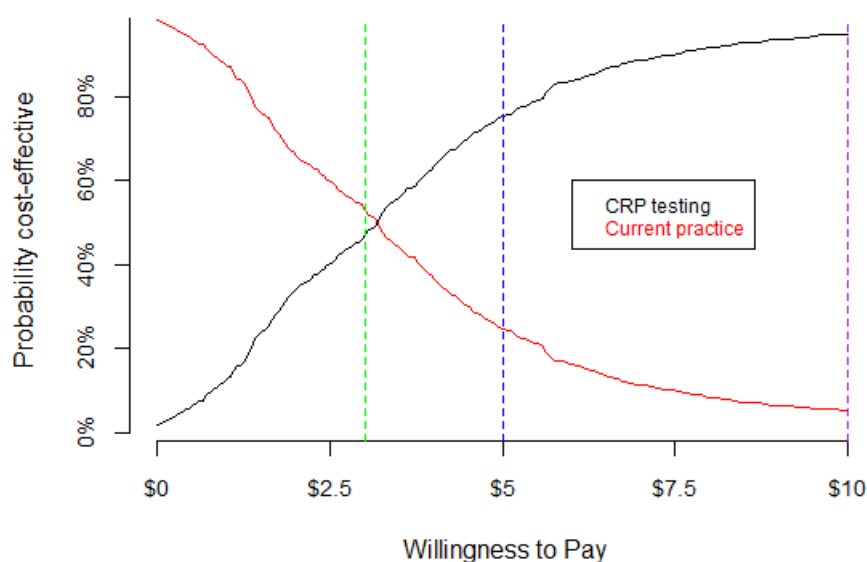
**Figure 4-3 Cost-effectiveness plane showing the output of 200 Monte-Carlo simulations.**

*The graph illustrates the simulation outputs, showing the incremental costs and gains for each simulation, and its positioning in relation to three different WTP thresholds. If policy makers were willing to pay \$10 per antimicrobial prescription averted, CRP testing would be highly likely to be cost-effective, as indicated by the small proportion of instances where the simulation outputs are above this threshold.*

In all modelled instances CRP testing safely reduced antimicrobials in a range of 10% - 50%. While there were a small number of instances where the CRP test was also cost saving,



in most instances it was more costly, and in over 55% of instances the incremental cost-effectiveness ratio was above the WTP threshold of \$3. This is indicated in the cost-effectiveness acceptability curves in figure 4-4, showing that the point at which there was over a 50% probability of CRP testing being cost effective was at a WTP value of between \$3 to \$5 per antimicrobial prescription averted. A WTP threshold of \$10 would imply close to 100% certainty of CRP testing being cost-effective, given the model assumptions.



**Figure 4-4 Cost-effectiveness acceptability curves for CRP testing and current practice**

*Given the model assumptions and parameter uncertainties, CRP testing (black curve) is more likely to be cost-effective if policy makers are willing to pay over approximately \$3.5 per antimicrobials prescription averted.*

#### **4.3.4 Budget impact analysis**

Lastly, we estimated the total cost and impact of CRP testing if these were to be adopted across the Vietnamese community health clinics and at outpatient departments of

district level hospitals. Using the baseline estimates of \$1 for the unit cost of the test and 64% adherence, the model suggested that implementation of the tests at this scale would result in an additional annual cost of \$4.6m, and avert the prescription of 1.3 million courses of antimicrobials. The best case scenario with a low-cost test (\$0.5) and 100% adherence with test results implies a cost saving of \$1.6m and 3.2m antimicrobials avoided. A worst-case scenario with a \$3 test and 50% adherence implies a budget impact of \$19m and 480 thousand courses of antimicrobial prescriptions averted.

#### **4.4 Discussion**

Previously, a trial based cost-effectiveness analysis conducted in the Netherlands had shown that although CRP tests cost more per patient in the short term, with a mean cost per patient of €37.6 compared to €36.0 in the routine arm, this was balanced by a reduction in antimicrobial prescriptions (39% versus 68%, ICER €5.79) and improved quality of life (156). A modelling based evaluation largely based on this trial considered the cost-effectiveness of CRP guided treatment of ARIs in primary care in the UK setting, also concluding that it would result in a gain in QALYs, minor cost-savings, and a reduction in antimicrobial prescriptions (247). Another observational based economic evaluation conducted in Sweden and Norway showed a higher but non-significant increase of €11.3 ( $p=0.09$ ) in health care cost and a reduction in antimicrobial prescription of 10% associated with CRP POC testing ( $p=0.08$ ) (155). All three of these studies concluded that CRP POC testing was cost-effective in reducing antimicrobial prescription and in cost per QALY gained in these high income settings. This study is the first economic evaluation of CRP guided treatment in an LMIC.

The trial results demonstrated that CRP testing could safely reduce antimicrobial prescription rates on first attendance by 20%, and that these gains were largely sustained at two weeks' follow up, with a 14% absolute difference. Here we investigated the economic

implications of the use of CRP tests from the patient and health system perspectives. The use of the CRP test resulted in small and non-significant decreases in direct medical and non-medical costs for patients and healthcare providers on first attendance and during the two weeks' follow-up.

When considering the added cost incurred by a CRP test at a unit cost of \$1, the reduction of approximately 20% in antimicrobial prescription rates would imply a cost of \$3.7 per antimicrobial prescription averted. If used across the network of community health centres and in outpatients attending district hospitals, CRP testing would incur approximately \$4.6m and avert the prescription of 1.3 million courses of antimicrobials; assuming a weight of 5g per full course (e.g. amoxicillin 500mg tablets taken up to three times daily for five days; ampicillin 500mg twice daily over five days), this would be equivalent to avoiding the consumption of over six tons of antimicrobials every year by primary care patients with ARIs in Vietnam.

Even in high income countries, primary care practices cannot use the test unless it is properly resourced (250). Whether such safe reductions in the use of antimicrobials justify this use of scarce resources is a challenging question. In LMIC settings this added cost should not be shouldered by patients' out-of-pocket payments, and in the poorest countries it is highly unlikely that health systems would or should view this as a priority over interventions with more tangible benefits, therefore leaving the funding to patients or health systems will result in sub-optimal uptake from a global perspective. Furthermore, different reimbursement structures exist among European countries: some may encourage inappropriate use or overuse of the test. Pay for performance (P4P) that offers financial incentives to physicians, or healthcare providers for meeting certain performance measures can be an effective payment model to enhance financial savings and quality improvement (251). P4P metrics may include:

(1) Process metrics: to assess if patients are undergoing appropriate CRP testing, as defined by evidence-based best practices.

(2) Outcome metrics: Antimicrobial prescribing rates? Is this improving over time?

(3) Cost or Utilisation metrics: Are resources being used appropriately? Specific measures may include re-consultation rates, algorithm adherence.

(4) Patient satisfaction metrics: Are patients satisfied with their overall experience?

A longer term, global public health perspective could well dictate that these added costs represent a small fraction of the potential impact of AMR, and such views have recently encouraged governmental and international bodies to dedicate large investment to mitigating its spread. Recent reports estimating the global impact of AMR have highlighted the need for a global funding mechanism such as *Diagnostic Market Stimulus pots* and Longitude fund, similar to the Global Fund for Aids Tuberculosis and Malaria that would be dedicated specifically to the development and scale-up of diagnostics and other interventions that improve the targeting of antimicrobials and mitigate the impact of AMR (7, 252). Economic evaluations such as these can help ensure efficient targeting of this funding. Before scale-up, a health technology assessment (HTA) should be performed to assess the opportunity costs of implementing as resources for health are always limited. Lessons can be learnt from HTA quality standards for stroke in Vietnam. Based on the previous success to establish national quality standards for acute stroke in Vietnam, quality standards for appropriate antimicrobial use for inpatients with certain conditions (community-acquired pneumonia and acute exacerbation of COPD) have been developed by the Vietnam Ministry of Health with support from OUCRU and NICE International (80). Linking reimbursement programmes to clinical guidelines may improve appropriate antimicrobial use if payment is only made when the prescription is performed according to guidelines.

The longer term implications of AMR should not be the only incentive for more judicious use of antimicrobials. While data to quantify the impact of adverse drug reactions (ADR) in the community in low income contexts are scarce, a meta-analysis of prospective studies in US hospitals found ADRs to be between the fourth and sixth cause of death during admission (253). Although adverse events occur in a small proportion of antimicrobial courses, the frequency of antimicrobial use makes them account for approximately a quarter of all adverse events recorded in the hospital setting (254, 255). A study of ADR associated emergency department visits found antimicrobials to be implicated in a fifth of cases (256). Averting such adverse events by reducing antimicrobial consumption is an additional argument for the introduction of CRP POC in the primary healthcare setting.

There were several limitations that need to be discussed. The primary measure of effectiveness used in the model was antimicrobial prescriptions averted; this is not equivalent, however, to actual antimicrobial consumption averted. In the trial there was indeed a sizable proportion of patients that were not prescribed an antimicrobial that opted to purchase these in the private sector – approximately a third of patients that were not prescribed an antimicrobial. This dilution of the initial effect on prescription is considerable, implying a proportional increase in the ICER to ~\$5 to avert the consumption of an antimicrobial. If the intervention were to be rolled out in routine care, this can and should be supplemented by further training and education for health workers and patients to ensure better adherence and high efficiency of the test. It is also likely that as with malaria rapid tests, over time these could gain greater traction as they become more familiar and trusted (257).

It is near impossible to quantify the link between current consumption and future costs of resistance. In this study, a rudimentary method was used to place a monetary value on the avoidance of the consumption of an antimicrobial, using a single available study to enumerate this link and place a monetary value representing the cost of AMR per antimicrobial

consumed. Even after adjustment, the relevance of this estimate is questionable and methods tailored to different contexts, drugs and infections are much needed.

Similarly, the interpretation of the ICER, the cost per antimicrobials prescription averted, is challenging, as compared with for instance the cost per DALY averted which is more familiar to policy makers and for which some (albeit highly imperfect) thresholds and frames of reference are available. With increasing awareness and resources dedicated specifically to interventions targeting safe reductions in antimicrobial consumption, economic evaluations using this as a shared measure of outcome will be useful in guiding these resources, even if comparison with other health interventions is not clear.

This analysis was limited in scope to the incremental costs of CRP testing, rather than a full economic evaluation, extrapolating to the health and economic benefits of the intervention. There are numerous possible cost and health implications associated with CRP testing that were not accounted for, including for instance the impact on hospital admission rates and their associated high costs, costs of potential reactions to antimicrobials (both allergic and other common reactions, such as nausea, vomiting and diarrhoea), as well as the potential direct health benefit to patients in better identification of cases that require treatment or the avoidance of side-effects and allergic reaction in patients receiving antimicrobials unnecessarily. While over-treatment is a huge problem in most areas in both low and high income settings, there are still many others where under-treatment of respiratory infection in patients with restricted access to antimicrobials still imposes a huge morbidity and mortality toll (2, 7). CRP testing in LMICs could therefore have a broader impact on costs and health outcomes than those at the focus of the current trial and cost analysis. Nevertheless, the introduction of a single test will not bring an improvement in AMR unless it's placed in a comprehensive stewardship program that include education, vaccination and other proper

preventive measures such as implementation of quality standards or evidence based guidelines for antimicrobial use (258).

## Chapter 5

### **Acceptance of C-reactive protein (CRP) point of care (POC) testing for non-severe acute respiratory infections (ARIs) among patients and health care workers in the primary health care setting of Vietnam – A qualitative study**

#### **5.1 Introduction**

Due to similar presentation of clinical symptoms, clinical differentiation between viral and bacterial acute respiratory infections (ARIs) is difficult, driving irrational use of antimicrobials (259-262). New approaches to reduce irrational antimicrobial use without compromising patient recovery must be an urgent priority. While tremendous incentives from the Global Innovation Fund and Longitude prize are being given to encourage the development of rapid tests which can diagnose bacterial infection (263, 264), there are several commercially available point-of-care (POC) tests for biomarkers of bacterial infection that can be performed at the site of patient care and can influence clinical decision making by providing rapid test results (265-267). One of these biomarkers is C-reactive protein (CRP), which has been assessed for clinical and cost-effectiveness in primary care settings of high income countries and recommended to guide antimicrobial prescription for bacterial pneumonia in primary care (155-157, 268, 269).

In Vietnam CRP POC testing evaluation has been conducted by our group in a randomised controlled trial (RCT) [see chapter 3] and we found this test can significantly reduce inappropriate antimicrobial prescription with an overall absolute reduction of 13.5% (77.9% versus 64.4%; odds ratio [OR] 0.49, 95% confidence interval (CI) 0.4 to 0.61) (216). Our finding supported previous evidence from systematic reviews of individual and cluster RCTs in European settings that CRP POC testing offer a significant reduction in antimicrobial



use (pooled risk ratio (RR) 0.78, 95%CI 0.66 to 0.92,  $I^2$  statistic=68%) (225). The trial-based economic evaluation in this setting showed that CRP testing could be cost saving if the unit cost per test was \$0.5 and adherence exceeded 80% (Chapter 4).

However, interventions that are proven effective may not be feasible in daily practice for a variety of reasons. Careful consideration of potential barriers in daily operation is required for effective large-scale implementation of any evidence-based intervention. To identify the potential obstacles, it is important to gain insight into the attitudes of patients (or their parents if patients were children, hereafter called relatives) and health care workers (HCWs) who participated in the trials toward the interventions. This study aims to assess the acceptance of CRP POC testing to reduce inappropriate antimicrobial use for self-limiting ARIs among patients (or relatives) and HCWs in Vietnam.

## **5.2 Methods**

### **5.2.1 Study design**

In this qualitative study in northern Vietnam, we combined both focus group discussions (FGDs) and in-depth interviews (IDIs). Individual interviews were used when gathering people for FGDs was challenging to arrange. One FGD was held with representative HCWs from ten district health centres that participated in the CRP trial (Chapter 3 in this Thesis, [clintrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01918579) number: NCT01918579). Two individual IDIs were performed with HCWs who were not able to participate in the FGD. One FGD with patients/relatives in a rural area was conducted in Ba Vi General Hospital, Ba Vi district, Hanoi (figure 5-1). Two FGDs and a total of nine individual IDIs with patients and relatives were performed in four selected urban districts in Ha Noi (Long Bien, Ha Dong, Dong Da, Hai Ba Trung). Participants were invited to these selected sites or to National Hospital for Tropical Diseases, Ha Noi, depending on their preference.



**Figure 5-1 Focus group discussion with patients and relatives in one rural site**

Interview guides were developed in English to cover general and specific issues for asking participants to discuss their own knowledge, experience and opinions regarding CRP POC testing. The English guides were sent to experts in the field for peer review. The revisions were subsequently translated into Vietnamese following by back translation into English to check consistency and piloting before use. Two pilots were conducted including one with HCW and one with patients to test the questionnaires and revise if needed. Both discussion and interviews included the following themes: (1) Attitude towards CRP POC testing, (2) Perceived impact of the test on antimicrobial prescription (3) Perceived impact of the test on consultation, (4) Suggestions for improvement (table 5-1 & table 5-2).

**Table 5-1 Interview guide for HCWs**

<b>Type of question</b>	<b>Content</b>
Perception of CRP testing	<ol style="list-style-type: none"> <li>1. What do you like/dislike about the test? (eg, sampling/turnaround time)</li> <li>2. Does the test need to be improved? If yes, how should it be improved?</li> <li>3. What factors make you trust the test/ not trust the test? What could make you trust it more?</li> </ol>
Impact on antimicrobial prescription	<ol style="list-style-type: none"> <li>4. How did the test support your treatment decision? Any differences between adult/children</li> <li>5. What do you think your patients are expecting from seeing doctor? (Drugs/Antimicrobials/Advice/Reassurance/Diagnosis/Others)</li> </ol>
Impact on consultation	<ol style="list-style-type: none"> <li>6. Did you use the CRP result to discuss with patients about your treatment decision?</li> <li>7. If not, why not?</li> <li>8. If yes, how did it help in persuading patient in case no antimicrobials are prescribed? Any differences between adult/children</li> </ol>
Recommendations	<ol style="list-style-type: none"> <li>9. In your opinion, should CRP test be introduced in routine practice of your setting? Why/Why not?</li> <li>10. What are your recommendations to improve current situation</li> </ol>

**Table 5-2 Interview guide for patients**

Type of question	Content
About Acute Respiratory Infections and health care seeking behaviour	<ol style="list-style-type: none"> <li>1. What is your understanding about the causes of ARI and it's natural history?</li> <li>2. Do individuals use multiple resources when you/your child is ill (pharmacy, clinic, hospital...) or do you tend to go for the same place each time?</li> <li>3. Why did you choose clinic on this occasion?</li> </ol>
Perception of CRP testing	<ol style="list-style-type: none"> <li>4. What do you like/dislike about the test?</li> <li>5. Does the test need to be improved? If yes, how should it be improved (eg. time, sampling) Any different for adult/children?</li> <li>6. What factors make you trust the test/ not trust the test?</li> <li>7. What could make you trust it more?</li> <li>8. In case, CRP test is not covered by health insurance, would you be willing to pay for the test? Why/why not?</li> </ol>
Impact on antimicrobial use	<ol style="list-style-type: none"> <li>9. What do you expect from seeing the doctor with ARI? (Drug/Antimicrobial/Advice/Reassurance/Diagnosis/Others)</li> <li>10. Did you seek for subsequent antimicrobials if your doctor did not give you antimicrobial? If yes, which sources? (eg. pharmacy, other clinic, self-treatment)</li> </ol>
Impact on consultation	<ol style="list-style-type: none"> <li>11. Did your doctor discuss with you about test result? If yes, did you feel persuadable if doctor said no antimicrobials are needed? Why/why not?</li> <li>12. What other information would you need to help you fully trust the test and trust the doctor's opinion that you do not need antimicrobials?</li> </ol>
Recommendations	<ol style="list-style-type: none"> <li>13. In your opinion, should CRP test be done as a part of routine diagnosis for ARI patients in primary care settings</li> <li>14. What are your recommendations to improve current situation</li> </ol>

All discussions and interviews were sound recorded and I was the moderator. An assistant took notes during the discussion, including the non-verbal communication of participants during the talks, which were used during transcribing of the sound recordings to better reflect the discussion. Each FGD lasted approximately 1.5 hours and IDI lasted 30 to 45 minutes. All FGDs and IDIs were sound recorded and transcripts were made followed by coding and thematic analysis for major themes.

The study was performed as part of the randomised trial (CRP trial) as described in Chapter 3, which was approved by the Institutional Review Board of the National Hospital for Tropical Diseases, Ha Noi (approval code: 39/IRB-NHTD) and the Oxford University Tropical Research Ethics Committee (OxTrec Reference: 176-12). Participant's permission was obtained by written informed consent.

### **5.2.2 Selection of participants**

Participants included HCWs and patients (or their parents if patients were children). They were sampled from those who participated in the previous conducted randomised trial evaluating CRP POC testing (216). Doctors in six centres where there was only one per centre participated in the trial were all invited to the FGD. Two centres had more than one doctor involved in patients recruitment, a main study doctor who enrolled more than 80% of centre's sample size was invited to attend in the group discussion. Doctors who enrolled only few patients during the trial were not invited because of their limited experience. Two remaining sites (Ha Dong centre and Ba Vi hospital) where there were two doctors equally involved in the patient enrollment, one per site was invited to participate the discussion, the latter were interviewed individually. In the FGDs with patients and relatives, participants were randomly selected from the CRP guided group only from all participating study sites, and included both those who were not given an antimicrobial and those who did receive an antimicrobial prescription regardless of the CRP test result. The rationale of putting those people in the same focus group is to stimulate discussion between the two types of participants. Enrolment ceased when no new themes arose from two consecutive FGDs/IDIs (saturation criterion met). In qualitative research, methods to reach data saturation are different across study designs. However, some general principles and concepts are agreed to assess data saturation including: no new data, no new themes, no new coding, and ability to replicate the study (270-272).

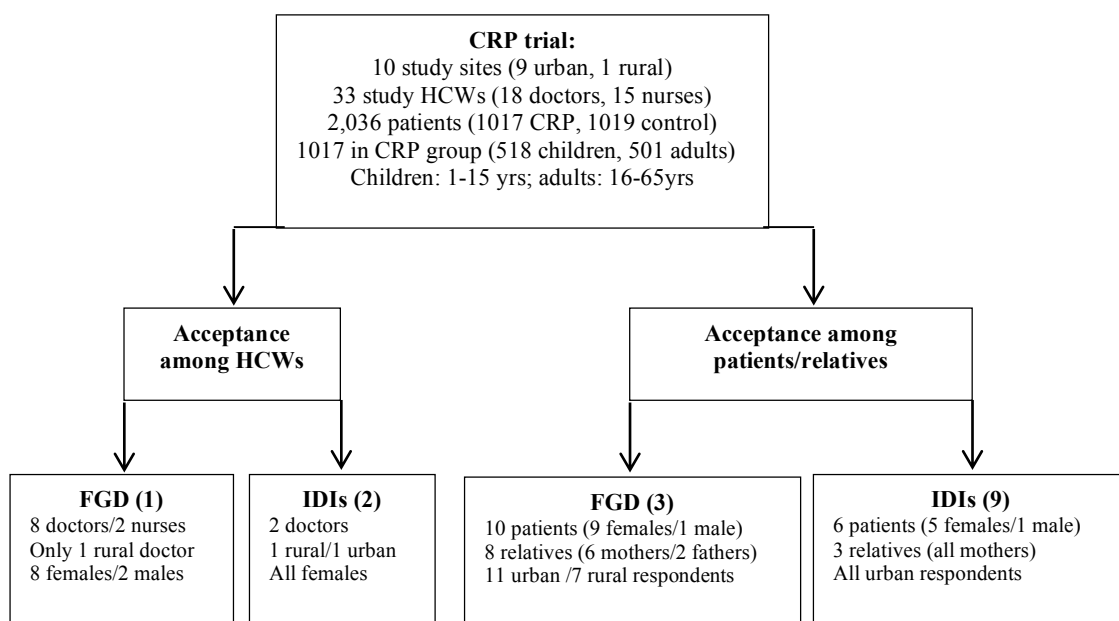
### **5.2.3 Data analysis**

Data from transcripts were analysed using content analysis as described in Chapter 2. The content can be analysed on two levels: (1) Basic level or manifest level: a descriptive account of the data; (2) Higher level or latent level of analysis: a more interpretive analysis that is concerned with the response as well as what may have been inferred or implied. Vietnamese verbatim transcripts were made from the tapes and notes of the FGDs and IDIs. I listened to the tapes and read through the text to become familiar with it and to obtain an overall view of key contents. Meaning units reflecting the same content were identified, abstracted, and then allocated a code. The codes were sorted into coding categories related to main themes, according to the procedures of basic content analysis which is a descriptive account of the data (202). Connections between and within themes were identified for further interpretive analysis. Common themes and quotes were translated into English.

## **5.3 Results**

### **5.3.1 Demographics of study population**

A total of four FGDs with five to ten participants per discussion and eleven individual IDIs were conducted. Three of these FGDs were with patients/relatives and one with HCWs due to characteristics of study doctors as mentioned in the method section (table 5-3). Two individual interviews were with HCWs and nine were with patients/relatives. Of the 39 total participants, 33 (85%) were women. Among 27 community members, 11 (41%) were relatives and 9 of these were patient's mothers. 10/12 HCWs were medical doctors, and the remaining two were nurses (figure 5-2).



**Figure 5-2 Flow chart of sampling procedure and study sample**

**Table 5-3 Data collection methods and participants involved**

Data collection method (n)	Participants (n)
FGD (1)	HCWs (8 doctors, 2 nurses)
IDIs (2)	HCWs (2 doctors)
FGD (3)	Patients (10), Relatives (8)
IDIs (9)	Patients (6), Relatives (3)

The youngest participant was 23 years old and twelve participants were above the age of 50. The majority of rural participants were farmers (6/7) and the highest level of education was higher elementary grade (1/7). The highest level of education among urban respondents was university degree (3/24). Of the twenty urban participants, occupation was variable and included: officer (5), tailor (4), business (4), housewife (2) and retired officer (5) (table 5-4).

**Table 5-4 Demographics of health care workers and patients/relatives**

General characteristics	HCWs (n=12)	Patients (n=16)	Relatives (n=11)
Gender – female (n, %)	10 (83.3)	13 (81.2)	9 (81.8)
Age (median, range) (years)	41 (30-51)	60 (37-63)	41 (23-50)
Rural/Urban (n/n)	2/10	4/12	3/8
Occupation	Doctor (n=10)	Farmer (n=4)	Farmer (n=2)
	Nurse (n=2)	Retired (n=5)	Official (n=5)
		Other (n=7)	Other (n=4)

Four main themes were included in the FGDs and IDIs including: (1) perception of testing, (2) impact of testing on antimicrobial prescribing, (3) impact of testing on consulting, and (4) proposed suggestions for improvement. The main themes, their categories, and examples of codes are shown in table 5-5. Quotes from participants, from both the FGDs and the IDIs, are presented in italic in the text that follows.



**Table 5-5 Themes, categories and a selection of codes**

Themes	Categories	Codes
Perception of testing	Time and convenience Perception of the illness Health care cost Scepticism	Short waiting time Easy to use Does not hurt Minor illness Need to co-pay Whether the test is accurate Is there something wrong
Impact on prescription	Awareness Poor adherence  Financial incentive	Prescribe more cautiously Habit of empirical treatment Patient expectation Concern of complication Self-treatment Antimicrobials in stock
Impact on consultation	Support clinical findings Problem when CRP results were low	Stronger evidence High expectation of antimicrobials Poor communication skills Insufficient information about the test and its result
Proposed suggestions	Education  Affordability	Less pressure to prescribe antimicrobial Be more acceptable if the test is free

### 5.3.2 Perception of CRP POC testing and identified barriers to implementation

A large majority of both patients/relatives (25/27 participants) and HCWs (12/12) expressed positive attitudes towards CRP POC testing, and found it relatively simple to perform using finger prick capillary blood and found that the results were rapidly available.

*“I believe that equipment-based diagnosis is better than solely clinical examination. I think this rapid test is enough for mild respiratory disease because it’s convenient for the patient and the doctor will know how to treat my disease correctly”*. (FGD2, Respondent 2)

*“It’s especially good for children because it does not hurt. I think paediatric hospitals should use this kind of testing”*. (IDI 7, urban relative)

All clinicians responded that CRP POC testing was a useful diagnostic tool without adding any burden on their workload. *“Compared to other diagnostic methods such as X-ray or endoscopy, this test is very simple and does not require expertise and time-consuming performance”*. (FGD4, Respondent 10)

In contrast, negative opinions were also expressed. Considering that non-severe ARI is not a serious condition, patients may not be willing to pay extra costs for a test like CRP POC. According to the regulation of health insurance, patients will need to co-pay 20 percent of health care costs once it exceeds allowed limitation (159, 273). Therefore, any extra services added would increase the risk of co-payment. All rural participants and two urban patients expressed this concern.

*“The more tests you have to take, the more money you need to pay”* (IDI5, Urban patient).

Regarding the belief in the test results, only one patient and one HCW noted scepticism.

*“Whether the test is accurate with such a fast provided result?”* (FGD1, Respondent 4). *“Most CRP results are below 8mg/ml even in patients who seem to have quite severe symptoms that make me wonder if something is wrong with this equipment.”* (FGD4, Respondent 6)

### **5.3.3 Impact of CRP POC testing on antimicrobial prescribing**

All clinicians reported that after gaining experience with the CRP POC test, this intervention helped them to prescribe fewer unnecessary antimicrobials.

*“This intervention makes us more aware that we are prescribing antimicrobials too often so with CRP POC testing we prescribe more cautiously.”* (FGD4, Respondent 8)

*“Before, nearly 100% ARIs patients were treated with antimicrobials. Now, for patients having mild symptoms and low CRP values, delayed antimicrobials prescription would be applied more frequently”* (FGD4, Respondent 7)

However, there was still resistance among HCWs to accept test results with low CRP values. The main reasons for ignoring low test result mentioned were: (1) the habit of treating

even mild respiratory symptoms with antimicrobials among HCWs, (2) incorrect knowledge of benefit of antimicrobial in preventing complications of ARIs and (3) doctor's concern about "losing patient's trust" resulting in antimicrobial prescription even when CRP results were low.

All HCWs shared the same opinion that: *"I know it's not necessary to prescribe an antimicrobial for ARI but because co-infections often occur, I need to give my patient antimicrobials to prevent disease from becoming worse"* (FGD4, Respondent 1).

Three HCWs mentioned: *"I want to comply with CRP results and avoid overuse of antimicrobials but if I do not prescribe antimicrobials, when my patients get worse, they will go to higher healthcare facility and they no longer trust me"* (FGD4, Respondent 4)

The opinion of preventing pneumonia complications, especially in children, by antimicrobials was widely reported among HCWs (10/12).

*"If children have fever, it's necessary to prescribe antimicrobials even with low CRP results. Complications of pneumonia easily occurs in these children if they are not treated with antimicrobials at beginning"* (FGD4, Respondent 3).

HCWs acknowledged that they prescribed antimicrobials much less based on CRP testing than previous empirical treatment. Nevertheless, it was stated by all HCWs that clinical examination is more valuable than CRP values in making treatment decision with low CRP results.

*"I agree that the test added a supportive value to the clinical findings. However, it could not replace clinician's experience"*. (FGD4, Respondent 2)

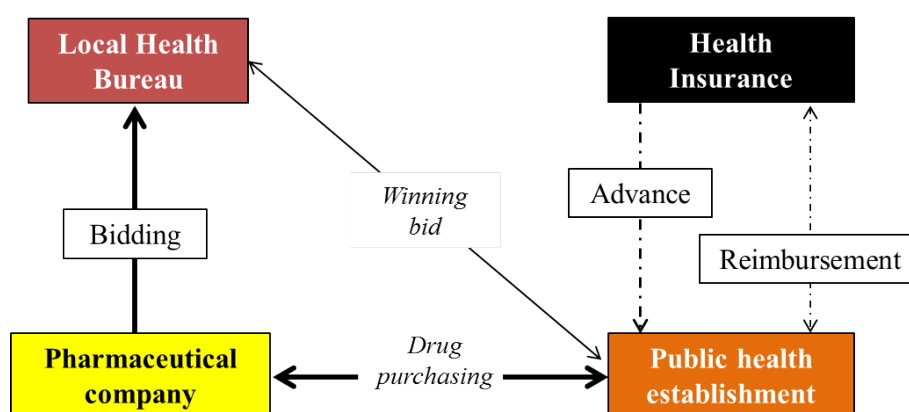
We also detected a contrast between doctors' thinking and patients' expectation. Whilst almost all doctors thought their patients wanted antimicrobials, just one-third of the patients state they expected an antimicrobial prescription.

“Without antimicrobial prescription, patients are not satisfied. Medicines are covered by health insurance, so they prefer to receive as many as possible. In case they do not use it, they can reserve it for future use”. (FGD4, Respondent 9)

Occasionally, one HCW stated that they were put under pressure to get rid of antimicrobial stocks as much as possible by the health centres to get reimbursement from health insurance agency. Normally, health insurance advance 80% of estimated drug expenditure for health establishments. Quarterly, health insurance will audit and make a final payment to clinics based on dispensed medicines (figure 5-3) (274). Therefore, they kept prescribing antimicrobials despite low CRP values.

“There are a lot of antimicrobials in stock that need to be dispensed. Depending on CRP results, I tell my patients to use the antimicrobial immediately or keep for another illness episode”. (FGD4, Respondent 4)

Expiry dates of these stocks were not mentioned. However, other respondents did not agree with this opinion.



**Figure 5-3 Central drugs bidding model for public health establishments**

*Source: Hanoi Health Bureau Office*

In fact, it was commonly reported that patients/relatives (7/27) reserve medicines including antimicrobials at home from the last sickness and use it when they or their children have similar symptoms or use previous prescription (5/27 respondents) to buy antimicrobials from private pharmacy. Some of them said that they sought antimicrobials from other sources such as private clinics or pharmacy when duration of symptoms lasted too long due to delayed antimicrobial dispensing.

Finally, all prescribers said they returned to their old prescribing habits after the CRP POC intervention study was stopped as they believe that antimicrobials help shorten the duration of symptoms and their patients expect an antimicrobial.

#### **5.3.4 Impact of CRP POC testing on consulting**

Three-quarters (9/12) clinicians reported that a rapidly available test result supported their clinical findings and provided a stronger evidence to convince patients to not use antimicrobials.

*“We showed the test result to the patient and said “look, yours is below 8” and compared to the recommended cut-offs, you do not need antimicrobials for your sickness. Patients are convinced and reassured”.*

However, one-third (4/12) of respondents expressed that it was difficult to consult patients who expect an antimicrobial prescription even with low CRP values.

*“Convincing patients who are asking for antimicrobials to accept non-antimicrobial management remains a challenge. Because patients are not assured that they will get better without antimicrobial treatment.” (FGD4, Respondent 5)*

Contrasting views were seen among patients/relatives regarding doctor’s consultation. Whilst only one-quarter (7/27) respondents acknowledged sufficient explanation from doctors/nurses that the test did not indicate anything serious as a reason for not prescribing antimicrobials for their sickness, others announced that they did not receive sufficient

information including purpose of performing the test and/or how to interpret the results. All of them said they would trust the test more if more sufficient information would be provided.

*“Taking an antimicrobial makes me tired; especially it is difficult to finish a full course of seven days so normally I stop using it after 2-3 days when symptoms are better or recovered. If a doctor can confirm the self-limiting nature of symptoms through elaborate examination following by testing, I feel my sickness was being taken carefully and I will be totally reassured without antimicrobial treatment.”* (IDI1, urban patient)

*“There is hesitance among parents to administer antimicrobials to their baby due to a fear of negative impact on their children. Therefore, if doctor said antimicrobials were not needed for my children, I have no reason to not be satisfied”* (IDI4, urban relative)

### **5.3.5 Proposed suggestions for improvement**

Both prescribers (12/12) and patients/relatives (27/27) considered that mass educational campaign for the general population would be needed to improve public knowledge and awareness about antimicrobials and resistance. This would likely have a significant impact on improving appropriate antimicrobial use in the community.

*“There will be less pressure to prescribe antimicrobials if patient’s awareness is improved”.* (FGD4, Respondent 2)

*“Through mass media, there should be several health programs focusing on antimicrobials to improve public awareness about side effects of antimicrobials. By achieving better understanding about antimicrobial and resistance, people will be encouraged to limit overuse or self-treatment with antimicrobials.”* (IDI2, rural patient)

Secondly, it was widely mentioned that the introduction of CRP POC testing into practice would be more adopted if it is well resourced by existing budgets rather than charged to patient’s pocket due to low affordability.

*“Majority of patients seeking primary healthcare facilities are non-rich citizen. Therefore, it would be more acceptable if the test cost is free of charge” (FGD4, R8).*

#### **5.4 Discussion**

This is the first qualitative study to assess the perceptions of both HCWs and patients/relatives (if patients were children) regarding the use of CRP POC testing to reduce unnecessary antimicrobial use for non-severe ARIs. Earlier qualitative studies conducted in the European setting included HCWs only. In general, positive attitudes toward the test were widely seen among respondents regarding convenience in performance and its impact on reducing unnecessary antimicrobial prescription, which were similar to previous qualitative findings in European countries (230, 275).

Discussing the impact of CRP POC testing illustrated that there is a clear need for improved information provision to both HCWs and patients/relatives regarding the test and the result. There have been several successful complementary interventions in developed countries that brought important changes in antimicrobial prescription whilst maintaining patient’s satisfaction (151, 156). As reported from a cluster RCT conducted in primary care practices in six European countries, the combined intervention between CRP POC testing and enhanced communication skills through internet training produced the greatest reduction in antimicrobial prescription without estranging patients (151). Doctors in this setting recommended using a patient information booklet, which helps explain the intervention more fully and makes patients feel more comfortable with the decision not to be prescribed antimicrobials. It has also been reported that such information booklets are particularly helpful when providing decisions not to prescribe antimicrobials, as they address patient’s concerns by providing a written reminder of ‘alarm symptoms’ suggestive of a more severe illness that should prompt re-attendance (275). However, we did not discuss this with HCWs as well as patients/relatives so its impact remains unknown among our population. To

improve public awareness, visual tools such as DVD, posters, leaflets or the old-fashioned / traditional commune loud speaker can be an effective way of spreading messages.

Clinical findings were acknowledged more valuable than CRP values in making decision by HCWs. However, a systematic review showed that the predictive value of the clinical findings and CRP separately for antimicrobial prescribing in adults presenting with acute cough was similar (AUC = 0.89) (244).

A qualitative approach to study the obstacles to effective implementation is an accepted and useful research design for deeper understanding of the reasons for non-adherence to a specific intervention (276, 277). Factors associated with low acceptance of the CRP POC test among HCWs included: (1) incorrect knowledge of the need for antimicrobials for mild ARI, and (2) perceived patient expectations of an antimicrobial prescription. The documented scepticism in some HCWs and patients suggests that they may need time to familiarise themselves with the test and gain experience in interpreting and applying the results. Additionally, we found that financial incentives in dispensing antimicrobials existed as they had antimicrobial stock. Furthermore, after the trial, doctors went straight back to keep prescribing antimicrobials indicating that not only patients but also prescribers should be targeted with proper interventions to change their behavior. These findings emphasise that different settings with country-specific health system and cultural features likely have different barriers that need to be identified and addressed with appropriate interventions to achieve optimal effectiveness in uptake of any new strategy.

Regarding the cost concerns and accessibility of CRP POC testing in resource constrained settings, our economic analysis showed that the CRP POC test added cost which should not be shouldered by patients' out-of-pocket payments, and in the poorest countries it is unlikely that health systems should view this as a priority over interventions with more obvious benefits. Also, as in the European setting, large scale roll out of the test in primary



care practices would need to be properly resourced (250). Therefore leaving the funding to patients or health systems will result in sub-optimal uptake from a global perspective. To control the global threat of antimicrobial resistance, global funding mechanisms for this evidence based intervention are highly recommended to encourage the adoption at scale, including LMICs (Chapter 4). On the other hand, further development of cheaper versions of the test without requirement for a costly reader would make it more affordable in resource limited settings.

The strength of this study is that we involved patients or relatives who had their children managed with the aid of CRP testing to achieve a more objective view on patient-related factors such as their acceptance of the test and satisfaction. Secondly, using both FGDs and IDIs facilitated the attendance of participants. Gathering people in the FGDs would help to gain a broader scope of topics, while IDIs prevent participants from being affected by other's opinions. Though the number of FGDs and IDIs were relatively small, no new ideas were recorded at the end of these, implying saturation was achieved.

While it offers useful findings, we found several limitations that need to be discussed in our study. Firstly, the predominance of female patients/relative may reflect selection bias and affect the results as males may have a different point of view. However, in the trial from which patients/relatives were selected, female patients accounted for substantial part of 60% and mothers were reported to be main caregivers of 83% (687/828) for children under five in rural Vietnam (224). Therefore, we believe the impact of this selection bias is minimal. Secondly, the refusing rate among young patients was higher than old patients due to their availability that may have biased the findings since young patients may have different views and awareness.

CRP POC testing contributes to antimicrobial stewardship in the primary health care setting, resulting in declining pressure for antimicrobial resistance development (269, 278).

Therefore, long-term and large-scale investment in this intervention offers wider societal implications. In order to make this investment as successful and effective as possible in resource limited settings such as Vietnam, the identified barriers need to be addressed with rational strategies for both HCWs and patients/relatives to improve their acceptance and compliance with the CRP POC testing. Furthermore, to promote the systematic uptake of research findings into routine practice, implementation science which has been developed to address implementation challenges should be studied (279). Proposed approaches include

(1) theories to understand/explain what influences implementation outcomes (e.g, to what extent do health care providers' attitudes and beliefs concerning CRP POC test predict their adherence to the test algorithm in clinical practices?).

(2) process models which guide stages/phases to implement CRP POC testing into practice.

(3) contextual frameworks, which are checklists of factors relevant to various aspects of implementation (e.g, budget, human resource, infrastructure, training, etc) which could be evaluated to determine implementation success.

## Chapter 6

### General discussion, implications & recommendations for future work

#### 6.1 Contribution of this thesis to existing evidence

The research presented in this thesis was set out to better understand the incentives that support (inappropriate) antimicrobial dispensing in private pharmacies in Vietnam. This understanding is important for designing effective interventions to partly improve rational antimicrobial consumption. Several proposed solutions including sanctions to improve GPP compliance/enforcement, availability of a rapid blood test in addition to history taking and physical examination to determine which customers should use antimicrobials, and education for both dispensers and customers to improve the current situation were discussed with dispensers. Based on the findings from the pharmacy study (chapter 2), settings for the next study were selected where we evaluated whether a rapid point of care C-reactive protein test is safe and effective to reduce (unnecessary) antimicrobials prescribing for patients with ARIs in a randomised controlled trial (chapter 3). Furthermore, the economic impacts of this strategy (chapter 4) as well as the acceptability of the test among healthcare workers and patients (chapter 5) were investigated.

In my thesis I sought to answer the following questions:

- What are financial and behavioural incentives of private pharmacies driving inappropriate antimicrobial dispensing in the community to develop potential effective intervention strategies? (Chapter 2)
- Can a Point-of-Care diagnostic, C-reactive protein (CRP) test reduce antimicrobial prescribing safely for acute respiratory infections (ARI) use in the primary care, and to what extent? (Chapter 3)

- What are the economic impacts of a CRP POC test in the LMIC setting of Vietnam? (Chapter 4)
- What is the acceptance of using a CRP POC test among patients and health care workers? (Chapter 5)

The key findings are synthesised below.

### **6.1.1 Antimicrobials dispensing in the private pharmacies**

Antimicrobial dispensing practice in Vietnamese community is characterised by poor adherence to regulation. ~90% of the antimicrobials are sold over the counter despite the existence of prescription regulation. This situation is similar to what was reported nearly twenty years ago when less than 1% of customers had a prescription (280). The considerable contribution of antimicrobials sales to the total revenue of private pharmacies (24% in urban and 18% in rural) is likely a key driver. Implementation of the Good Practice for Pharmacy (GPP) system alone is not effective to improve dispensing practices as non-compliance with regulations is not sanctioned. Better practices have been observed in stores with an on-site pharmacists (Chapter 2). However, having an on-site pharmacist is often not feasible due to cost and the small number of pharmacists with a degree, especially in remote areas (281, 282). Profit incentives the regulatory compliance must be taken into consideration when designing interventions to improve antimicrobial dispensing in this setting.

Most antimicrobials are dispensed for acute respiratory infections (ARIs) which are mainly viral in origin. In a recent Vietnamese study it was found that viral pathogens account for 72% of all detected respiratory pathogens in ARI outpatients and only 7% are bacterial (283). Using a rapid POC test to determine which customers may need antimicrobials could be a solution in improving antimicrobial use. Though concerns about losing income when the test result recommends to not prescribe antimicrobial were noted among dispensers (250).

Proper reimbursement mechanisms could be applied to compensate loss of income due to negative test results.

Although this study revealed the magnitude of inappropriate antimicrobial dispensing in the Vietnamese community, there were several limitations that need to be addressed in future research. One of the challenges we were confronted with was the variety in the antimicrobial inventory of a private pharmacy (figure 6-1). There were hundreds of brand antimicrobials in the pharmacies making an inventory during three observation days difficult. In future research, this would be possible with for instance five essential systemic generic antimicrobials to be inventoried. Furthermore, the chosen observation time was working hours only (from 9AM-5PM) while most pharmacies' opening hours were 8am – 6 or 9pm. In the context of high pressure from customers, interviewing customers need to be considered in future studies to understand drivers for supporting their self-medication with antimicrobials. To change behavioural incentives, education campaigns targeting both providers and consumers on AMU and AMR needs to be a component of any intervention strategy (217).



**Figure 6-1 Antimicrobials sold in a small rural private pharmacy**

*Source: Picture has been made by Prof. Heiman Wertheim in a field trip to Thanh Ha commune, Thanh Liem district, Hanam province, Vietnam.*

### **6.1.2 Potential of CRP POC testing in reducing antimicrobials prescription for non-severe acute respiratory infections in primary care settings**

With a large sample size, our individual randomised control trial is sufficiently powered to assess the effectiveness of C-reactive protein point of care testing in reducing inappropriate antimicrobial prescription for non-severe ARIs in both adults and children. Presently there is a lack of studies from primary care settings addressing POC biomarkers to reduce antimicrobial prescribing, especially in low and middle income countries. Also, virtually no data exist on CRP POC testing in children. Using POC tests to reduce

antimicrobial prescribing is an ongoing debate to which we believe this study adds new and useful information (225, 284, 285).

Large between-site heterogeneity was found in the effect of CRP POC testing across ten study sites ( $I^2=84%$ , 95%CI 61%-96%), an important limitation. This heterogeneity was significantly higher than what has been reported in Denmark with  $I^2=47%$  (152). There was no single reason that fully explains the observed between-site differences, though varying levels of adherence to the CRP algorithm is part of this story. Further qualitative investigations are needed to identify the potential barriers that need to be overcome to make the intervention even more effective (Chapter 5).

The rate of pneumonia was assumed very low in our population basing on previous work showing that, among 563 ARIs outpatients visiting a tertiary referral hospital for paediatrics in Vietnam, only 1.2% was clinically classified as pneumonia (283). Still, a very high proportion of those with low CRP values that rule out the risk of pneumonia were prescribed antimicrobials, indicating poor adherence to the CRP value and treatment guidelines. Notably, these prescriptions were made by well-trained doctors, illustrating that either the limited knowledge and awareness in responsible use of antimicrobial also exist among health care workers or prescribing antimicrobials is considered as a defensive measure. Whichever the cause was, these barriers need to be addressed. Lessons can be learned from high-income settings where the combination of CRP POC testing and education showed the highest impact on improved prescribing (151).

To reduce the total antimicrobial consumption and thus resistance in low-middle income countries where most antimicrobial utilisation decisions are made outside of the health care facility (Chapter 1), investigating the potential for POC CRP testing in pharmacies and drug stores will still be needed. Given the mild to moderate clinical symptoms with virtually no adverse outcomes (1%), it is hard to assess safety of the trial in more severe

conditions of ARIs. Further evidence on the risks of not prescribing based on POC CRP and guidance in the application of test results to different populations, including patients with comorbidities associated with elevated systemic inflammatory CRP (such as rheumatoid arthritis and chronic obstructive pulmonary disease) also needs to be investigated (250, 286-288).

### **6.1.3 Economic impact of CRP POC testing**

Utilising primary cost and clinical outcome data from the CRP trial, we were able to explore the cost-effectiveness of the intervention, its economic implications for households, as well as for the health system in Vietnam if implemented at scale, and places this in the broader context of global efforts and financing for interventions to reduce the burden of AMR.

Although these findings indicate that CRP testing can avert a significant proportion of human antimicrobial consumption, the answer for justified investment of this strategy in LMICs remains unclear. Neither patients nor highly resource constrained health care settings in these countries should bear this added cost. To balance the cost for reducing antimicrobials consumption and potential global impact of AMR in a longer term, a similar global funding mechanism which has been aided for improving diagnostics and thus controlling tuberculosis and malaria is highly recommended.

There are several major problems with health economics models for AMR. As it is difficult to quantify the long term clinical consequences of AMR, current estimates may be over- or underestimating the real costs. Furthermore, not all reductions in antimicrobials are equal as antimicrobials are differently associated with the development of resistance. The value of reducing antimicrobial overuse in different settings, such as pharmacies/communities or hospitals, will also not necessarily be the same. Thus, this needs to be considered when comparing the results of different antimicrobial stewardship interventions. It is possible that



antimicrobial stewardship interventions may result in negative health outcomes. It is difficult to account for these negative health outcomes without using DALY and QALYs within a cost-effectiveness analysis. They would not be captured by a cost per prescription averted, which has been used in our current cost analysis. However, economic evaluations using this as a shared measure of outcome will be useful in guiding investment resources, even if comparison with other health interventions is not clear.

#### **6.1.4 Acceptance of CRP POC testing among HCWs and patients/relatives**

By discussing with HCWs and patients or their legal guardians who experienced the additional diagnostic support of CRP POC testing in making treatment decision and consultation, we were able to understand their perceptions towards the test and how these affect subsequent HCW prescription practices, patient adherence and behaviour. This knowledge is vital in improving the uptake of POC CRP at large scale in Vietnam as well as similar contexts in other LMICs.

Both patients and HCWs showed positive attitudes towards CRP POC, similar to findings in high-income settings (230, 275). However, there was still poor adherence to CRP test results indicates that overcoming the habit of treating even mild respiratory symptoms with antimicrobials among HCWs or self-medication with antimicrobials among patients/relatives is the main challenge. Previous studies have used educational approaches with success to improve awareness among HCWs and reduce inappropriate antimicrobial prescribing (151, 289, 290).

Besides identified knowledge and awareness related barriers that could be addressed by educational approaches (151), there was also a financial obstacle that needs to be overcome. It was stated that there was pressure to get rid of antimicrobial stocks for insurance reimbursement. Findings from Europe suggest that a reimbursement program where payment is only made when the tests are performed according to guidelines. Similar pay for

performance mechanisms for antimicrobials prescribing could also be applied to address financial incentives (250). Since the intervention will be further evaluated for use in the private sector (pharmacies, drug outlets) where many ARI patients seek care, the considerations of the pharmacies and customers regarding what costs of a CRP rapid test is acceptable for stocking, selling and purchasing them to guide treatment recommendation need to be discussed.

## **6.2 Implications for practice and policy**

In 2015 a global action plan on antimicrobial resistance was issued by WHO that emphasises the need for more evidence to develop effective policy interventions in the struggle against the global problem of antimicrobial resistance, especially in LMICs (286). Along with surveillance and infection control, responsible use of antimicrobials is considered to be the most effective policy area within and between nations with different income levels (8).

While investigations of new biomarkers and diagnostic tests to further improve antimicrobial targeting in ARI continue, this study confirms that use of commercially available CRP tests can be an effective, scalable and economically viable approach, even in highly resource constrained settings. Without proper resources, adoption of the POC test in primary settings is impossible even in high-income countries (250). Encouraging such an approach with support of global financing mechanisms can ensure that such policies are implemented in low and middle income countries, which often face more tangible causes of morbidity and mortality than the insidious, global public health threat posed by antimicrobial resistance (291).

## **6.3 Future research recommendations**

Besides biomarkers such as CRP and procalcitonin, other diagnostic indicators such as 2-transcript host RNA signatures were shown to be useful in distinguishing bacterial from

viral infection in febrile children, though further investigations of this test in different populations and clinical settings are needed (146). Currently, the Longitude prize offers an awards of £10 million for the development of a toolkit for overall antimicrobial stewardship, in particular a cost-effective, accurate, rapid and easy-to-use POC test kit for bacterial infections to support a long-term path in smarter antimicrobial use, indicate a tremendous effort is being put into this approach to combat antimicrobial resistance (59). In line with the international and national current efforts, and based on the results of this thesis, we propose the recommendations and future work as follows:

1. Findings from our trial showed that the large heterogeneity of the effect across studied sites is likely attributable to different adherence to the algorithm. Evidence from previous cluster RCT studies in the primary care settings of six European countries indicated that the combined intervention of the CRP POC test and enhanced communication skills were associated with the largest reduction in prescribing rates (151). Therefore, investigating this combination in both primary healthcare stations and drug stores in a cluster RCT design is being considered to gain optimal impact on reducing community antimicrobial consumption.
2. A full economic evaluation of the trial, that also takes into account the potential cost, health benefit and negative health outcomes associated with CRP testing by using DALY or QALYs within a cost-effectiveness analysis is needed to more accurately quantify the economic benefits of the intervention in resource constrained settings. Future trials under consideration will include this.
3. Rapid detection of pathogens by detection of pathogen RNA/DNA enables appropriate antimicrobial therapy prescription, and is currently being investigated (292). A diagnostic strategy that includes sensitive biomarkers and pathogen-specific tests needs to be further investigated for improving antimicrobial use management.

4. Since financial incentives play an important role in current antimicrobial dispensing practices in the community, using pay for performance (P4P) incentives could be a prospective intervention to evaluate. Lessons can be learnt from the association of facility-based incentives coupled with training and improvement in treatment of non-malarial fevers in Kenya (293) and the Antimicrobials Smart Use (ASU) programme where a P4P model was integrated in a multifaceted intervention and was associated with promoting rational use of medicines in Thailand (294).
5. To date, there is limited evidence of over-the-counter medicines such as non-steroidal anti-inflammatory drugs or cough preparations in reducing symptoms of ARIs (295, 296). In the context of high prevalence of self-treatment with antimicrobials, investigation of effectiveness and safety of alternative over the counter medications for self-limiting infections is further needed.

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## **Appendix A**

### **Questionnaires - Pharmacy study**

**Antibiotic sales in public and private pharmacies in rural and urban Vietnam:  
an observational study**

**Investigators:**

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**Appendix A1 Pharmacy observation form**

**Q1.** Pharmacy’s Code \_\_\_\_\_

**Q2.** Opening times (24 h clock)

	Monday	Tuesday	Wed	Thurs	Fri	Sat	Sun
From							
To							

**Q3.** Estimated average number of customers per day: \_\_\_\_

**Q4.** Does pharmacy have GPP certificate:            yes                                   not yet

**Q5.** Pharmacy’s owner is a:                                  Pharmacist                                       License renter  

**Q6.** Pharmaceutical background of pharmacy owner [mark highest level attained]

Pharmacist (Pharmacy degree)

Assistant pharmacist (college pharmacy degree)

Elementary pharmacists (six month course)

High school

Primary school

Other \_\_\_\_\_

**Q7.** Pharmaceutical background sellers. Total number: \_\_\_\_\_

Background:    Assessable (number)

Pharmacist and higher    \_\_\_\_\_

Assistant pharmacist    \_\_\_\_\_

Elementary pharmacist    \_\_\_\_\_

High school \_\_\_\_\_

Primary \_\_\_\_\_

Other \_\_\_\_\_

**Q8.** Is there a drug manual present (e.g. MIMS, Vidal, other)?

Yes  1. \_\_\_\_\_ (EN/VN) Publ Year \_\_\_\_\_  
2. \_\_\_\_\_ (EN/VN) Publ Year \_\_\_\_\_  
3. \_\_\_\_\_ (EN/VN) Publ Year \_\_\_\_\_

No

**Q9.** Is there a therapy guide or tool available for drug sellers that will help to decide what drug to give based on symptoms?

Yes  Specify \_\_\_\_\_

No

**Q10.** Have you seen these manuals or tools being used during observation?

Frequently

Occasionally

Rarely

Never

**Q11.** Inventory drugs pharmacy:

Generic Name	Brand name	Unit	Dose per unit	Selling Price per unit	Purchase Price per unit
antibiotic					



**A2. Transaction observation form**

Observation date \_\_\_/\_\_\_/2010 Day 1 / 2 / 3 Time \_\_\_:\_\_\_ (24h clock)

Observer name \_\_\_\_\_ Pharmacy's Code \_\_\_\_\_

Customer number (sequential order) \_\_\_\_\_

**Q1.** Gender Male  Female

**Q2.** Estimated age: 10-15  16-25  26-40  41-60  >60

**Q3.** Visit for: self  other person  If other child  adult

**Q4.** Reason for visit [check all that apply]:

- I A00-B99 Infectious and parasitic diseases
- Upper respiratory tract infection
- Lower respiratory tract infection
- Diarrhoea
- Intestinal worms
- Ear infection
- Eye infection
- GU infection
- Skin infection
- Other infection: \_\_\_\_\_
- II C00-D48 Neoplasms
- III D50-D89 Diseases of blood(forming organs), immune system
- IV E00-E90 Endocrine, nutritional and metabolic diseases
- V F00-F99 Mental and behavioural disorders
- VI G00-G99 Diseases of the nervous system

- VII H00-H59 Diseases of the eye and adnexa
- VIII H60-H95 Diseases of the ear and mastoid process
- IX I00-I99 Diseases of the circulatory system
- X J00-J99 Diseases of the respiratory system
- XI K00-K93 Diseases of the digestive system
- XII L00-L99 Diseases of the skin and subcutaneous tissue
- XIII M00-M99 Diseases of the musculoskeletal system and connective tissue
- XIV N00-N99 Diseases of the genitourinary system
- XV O00-O99 Pregnancy, childbirth and the puerperium

Q5. Does customer bring a prescription?      Yes                                          No   

Q6. If prescription available, are drugs sold according to prescription?  
Yes                                          No    , because \_\_\_\_\_

Q7. Who made final choice of drugs in case no prescription:  
Customer requested                                          Seller recommended

Q8. List of sold drugs

No	Name	Unit (tablet, solution, injection, suppository	Dose per unit	Number of units sold	Price per unit	Total money

**Appendix A3 Questionnaire for owners and drug sellers**

Interview date \_\_ / \_\_ / \_\_\_\_

Interviewer's Name \_\_\_\_\_

**Q1.** Pharmacy Code \_\_\_\_\_

**Q2.** Interviewee      pharmacist       owner       seller

**Q3.** Age \_\_\_\_\_

**Q4.** Gender               Male       Female

**Q5.** How many different generic drugs do you sell in your pharmacy?

1       2       3       other, specify \_\_\_\_\_

**Q6.** Which type of drug do you sell most? VIDAL / IMS categories (one option only, and write down the subcategory for type chosen)

- |  |   |
|--|---|
| <input type="checkbox"/> Gastro-intestinal/hepatobiliary | <input type="checkbox"/> Hematopoietic                |
| <input type="checkbox"/> Respiratory                     | <input type="checkbox"/> Neuro-muscular system        |
| <input type="checkbox"/> Hormones                        | <input type="checkbox"/> Contraceptives               |
| <input type="checkbox"/> Antibiotic                      | <input type="checkbox"/> Other chemotherapeutics      |
| <input type="checkbox"/> Genito-urinary system           | <input type="checkbox"/> Endocrine / metabolic system |
| <input type="checkbox"/> Vitamins / minerals             | <input type="checkbox"/> Nutrition                    |
| <input type="checkbox"/> Eye/Ear, mouth, throat          | <input type="checkbox"/> Dermatological / skin        |
| <input type="checkbox"/> Anesthetic local / general      | <input type="checkbox"/> Allergy / immune system      |
| <input type="checkbox"/> Antidotes, detoxifying          | <input type="checkbox"/> Intravenous solutions        |
| <input type="checkbox"/> Other _____                     | <input type="checkbox"/> No answer                    |

**Q7.** Do you regularly co-sell drugs with antibiotics?

1.  Yes, I co-sell with (more than one answer allowed): .....
2.  No

**Q8.** Who supplies antibiotics to your pharmacy and/or where do you buy? (more than one answer allowed)

**Q9.** Domestic antibiotics from .....

Foreign antibiotics from.....

**Q10.** Which type of drug brings the highest profit for your pharmacy? (one option only, and write down the subcategory for type chosen)  gastro-intestinal/hepatobiliary

Hematopoietic

Respiratory

Neuro-muscular system

Hormones

Contraceptives

Kháng sinh

Other Chemotherapeutics

Genito-urinary system

Endocrine / metabolic system

Vitamins / minerals

Nutrition

Eye/Ear, mouth, throat

Dermatological / skin

Anesthetic local / general

Allergy / immune system

Antidotes, detoxifying

Intravenous solutions

Other \_\_\_\_\_

No answer

**Q11.** From your total profit, what is the contribution of antibiotic sales? (one option only)

1.  <20%

5.  >80%

2.  >20%-40%

6.  Don't know

3.  >40%-60%

7.  No answer

4.  >60%-80%

**Q12.** Which Antibiotic brings more profit to your total profit? (1 option only)

Domestic

Don't know

Imported

No answer

Same

**Q13.** What type of antibiotic do you sell most? (1 option only).  Domestic

Imported

Same

Don't know

No answer

**Q14.** Do you use information on antibiotic resistance to guide your antibiotic dispensing practices?

- Yes  Don't know  
 No  No answer

**Q15.** Do you have promotional agreements with any pharmaceutical companies / distributors to sell foreign branded antibiotics?

- Yes  Don't know  
 No  No answer

**Q16.** Do you have promotional agreements with any pharmaceutical companies / distributors to sell domestic antibiotics?

- Yes  Don't know  
 No  No answer

**Q17.** Do you have promotional agreements with any health workers to prescribe specific drugs?

- Yes  No  Don't know  No answer

**Q18.** Which of the following do you think are important causes for inappropriate AB selling in your region? State if you strongly disagree, disagree, agree, strongly agree or if you are neutral by circling.

1. There is too much pressure from patients that demand antibiotic  
 strongly disagree –  disagree –  neutral –  agree –  strongly agree  
 Don't know  Refused to answer
2. If I did not sell antibiotics without prescription I would lose many customers.  
 strongly disagree –  disagree –  neutral –  agree –  strongly agree  
 Don't know  Refused to answer
3. Pharmacy quality standards are low and current GPP policy is a good policy.  
 strongly disagree –  disagree –  neutral –  agree –  strongly agree  
 Don't know  Refused to answer
4. Antibiotics should only be sold with a prescription

strongly disagree –  disagree –  neutral –  agree –  strongly agree  
 Don't know  Refused to answer

5. Antibiotic resistance is an important health problem in Vietnam.

strongly disagree –  disagree –  neutral –  agree –  strongly agree  
 Don't know  Refused to answer

6. Over-use of antibiotics contributes to antibiotic resistance.

strongly disagree –  disagree –  neutral –  agree –  strongly agree  
 Don't know  Refused to answer

7. Doctors do not prescribe appropriately

strongly disagree –  disagree –  neutral –  agree –  strongly agree  
 Don't know  Refused to answer

8. Knowledge seller insufficient to do appropriately

strongly disagree –  disagree –  neutral –  agree –  strongly agree  
 Don't know  Refused to answer

9. Pharmaceutical companies and distributors promote selling antibiotics.

strongly disagree –  disagree –  neutral –  agree –  strongly agree  
 Don't know  Refused to answer

10. Antibiotic sales are too profitable, I cannot stop otherwise I will lose too much income.

strongly disagree –  disagree –  neutral –  agree –  strongly agree  
 Don't know  Refused to answer

11. Other.....

strongly disagree –  disagree –  neutral –  agree –  strongly agree  
 Don't know  Refused to answer

12. Antibiotics are sold appropriately in Vietnam and we should not change the way we work.

strongly disagree –  disagree –  neutral –  agree –  strongly agree  
 Don't know  Refused to answer

### **Appendix A3 Focus Group Discussion**

- 1) Financial incentives (touch on themes below)
  - a) The importance of Ab sales in comparison with other drugs for profit?
  - b) What factors affect the sale of antibiotics? Can we change these factors or not?
  - c) What is the role of the pharmaceutical industry and distributor?
  - d) What is the role of the doctor?
  - e) Role of patient/customer? What type of patient demands antibiotic without prescription and is this common?
  - f) Why are antibiotics still sold even if there is no prescription?
  - g) If customer request antibiotics in unnecessary cases, would you sell or not? Why?
- 2) Knowledge and government regulation
  - a) Is there enough attention to antibiotics and resistance in training curriculum of pharmacists/sellers?
  - b) What about knowledge patient? If better knowledge, will there be less pressure to give them antibiotics?
  - c) Do you use guides in pharmacy to dispense antibiotics?
  - d) Is regulation sufficient? Why?
  - e) What do you know about antibiotic resistance and the role of inappropriate antibiotic use?
  - f) Will GPP help to improve this? Why?
- 3) Solutions
  - a) What would happen if AB's sale decline due to compliance with regulations of selling drugs (antibiotics)? (e.g. sell more vitamins? Have financial problem??)

- b) Do you think a rapid blood test to determine which customers should use antibiotics is a good idea?
- c) What do we need to do to improve the situation of Abs use and resistance in Vietnam? With the role of pharmacists (or pharmacy's owners), what can you do? Role industry? Role government?
- d) GPP?



## **Appendix B**

### **CRP trial – Study protocol and case report forms**

**Efficacy of point-of-care C-reactive protein testing to reduce inappropriate use of antibiotics for acute respiratory infections in the primary health care setting of Hanoi – a randomized controlled trial**

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## **1. Background**

Around the world, bacterial pathogens are becoming ever more resistant to antibiotics. The global problem of antimicrobial resistance is particularly pressing in developing countries, where the burden of infectious disease is high and cost constrains the replacement of older antibiotics with newer, more expensive ones [1].

Vietnam already experiences high levels of antibiotic resistance in both the community and hospital setting (GARP report 2012). Development of resistance is multi-factorial but primarily it is caused by injudicious use of antibiotics in both human and animal medicine [2-4]. According to a community-based study undertaken in 1999, 78% of antibiotics were purchased in private pharmacies without a prescription. 67% of the participants consulted the pharmacist while 11% decided themselves about antibiotic use [5]. Only 27% of the pharmacy staff had correct knowledge about antibiotic use and resistance [6]. Some studies report the prevalence of “Tu Lam Bac Sy” – patients being their own doctors – to be even higher [7].

The results from this data raise concern about drugs being sold without prescription and the common practice of self-medication. Importantly, decreasing antibiotic use will limit the spread and development of antibiotic resistant bacteria. The goal is that antibiotics are used only in people with bacterial infections that can be cured by antibiotics, and not by people who will not benefit from them [8].

Inappropriate antibiotic prescribing is a particular problem for acute respiratory tract infections (ARI) presenting to primary care throughout the world and studies have shown this to be the case in Vietnam too [9]. Distinguishing serious from self-limiting ARI is a challenging task, with the primary care physician often forced to rely solely upon careful history and examination. Concern over missing a serious infection often influences an understandably cautious approach. In lower-income settings, where health infrastructure is less developed, physicians may also be concerned about patients’ ability to access healthcare if their condition deteriorates further. These factors often motivate inappropriate antibiotic use for self-limiting infections. Implementation of an objective, quantitative, affordable and practical point-of-care test (POC) to aid diagnosis is therefore an attractive prospect.

This study sets out to assess the effect of implementing a simple POC diagnostic, C-reactive protein (CRP) test, to improve rational antibiotic use in the community setting.

## **2. Rationale**

CRP, a 24kDa protein synthesized by hepatocytes, is normally present at very low serum concentrations of a few micrograms per milliliter. In the presence of infection, transcription of CRP is rapidly induced by pro-inflammatory cytokines, particularly IL-6, and serum concentration can rise 1000-fold within 24-48 hours [10]. Transcription is also rapidly switched off after the acute phase response has subsided. Acting as an opsonin, CRP flags up

pathogens and damaged host cells for phagocytosis by binding to ligands on their cell surfaces. Apart from deranged liver function, very little is thought to interfere with CRP production. These characteristics make it a good biomarker for the presence of a significant inflammatory process – a process that may benefit from antibiotic intervention.

The idea that CRP is elevated in bacterial and not viral ARI presenting to primary care has recently come under scrutiny. Whilst an elevated CRP can aid differentiation between bacterial and viral infections in intensive care units[11] the situation in primary care is not as clear-cut: rises in CRP may be influenced by other factors, for example adults vs. children[12-14] and lower respiratory tract infections (LRTI) vs. upper respiratory tract infections (URTI) [15]. In addition, the majority of studies were performed using laboratory CRP values rather than the newer POC test methodology proposed in this study.

However, in order to reduce inappropriate community antibiotic prescribing safely (the proposed aim of this study), it is more important to distinguish self-limiting from serious infections, than bacterial from viral. Many studies have shown that POC CRP tests can do this: a study in the Netherlands showed that general practitioners who used the POC CRP test prescribed fewer antibiotics (31% vs. 53%) in patients with cough, without adversely affecting patient recovery [16, 17]. A result of a POC CRP test is available within 3 minutes and studies have shown that the result can exert a strong influence on antibiotic prescribing rates in primary care [16, 18]. Given the large number of self-limiting ARI that present to primary care in Vietnam, similar results would greatly reduce the absolute number of antibiotic prescriptions and thus one of the major drivers for bacterial resistance.

A significant proportion of antibiotic overuse for community ARI in Vietnam occurs in children. A study of 100 Vietnamese children found that only 17% of those that received antibiotics had a laboratory confirmed CRP > 10mg/mL [9]. Whilst data for POC CRP testing in children in primary care are lacking, there is much evidence that POC CRP test results in children corroborate well with laboratory CRP measurements [19][20]. Hence, the effects of POC CRP testing on antibiotic prescribing rates in adults detailed above, can safely be extended to children above 5 years of age with non-severe ARI. [21] Based on a recent study, for children aged 1 to 6 years old, CRP values should be combined with fever duration to rule in or rule out bacterial infections. CRP cut-off level of 11 mg/dl or higher obtained >24h of fever corresponding with the risk of 75% of bacterial infection could be used to rule in bacterial infection. [22]

### **3. Objectives**

To assess the efficacy of CRP POC testing for patients presenting with non-severe ARI at primary healthcare centers in Vietnam in reducing inappropriate antibiotic use safely.

### **4. Study design**

Open-label 1:1 randomized controlled clinical trial of CRP POC test (Nycocard, Axis-Shield or equivalent) guided antibiotic prescription versus standard-of-care prescription without a CRP POC test result. The CRP POC tests are easy to use with time from sample collection to result of about 5-10 minutes. Patients, aged 1 to 65 years, that visit one of 10 selected primary healthcare centers in northern Vietnam, with symptoms of non-severe ARI, among them, patients aged 1 to 6 with fever duration >24h, are eligible for this study. All patients will be followed-up at 2 weeks after the initial health clinic visit with a structured telephone interview.

As participation in the study itself may raise awareness amongst the health center staff and local community, current antibiotic prescribing rates will be assessed in an observational run-in period before the intervention. Doctors will be asked to complete (CRF) record forms for patients presenting to their health center with non-severe ARI. This aims to capture current antibiotic prescribing habits before the study is launched.

Inclusion criteria:

- Patients, aged 1 to 65 years, that visit one of the 10 selected primary healthcare centers. Among them, patients aged 1 to under 6 must have fever duration >24h at the time of presentation.
- Suspected to have acute respiratory tract infection (ARI) by treating physician. Informed consent

An ARI is defined as:

First consultation for the current episode of ARI (duration less than 2 weeks) regarded by the physician to be caused by an ARI with at least 1 of following focal signs and symptoms: (1) cough, (2) rhinitis (sneezing, nasal congestion, or runny nose), (3) pharyngitis (sore throat), (4) shortness of breath, (5) wheezing, (6) chest pain, or (7) auscultation abnormalities. At least 1 of the following systemic signs and symptoms had to be present: (1) fever, (2) perspiring, (3) headache, (4) myalgia, and (5) feeling generally unwell.

Exclusion criteria:

- Severe respiratory disease as determined by treating doctor
- Any disease or symptom requiring hospital referral as determined by treating doctor
- Immunosuppressed patients (e.g. HIV, long term steroid use)
- Suspicion of tuberculosis
- Evidence of acute or chronic liver disease (e.g. hepatitis or cirrhosis due to any cause)
- Past medical history of: neoplastic disease, congestive cardiac failure, chronic obstructive pulmonary disease, insulin-dependent diabetes or renal disease

- Pregnancy
- No access to telephone
- Not able to come for follow up visit on day 4 ( $\pm 1$ ).
- Already taking antibiotics at the time of presentation
- Symptoms present for more than 2 weeks
- Meeting any of the criteria below (referral recommended)

#### *Adults*

Presence of any of the following is a sign of severe disease and an exclusion criterion: age  $> 65$ , altered mental status (Glasgow Coma Score  $< 15$ ), respiratory rate  $\geq 30$  breaths per min, systolic blood pressure  $< 90$  mmHg, diastolic blood pressure  $< 60$  mmHg, temperature  $\leq 35$  °C or  $\geq 40$ °C, pulse of  $\geq 125$ /min. These exclusion criteria are based on a modified CRB-65 system as recommended by the British Thoracic Society for severity scoring of pneumonia in primary care [23]. It has been validated as the simplest (albeit in elderly patients)[24] and most cautious[25] of primary care scoring systems and is therefore appropriate for our study.

#### *Children (Age $\geq 1$ years and $< 16$ years)*

In addition to the above criteria the following are additional exclusion criteria relevant to children (age  $\geq 1$  years and  $< 16$  years). Children are defined as  $< 16$  years old consistent with the age cut off used in Vietnam.

Tachypnea, signs of chest wall in drawing, reduced consciousness, confusion, dehydration, hypothermia, severe malnutrition, unable to feed or drink, vomiting, and convulsions.

These danger signs in children are based on the integrated management of common childhood illnesses (IMCI) of the World Health Organization (WHO, 2012). Whilst they were primarily developed for children  $\leq 5$  years of age they are included here as an extra precaution.

- Randomisation

Eligible patients are 1:1 randomised to CRP testing or control by the health station's doctor using an individual randomisation method, stratified by health station and age category (child versus adult). This SNOSE randomisation method was used successfully in a similar study in Europe[17, 26] and ensures that a patient is irrevocably allocated to one arm of the trial immediately on enrollment, i.e. the treating physician finds out which arm of the trial the patient is allocated to only after they have committed to enrolling them. The allocation is concealed by envelope.

- Intervention

For patients aged 6 to 65 years old:

- CRP levels  $\leq 20$  mg/L, a ‘wait and see’ policy (no antibiotics) is recommended
- CRP levels  $> 20$  mg/L will be treated with antibiotics as clinically indicated in consultation with existing local guidelines

For patients aged 1 to under 6 years old with fever duration  $> 24$ h:

- CRP levels  $\leq 10$  mg/L, a ‘wait and see’ policy (no antibiotics) is recommended
- CRP levels  $> 10$  mg/L, will be treated with antibiotics as clinically indicated in consultation with existing local guidelines

Doctors will be trained that adult patients with CRP levels of  $\geq 100$  mg/L and children with CRP levels of  $\geq 50$  mg/L should in principle be treated with antibiotics. All enrolled patients will be evaluated clinically at the health center on day 4 ( $\pm 1$  day) after enrollment (day 0). This in the CRP test arm will be also be retested for CRP on day 4 ( $\pm 1$  day). Clinical features and CRP levels will be interpreted as on day 0.

Patients randomized to the control arm will be treated according to routine practice and local implemented treatment guidelines. Each site will only get enough CRP tests for the intervention group and will be numbered to ensure that no CRP tests are used for control patients.

As the study progresses the treating physician may begin to recognize patterns in the presenting symptoms of patients who are later verified to have a high CRP. This may result in more appropriate prescribing of antibiotics even for the patients who are randomized to the non-CRP test arm. To counteract this two steps have been taken. Firstly, the observational run-in period before the intervention aims to capture current antibiotic prescribing habits and secondly, this has been accounted for in the sample size calculation.

## **5. Training of physicians and centers**

Training will be based on a model developed for a similar study in Maastricht, contextualized to the Vietnamese setting. Training will be both verbal and written, consisting of oral presentations and written information leaflets for the doctors and health centers to keep for future reference. All training (both written and verbal) will be carried out in Vietnamese.

Training will be carried out at a workshop in Hanoi and at on-site implementation visits at the 10 health centers. Members of the study team will conduct all training. The health centers and doctors will be given a telephone number to contact should any queries arise during the study. Doctors and centers will also be given laminated posters and desk reminders with cut-off values for the specific age groups.

Training will be conducted after the observational run-in period so that new knowledge about ARI and the role of antibiotics can be shared with them.

## **6. Study location**

Ten primary healthcare stations in northern Vietnam. The health stations will be selected within a 60 km radius of Hanoi and need to have a sufficient caseload of approximately 5 ARI cases per day and an on-call certified clinician.

## **7. Primary and secondary endpoints**

Primary endpoints: proportion of patients receiving any antibiotic within 2 weeks of study enrollment.

Secondary endpoints: treatment cost on Day 0 and at 14 days, duration of symptoms (fever, any respiratory symptom), proportion of patients with an immediate versus subsequent prescription within 2 weeks, frequency of re-consultation, source of any subsequent antibiotic (self-medication vs. pharmacist vs. doctor vs. other), serious adverse events (admission to hospital or death), presence of antibiotics in urine on day 4 ( $\pm 1$  day). Furthermore we will assess the number of patients that needed their clinical management changed based on evaluation on the second visit. The attitudes and satisfaction of patients and health center staff towards the POC test.

## **8. Sample size calculation**

In general, we expect CRP-guidance to reduce antibiotics prescription for ARI by at least 20%: from 80% to 60%. However, it may be that the participation of the health station in a randomized trial and the overall awareness in the community due to the study by themselves bring antibiotics prescriptions down and hence reduce the CRP effect. Therefore, the trial is powered to detect a reduction of the antibiotics prescription rate from 70% to 60%. To detect such a difference in an individual randomized trial with 90% power and two-sided 5% significance level, a total of 477 patients are required per arm.

As community health stations may vary regarding quality, urban versus rural and patient caseload, and we want to analyze both adults and children, we will enroll 2000 patients (two strata: 50% children and 50% adults); i.e. 200 per health station. This sample size will allow us to robustly assess the CRP effect in both the subgroups of children and adults separately and to assess potential differential CRP effects in these subgroups.

In addition, with 1000 patients per stratum (child – adult), we will have sufficient power to show whether the duration of symptoms is similar in the two arms (CRP test versus no CRP test), i.e. that the intervention is safe: if CRP-guidance truly doesn't result in a longer durations of symptoms and the (between-patient) standard deviation of the duration of symptoms is 4 days, the 95% confidence interval for the difference in the duration of symptoms between the two arms for each stratum will exclude differences of  $>0.7$  day in favor of the control arm with 80% power.

## **9. Definitions**

- Acute respiratory infection

A first consultation for a current episode of ARI (duration less than 2 weeks) regarded by the physician to be caused by an ARI with at least 1 of following focal signs and symptoms: (1) cough, (2) rhinitis (sneezing, nasal congestion or runny nose), (3) pharyngitis (sore throat), (4) shortness of breath, (5) wheezing, (6) chest pain, or (7) auscultation abnormalities. At least 1 of the following systemic signs and symptoms had to be present: (1) fever, (2) perspiring, (3) headache, (4) myalgia, and (5) feeling generally unwell.

- Severe ARI

Presence of any of the following is a sign of severe disease and an exclusion criterion for adults: age > 65 years, altered mental status (Glasgow Coma Score < 15), respiratory rate  $\geq 30$  breaths per min, systolic blood pressure < 90 mmHg, diastolic blood pressure < 60 mmHg, temperature  $\leq 35$  °C or  $\geq 40$ °C, and pulse of  $\geq 125$ /min. These exclusion criteria in adults are based on a modified CRB-65 system.

- Danger signs in children

Tachypnea, signs of chest wall indrawing, reduced consciousness, confusion, dehydration, hypothermia, severe malnutrition, unable to feed or drink, vomiting, and convulsions.

These danger signs in children are based on the integrated management of common childhood illnesses (IMCI) of the World Health Organization (WHO, 2012). Whilst they were primarily developed for children  $\leq 5$  years of age they are included here as an extra precaution.

## **10. Patient enrolment & consent**

Patients with non-severe ARI presenting at participating primary healthcare centers will be approached and informed about the study and asked if they would like to learn more about what the study involves. If so, a health station nurse will assist the health station study doctor in obtaining consent by describing the study, answering relevant questions and referring any clinical queries to the study doctors.

A study team doctor will take the consent by ensuring the participant has understood all aspects of the study and signs an informed consent form. Patients who are illiterate will have a witness present while the consent form is read to them and while their questions are answered. The witness will confirm this procedure by signing the consent form.

Once consent is obtained a CRF will be completed for each patient containing all the information related to the study variables. The patient will be randomly and irrevocably assigned to one arm of the study immediately at enrollment. Each patient will be assigned a



study number which will increase sequentially e.g. 0111, 0112, 0113 etc. These numbers will be used on all labels, data collection sheets and the database in order to protect the patient's identity. The study number is made up of a health center code (0 to 9 relating to the different health centers), age stratum (1 for child and 2 for adult), study code (corresponding to one of the two interventions: to test, 1, or not to test CRP, 2) and patient code (relating to the order of patient recruitment, 1 to 200 at each health center)

## **11. Study procedures**

- Enrollment

Eligible subjects will be approached for consent to participate in the study. The consent form will be in Vietnamese and patients/their relatives will be explained all of the study procedures, tests, risks, benefits and other details of the informed consent form. All questions asked by the patient or relative will be answered until the study staff is sure that all aspects of the study are understood. After that, they will be asked to sign the consent form if they agree to participate.

- Randomisation

Before randomisation, patients will receive a brief medical examination to verify absence of exclusion criteria. In case no exclusion criteria are present the patient will be individually randomized as detailed above.

- Enrollment Case Record Forms

Interview and clinical examination will be done on the day 0, and a telephone interview on day 14 (+1 day) for all study participants. Participants in CRP test arm will be evaluated again on day 4 ( $\pm$  1 day) (depending on their availability and weekend) by clinical examination and 2nd CRP test. A telephone number needs to be provided and the documentation will therefore not be anonymous until end of follow up. Patients will be asked about costs relating to ARI treatment on Day 0 and at Day 14.

- Assessments

All patients will receive a routine medical history and examination as part of the enrollment process, consisting minimally of: medical history (including duration of symptoms, fever, cough, dyspnea, throat ache), mental status (Glasgow coma score), hydration status, blood pressure, pulse, respiratory rate, temperature (ear thermometer), Ear-nose-throat (ENT) examination and lung auscultation. Depending on presenting symptoms and underlying illness further examinations are performed at the discretion of the treating physician.

For those in the CRP test arm, a finger prick to collect capillary blood will be performed and analyzed using the Nycocard analyzer (Axis Shield, Norway or equivalent) on day 0 and day

4 ( $\pm$  1 day). Those in the control arm will receive treatment according to local guidelines, which is generally ampicillin or oral 2nd generation cephalosporins for non-severe ARI and will be re-evaluated on day 4 ( $\pm$  1 day).

Patients in the CRP test arm will receive treatment that is guided by the CRP level and clinical symptoms on day 0 and day 4 ( $\pm$  1 day). The treating physician will decide based on his/her clinical evaluation whether or not to comply with the guidance below (provided at the training sessions).

For patients aged 6 to 65 years old:

- CRP levels  $\leq$ 20 mg/L, a 'wait and see' policy (no antibiotics) is recommended;
- CRP levels  $>$ 20 mg/L will be treated with antibiotics as clinically indicated in consultation with existing local guidelines

For patients aged 1 to under 6 years old with fever duration  $>$ 24h:

- CRP levels  $\leq$ 10 mg/L, a 'wait and see' policy (no antibiotics) is recommended ;
- CRP levels  $>$ 10 mg/L, will be treated with antibiotics as clinically indicated in consultation with existing local guidelines
- Doctors will be trained that adults with CRP  $\geq$  100 mg/L and children with a CRP  $\geq$  50 mg/L should generally be treated with antibiotics. Referral to a hospital for further diagnosis needs to be considered for these cases.

Immediate antibiotic prescribing rates and type of antibiotic at the initial primary healthcare center visit will be recorded for both arms.

On the follow up visit on day 4 ( $\pm$  1 day), urines will be collected from all enrolled patients and checked for presence antibiotics using a bio-assay. All these samples will be stored up to 5 years after study completed. Antibiotic use will be assessed by interviewing the caretaker and checking the diary. For children that cannot urinate on command, special urine collection bags will be provided.

After 2 weeks, enrolled patients will be assessed by telephone and receive an interview to assess; whether they have been to any health clinic since the last health station visit; subsequent medication use for the same ARI; source of medication; serious adverse events (e.g. admission to hospital); and duration of ARI symptoms. The attitudes and satisfaction of patients and health center staff towards the test will also be assessed.

The patient will be given a simple symptom diary as a memory aid, to reduce recall bias at the follow-up telephone call. They will also be educated with regards the following alarm symptoms; breathlessness on minimal exertion; severe coughing interfering with breathing;

seizures or fits; coughing up blood; confusion; and loss of consciousness. They will be given a telephone number they can ring if they are concerned.

The 14-day (+1 day) telephone interviewer will be blinded for the intervention. However, the information regarding the intervention may be revealed by information provided by the patient or his/her legal guardians. The interviewer will be trained to assess in a non-biased way. No one in the study team has a conflict of interest in the favor of the CRP POC test. In case of persistent symptoms or progression, the patient is recommended to seek medical attention.

## **12. Data management**

- Data entry

All clinical information will be recorded or placed in the patient's notes, in keeping with local practice. Relevant data will be recorded onto a CRF and checked for accuracy before single data entry onto an electronic database (CLIRES). Internal checks of the entered data will be done to look for outliers and errors. After the follow up is finished the CRFs will be anonymized by removing patient identifiers and telephone numbers. Data entry will therefore be anonymous.

- Data analysis

Analysis of the primary endpoint and the total probability of an antibiotics prescription:

The primary endpoint of this trial is the proportion of any antibiotic prescriptions within 2 weeks of randomisation between the two arms. The primary comparison between the treatment arms will be a logistic regression with the treatment assignment, and the age stratum (children vs. adults) as fixed effects and the healthcare center as a random effect. P values (2 sided) below 0.05 are considered significant. A two-sided 95% confidence interval (CI) for the odds ratio of receiving antibiotics prescription rate (primary endpoint) will be calculated.

The primary endpoint (total proportion of patients with any antibiotic prescriptions within 14 days, both immediate and subsequent) will also be investigated in subgroups to assess whether the reduction in antibiotics prescribing is homogeneous across subgroups. Specifically, intervention effects and appropriate interaction tests for heterogeneity will be calculated in the following pre-defined subgroups:

- Age stratum (adults vs. children)
- Healthcare center
- Febrile versus non-febrile patients

Additionally, we will compare the proportion of ‘intervention failures’ in both treatment arms, i.e. the proportion of patients without initial antibiotics prescriptions who received antibiotics for any reason before the end of follow up.

Analysis of secondary endpoints:

The duration of symptoms will be visualized using Kaplan-Meier curves and estimates (and 95% confidence intervals) of median durations in both groups. Formal comparisons between the two treatment arms will be based on Cox proportional hazards model with the treatment assignment, and the age stratum (children vs. adults) as fixed effects and the healthcare center as a Gaussian random effect (frailty). Subgroup analyses for the same subgroup analyses as for the primary endpoint will be performed.

The proportion of patients in the CRP test arm that need adjustment of their treatment based on a change in the CRP levels and clinical evaluation on day 4 ( $\pm 1$ ) will be calculated.

The proportion of urines in which antibiotic activity has been detected by the bioassay will be compared between both groups.

The frequency of re-consultation will be compared between the two arms in the same way as the primary endpoint.

The other secondary endpoint will be summarized by using descriptive statistics.

Serious adverse events monitoring:

Data on SAEs will be sent each week to an independent study statistician who will monitor for serious adverse events (SAE): admission to hospital or death between initial consultation and follow-up telephone call, in both arms. If a total of 10 SAE are reported, an interim analysis between the two study arms will be conducted and the study team will decide whether it is safe to continue with the study in case of statistical significance. In case the study continues the next SAE interim analysis will be done after the next 10 SAEs, and so on.

### **13. Ethical considerations**

The protocol will be submitted for external peer review as well as for review by the ethical committees of the National Hospital for Tropical Diseases in Hanoi and the Oxford University Tropical Research Ethics Committee (OxTrec). Permission for this study also will be obtained from local authorities.

- Informed consent

The patients will be asked to provide informed consent to participate in the study, receive a medical examination (5 minutes) and, possibly, a capillary blood sample (2 minutes). Patients will be asked to come back on day 4 ( $\pm 1$  day) for a 2nd medical evaluation and a urine test.

Those in the CRP arm will be retested for CRP. Patients or their relatives or legal representative will be approached and told about this study. They will be informed of the aims, methods, urine storage time, possible risks and benefits of the study by a member of the research team.

If the patient is willing to join the study, he/she will sign the consent form; the same will apply to relatives or legal representative. The consent form will be countersigned by the attending doctor. A copy of the consent form will be given to the patient or his/her relative/legal representative. As this study concerns patients with non-severe ARI, and who need to be able to keep a diary, adults will be able to provide informed consent without the need of a legal representative.

- Alternatives to enrolling

If informed consent is not obtained, then the patient will not be part of this study. He/she will receive the usual care for ARIs according to implemented treatment guidelines.

- Study withdrawal

Patients or parents / guardians are free to withdraw their consent / consent for their relative at any time. Patients will still be entitled to study related benefits, as outlined in the consent form, up to the point of withdrawing their consent.

- Risks & Benefits

- Risk

Risks for participating in this study is that the medical visit will take longer than usual and mild discomfort due to the capillary blood collection. Another risk is in cases needing antibiotics and the CRP test shows a low level. However, as these are non-severe ARI, the risk of a delay in antibiotics is minimal. Patients will be informed to seek new medical consultation in case the symptoms progress or persist. They will also be provided with a study telephone number to call if they are concerned, given a patient information leaflet and educated about the following alarm symptoms; breathlessness on minimal exertion; severe coughing interfering with breathing; seizures or fits; coughing up blood; confusion; loss of consciousness.

SAE will also be monitored as detailed above to detect any difference between the intervention and control arms of the study.

- Benefits

Patients will receive a more thorough examination than usual and may receive a better diagnosis of their disease. Furthermore, through information provided by this study, patients

will be more educated in management of ARI, a common illness. Patients will receive compensation (value not exceeding 1 US dollar) as a token of appreciation for their participation and reimbursed for travel expenses, if any.

- Patient confidentiality

Patients will be assured that all information generated in this study will remain confidential. Their names will not appear in the database. Any scientific publications or reports will not identify any patient by name or initials. When the research team review the patient notes, they are also bound by professional confidentiality.

#### **14. Management of the study**

The execution of this study will be a joint effort between the Oxford University Clinical Research Unit (OUCRU) and the National Hospital for Tropical Diseases (NHTD). The investigators have overall responsibility for managing this study.

#### **15. Financing and Insurance/indemnity**

CRP test will be funded by the Oxford University Clinical Research Unit. Indemnity will be provided by the University of Oxford.

#### **16. Publications**

Data from this study will be published in peer-reviewed journals. Authorship and reporting of this work will follow international guidelines. Authors will have made a note worthy contribution to the work.

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**Appendix B1 Inclusion – Exclusion form for 1-5 years-old**

<b>Inclusion-Exclusion (1-5 years old)</b>		
Site code [ ][ ]	Screening number [ ][ ][ ][ ]	Initials [ ][ ][ ][ ][ ]
<b>Inclusion criteria</b>		
<i>Must be “Yes” for criteria from 1-4</i>		
1. Age $\geq 1$ and $\leq 5$		<input type="radio"/> Yes <input type="radio"/> No
2. Clinical examination:		
a. Suspected to have acute Respiratory tract infection		<input type="radio"/> Yes <input type="radio"/> No
b. Respiratory rate $< 40$ [ ][ ]/min		<input type="radio"/> Yes <input type="radio"/> No
c. GCS=15 (normally communicate)		<input type="radio"/> Yes <input type="radio"/> No
d. Temperature $\geq 38^{\circ}\text{C}$ [ ][ ][ ][ ] $^{\circ}\text{C}$		<input type="radio"/> Yes <input type="radio"/> No
e. Fever duration $> 24\text{h}$ [ ][ ]h		<input type="radio"/> Yes <input type="radio"/> No
3. Symptom duration $\leq 2$ weeks		<input type="radio"/> Yes <input type="radio"/> No
4. Informed consent		<input type="radio"/> Yes <input type="radio"/> No
<b>Exclusion criteria</b>		
<i>If any questions is answered “YES”, the patient is NOT eligible</i>		
5. Severe respiratory diseases		<input type="radio"/> Yes <input type="radio"/> No
6. Any disease or symptom requiring hospital referral		<input type="radio"/> Yes <input type="radio"/> No
7. Danger signs (signs of chest wall indrawing, reduced consciousness, confusion, dehydration, hypothermia, unable to feed or drink, malnutrition, vomiting and convulsions)		

	<input type="radio"/> Yes <input type="radio"/> No
8. Immunosuppressed patients (e.g. HIV, long term steroid use)	<input type="radio"/> Yes <input type="radio"/> No
9. Suspicion of TB	<input type="radio"/> Yes <input type="radio"/> No
10. Evidence of acute or chronic liver disease	<input type="radio"/> Yes <input type="radio"/> No
11. Past medical history of: neoplastic disease, congestive cardiac, failure, COPD, insulin-dependent diabetes or renal disease	<input type="radio"/> Yes <input type="radio"/> No
12. No access to telephone	<input type="radio"/> Yes <input type="radio"/> No
13. Already taking antibiotics at the time of presentation	<input type="radio"/> Yes <input type="radio"/> No
14. Can't come on day 3/4	<input type="radio"/> Yes <input type="radio"/> No
<b>Enrollment</b>	
15. Patient code	05HN-[ ][ ]-[ ][ ][ ][ ]

**Appendix B2 Inclusion-Exclusion form for 6-65 years-old**

<b>Inclusion-Exclusion (6-65 years-old)</b>		
Site code [ ][ ]	Screening number [ ][ ][ ][ ]	Initials [ ][ ][ ][ ][ ]
<b>Inclusion criteria</b>		
<i>Must be "Yes" for criteria from 1-4</i>		
16. Age $\geq 6$ and $\leq 65$		<input type="radio"/> Yes <input type="radio"/> No
17. Clinical examination		
f. Suspected to have acute Respiratory tract infection		<input type="radio"/> Yes <input type="radio"/> No
g. Respiratory rate $<30$ [ ][ ]/phút		<input type="radio"/> Yes <input type="radio"/> No
h. Heart rate $<125$ [ ][ ][ ]/phút		<input type="radio"/> Yes <input type="radio"/> No
i. GCS=15 (normally communicate)		<input type="radio"/> Yes <input type="radio"/> No
j. Systolic BP $\geq 90$ and diastolic BP $\geq 60$ (for adults only) [ ][ ][ ]/[ ][ ][ ] mmHg		<input type="radio"/> Yes <input type="radio"/> No
k. Temperature $>35^{\circ}\text{C}$ and $<40^{\circ}\text{C}$ [ ] $^{\circ}\text{C}$		<input type="radio"/> Yes <input type="radio"/> No
18. Symptom duration $\leq 2$ weeks		<input type="radio"/> Yes <input type="radio"/> No
19. Informed consent		<input type="radio"/> Yes <input type="radio"/> No
<b>Exclusion criteria</b>		
<i>If any questions is answered "YES", the patient is NOT eligible</i>		
20. Severe respiratory diseases		<input type="radio"/> Yes <input type="radio"/> No
21. Any disease or symptom requiring hospital referral		<input type="radio"/> Yes <input type="radio"/> No

22. Danger signs in children (signs of chest wall indrawing, reduced consciousness, confusion, dehydration, hypothermia, unable to feed or drink, malnutrition, vomiting and convulsions)	<input type="radio"/> Yes	<input type="radio"/> No
23. Immunosuppressed patients (e.g. HIV, long term steroid use)	<input type="radio"/> Yes	<input type="radio"/> No
24. Suspicion of TB	<input type="radio"/> Yes	<input type="radio"/> No
25. Evidence of acute or chronic liver disease	<input type="radio"/> Yes	<input type="radio"/> No
26. Past medical history of: neoplastic disease, congestive cardiac, failure, COPD, insulin-dependent diabetes or renal disease	<input type="radio"/> Yes	<input type="radio"/> No
27. Pregnancy	<input type="radio"/> Yes	<input type="radio"/> No
28. No access to telephone	<input type="radio"/> Yes	<input type="radio"/> No
29. Already taking antibiotics at the time of presentation	<input type="radio"/> Yes	<input type="radio"/> No
30. Can't come on day 3/4	<input type="radio"/> Yes	<input type="radio"/> No
<b>Enrollment</b>		
31. Patient code	05HN-[ ][ ]-[ ][ ][ ][ ]	

### Appendix B3 Examination at enrolment (Day 0)

Examination on Day 0	
Patient Code 05HN-[ ][ ]-[ ][ ][ ][ ]	Patient initials [ ][ ][ ][ ][ ]
1. Symptom	
Cough	<input type="radio"/> Yes <input type="radio"/> No
Sputum	<input type="radio"/> Yes <input type="radio"/> No
Coryza	<input type="radio"/> Yes <input type="radio"/> No
Dyspnea	<input type="radio"/> Yes <input type="radio"/> No
Wheeze	<input type="radio"/> Yes <input type="radio"/> No
Earache	<input type="radio"/> Yes <input type="radio"/> No
Chills	<input type="radio"/> Yes <input type="radio"/> No
Sore throat	<input type="radio"/> Yes <input type="radio"/> No
Fever	<input type="radio"/> Yes <input type="radio"/> No
Sweating	<input type="radio"/> Yes <input type="radio"/> No
Rigors	<input type="radio"/> Có <input type="radio"/> No
2. Duration of symptom (from the first symptom)	[ ][ ] Days
3. Vital signs	
Heart rate	[ ][ ][ ]/min
Blood pressure (for adult only)	[ ][ ][ ]/[ ][ ][ ] mmHg
Respiratory rate	[ ][ ][ ]/min
4. Respiratory Examination	

Respiratory Distress	<input type="radio"/> Yes	<input type="radio"/> No
Crepitations	<input type="radio"/> Yes	<input type="radio"/> No
Wheeze	<input type="radio"/> Yes	<input type="radio"/> No
Other	_____	
5. ENT Examination		
Throat red	<input type="radio"/> Yes	<input type="radio"/> No
Throat pus	<input type="radio"/> Yes	<input type="radio"/> No
Tympanic membrane red	<input type="radio"/> Yes	<input type="radio"/> No
Other	_____	
6. CRP test	<input type="radio"/> Yes	If Yes, answer Q.6a <input type="radio"/> No
6a. CRP value	<input type="radio"/> >200 [ ][ ][ ][ ]	<input type="radio"/> <8 mg/L
7. Antibiotics prescribed	<input type="radio"/> Yes	<input type="radio"/> No
8. Antibiotics details		
<input type="radio"/> Amoxicillin	<input type="radio"/> Ampicillin	<input type="radio"/> Azithromycin
<input type="radio"/> Cephalexin	<input type="radio"/> Cefaclor	<input type="radio"/> Cefixim
<input type="radio"/> Cefuroxime	<input type="radio"/> Clindamycin	
Other:	_____	
9. Date to come back on day 3/4 [ ][ ]/[ ][ ]/[ ][ ][ ][ ] (dd/mm/yyyy)		
10. Date for telephone follow-up [ ][ ]/[ ][ ]/[ ][ ][ ][ ] (dd/mm/yyyy)		

**Appendix B4 Examination on follow-up visit day (Day 4)**

<b>Examination on Day 4</b>	
<b>Patient Code: 05HN-[ ]-[ ]-[ ]-[ ]-[ ]</b>	<b>Patient initials: [ ]-[ ]-[ ]-[ ]</b>
1. Show up on Day 3/4	<input type="radio"/> Yes <input type="radio"/> No, reason: _____
2. Since the last visit, have you used any antibiotics	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unknown
3. Since the last visit, have you admitted to hospital	<input type="radio"/> Yes <input type="radio"/> No
4. Symptom	
Cough	<input type="radio"/> Yes <input type="radio"/> No
Sputum	<input type="radio"/> Yes <input type="radio"/> No
Coryza	<input type="radio"/> Yes <input type="radio"/> No
Dyspnea	<input type="radio"/> Yes <input type="radio"/> No
Wheeze	<input type="radio"/> Yes <input type="radio"/> No
Earache	<input type="radio"/> Yes <input type="radio"/> No
Chills	<input type="radio"/> Yes <input type="radio"/> No
Sore throat	<input type="radio"/> Yes <input type="radio"/> No
Fever	<input type="radio"/> Yes <input type="radio"/> No
Sweating	<input type="radio"/> Yes <input type="radio"/> No
Rigors	<input type="radio"/> Có <input type="radio"/> No
5. Vital signs	
Heart rate	[ ]/[ ]/min
Blood pressure	[ ]/[ ]/[ ] mmHg
Respiratory rate	[ ]/[ ]/min
6. Respiratory Examination	
Respiratory Distress	<input type="radio"/> Yes <input type="radio"/> No



Crepitations	<input type="radio"/> Yes	<input type="radio"/> No
Wheeze	<input type="radio"/> Yes	<input type="radio"/> No
Other _____		
<b>7. ENT Examination</b>		
Throat red	<input type="radio"/> Yes	<input type="radio"/> No
Throat pus	<input type="radio"/> Yes	<input type="radio"/> No
Tympanic membrane red	<input type="radio"/> Yes	<input type="radio"/> No
Other _____		
<b>8. Symptom progress</b>		
<input type="radio"/> Better		
<input type="radio"/> Not change		
<input type="radio"/> Worse		
<b>9. CRP test</b>		
	<input type="radio"/> Yes	<input type="radio"/> No
If Yes, answer Q.9a		
9a. CRP value	<input type="radio"/> >200	<input type="text" value="[_][_[_]"/> <input type="radio"/> <8 mg/L
<b>10. Antibiotics prescribed at this visit</b>		
	<input type="radio"/> Yes	<input type="radio"/> No
<b>11. Antibiotics details</b>		
<input type="radio"/> Amoxicillin <input type="radio"/> Ampicillin <input type="radio"/> Azithromycin <input type="radio"/> Cephalexin <input type="radio"/> Cefaclor <input type="radio"/> Cefixim <input type="radio"/> Cefuroxime <input type="radio"/> Clindamycin    Other _____		
<b>12. Urine sample provided</b>		
	<input type="radio"/> Yes	
	<input type="radio"/> No, reason	_____

## Appendix B5 Interview on Day 14

Interview on Day 4	
<b>Patient Code:</b> 05HN-[ ][ ]-[ ][ ][ ][ ][ ]	<b>Patient initials:</b> [ ][ ][ ][ ][ ][ ]
1. Informant	<input type="radio"/> Patient <input type="radio"/> Mother <input type="radio"/> Father <input type="radio"/> Other _____
2. Since visiting the centre 14 days ago, how long do the symptoms last (from Day 0)	[ ][ ] (days)
3. Within 14 days, did you use any antibiotics?	<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Don't know
3a. If yes, what source of antibiotics:	<input type="radio"/> Doctor <input type="radio"/> Pharmacist <input type="radio"/> Self-medication <input type="radio"/> Other, specify: _____
4. In your opinion, has the illness improved, worsened, or remained the same since you left the clinics 14 days ago?	<input type="radio"/> Recovered <input type="radio"/> Improved <input type="radio"/> Stayed the same (if yes, ask to Q9) <input type="radio"/> Worsened (if yes, ask Q9) <input type="radio"/> Not sure
5. Is there any serious adverse events (SAEs) occurred during 14 days?	<input type="radio"/> No <input type="radio"/> Yes, please specify as below <ul style="list-style-type: none"> <li>1. Hospitalisation <input type="checkbox"/></li> <li>2. Death <input type="checkbox"/></li> </ul>
5a. For any SAEs as above, please specify:	Occurred date [ ][ ]/[ ][ ]/[ ][ ][ ][ ] (dd/mm/yyyy) Reason: a. Related to current disease <input type="checkbox"/> b. Other diseases <input type="checkbox"/> specify _____ c. Other <input type="checkbox"/> specify _____
6. Patient's satisfaction score (range: 0-10):	_____

### Appendix B6 Patient contact form

Interview on Day 4	
<b>Patient Code: 05HN-[_ _]-[_ _ _ _]</b>	<b>Patient initials: [_ _ _ _]</b>
1. Informant	<input type="radio"/> Patient <input type="radio"/> Mother <input type="radio"/> Father <input type="radio"/> Other _____
2. Contact Date:	[_ _]/[_ _]/[_ _ _ _] (dd/mm/yyyy)
3. Reason for contact :	_____ _____ _____
4. Action of study team with agreement of patient	_____ _____ _____

### Appendix B7 Patient symptom diary

Patient Code: 05HN-[_ _]-[_ _ _ _]		Patient initials: [_ _ _ _]													
DAY	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Fever															
Cough															
Sputum															
Coryza															
Dyspnea															
Wheeze															
Earache															
Chills															
Sweating															
Rigors															
Sore throat															

## **Appendix C**

### **Cost survey forms – Economic Impact analysis**

#### **Economic Implications of C-Reactive Protein Point of Care Testing in the Management of Acute Respiratory Infections in the Vietnamese Primary Health Care Setting**

**Principal investigator** Yoel Lubell, Mahidol Oxford Research Unit

**Co-investigator** Heiman Wertheim, Oxford University Clinical Research Unit

Do Thi Thuy Nga, Oxford University Clinical Research Unit

### Appendix C1 Cost survey on Day 0

Cost survey on Day 0				
Patient Code: 05HN-[ ]-[ ]-[ ]-[ ]-[ ]		Patient initials: [ ]-[ ]-[ ]-[ ]		
1. Informant	<input type="radio"/> Patient	<input type="radio"/> Mother	<input type="radio"/> Father	<input type="radio"/> Other _____
PRE-CLINIC, TREATMENT & TRAVEL COST TO CLINICS (in vnd)				
2. Before coming to the clinics today, what did you do to treat this illness? (Tick all that apply)				
<input type="checkbox"/> Nothing				
<input type="checkbox"/> Went to a clinic/hospital				
<input type="checkbox"/> Got drugs from pharmacy				
<input type="checkbox"/> Other, specify _____				
3. How much have you spent in treating this illness before coming to the clinics today, including costs of any medicines and any fees charged by providers?				
Medicines fee: [ ]-[ ]-[ ]-[ ]-[ ]-[ ]-[ ]-[ ]				
Examination fee: [ ]-[ ]-[ ]-[ ]-[ ]-[ ]-[ ]-[ ]				
Diagnosis fee: [ ]-[ ]-[ ]-[ ]-[ ]-[ ]-[ ]-[ ]				
Other: [ ]-[ ]-[ ]-[ ]-[ ]-[ ]-[ ]-[ ]				
4. How much money did you spend on transport to come to the clinics today?				
[ ]-[ ]-[ ]-[ ]-[ ]-[ ]-[ ]-[ ]				
CLINICS DIAGNOSIS AND TREATMENT ON DAY 0				
5. How much have you pay for examination fee today?				
<input checked="" type="checkbox"/> Cover by HI: [ ]-[ ]-[ ]-[ ]-[ ]-[ ]-[ ]-[ ]				
<input checked="" type="checkbox"/> Self-paid: [ ]-[ ]-[ ]-[ ]-[ ]-[ ]-[ ]-[ ]				
6. Have any diagnostic tests been performed at the clinics today?				
Test	Covered by HI	Cost	Self-paid	Cost
<input checked="" type="checkbox"/> None				
<input checked="" type="checkbox"/> X-ray	<input checked="" type="checkbox"/>	[ ]-[ ]-[ ]-[ ]-[ ]-[ ]-[ ]-[ ]	<input checked="" type="checkbox"/>	[ ]-[ ]-[ ]-[ ]-[ ]-[ ]-[ ]-[ ]
<input checked="" type="checkbox"/> Blood test	<input checked="" type="checkbox"/>	[ ]-[ ]-[ ]-[ ]-[ ]-[ ]-[ ]-[ ]	<input checked="" type="checkbox"/>	[ ]-[ ]-[ ]-[ ]-[ ]-[ ]-[ ]-[ ]
<input checked="" type="checkbox"/> Endoscopy	<input checked="" type="checkbox"/>	[ ]-[ ]-[ ]-[ ]-[ ]-[ ]-[ ]-[ ]	<input checked="" type="checkbox"/>	[ ]-[ ]-[ ]-[ ]-[ ]-[ ]-[ ]-[ ]
<input checked="" type="checkbox"/> Other:	<input checked="" type="checkbox"/>	[ ]-[ ]-[ ]-[ ]-[ ]-[ ]-[ ]-[ ]	<input checked="" type="checkbox"/>	[ ]-[ ]-[ ]-[ ]-[ ]-[ ]-[ ]-[ ]

7. Have any medications have been prescribed to you today?				
	Covered by HI	Cost	Self-purchased	Cost
<input checked="" type="checkbox"/> Nothing				
<input checked="" type="checkbox"/> Antibiotics	<input checked="" type="checkbox"/>	_ _ _ - _ _ _	<input checked="" type="checkbox"/>	_ _ _ - _ _ _
<input checked="" type="checkbox"/> Cough preparations	<input checked="" type="checkbox"/>	_ _ _ - _ _ _	<input checked="" type="checkbox"/>	_ _ _ - _ _ _
<input checked="" type="checkbox"/> Fever, pain killer	<input checked="" type="checkbox"/>	_ _ _ - _ _ _	<input checked="" type="checkbox"/>	_ _ _ - _ _ _
<input checked="" type="checkbox"/> Anti-histamin	<input checked="" type="checkbox"/>	_ _ _ - _ _ _	<input checked="" type="checkbox"/>	_ _ _ - _ _ _
<input checked="" type="checkbox"/> Corticoids	<input checked="" type="checkbox"/>	_ _ _ - _ _ _	<input checked="" type="checkbox"/>	_ _ _ - _ _ _
<input checked="" type="checkbox"/> Vitamin	<input checked="" type="checkbox"/>	_ _ _ - _ _ _	<input checked="" type="checkbox"/>	_ _ _ - _ _ _
<input checked="" type="checkbox"/> Other	<input checked="" type="checkbox"/>	_ _ _ - _ _ _	<input checked="" type="checkbox"/>	_ _ _ - _ _ _

## Appendix C2 Cost survey on Day 14

Cost survey on Day 14	
Patient Code: 05HN-[ ]-[ ]-[ ]-[ ]-[ ]	Patient initials: [ ]-[ ]-[ ]-[ ]
1. Informant	<input type="radio"/> Patient <input type="radio"/> Mother <input type="radio"/> Father <input type="radio"/> Other _____
<b>TREATMENT AND COURSE OF ILLNESS SINCE DAY 0 (in vnd)</b>	
2. Since leaving the health centre 14 days ago, what have you done to treat this illness, and how much have you spent including 2 <sup>nd</sup> visit?	
<input checked="" type="checkbox"/> Nothing <input checked="" type="checkbox"/> Went for 2nd study visit <input checked="" type="checkbox"/> Went to drug store <input checked="" type="checkbox"/> Returned to this clinics (except 2nd <input checked="" type="checkbox"/> Went to another clinics <input checked="" type="checkbox"/> Went to hospital <input checked="" type="checkbox"/> Hospital admission <input checked="" type="checkbox"/> Consulted traditional healer <input checked="" type="checkbox"/> Other, specify _____	
3. For each option about, please specify the cost for	
Transportation fee:	[ ]-[ ]-[ ]-[ ]-[ ]-[ ]
Examination fee:	[ ]-[ ]-[ ]-[ ]-[ ]-[ ]
Diagnosis fee:	[ ]-[ ]-[ ]-[ ]-[ ]-[ ]
Medicine fee:	[ ]-[ ]-[ ]-[ ]-[ ]-[ ]
Other:	[ ]-[ ]-[ ]-[ ]-[ ]-[ ]
4. Since leaving the health centre 14 days ago, what kind of medications you had to buy for this illness, and how much did they cost?	
	Cost (vnd)
<input checked="" type="checkbox"/> Nothing	
<input checked="" type="checkbox"/> Antibiotics	[ ]-[ ]-[ ]-[ ]-[ ]-[ ]
<input checked="" type="checkbox"/> Cough preparations	[ ]-[ ]-[ ]-[ ]-[ ]-[ ]
<input checked="" type="checkbox"/> Fever, pain killer	[ ]-[ ]-[ ]-[ ]-[ ]-[ ]
<input checked="" type="checkbox"/> Vitamin	[ ]-[ ]-[ ]-[ ]-[ ]-[ ]

## **Appendix D**

### **NATIONAL ACTION PLAN ON COMBATTING DRUG RESISTANCE**

**in the period from 2013 - 2020**

(Approved with the Decision No. 2174/QD-BYT

dated 21st June 2013 of the Minister of Health)



**Part one**  
**RATIONAL**

**BACKGROUND**

Since the discovery of penicillin antibiotics, hundreds of antibiotics and similar drugs have been invented and used. The discovery of antibiotics marked a new era of medicine development for the treatment of bacterial infections.

In addition to the role of medicine known to man, anti-bacterial drugs have been widely used in livestock, poultry, aquaculture and cultivation for the treatment, prevention and control of animal diseases, as well as for production purposes. As a result of continuous exposure to antimicrobial drugs, the proportion of drug-resistant bacteria in the feces of these animals is relatively high.

Antibiotics are of great benefit in the treatment and care of patients and the veterinary if they are prescribed and used properly. However, that these drugs have been widely used, prolonged and abused would make microbes adaptable to drugs, enabling many bacteria to become resistant and as a result, the drugs are becoming less effective or ineffective. Drug resistance is not only a concern of clinicians in the treatment but also the concern of the whole society for public health.

Drug resistance (AMR) is a condition of microorganisms (such as bacteria, viruses, fungi and parasites) are resistant to the antibiotics which used to be susceptible to microorganisms. Resistant organisms (bacteria, viruses, parasites) that can withstand the attack of anti-bacterial drugs (such as antibiotics, antiviral, anti-malarial drugs), therefore, the application of methods, specific therapy, drugs becomes ineffective, the infection will be prolonged (even fatal) and can spread to others. AMR is the corollary of the process of drug use in the treatment and particularly becomes more serious where abuse of antibiotics is increasingly more common. Bacteria resistant to most antibiotics have appeared in the world, also called XDR bacteria.

In Vietnam, most of the examination and treatment facilities are facing with of spread of bacteria resistant to many antibiotics. The level and speed of drug resistance are increasing, at alarming level. The burden of drug resistance is increasing due to the increasing cost of treatment, prolonged treatment,. That will affect patients' health, community and social development. In the future, many nations will be able to face the possibility of having no effective drugs to treat infectious diseases if they do not make appropriate interventions.

Currently, drug resistance is not a new issue, but it has become dangerous and urgent, requiring the comprehensive effort to help the humankind avoid the risk of returning to the era without antibiotics. The World Health Organization (WHO) said that we live in the era dependent on antibiotic and requires global responsibility to protect valuable source of antibiotics for the next generation.

On the World Health Day 2011, WHO chosen the drug resistance prevention slogan “No action today, no cure tomorrow” and urged the nation to have timely plan to deal with drug resistance.

Hence, it is essential for Vietnam to build a comprehensive, overall, long-term Plan for the prevention of drug resistance in the current period.

## **I. PRACTICAL BASIS**

### **1. Status of drug resistance**

#### **1.1. Drug resistance in the world**

The problem of drug resistance has become alarming around the world, especially the developing countries. The burden of the cost for treating infectious diseases is relatively large due to the replacement of older antibiotics with new expensive antibiotics.

In 2011, drug-resistant TB situation was happening in most countries. There are about 640,000 cases of multidrug-resistant tuberculosis (MDR - TB) worldwide, about 9% of which is XDR - TB [1].

Falciparum malaria parasites resistant to artemisinin is emerging in Southeast Asia. Resistance to anti-malarial drugs of previous generation such as chloroquine and sulfadoxine-pyrimethamine is widespread in most endemic countries [2].

The global approach to antiretroviral drugs to treat HIV patients increases the risk of drug resistance. The resistance of the virus to drugs is a threat to humanity. Approximately 15% of patients treated have resorted to second and tertiary drug regimen. The cost of this drug is 100 times higher than primary regimen. The increasing resistance of HIV poses a challenge to maintain global outreach programs in low-income countries. These countries need to strengthen health services and improve the quality of care for people with HIV to minimize the spread of resistant viruses.

Data of ANSORP monitoring studies from 1/2000 to 6/2001 of 14 centers from 11 countries in Southeast Asia shows the high proportion of resistance of bacteria *S. pneumoniae*. 483 of the 685 strains of *S. pneumoniae* isolated from patients (52.4%) are not susceptible to penicillin, 23% at intermediate level and 29.4% resistant to penicillin (MIC  $\geq$  2 mg/l). Results of bacterial isolation showed the highest rate of resistance to penicillin in Vietnam (71.4%), followed by South Korea (54.8%), Hong Kong (43.2%) and Taiwan (38.6 %). Erythromycin resistance rate is also very high in Vietnam 92.1%, Taiwan 86%, South Korea 80.6%, and Hong Kong 76.8% and China 73.9%. Data from multicenter surveillance studies clearly demonstrated the speed and resistance rate of *S. pneumoniae* in Asian countries, where the most incidence of diseases in the world [3].

According to data from the 2005-2007 KONSAR study in South Korea hospitals showed that Methicillin-resistant *S. aureus* (MRSA) was 64%; *K. pneumoniae* resistant to third-generation cephalosporins was 29%; *E. coli* resistant to fluoroquinolone 27%, *P. aeruginosa* resistance 33%, *Acinetobacter* spp. resistance 48%, *P. aeruginosa* resistant to amikacin 19%, *Acinetobacter* spp. resistance 37%. vancomycin-resistant *E. faecium* and imipenem-resistant *Acinetobacter* spp. is increasing. Resistance rate detected in the laboratory of *E. coli* and *K. pneumoniae* to third-generation cephalosporins and *P. aeruginosa* to imipenem is higher in hospitals [4].

Antibiotics effectively treated for *Shigella* dysentery were previously resistant, so WHO is currently recommending ciprofloxacin. However, the rate of ciprofloxacin resistance increasing rapidly reduces both the safety and effectiveness of treatment, especially for children.

AMR has become a serious problem in the treatment of gonorrhoea (caused by *N. gonorrhoeae*), even related to the oral cephalosporin (final treatment remedy) and is increasing worldwide. That Gonococcal infections can not be treated will lead to increasing morbidity and mortality, thus reversing the gains made in the program to control the sexually transmitted diseases. The control of these diseases has been badly affected by the development and spread of drug resistance.

New resistance mechanism such as beta-lactamase NDM-1 has emerged among gram-negative bacilli. This may invalidate the result of strong antibiotics - usually only final prescription against multidrug-resistant strains of bacteria.

## **1.2. Situation of antibiotic use and resistance in Vietnam**

### **1.2.1. Antibiotic use in community:**

According to the survey results of the antibiotics sold in pharmacies in urban and rural areas of Northern provinces showed poor awareness of antibiotics and antibiotic resistance of the people and drug sellers, particularly in rural areas. Among the total 2,953 pharmacies under investigation: 499/2,083 pharmacies in urban areas (accounting for 24%) and 257/870 pharmacies in rural areas (accounting for 29.5%) sold antibiotics prescribed. Antibiotics accounted for 13.4% (urban) and 18.7% (rural) in pharmacies' total sales. Most antibiotics are sold without a prescription: 88% (urban) and 91% (rural). Antibiotics are sold to treat cough 31.6% (urban) and fever 21.7% (rural). Three antibiotics are sold the most: ampicillin/amoxicillin (29.1%), cephalexin (12.2%) and azithromycin (7.3%). People often ask for antibiotics without a prescription: 49.7% (urban) and 28.2% (rural) [5].

### **1.2.2. Antibiotic use and antibiotic resistance in hospitals**

The review of results of the sensitivity of antibiotics carried out in 2003-2006 showed that resistance rate of *Klebsiella* spp. to cephalosporins of 3rd generation, 4th generation, fluoroquinolones and aminosid has increased from > 30% in 2003 to > 40% in 2006; to *Pseudomonas* spp. from > 40% in 2004 to > 50% in 2006 and to *Acinetobacter* spp. from > 50% in 2004 to > 60% in 2006. Although imipenem/cilastatin, carbapenem have just been put into Vietnam markets for nearly 10 years, their susceptibility to gram-negative bacilli with no enzymatic generation is reducing. Imipenem /cilastatin resistance rate of *Pseudomonas* spp. has increased over the years: 12.5% (2003), 15.5% (2005) and 18.4% (2006) [5].

According to data reported by 15 hospitals under the Ministry, Provincial General Hospitals in Hanoi, Hai Phong, Hue, Da Nang, Ho Chi Minh city, ... about the use of antibiotics and antibiotic resistance in the period 2008 - 2009 showed that, 30-70% of gram-negative bacteria resistant to cephalosporins of 3rd generation and 4th generation, nearly 40-60% resistant to aminoglycosides and fluoroquinolones in 2009. The sensitivity to imipenem of nearly 40% of *Acinetobacter* strains decreased.

Using antibiotics averagely 274.7 DDD/100 day-bed. This rate is significantly higher compared with Dutch report at the same period as 58.1 DDD/100 day-bed and higher than that of 139 reports from hospitals of 30 European countries in 2001: 49.6 DDD/100 day-bed.

The correlation between antibiotic use and antibiotic resistance is evident when the ratio of gram-negative bacteria resistant to cephalosporins of 4<sup>th</sup> generation is high in places with greater consumption of antibiotics [6].

According to the results “study antibiotic use in hospital-acquired infections in intensive care units in some health facilities” shows the most four isolated strains *Acinetobacter* spp, *Pseudomonas* spp, *E. coli*, *Klebsiella* spp. Frequency of *Acinetobacter* spp or *Pseudomonas* spp. infections marked dominant proportion (> 50%) in nosocomial pneumonia (ventilator or no ventilator). These 4 isolated strains were multidrug-resistant bacteria. A specially high resistance is detected in cephalosporin of 3<sup>rd</sup> and 4<sup>th</sup> generations (66-83%), followed by the group of aminosid and fluoroquinolones with resistance ratio over 60%.

The high resistance is also reflected in the use of antibiotics in the initial empirical results inconsistent with antibiotic regimen 74% [7].

### **1.2.3. Use anti-TB and drug-resistant TB**

Report of WHO 2012 estimates, Vietnam ranks 12 of the 22 countries with high tuberculosis burden globally, ranking 14th out of 27 countries with MDR-TB burden in the world.

MDR-TB rate was 2.7% among new TB patients (approximately 4,800 patients), 19% of re-treatment TB patients (approximately 3,400 patients). In 2011 WHO estimated about 3,500 MDR-TB patients (95% CI: 2,600-4,700) among TB patients detected [8].

However, in recent years, tuberculosis has become more complicated due to the impact of HIV/AIDS and drug resistance.

According to WHO, drug-resistant TB is a particularly serious problem. Result of treatment for patients with drug-resistance is often poor, especially MDR-TB patients. The cost of treating MDR-TB patients is hundreds of times higher than the non-drug-resistant TB patients and some cases can not be treated. Currently, the proportion of MDR in new TB patients in Vietnam is at <3%, but it is not small in comparison with the big number of patients with smear positive pulmonary TB (+) recently detected in Vietnam each year. Moreover, there are about 350 people with chronic tuberculosis each year, and most of them are MDR-TB patients. This is worsening the current status of drug resistance.

The cause of drug resistant TB bacteria may be due to bacteria transforming themselves to survive; patients do not comply with the treatment regimen, voluntary discontinuation, dose reduction ...; due to environmental pollution, spitting, littering in public places ... These causes are main factors which increase TB patients and drug resistance in Vietnam.

### **1.2.4. Use of HIV drug and HIV resistance**

Since the first cases had been detected in 1990, up to 31th March 2012, the number of people living with HIV was 199,744, of which 49,369 people entered AIDS phase, 52,681 people died from AIDS. The speed is still on the rise, but there are signs of slowing down in recent years due to the implementation of the intervention program.

In Vietnam, ARV drugs have been used from the mid-1990s but have been limited in some provinces and cities, especially in Hanoi and Ho Chi Minh City with a one-drug regimen or combination of the two types of ARVs.

Since 2005, the three-drug combination regimen in highly active antiretroviral therapy

(HAART) has been mentioned in national guidelines for diagnosis and treatment of HIV/AIDS of the Ministry of Health. In particular, the issue of compliance with antiretroviral therapy is considered as one of the prerequisite for the success of treatment.

The use of ARV also created the appearance of strains of HIV resistant to ARV and the risk of the spread of drug-resistant strains in the community. In countries where ARV has been put in use for many years, 5-27% of people newly infected with HIV carry the virus HIV-1 strains resistant to one or more antiretroviral drugs.

In a study on drug resistance conducted in Ho Chi Minh City, the rate of HIV drug resistance of people who are drug addicts, prostitutes and patients with sexual transmitted diseases unprecedented access to ARV was 6.5%. The research results of Pasteur Institute in Ho Chi Minh City in pregnant women without access to ARV and new HIV infections (under the age of 30, the number of lymphocytes  $CD4^+ > 500$  cells/mm<sup>3</sup> without ARVs) showed that the rate of HIV resistance is low <5%. Another study in Ho Chi Minh City showed that, the rate of drug-resistant HIV in pregnant women participating in PMTCT at the time before taking drug was relatively low 0.6%. Two weeks after birth, the percentage of pregnant women were found to be carrying drug-resistant HIV reduced to 17.53% and down to 3.06% two months after birth. 3TC resistance mutations often found in groups of pregnant women using combination regimens AZT+3TC and NVP resistance mutations in pregnant women using sd-NVP. The 3TC resistance mutations often found among women taking combination therapy and the AZT +3 TC NVP resistance mutations in pregnant women using sd-NVP. Although after discontinuing oral prophylaxis, the rate of virus with resistance mutation decreases gradually, drug-resistant strains can persist at levels below the detection threshold and are possible to reoccur when mothers are treated with the regimens using resistant drugs.

In 2008, the Ministry of Health developed the national plan for prevention, monitoring HIV drug resistance as recommended by WHO. The national plan includes contents related to: (1) collect early warning indicators of drug-resistant HIV; (2) monitor the appearance of drug-resistant HIV among patients on ARV therapy grade 1; and (3) investigate the appearance of drug-resistant HIV among HIV-infected people without ARV.

Since 2008, Vietnam has annually collected data regarding ARV treatment results along with the collection of early warning indicators of HIV drug resistance in representative antiretroviral treatment facilities nationally .

The monitoring of HIV drug resistance among newly HIV-infected people without ARV showed the rate of HIV resistance below 5%.

#### **1.2.5. Use of antibiotics and antibiotic resistance in livestock, cultivation**

In order to limit the risk of diseases in livestock industry, people have the habit of using many antibiotics, stimulants including prohibited active ingredients and veterinary drugs to stimulate growth or prevention and treatment for animals. If it is not well controlled, the use of the active ingredient, veterinary drugs in livestock production will cause a great risk for the environment and human health such as drug resistance, antibiotic resistance in humans, residual antibiotics from feces, urine to plants and to humans through water resources, ... In livestock industry, there is so much abuse of synthetic antibiotics. The number of households using antibiotics 3-6 active elements accounts for 27% of pig farms for meat, 24% of farms of small pigs and 10% of chicken farms (Vu Dinh Ton et al 2010). The use of antibiotics and veterinary chemicals based primarily on experience will often lead to the increase of doses

and treatment regimen. Use of antibiotics in disease symptoms (44%), as directed by veterinary staff 33%, the use of antibiotics as recommended by the manufacturer for 17% and only 6% of the farms use antibiotics following the antimicrobial susceptibility testing results (Nguyen Quoc An, 2009) [5].

### **1.2.6. Hospital infections and infection control in hospitals**

Hospital infection is one of the challenges and concerns in Viet Nam and around the world. Many studies show that hospital infection increases mortality, prolongs hospital stay, increases duration of antibiotic use, increases antibiotic resistance and increases treatment costs.

U.S. statistics show that the cost of a hospital infection case is usually 2 to 4 times higher than a case without hospital infection. Of which, costs incurred by sepsis related to intravascular devices is set from 34,508 dollars to 56,000 dollars and pneumonia in patients with ventilation support is from US \$ 5,800 to US \$ 40,000. In the U.S., each year 2 million patients are estimated to be hospital infections, causing 90,000 deaths, costs US \$ 4.5 billion of hospital fees.

Hospital infection in Vietnam has not been fully determined. Very little document and monitoring of hospital infection has been published. The expenditure for manpower and financial resources to cope with nationwide hospital infection has not yet determined. Three national cross-sectional surveys were carried out. The 1998 survey on 901 patients in 12 hospitals nationwide showed that the rate of hospital infection was 11.5%, of which, wound infections accounted for 51% of the cases of hospital infection. In 2001, the rate of hospital infection was 6.8% in 11 hospitals and hospital pneumonia was the most common cause (41.8%). That in 1998 survey in 19 hospitals nationwide was 5.7% and hospital pneumonia was the most common cause (55.4%). There have never been a national study to assess the cost of hospital infection.

The diseases caused by hospital infection has higher level of MDR than infectious diseases in community. Hospital infection is caused by bacteria with high resistance such as *S. aureus* resistant to methicillin (MRSA) and vancomycin-resistant enterococci, multidrug-resistant *A. baumannii*, *P. aeruginosa* accounted for considerable proportion.

Situation of hospital infection control: The BCC system is not completed as required; staff for management of BCC are insufficient, not qualified, most of them have not been trained; lack of infrastructure and necessary facilities for BCC particularly in district hospitals; many critically professional missions on BCC have not been done; lack of a database of hospital infection, diseases, drug-resistant microorganisms, ...

## **2. Causes of resistance**

### **2.1. Use of inappropriate antimicrobial drug**

The overdose, insufficient dose or abuse of antimicrobial drug has caused resistance, creating favorable conditions for resistant microorganisms to emerge, change and spread. In fact, many patients buy antibiotics for self-treatment without prescription, use of antibiotics for treatment of cases which are not caused by pathological infections; inappropriate use of antibiotics and drug to bacteria, viruses, parasites .... use of improper dosage, and time ...

### **2.2. Control and inspection of drug quality are limited**

Quality control system can not meet the actual needs due to lack of testing capacity for many active ingredients; can not control the quality of all production lots of each product circulating in the market.

### **2.3. Prevention and control of infectious diseases are ineffective**

Ineffective prevention and control of infectious diseases help increase the spread of drug-resistant bacteria. The patients treated in hospitals are the major source of spread of resistant microorganisms from one person to others.

### **2.4. The monitoring system of drug resistance has not been established**

At present, there is not a national network for monitoring drug resistance in Vietnam. The monitoring of drug resistance is only set up and implemented in some hospitals, such as the Central Tropical Diseases Hospital, Bach Mai Hospital, Children's Hospital No.1...

However, the monitoring activities are not done frequently. The lack of testing facilities accurately identifying microbial resistance leads to difficulties in the detection of newly emerging resistant microbes, therefore, it is impossible to act quickly to control the drug resistance.

### **2.5. Use of antimicrobial drugs in livestock is not properly controlled**

Antibiotics are increasingly widely used in livestock to promote growth and prevent diseases. This can lead to microbial resistance and cause drug resistance in humans.

### **2.6. The expertise regulations of health care is not regularly updated**

There have not been enough instruction for diagnosis and treatment or updated guidelines for many infectious diseases. In addition, the regulation on the use of antibiotics, antibiotic regimen, microbiological testing has not been completed; the inspection and supervision of the implementation process at the local level is not frequent enough.

### **2.7. Awareness of community, health workers on drug resistance is limited.**

People's habits "heal myself" and "imitate" prescriptions lead to the arbitrary use of antibiotics, contributing to increased drug resistance. In addition, limitations of health workers, equipment of some health facilities, especially at the lower levels, regional and remote areas, lack of conditions for antibiotic regimen lead to improper use of antibiotics by patients.

## **3. The consequences and the burden of drug-resistance**

Drug resistance is not a new phenomenon, however, it is becoming more serious and its growth rate is badly affecting community health. As a result, after 70 years since the introduction of antibiotics, we have to face with the possibility of a future without effective antibiotics for treatment for a number of infectious diseases, especially the surgery and treatments such as cancer chemotherapy and human body parts, tissue transplant.

In addition, drug resistance has induced scarcity, lack of new antimicrobial drugs, especially in patients with infections caused by multidrug-resistant organisms (MDR). The social costs and financing in the treatment of drug-resistant infections put a significant burden on individuals, families and society, due to prolonged duration of treatment, bad prognosis and waste of costs for drugs due to inappropriate medication use.

## **II. LEGAL BASIS**

1. Law on health examination and treatment No. 40/2009/QH12 dated November 23<sup>rd</sup> 2009
2. Law on Pharmacy No. 34/2005/QH11 dated June 14<sup>th</sup>, 2005
3. Law on Prevention and Control of Infectious Diseases No. 03/2007/QH12 dated November 21<sup>st</sup>, 2007.
4. Law on prevention and control of viral infection causing immunodeficiency syndrome (HIV/AIDS) No. 64/2006/QH11 dated June 29<sup>th</sup>, 2006.
5. Decree No. 63/2012/ND-CP dated August 31<sup>st</sup>, 2012 of the Government defining the functions, tasks, powers and organizational structure of the Ministry of Health.
6. Decision No. 1208/QD-TTg dated September 4<sup>th</sup>, 2012 approving the national target program on Health for the period 2012-2015 by the Prime Minister.



**Part two**  
**CONTENTS OF PLAN**

**I. OBJECTIVES**

**1. The overall objective**

Promote prevention of drug resistance, contributing to improving the quality and effectiveness of the prevention and control of epidemics, medical examination and treatment to protect, care for and improve people's health.

**2. Specific objectives**

2.1. Raise awareness of community and health workers on drug resistance.

2.2. Strengthen, improve national surveillance system on the use of antibiotics and drug resistance

2.3. Ensure adequate supply of quality medicines to meet the needs of people.

2.4. Promote proper safe use of drugs

2.5. Promote infection control.

2.6. Promote proper safe antibiotic use in livestock, poultry, aquaculture and cultivation

**II. ACTIVITIES**

**1. Raising awareness of the community and health workers about drug resistance**

**1.1. Activities**

a) Compile documents for continuous training and develop IEC communication materials.

b) Organization of communication activities, including direct communication (seminars, talks, consultations, ...) and indirect communication in mass media (TV spots, radio spots, knowledge, articles, ...).

**1.2. Time and schedule for implementation**

**Phase 1 (from 2013 to 2016):**

a) Develop communication materials: brochures, posters, flip pictures, video spot, television spot for propaganda, dissemination on the causes and consequences, measures to prevent drug resistance.

b) Develop materials to guide health workers, community on prevention of drug resistance.

c) Organize seminars, talks and consultation to answer questions about prevention of drug resistance on mass media.

d) Organization of communication and education activities on the prevention of drug resistance on mass media from the central to local levels.

e) Launch the month for prevention of drug resistance in the country.

e) Organize training conferences, disseminate and educate laws on on the prevention of drug resistance

g) Organize continuous training, training in communication skills, monitoring and evaluation of prevention of drug resistance.

**Phase 2 (from 2016 to 2020):**

Maintain communication activities in addition to the survey, assessment of community's knowledge about drug resistance.

## **2. Enhance, improve the capacity of the national surveillance system on antibiotic use and resistance**

### **2.1. Activities**

- a) Developing and completing documents regulating clinical microbiology laboratory; standard testing procedures, building standard microbiology laboratories and reference laboratories;
- b) Establish drug resistance surveillance system;
- c) Participating in curriculum development for training in microbiology and antibiotics in universities, medical- pharmacy schools;
- d) Continuing education and training to enhance the capacity of the clinical microbiology laboratory, scientific research capacity of staff on the resistance;
- e) Developing training cooperation programs on drug resistance prevention between domestic and abroad medicine – pharmacy schools;
- e) Developing a database of antibiotic use and resistance.

### **2.2. Time and schedule for implementation**

#### **2.2.1. Phase 1**

- a) Develop and improve standard test procedures, guidelines for clinical microbiology laboratory.
- b) Establish the National Center of clinical microbiology laboratory.
- c) Conduct training, continuous training on technical expertise of the clinical microbiology for laboratory staff at the national standard center and 30 laboratories nationwide.
- d) Build functions, tasks, organizational structure, human resources and equipments for laboratories of clinical microbiology.
- e) Organize abroad training courses on drug resistance surveillance system.
- e) Set up a network of monitoring of antibiotic use and resistance in 30 laboratories across the country.
- g) Develop forms, tracking software and reports of the use of antibiotics, reports of drug resistance.
- h) Carry out scientific research on drug resistance.
- i) Participation in scientific conferences on drug resistance in the country and abroad.

#### **2.2.2. Phase 2**

- a) Develop a database of antibiotic use and resistance.
- b) Develop evaluation indicators, establish a system for collecting and processing information, develop websites for tracking, monitoring and evaluation of drug resistance.
- c) Organize scientific conferences on drug resistance prevention.

## **3. Ensure adequate supply of quality essential drugs**

### **3.1. Activities**

- a) Improving, updating the documents defining the list of essential medicines, major drug categories used in the examination and treatment;
- b) Investing in production supply the market with drugs of good quality, reasonable price;

c) Implementing comprehensive management of drug quality during the entire process of production, export, import, distribution and use of drugs.

### **3.2. Time and schedule for implementation**

#### **3.2.1. Phase 1**

- a) Update list of essential medicines, major drug categories that are consistent with the pattern of disease and socio-economic conditions of Vietnam; in line with advances in science and technology in healthcare in each specific stage and technical capabilities of each level.
- b) Monitoring and surveillance of counterfeit drugs circulating in the market.
- c) Continue to promote the implementation of the project “The Vietnamese use drugs made in Vietnam with priority”.
- d) Develop and propose mechanisms to prioritize the production of generic drugs for pharmaceutical companies in the country.
- e) Investment in production to supply the market with drugs of good quality, reasonable price.

#### **3.2.2. Phase 2**

Continue some activities of the phase before 2015 combined with topical scientific workshop on enhancing patients’ access to essential medicines.

### **4. Strengthen safe and rational use of drugs**

#### **4.1. Activities**

- a) Developing and completing documents and manuals regulating rational drug use, antibiotics and treatment;
- b) Conducting workshops, seminars, training, ongoing training on good prescribing practice, clinical pharmacy practice.
- c) Building capacity for the Council of Drugs and Treatment;
- d) Conducting workshops, seminars on evaluation of the rational safe use of drugs, assessment of activities of Council of Drugs and Treatment.
- e) Monitoring , inspecting and supervising the rational safe use of drugs in the examination and treatment facilities.
- e) Developing and completing the training program, ongoing training on clinical pharmacy practice.

#### **4.2. Time and schedule for implementation**

##### **4.2.1. Phase 1**

- a) Develop, update and promulgate treatment guidelines.
- b) Develop guidelines for the use of antibiotics for medical staff and community.
- c) Conduct training, continuous training of clinical pharmacy practice, good prescription.
- d) Develop regulations for the operation of the Council of Medicines and Treatment.
- e) Conduct training, continuous training in treatment guidelines for health workers.
- e) Evaluate the compliance to treatment guidelines in health facilities.
- g) Develop documents defining the assessment of drug use.
- h) Develop indicators for the assessment of drug use in hospitals and community.
- i) Do monitoring and evaluation of drug use, monitoring the treatment compliance and operation of Council of Medicines and Treatment in health facilities.
- k) Conduct conference on the assessment of drug use, operation of Council of Medicines and

Treatment in health facilities.

#### **4.2.2. Phase 2**

- a) Cooperate in research on the use of drugs, especially antibiotics
- b) Do continuous training and training nationally and internationally on drug information, drug use, clinical pharmacy practice
- c) Conduct management, information collection, evaluation of indicators of drug use
- d) Conduct scientific conferences on antibiotics and antibiotic resistance.

### **5. Strengthen infection control.**

#### **5.1. Activities**

- a) Improve and update documents on infection control;
- b) Continuing education, training, inspecting, monitoring and evaluating the implementation of infection control for health workers.
- c) Promote the monitoring system and report of data to form the database of national infection control.

#### **5.2. Time and schedule for implementation**

##### **5.2.1. Phase 1**

- a) Add, update and promulgate legal documents, policies, national technical regulations and BCC hospital guidelines.
- b) Improve the organization of infection control in accordance with Circular No. 18/2009/TT-BYT dated 14/10/2009 guiding the implementation of BCC in the examination and treatment facilities.
- c) Conduct continuing training and training to improve their knowledge and skills to practise infection control for health workers and specialized BCC staff at health facilities.
- d) Develop the monitoring indicators in infection control.
- e) Establish monitoring systems and reporting data on hospital infections from hospitals under the Ministry of Health and provincial hospitals.

##### **5.2.2. Phase 2**

- a) Promote scientific research in the BCC field.
- b) Regularly organise national scientific workshops once/year and international scientific workshops on infection control once/5 years.

### **6. Strengthen safe, appropriate antibiotic use in livestock, poultry, aquaculture and cultivation**

#### **6.1. Activities**

- a) Develop documents and manuals prescribing antibiotics, growth drug in livestock, poultry, aquaculture and cultivation.
- b) Develop list of permitted antibiotics and prescribe limitations of antibiotic residues in livestock, poultry, aquaculture and cultivation
- c) Establish monitoring system of safe **appropriate** use of antibiotics in livestock, poultry, aquaculture and cultivation.

#### **6.2. Time and schedule for implementation**

### **6.2.1. Phase 1**

- a) Develop documents prescribing antibiotic use in livestock, poultry, aquaculture and cultivation.
- b) Make the list of antibiotics and prescribe restricted antibiotic residues in livestock, poultry, aquaculture and cultivation
- c) Establish the monitoring system of antibiotic use in livestock, poultry, aquaculture and cultivation.

### **6.2.2. Phase 2**

- a) Cooperate in research and evaluation of antibiotic use and resistance in livestock, poultry, aquaculture and cultivation.
- b) Evaluation of antibiotic use and resistance in livestock, poultry, aquaculture and cultivation.
- c) Continue to implement activities to prevent drug resistance.

## **Part three**

### **SOLUTIONS**

#### **I. POLICY AND MANAGEMENT**

1. Gradually improve the system of legal documents and instructions on technical expertise in infectious disease control, infection control, surveillance of drug resistance, enhancing rational drug use.
2. Improve the system of documents on antibiotic use in livestock, poultry, aquaculture and cultivation.
3. Strengthen inspection and supervision of the implementation of professional rules relating to treatment guidelines, medication use, hospital pharmacy, infection control in health facilities.
4. Enhance the assessment of tuberculosis epidemiology, medicine and equipment, tuberculosis with HIV/AIDS, situation of TB drug resistance.
5. Closely monitor the quality of drugs, prevent poor quality drugs, counterfeit drugs from circulating in the market.
6. Increase the capacity of program management: prevention of tuberculosis, HIV/AIDS, drug resistance, infection control.

#### **II. INFORMATION, EDUCATION AND COMMUNICATION,**

1. Promote dissemination, advocacy, legal education on the rational safe use of drugs.
2. Raise awareness of community, health workers, people who work in the fields of livestock, poultry, aquaculture and cultivation on antibiotics and drug resistance.
3. Mobilize people to follow The month for prevention of drug resistance.
4. Strengthen education and communication for the entire population, gradually socializing TB prevention: advocacy, requirement, use of all society components, relatives of patients participating in the tuberculosis prevention at all levels and under different forms.

#### **III. TECHNICAL EXPERTISE AND TRAINING**

1. Complete expertise guidance, technical procedures in health examination and treatment, microbiology testing, drug resistance surveillance as the basis for the implementation of units.
2. Enhance training, improve qualification for health workers, diversifying forms of training, continuous training, additional training, domestic and international training on diagnosis and treatment of diseases, especially infectious diseases; microbiology testing, infection control, surveillance of drug resistance in health facilities.
3. Complete training frame, curriculum in microbiology and antibiotics in universities, health schools.
4. Increase investment in infrastructure, support facilities and equipment to meet the demands of infection control, microbiology testing, monitoring drug resistance, drug quality control.
5. Upgrade laboratories, research centers on microbiology at central hospitals, universities.
6. Continuously improve the quality of drugs and bioequivalence assessment.
7. Ensure adequate supply of medicines in the list of essential drugs used in the examination and treatment.
8. Complete system for collecting statistical data and reports, gradual modernization,

application of information technology to manage information on the national network.

9. Coordinate activities between the national TB control and other national health programs at district, commune and village levels.

#### **IV. FINANCE**

Investment from the state budget, ODA funding and other legitimate funds to implement the National action plan to combat antimicrobial resistance in the period from 2013 to 2020:

1. In the country: the units ensure funding to implement activities within assigned missions and state budget distributed in the annual and 5-years plan.

2. Mobilize resources from international organizations, non-governmental organizations: WHO, UN forestry fund, GARP - Vietnam, UNAIDS, WB, ...

#### **V. SCIENTIFIC RESEARCH AND INTERNATIONAL COOPERATION**

1. Strengthen research and transfer of new techniques in the diagnosis and treatment of infectious diseases, microbiology testing, quality control, microbiology laboratory.

2. Enhance the capacity of study on drug use, drug resistance research, especially research on multi-drug resistant bacteria.

3. Promote research on hospital infections.

4. Coordinate with relevant agencies to promote cooperation in research: assessment of antibiotics use, antivirals, parasite; study on drug resistance especially study on multi-drug-resistant bacteria.

5. Strengthen international cooperation, experience exchange and sharing, participate in workshops, specialized scientific conferences, forums on prevention and control of infectious diseases, rational drug use, hospital infection, quality control of microbiological testing, drug resistance.

6. International cooperation on continuous training, research on drug use, clinical pharmacy practice.

## Part four

### IMPLEMENTATION

#### I. ESTABLISHMENT OF STEERING COMMITTEE

**1. Chairman:** Minister of Health

**2. The Deputy Chairmen:** Deputy Minister of Health, Ministry of Agriculture and Rural Development

**3. The Commissioners:** Leaders of Departments of examination and treatment Administration, Food Safety, Preventive Medicine, HIV/AIDS, Drug Administration, Health Environmental Management, Science Technology and Training ... Leaders of Departments of Planning - Finance, Facilities and health services Works, Health Insurance, ... Inspector of the Ministry of Health; relevant Departments of Ministry of Agriculture and Rural Development.

**4. Secretaries:** Representatives of relevant Departments, agencies of Ministry of Health, Ministry of Agriculture and Rural Development.

**5. The sub-committees:**

a) Sub-Committee on infection control

b) Sub-committee on treatment (Infection, intensive care, HIV/AIDS, TB)

c) Sub-Committee on monitoring, inspection and examination of the use of antibiotics:

- Prevention, diagnosis and treatment in health facilities and communities

- Livestock, poultry, aquaculture and cultivation.

d) Subcommittee on logistics

e) Sub-committee on education and communication

**6. Permanent Division:** Department of examination and treatment Administration

#### II. ASSIGNMENT OF RESPONSIBILITY

##### 1. The agencies of the Ministry of Health

###### 1.1. Department of Examination and treatment administration:

a) Act as the focal point to collaborate with other relevant units to direct and guide the implementation; summing up the results of operations in the plan to report to the Ministry of Health;

b) Develop technical expertise guidance on infection control, treatment regimens, surveillance of drug resistance and drug use;

c) Examine and supervise the implementation of professional rules relating to treatment guidelines, drug use, infection control in health facilities;

d) Establish the system of national drug resistance surveillance; monitoring, management, warning of the resistance and the danger of drug resistance; develop the database on antibiotic use and resistance; training, continuous technical professional training on clinical microbiology for laboratory staff at the national standard center and 30 laboratories throughout the country;

e) Establish the system of monitoring and reporting data on hospital infections from hospitals under the Ministry of Health and provincial and cities hospitals under central authority;

e) Monitoring and evaluation of drug use, compliance monitoring, promoting activities of the



Council of Drug and Treatment in health facilities;  
g) Evaluate TB epidemiology, drugs and equipment, tuberculosis with HIV/AIDS, TB drug resistance.

### **1.2. Drug Administration**

- a) Implement measures to improve the quality of drugs and bioequivalence assessment.
- b) Provide enough drugs in the list of essential drugs mainly used in health facilities.
- c) Monitoring and surveillance of counterfeit drugs circulating in the market.

### **1.3. Bureau of HIV/AIDS prevention and control**

- a) Collect data regarding antiretroviral treatment outcomes; collecting early warning indicators of HIV drug resistance in nationally representative facilities treating HIV/AIDS.
- b) Monitoring, supervision and evaluation of HIV drug resistance in patients receiving therapy and new HIV infected patients without ARV.
- c) Implement measures to improve capacity for HIV resistance testing laboratory.

### **1.4. Department of Preventive Medicine**

Tracking, monitoring, doing research, evaluation of the use of antibiotic and antibiotic resistance in community

### **1.5. Department of Food Safety**

Tracking, monitoring antibiotic residues in foods directly affecting people's health.

### **1.6. Inspector of the Ministry**

Inspecting the sale of antibiotics without prescription.

### **1.7. Department of Planning – Finance**

- a) Guide relevant departments in estimating the annual budget as assigned in the plan.
- b) Investments from the state budget, official sources for development assistance and other legitimate funding sources to implement the National Action Plan to Combat Antimicrobial Resistance in the period 2013-2020.
- c) Arrangement, allocation of regular budget for hospitals to implement solutions of prevention of drug resistance.

### **1.8. Health Insurance Department, Bureau of Environmental Health Management**

Coordinate with relevant agencies to implement the Action Plan in accordance with the functions assigned.

### **1.9. Bureau of Science, Technology and Training**

- a) Propose, support, give priority to research and new techniques transfer in diagnosis of infectious diseases, microbiology testing.
- b) Training to strengthen the capacity of study on assessment on drug use, drug resistance studies, especially study of multidrug-resistant bacteria, study of hospital infection.
- c) Strengthen continuous training with appropriate forms domestic and abroad to improve the qualification of health workers.
- d) Improve the curriculum frame, curriculum for microbiology, antibiotic in medical and pharmaceutical training units.

### **1.10. Department of Communications and emulation, commendation**

Assume the prime responsibility and coordinate with the relevant departments in the dissemination and propagation, education to raise awareness of community and health workers on prevention of drug resistance and mobilize them to perform the month for actions against drug resistance.

### **1.11. Department of Health in provinces and cities under central management**

Guide provincial health facilities in plan development and implementation; allocating resources to implement the national action plan against drug resistance in the period 2013-2020 in accordance with the specific circumstances of each locality.

### **1.12. Hospitals**

- a) Develop a specific plan in accordance with the conditions of each unit to implement the National action plan against drug resistance in the period 2013-2020.
- b) Allocate resources for the prevention of drug resistance: upgrade microbiology laboratories; strengthening infection control; monitor and control the use of inappropriate antibiotics, ...

## **2. Ministry of Agriculture and Rural Development**

Ministry of Agriculture and Rural Development assigns its agencies in collaboration with the Ministry of Health to direct and guide relevant agencies to develop regulations on the use of antibiotics, list of antibiotics, antibiotic residues limits used in livestock, poultry, aquaculture and cultivation. Inspection, testing and monitoring the use of antibiotics in livestock, poultry, aquaculture and cultivation.

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