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Lung Health in Rural Nepal

Multi-State Modeling of Health Status and Economic Evaluation of Integrated Respiratory Care Guidelines

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Lung Health in Rural Nepal

Multi-State Modeling of Health Status and Economic Evaluation of Integrated Respiratory Care Guidelines

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Preface

More than seven years ago, while I was working as a biostatistician at the Nepal Health Research Council, I got a call from Naveen Shrestha from the Institute of Medicine at the Tribhuvan University, where I was also teaching part time. He asked me to visit him with my biodata the same day – I thought it was for some sort of research proposal. I was completely unaware of what was coming – something that completely changed my future. At the meeting I found Naveen Shrestha and Guus ten Asbroek waiting for me, where they offered me the opportunity to work on a PhD in The Netherlands. It took me by surprise; however, I immediately agreed to take it. At that time, I did have the desire to pursue further studies abroad, but had not thought that the opportunity would come in such a package. With the support from Prof. Bimala Shrestha, Head of the Department of Community Medicine, and the honest advice from Prof. Ramesh Adhikari, Dean of the Institute of Medicine, I travelled to Groningen at the end of August 2001 to start the new journey which culminated in this book.

In Groningen, I spent the first year (August 2001–July 2002) mostly attending the Master's courses at the Population Research Center (PRC) along with Vanessa, Jan Willem, and others. I had a hard time with the first course on demographic theories, which was coordinated by Inge Hutter, as I was not used to studying social science theories. At the end of three months I was quite relieved, as I completed the course satisfactorily. In the later courses I learned a lot about technical demography. Frans Willekens' courses on multi-state demography and event-history analysis were fundamental to this thesis. I met Sergei Scherbov during his course on computing in demographics where I learned to do programming, which was very useful for me in this analysis and also in my other work.

The social life in Groningen was mostly spent with Vanessa, Tomas, and Rob. For almost 11 months of my stay in Groningen, I lived in a guest house next to a very big and well maintained garden of the Dekker family, and I thank them for their hospitality, and introducing me to the culture and ways of European life. Frans and Maria were always there to support me in all matters. I am indebted forever to all my friends and colleagues with whom I had a very wonderful time. I was lucky to have Karen as my office mate and I praise her for her patience while listening to my sometime strange chatting and answering my weird questions. I thank Stiny for making sure that all the administrative matters were perfect during my stay in Groningen, as well as during the preparation of my PhD defense. I share a lot of

memories with all my colleagues and friends at Groningen including Jan Willem, Sarbani, Mamun, Mauri, and Maaike.

All through the year, I was working on specifying a multi-state model for the PAL project and was waiting for the day to get back to Nepal and get involved in the data collection process, which was initially planned for six months, and would start while I was still in Groningen, being undertaken by Naveen Shrestha and Guus ten Asbroek in Nawalparasi, Nepal. I was supposed to take over the last two months of the data collection and then continue with the data-entry. However, due to various reasons, the data-collection started only after I got back to Nepal and I spent almost 17 months in Nepal before the final set of data was prepared, of which about 12 months were spent on data collection alone, as the expected number of samples was not achieved during the initially-planned six months.

When I came back to Kathmandu from Groningen, I had to travel to Nawalparasi four days later (at the beginning of August 2002) to get involved in the selection and training of around 50 field assistants. I met Pralhad Bhattarai and Sagar Ghimire who were field research officers responsible for the day-to-day field operation. The PAL-Nepal project had rented an apartment which was used as both the office for PAL-Nepal and a residence for the four of us. The biggest room was partitioned halfway by a thin board – one side was the office for PAL-Nepal and the other side was a bedroom for all of us. Each of us had a small bed with a mosquito net, and two ceiling fans were running all the time. I will never forget the first night; around 1am the electricity went off and I found myself drowning in my own sweat as all the windows were closed. I realized that the rest of my roommates were also awake and the heat was unbearable. It took some hours before we got the light back. This became a routine and it was exactly the reverse during winter; it was so cold that I was wearing layers and layers of clothes all the time 24–7. After a few days, Naveen Shrestha left for the Erasmus University in Rotterdam to study for his Master's degree, following the training of the field assistants.

During the data collection phase, field assistants were stationed in each of the selected health centers spread all across the district. All the health centers were accessible either by bitumen or dirt road. In order to supervise the field assistants, we bought two 100cc Indian motorcycles and rode them all day, sometimes into the evening, often travelling more than a hundred kilometers to visit the health centers and the patients' homes. At one point, we had to pull out of one of the sub-health posts for security reasons as the Maoist insurgency was at its peak during the period.

I am highly grateful, and express my sincere appreciation, to all my colleagues, starting with Naveen Shrestha and Guus ten Asbroek, who paved my way in the initial steps of the data collection. I thank Pralhad, Sagar and Prem Bhusal for their efforts in managing and supervising the entire data collection process in Nawalparasi, and I extend my thanks to Jogendra and Sarbatiya for their continuous support in helping with local logistics and issues. I acknowledge the work done by Binjwala

Shrestha, Bimala Shrestha, and Ram Prasad Pathak as external supervisors of the whole process of data collection. Most importantly, I am grateful to the field assistants who were doing the actual data collection at the health centers, as well as visiting the respondents' residences, in spite of all the difficulties associated with working in rural Nepal at that time. I am highly indebted to the health workers in the medical facilities, as well as the patients, who willingly and patiently provided their time and responses to our questions. I also extend my gratitude to the students BPH from IOM who helped us collect data related to facilities on two occasions. Finally, I would like to thank all those who helped me during the data-entry process; Hitesh, Madhusudan, Deepak, Archana, Sushma, and Jeevana.

In January 2004, I returned to Rotterdam, instead of Groningen, for two reasons. Firstly, the PAL project was coordinated by Louis Niessen who was at the Erasmus University and, secondly, Frans Willekens has moved to Den Haag as a Director of NIDI. At the first meeting with Frans and Louis we planned to finish everything in one year. I had the data, but was still not sure about the model to be used. I struggled quite a lot in defining appropriate multi-state models for evaluation purposes and, with the advice and support from colleagues at the Erasmus University, Naveen Shrestha, Louis, Rob Baltussen, and Frans, I managed to come out with the two multi-state models presented in this book. At the end of that year (2004) the drafts of all the chapters were ready and I thought that it would be few more months before I could apply for the defense, as I was leaving for Vienna to work at IIASA staring in May 2005. However, things were not as simple as I thought, as it took me another three and half years to finally get the thesis ready. It was a difficult time for me to work on all the comments that I was receiving from Frans and Louis while simultaneously undertaking my usual research work at IIASA, where I was mostly working with population projection by age, sex and educational level for many countries of the world – the two jobs having nothing in common. However, I believe that this manuscript got better in terms of the additional analysis, as well as the insights, that I started developing while working at IIASA. I can see a big difference between the first draft that I prepared before I left Rotterdam in late February 2005 and the one that is in this book.

While living in Rotterdam, unlike Groningen where I was like a 'regular student', I made fewer friends. I was mostly with Naveen Shrestha and Pralhad. I started playing football with Arthur, and Louis also joined in a few games. Because of that I am still playing football in two hobby football teams in Vienna, and I still remember cheering the Dutch team in the Eurocup 2004 at the Dutch bars, as well as at Louis's house. Bart and Merijn took good care of me whenever I visited them in Amsterdam.

When I joined IIASA in May 2005, I moved to Vienna along with my wife and daughter. I thought that it would be a few more months before I could finalize the thesis. I thank all of my colleagues at IIASA and also friends at the Vienna

Institute of Demography who kept on encouraging me and pushing me to finish the PhD, especially Wolfgang, Anne, and Tapas. It took a long time to get to this position and I am very happy and relieved to present the book in its current form. I am quite satisfied with the outcome and I hope it can be useful to others, particularly to people at the WHO. I would like to thank the Publication Committee at IIASA for publishing the book and to thank my colleagues in the IIASA Communications Department, especially Iain for managing the publication procedure, Ingrid for type-setting, Anka for cover designing, and others who worked for this book. I extend my appreciation to Niki who did the English editing and I am very grateful to Biswamitra Sahu for the last minute printing and binding of the dissertation and submitting it to the University.

Finally, this work would not have been a possible without the constant support and encouragement from my family. While in Groningen and in Rotterdam, it was sometimes very painful to be away from them. Also, during the data collection, I spent more than half of my time in Nawalparasi, which is a long way from Kathmandu. I missed all of them during these periods; however, I was constantly encouraging myself that one day this would pay off. I dedicate this work to my parents, to my wife Binita, my daughter Aayu and to the rest of the K.C. family.

Samir K.C.

Acknowledgments

Project

The author expresses his gratitude to the NWO-WOTRO (Netherlands Foundation for the Advancement of Tropical Research) for financial support. He conveys genuine appreciation to the Department of Community Medicine and Family Health, Institute of Medicine, Tribhuvan University, Kathmandu, Nepal; to the Institute of Health Policy and Management, Erasmus University Rotterdam, and the Population Research Center of the University of Groningen (both in The Netherlands); and to the World Population Program, IIASA, Laxenburg, Austria, for hosting the author to do the analyses and to write this book.

Book

The author acknowledges the spirit of teamwork in the PAL evaluation study. In relation to the content of this book, he would specifically like to thank Naveen Shrestha for his contributions to the analysis, writing and field work, and Pralhad Bhattarai for his initial work as part of his master's thesis (Chapter 3). The author recognizes the contributions made by Guus ten Asbroek, Rob Baltussen, and David Bishai for their advice and suggestions during preparation of this thesis. Finally, the author expresses thanks to the people of Nawalparasi for their time, patience and willingness to participate in the research.

To

Binu and Aayu

Summary

Human beings are susceptible to many different diseases which may cause death. However, many diseases can be prevented, mitigated, and cured. People suffer from different diseases in different parts of the world. People living in poor countries continue to suffer from diseases that no longer exist in high-income countries. The transfer of knowledge and technology helps to narrow this health burden through the training of health care providers, along with the necessary investments, for example, in new medicines, equipment, and management strategies, etc. These interventions need to be adapted and contextualized to local settings and evaluated *ex ante* to determine the potential health effects in relation to cost.

This book presents the findings of a cost-effectiveness analysis of an integrated lung health strategy i.e., the Practical Approach to Lung health (PAL) strategy, developed by the World Health Organization (WHO) and implemented in a rural pilot setting in Nepal. Lung diseases, such as pneumonia, tuberculosis, chronic obstructive pulmonary disease (COPD), and asthma, pose major health problems in Nepal, especially in rural areas where proper facilities and well-trained health staff are lacking.

The PAL strategy for primary health care centers is specifically designed for health care providers with limited health care training. The program in the pilot district trained at least one health care provider in the PAL guidelines at twenty-two randomly-chosen, rural primary health care facilities (out of forty-two). Twenty facilities in the same district, where the standard health care procedures were followed, were selected as control areas. Data were collected from patients with lung disease-related symptoms, namely fever, cough or breathing difficulties, during visits to both types of health facilities during a one year follow-up period. The book presents the results of the economic evaluation of the PAL pilot in terms of costs, health effects, and cost-effectiveness, as compared to existing standard care procedures.

Our research shows, as expected, that the implementation of PAL increases the government's health expenditure, due to the increased costs associated with the training and supervision of health care providers, by US$ 1.04 per disease episode. Therefore, before PAL is adopted, the initial increase in budget has to be guaranteed, either from the national budget or through international support. However, the cost per episode can be reduced significantly once the PAL strategy is adopted nationwide and integrated into the basic training of health care providers.

At the patient level, we demonstrated that implementing PAL reduces patients' out-of-pocket expenses, mostly due to the lower average cost per drug prescription. The PAL strategy is designed to enhance the rational use of drugs; it reduces multi-drug prescriptions, the number of antibiotic prescriptions, and increases generic drug prescriptions, as well as drug use from the essential drugs list. Overall, patients visiting PAL facilities, on average, spent less on health care related costs per episode, including expenses for drugs, fees, and diagnostic tests (US$ 0.83 vs. US$ 1.01), as well as on non-health care related costs (US$ 2.00 vs. US$ 2.20). This is an important finding, as most people visiting government facilities are poor, and saving a few Rupees makes a difference to them.

Next, we found greater effectiveness of the treatment provided at PAL facilities in patients with breathing difficulties with a non-chronic cough (lasting less than two weeks). Better health for patients visiting PAL facilities is also linked to the improvement in the prescribing behavior of health care providers, thereby reducing costs, and increasing health benefits. These effects, though not all statistically significant, may ultimately lead to the improved health status of patients. Measuring the health effects in terms of standard disease-specific indicators was not possible in the context of rural Nepal. The remoteness, as well as the lack of resources at the facilities, restricted us from using appropriate equipment to measure patients' health status. Also, the PAL intervention is a symptom-based approach and not diagnosis-based, hence, it was actually not designed to use diagnosis-based techniques. Therefore, we used several different questionnaires, as well as own researcher observations to measure patient health. We measured the general health effects of patients by means of generic health-related quality-of-life measurements, adapted and contextualized within the local setting, after validation. We demonstrated that patients treated at PAL facilities had increased health-related quality-of-life outcomes compared to patients who were treated at non-PAL facilities, although this was only observed in patients with a chronic cough.

For evaluation purposes, it was essential to develop disease models to study the evolution of disease over time. This study developed two multistate models, the first being a multistate approach to modeling generic health-related quality of life outcomes, and the second being an integrated lung disease multi-state model. The development of these models is based on an extensive literature review on modeling lung diseases. The review found that models exist for single diseases based on disease-specific measures. However, the review of multistate models for lung diseases lead to the selection of the appropriate number of states and an appropriate time period for modeling each of the four lung diseases.

The multistate model based on health-related quality of life was used to study the evolution of patients in different health states defined by their generic health-related quality-of-life (EuroQOL) scores during the follow-up. This model will be useful in contexts in which diagnoses, or disease-specific measurements, are not

available or difficult to establish. Also, this model can be useful in studying and comparing multiple diseases. The present model application showed that patients with a non-chronic cough who visited PAL facilities benefited from and increased health-related quality of life than those who visited the control facilities, which was consistent with what we found in the empirical analysis.

The second multistate integrated lung disease model was developed to analyze the cost-effectiveness of the PAL guidelines compared to the standard practice. Patient categories are healthy, diseased with acute symptoms, or diseased with chronic stable symptoms. The time spent in each state by the population is calculated and weighted through any health-related measurement. At the same time, cost can be associated with the incidence of transition from one state to another, as well as with the time spent in each state. The model outcomes revealed that the PAL implementation pilot was cost-effective at various levels based on standard economic benchmarks. Uncertainty analysis showed that the probability of PAL being effective was 54% in all patient groups together. As such, it is difficult to conclude that PAL would be effective as a program as a whole.

Considering the results of this PAL pilot and the conditions associated with a full-scale implementation of PAL – especially the limited dedication and potential commitment of the national and international implementers – the PAL strategy deserves the benefit of doubt. The partially-positive results and the possibility for further improvement at different levels of implementation should help keep the next PAL implementation phase flexible, taking into account the lessons learnt and allowing for future evaluation and monitoring.

1
Introduction

1.1 Introduction

Human beings are susceptible to different, sometimes fatal, diseases. However, diseases can be prevented, controlled (i.e. less suffering), and cured. People are affected differently by the same diseases in different parts of the world. Those who live in poor countries are still suffering (or dying) from diseases that are virtually non-existent in wealthier countries. The reasons are mainly technical, including lack of knowledge, manpower, equipment, infrastructure, and other facilities required for the provision of efficient health care services. Secondly, from the societal and policy-related perspective, the general inability and lack of commitment by society and government to plan and implement policies in a (self-) sustainable way as a result of poverty, such as less-educated population, lack of knowledge, poor governance, corruption, etc., plays a significant role as well.

In order to effectively deal with diseases existing knowledge and technology can be introduced through 'interventions' by individuals or institutions. However, an adaptation process should precede the introduction of an intervention in a new setting or context. The adaptation process contextualizes the intervention, thus making it more effective during the implementation phase. Prior to full implementation it is important to assess the value of the new or additional health benefits the intervention provides for individuals and society. The health benefits need to be evaluated with respect to costs given that resources are always limited. Hence, economic evaluations are often carried out to determine the costs and effectiveness of new or former interventions within a new setting.

This publication is the outcome of an evaluation study on the implementation of an international health intervention in a poor, rural setting in a developing country, namely in the lowland district of Nawalparasi in Nepal. The intervention selected for the evaluation study is the Practical Approach to Lung Health (PAL) [1, 2], respiratory care guidelines developed by the World Health Organization (WHO). Specifically, the study underlying this book assessed the effectiveness of the PAL intervention's implementation in relation to the costs involved at individual and national levels.

1.1.1 Intervention Practical Approach to Lung Health

Lung disease is one of the leading causes of death in developing countries. Lower respiratory infection (LRI), tuberculosis (TB), chronic obstructive pulmonary disease (COPD), and asthma amount to 15.4% of all disability-adjusted life years (DALYs) lost in the South East Asia Region [3, 4]. Health interventions are continuously being developed to improve individuals' health. Interventions in the form of health care guidelines are implemented by trained health care workers who base the treatment of patients on these guidelines. Guidelines are developed to establish consistency and specific standards in the treatment of diseases within a given health care setting.

In light of the progress made in the Integrated Management of Childhood Illness (IMCI) [5] – an integrated case management strategy – the World Health Organization (WHO) together with several countries across the globe initiated the Practical Approach to Lung Health (PAL) [1, 2], developing guidelines for an integrated case management of tuberculosis, COPD, asthma, pneumonia, and other respiratory diseases. The PAL guidelines aim to improve the quality and efficiency of respiratory health care services by providing standardized tools for primary health care and district hospital workers to effectively manage respiratory infections, tuberculosis, asthma, and chronic obstructive lung diseases in adults. Trained health care workers at primary health care facilities implement the PAL guidelines to evaluate a patient's condition using algorithms that follow a syndromic approach to disease. Health care providers use the guidelines to carry out patient evaluations step-by-step, arriving at a specification of the most suitable form of disease management and, where required, of treatment [6]. This initiative aims to promote better lung health care of adult patients at first level government health care facilities.

The PAL guidelines' effects and costs had not yet been tested in a real life setting. Only few countries participated in the first phase of the pilot implementation and evaluation, Nepal being one of the countries. PAL-Nepal [4], a research strategy by the Nepal Tuberculosis Center (NTC) under the Ministry of Health, Nepal (MoH-N), and the WHO-Nepal as an implementing partner, alongside a team of researchers from national and international institutions as evaluating partners, was developed in the Netherlands in 2001.

1.1.2 Nepal

In 2003 Nepal's population size was estimated at over 26 million [7]. According to a 2001 census [8], the population's growth rate was 2.25%, with 86% of the population residing in rural areas. The country can be divided into three ecological zones, namely mountains, hills, and Terai (lowlands), covering 35%, 42%, and 23% of Nepal's total area, respectively. The Terai region, which is flat and more fertile, is

inhabited by 48.4% of the population, while 7.3% and 44.3% of the population live in the mountainous and hills regions, respectively. Nepal's population is relatively young with a median age of 20.1 years (19.7 for males and 20.5 for females) (2001).

Life expectancy at birth is 62.2 years (2004); life expectancy of females (62.5 years) only recently surpassed that of males (61.8 years) due to the successful reduction in maternal deaths (from 539 per 100,000 births between 1989–1995, to 281 between 1999–2005) (DHS). In 2005 the infant mortality rate was 56 per 1000 live births (WHOSIS).

According to a 2001 census [8], 42.8% of women in Nepal are literate, compared to 65.5% of men. Nepal is one of the poorest countries in the world with a GDP per capita of US$240 ($168^{th}$ in the world) and GDP (PPP) of US$1,402 ($153^{rd}$ in the world) [9].

1.1.3 Health Expenditure in Nepal

According to Hotchkiss *et al.* (1998) [10], 75% of the total health care expenditure in the fiscal year 1994/1995 was out-of-pocket, amounting to 3.9% of the total GDP. Health care costs added up to 5.02% of the average household budget, the percentage among the wealthiest rural quartile being highest at 8.72% and lowest at 1.11% among the urban poorest quartile. Additionally, donors (13%), the government (10%), and private companies (2%) contributed to the total health expenditure. More recent figures reveal a similar distribution of health care costs. Total expenditure on health per capita amounted to US$12 in 2002, of which US$3 (25%) derived from public funds [11]. Some 6.2% of the total national budget was allocated to health care [11]. This highlights the weight of out-of-pocket expenditure on health care in Nepal. That is, policies targeting the reduction of medical costs should focus on the reduction of out-of-pocket costs. These include travel (8%) and consultation fees (92%). Consequently our evaluation of the cost-effectiveness of implementing PAL in Nepal considers health expenditure from a public perspective, as well as from the patient's perspective.

1.1.4 Health in Nepal

According to the 2002 WHO Global Burden of Disease study [12], 49% of all deaths in Nepal (233,000) are caused by diseases and conditions classified by the WHO under Group I diseases (communicable, maternal, perinatal, and nutritional conditions); in South Asia, only Pakistan (52.8%) has a higher mortality rate. This measurement can be used as an indicator of the status of health care services, denoting a negative association between the percentage of deaths linked to Group I causes which correlates negatively with development as indicated by the following figures – EU-25 (5.7%), US/Canada (6.0%), Sri Lanka (13.4%), Southeast Asia

(29.1%), South Asia (42.2 %), and Africa (72.3%). The primary reason for a high mortality rate from Group I causes is directly linked to poverty and illiteracy, which impact the general health of the population, while many of the diseases and conditions classified in this group have been eradicated or are prevented and controlled in more developed countries. Tuberculosis and respiratory infections, which are of particular interest for our study, are classified in this group. In 2002 6,000 deaths in Nepal were linked to tuberculosis (2.6% of the country's total mortality rate) and 23,800 to lower respiratory infections (10.2%).

The second group (Group II) in the WHO's burden of disease study comprises non-communicable diseases. The diseases in this group do not spread from one person to the other, but are generally chronic in nature. Approximately 42% of the deaths in Nepal in 2002 were linked to diseases in this group. In developed countries more deaths are linked to diseases from this group than from communicable diseases. Asthma and chronic obstructive pulmonary disease (COPD), which are also of particular interest for us, are classified in this group and are the cause of 2.2 (0.9%) and 6.6 (2.8%) deaths in Nepal, respectively. Nine percent of deaths are caused by injuries (Group III) and 'unclassified' causes.

In addition to mortality estimates, the WHO burden of disease study also provides data on disability-adjusted life years (DALYs), that account for lives lost due to both morbidity and mortality. In Nepal the total number of DALYs lost in 2002 was estimated at 7.5 million years, of which approximately 36% were lost as a result of disability caused by disease (estimated by the number of incidents, disability weight of the disease, and duration of the disease). About 64% of the total number of DALYs lost is caused by premature death, which is estimated with reference to the person's remaining average life expectancy at the time of death [13]. The percentage of total DALYs lost due to tuberculosis, lower respiratory disease, asthma, and COPD was 1.9, 7.6, 1.1, and 1.1, respectively.

The data clearly illustrate the impact of respiratory diseases in Nepal. A baseline study conducted by the WHO and the Global Tuberculosis Initiative (GTB) in Nepal revealed that 8.5% of patients aged five and older, who visited primary health care facilities with no on-site physician, had symptomatic respiratory problems [14]. Nepal has an extensive network of primary health care facilities offering basic medical services to the majority of Nepalese living in rural areas [15]. The lowest level unit is known as the *Sub-Health Post* (SHP), and the staff providing services at this level only have a few years of basic medical training. The staff at the higher-level units, the *Health Posts* (HP) and *Primary Health Care Centers* (PHC), have more advanced medical training and the facilities are equipped with some basic laboratory services. A referral system exists; patients are referred to higher level facilities when complications arise or when the nature of the patient's disease is complex. Hospitals represent the highest health care facility level and are generally located in big cities or urban areas. This study evaluates the effectiveness

of the PAL guidelines in primary health care facilities, namely sub-health posts, health posts, and primary health care centers.

1.1.5 PAL-Nepal

Researchers in Nepal, The Netherlands, and the USA developed a research plan to assess the health outcomes and costs of implementing PAL in Nepal [4]. The main research question was how cost-effective the implementation of PAL in Nepal is. Specifically, the objectives of the study were:

1. To weigh the costs of implementing the PAL guidelines in government facilities against the costs of retaining the existing range of medical services. Costs were considered from a societal and health sector perspective.

2. To compare the outcome for patients treated at PAL facilities to that of patients treated at facilities employing standard medical services.

3. To compare the cost-effectiveness of the PAL guidelines strategy to other possible national health schemes. Such a comparison must take the actual prevalence of disease into account, as well as the existing quantity and quality of services being provided.

The researchers selected the lowland district Nawalparasi in Nepal in coordination with the WHO and the Nepal Tuberculosis Center (NTC), since it met all the required preconditions for the implementation of the PAL guidelines. The preconditions include the implementation of other WHO programs and availability of experienced health care workers [16] for TB and Integrated Management of Childhood Illnesses (IMCI) [17]. DOTS (Directly Observed Treatment Schedule) for TB was first introduced in Nepal in 1996 by NTC, and IMCI in 1995. The DOTS strategy is a combination of technical and managerial components which quickly transforms infectious TB cases into non-infectious ones and interrupts the transmission of the disease [16]. Similarly, IMCI is a strategy to improve children's health and includes a number of complementary interventions for various childhood illnesses, mainly pneumonia, diarrhea, malaria, measles, and malnutrition at the community, health care facility, and health system level [17]. The integrated strategy refers to the treatment, or case management, in which the health care worker uses a color-coded triage (algorithm) system to classify the child's condition as urgently requiring a referral to a more specialized facility that can evaluate the child's condition more accurately and provide the necessary care, or whether the child can be treated on site, or whether the child can convalesce at home [17]. The availability of health care workers with experience in using these two strategies (DOTS and IMCI) is crucial for the effective implementation of the PAL strategy [4]. PAL's algorithmic approach has a similar format as IMCI's [4].

After it was agreed that a pilot implementation would be launched, a group of health professionals and researchers at local, national, and international levels were assigned to devise an implementation plan. A research group was established under the umbrella of the Nepal Health Research Council (NHRC), an ethics committee under the MoH-Nepal. The WHO's PAL guidelines were reviewed and an adaptation process initiated at the national level. The PAL guidelines were translated into Nepali and tested by local health professionals. The processes implemented at this level are well documented in a thesis by Ten Asbroek (2006) [18].

Parallel to the implementation process, another group of researchers (which included the author) was involved in designing a research plan to evaluate PAL's cost-effectiveness in relation to the standard treatments available. Data were continuously collected at the facility level. Data on infrastructure, costs, time, etc. were gathered before and after the implementation of the PAL guidelines. Forty-two of 67 health care facilities in Nawalparasi were selected for inclusion in our study on cost-effectiveness based on their high patient turnout.

Once nationally adapted PAL guidelines had been prepared, health care workers from 22 randomly selected governmental first-level health care facilities were trained in June and July 2002. The training was conducted by trainers who had previously been trained by experts from the NTC and WHO. The training of trainers and the training of health care providers by these trainers are the most important steps in the implementation process. Twenty primary health care facilities were randomly selected in the same district to function as control facilities, representing standard practice facilities.

Two months after the last training took place, field assistants (FAs) were sent to all 42 health care facilities to collect data from individual patients with lung disease-related symptoms. We waited two months to determine the actual effect of the knowledge generated by the PAL guidelines in a real setting, since we believed that the training's immediate result would be misleading. Data from the two primary health care facility types were collected at patient- and facility-level from September 2002 to September 2003. Baseline data from the facilities had been collected since 2001. Data analyses were carried out in The Netherlands throughout 2004, the results of which are reported here.

1.2 Structure of This Book

This book is about assessing the costs and effectiveness of implementing PAL guidelines and, ultimately, to estimating the cost-effectiveness of the PAL guidelines in comparison to standard practice. The analysis of the intervention type and context required tailor-made techniques. The first step involved conducting an empirical assessment on which to build a model for long-term predictions or for

better understanding the process and including additional factors from secondary sources. The first part of the book focuses on empirical analyses of costs, effects, and on cost-effectiveness analysis. The second part presents a multistate modeling technique to describe and simulate the evolution of PAL diseases. The results of the model are elucidated in terms of standard outcomes, as well as in terms of new outcome measures in six chapters.

The first three chapters (Chapters 2 to 4) depict the empirical analysis. Chapter 2 analyzes the divergence in the health effects experienced by patients with respiratory problems who visited a PAL facility, and the health effects experienced by those who were treated at a conventional health care facility (control group). The analysis involved two groups of patients who were classified in accordance with their initial condition prior to visiting a facility, namely determined by the duration of their cough. Those who had a *chronic cough* – defined as a cough that had already lasted more than two weeks by the time the patient visited the health care facility – were believed to have TB or COPD. The recovery period for TB and COPD is longer than for other respiratory diseases, and hence, a follow-up interview with patients diagnosed with either of the two conditions was conducted two months later, while patients without a chronic cough were interviewed again after two weeks. The results were mixed, although the patients that had been treated at facilities implementing the PAL guidelines showed slightly better results.

Chapter 3 describes the tool used in the data collection to measure individual patient's Health-Related Quality of Life (HRQOL). Health-Related Quality of Life is a recommended outcome variable in health economics and epidemiology to measure individuals' health status [19, 20]. The HRQOL data were collected using two sets of standard HRQOL questionnaires addressing all patients at the time of their first visit to a health care facility, and selected patients after two weeks or two months, depending on the initial duration of their cough. As far as we know, we are the first to use Health-Related Quality of Life questionnaires to assess patients' health status. In this book we describe the process of adapting the questionnaires, and present the results of the patients included in the PAL study. We found that the questionnaires adequately measured the changes in the health status of the two groups of patients with respiratory symptoms within a time period of two weeks, as well as two months.

In Chapter 4 we compare the prescription behavior of health care providers in the PAL facilities and in the standard practice facilities. One of the aims of the PAL intervention is to enhance efficient prescription behavior to promote the rational use of drugs for selected respiratory diseases. Patients often pay for their drugs out-of-pocket, and we presume that PAL's impact on the rational use of drugs will lower patients' out-of-pocket costs by lowering excess expenditure on drugs. We found the PAL guidelines to be more suitable for promoting rational use of drugs in terms

of improved prescription behavior, as well as reducing the average prescription costs.

Subsequently, we developed multistate models for lung diseases and used these models to perform a cost-effectiveness analysis. Multistate models are useful for studying life histories in terms of incidents, such as disease occurrence, progression, and mortality. Multistate models are widely used in the field of medical prognosis, as well as in the study of model-based economic evaluation and medical decision making. The section on models comprises three chapters (Chapters 5 to 7). Chapter 5 reviews existing multistate models for lung health (tuberculosis, asthma, and COPD). We did not find any other study that applied multistate models for lower respiratory infections.

We then present an in-depth review of lung disease models and draw inferences to build PAL multistate models. The definition of state-space, assumptions in the model, the measurement of transition rates/probabilities, and uncertainty analysis were reviewed. These are important steps in the establishment of a PAL model, however, exact state-space and the measurement of transition rates/probabilities were difficult or impossible to replicate, since most of the lung models studied had in fact been implemented in the developed world with its abundant resources. In the context of PAL, the measurement of individual disease states is difficult because of a lack of resources, and the distinct design of the PAL strategy. In the subsequent two chapters we present the multistate models based on health-related quality of life states as an alternative to the states of disease.

In Chapter 6, we propose a state-space for health-related quality of life using the European Quality of Life Questionnaire (EuroQOL), commonly known as EQ-5D (EuroQol with 5 Dimensions) [21]. Most research on the HRQOL assesses the mean HRQOL or the mean change in HRQOL. That is, it is not possible to model HRQOL directly in, for instance, a Markov model with states defined by HRQOL. In fact, when HRQOL is an outcome of a modeling exercise, it is a value attributed to the categorized prognostic variables of the diseases [22–25]. In that regard one could say that HRQOL is always modeled indirectly. If HRQOL is genuinely considered an important feature of health, then direct modeling of HRQOL is indeed useful and the classification of health states based on HRQOL should be explored. We propose several methods of classification and use empirical data from PAL for demonstration purposes. After HRQOL is classified into appropriate states (with discriminative and evaluative values), the divergence in the transition probabilities between HRQOL states as a result of different interventions can be considered an effect in the cost-effectiveness evaluation.

Finally, in Chapter 7 we address the question whether PAL, as implemented in Nawalparasi Nepal, by the WHO-Nepal and NTC, is cost-effective. The implementation of the PAL guidelines in general is considered a better alternative to the standard health care available at primary health care levels. However, health care

providers who actually apply the PAL guidelines to treat patients are either the key to the intervention's success or the key to its failure. Hence, the intervention's implementation is one of the most crucial aspects. Moreover, its success depends on the patients who have to follow the treatment guidelines and the recommendations of the health care workers. Failure to understand or comply with the prescription and advice makes even the best intervention ineffective and sometimes even costlier. Costs are estimated from a societal, as well as from an individual perspective. The expenses covered by the government and the community include training the health care workers, investments in infrastructure, equipment acquisition, payment of salaries, provision of subsidies for drugs/services, etc.

At the same time, individual patients have to also pay out-of-pocket for various health care-related and non-health care-related costs. We expect that the implementation of PAL will also help lower patients' out-of-pocket costs, while the government will have to spend more on the training and supervision of health care providers during the implementation phase of the PAL strategy. We have developed a single integrated multistate model for four PAL diseases. Based on data from the WHO on lung diseases, as well as on data of costs and effects derived from the PAL survey, we assessed the long-term cost-effectiveness of the PAL implementation in Nepal.

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Part I

PAL: EMPIRICAL ASSESSMENT

2

Effectiveness of Integrated Syndromic Lung Health-Guidelines in Patients with Breathing Difficulties in Rural Nepal

The health effects of an integrated symptom-based approach to lung health, the Practical Approach to Lung Health (PAL) guidelines developed by the World Health Organization, were unknown in real-life settings. The PAL guidelines were adapted to the Nepalese setting and health care providers from randomly selected facilities (referred to in this study as PAL facilities) in a Nepalese rural district were trained in applying the guidelines. We compared the health effects in patients with breathing difficulties who has been treated at a PAL facility with those in patients who had visited a facility using the standard treatment schedule (i.e. STS facilities).

We identified two groups of patients with breathing difficulties when the first interview was conducted, namely, those with a cough that had lasted over two weeks by the time of the visit to the health care facility (i.e. 'with a chronic cough'), and those 'without a chronic cough'. Data were collected during the first visit (baseline) to a given facility and during a follow-up visit at the patient's place of residence. The follow-up interview of patients with a chronic cough (n = 296) and of those without a chronic cough (n = 270) took place two months and two weeks later, respectively. We used five symptom-based questions derived from Juniper's Asthma Control Questionnaire (ACQ) to obtain ACQ5 scores. T-tests and a linear regression analysis compared the health effects in patients treated at PAL and at STS facilities.

At baseline, the mean ($\pm$ standard deviation) of the ACQ5 score was higher for patients without a chronic cough than for patients with a chronic cough (1.95 $\pm$ 1.05 vs. 2.41 $\pm$ 0.96, $P < 0.001$). Patients' conditions generally improved following a visit to a health care facility. After correcting for age, the change in the health states of patients with a chronic cough, who had been treated at a PAL facility, resulted in a reduction of the ACQ5 score by 0.166 (P-value = 0.505) compared with visitors of a STS facility, and by 0.360 (P-value = 0.008) among patients without a chronic cough.

The treatment patients, who did not have a chronic cough, received at PAL facilities seemed to be more effective than the treatment provided at STS facilities. Are PAL guidelines thus more effective than the STS? This may depend on various factors, including training, use of the skills acquired, etc. Differences may also be

explained by the way the chosen instruments were implemented. The project trained one person per facility, i.e. a 'trained person-effect' may be evident. Since the facilities were randomly divided into two groups – into PAL and STS – at the onset of the study, the only difference between the health facilities and the patient groups was the training of the health care providers on how to apply the PAL guidelines in the intervention. Pooled data in each group and averages were computed in the assumption that any additional effects were random. Other factors may also explain the results. The intervention strategy presumes that the trained health care worker disseminates his/her acquired knowledge to others. From a clinical point of view, patients with both breathing difficulties and a chronic cough are less likely to be asthma patients. The Asthma Control Questionnaire is therefore less suitable for bringing about health improvements for this patient group than for patients who only suffer from breathing difficulties. This might very well explain why patients with a chronic cough and who were treated at PAL facilities, did not display any additional health benefits compared to those who visited STS facilities.

2.1 Introduction

A baseline study conducted by the World Health Organization (WHO) and the Global Tuberculosis Initiative (GTB) in Nepal indicated that 8.5% of all patients aged five and up, who visited a primary health care facility without an on-site physician, were classified as symptomatic respiratory cases [1]. Among these symptomatic respiratory cases, 22.5% were chronic respiratory cases, with 12.5% suffering from asthma and 10% from a chronic cough [1]. With the exception of tuberculosis case management, Nepal's health system does not employ a standard strategy to deal with the large number of patients with lung diseases. This is reflected in the low quality of health care delivery and leads to unnecessary financial burdens for both the health care system and the individual patient [2].

To date only few studies measuring the health effect of patients with lung diseases in Nepal have been conducted. A study carried out by Melsom *et al.* (2001) analyzed the implication of indoor environmental factors on childhood asthma, but the health effects as such were not assessed [3]. The health effects of an integrated symptom-based approach to lung health, the Practical Approach to Lung Health (PAL) guidelines developed by the WHO, which covers four lung diseases (tuberculosis, asthma, chronic obstructive pulmonary diseases, and pneumonia) were unknown [2, 4, 5]. Consequently, the PAL guidelines were adapted to the Nepalese context and health care providers from randomly selected facilities in a rural Nepalese district were trained in how to apply them.

This chapter focuses on the case management of patients with breathing difficulties. Specifically, the health effects in patients with breathing difficulties are

measured within the context of the PAL guideline implementation in Nepal [2, 4, 5]. Hence, our first task was to define standard tools – be they generic, disease- or condition-specific – to measure health effects. Below we will describe the tool used to measure the condition-specific health effects in patients with breathing difficulties.

The general objective was to compare the health effects of patients with breathing difficulties who sought treatment at facilities that used the PAL-guidelines with those of patients who visited facilities using the current standard treatment schedule (STS). We established the baseline measures for breathing difficulties during the patients' first visits to the health care facility, taking some important covariates into account. Subsequently, in a follow-up interview, the health effects in patients who had been treated at a PAL or STS facility were assessed with reference to the covariates age and sex. In addition, we studied the correlation between the health effects in patients and an objective measurement of lung function, namely peak flow measurements.

2.2 Methods

2.2.1 Background on the Design of PAL's Field Trial in Nepal

A trial of the PAL-Nepal program was tested between 2001–2003, during which 42 health care facilities were randomized into a control group of 20 facilities, whose staff applied the standard treatment schedule (STS) for lung disease being used in community practices, and into an intervention group of 22 facilities, whose staff received six days of training by the Nepal Tuberculosis Center (NTC) on how to apply the PAL guidelines. The health care facilities selected included Sub-Health Posts (SHP), Health Posts (HP), and Primary Health Care Centers (PHCC). The patient cases are classified in accordance with this hierarchical system, though patients are free to choose which health care provider to turn to [6]. SHPs are the smallest of the three health care units, with a staff of only three health care workers, of which only one has completed a two year professional training program and is thus the only one qualified to treat adults. The staff at HPs and PHCCs include higher level medical personnel. PHCCs are the most advanced and also the largest health care units included in our study with a medical officer (doctor) on site. The details of the intervention, as well as the general context, is explained in more detail in Ten Asbroek (2005) [6]. Between June and July 2002, at least one health care provider from each of the 22 selected health care facilities was trained in how to apply the PAL guidelines. From September 2002 to July 2003 (ten months), patients aged 15 years and older who visited one of the 42 health facilities and reported having at least one of the following symptoms – fever, coughing, and/or breathing difficulties – were included in our study and followed-up during their treatment period at the

given health care facility. We obtained a clearance from Nepal's national ethics committee and a written consent from the patients who participated in the data collection process. Follow-up interviews were not conducted with patients who only had a fever or a cough that lasted less than 15 days, since the likelihood that these patients had one of the target diseases was rather low. Patients with a chronic cough that lasted 15 or more days were interviewed again two months later, while the remainder were interviewed two weeks after the initial interview, usually at the patient's home. A maximum of three attempts were made to schedule a follow-up interview at the patient's home. Data were collected from 2243 patients visiting one of the 42 selected facilities between September 2002 and September 2003 (ten months for the baseline interviews and two months for the follow-ups).

2.2.2 Materials and Methods Used in This Study

One of the main assumptions of the PAL-Nepal strategy was that patients were likely to be misdiagnosed, because of the health care providers' (mostly nurses) lack of knowledge, the insufficient equipment, and inadequate infrastructure. To reiterate, the four diseases included in the PAL guidelines are pneumonia, tuberculosis, chronic obstructive pulmonary disease, and asthma. According to the guidelines, pneumonia can be diagnosed at the facility level, while most of the other lung diseases' symptoms are recognizable and can subsequently be treated on site, or patient referrals made to higher level health care facilities for further testing [4]. Known cases of asthma or chronic obstructive pulmonary disease can be diagnosed for obvious reasons. Hence, our study was designed independently of a patient's diagnosis. Patients who answered "yes" to having any of the three PAL entry symptoms (breathing difficulties, a cough, and fever) were included in our sample. This approach was validated in advance [7–9].

The PAL guidelines' effectiveness for patients with breathing difficulties was analyzed using Juniper's Asthma Control Questionnaire (ACQ) [10]. Juniper developed and validated the ACQ which comprises seven questions on all criteria to determine whether a patient has asthma (symptoms, airway caliber, and rescue beta-two-agonist use) [11]. Juniper concluded that the force expiratory volume in one second (FEV_1) and beta-two-agonist questions could be omitted from the ACQ for large clinical and epidemiological trials, without modifying the instrument's validity or measurement properties [11].

The unavailability and cost of beta-two-agonist in Nepal's rural areas reduces the likelihood that patients use a beta-two-agonist. The evaluation research consisted of one follow-up visit to the patient's home, which was sometimes inaccessible for all types of vehicles. Hence, it was not practical in terms of costs and management to include spirometry to measure peak expiratory flow. We therefore used a peak flow meter instead and verify this instrument's validity in our study.

We used questions on symptoms from the ACQ for the analysis. There are five questions on symptoms, referred to as ACQ5. We calculated ACQ5 scores by taking the mean of responses related to symptoms (the first five) as described by Juniper *et al.* [10]. The score ranges from 0 to 5, with a lower score indicating better control of the disease.

A literature review revealed that ACQ had not yet been used in lung health-related research in Nepal. This chapter presents the distribution of ACQ scores and their association with the covariates age and sex. Furthermore, ACQ5 scores were used to assess PAL-Nepal's effectiveness in controlling asthma among asthma patients. According to the PAL guidelines, breathing difficulties are one of the leading symptoms of asthma, as well as of chronic obstructive pulmonary disease. We evaluated patients with breathing difficulties and defined those whom we followed-up after two months or after two weeks as 'difficulties breathing with chronic cough' (DBWCC) and 'difficulties breathing without chronic cough' (DBWoCC), respectively.

2.2.3 Analysis

Table 2.1 illustrates patient characteristics. We include the descriptive statistical mean and standard deviation of ACQ5 scores for the different values of the covariates age, sex, and health care facility level (PHCC, HP, and SHP). We also applied independent t-tests and chi-square tests to examine the effect of randomization using baseline data. At the baseline, a stepwise linear regression analysis was performed to assess the relationship between the ACQ5 score and the variables age and sex.

The PAL effect was first measured using a paired t-test of the ACQ5 scores during the baseline and follow-up. A stepwise linear regression was performed to assess the relationship between the ACQ5 score and each covariate. Huber & White's variance estimator was used to adjust the effect of patient clustering in a given facility. The relationship between the ACQ5 score and the peak flow measurement was explored using Pearson's correlation coefficient. Separate analyses were conducted for patients with DBWoCC and DBWCC. We used STATA 8.2, STATACORP LP for all statistical analysis.

2.3 Results

In total we interviewed 2243 patients with PAL-related symptoms who visited one of the select health care facilities for the first time during the disease episode. Six hundred and sixty (29.2%) patients reported that breathing difficulties were one of the reasons for visiting the facility. We first identified cases with complete data for the ACQ5; for the baseline assessment, we compiled a total of 638 cases with

complete ACQ5 data during their first visit to the health care facility. Among these, 566 cases with complete ACQ5 data were interviewed during a visit to their home, which subsequently were used for the effectiveness analysis. We identified 270 patients with DBWoCC and 296 patients with DBWCC.

Table 2.1 shows the distribution of patients with respect to the covariates used in our analysis, as well as the distribution of the symptoms of patients having breathing difficulties. Patients with DBWCC were older than patients with DBWoCC: the mean (SD) age in years was 51.2(17.8) vs. 46.7(18.8) with $|t| = 3.16$ and P-value = 0.0016. In patients with DBWCC, the mean age was higher among those visiting STS facilities than among those being treated at PAL facilities (53.5 years vs. 49.3 years, $|t| = 2.19$, P-value = 0.029). The difference was not statistically significant among patients with DBWoCC (P-value = 0.202). The distribution of the covariate sex among patients with either DBWoCC or DBWCC who sought treatment at the PAL or STS facilities was similar.

Overall, the mean baseline ACQ5 score was lower among patients with DBWoCC (*Table 2.2*). With regard to sex, we found that the mean baseline ACQ5 score was lower in women than men across all categories. However, a statistically significant difference between the two sexes was only found among patients with DBWoCC who visited PAL facilities (1.77 vs. 2.14: $|t| = 2.37$, P-value = 0.02). We found no significant difference in the ACQ5 scores of men and women who sought treatment at PAL and STS facilities. Patients visiting PAL facilities had a slightly higher baseline ACQ5 score than patients visiting STS facilities in both symptom categories (*Table 2.2*). However, the t-test revealed no significant difference. The divergence in the ACQ5 scores is low (0.157), possibly due to an initially higher ACQ5 score for patients visiting PAL facilities. The difference in the 'Both Sexes' column with regard to DBWoCC is 0.05 higher in the PAL facilities, but when compared separately, we actually see mixed results. Among males, the score is 0.16 higher in PAL facilities; among females, the difference is 0.08 higher in STS facilities. Moreover, the reduction in the ACQ5 score by 0.157 (not statistically significant) is found among patients with a chronic cough.

We performed a linear regression on the baseline ACQ5 score, including age as a covariate, and found that an increase in age by one year increases the score by 0.013 (P-value < 0.001) and 0.007 (P-value = 0.014) in patients with DBWoCC and with DBWCC, respectively.

The mean $\pm$ standard deviation of the change in the ACQ5 score was found to be -1.047 and 1.24 among all patients with breathing difficulties. The results for patients with DBWoCC and with DBWCC were -1.188 ± 1.34 and -0.901 ± 1.11. Mean differences were significant, with a P-value < 0.001 and a low standard error of 0.00504 in the DBWoCC group ($= 1.27/126^{0.5}$). The result shows that these patients' conditions improved after they visited a health care facility in general.

Table 2.1. Patients' Attributes by Facility Type

		Total		DBWoCC		DBWCC	
		PAL	STS	PAL	STS	PAL	STS
Age	15–29	83 (21.7%)	41 (14.7%)	45 (23.6%)	24 (18.9%)	38 (19.9%)	17 (11.3%)
	30–39	46 (12.0%)	35 (12.6%)	30 (15.7%)	15 (11.8%)	16 (8.4%)	20 (13.2%)
	40–49	62 (16.2%)	33 (11.9%)	27 (14.1%)	22 (17.3%)	35 (18.3%)	11 (7.3%)
	50–59	59 (15.4%)	48 (17.3%)	26 (13.6%)	20 (15.7%)	33 (17.3%)	28 (18.5%)
	60–69	77 (20.2%)	67 (24.1%)	42 (22.0%)	26 (20.5%)	35 (18.3%)	41 (27.2%)
	70+	55 (14.4%)	54 (19.4%)'	21 (11.0%)	20 (15.7%)	34 (17.8%)	34 (22.5%)
Sex	Male	209 (54.7%)	150 (54.0%)	102 (53.4%)	68 (53.5%)	107 (56.0%)	82 (54.3%)
	Female	173 (45.3%)	128 (46.0%)	89 (46.6%)	59 (46.5%)	84 (44.0%)	69 (45.7%)
Symptoms*	DB Only	10 (2.6%)	11 (4.0%)	10 (5.2%)	11 (8.7%)	–	–
	DB +Fever	4 (1.1%)	3 (1.1%)	4 (2.1%)	3 (2.4%)	–	–
	DBWoCC	73 (19.1%)	43 (15.4%)	73 (38.2%)	43 (33.9%)	–	–
	DBWoCC +Fever	104 (27.2%)	70 (25.2%)	104 (54.5%)	70 (55.1%)	–	–
	DBWCC	106 (27.7%)	69 (24.8%)	–	–	106 (55.5%)	69 (45.7%)
	DBWCC +Fever	85 (22.3%)	82 (29.5%)	–	–	85 (44.5%)	82 (54.3%)
	Total	382 (100%)	278 (100%)	191 (100%)	127 (100%)	191 (100%)	151 (100%

*DB = Difficulties Breathing

Table 2.2. Mean baseline ACQ5 scores among patients with breathing difficulties, with and without a chronic cough, visiting PAL and STS facilities

		Mean ± Standard Deviation (size)	
		STS	PAL
Both Sexes	Total	2.19 ± 1.01 (266)	2.20 ± 1.05 (372)
	DBWoCC	1.92 ± 1.05 (119)	1.97 ± 1.06 (185)
	DBWCC	2.40 ± 0.92 (147)	2.42 ± 0.99 (187)
Male	Total	2.23 ± 1.00 (142)	2.29 ± 1.01 (203)[1]
	DBWoCC	1.98 ± 1.09 (62)	2.14 ± 1.14 (100) [2]
	DBWCC	2.43 ± 0.87 (80)	2.43 ± 1.00 (103)
Female	Total	2.13 ± 1.02 (124)	2.09 ± 1.01 (169)
	DBWoCC	1.85 ± 1.00 (57)	1.77 ± 0.93 (85) [1]
	DBWCC	2.37 ± 0.99 (67)	2.37 ± 0.99 (67) [2]

T-test Male vs. Female: [1]P-value < 0.10; [2]P-value < 0.05

Table 2.3. Test of the significance of the difference in mean change in the ACQ5 score between PAL/STS, in patients with DBWoCC and DBWCC

		Mean ± Standard Deviation (size)		t-statistic (P-value)
		STS	PAL	t (P-value)
Change in	Total	–0.88 ± 1.21 (230)	–1.17 ± 1.25 (336)	0.296 (0.005)
ACQ5 Score	DBWoCC	–1.04 ± 1.27 (126)	–1.29 ± 1.38 (170)	0.374 (0.007)
	DBWCC	–0.68 ± 1.12 (104)	–1.05 ± 1.09 (166)	0.250 (0.112)

The mean difference of the change in the ACQ5 score between patients visiting PAL and STS facilities was –0.25 (P-value = 0.112) and –0.37 (P-value = 0.007) in DBWCC and DBWoCC, respectively (see Table 2.3). The results indicated a lower ACQ5 score following treatment at a PAL facility, consistent with an improvement in respiratory health. However, the difference was statistically significant only among patients who did not have a chronic cough.

Two sets of stepwise multiple regression analyses for patients with DBWoCC and DBWCC were performed to explain the change in the ACQ5 score during the follow-up, by testing independent variables including: facility-type (PAL/STS), age, sex, baseline ACQ5 score, and facility-level (see *Table 2.4*).

The variables age, sex, baseline ACQ5 score, and facility-level (two dummy variables) were introduced in the model as covariates, since they (could) affect the change in the ACQ5 score and, hence, we separated the main effect, i.e. the effect of facility type visited (PAL/STS) on the change in the ACQ5 score. We included the baseline ACQ5 score in the model, since the baseline score among patients visiting PAL facilities was higher (though statistically insignificant) (*Table 2.2*). In

Table 2.4. Linear regression models of change in the ACQ5 score, based on different variables

	Regression coefficients (P-values) of change in the ACQ5 score based on variables				
DBWoCC	Model 1	Model 2	Model 3	Model 4***	Model 5
Constant	–0.675 (0.000)	–1.134 (0.000)	–1.107 (0.000)	–0.315 (0.070)	–0.317 (0.072)
Group (PAL = 1)	–0.374 (0.008)	–0.344 (0.009)	–0.341 (0.008)	–0.360 (0.008)	–0.361 (0.007)
Age		0.009 (0.008)	0.010 (0.007)	0.016 (0.000)	0.016 (0.000)
Sex (male = 1)			–0.118 (0.358)	–	–
Baseline ACQ5				–0.583 (0.000)	–0.579 (0.000)
PHCC					–0.181 (0.197)
HP					0.015 (0.929)
DBWCC	Model 1	Model 2	Model 3	Model 4	Model 5***
Constant	–1.044 (0.000)	–1.849 (0.000)	–1.792 (0.000)	–0.526 (0.181)	–0.345 (0.388)
Group (PAL = 1)	–0.249 (0.354)	–0.184 (0.481)	–0.181 (0.483)	–0.158 (0.566)	–0.166 (0.505)
Age		0.015 (0.006)	0.015 (0.005)	0.02 (0.000)	0.019 (0.000)
Sex (male = 1)			–0.13 (0.400)	–	–
Baseline ACQ5				–0.658 (0.000)	–0.651 (0.000)
PHCC					–0.462 (0.034)
HP					–0.375 (0.218)

***Final Model

addition, patients with a lower ACQ5 score (i.e. whose health condition was better) recovered sooner than patients with a higher ACQ5 score.

At the same time, the minimum value ACQ5 could have was 0, implying that no problems were associated with breathing difficulties. It also means that the reduction of the ACQ5 score is limited, and for those with a lower ACQ5 score the limit is smaller. In line with this argument, age and sex were included, since an increase in age leads to a higher ACQ5 score at baseline, and females have lower ACQ5 scores (though statistically insignificant). Regarding the variables related to facility level, we expected that receiving treatment from higher level facilities would have a positive effect on the patient's health, considering that the medical competency and resources of higher level facilities are more advanced. We introduced two dummy variables for facility level, with PHCC = 1 and HP = 0 indicating facility visited as PHCC; with PHCC = 0 and HP = 1 indicating HP; and with PHCC = 0 and HP = 0 indicating SHP.

Our main hypothesis is that the reduction in the ACQ5 score is higher among patients who seek treatment at PAL facilities than among those visiting non-PAL facilities, correcting for other relevant characteristics, including baseline ACQ5 scores, as these may be effect modifiers. We considered several stepwise regression models as illustrated in *Table 2.4*. Variables with a statistically insignificant effect were excluded from the model at each step. That is, the final model only consists of statistically significant dependent variables.

Table 2.4 represents the individual results of the regression analysis of change in the ACQ5 scores with reference to the different (previously described) covariates for the two groups of patients, DBWoCC and DBWCC. Our main independent variable in Model 1 (*Table 2.4*) is 'Group', which either has a value of 0 for a STS facility or a value of 1 for a PAL facility. A higher reduction in the ACQ5 score for patients visiting PAL facilities is evident with 0.374 (P-value = 0.008) for patients with DBWoCC, and 0.249 (P-value = 0.354) for patients with DBWCC. This implies that a PAL facility provides better health care than a STS facility, which applies to patients with DBWoCC, but not to those with DBWCC.

To control for other covariates' effects on the ACQ5 score, we included each covariate separately, as demonstrated in Models 2 to 5 (*Table 2.4*). In Model 2, we introduced the patient's age, which has a significant positive effect (i.e. deteriorating health effect) on the ACQ5 score for both groups of patients, with each additional year in age lowering the total reduction in the ACQ5 score by 0.009 (P-value = 0.008) among patients with DBWoCC, and by 0.015 (P-value = .006) among patients with DBWCC.

Next we introduced the patients' sex. Model 3 in Table 2.4 indicates that the reduction of males' ACQ5 score is higher than females'. The additional reduction for male patients with DBWoCC is 0.118 (P-value = 0.358), and 0.13 (P-value = 0.400) for those with DBWCC. Based on the P-values, the sex of a patient had no

statistically significant effect on the ACQ5 score, therefore, we excluded patients' sex from the model. We also introduced patients' baseline ACQ5 score in Model 4 (in addition to facility type and age), which reveals that the effect on the reduction in ACQ5 is statistically significant in both groups of patients, with a reduction of 58.3% of the initial ACQ5 score. To further explain this result, let us assume two patients, both aged 40, visited a PAL facility. The initial ACQ5 score was 2.5 for Patient 1 and 1.5 for Patient 2. According to Model 4, the reduction in the ACQ5 score for patients with DBWoCC would, two weeks later, lie at 1.503 (–0.325 – 0.36 + 0.016 $*$ 40-0.583 $*$ **2.5**) for Patient 1 (with a final ACQ5 score of 0.997), and 0.920 (–0.325-0.36 + 0.016 $*$ 40 – 0.583 $*$ **1.5**) for Patient 2 (with a final ACQ5 score of 0.581). This implies that the reduction in the ACQ5 score is higher if the patient's initial score was higher.

Lastly, in Model 5 we introduced a variable indicating the level of the health care facility visited by the patient. As mentioned above, we included two dummy variables, PHCC (1/0) and HP (1/0). The ACQ5 score of patients with DBWoCC who visited a PHCC reduced by -0.181 (P-value = 0.197) and by -0.462 (P-value = 0.034) for patients with DBWCC. That is, visiting a PHCC makes a difference, which comes as no surprise, since PHCCs employ more competent health care providers and, at the same time, are better equipped than the other facilities. However, the effect of facility level is only statistically significant among patients with DBWCC, and not among patients with DBWoCC. The effect of visiting a HP is statistically insignificant for both groups of patients.

Based on this regression analysis, Model 4 is the most appropriate model for patients with DBWoCC in terms of change in the ACQ5 score within a two week period (change in ACQ5 score = facility type + age + initial ACQ5 score). Similarly, Model 5 is the best model for change in the ACQ5 score for patients with DBWCC within two months (change in ACQ5 score = facility type + age + initial ACQ5 score + level of facility). Controlling for age, sex, baseline ACQ5 score, and facility level, our findings showed that the ACQ5 score of patients visiting a PAL facility further reduced by 0.36 (P-value = 0.008) compared to those visiting a STS facility. Among patients with DBWCC, the additional reduction was 0.166 (P-value = 0.505), which was not statistically significant.

To support the validity of the ACQ5's use, we confirmed the scores against those from the peak flow meter measurements and computed the Pearson correlation. Along with the ACQ5 questionnaire, peak flow measurements were obtained from the patients as an objective measurement of their lung function. A higher value for the peak flow measurement indicates better lung function. A strong correlation between the peak flow measurement and the ACQ5 score verified the "field level" validity of the ACQ5 in the Nepalese context, considering that the peak flow measurement is a valid and objective measurement of lung function. Hence, we calculated Pearson's correlation as being between the peak flow measurement and

the ACQ5 score. We found a significant negative correlation coefficient, r = –0.21 (P-value < 0.001) between the baseline ACQ5 score and the peak flow measurement; and r = -0.44 (P-value < 0.001) between the follow-up ACQ5 score and the peak flow measurement. The correlation between the change in the ACQ5 score and in the peak flow measurement was negative with r = -0.30 (P-value < 0.001). The negative correlation seems to confirm that both the ACQ5 and the peak flow measurement provide similar estimates: the ACQ5 decreases with improved lung function, while the peak flow measurement increases. Earlier, we used the term "rough" validity because the primary device for testing lung function is, in fact, the spirometer; however, using a spirometer was not feasible in our case due to limited resources, as well as the local terrains, which made it impossible to bring a spirometer along when visiting patients at home. Concurrently, measurements using a peak flow meter were made under comparable conditions to ensure that the measurement was applicable either between individuals or to one individual at a specific time. Hence, a weaker correlation in the expected direction is an indication of the ACQ5 questionnaire's validity within the Nepalese context. The ACQ5 is a simple and easily understandable questionnaire that is used worldwide and does not necessarily require further validation for use within the local Nepalese context.

2.4 Discussion and Conclusion

Symptoms related to breathing difficulties improved after patients visited a health care facility, demonstrated by the difference between the ACQ5 baseline scores and those of the follow-up among patients with and without a chronic cough (*Table 2.3*). Health improvement was significantly higher among patients who did not have a chronic cough and visited a PAL facility than for those who visited a STS facility. The higher degree of improvement may be attributable to the use of the PAL guidelines by the health care providers, since one of the objectives of implementing the PAL guidelines is to improve the quality of respiratory care management [5]. However, the degree of improvement was higher among patients without a cough or with a non-chronic cough than among patients with a chronic cough. There are three possible reasons that may explain this finding; the condition of patients without a cough or with a non-chronic cough is acute or short-term, and these patients are more likely to be healthier than patients with a chronic cough, even before any symptoms have appeared. Appropriate treatment reduces the symptoms immediately and the patient's former health condition is more easily restored.

The second reason could be related to the design of the survey. Patients with a chronic cough were followed-up two months after the first interview, while patients without a cough or with a non-chronic cough were followed-up after two weeks. We already asserted that a patient's condition improves after he/she visits a health

care facility in general. Hence, the speed of recovery becomes the crucial factor. When a patient is followed-up after a prolonged time lapse, it is more likely that his/her health status is similar to other patients', irrespective of which type of health care facility was visited. This could explain why we found a statistically significant difference in the average decline in ACQ5 scores between patients who had visited a PAL facility (higher degree of improvement) and those who visited a STS facility, though this applied only to patients with no cough or a non-chronic cough. Another reason may be the selected measuring instrument, in our case the ACQ. Since the ACQ was developed to measure the control of asthma but was used here for patients with a chronic cough who were more likely to have tuberculosis or chronic obstructive pulmonary disease with or without an asthmatic component, the result may not be valid. ACQ is not used to measure the change in the health status of patients with a chronic obstructive pulmonary disease or tuberculosis, since it is a valid instrument used for asthma patients. Unfortunately, other simple instruments or questionnaires were not available. The ACQ was the most appropriate tool we could find to measure the health effect among patients with breathing difficulties. We used the ACQ questionnaire to measure the health status of patients with asthma – the main symptom being breathing difficulties – by interviewing all the patients who reported having these symptoms (with the exception of those patients who were previously diagnosed with chronic obstructive pulmonary disease, tuberculosis, or asthma),,since the PAL guidelines are based on a syndrome approach.

At the baseline we found that the severity of symptoms measured by the ACQ5 increased with age, which can be explained by aging in general and secondly, by the chronic nature of diseases. Severity was lower among women than men. The reason for this could be age rather than sex since the women in our sample were younger than the men. Severity is higher among patients with chronic conditions, and due to the younger age of the women in our sample, there were fewer cases of chronic conditions among the women included. Among patients with DBWoCC, the sex difference in the baseline ACQ5 score was significant.

Some discussion points on the introduction of the WHO PAL program must be raised here. Firstly, this is a symptoms-based study and not a diagnosis-based study, as it involved primary health care facilities in real-life settings. At this level, the health care providers in Nepal have one to two years of basic training and, in addition, the lack of resources makes it difficult to correctly diagnose a disease. Hence, diagnosis-confirmed studies cannot (and should not) be conducted at this level, given the PAL program's objectives. Consequently, the possibilities of comparing our results with those from other studies were limited, with the exception of a comparison with other PAL evaluation studies [8, 9]. Our study is the first symptom-based study on patients with breathing difficulties in Nepal, and in fact, in all of South-East Asia.

Secondly, the intervention in this study comprises the actual instruction and training of health care providers about how to apply PAL guidelines, which is different from providing direct treatment to patients in typical intervention-control trials. We can only presume that the quality and methodology of training, as well as the background of the trainees would influence the results of the analysis on the effectiveness of the guidelines. Also, this approach reflects real-life settings in the actual practice of promoting and implementing primary care in the Nepalese setting.

Thirdly, the research period of one year for assessing the effect of a one-time training may have two different consequences. The limited number of PAL patients required an extension of the study period to one year. With more practice, health care providers may have gained a better understanding of the guidelines. In the absence of proper supervision, however, health care providers may have reduced the level of adherence to the guidelines and returned to the standard treatment methods, since the guidelines are more complex to follow and more time consuming. In both cases, the effect of the guidelines may have varied throughout the one year period. A shorter evaluation timeframe would probably provide better results among the intervention groups. However, there is a wash-out of the training effect the more time passes. Fourthly, patients in the sample do not necessarily represent the area's general population because many patients visit private medical facilities, utilize traditional medicine, and travel to India or other facilities in neighboring districts in search of better care.

Finally, the use of the asthma control questionnaire to measure the severity of symptoms in patients with breathing difficulties should be seriously reconsidered given that not all patients with breathing difficulties are asthmatic. We recommend that more research be conducted to explore and establish simple generic tools for measuring chronic health effects in lung patients, suitable for symptom-based algorithms and guidelines.

To conclude, tools for measuring the health effects of interventions using syndromic approaches to lung health should be explored further in order to more accurately describe (improvements in) patients with a chronic cough. The PAL guidelines were shown to be more effective than the Standard Treatment Schedules in patients who had breathing difficulties without a chronic cough.

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3

Health-Related Quality of Life of Adults in Nepal with Respiratory Symptoms, Using WHOQOL and EQ-5D

Only few studies on health-related quality of life have been carried out in Nepal using generic health-related quality of life (HRQOL) instruments. The aim of this chapter is to determine the HRQOL of patients with respiratory symptoms in Nepal with the use of the World Health Organization Quality of Life Questionnaire (WHO-QOL) and the European Quality of Life Questionnaire (EQ-5D), and to establish and compare their construct validity within the Nepalese context.

The English versions of the WHOQOL and EQ-5D were translated into Nepalese and Bhojpuri (a local dialect) and translated back into English, following the standard adaptation guidelines. Using WHOQOL and EQ-5D, we interviewed 2243 patients with respiratory symptoms (aged 15 years and older) who visited one of the 42 primary health care facilities selected for our study within a ten month period (September 2002–July 2003).

We found EQ-5D to be a valid instrument for measuring the Nepalese patients' health-related quality of life. We established the validity of EQ-5D with reference to different WHOQOL domains by comparing EQ-5D's utility score with the median scores of each WHOQOL domain. We found a higher degree of association between the EQ-5D utility scores and the physical (r = 0.533) and psychological (r = 0.393) domains of the WHOQL.

We also determined that breathing difficulties are among the most prevalent respiratory problems that significantly reduce patients' health-related quality of life. Fever and chronic cough also contribute to the reduction of patients' HRQOL, but to a lesser degree. Younger patients have a better HRQOL; patients with a higher level of educational attainment also have a better HRQOL; while patients who are separated, divorced or widowed have lower HRQOL levels. Patients' sex was found to only have an insignificant effect on the level of HRQOL.

This publication is the first of its kind to describe the HRQOL of patients in Nepal. More research on the validation of generic and disease-specific HRQOL should be carried out to facilitate future economic evaluations.

3.1 Introduction

Health-related quality of life (HRQOL) plays an important role in assessing the effectiveness of health care [1–3]. General health-related quality of life scales assess the impact of illness and individuals' experiences with health [4]. An individual's general health-related quality of life is often measured by using a set of questions representing different dimensions. Demands for measuring health-related quality of life is increasing worldwide [5]. Several questionnaires have been developed in the past with many more to be developed in the future. The World Health Organization Quality of Life Questionnaire (WHOQOL) [6] and the European Quality of Life Questionnaire (EuroQOL, but referred to here as EQ-5D) [7] are commonly used instruments to determine the general population's health-related quality of life or that of a disease-specific group of patients. We used these two questionnaires to measure the health-related quality of life of patients with respiratory symptoms within the context of a study on the cost-effectiveness of an intervention in Nepal.

3.1.1 Intervention

The intervention is an integrated symptom-based approach to lung health, namely the Practical Approach to Lung Health (PAL) guidelines developed by the World Health Organization, targeting four lung diseases including tuberculosis, asthma, chronic obstructive pulmonary diseases, and pneumonia [8-10]. The PAL guidelines were adapted to the Nepalese setting and health care providers at randomly selected facilities in a rural Nepalese district were trained to apply them. We conducted a one-year intervention-control prospective trial during which – along with other patient-related data – we collected patients' health-related quality of life using the translated and locally adapted WHOQOL and EQ-5D. The trial's aim was to assess the cost-effectiveness of the PAL guidelines' implementation in Nepal

3.1.2 Quality Adjusted Life Years

The two key purposes of the HRQOL measurement are to either compare the level of HRQOL between people as a discriminative instrument or as an evaluative instrument to compare the change in individuals' HRQOL levels over time [11]. In cost-effectiveness studies, effectiveness is often measured in terms of quality adjusted life years (QALYs) gained/lost for which an evaluative tool is needed. Individuals' QALYs for a certain period is estimated by multiplying that particular time period by a specified weight (ranging from 0 to 1) that is associated with the individual's health-related quality of life during the given period of time. What we need is an index, preferably between 0 and 1, that corresponds to an individual's health-related quality of life. In the PAL study, we included the EQ-5D as our evaluative instrument of choice, since it was developed to produce a single value that

can be used to estimate QALYs. Numerous cost effectiveness studies have used EQ-5D to estimate QALYs. The purpose of WHOQOL, on the other hand, is to describe individual's self-assessed health status in detail for the different domains of health-related quality of life. Notably, the WHOQOL has already been adapted, tested, and implemented in India [12], and since the conditions in Nepal are similar to India's, the use of the WHOQOL in Nepal did not have to be re-adapted to an entirely new setting (which was actually a requisite by the developers of WHOQOL) [13]. An algorithm has been developed to compute a single value for individuals' health-related quality of life using the WHOQOL; however, the (implicit) assumptions in the summarization process preclude a single value from being used as a weight to estimate the QALYs. This is discussed in detail later in the chapter.

3.1.3 Validity of HRQOL Instruments to Measure Patients' HRQOL within the Nepalese Context

An efficient measurement tool should generally have the following instrumental properties: reproducibility, accuracy, validity, and interpretability [11]. Reproducibility is measured by reliability and responsiveness when using discriminative and evaluative instruments, respectively. The validity of an instrument must be determined prior to using the measurements' results. The validity of an already established instrument should also be tested when measuring a property in a new context. Measuring the validity of an instrument involves verifying whether or not the instrument measures the targeted domain, which is also referred to as face validity [11]. An instrument's face validity can easily be established either through empirical evidence or by theoretical consideration (examining how the measure was established and whether existing theories confirm that the indicators used for the instrument are directly – or indirectly – associated with the domain), or both. Once the instrument's face validity has been established, the second question is how accurately the instrument measures a given property. This can be determined through construct validation, which is used to compare the different measures, and to explore the logical relationship that ought to exist between a given measure and the characteristics of a patient or a patient group [11]. The comparison is typically carried out by estimating the correlation coefficient between the test instrument's measurements and the existing standard instrument. In this study, we describe and present the results of the validation of the EQ-5D (test instrument) in relation to the WHOQOL (standard instrument). Finally, a HRQOL measuring instrument should be interpretable. For a given HRQOL score it should be possible to categorize individuals' condition into "*normal, mild, moderate or severe impairment of HRQOL*" [11] and, if the change in HRQOL level is being measured over time, it should be possible to interpret the change as being "*trivial, small but important, moderate, or large improvement or deterioration*", an aspect we address in Chapter 6 [11].

3.1.4 Objective

The main objectives of this chapter are to describe the variation in the health-related quality of life of patients with respiratory symptoms with reference to precisely these symptoms and to various other demographic and socio-economic variables. We furthermore aim to analyze the change in the impairment of HRQOL over time. To achieve these objectives, it is important to establish the validity of the measuring instruments. Therefore, the second objective is to establish the validity of the EQ-5D with reference to WHOQOL's different domains. The validation of EQ-5D will be the starting point for using the EQ-5D measurement as an evaluative instrument in the analysis of the PAL intervention's cost-effectiveness.

In the following section, we describe the two HRQOL instruments, WHOQOL and EQ-5D, in detail. Next, in the methods section, we explain the PAL study design and describe the process of adapting the HRQOL instruments to the Nepalese context. The methods section also describes the statistical analysis used to achieve our objectives. The results and inferences are presented in the results section. Finally, the chapter concludes with a discussion and general conclusions.

3.2 HRQOL Instruments

3.2.1 WHOQOL

The developers of the WHOQOL defined the quality of life as an individual's perception of his/her position in life within the context of his/her culture and value system, and in relation to the individual's goals, expectations, standards, and concerns [6, 13, 14]. It is viewed as a subjective, multidimensional concept [15, 16], which places emphasis on the individual's self-perception of his/her current health state. WHOQOL was used in the trial to assess the health-related quality of life of patients with respiratory symptoms. We chose the WHOQOL, since the Indian version, WHOQOL-Hindi, was verified as a valid instrument for comprehensively assessing the quality of life in health care settings in India [12]. Due to the geographical proximity and historical relationship between the two countries, people from India and Nepal have a lot in common, including culture, religion, value systems, etc. It is therefore justifiable to infer that the WHOQOL is a valid instrument for measuring the Nepalese population's generic health-related quality of life. We did not conduct a validation process of the Nepali and Bhojpuri (local dialect) WHOQOL independently as recommended by the developers of WHOQOL, since it was beyond the scope of the PAL evaluation study. We translated the WHOQOL-Hindi into the local language and made context-specific adaptations following repeated field testing. We then used the translated and locally adapted WHOQOL (WHOQOL-Nepali and WHOQOL-Bhojpuri; we did not distinguish between the

two versions in our analysis and for simplification purposes, we will refer to both as WHOQOL) as a valid instrument to measure health-related quality of life in the study on cost-effectiveness, and also used it to test the validity of EQ-5D.

The WHOQOL questionnaire consists of 26 items [17]. The first two items are global indicators for quality of life and satisfaction with general health. The remaining 24 items are grouped into 4 domains: physical health (7 items), psychological health (6 items), social relationships (3 items), and environment (8 items). Each item is rated on a 5-point Likert scale. Hence, one of the 6 x 10^{16} (5^{24}) states of the WHOQOL's overall states may be attributable to an individual, or one of the 78125, 15625, 125, and 390625 states of the WHOQOL's domains physical health, psychological health, social relationships, and environment, respectively. To narrow it down, the WHOQOL group proposes the calculation of the responses' mean (recoded as 1, 2, 3, 4 or 5 with a higher value indicating an improved status) in each domain. The means were multiplied by 4 to obtain domain scores ranging from 5 to 20. Finally, the overall WHOQOL score was calculated as a sum of these domain scores, resulting in a range of 20 (for worst health state) and 100 (for best health state).

At the domain level, the use of the mean implicitly assumes that the responses are summed in an interval scale, which, however, is not the case since they are summed in an ordinal scale. We propose using the median as a more suitable alternative for representing the HRQOL level in each of the WHOQOL's domains, considering that the median as a measure better represents central tendencies when averaging values in an ordinal scale. Next, at the general level, the summing of domain scores to obtain the overall WHOQOL score implicitly assumes equal HRQOL weight for all domains, which is also erroneous because the perceived value of these weights differs between individuals and communities. Therefore, the current developmental status of the WHOQOL cannot be used to calculate QALYs that require a single utility measure. In this study, for descriptive purposes, we calculated the median response for each WHOQOL domain. Using the median scores for each domain, 625 WHOQOL states were defined, and with some additional modifications on weight estimation, the WHOQOL could be used in the study on QALYs. For the purpose of validating EQ-5D using WHOQOL, we limited our validation to the domain level.

3.2.2 EQ-5D

The EQ-5D questionnaire [18] is a commonly used tool to measure health-related quality of life. It contains five dimensions for health (*mobility, self-care, usual activities, pain/discomfort, anxiety/depression*) with three levels of response (*1* for "no problem"; *2* for "some problem"; *3* for "severe problem"), which represent 243 (3^5) health states. We included EQ-5D in the cost-effectiveness analysis to

estimate the QALYs of patients. The original version of the EQ-5D was translated and locally adapted for this purpose, and the validation of EQ-5D performed by using WHOQOL as a valid standard measurement of health-related quality of life in Nepalese patients.

A unique feature of the EQ-5D is that former validation research facilitates the measuring of severity of the 243 health states [19]. This measure of severity in HRQOL impairment is often expressed in terms of utility as perceived by patients with a decline in utility, signifying a more serious HRQOL impairment. It has a value of 1.00 when the individual is healthy (11111) and 0.00 when the person is deceased. Very severe health states, e.g. 33333, have negative values (–0.59). The utilities were calculated using a reference set of preference weights derived from a representative sample of the UK's general population, known as the UK weights [5]. We used the UK weights since no such weights exist for Nepal's population. The possibility to attribute a measure of severity to the EQ-5D health states eliminates the problem of multiple outcomes, which is inextricably linked to the use of multidimensional HRQOL measures (e.g. the WHOQOL). For this reason, the utility score of the EQ-5D provides an especially suitable result for modeling purposes, when the burden of disease or the effectiveness of a health care intervention is evaluated in terms of health-related quality of life [19]. The utility score, which corresponds to the specific condition a patient is in, can be understood as the amount of ideal quality time a patient is ready to trade for one unit of (less) quality time.

Additionally, the EQ-5D consists of a single rating scale of health impairment, a vertical calibrated 20 cm Visual Analogue Scale (VAS) with ratings of 'worst imaginable health state' (0) at one end, and 'best imaginable health state' (100) on the other [18]. The objective when using the VAS in valuation studies is to attach values (or utilities) to all EQ-5D statuses according to the protocol described on EuroQol's official Web site (http://www.euroqol.org). Even though the PAL study is not a valuation study of the EQ-5D, local versions of EQ-VAS were developed through repeated field testing. Later, we collected the responses to the modified EQ-VAS (*Figure 3.1*) along with the EQ-5D questionnaire (this is mentioned here for information purposes for future EQ-5D users in Nepal). The respondents were asked to mark the point on the scale that they felt best described their current state. The rating scale in this study differs from the EQ-VAS, since we added three pictures to indicate 'best' (100), 'worst' (0), and 'average' (50) health states. These were repeatedly field tested among health professionals, students, patients, and the general population in the area under investigation. Interviews based on an early version of the survey indicated some confusion between the verbally presented concept of "full health" and material or monetary well-being. After the pictures were introduced, this confusion no longer emerged (see *Figure 3.1*). We used VAS results as an additional instrument to measure health status.

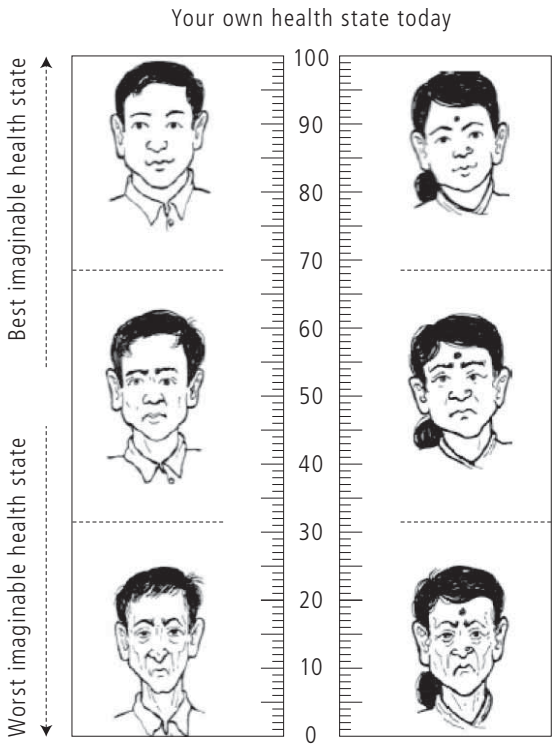

Figure 3.1. Modified visual analogue scale.

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer). On this scale the best health state you can imagine is marked 100 *(Field assistant: point now with your finger to figure 100)* and the worst state you can imagine is marked 9 *(point now with your finger to figure 0)*.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

3.3 Methods

3.3.1 Study Design

The stratified intervention-control cluster randomized trial was conducted in the rural lowland district of Nawalparasi in Nepal between 2002 and 2003. The details of the trial are described in Chapter 2. To recapitulate, two primary health care centers, eight health posts, and 32 sub-health posts were randomly selected and grouped into intervention facilities (PAL) and standard practice facilities (STS) at which health care providers followed standard treatment schedules, with a total of 22 and 20, respectively. At least one health care provider per PAL facility partici-

pated in a five-day training program on how to apply the PAL guidelines. After the intervention, data were collected from patients aged 15 and above, who visited a PAL or STS facility and reported having one or more of the following respiratory symptoms: fever, a cough (duration less than, equal to, or more than two weeks), and breathing difficulties. Patient-level data were collected directly at the facility from all patients included in the trial and later from patients with specific symptoms at their home. Along with other data, facts on patients' health-related quality of life were collected using locally translated and adapted WHOQOL and EQ-5D questionnaires. A total of 2243 patients were interviewed during this period.

3.3.2 Translation and Validation of the Questionnaire

WHOQOL

We used the WHOQOL-Bref-Hindi questionnaire to measure general health status [12]. This instrument had already been tested in Delhi, India [12] and was translated into Nepalese and Bhojpuri following the standard methods described below.

EQ-5D

The EQ-5D questionnaire has been tested worldwide and the standard questionnaires are available in different languages. The English version of the questionnaire was translated into Nepalese and Bhojpuri following the standard guidelines.

Translation

Both questionnaires were first translated from English into Nepali and Bhojpuri by two qualified translators who were native speakers of these two languages. The translated questionnaires were then independently translated back into English (2^{nd} English version). The second English version was then compared with the original version and the divergences taken into consideration to produce a second Nepali and Bhojpuri version of the questionnaire. This version was then piloted by conducting interviews with a few people. Based on the pilot test, a third version of the questionnaire was prepared and used for data collection. The score of the EQ-5D ranges from –0.59 to 1, while the range is 1 to 5 for the domains included in the WHOQOL.

Validation

To test construct validity, we estimated that Spearman's correlation coefficients were situated between the EQ-5D score and each dimension of the WHOQOL. A

stronger correlation indicates a higher level of EQ-5D validity with regard to the WHOQOL. The quantitative significance of the correlation coefficient is based on the recommendation by Burnand *et al.* [20]. According to Burnand *et al.*, a correlation coefficient's value, r, that is less than 0.30 indicates an insignificant association; a range of 0.30–0.45 signifies a moderate degree of association; a range of 0.45–0.60 indicates a substantial level of association, and a correlation coefficient value that is greater than 0.60 denotes a high level of association. In our analysis, we expected to at least detect a moderate level of association between the EQ-5D and similar domains of the WHOQOL.

As explained earlier, the dimensions of the EQ-5D include mobility, self-care, usual activities, pain/discomfort, and anxiety/depression; the domains of the WHOQOL are physical, psychological, social, and environmental. We used a single score for the EQ-5D, and the correlation coefficients were calculated as being situated between the EQ-5D's single score and the individual domain scores of the WHOQOL. When comparing the dimensions of the EQ-5D with the WHOQOL's domains, we noticed that the first four EQ-5D dimensions matched the WHOQOL's physical domain, and the EQ-5D's fifth dimension (anxiety/depression) matched the WHOQOL's psychological dimension. Therefore, we expected the EQ-5D score to reveal a higher degree of positive association with physical attributes, and a lower degree with psychological attributes. We did not expect the EQ-5D's dimensions to be associated with the WHOQOL's social and environmental domains.

3.3.3 Statistical Analysis

After the validation exercise, for descriptive purposes, we estimated the mean and standard deviation of the HRQOL score for the EQ-5D and the domains of the WHOQOL for the patients in general, as well as for sub-groups of patients by sex, age group, marital status, level of educational attainment, and, most importantly, by the patients' respiratory symptoms. We expected patients with a chronic cough and breathing difficulties to have a lower HRQOL compared to those with a shorter cough duration or with only a fever. At the same time, we expected younger patients, as well as more educated patients to have a higher HRQOL level. We also included marital status in our model. We assumed that patients who were separated, divorced or widowed would have a lower HRQOL level. The majority of the population in Nepal marries at a relatively young age and the rate of separation and divorce is very low. To test these hypotheses, we used a t-test for sex (two sub-groups) and for the rest, with more than two sub-groups, we used a one-way ANOVA.

Finally, to analyze the variation in HRQOL with respect to the above-stated explanatory variables, we performed two linear regression analyses of health-related quality of life scores – one for the EQ-5D dimensions and one for the domains

of the WHOQOL – on respiratory symptoms and various socio-demographic variables. The results from the regression analyses were used to test the hypotheses stated earlier.

3.4 Results

A total of 2243 patients aged 15 or older were included in the PAL study. The response rate to the four domains of the WHOQOL, namely physical, psychological, social, and environmental, were very high with 98%, 97%, 97%, and 97% of the total respondents (2243) rating them, respectively. According to the WHOQOL protocol, if the number of questions answered for each domain is less than 80%, the response to the domain is considered incomplete. The response rate to the overall WHOQOL was 90.5%, which is quite low in relation to the response rate for each domain. This indicates that non-response at the individual level was limited mostly to one domain, since the response rate at the general domain level was quite high. Similarly, the EQ-5D demonstrated a higher response rate (95.5%). The higher response rate for the EQ-5D is attributable to the fact that the EQ-5D consists of fewer (five) questions that are easier to answer than those posed by the WHOQOL (26 questions). *Table 3.1* presents the distribution of patients who responded in full to the EQ-5D and to each of the WHOQOL's different domains by age, sex, marital status, level of educational attainment, and symptoms.

A similar proportion of male and female patients responded to the WHOQOL's different domains in full (51% males) and to the EQ-5D (51% males) (see *Table 3.1*). The second to last block in *Table 3.1* represents the distribution of respondents by respiratory symptom at the time of their visit to a health care facility. Around 40% of the patients either had a cough that lasted less than 2 weeks or fever. These patients were not included in the follow-up stage, since – in accordance with the PAL guidelines – they were less likely to have a PAL target disease, namely tuberculosis, chronic obstructive pulmonary disease, pneumonia, or asthma. Some 30% of the patients had breathing difficulties as an individual or one of several symptoms, and for these patients, a separate questionnaire (a modified Asthma Control Questionnaire) was administered. Some 21% of the patients had a chronic cough as an individual or one of several symptoms, and these patients were followed-up two months later. The remaining patients (39%) were followed-up after two weeks. A higher proportion of patients (around 44%) belonged to the younger age groups (15–34 year olds). Around 79% of the patients were married, while approximately 9% were either separated, divorced, or widowed. The majority of patients had a low level of education (76%) (see *Table 3.1*).

In the EQ-5D, the majority of patients reported having *no problem at all* in the dimensions mobility (59.4%) and self-care (75.1%), whereas the majority of

Table 3.1. Distribution of patients by age, sex, marital status, level of educational attainment, and symptoms of patients who responded to the different domains of the WHOQOL and the EQ-5D in full (total patients = 2243)

	WHOQOL - number (%)								EQ-5D	
	Physical		Psychological		Social		Environmental		Number (%)	
All patients	2189	(100%)	2185	(100%)	2170	(100%)	2181	(100%)	2164	(100%)
Sex										
Male	1115	(51%)	1113	(51%)	1111	(51%)	1114	(51%)	1104	(51%)
Female	1074	(49%)	1072	(49%)	1059	(49%)	1067	(49%)	1060	(49%)
Age Group										
15–24	536	(24%)	536	(25%)	534	(25%)	536	(25%)	527	(24%)
25–34	442	(20%)	442	(20%)	436	(20%)	441	(20%)	437	(20%)
35–44	370	(17%)	369	(17%)	367	(17%)	368	(17%)	360	(17%)
45–54	293	(13%)	293	(13%)	292	(13%)	292	(13%)	294	(14%)
55–64	274	(13%)	273	(12%)	271	(12%)	272	(12%)	273	(13%)
65–74	199	(9%)	197	(9%)	195	(9%)	197	(9%)	200	(9%)
75+	74	(3%)	74	(3%)	74	(3%)	74	(3%)	72	(3%)
Marital Status[*]										
Single	255	(12%)	255	(12%)	255	(12%)	255	(12%)	251	(12%)
Other	197	(9%)	196	(9%)	192	(9%)	193	(9%)	196	(9%)
Married	1732	(79%)	1729	(79%)	1718	(79%)	1728	(79%)	1712	(79%)
Symptoms										
Fever or Cough	882	(40%)	881	(40%)	875	(40%)	879	(40%)	871	(40%)
Fever and Cough	429	(20%)	429	(20%)	427	(20%)	429	(20%)	423	(20%)
Breathing Difficulties	20	(1%)	20	(1%)	20	(1%)	20	(1%)	20	(1%)
DiB and Fever/Cough	121	(6%)	121	(6%)	117	(5%)	119	(5%)	117	(5%)
DiB, Fever and Cough	170	(8%)	170	(8%)	169	(8%)	169	(8%)	168	(8%)
Chronic Cough	105	(5%)	105	(5%)	105	(5%)	105	(5%)	103	(5%)
C-Cough and Fever	129	(6%)	128	(6%)	127	(6%)	129	(6%)	128	(6%)
C-Cough and DiB	170	(8%)	169	(8%)	169	(8%)	169	(8%)	173	(8%)
C-Cough, DiB, and Fever	163	(7%)	162	(7%)	161	(7%)	162	(7%)	161	(7%)
Level of Education										
No education	1669	(76%)	1665	(76%)	1653	(76%)	1661	(76%)	1654	(76%)
Primary	266	(12%)	266	(12%)	265	(12%)	266	(12%)	261	(12%)
Secondary	215	(10%)	215	(10%)	213	(10%)	215	(10%)	211	(10%)
Tertiary	39	(2%)	39	(2%)	39	(2%)	39	(2%)	38	(2%)

[*]Total does not add up due to missing information

patients reported having *some problem* in the dimensions pain/discomfort (63.3%) and anxiety/depression (57.3%). Some 16% of the patients reported having *severe problems* with pain/discomfort, while less than 3% of the patients indicated having *severe problems* in the dimension mobility, and less than 2% reported having *severe problems* in the dimension self-care.

Table 3.2 demonstrates the results of the average scores and their standard deviation for the different domains of the WHOQOL and EQ-5D by sex, age, marital

Table 3.2. Mean and standard deviation of the WHOQOL domain scores and the EQ-5D utility score

	Mean ± Standard Deviation				
	Physical	Psychological	Social	Environmental	EQ-5D
All patients	3.12 ± 0.7	3.22 ± 0.6	3.50 ± 0.7	2.95 ± 0.6	0.55 ± 0.3
Sex					
Male	3.16 ± 0.7	3.28 ± 0.7	3.55 ± 0.6	3.02 ± 0.6	0.56 ± 0.3
Female	3.08 ± 0.7	3.15 ± 0.6	3.46 ± 0.7	2.88 ± 0.6	0.53 ± 0.3
Age Group					
15–24	3.34 ± 0.7	3.44 ± 0.6	3.56 ± 0.7	3.11 ± 0.6	0.63 ± 0.3
25–34	3.22 ± 0.7	3.31 ± 0.6	3.57 ± 0.6	2.95 ± 0.6	0.58 ± 0.3
35–44	3.15 ± 0.7	3.22 ± 0.6	3.54 ± 0.6	2.87 ± 0.6	0.56 ± 0.3
45–54	3.11 ± 0.7	3.12 ± 0.6	3.48 ± 0.7	2.90 ± 0.6	0.54 ± 0.3
55–64	2.94 ± 0.7	3.02 ± 0.7	3.45 ± 0.6	2.90 ± 0.7	0.53 ± 0.3
65–74	2.71 ± 0.7	2.91 ± 0.6	3.28 ± 0.7	2.87 ± 0.6	0.32 ± 0.4
75+	2.62 ± 0.7	2.95 ± 0.7	3.43 ± 0.6	2.87 ± 0.6	0.37 ± 0.4
Marital Status					
Single	3.47 ± 0.6	3.48 ± 0.6	3.50 ± 0.7	3.18 ± 0.6	0.66 ± 0.2
Other	2.70 ± 0.8	2.81 ± 0.7	3.05 ± 0.7	2.77 ± 0.6	0.34 ± 0.4
Married	3.12 ± 0.7	3.23 ± 0.6	3.56 ± 0.6	2.94 ± 0.6	0.55 ± 0.3
Symptoms					
Fever or Cough	3.30 ± 0.7	3.40 ± 0.6	3.55 ± 0.6	3.00 ± 0.6	0.62 ± 0.3
Fever and Cough	3.19 ± 0.7	3.25 ± 0.6	3.56 ± 0.7	3.01 ± 0.6	0.55 ± 0.3
Breathing Difficulties	2.90 ± 0.8	3.18 ± 0.6	3.48 ± 0.8	3.08 ± 0.7	0.50 ± 0.4
DiB and Fever/Cough	3.04 ± 0.7	3.11 ± 0.7	3.41 ± 0.7	2.96 ± 0.6	0.54 ± 0.3
DiB, Fever, and Cough	2.90 ± 0.7	2.99 ± 0.7	3.49 ± 0.7	2.86 ± 0.6	0.40 ± 0.4
Chronic Cough	3.32 ± 0.7	3.35 ± 0.6	3.53 ± 0.7	3.00 ± 0.6	0.70 ± 0.2
C-Cough and Fever	3.02 ± 0.8	3.13 ± 0.7	3.44 ± 0.6	2.95 ± 0.6	0.52 ± 0.3
C-Cough and DiB	2.67 ± 0.7	2.86 ± 0.7	3.39 ± 0.7	2.76 ± 0.6	0.41 ± 0.3
C-Cough, DiB, and Fever	2.71 ± 0.7	2.85 ± 0.6	3.35 ± 0.7	2.80 ± 0.6	0.33 ± 0.4
Level of Education					
No education	3.02 ± 0.7	3.13 ± 0.6	3.45 ± 0.7	2.87 ± 0.6	0.51 ± 0.3
Primary	3.37 ± 0.7	3.42 ± 0.6	3.64 ± 0.6	3.15 ± 0.6	0.62 ± 0.3
Secondary	3.50 ± 0.6	3.58 ± 0.6	3.72 ± 0.7	3.28 ± 0.6	0.68 ± 0.2
Tertiary	3.69 ± 0.6	3.62 ± 0.6	3.74 ± 0.6	3.28 ± 0.6	0.67 ± 0.2

*C-Cough = Chronic Cough; DiB = Breathing Difficulties

status, symptoms, and level of educational attainment. The average score of the WHOQOL's domains ranges between 1 (i.e. worst HRQOL) and 5 (best HRQOL). When looking at the different WHOQOL domains for all patients, we determined a minimum average score of 2.95 in the environmental domain and a maximum average score of 3.50 in the social domain. This could indicate that social relations do not change much when an individual falls sick. Similarly, the mean EQ-5D score is 0.55 for all patients, with the range of the EQ-5D score lying between –0.59 to 1 (best health).

Using the results in *Table 3.2*, we found higher mean scores (between 0.08 and 0.14) among males for all domains, the difference in all domains being statistically significant with a P-value < 0.001 in the physical, psychological, and environmental domains, and a P-value < 0.01 in the social domain. The same holds true for the average EQ-5D score of 0.03, with a P-value < 0.05. As expected, we found a higher HRQOL level among younger patients with a consistent decline (ANOVA: P-value $< .001$) in the mean scores among higher age groups in all WHOQOL domains and in EQ-5D (with the exception of the last age group for psychological, social domains, and for EQ-5D). The difference between the age groups (0.72) was highest in the physical domain and lowest (0.24) in the environmental domain. The largest divergence was at 0.31 in the EQ-5D between the age groups 65–74 and 15–24.

Next, we found higher HRQOL scores among patients who were single, followed by those who were married, and by the remainder (widowed, separated, or divorced) (see *Table 3.2*) (ANOVA: P-value < 0.001). As expected, patients who were either widowed, separated or divorced had a lower HRQOL level. However, as singles are most likely to be of younger age than members of the other groups, the effect of age must be taken into account before making any inferences. The largest disparity between married couples, singles, and the remainder was at 0.77 in the WHOQOL's physical domain and the lowest level of divergence was at 0.41 in the environmental domain. The difference in the EQ-5D score was 0.32.

Regarding the patients' education, as anticipated, we found that patients with a higher level of educational attainment also had significantly higher (ANOVA: P-value < 0.001) mean HRQOL scores in all domains and in the EQ-5D than patients with lower educational attainment levels. Between the different educational groups, the highest disparity was at 0.67 in the WHOQOL's physical domain with the lowest level of divergence being in the social domain. The difference in the EQ-5D score was 0.17.

Average HRQOL scores varied significantly (ANOVA: P-value < 0.001) between patients with different symptoms (individual or combined symptoms). The disparity in the average HRQOL between patients from different symptom groups was highest in the WHOQOL's social and psychological domains (0.55 each), and lowest in the social domain (0.21). The highest value in all domains was found among patients who only had either a cough, a chronic cough, or fever. The lowest value was established predominantly among patients with a chronic cough, fever, or breathing difficulties. EQ-5D had a similar pattern with a divergence of 0.37 between patients with only a chronic cough and patients with a chronic cough, fever, and breathing difficulties. Below we will present the results of the multivariate regression analyses of the HRQOL scores on the different symptoms controlling for sex, age-group, marital status, and patients' level of educational attainment. Prior

Table 3.3. Spearman's correlation (r) coefficients between the EQ-5D score and the average WHOQOL domain scores

	Physical	Psychological	Social	Environmental	EQ-5D
Physical	1.000	0.544	0.249	0.419	0.533
Psychological	0.544	1.000	0.331	0.503	0.393
Social	0.249	0.331	1.000	0.354	0.146
Environmental	0.419	0.503	0.354	1.000	0.283
EQ-5D	**0.533**	0.393	**0.146**	0.283	1.000

to presenting the results of the regression analysis, the results of EQ-5D's validity test in the Nepalese context are introduced.

The results (means) presented above point to an association between the average HRQOL scores in the different WHOQOL domains and the average EQ-5D utility score. We could consider the above results a face validity of the EQ-5D for measuring patients' HRQOL as compared with the WHOQOL's different domains, which is considered a valid HRQOL measure in the Nepalese context (as described earlier). Furthermore, the direction of change in the average EQ-5D utility score is the same as the average WHOQOL domain scores in nearly all cases. In *Table 3.3*, we present the results of the verification of EQ-5D's construct validity with reference to the WHOQOL's different domains by estimating the correlation coefficients as being located between the average EQ-5D utility score and the average WHOQOL domain scores.

Based on the the results presented in *Table 3.3*, we determined that the EQ-5D score has the highest degree of correlation with the physical domain of the WHOQOL (r = 0.533) and the lowest degree of correlation with the WHOQOL's social domain (r = 0.146). As stated earlier, the quantitative significance of the correlation coefficient is based on Burnand *et al.'s* recommendation [17], therefore, the association of EQ-5D scores with the WHOQOL's social and environmental dimension (r = 0.283) is considered insignificant. While the degree of association with the WHOQOL's psychological domain (r = 0.393) is considered to be moderate, the association with the physical domain is regarded as being substantial. These results are as expected; as mentioned earlier, the EQ-5D dimensions are mostly related to physical health (four questions out of five in the EQ-5D) and one is related to the WHOQOL's psychological domain. Hence, we consider the EQ-5D to be a valid instrument for measuring the HRQOL of Nepalese patients with lung diseases, and proceed to the next step of describing the HRQOL in patients with respiratory symptoms, using the EQ-5D and WHOQOL. We acknowledge that the statement on validity would be stronger if the values of r were higher.

After having accepted EQ-5D as a valid tool to measure HRQOL, the next task was to describe the variation in HRQOL impairment as measured by the EQ-5D and the different domains of the WHOQOL with respect to respiratory symptoms and

Table 3.4. Multivariate regression model describing EQ-5D and four dimensions of the WHOQOL by symptoms, age, sex, marital status, and level of education

	Regression coefficients (P-values) of EQ-5D utility scores on variables				
	EQ-5D	Physical	Psychological	Social	Environmental
Constant	0.75 (0.000)	3.51 (0.000)	3.54 (0.000)	3.40 (0.000)	2.90 (0.000)
Breathing Difficulties	–0.16 (0.000)	–0.29 (0.000)	–0.26 (0.000)	–0.07 (0.031)	–0.11 (0.000)
Fever	–0.12 (0.000)	–0.12 (0.000)	–0.08 (0.009)	–	–
Chronic Cough	–0.03 (0.058)	–0.14 (0.000)	–0.12 (0.000)	–	–
Age Groups (10-year)	–0.02 (0.000)	–0.04 (0.000)	–0.04 (0.000)	–	–
Sex (female)	–0.03 (0.091)	–	–0.10 (0.000)	–	–
Married	–	–0.13 (0.013)	–	0.13 (0.006)	–
Divorced/Widowed/ Separated	–0.13 (0.000)	–0.36 (0.000)	–0.21 (0.000)	–0.32 (0.000)	–
At Least Secondary Education	0.09 (0.000)	0.33 (0.000)	0.29 (0.000)	0.25 (0.000)	0.40 (0.000)
Primary Education	0.05 (0.018)	0.23 (0.000)	0.16 (0.000)	0.16 (0.000)	0.27 (0.000)
R-Square	0.127	0.14	0.14	0.057	0.055

various demographic and socio-economic variables. We performed multivariate regression analyses of different WHOQOL domains and EQ-5D scores on symptoms, controlling for age, sex, level of educational attainment, and marital status. We built on the notion of symptoms as independent variables in the regression model. Other variables were gradually introduced and only those which were statistically significant (P-value < 0.10) were included in the final model. The results of the final model are presented in *Table 3.4*.

The results of the regression analysis show that for all health-related quality of life measurements compared to the results of the patient group with non-chronic coughs (reference group), breathing difficulties reduced the HRQOL scores significantly compared to fever and chronic cough. For example, breathing difficulties reduce the EQ-5D's utility score (range: –0.59 to 1) by –0.16, which can be considered significant. We also found that patients with a higher level of educational attainment had better HRQOL levels than patients with lower levels of education. The advantage of having at least a secondary education was higher in all HRQOL measurements than having only a primary level education. The HRQOL scores for the EQ-5D and for the physical, psychological, and social domains of the WHOQOL were lower for patients who were either separated, divorced, or widowed. The patients' sex did not affect the HRQOL score except in the WHOQOL's psychological domain, where females demonstrated a slightly lower HRQOL. Older people generally had lower levels of HRQOL. However, the effect of age is not evident in the case of the WHOQOL's social and environmental domains. Marital status also did not influence the HRQOL scores in the environmental domain, but was the

most significant factor in the social domain. The effect of breathing difficulties was also smaller in these two dimensions.

In *Table 3.5* we present the results of a similar exercise with the dependent variable being the change in HRQOL score between the first visit to the health care facility and the follow-up for the two groups of patients, i.e. patients with a chronic cough who were followed-up after 2 months, and patients without a chronic cough who were followed-up after 2 weeks.

Among the patients who were followed-up 2 weeks after the initial interview (shown in the first block in *Table 3.5*), breathing difficulties, age, and patients' marital status (being separated/divorced/widowed) were found to be significant explanatory covariates of variation in the change in EQ-5D score. In the WHOQOL domains, the variations in the change in the physical and psychological domains were explained by breathing difficulties, age, and sex (being female), in addition to the cough in the psychological domain. Similarly, the change in HRQOL score in the WHOQOL's social dimension depended on marital status only (being separated/divorced/widowed), and for the environmental domain, age was the only explanatory variable. The associations between the explanatory variables and dependent variables were negative as indicated by the negative values of the regression coefficients.

Among the patients with a chronic cough (second block in *Table 3.5*), breathing difficulties and age were explanatory variables for the change in HRQOL scores as measured by the EQ-5D, and the physical and psychological domains of the WHOQOL. Moreover, we found that being married was an explanatory variable (with a positive association) for the change in the HRQOL score in the WHOQOL's social domain. Finally, in the environmental domain, breathing difficulties, fever, and level of educational attainment (with a minimum of secondary education indicating a positive association) were found to be explanatory variables. All the associations are negative, except where indicated otherwise.

Among all patients, the initial HRQOL score affects the change in the HRQOL score with a higher degree of change among patients with lower levels of initial HRQOL scores, as indicated by negative coefficients. To explain the coefficients, let us consider a married male patient, aged 40, with secondary education, who has breathing difficulties accompanied by a fever (no cough), and with an initial EQ-5D score of 0.65. For comparative purposes, a second patient with similar attributes has an initial EQ-5D score of 0.50. Both patients visit one of the study facilities. Since neither has a chronic cough, our regression model can predict the EQ-5D score of the patients after two weeks, using the coefficients from the first block. For the patient with the 0.65 EQ-5D score, the predicted increase in his/her HRQOL in two weeks is 0.18, while it is 0.29 for the second patient. The overall picture based on *Table 3.5* indicates that it is much more difficult for older patients who have breathing difficulties to recover.

Table 3.5. Multivariate regression model explaining the change in EQ-5D and in the four dimensions of the WHOQOL with reference to symptoms, health care facility type, age, sex, marital status, and level of education

	Regression coefficients (P-values) of Change in EQ-5D utility score and in the WHOQOL domains on variables				
	EQ-5D	Physical	Psychological	Social	Environmental
Without Chronic Cough (follow-up in 2 months)					
Constant	0.84 (0.000)	3.31 (0.000)	2.27 (0.000)	2.38 (0.000)	1.76 (0.000)
Initial HRQOL	–0.76 (0.000)	–0.80 (0.000)	–0.64 (0.000)	–0.63 (0.000)	–0.51 (0.000)
Breathing Difficulties	–0.08 (0.000)	–0.24 (0.000)	–0.09 (0.073)	–	–
Cough	–	–	0.20 (0.087)	–	–
Age Group (5-year)	–0.03 (0.000)	–0.10 (0.000)	–0.05 (0.000)	–0.02 (0.124)	–0.03 (0.006)
Sex	–	–0.13 (0.019)	–0.09 (0.036)	–	–
Separated/Divorced/ Widowed	–0.10 (0.011)	–	–	–0.35 (0.000)	–
R-Square	0.56	0.45	0.36	0.37	0.29
With Chronic Cough (follow-up in 2 months)					
Constant	0.83 (0.000)	3.34 (0.000)	3.00 (0.000)	2.05 (0.000)	2.16 (0.000)
Initial HRQOL	–0.77 (0.000)	–0.80 (0.000)	–0.79 (0.000)	–0.65 (0.000)	–0.65 (0.000)
Breathing Difficulties	–0.04 (0.169)	–0.14 (0.051)	–0.09 (0.175)	–	–0.12 (0.052)
Fever	–	–	–	–	–0.13 (0.022)
Age Group (5-year)	–0.05 (0.000)	–0.15 (0.000)	–0.09 (0.000)	–	–
Married	–	–	–	0.24 (0.000)	–
At least Secondary Education	–	–	–	–	0.24 (0.041)
R-Square	0.44	0.42	0.39	0.34	0.33

3.5 Discussion

In this chapter we presented the results on the health-related quality of life of individual patients with respiratory symptoms at the time of their visit to a health care facility, as well as at the time following their approximated recovery period. We analyzed and explained the variations in the HRQOL by key socio-demographic factors, as well as by different respiratory symptoms. We found that breathing difficulties are the most significant respiratory symptom that reduces patients' health-related quality of life considerably. Fever and a chronic cough also contribute to the reduction of a patient's HRQOL, however, to a lesser extent than breathing difficulties. We determined that younger patients have better HRQOLs; patients with higher levels of educational attainment also have better HRQOLs; while patients who are either separated, divorced, or widowed have lower HRQOL levels. Sex was found to have an insignificant effect on the level of HRQOL.

It is crucial to test the validity of a measurement instrument in a new context. Since we considered the WHOQOL as being a valid instrument to measure HRQOL in the South Asia region, we tested the validity of the EQ-5D scores with

regard to different WHOQOL domains. We have already shown that EQ-5D scores are extensively associated with the WHOQOL's physical domain and only moderately with its psychological domain. We did not discover a significant association between EQ-5D scores with the social and environmental domains of the WHOQOL. Based on these results, we concluded that the EQ-5D is a valid instrument to measure the HRQOL among Nepalese patients, and that the description above of the HRQOL of patients with respiratory symptoms in Nepal to be valid. In the next section, we will discuss these results with regard to each studied explanatory variable.

The symptom breathing difficulties was identified in approximately 30% of the patients included in our study. Breathing difficulties are a common symptom during exacerbations in patients with asthma and chronic obstructive pulmonary disease. In many cases of exacerbation, urgent health care is required, since the patient's health deteriorates quite rapidly. For this reason, patients' HRQOL is generally lowest during episodes of exacerbations. Associating exacerbations with breathing difficulties may explain the higher impact of this symptom on the reduction of patients' HRQOL. *Table 3.5* shows that patients with breathing difficulties had significantly lower HRQOL scores even after the approximate recovery period. There might be two explanations for this: first, patients with breathing difficulties have longer recovery periods, indicating the symptom's longer-lasting impact on the patient's health. Alternatively, these patients could be individuals who suffer from asthma or chronic obstructive pulmonary disease, and due to the chronic nature of these diseases, the affected patients have lower levels of HRQOL than the general population. As a period of two weeks (in cases of non-chronic coughs) and two months (in the case of a chronic cough) is a sufficient recovery period, the second explanation seems more plausible.

Next, we found age to be an important factor, a well-known fact in HRQOL studies in general. We did not find a significant effect of sex on patients' level of HRQOL. The most important demographic factor affecting the HRQOL level (in the EQ-5D model) was found to be the patient's marital status. Single and married patients had a higher level of HRQOL compared to those who were separated, divorced, or widowed. The results are based on a regression model including age, gender, marital status, level of educational attainment, and symptom(s). The explanation, therefore, lies mainly in the social and situational consequence of being 'single' (following the death of a spouse or a separation or divorce) within the patient's context. Among this group of patients, most are widowed (86%), older (mean age around 60 years), and primarily female (close to 75%). That is, the patients in this group are mostly dependent on their children and have very little income of their own (especially the women), since most of the people in the region are farmers. The economic situation is better for men in this group than for women, however, men who have lost their wife are more likely to receive lower

quality of care at home than they did prior to their wife's death. Hence, loneliness and poverty may also lead to a lower HRQOL level in general, a level that may reduce even more during illness.

Another important factor we found is the positive effect of a higher level of educational attainment on patients' HRQOL. Our results indicate that patients with a higher educational level also have higher levels of HRQOL. Education here can be seen as a proxy for socio-economic status. In a rural community people with a higher education have a higher social status, as they are more likely to have been born into a higher class/caste. In rural Nepalese villages education is usually followed by good fortune rather than the other way around. In any case, people with a higher educational level can make informed decisions quicker than those who are uneducated. In particular, more educated people are more likely to choose the best opportunities available to them and subsequently prefer to visit modern health care facilities over the traditional ones.

Our study has some limitations. These are mostly related to the first time application of the HRQOL questionnaire in the Nepalese context. Both the WHOQOL and EQ-5D were used in a study in Nepal for the first time. We took the validity of the WHOQOL to measure the HRQOL of Nepalese patients for granted, based on the verification of validity of the WHOQOL in the Indian context. Though the socio-cultural situations in India and Nepal are similar, our study would have been reinforced had we validated the WHOQOL in the Nepalese context as prescribed by the WHOQOL group. However, it was not within the scope of the PAL research study to carry out the WHOQOL's validity and hence, we acknowledge it as a weakness of our study.

Secondly, we also acknowledge a similar caveat in the calculation of the EQ-5D score where we used the utility score as defined for the UK's population. Due to the sizable difference between Nepal and the UK in terms of value-system and utilities, the loss of utility attached to various levels of disability might significantly differ. At the onset of our study, we searched for a community with an already established EQ-5D utility score that was geographically closer to Nepal than the UK. We found Japan to be the closest match, and in terms of Japan being an Asian country, we could have used Japan's utility score. However, after careful consideration of the differences between the two countries' value-systems and the different levels of socio-economic development, Japan was found to not be a more suitable alternative. The main reason for choosing the UK's utility measurements over Japan's was that the EQ-5D was initially developed in the UK and holds greater credibility in terms of quality and diligence in the research to estimate the utility measurements.

The limitation of our study is the lack of an objective generic measurement of health in at least an ordinal scale, to facilitate the validity of the EQ-5D other than using the WHOQOL. The nature of the PAL guidelines, which limited us

to mostly recording the symptoms of patients, and the limitation of available resources in terms of manpower (i.e. more trained health care professionals) and medical equipment at the interview location compelled us to include such objective measurements. Finally, the data on the HRQOL was not available for the general population, which limited us from making any inference regarding the patients' HRQOL relative to the general population's.

We end this chapter with a recommendation for future research; additional studies to validate generic health-related quality of life questionnaires, as well as disease-specific HRQOL in Nepal should be conducted. Since many such questionnaires already exist, we recommend choosing those which are proven most suitable in other countries and to carry out the validity of these questionnaires for future use, especially for economic evaluations.

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4

Practical Approach to Lung Health in Nepal: Improving Prescription Behavior and Reducing Costs

This chapter assesses the impact of the Practical Approach to Lung Health (PAL) guidelines in terms of prescription behavior and the total costs of prescriptions for patients with asthma, chronic obstructive pulmonary disease, and pneumonia.

The study is a pre-post intervention comparison in a cluster-randomized trial of primary health care facilities. Forty health care facilities (7 health posts and 33 sub-health posts) in Nepal were stratified by type and subsequently randomized into intervention and control groups. Health care providers from the intervention facilities participated in a five-day training program to familiarize themselves with the adapted PAL guidelines and to learn how to apply them. Carbon-copy prescription pads were used to collect prescription details from both groups. Two sets of indicators were applied to measure the PAL guidelines' impact in a multivariate regression analysis: the World Health Organization's rational-use-of-drug indicators and drug cost indicators.

The PAL guidelines were linked to a reduction in poly-pharmacy and to an increase in the prescription of generic drugs, as well as prescriptions from the essential drug list. The PAL guidelines were also associated with a decrease in the average prescription and wastage costs for the diseases under consideration here, except for COPD; however, these correlations were not statistically significant. Similarly, the PAL guidelines' effect was also linked to an increase in the prescription of antibiotics and adherence to the prescription guidelines, though it was statistically insignificant.

There is evidence that the PAL guidelines' implementation is effective in promoting the rational use of drugs for certain respiratory diseases. Furthermore, a cost-effectiveness analysis should be carried out to compare the PAL guidelines' expected health effects with the actual implementation costs before continuing similar forms of lung health training. In addition, the development of further managerial strategies to guarantee the guidelines' sustainability is encouraged.

4.1 Introduction

Increasing drug costs are a burden for many health care delivery systems in both developed and developing countries. Only operational costs, such as the salaries of health care providers, are higher than the expenditure on drugs, a significant impact on the already scarce resources [1]. Drug costs could be reduced if the prescription behavior of health care workers improved. The non-rational prescription of drugs promotes multi-drug resistance [2] and was estimated to increase drug costs by 33% in India [3] and by 20–52% in rural Nepal [4]. Increasing drug prescription costs influences patients' purchasing decisions where out-of-pocket costs are common [5]. Various educational, managerial, as well as financial strategies have been introduced to alter the prescription behavior of health care providers in developing countries [6], including Nepal [7, 8], to promote 'value for money' in the health sector. Providing training on the standard treatment guidelines (STG) is one of the educational strategies being implemented in many countries to reduce non-rational prescription behavior.

Nepal is one of the poorest countries in the world and spends 5.4% of its gross domestic product (GDP) on health. Of this, only 23.5% is financed by the public sector with the private sector, and especially consumers financing the rest on their own (i.e. 72.4% is paid out-of-pocket) [9]. Thus, rising drug costs directly affect patients' decisions to purchase drugs, which ultimately influences access to health care.

Based on encouraging experiences with the Integrated Management of Childhood Illness program (IMCI), the World Health Organization (WHO) recently developed generic clinical practice guidelines to improve the management of respiratory diseases in adults, the Practical Approach to Lung Health (PAL) [10]. In Nepal, the Ministry of Health (MoH) introduced the generic PAL guidelines in one district, adapting them to the national setting [11]. Primary health care providers from select pilot health facilities were trained in applying the PAL guidelines. One of the aims of the PAL guidelines' implementation is to enhance efficient prescription behavior and to thus promote rational drug use for certain respiratory diseases.

This chapter assesses the impact of the PAL guidelines on prescription behavior and prescription costs of PAL-targeted diseases, i.e. asthma, chronic obstructive pulmonary disease (COPD), and pneumonia.

4.2 Methods and Materials

4.2.1 Design

This study was part of the international pre-post evaluation program *"Assessing the cost effectiveness of integrated respiratory care guidelines in Nepal"* [12] which in-

cluded a stratified cluster randomized trial [13] in the Nepalese lowland district of Nawalparasi. The Nawalparasi district was selected because it met two prerequisites for launching a pilot PAL program, namely a district in which both IMCI and DOTS is implemented. The program included both locally adapted guidelines and subsequent training.

Health care facilities

Of the 76 health care facilities in the Nawalparasi district, 40 were included in our study based on highest patient turnout. The selected health care facilities included 7 health posts (HPs) and 33 sub-health posts (SHPs). These 40 facilities were stratified by type and subsequently randomized into PAL intervention (21) and standard practice control (19) groups. Both groups received a copy of the Standard Treatment Schedule (STS) [14] prior to the PAL intervention. Each health care facility in both groups employed a Community Drug Program (CDP) to ensure the availability of drugs throughout the year, and had received CDP training prior to the program's implementation. Rational drug prescription is one of the components of CDP training [15].

Description of the intervention

The WHO's generic PAL guidelines were developed in an international context [16]. To complement its successful tuberculosis control program, Nepal was selected as one of the countries that would benefit from the implementation of the PAL guidelines. The implementation involved a number of steps. First, the generic guidelines were adapted to the national Nepalese setting. Together with the National Tuberculosis Centre (NTC), the WHO took the initiative to facilitate the adaptation of the guidelines and the implementation process. Several professionals and different organizations, along with health care providers from a pilot project being carried out in a Nepalese district participated in the process and reached a consensus on the content of the PAL-Nepal guidelines [17]. The guidelines target health care workers at HPs and SHPs and follow the same format as the IMCI first-level facility guidelines. Secondly, the NTC developed training materials and conducted the training of health care providers from the selected intervention facilities on the application of PAL-Nepal guidelines. At least one health care provider from each facility participated in the training. The NTC organized a training of trainers (ToT) with the assistance of WHO consultants in June 2002. Respiratory physicians, trainers from the District Health Office (DHO) and the NTC participated in the ToT. The five-day training program of health care workers was conducted at the district level in July/August 2002, with the support of the ToT participants.

Trainings were conducted in three small groups at the local hospital. Thirdly, following the completion of the training program, NTC supplied all PAL intervention facilities with examination formats and wall posters.

4.2.2 Indicators and Coding

Indicators

We used the WHO's Rational-Use-of-Drugs (RUD) indicators [18] to measure the prescription behavior of health care providers in both groups before and after the PAL intervention. These include the average number of drugs prescribed per patient encounter, prescription of generic drugs (in %), prescription of drugs from the Essential Drug List (EDL) (in %) [19], prescription of an antibiotic (in %), and adherence to the prescription guidelines (in %). We used three types of cost indicators, i.e. expected costs, actual costs, and wastage costs, to assess the impact of the PAL guidelines on overall prescription costs. We were not able to calculate the costs for a full course of treatment because the available information on prescriptions was incomplete. Instead, we calculated the drug costs on the basis of the Defined Daily Doses (DDD) for solid oral preparations. For liquid oral and topical preparations we used the unit costs of the product available in the local setting. Actual costs were calculated as the unit price of drugs prescribed, multiplied by each drug's DDD. Expected costs were calculated as the unit price of drugs for a particular disease as recommended by the PAL guidelines and multiplied by the DDD of the proposed drugs. Wastage costs were calculated by subtracting the expected costs from the actual costs.

Carbon-Copy Prescription Pads (CCPPs) were used to collect information on prescription patterns. Many studies on drug use apply this method of data collection since its format does not differ from existing prescription pads, except for the additional carbon-copy sheet. CCPPs had been in use in the 40 Nawalparasi pilot facilities since the beginning of 2002, with the approval of the MoH. A one-day orientation program for health care providers was organized prior to the introduction of the CCPPs to explain their purpose and demonstrate their use. Field assistants distributed and collected the CCPPs, including the prescription data. We collected all disease-specific prescriptions made at each facility during each phase of the study from February to May 2002, prior to the implementation of the PAL (baseline) guidelines. Similarly, to assess post-intervention prescription behavior, we collected all disease-specific prescriptions made at each facility during every phase of the study from October 2002 to January 2003. The total number of prescriptions (407) by groups is illustrated in *Figure 4.1*. In addition, field assistants collected the individual drug prices at local health care facilities, as well as from nearby drug retailers between July and October 2003.

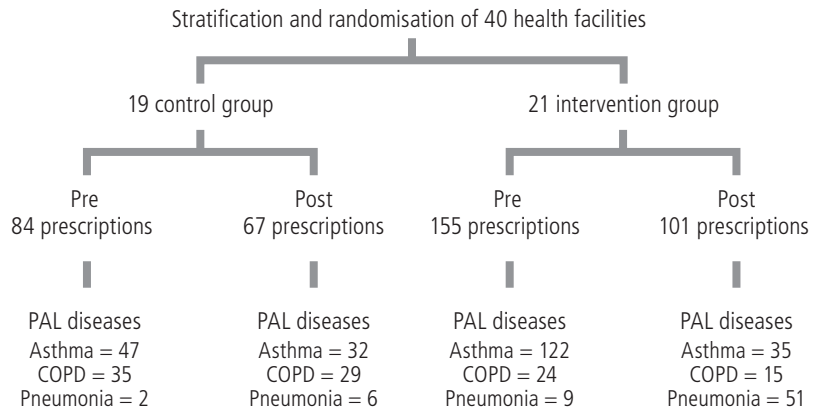

Figure 4.1. Number of prescriptions stratified by study group and diseases.

Coding

For the comparison to be feasible, we used two sets of disease-specific indicators to determine appropriate prescription behavior: one set for selected lung diseases that were to be treated according to the PAL-Nepal guidelines within the PAL intervention group, and one set for selected lung diseases to be treated according to the STS guidelines [14] in a standard practice control group. In the PAL intervention group, asthma was coded as having been correctly treated when it was treated according to the PAL guidelines, i.e. when the health care provider prescribed salbutamol tablets or an inhaler; COPD was coded as having been correctly treated when the health care worker prescribed either salbutamol tablets or an inhaler; and pneumonia was coded as correctly having been treated when either cotrimoxazole, amoxicillin, chloramphenicol, or penicillin VK with or without paracetamol was prescribed. Similarly, in the standard practice control group, asthma was coded as having been correctly treated when it was treated according to the STS guidelines, i.e. when the health care provider prescribed salbutamol or aminophylline tablets; COPD was correctly treated if the health care worker prescribed salbutamol or aminophylline tablets; and pneumonia when cotrimoxazole or amoxicillin with or without paracetamol was prescribed. Treatment was only classified as being appropriate if the health care provider had prescribed the correct drug in accordance with the PAL or STS guidelines. We coded all diseases into one aggregate group, since our aim was to measure and evaluate whether the PAL guidelines promote rational drug prescription for lung disease in general. Using regression analysis, we accounted for the low number of prescriptions for individual diseases.

4.2.3 Data Analysis

Data were entered using the software SPSS-Data Entry 3.0, SPSS, Inc. and analyzed using SPSS 11.0, SPSS Inc., and STATA 8.2, Stata Corp. The median price per unit for each drug was calculated by pooling the price of the particular drug at different health care facilities and retailers, and by pooling together the price of the drug under its traded and its generic name. Separate prices were calculated for different modes of administration. To compute the total drug costs for the entire prescription dataset, the costs datasets were merged using a unique identifier for each combination of a drug's generic name drug and its mode of administration.

We used multiple linear regression models to explain the variation in each of the outcome variables, namely the total costs of a prescription, total number of drugs prescribed for each prescription, number of drugs prescribed from the essential drugs list per prescription, and the number of generic drugs prescribed for each prescription [20, 21]. We grouped the prescriptions by time period (pre- and post-intervention), PAL facility status (PAL facility and non-PAL or control facility), and existence of an intervention (PAL post-intervention). We used the pre- and post-independent variable labeled 'Non-PAL' and 'PAL' to measure the changes in relation to time trends. Next, we used the 'PAL post' parameter to measure the real changes attributable to the PAL intervention, hence controlling for a secular trend. In all regression analyses, we also controlled for other variables such as health care facility level (HP and SHP), diagnosis, i.e. asthma, COPD, and pneumonia, as well as for patient characteristics (age and sex). The distribution of total costs was found to be skewed, and, therefore, a log-transformation on the total costs was used in the regression model, as is common in cost studies. In total, we dropped three extreme observations as outliers, which were possibly a result of an error in data entry.

In a second regression analysis, we calculated the odds of prescription guideline adherence (as a yes/no criterion) and prescription of antibiotics (also as a yes/no criterion) using logistic regression. The independent variables used in the model were the same as in the multiple linear regression models. To account for clustering of patients visiting a specific health care facility, we used the random-effect model Huber-White, a solid method for calculating standard errors in cluster effects, as part of the STATA 8.2 version [21, 22].

4.3 Results

4.3.1 Patients' Characteristics

There was a slightly higher percentage of male patients in both groups throughout the different phases of data collection. The median age of patients was similar in both the control and intervention groups (during the pre- and post-intervention

Table 4.1. Age and sex distribution of patients

	Control		Intervention	
Prescriptions	Pre	Post	Pre	Post
Male (%)	49 (58.3)	41 (61.2)	88 (56.8)	55 (54.5)
Female (%)	35 (41.7)	26 (38.8)	67 (43.2)	46 (45.5)
Median age (IQR)	60 (49–65)	60 (41–70)	60 (45–69)	52 (34–62)

IQR = Inter-Quartile Range

period); the median age was slightly lower for the intervention group during the post-intervention period (see *Table 4.1*).

4.3.2 Prescription Behavior and Prescription Costs

We calculated the mean and standard deviations of the specific indicators for rational prescription behavior (*Table 4.2*). The average number of drugs per prescription increased in both groups following the PAL intervention, but was far more evident in the control group. The pre-post difference with reference to generic drug prescriptions increased in both groups, but was slightly higher for the control group. The percentage of drugs prescribed from the EDL declined in the control group but increased in the intervention group. The percentage of prescriptions including at least one antibiotic per patient encounter increased in both groups, whereas the percentage of patient encounters indicating prescription guideline adherence decreased in the control group. Concomitantly, the aggregate average and aggregate wastage costs for all lung diseases combined increased in both groups.

In the PAL intervention group a shift in diagnoses toward more pneumonia cases and fewer chronic lung diseases was apparent. As such a shift was not observed in the control group, it could be attributable to the PAL intervention. Changes in absolute turnout were not analyzed, since they are subject to a number of influences both at the district and local levels, e.g. seasonal changes, availability of health care staff and of drugs. All these influences were accounted for in the randomization process.

We used a linear regression to examine the PAL guidelines' effect and to control for a variation in case-mix, patients' characteristics, as well as facility features. *Table 4.3* presents a summary of the linear regression models by different outcome parameters for prescription behavior and prescription costs. The PAL guidelines were particularly effective in reducing the average number of drugs prescribed per prescription at PAL facilities, by six drugs for every 10 prescriptions. Generic drug prescription and the prescription of drugs from the EDL also increased by 6% and 10%, respectively, but this effect was not statistically significant. The average amount of drug prescriptions reduced by 34% and wastage costs per prescription

Table 4.2. Pre-post and intervention-control values of selected indicators for all diseases, expressed in mean (standard deviations)

Indicators	Pre-Post prescriptions (n)	Drugs per prescriptions	Percentage of generic prescriptions	Percentage of drugs prescribed from the Essential Drug List	Percentage of at least one prescribed antibiotic per encounter	Percentage of encounters indicating adherence to guidelines	Cost per prescription (NRs.)*	Wastage cost per prescription (NRs.)*
Control	Pre (84)	2.56 ± 1.13	51.3 ± 35.9	71.3 ± 26.2	42.9 ± 49.5	21.4 ± 41.3	11.2 ± 16.0	9.8 ± 16.1
	Post (67)	3.10 ± 1.22	56.3 ± 31.8	62.4 ± 28.8	62.7 ± 48.7	11.9 ± 32.7	17.0 ± 18.1	15.4 ± 18.2
a. Pre-Post change		0.54	5.0	–8.9	19.8	–9.5	5.8	5.6
Intervention	Pre (155)	2.52 ± 0.98	55.8 ± 31.5	64.1 ± 27.5	41.9 ± 49.5	14.8 ± 35.7	8.41 ± 11.4	6.94 ± 11.4
	Post (101)	2.58 ± 0.97	56.8 ± 38.9	69.1 ± 28.5	66.3 ± 47.5	19.8 ± 40.0	17.9 ± 26.9	15.2 ± 27.0
b. Pre-Post change	0.06	0.06	1.0	5.0	24.4	5.0	9.5	8.3
Relative change (a–b)		–0.48	–4.0	13.9	4.6	14.5	3.7	2.7

*US$ 1 = NPR 75.

Table 4.3. Linear regression models for indicators of rational prescription behavior and beta coefficients (standard error) for various explanatory parameters[†]

Indicators	Drugs per prescription (n = 407)	Percentage of generic prescriptions (n = 407)	Percentage of drug prescriptions from Essential Drug List (n = 407)	Cost per prescription*** (NPR) (n = 407)	Wastage cost per prescription (NPR) (n = 407)
Constant	2.69 (0.3)	38.15 (7.6)	78.21 (8.6)	2.09 (0.3)	5.92 (3.6)
Post vs. Pre	0.45 (0.2)*	6.79 (7.5)	–6.98 (4.6)	0.51 (0.3)	4.63 (3.6)
PAL vs. Non-PAL	0.1 (0.2)	3.36 (7.1)	–7.64 (4.6)	0.11 (0.2)	–0.93 (2.9)
PAL post	–0.65 (0.2)**	6.22 (9.4)	9.89 (6.0)	–0.41 (0.3)	–2.46 (4.1)
Asthma	–0.58 (0.2)**	7.32 (4.5)	1.69 (4.0)	–0.94 (0.2)**	–4.34 (2.8)
COPD	Dropped	Dropped	Dropped	–0.34 (0.2)	2.49 (3.0)
Pneumonia	–0.07 (0.2)	–17.24 (6.1)**	9.07 (6.4)	Dropped	Dropped
Health care facility level	0.3 (0.2)	–0.9 (6.6)	–10.99 (2.9)**	0.34 (0.2)	4.47 (3.1)
Age	0.004 (0.003)	0.15 (0.1)	–0.1 (0.1)	0.002 (0.003)	0.08 (0.1)
Gender	–0.2 (0.1)	2.6 (3.6)	–0.18 (0.1)	–0.09 (0.1)	–1.13 (1.8)
R^2	11%	7.5%	6%	15.92%	9.2%

[†]Selected indicators = constant + b_1 (post) + b_2 (PAL) + b_3 (PAL Post) + b_4 (Asthma) + b_5 (COPD) + B_6 (Pneumonia) + b_7 (Health Post) + b_8 (Age) + b_9 (male) + residual error. Between brackets: Huber-White robust standard error accounting for potential cluster-effects (Williams, 2000; Ukoumunne et al., 1999).

*P-value = < 0.05;**P-value = < 0.01;***Log transforms

fell by NPR 2.46 (US$ 1 = NPR 73.15), but these findings were also not statistically significant.

We performed another logistic regression for two specific indicators to examine prescriptions including antibiotics and adherence to the prescription guidelines, and to control for variation in the case-mix, patients' characteristics, as well as health care facility level. *Table 4.4* indicates the summary of the logistic regression model. We determined a low odd ratio[1] in the prescription of antibiotics and a high odd ratio in the adherence to prescription guidelines (2.29)[2] as an effect attributable to the PAL guidelines, but these findings were not statistically significant.

4.4 Discussion

There is evidence that implementation of the PAL guidelines is effective in promoting the rational use of drugs for select respiratory diseases. The PAL guidelines

[1]Calculated as: $e^{-1.0} = 0.37$

[2]Calculated as $e^{-0.83} = 2.29$

Table 4.4. Logistic regression model for specific bi-nominal indicators for rational prescription behavior and beta-coefficients (standard error) for various explanatory parameters

	Antibiotics per encounter (n = 407)	Adherence to guidelines (n = 407)
Constant	0.33 (0.42)	–1.68 (0.62)
Pre vs. Post	0.72 (0.45)	–0.72 (0.43)
PAL vs. Non-PAL	0.14 (0.41)	–0.63 (0.44)
PAL Post	–1.00 (0.67)	0.83 (0.64)
Asthma	–1.00 (0.48)*	0.67 (0.49)
COPD	Dropped***	Dropped***
Pneumonia	3.31 (0.95)**	1.2 (0.6)*
Health care facility level	–0.01 (0.19)	–0.19 (0.39)
Sex	–0.2 (0.29)	–0.03 (0.39)
R^2	19.33%	19.2%

*P-value = < 0.05; **P-value = < 0.01; ***Due to co-linearity
Between brackets: Huber-White robust standard error accounting for cluster-effects (Williams, 2000; Ukoumunne et al., 1999).

were associated with a reduction in poly-pharmacy, as well as an increase in the prescription of generic drugs and drugs from the EDL. The PAL guidelines were also linked to a decrease in average prescription and wastage costs, although these links were not statistically significant. Similarly, there is a positive but not significant effect of the PAL guidelines on the prescription of antibiotics and the adherence to prescription guidelines. The fact that only one outcome variable, out of seven being regressed, was found to be statistically significant might raise the suspicion that the significance occurred by chance. However, the high level of significance of the P-value of less than 1% can be taken as a strong reason for stating such a chance is very unlikely.

The study reveals an increase in the number of drug prescriptions over time. This may be the result of the community drugs program that was introduced in 2000 to ensure year-round availability of essential drugs. The program may also have led to some supplier-induced demand, since health care providers can prescribe more (yet unnecessary) drugs to increase drug revenues at the health care facilities.

Health care workers' adherence to drug prescription guidelines was very low, around 10–20%. The reason for this result may have been that the study selection criteria only included patients in which one particular disease had been diagnosed, although in reality patients may have suffered from a comorbid condition which required the prescription of other drugs. This reduced the number of prescriptions that indicated an adherence to the prescription guidelines.

Our study has several limitations. First, the monitoring of health care providers by field assistants and the use of CCPPs may have influenced their prescription

behavior. Secondly, the number of overlooked cases may have been high if the health care provider did not mention the diagnosis or syndrome in the patients' prescriptions. Third, drug prescription costs were calculated based on DDD and not on actual costs. Actual costs may differ from our result on drug prescription costs if the prescribed dosage is different from the DDD. Fourth, because of a low patient inclusion in our study, drug prescription patterns were not analyzed with reference to conditions, and important disease-specific findings may have therefore been missed.

The PAL guidelines' ultimate aim is to deliver more effective and efficient health care services. Our study indicates that the guidelines do indeed promote rational prescription behavior, although a reduction in treatment costs was not apparent. When the costs of guideline implementation and supervision are considered as well, the question is whether the additional costs related to the implementation of PAL guidelines are worth the benefits. We recommend further analysis on cost-effectiveness to compare the final costs and derived benefits. Furthermore, training alone on the application of guidelines may not be a sufficient form of intervention to ensure a modified prescription behavior in the long-term. Further training to bring the staff at health care facilities up to date, as well as other managerial strategies may be needed to foster permanent effects [23].

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Part II

PAL: MODELING POPULATION LUNG HEALTH

5

Multistate Models to Study Lung Diseases: A Review

Multistate models are useful for studying life histories in terms of events such as disease incidence, progression, and mortality. Multistate models are widely used in the study of medical prognosis, as well as in model-based economic evaluation and medical decision making. For our study we reviewed journal articles on the implementation of multistate models for lung health.

5.1 Introduction

A disease process is inherently a multistate process. At any point in time, individuals are either in good or in poor health. In terms of a specific disease, individuals are either diseased or non-diseased. In the course of time, the disease process continues up until death. In health care, the purpose of preventive intervention is to prevent people shifting from a state of good health to one of poor health, or from a non-diseased state to a diseased state. Likewise, curative interventions are aimed toward increasing the rate of transition from a diseased to a non-diseased state, or from poor to good health. The effect of such interventions on the process of change in health-related states is studied by using multistate models. The models are estimated through longitudinal data that record health status changes or the health state of an individual at various points in time.

Multistate models are useful for studying life history events such as disease incidence, progression, and mortality [1, 2]. Markov models are an example of multistate models and are widely used in the study of medical prognosis [3], as well as in the study of model-based economic evaluation and medical decision making [4–6]. In this study, we review the use of multistate models to study lung health.

This chapter is part of a research study aimed at developing a multistate model to evaluate the cost-effectiveness of the implementation of the Practical Approach to Lung Health (PAL) guidelines in Nepal [7]. The guidelines initiated by the World Health Organization (WHO) aim to improve the syndromic management of lung diseases in youths (over 5 years of age) and adults in middle and low-income countries. The guidelines target four main respiratory diseases: tuberculosis, asthma, chronic obstructive pulmonary diseases, and pneumonia, collectively referred to as PAL-diseases. In Nepal, PAL has been adapted to local contexts and a pilot

implementation of the nationally adapted package, PAL-Nepal, was tested in primary health care centers, health posts, and sub health posts in Nawalparasi, a rural lowland district [8].

This chapter consists of two main sections. The first section presents a brief description of PAL diseases and the relevant publications identified. The second section addresses conceptual and measurement issues in intervention studies. One measurement issue is the definition of the state-space, i.e. the disease states to be distinguished. A second issue is the measurement of transitions from available data which are often incomplete.

The definition of disease states is sometimes difficult to establish, mostly due to the lack of proper knowledge of the disease processes and, even if the disease states are well defined, it is sometimes difficult to measure them on account of lack of resources in terms of human capital, infrastructure, and medical equipment. For example the lack of properly trained doctors in rural Nepal makes it difficult to assess the severity of a disease condition. Even in the presence of a doctor, the lack of diagnostic equipment often makes the task of determining the severity of a disease virtually impossible.

Once the state-space is defined, transitions between different states of health are measured. For this, patients are continued to be monitored and data are collected at certain intervals. We focus on the questions about when and what should be measured. Based on the measurement, transition rates or transition probabilities are calculated. In some cases, transition rates are needed for shorter periods. In others, transition rates need to first be modeled and the effects of various covariates studied. The uncertainty in the measurements' estimation process must be reported. Failing to do so makes the description of the disease process incomplete, and reduces the usefulness of the measurement for future statistical inferences.

A literature review on the use of multistate models to study lung health contributed to the establishment of a multistate model that could be used in our evaluative study. In Section 2, we briefly describe the PAL diseases and the articles included in the review. We included eleven articles published between 1995 and 2005. Subsequently, in Section 3, we consider each aspect individually and describe and assess the current state of the art. In Section 4, we discuss how the findings in this chapter contribute to the development of a multistate model for PAL and, finally, draw some conclusions.

5.2 PAL Diseases

The next section briefly describes PAL diseases, namely asthma, chronic obstructive pulmonary disease, tuberculosis, and pneumonia.

5.2.1 Asthma

Asthma is a chronic disorder of the airways that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. Based on the level of airflow limitation and its variability, asthma has broadly been classified in a progressive level of severity as intermittent, mild persistent, moderate persistent or severe persistent [9]. In addition, episodes triggered by asthma exacerbations (attacks or worsening of asthma symptoms and lung function) can be classified in different levels of asthma control, such that a mild level on a severity basis may become a severe acute exacerbation. The chronic-episodic nature of asthma makes the disease a good candidate for a multistate modeling framework. The disease can develop at any age, though childhood asthma, especially in boys, may disappear during puberty, but reappear again at a later stage [9]. The prevalence of asthma is quite high; for example, the prevalence of asthma among children in Nepal is up to 30% [9]. Deaths linked to asthma are mostly attributable to failed disease management. Morbidity linked to asthma is usually caused by increased severity, under-treatment of patients with anti-inflammatory therapy, over-reliance on bronchodilators, and a delay in medical help during an exacerbation.

We found eight papers of which we chose five for inclusion in this review. An article by Boudemaghe was in French and was thus excluded on the grounds of the language barrier. The first article by Soriano *et al.* [10] is based on cross-sectional data and, hence, we will limit the review to the definitions of state, as longitudinal data required to carry out transitional measures was not collected. Among the remaining four publications, the multistate model was applied to examine the long-term evolution of asthma in two papers by Combescure *et al.* and by Saint Pierre *et al.* [11, 12]. In the last two articles by Paltiel *et al.* and Price and Briggs, the multistate model was used to assess the cost-effectiveness of different interventions [13, 14].

5.2.2 Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease is a chronic disease characterized by a decline in lung function over time. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) [15] defined chronic obstructive pulmonary disease as "... a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases". According to the GOLD, a diagnosis of chronic obstructive pulmonary disease should be considered

in any patient with a cough, sputum production, dyspnoea, and/or a history of exposure to the disease [15]. The diagnosis is confirmed by spirometry. Based on the spirometry, the GOLD defines four levels of chronic obstructive pulmonary disease: *mild*, *moderate*, *severe*, and *very severe*. The prevalence of chronic obstructive pulmonary disease is highest in countries where cigarette smoking has been, or still is, very common [15]. The morbidity and mortality rate linked to chronic obstructive pulmonary disease is among the highest in the world, ranked 12^{th} in the WHO's Global Burden of Disease Study in the year 2002 with 1.9% of the Disability Adjusted Life Years (DALYs) lost worldwide [15]. Dyspnoea and exacerbation of chronic obstructive pulmonary disease are the main reason for seeking medical attention [15].

We also included three articles that applied a multistate modeling framework to study chronic obstructive pulmonary disease [16–18]. Sin *et al.* use the Markov model in a cost effectiveness analysis in patients with varying severities of chronic obstructive pulmonary disease defining state by level of severity [16]. Borg *et al.* describe chronic obstructive pulmonary disease by means of a two-dimensional Markov model [17]. The model consists of several primary states which refer to the disease's severity and several secondary states relating to exacerbation. They tested their model in an evaluation of two hypothetical interventions treating different mechanisms of the disease, namely irreversible lung function decline and exacerbation frequency [17]. Similarly, Oostenbrink *et al.* use a Markov model to study the cost effectiveness of different treatments for chronic obstructive pulmonary disease. The states are defined by levels of severity and of exacerbation [18].

5.2.3 Tuberculosis

Tuberculosis is an infectious disease which appears as a progressive primary disease in persons who have been newly infected, or through endogenous reactivation (post-primary disease), or exogenous re-infection in individuals with remote (latent) infections [19]. Cases of tuberculosis can be infectious or non-infectious. An infection with tuberculosis begins with the transmission of *Mycobacterium tuberculosis*. Infected persons either develop active tuberculosis or become latently infected and may develop active tuberculosis at a future stage. Active tuberculosis can develop more than once. Some crucial points in time in the tuberculosis process are time of infection, onset of disease, case detection, duration of treatment, relapse, smear conversion, and endogenous reactivation.

We have also included three articles by Blower *et al.*, Vynnycky and Fine, and Dye, in which a multistate approach was used in the analysis of tuberculosis [20–22]. Blower *et al.* present two models of the transmission dynamics of M. Tuberculosis. The first model distinguishes between three and the second between

five states [20]. The models were applied to determine the reasons for the sudden rise and drastic decline of major epidemics in developed countries prior to the availability of an effective therapy.

Vynnycky and Fine employed a *compartmental model* to assess the relative contribution of different disease mechanisms in the decline of tuberculosis in England and Wales in 1900. The model is an extension of the one introduced by Sutherland *et al.* [23]. It distinguishes between eight active states and estimates the age-specific risks for developing *primary*, *endogenous*, and *exogenous* tuberculosis.

Dye *et al.* extended and merged the models by Blower et al. and Vynnycky and Fine to produce an age-structured compartmental tuberculosis model. The model was applied to assess the potential effect of DOTS in developing countries with a high prevalence of tuberculosis.

5.2.4 Pneumonia

Pneumonia is an acute infectious disease that is reversible, and has a short incubation period. A multistate model of three states applies characterized by short time-steps: *healthy-diseased-deceased*. We did not find any multistate or Markov model that has been applied specifically to pneumonia.

5.3 Review

In this review our focus is on multistate modeling. We consider the state-space, model assumptions, measurement of transitions, and the reporting of uncertainties.

5.3.1 State-Space

A multistate model is specified by a state structure and a set of rates or probabilities of transition from one state to another [24]. The state-space consists of every distinct health state [2]. Therefore, the first step in building a multistate model is the enumeration of all distinct states of health that should correspond to standard or literature-based notions of the disease [3]. An individual can display various states of health at different points in time. The states distinguished in multistate modeling, i.e. the choice of the state-space, depend on the research question. For example, if the research question is to assess the impact of treatment on the duration of hospital stay, the states may be defined as: healthy, diseased – not in hospital, diseased – in hospital. If instead the research question is about the impact of the treatment on health-related quality of life (HRQOL), the states could be defined as ‘with-good-HRQOL’ and ‘with-bad-HRQOL’.

Asthma

The state-spaces for asthma in all but one study included in this review were based on asthma control programs focused on short-term change. The level of asthma severity, which only changes very slowly, is used to categorize patients into three main groups: mild, moderate, and severe. The severity of asthma is measured by both the level of airflow limitation and its variability [9]. Most studies use asthma severity as a criterion for the inclusion of patients in the studies. To study the change in severity, a longer study period is required and not much data on the transition between severity groups are available.

Soriano *et al.* define states of asthma control as *good*, *moderate*, and *poor control*. Soriano *et al.* determine these states on how many of the GINA goals (goals set by *Global Initiative for Asthma*) are not achieved [9]. Achieving all goals means that the patient does not experience any asthma-related symptoms that carry any significance. The patients' responses to straightforward questions are recorded. These concern their experiences at different times: present day (5^{th}), past week (1^{st} and 2^{nd}), past month (3^{rd}), and past year (4^{th}). In a multistate modeling framework, the incidents that are of particular interest are those that occurred between two points in time, typically the time-steps between the last and the present interview. Therefore, the state-space of asthma control based on the GINA goals is problematic.

Combescure *et al.* and Saint Pierre *et al.* define state-space through three "control" states [11, 12]. These states are defined based on a list of asthma-related incidents and 'activities'. Combescure *et al.* and Saint Pierre *et al.* used data from ARIA (*Association pour la Recherche en Intelligence Artificelle*) and the definitions of a state-space in both cases are the same. Data were collected over a four year period (1997–2001) from several French chest physicians reflecting a hospital's real life activity. At each visit, patients were categorized into one of three asthma control states, namely *optimal*, *sub-optimal*, and *unacceptable*, based on the frequency of symptoms, their duration, the degree of bronchial obstruction, and the need for rescue medications. For the multistate analysis, data were collected from visits that were at least four weeks apart. Visits that took place less than four weeks following the preceding visit were not included in the study. Most of the variables used to define the states were measured by posing questions on past experience, practice, and incidents, as well as a measurement of FEV_1 (Force Expiratory Volume in 1 second). In poor medical settings, for example in rural parts of developing countries, FEV_1 measurement may not be possible; however, other variables can be used to assess the state of the patient's asthma control. Hence, the overall definition of the states of asthma control can be considered an important contribution made by this dissertation to the study of asthma control over time in different settings.

Paltiel *et al.* [13] define four states of *exacerbation* based on the patient's exacerbation experience in the preceding month, such as *chronic/stable* (no exacerbation), *exacerbation involving urgent-care, exacerbation involving the emergency department*, and *exacerbation involving hospitalization*. Twelve strata are formed based on a combination of lung function (mild, moderate), prior hospitalization (none, once, or more than once), and age groups (18–35, $>$35). Each stratum then has a state-space comprising four *exacerbation* states. Patients who are over 35 years move to the subsequent age strata in which new rates of transition apply. Transitions between the four states are all possible. Two *deceased* states (asthma-related and others) are included in the state-space. The state-space used for the cost-effectiveness analysis consists of 48 active states comprising twelve strata with four exacerbation states each. The time-steps is one month and the model runs for ten years. The model is data intensive (which is acknowledged by the authors who consequently did not include additional dimensions, e.g. socio-demographics, risk factors, and environmental exposure) [13], and all data are obtained from published sources, except for the data for quality of life. At the core of the model lie four exacerbation states and two deceased states which are similar to the asthma control states of other studies. Death is rare in asthma studies hence, general death rates can be applied which lead to a single deceased state. The authors included two asthma-related death rates for the two age groups. The strata can be included in the model as covariates following Saint-Pierre *et al.* [12]. This states structure is easy to apply, convenient for data collection, and does not require much resources, like a doctor or medical equipment.

In Price and Briggs [14], the different states of asthma control are based on the patient's exacerbation experience in the past week. They define five states: successful control, sub-optimal control, primary care managed exacerbation, hospital-managed exacerbation, and treatment failure exacerbation. The time-step between space-states is one week, the reason for this being the chronic episodic nature of asthma, with patients typically deteriorating within a relatively short period of time, but also improving very quickly.

To summarize, asthma is modeled by multistate models with a state-space based on asthma control. Asthma control is acute in nature and defined in accordance with the severity of exacerbation and resources used to treat the exacerbation, and not based on asthma severity, which is chronic in nature. The severity of exacerbation is usually measured in 3–4 states and can easily be estimated by using a questionnaire that focuses on resources needed to treat the exacerbations, thus facilitating data collection. In addition, trained doctors and medial instruments are used in some cases to define states in asthma. A *deceased* state is not included in most of the models, since asthma-related deaths are rare, but also because the timesteps of the clinical trials are short. The time-step is usually one month, except in Price and Briggs' model (2002), where the time-step is one week. Since all incidents and

durations are important for such research studies, the time-step should be such that the likelihood of more than two incidents occurring during the period of a given time-step is minimal. This argument is made by Price and Briggs and is an important factor to consider when planning the data collection process.

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease is a progressive, irreversible disease with an increasing degree of airflow limitation and periods of acute worsening of the disease, also referred to as exacerbations [17]. The chronic-episodic nature of chronic obstructive pulmonary disease is similar to asthma and hence, we would expect the disease to have a similar state-space as is the case for asthma.

Sin *et al.* present a model to study the natural history of chronic obstructive pulmonary disease with a long-term severity of the disease measured by the FEV_1, as recommended by the American Thoracic Society [25]. Three severity states (stages) are defined: stage 1, 2, and 3 (FEV_1: $>=$50% predicted, $<$50 but $>=$30% predicted, and $<$30% predicted). Data are mostly obtained through published sources and surveys. The simulation runs for three years with twelve trimonthly time-steps. Patients often move to either higher stages of the disease or die. The transition to higher stages, as is similar to the aging process in a life table, is associated with a decline in FEV_1 at a constant rate of decline of 47 mL per patient per year. Hence, with this steady decline in FEV_1, a patient in stage 1 (FEV_1 $>=$50% predicted) will reach stage 2 (30% $=<$ FEV_1 $<$50% predicted) within a few years. During each time-step, the number of different exacerbation types is derived from a given rate of exacerbations. Exacerbations are then classified into three mutually exclusive categories, namely, mild, moderate, and severe, depending on the type of intervention required. The mean durations are 1, 2, and 4 weeks, respectively. However, they are not defined as states, but rather as events. This can be translated as each stage having 4 sub-states, namely *stable*, *mild*, *moderate*, and *severe exacerbation*. Following incidents of exacerbation, patients move about between these states for some time before arriving at a stable state again. This model is similar to the Asthma Policy Model by Paltiel *et al.*, which is suitable for a life course analysis of chronic diseases with acute episodes occurring at various time-steps. In this model, the possibility of moving to higher stages does not depend on the occurrence and type of exacerbation as cited by Borg *et al.* [17]. In Sin *et al.*, exacerbations are not treated as sub-states and the effect of exacerbation on lung function decline has not been considered. Borg *et al.* address these issues in their two-dimensional Markov chain to represent disease severity and exacerbation status.

In their multistate model, Borg *et al.* cover four states of severity: *I*, *IIA*, *IIB*, and *III* based on the GOLD definition using FEV_1 [15, 17]. States *IIA* and *IIB* are

further sub-divided into two states each, as *IIA1*, *IIA2*, *IIB1*, and *IIB2*, amounting to a total number of severity states of six. Unlike in Sin *et al.*, a patient can regress one step to a milder severity state (within half a year). However, a patient who has regressed one step cannot regress any further, so in order to differentiate between patients who regressed to a milder severity state, two additional states *IIA2* and *IIB2* were introduced. A *deceased* state is also included in the model. Each of the six severity states has four exacerbation states, namely *none*, *mild*, *moderate*, and *severe*. The definition of exacerbation is based on the symptom-driven definition of exacerbations in accordance with Seemungal *et al.* (cited by the authors on page 156) [17]. The states of exacerbation are defined based on Rodriguez-Roisin's resource-driven staging development (cited by the authors on page 156) [17]. The time-step is one week.

Oostenbrink *et al.* defined four severity states (mild, moderate, severe, and very severe) based on the GOLD definition [18]. However, they do not include the mild state in their study. The study period consist of only one year, hence the state 'deceased' is also excluded. The time-step for the first cycle is eight days and, thereafter, one month. In each cycle, a patient can have none, or one exacerbation which is either non-severe or severe. The data used derived from five clinical trials. The change in severity states as observed in eight days and one month is too insufficient to conclude that change occurs at the severity level of chronic obstructive pulmonary disease. Instead, only the change in FEV_1 due to an alteration of an acute condition, i.e. exacerbation, is taken into account.

In conclusion, due to the chronic-episodic nature of both asthma and chronic obstructive pulmonary disease, both diseases can have a similar state structure. The number of severity states is clearly defined by GOLD, namely *mild*, *moderate*, *severe*, and *very severe* states. In most cases the number of exacerbation states are defined by the type of resource needed to control the exacerbation, which ranges from 3 to 4.

It would be helpful to have a two-dimensional definition of a patient's state (severity state, exacerbation state) at every phase. Severity-based models are not useful in short-term studies. The time-step for severity is obviously longer than that for exacerbation; since the change in severity level is a very slow process, the time-step for severity should be a multiplication of the exacerbation dimension's time-step so that at the end of a severity episode, the transition between the states of both dimensions can be examined. The time-steps of severity-based multistate models comprise three months in Sin *et al.*'s study [16], six months in Borg *et al.*'s [17] and one month in Oostenbrink et al.'s studies [18]. Similarly, the time-steps of exacerbation-based multistate models range from one week in Borg *et al.* to one month in Oostenbrink *et al.* Though Sin *et al.* assert that the average duration of exacerbation is either one, two, or four weeks, depending on severity, it is not considered a time-step per se. As stated earlier in the case of asthma, the decision

on which time-step to use should be such that the probability of occurrences of multiple incidents is minimized.

Tuberculosis

Unlike asthma and chronic obstructive pulmonary disease, tuberculosis is not a chronic disease. Once a person is infected by *m. tuberculosis*, individuals become diseased by either direct progression (the disease develops shortly after infection) or endogenous reactivation (disease develops many years after infection) or never develop active tuberculosis. A simple three-state tuberculosis model (*also called SLT model*) is presented by Blower *et al.* [20] with the following states: *susceptible* (no tuberculosis, S), *latently infected* by tuberculosis (no clinical illness and non-infectious, L), and *actively infected by tuberculosis* (infectious tuberculosis, T). A *deceased* state (D) is added to the model. Individuals shift from the state *susceptible* to either *latent* or to *actively infected by tuberculosis*. Once an individual is infected by tuberculosis, he/she remains infected for his/her entire life (and is hence less likely to be infected again for immune-related reasons). Hence, there is no transition back to the state *susceptible*. Transitions from the state *latent* to *actively infected by tuberculosis* are possible as a result of an endogenous reactivation at a later stage and vice versa, following recovery from active tuberculosis. Individuals in a state of *active tuberculosis* can die from tuberculosis-related or other causes, while individuals in other disease states die only from other causes. This is a simple "*SLT*" model of tuberculosis. It is suitable for a quick analysis, since the data needed for the *SLT* model is readily available in most countries of the world.

To study complexities in the tuberculosis disease process, the *SLT* model is further modified to become a detailed model of tuberculosis transmission. The model is then expanded with three refinements, with the state *active tuberculosis* being divided into two sub-states: *active non-infectious tuberculosis* and *active infectious tuberculosis*. Instead of allowing the (either with or without treatment) recovered individual to return to a separate *latent* state, a *recovered* state is added to differentiate between infected people who never developed active tuberculosis (i.e. remained in a *latent* state) and those who developed active tuberculosis and eventually recovered. Those who recovered can have a relapse and develop active tuberculosis or die from other related causes. Models are then run with a set of differential equations using secondary equations to study the transmission dynamics of tuberculosis.

Vynnycky and Fine [21] developed a tuberculosis model which is similar to that of Blower *et al.*'s detailed tuberculosis transmission model. It distinguishes between the intermediate state *infected*, which people enter after being infected by tuberculosis. Individuals shift from the state *infected* either by developing primary tuberculosis within five years of getting infected, or by moving to the state *latent* when they do not develop active tuberculosis. The difference of Blower *et al.*'s

detailed model is that infected individuals move to a *latent* state if they do not develop primary tuberculosis shortly after infection. In Vynncky and Fine, those who recovered from a primary infection episode moved to the *latent* state. In Vynncky and Fine's model, no distinction is made between infectious and non-infectious tuberculosis. Instead, exogenous and endogenous tuberculosis are differentiated from the *latent state* and a state of *re-infection* is included, which follows the same course before reaching the *latent* state within a timeframe of five years, complicating data collection. The state *re-infected* is not included in Blower *et al.'s* model, since their model addresses an immunocompetent population, implying that individuals who were infected with tuberculosis are less likely to be infected again. Hence, these individuals do not have an exogenous disease state. Lastly, in Vynncky and Fine's model, those who are infected but not diseased, as well as those who recover after being diseased, will eventually arrive at the *latent* state unlike Blower *et al.'s* state *recovered*. The time-step in Vynncky and Fine's model is one year.

Dye *et al.* [22] aimed to assess the potential effect of DOTS in those developing countries in which the disease is most prevalent. They developed an age-structured tuberculosis model based on the two models discussed above. Their model includes two active tuberculosis states like Blower *et al.'s* model, namely *infectious tuberculosis* and *non-infectious tuberculosis*, but only one *latent* state for those who never develop tuberculosis and for those who recover from active tuberculosis. Individuals who are in a *non-infectious tuberculosis* state can move to *infectious tuberculosis* with smear conversion. In addition, individuals in *active tuberculosis* states and poor treatment can move to the state *treatment failure* (classified in cohort analysis as *failed, defaulted or transferred out*). Similarly, individuals can be self-cured and move from an *active tuberculosis* state to the *natural cure* state. The states *treatment failure* and *natural cure* each have two separate sub-states for infectious and non-infectious tuberculosis. Among the *susceptible*, those who are immunized move to an *immunized* state but can potentially revert back to the state *susceptible* after the effect of immunization wears off. The time-step is one year and the simulation runs with different equations from 1998 until 2020.

Based on these studies it is clear that tuberculosis models involve a range of states, from a simple three-state SLT model (Blower *et al.*) to a more complex model including nine states (Dye *et al.*). More states can be added or removed, depending on the research question and availability or feasibility of data. For example, states for those who are sensitive to a single or to multiple tuberculosis drug(s) can be added, and could, for example, be referred to as *drug-sensitive state* or *multi-drug sensitive state* [26]. More states could also be included by adding an HIV/AIDS dimension.

In the PAL studies, patients were interviewed twice in a time-step of two weeks or two months (depending on the duration of their cough). The first interview took place directly at the health center during the patients' first visit, while the second

interview was (for the most part) conducted at the patient's home two months later. Patients were generally in an acute condition during the first interview. The effect of treatment and follow-ups (either at the same health facility or at higher level facilities) following the initial visit were recorded in the second interview. As our aim was to test the effectiveness of the PAL guidelines' implementation at the local rural level, we were particularly interested in how acute cases are treated. Hence, a longer time-step, commonly of one year, is too long for most clinical studies, such as ours, where the effectiveness has to be visible within a short period of time, e.g. within two weeks time.

The states that apply for tuberculosis generally include three different states in addition to the state *deceased*, depending on the availability of data and the purpose of the research. Additional sub-states can be added to the three main states in the general model (Susceptible-Latent-Active). The time-step is usually one year. Unlike asthma and chronic obstructive pulmonary disease, where the aim of medical treatment is typically to alleviate the disability caused by recurrent exacerbations, the aim in cases of tuberculosis is to treat the actual disease and ensure that it remains latent. In other words, tuberculosis is similar to the cases of asthma and chronic obstructive pulmonary disease with the difference being the number of incidents. These are less frequent in active tuberculosis cases than the exacerbations, but the duration of active tuberculosis lasts longer than the states of exacerbation, though the acute phase is normally not very long.

5.3.2 Estimation of Transition Rates and Their Standard Error

In this section, we review the assumptions with regard to transitions between different states and how the transition rates and probabilities are related in the modeling process. We are interested in the data sources being used and how measurements are taken, whether transition parameters are based on incidents measured during a given period (incidents of exacerbation, the onset of symptoms, etc) or status measured at a given point in time (lung function, sick or healthy, etc). To estimate transition rates, the timing of the incident needs to be determined. If the timing of the incidents is unknown, what assumptions can be made? Does the length of time spent in a given state actually matter? We examined how transition rates and probabilities are related and calculated. Not all models reviewed here are referred to as multistate models by the authors, e.g., the compartmental model in the case of tuberculosis. Different methods are used for the transitions in the different multistate models including the compartmental models including matrix equations, differential equations, and difference equations. In this review, we focus on the multistate model aspects of the articles and on specific issues related to lung diseases.

Next, we review the model's uncertainties. Uncertainties related to the estimates are often addressed in studies, and we have therefore included a synopsis of

the related uncertainties in this section, along with a review of the transition parameters. Uncertainties with reference to the sampling method in the multistate model are considered and, consequently, point estimates, along with the standard error, for example of initial distribution and the transition rates/probabilities, should be included in the description of these parameters, and when providing details on the results. With regard to forecasting, uncertainty is also associated with assumptions about the future. These uncertainties could be random in nature due to sampling errors, or they could be systematic owing to different model assumptions such as the choice of time-step and the timing of incidents, the use of different methods for calculating the flow in the model, and assumptions about the future for forecasting purposes. Next, we review different methods used for the reporting of uncertainties.

Asthma

State-space in asthma models are either based on the severity of asthma measured by lung function or on the control of asthma measured by the incidents of exacerbation. The change in the severity dimension is a slow (continuous) process and it takes years for patients to move into states of higher severity. Asthma severity can be measured at any point in time, and therefore, is best measured as a status variable at the beginning and at the end of a time-step. On the contrary, the control of asthma is measured by different (discrete) incidents experienced by the patients. For example, an exacerbation incident requiring hospitalization leads to a transition from a state that is better controlled to one in which control worsens. In many instances, the severity of exacerbation is determined by the type of health care required to effectively treat the exacerbation. The exacerbation's timing and incident can easily be measured, and the change in status within a given time-step can largely be determined through the use of self-reporting, either at the time of the interview or through a patient's diary. Depending on the research question, the measurement of various covariates, time-dependent and independent are taken as well. These data can then be used in a regression analysis, as well as to explain uncertainties. Below we review some of the important covariates and assumptions related to the Markov processes in the multistate models.

Combescure *et al.* [11] and Saint Pierre *et al.* [12] studied the long-term evolution of patients with asthma in asthma controlled states. The authors assessed the transition between the asthma controlled states in a time-step of four weeks. The actual durations of exposure were used as denominator to obtain the transition rates (referred to as 'forces' by the authors). Six transition rates – expressed as transitions per day – are estimated for the various transition possibilities between the three states in terms of their maximum likelihood of occurring. The transition forces are presented for the entire population, as well as for two severity-based

strata individually. The transition forces are assumed to follow a continuous homogeneous Markov model, which implies that the transition rates are independent of time (period, age or since last transition). In addition, Saint Pierre *et al.* incorporated in their study the effect of covariates on the transition forces. The covariates included are Body Mass Index (BMI), severity index, and number of exacerbations. A time-dependent covariate (duration of a state) is also incorporated, assuming a piecewise but ongoing intensification. The probabilities of transitions are derived from the transition rates and are presented as results in the evolution of transition probabilities over time. The main outputs of the model are a series of graphs exhibiting the evolution of point estimates of the transition probabilities.

In both articles, authors reported on the standard errors of the transition forces estimates by inverting the empirical information matrix (for further details, the reader is referred to the relevant literature). No uncertainties are reported for the transition probabilities, the output of the model. Combescure et al. present a standard deviation of the mean time spent in each state as an outcome of the model, using the Delta method which is a method for deriving an approximate probability distribution, when knowledge of the estimator's variance is limited. No details are provided, however. Saint-Pierre *et al.* describe the regression coefficients of the covariates on the transition forces, along with the standard errors. In addition, Saint-Pierre *et al.* carried out a sensitivity analysis to test the assumption of time homogeneity in terms of a state's duration applying log-likelihood tests between a homogeneous model and a piecewise-constant model.

Paltiel *et al.* [13] developed an asthma policy model and, for demonstration purposes, mostly used data from literature sources. Exacerbation rates are estimated by establishing a relationship between the rate and the FEV_1-predicted, using the results from various studies. These rates are then adjusted to the distinct (origin) states which differ by prior hospitalization status, again using a secondary source. The number of patients requiring different types of urgent care is estimated using a secondary database, and the transition rates to the various (destination) states which differ by urgent care types are determined. These dimensions are calculated for different age groups and severity states. The effect of different interventions on transition rates were also derived from the literature and adjusted. Likewise, data on mortality rates were collected from the literature. All transition rates were then transformed to the monthly probability transition matrix (without, however, mentioning which transformation method was used). The modeling time is 10 years and all rates are assumed to be homogenous during this time period and within each state (no more covariates).

Price and Briggs [14] noted the incidents of exacerbation within one week at the end of each week using data from a total period of 12 weeks. The exacerbation incident can occur at any time during any week. In the event of an exacerbation incident during a given week, an asthma control status based on the subsequent

intervention required (*Primary care managed exacerbation* or *Hospital managed exacerbation*) is defined for each patient. When no exacerbation incident occurs, an asthma control status (*Successfully controlled* or *Sub-optimal controlled*) is defined for the patient based on his/her experiences, which are recorded in the daily diary card. Next, based on the patients' asthma control status, transition probabilities are estimated between any two states. According to the authors, when no transition is recorded between any two states, a zero transition rate between any two states is theoretically not possible and, hence, Bayesian methods are applied to arrive at non-zero transition probabilities. A set of transition probabilities is then calculated based on the change in states during each of the 12 weeks. This indicates that the model is a time-homogenous Markov model. The authors did not consider any other covariates in their model – the Markov model is applied repeatedly using the set of weekly transition probabilities for the entire 12 week period. Each week is assigned a cost, depending on the control status of the given week.

Uncertainty in the transition probabilities was dealt with by assuming that the transition probabilities, considered input to the model, follow the Dirichlet distribution, which is a multinomial equivalent of the beta distribution. The authors employed *Probabilistic Sensitivity Analysis* to analyze the uncertainty in the outputs of the model. A second-order Monte Carlo simulation technique was used, in which for each simulation the transition probabilities and other variables (e.g. unit costs of primary care consultations, costs of an in-patient day and length of hospital stay, etc.) are randomly drawn from both the Dirichlet and the normal distribution, respectively. The distribution for the former is obtained empirically, and from published sources for the latter. The simulation is repeated 1000 times and the outputs (e.g. number of successfully controlled weeks, costs, cost-effectiveness ratios) are recorded and later used to report the distribution in a scatter diagram, and in 95% uncertainty intervals. Hence, the study can be considered complete in terms of addressing the issues of uncertainty at the input, as well as at the output level.

Among the articles reviewed, Paltiel *et al.* [13] include the severity dimension in their multistate model in addition to the control dimension. Events of exacerbation are measured and transition rates and probabilities estimated. Exacerbation incidents are, therefore, an important measure of effectiveness in the analysis of the asthma disease process. In the PAL study, Juniper's Asthma Control Questionnaire [27] was used for each interview with patients who had breathing difficulties to collect information on the incidents of exacerbation in the last week and, hence, can be used to define control states as was done in the reviewed papers. Finally, uncertainties regarding the transition rates and probabilities were presented.

Chronic obstructive pulmonary disease

Similar to asthma, the state-space in chronic obstructive pulmonary disease models are also centered on severity and exacerbations. The change in the severity dimension is – like for asthma – a slow (continuous) process and it takes years for patients to move into states of higher severity. Similarly, acute episodes are caused by an exacerbation incident and a patient's health status may change thereafter.

In Sin *et al.'s* multistate model [16], the initial compilation of patients according to their states of severity defined by their levels of lung function (FEV_1) were taken from a large health and nutrition survey. The mean rates of transition from a severity state to a state of higher severity (within three months) were estimated by a mean decline in lung function based on data from another large lung health study. The probability of transition was calculated based on these rates. Individual data on FEV_1 at the baseline could have been used as well and the transitions generated by applying the mean decline in lung function. In any case, the lung function for all patients was estimated as declining with a constant rate of 47 mL per year, in other words, the transition rate is constant, irrespective of any other variable. Hence, the model becomes a deterministic model. Furthermore, the assumption that the mean rate of decline is constant for patients within and between different severity states seems unconvincing, considering that the authors do not cite any other studies.

Incidents of exacerbation (mild, moderate or severe) can occur in every severity state (stage). The rates of different exacerbation incidents in various severity states were derived from the literature and are expressed in percentages over a 30-day period. Patients in severe states suffered more in terms of the number of exacerbation incidents, as well as in terms of the number of severe exacerbations. The authors assumed the duration of each exacerbation type to last one, two and four weeks for mild, moderate, and severe exacerbation, respectively. This is equivalent to having four exacerbation-related states (with fixed durations), i.e. an individual is, at any given point of time, either in a state of no exacerbation or in one of the three exacerbation states varying in degree. As soon as an exacerbation occurs, a time period depending on the type of exacerbation is weighted by a certain degree of utility, irrespective of when the exacerbation occurred. For example, a person who experiences an exacerbation at the end of a given time period will not spend his/her days with a reduced quality of life until the next period; however, in the model, the days in which the patient experiences a reduced quality of life arise in the period in which the incident actually occurred. By modifying the model to define exacerbation states in line with those used in other studies, and by reducing the cycle lengths for transitions between the exacerbation states, would greatly enhance this model.

The effect of an intervention is introduced in the model as a reduction of the exacerbation rate by 30%, with a 95% confidence limit derived from published

literature. All transition and incident rates are presented with a 95% confidence interval and with reference to published literature. However, the distributions these rates follow are not mentioned, and the uncertainty on the initial distribution is not mentioned. A Monte Carlo simulation with 100,000 sample sets is described in which the rates from its distribution were randomly selected. The uncertainty regarding the duration of an exacerbation state is not included, since fixed durations are used (one, two, and four weeks for mild, moderate, and severe exacerbations).

Unlike Sin *et al.*, Borg *et al.* [17] based the calculation of their data on a single follow-up study and defined the exacerbation states within each severity state. Data from a 10-year follow-up study was used to calculate the 10-year transition probability between the severity states of chronic obstructive pulmonary disease. The multistate model has a one-year time step. In the Appendix of their publication, Borg *et al.* explain how a one-year transition probability matrix is obtained by calculating the 10^{th} root of a 10 year transition probability matrix. The authors claim that the root is unique given the matrix's large number of constraints (and numerous transitions not being possible). A similar process was used to arrive at yearly rates of all-cause mortality. This process assumed homogeneity of transition probabilities throughout the entire 10 year period, ignoring any time and age effects. The data used comprised three broad age groups. Simple linear interpolation was carried out to obtain the transition probability matrix for the different age groups. Nonetheless, the assumption is too simplistic and the authors acknowledge the question of validity of such a method.

Exacerbation transition rates were based on data from a follow-up study and estimated at the end of the week by assessing the incidents of different types of exacerbation during a given week and the mean duration of these exacerbations. The distribution of patients in different states is assumed to follow a stationary distribution, given that the severity does not change. The aspect of a stationary population distribution was then used to estimate the stationary distribution of patients in various exacerbation-related states. The mean duration of exacerbations was calculated using the available data. The rate of transition out of the various exacerbation states were then calculated as the inverse of the mean duration of exacerbations (1 / mean exposure). The model does not include a *deceased* state, which is correct when the cycle length (time-step) is small. However, in the long-term perspective in a given cohort, the severity level of patients within a severity state is increasing, and since the authors also emphasize the relationship between severity and the rate of exacerbation, the stationary distribution assumptions may not hold true.

Borg *et al.* assume that the exacerbation process could affect both the progression toward severity and the mortality rates, and hence, proposed a simple mechanism by introducing two variables, alpha and beta, which denote a value between 0 (no effect) and 1 (completely dependent). Authors report a limitation of the data on the extent of the effect and hence, the mechanism was used in the sensitivity

analysis only. The authors use bootstrapping to estimate the standard error of the transition rates by re-sampling the data on the incidents and duration of the exacerbations numerous times.

Oostenbrink *et al.* [18] estimated the transition probabilities between severity states using primary data. The severity states are assessed at the beginning and at the end of each period. The transitions are assumed to occur mid-way in each cycle. Since the durations between the follow-ups are not identical in the different databases, the empirical transition probability matrices are converted for a period of eight days (first cycle) and one month (12 subsequent cycles) using a Taylor series expansion, which is explained in the Appendix of the paper. The transition probability matrix for the first cycle is based on data from the patient's first visit and the first follow-up. The transition probability matrix for subsequent cycles is based on data from the first and last follow-up visits. The assumption of a homogeneous Markov process was made for the subsequent periods.

Two sets of probabilities of exacerbation by severity state were calculated as the ratio of the number of exacerbations within a month and the number of patients (in a given severity state) at the beginning of the month. The number of exacerbations during each cycle was used in the model analysis and it was assumed that only one exacerbation per patient could occur in each cycle. Unlike in Borg *et al.*, the durations in exacerbation were not used. Instead, when an exacerbation occurred within a given cycle, the entire cycle was considered to be in a state of exacerbation, irrespective of the severity of the exacerbation, since the utility value was assumed to reduce by 15% for non-severe and by 50% for severe exacerbations, which were derived from the literature. However, the duration of exacerbations is usually shorter in non-severe cases and it may be possible that the 15% reduction in utility value only applies for a short period rather than for the entire month. In conclusion, the model can be seen as a two-dimensional multistate model (as in Borg et. al.) using the same time-step for both dimensions.

Oostenbrink *et al.* present standard errors together with the point estimates for the transition probabilities and the probabilities of exacerbation. To calculate standard errors of exacerbation probabilities, a simple simulation with 5000 iterations was performed. It is not clear how the simulation was carried out; most probably, a bootstrap method was used. To account for uncertainty in the results, a Monte Carlo simulation was conducted assuming transition probabilities following the Dirichlet distribution, similar to Price and Briggs in their article on asthma.

We found that all articles included the transitions between states based on severity. However, not all models reviewed explicitly defined states based on exacerbation. The rates and probabilities of exacerbation differ for varying severity levels. The purpose of the interventions is to reduce the rates of exacerbation. Hence, the modification of the models to include states that are based on exacerbation as an individual dimension would be more suitable for the modeling of the chronic

episodic nature of chronic obstructive pulmonary disease. Uncertainties in the inputs – transition rates – were included in the analysis of some of the authors, who presumed that the transition rates followed a Dirichlet distribution, as was the case in the asthma models. Monte Carlo simulations were used to estimate uncertainty in the results. In conclusion, a multistate model for asthma and chronic obstructive pulmonary disease can be identical with the states defined for both the chronic and acute dimension.

Tuberculosis

Tuberculosis is not a chronic disease and it is possible to completely cure the disease. However, once a person is infected with tuberculosis he/she can remain infected for his/her entire life with or without an incidence of the disease. The most important incidents in the tuberculosis disease process are infection with the disease, the incidence of disease, being cured, relapsing, etc. In terms of tuberculosis management, disease detection and the completion of a therapy are the most crucial elements. Although the tuberculosis models included in this review are not explicitly referred to as multistate models, they are all in fact multistate models, with state-space and transition rates being clearly defined. Unlike in standard multistate models, transition probabilities and matrix algebra are not used, instead, a set of differential equations and difference equations are applied.

Blower *et al.* [20] describe the transition rates between the different states using various tuberculosis-related rates, proportions, coefficients, and probabilities from the literature. The rate of change in the number of people in the given states is established through ordinary differential equations. These rates of change are then applied over time to obtain various tuberculosis-related outcomes. A set of model parameters, along with the assumed distribution (triangular or uniform), are used as input to the model.

The uncertainties in the results are dealt with by distributing 1000 points for each outcome. Each point is a result of a set of values of parameters randomly drawn without replacement from the parameters' distributions, using a Latin Hypercube (LHS) sampling method. In this method, each probability density function (pdf) is divided into equi-probable parts by n (1000 in this case) points. The LHS method then takes a random sample without replacement from each pdf to create a set of values of parameters. The sampling is repeated 1000 times, resulting in 1000 sets of parameter values. the authors acknowledge that the transition rates are time-homogenous and there is no mention of any covariates. Once a patient is (newly) infected by tuberculosis, the waiting period before he/she moves to the *latent* state is not included in the model. The model seems to be carried out in a yearly time-step. In that case, the waiting period for moving to the *latent* state would be one year.

Vynncky and Fine's model [21] comprises many transition rates. Infection and re-infection rates change over time (derived from the literature). Following infection (or re-infection), the rate of developing tuberculosis is high in the first year but diminishes in later years, and is age-dependent (also based on the literature). The rate of recovery depends on age, time, and the time since the onset of disease. The fatality rates are also drawn from various studies. Hence, in terms of a multistate Markov model, the model is non-homogeneous with reference to time. The time it takes to transition from an infected state to a latent one is exactly five years. State-specific mortality rates were also derived from various studies. A system of partial differential equations is reduced to one of ordinary differential equations, which are then solved using time-steps of one year and by applying the Euler method. Using the model and the tuberculosis notification database from national surveys in England and Wales, the age- and period-specific rates of developing active tuberculosis were estimated through different mechanisms. These mechanisms included primary tuberculosis (shortly after the initial infection – during the first five years of being infected), by endogenous reactivation (after five years), and by exogenous re-infection (also after five years).

The uncertainties in the inputs were estimated by calculating the standard errors of the estimates of these transition rates in the assumption that all forms of tuberculosis notifications follow a Poisson distribution. Fifty sets of tuberculosis notification rates were drawn, resulting in 50 notification data sets. Rates of developing tuberculosis were then matched to each dataset, and a 95% range of the resulting distribution was reported to represent the uncertainties around the point estimates calculated from the original dataset. Other inputs in the model were point estimates.

Dye *et al.* [22] prepared a set of difference equations for the flow (one year time-step) in the age-structured tuberculosis model. They estimated key indicators and variables based on the literature. As in Vynncky and Fine, the estimated rates of active tuberculosis was obtained through different mechanisms by matching the three states (*Susceptible-Latent-Tuberculosis*) to the 'compartmental' model on age- and period-specific data on tuberculosis incidents in The Netherlands. The incidence rates were assumed to be age-specific (defining two age groups, children $<=$15 and adults). These rates and other estimates (some region-specific) were used in the model to make a projection for six WHO regions, beginning in 1910 for Europe and 1950 for the remaining regions (depending on when the incidents of tuberculosis began to decline). The annual incidence rates and the proportion of tuberculosis cases or deaths prevented by the Directly Observed Treatment Short course (DOTS, a WHO recommended tuberculosis control strategy) were used as measures for the effectiveness of tuberculosis control. The rates and proportions are allowed to change over time based on historical facts, the model used, and future assumptions.

The ranges for all inputs and the standard deviations for the estimated rates of active tuberculosis were reported. Uncertainty in the results was dealt with by using Latin Hypercube Sampling and drawing 100 sets of parameters. All parameters were assumed to follow a rectangular distribution between their ranges. The result of the simulation was presented as a 90% uncertainty interval. The authors acknowledged that the uncertainty analysis was far from being complete, and hence reported only on comparative indicators in relative terms.

All tuberculosis models reviewed focus on the macro level and apply a time-step of one year. The transition rates between the different states are mostly drawn from country-level data. In terms of micro analysis to analyze the effects at the individual level, these models are not really useful in the context of PAL, since the models do not incorporate the acute episodes when patients suffer from active tuberculosis and seek health care. PAL aims to increase the case-detection rate of tuberculosis by filtering the suspected tuberculosis cases from the pool of patients with respiratory symptoms attributable to other diseases. States defined by incidents of case-detection, start of treatment, or completion of treatment, can be useful to determine the effectiveness of interventions. Regarding uncertainties, similar methods were used in the case of asthma and chronic obstructive pulmonary disease. Instead of a Monte Carlo simulation, the Latin Hypercube sampling method seems to be quite popular.

5.4 Conclusion and Inference for PAL

The review's main message is that the existing multistate lung health models can help us identify the states in the disease process with regard to disease management. In the case of asthma and chronic obstructive pulmonary disease, states can be defined by two dimensions, namely acute and chronic. Patients suffering from both diseases in the chronic dimension only experience a very gradual change in the course of the disease, with chronic states mainly being distinguished by the level of the patient's lung function. The acute dimension, in which a patient's health status changes more rapidly to poorer health states, is more critical but with proper care a transition to a better health status can be achieved in a short period of time. Without medical intervention, patients may seriously suffer and, in the worst case, die. We found that acute states of asthma or chronic obstructive pulmonary disease mostly depend on the level of medical intervention required to treat the exacerbations, in other words, are resource-driven. Many interventions and strategies are developed to improve patients' health in the acute dimension, with PAL being one such example.

Tuberculosis, on the other hand, is not a chronic disease. However, it is characterized by an acute phase in which patients' health states deteriorate considerably

once the person develops active tuberculosis. With proper treatment, the acute phase can be overcome in a short period of time. The patient has to take medication for a longer period of time, even though the patient feels as though he/she is in perfect health. However, if the patient does not complete the full course of treatment, the disease may potentially reappear and then in an even more serious form. Unfortunately, we did not find any article that captured this micro aspect of the disease process, as most of the tuberculosis models are studied at the macro level. Therefore, the knowledge derived from the review of tuberculosis models is useful for modeling tuberculosis at the macro level, but not suitable for studying the effect of interventions such as PAL.

The second message is that multistate models are gradually being applied to study the disease process of asthma, chronic obstructive pulmonary disease, and tuberculosis. Various methods to estimate transition rates are either developed or borrowed from other fields and are used quite effectively. Uncertainties in the estimation of transition rates are reported in many cases, making it easier to establish statistical inferences regarding the transition rates, as well as the multistate model's output. The review has revealed that the multistate model is, and can be, an important tool for studying the lung disease process.

This review was conducted to critically examine how multistate models are being used in lung health. We now have some insight on how multistate models can be applied to study individual disease processes, namely asthma, chronic obstructive pulmonary disease, and tuberculosis. However, we did not find any articles involving a multidisease model, i.e. modeling more than one disease simultaneously. Secondly, the data used in most articles was collected from developed countries, where human capital and medical resources are adequate. The different states are defined on measurements that are reliable, valid, and most importantly, disease-specific. In similar settings and in a single disease study, the knowledge gained from this review can be highly useful. However, the use of this knowledge is not so straightforward for PAL studies.

Based on the knowledge we acquired from this review, we developed two multistate models to study the cost-effectiveness of PAL in Nepal. In the following section, we discuss the inference we made for PAL. First, the PAL guidelines represent an integrated strategy for four lung diseases including pneumonia, asthma, chronic obstructive pulmonary disease, and tuberculosis. Secondly, PAL was implemented in rural health care settings in Nepal and the PAL guidelines were adapted in such a way that health care providers with lower levels of training could understand and implement them when treating patients. The health care providers are often the only persons working at the health facilities and have a minimal level of resources available to them in terms of infrastructure and other medical health care resources. Both of these 'constraints' demand a model that is generic and non-disease specific such that a single health dimension can detect the changes in the health status of

the ‘lung’ patients, which can be achieved when implementing the PAL guidelines, while the treatment of patients with respiratory symptoms does not always result in a diagnosis of a disease. At the same time, the generic measurement should be such that it can be easily implemented at low cost, and that the patients who are usually poor and less educated, can understand the measurement. Based on this review and the above discussion, we will briefly introduce how we went about to solve the above-mentioned problem. In the PAL system, patients are managed (treatment and/or referral to higher level health facilities) on the basis of their symptoms, unless the diagnosis is known in advance. The common symptoms of different respiratory diseases make it difficult to make a diagnosis when health care providers are not adequately trained and resources are limited. The PAL guidelines aim to reduce erroneous diagnoses by assessing the patient’s condition with algorithms that follow a syndromic approach to disease. Health care providers are guided through the assessment of a patient step-by-step to determine a specific disease classification resulting in either explicit disease management or, if necessary, in the treatment of the disease [8]. To test the effectiveness of such guidelines, the different states of the diseases have to be based on the symptoms or a general health status. States based on a generic measure of respiratory condition would be the ideal dimension. A simple two-state model (acute and chronic-stable states) can be used to model the patients in PAL. More states can be included in the acute dimension based on a generic measurement of (respiratory) health. Patients who suffer from chronic obstructive pulmonary disease or asthma (known or unknown) would suit this model, since exacerbation would lead to the acute state (or, one of the acute states), forcing patients to visit a health center. If followed-up, patients could recover and return to a better health state, or completely recover in the chronic state. The same could apply to tuberculosis – patients only visit the health center when the disease has reached an acute state. At the follow-up visit, a patient’s condition would either deteriorate to a worsening of the acute state (even death) or with case detection and the start of a therapy (DOTS) return to an improved state of health.

In the following two chapters, additional details are presented on the actual analysis of the effectiveness of implementing the PAL guidelines using a multistate model.

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6

Defining Disease States in Health Modeling Based on Quality of Life: An Alternative for Modeling Disease States Based on Prognostic Variables

The categorization of health states leads to the definition of distinct health states, which can be used in the study of disease evolution. The new classifications of health states are typically carried out on the basis of categorizing prognostic variables of diseases. Remarkably, despite its frequent use as an outcome variable, hardly any classification is performed on the basis of variables measuring quality of life. In this study, we propose several methods for the categorization of health states on the basis of Health-Related Quality Of Life (HRQOL).

6.1 Introduction

Researchers have been working on methods to classify heath states for modeling purposes for quite some time [1, 2]. In his paper "Note on grouping", Cox in 1957 proposed classifying individuals' health as "poor", "average", or "good", based on a variable X representing a property linked to the individual's health [1]. The categorization of health states leads to the definition of distinct health states, which can be used in the study of disease evolution. A common approach to the modeling of disease processes is the multistate approach, which includes the Markov process [3, 4]. The issue of categorizing health states continuously re-emerges in research, as new measures of health state are being used in epidemiological and health economic models. The new classifications of health states are typically performed on the basis of categorizing prognostic variables of diseases by first determining the variables that predict the outcomes of patients with distinct characteristics and then by categorizing the prognostic variable [5]. Prognostic variables could be an absence or presence (and level) of signs and symptoms, for example a cough, fever, etc. or diagnostic tests like level of blood sugar, blood pressure, etc.. For example, in patients with chronic obstructive pulmonary disease or asthma, the lung function measured by spirometry as FEV_1 (forced expiratory volume in one second) is used to categorize the severity of the disease.

Health-Related Quality Of Life (HRQOL) is a recommended outcome variable in health economics and epidemiology to measure individuals' health status [6, 7]. Especially when we are not able to measure the prognostic variables, HRQOL can be helpful in measuring a patient's state of health, though it might not necessarily identify the disease as such, for which a more disease-specific HRQOL would be required, but it certainly reveals the overall state of a person's health at the given point in time. The HRQOL measures are used in economic evaluations to measure the utility of patients (in terms of time trade-off, explained later), to estimate quality adjusted life years (QALYs) gained or lost, and the measurement of effect in the cost-effectiveness analysis used to calculate the cost per QALYs gained/lost. The general HRQOL measures can be used as a single instrument to measure the general population's health in multi-disease studies. Despite HRQOL's widespread use, the categorization of individuals' health based on HRQOL has not yet been taken up, except in a study on obesity [8]. In most cases, HRQOL functions as a continuous variable and the mean value or the changes in mean values are assessed. However, a good HRQOL instrument should be interpretable (for further details, see the introduction in Chapter 1) [9], in order to compare HRQOL impairment between patients (e.g., to determine whether an individual has a normal, mild, moderate, or severe impairment of HRQOL) [9]. Defining meaningful categories of HRQOL can make this possible. When measuring the change in HRQOL impairment of individual patients over time, the interpretability of the HRQOL measure reveals whether, for example, change is trivial, small but important, important, or very important, etc. [9]. Hence, two issues are essential, namely the definition of HRQOL states for discriminative usage and the definition of the scope of the changes for evaluative purposes. Defining such categories facilitates the use of multistate models – in which the state variables are generally discrete variables – to study the evolution of health in different HRQOL states. Indeed, when the determination of HRQOL is an outcome of a modeling exercise, its value is attributed to the categorized prognostic variables of a disease, meaning HRQOL is treated as an outcome or an indication of being in a particular disease state with a given value, for example, level of blood pressure, temperature, etc. specifying the state [10–13]. In that respect it could be claimed that HRQOL is always modeled indirectly. If HRQOL is really considered an important outcome of health, direct modeling of HRQOL is warranted and a categorization of health states on the basis of HRQOL should be explored.

The main objective of this chapter is to explore and develop methods for defining discrete health states based on HRQOL, which can then be used in multistate models, for example, to study the evolution of general or specific populations' HRQOL states. We propose several methods of categorization of health states on the basis of HRQOL and apply these methods on lung diseases, namely pneumonia, tuberculosis (TB), chronic obstructive pulmonary disease (COPD), and asthma in the context of the Practical Approach to Lung health (PAL) study in Nepal.

6.2 Methods

The EuroQol EQ-5D questionnaire [14] is a commonly used tool to measure health-related quality of life. It contains five dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with three levels of response (1 for "no problem"; 2 for "some problem"; 3 for "severe problem"), which define 243 (3^5) health states. A unique feature of the EQ-5D is that former validation research allows attributing a measure of severity to the 243 health states [15]. This measure of severity is often referred to as "utility". The utility score that corresponds to a condition a patient is in can be understood as the amount of perfect quality time a patient is willing to trade for one unit of his/her (lower) quality time. For example, if a person suffering from asthma is willing to trade 10 years of his/her life in his/her current state with 8 years of a perfectly healthy life, the utility of the patient's current state is said to be 0.8. In EQ-5D, the utility score has a value of 1.00 when morbidity is absent (person is healthy) (11111) and 0.00 when the person is dead. Very severe health states, like 33333, get negative values (–0.59). For details see Chapter 3, section 2.

The main issue here is that utility scores are available (a continuous variable) and we want to divide them into meaningful categories so the utility scores can be used as a discriminative measure, as well as an evaluative measure [9]. The question then is how the state of a person with a utility score of, say, 0.65 should be referred to – for example, in a good, bad, or worst health state – and how to refer to a change in the utility score from 0.65 to 0.85 – for example a trivial, small but important, or very important change in health status [9].

6.2.1 Categorization on the Basis of the Description of the 243 EQ-5D Health States

The unique feature of the uni-dimensional severity score of the multidimensional EQ-5D becomes apparent when we try to classify health states on the basis of the five-dimensional descriptive system. To begin, we could divide the 243-EQ-5D into two groups of health states: *full-health* and *poor-health*. A *full-health* state can be defined as a state in which there is "no problem" in all dimensions i.e., a score of 11111, and the *poor-health* state as one with at least "some problems" in one or more of the dimensions – in total, 242 states. This procedure can be extended to more than two states and the change in an individual's health over time can be studied by using multistate models with the state definitions described above. However, even with such a simple classification rule we are faced with the problem that we do not know what the distinctive contribution of different dimensions and levels on the overall HRQOL is. Indeed, 31111 must logically represent a more severe health state than 21111, but without additional assumptions or information,

there is no way of telling whether a score of 31111 is worse than, say, 12111. Fortunately, we have additional information on health state severity in the form of the utilities of the EQ-5D health states as valued in former research [15].

6.2.2 Categorization on the Basis of the Utility of the EQ-5D Health States

If we want to categorize health states on the basis of their utility score, we have to define cut-points. Before doing so, we should first determine the optimal number of categories. This will depend on the characteristics of the epidemiological models involved. In asthma [16] and chronic obstructive pulmonary disease [17], it is most common to model the disease using three or four categories of health. Therefore, we explored the effect of having three or four states as final outcomes. Secondly, the cut-points have to be defined. This is a research problem with only a metric solution. To facilitate the interpretation of the modeling results, the clinical relevance of the cut-points should be considered as well. We tried to include both considerations by taking the following steps:

Defining states by visual exploration of utility distribution

First, we began with an exploratory analysis by visualizing the distribution of the utility score. *Figure 6.1* illustrates the distribution of EQ-5D utility scores among 2164 patients with respiratory symptoms who visited health facilities in the rural Nepalese district of Nawalparasi (a brief description of the data is provided at the end of the methods section). The bar with utility score 1 (full health) is distinct. The distribution reveals a clustering of patients in three states: *full-health* (utility score of 1), *moderate-health* (utility score of 0.5 to 0.9), and *low-health* (utility score of less than 0.5), with *low-health* corresponding to the poorest health state. The three states are distinct in *Figure 6.1*; however, defining four states is not straightforward or even possible by just looking at the figure. This visual definition of states serves as a starting point in the process of defining utility-based HRQOL states.

Defining states using the concept of minimal important difference

The next step is to arrive at a metric definition of cut-points. First, we define a Minimal Important Difference (MID) in the EQ-5D, which serves as the minimum change in the EQ-5D utility score over time and is perceived by individuals as being important. There is no universally accepted MID for the EQ-5D utility score, although a change of 0.05 is considered reasonable [18]. However, in this analysis we define the MID as a difference of 0.10 in the utility score, in view of the fact that the decline in health from full-health (EQ-5D state “11111” with a utility

score of 1) as a result of an altered state of health in the EQ-5D's third dimension (pain/discomfort), leads to a state of health (EQ-5D state "11211") that has a smaller value (smaller than 1) and a utility score of 0.882, which is a decline of a little over 0.10.

For cross-sectional data on the EQ-5D, we can illustrate a metric method of categorization using Dalenius and Hodges' method (1959) [2]. We used this method for the sake of illustrating an existing method and to compare the result with those from other definitions of states in this chapter.

Dalenius and Hodges assert that a frequency table in ascending or descending order of the outcome variable's variable must first be prepared (example utility in our case). The square roots of the frequency are then calculated and a cumulative of the square root of the frequency determined. For a given number of states, the next step is to choose cut-points to create equal intervals on the cumulative scale established in advance. In our case, the outcome variable is the patients' utility score. We applied this rule for all 2164 utility scores and arrived at the following results: (i) three strata: full health (score 1), moderate health (score 0.5 to 0.89), and low health (score lower than 0.5); (ii) four strata: full health (score 1), mild health (score 0.6 to 0.89), moderate health (score 0.2 to 0.59), and low health (score lower than 0.2). This is a quick approximation of categories of a static variable in cross-sectional data. However, if longitudinal data is available for the variable to be categorized, changes in the score over time might be taken into consideration to determine the cut-points. This is important because our ultimate objective is to use the utility categories to define a multistate model, in which individuals' transitions between the different states will be modeled.

Defining states of health using Cox's method

According to Cox, the best system of grouping is the one that retains as much information as possible [1]. In our context of modeling the progress of a disease, we are interested in capturing the occurrence of incidents that trigger a change in the states of health or a *transition*, and the non-occurrence of incidents that do not cause any change in the states of health or to *non-transition* within a set of health states over a period of time, using a multistate model. Using a multistate model for a given state-structure defined by a set of cut-points, a loss of information over a period of time develops when actual incidents trigger transition (defined by certain criteria, for instance, the minimum change in the EQ-5D utilities) but are not recognized as having initiated a transition. Additionally, a loss of information may develop when the non-occurrence of incidents that cause *non-transitions* are recorded as being transitions, for example, if a cut-point is 0.60 and a patient has a value of 0.59 and 0.61 at two points in time, the definition of cut-point regards this change as a transition, when in reality, a change of 0.02 might not be significant enough to be

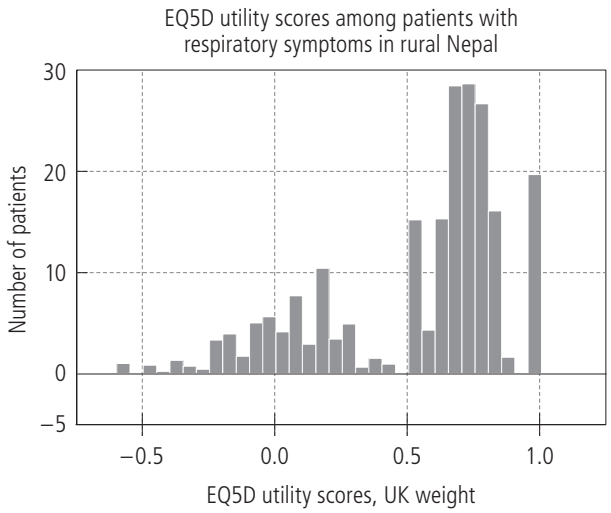

Figure 6.1. Histogram of utility scores using EQ-5D in all patients (n = 2164) with respiratory symptoms at their first visit to a health facility

considered an actual change. We refer to this as being a *false transition*. We propose a criterion for determining an optimum set of cut-points, one that maximizes the measurement of the suitability to categorize a set of cut-points, defined as the percentage of actual incidents (transition/non-transition) identified by the structure of health states among the total population at risk at the beginning of the period.

The first step in the establishment of the criterion was to define the occurrence of actual incidents that trigger *transition*, as well as the non-occurrence of incidents that cause *non-transition*. For this purpose, we defined a Minimal Important Transition (MIT) as the minimum change in utility that patients consider a significant change in their health status. Like for the MID, we chose this criterion to be at least 0.10 in terms of EQ-5D utility scores. Based on the MIT, a *true transition* was defined as a change of at least one MIT, while a *true non-transition* was defined as no change or a change of less than one MIT being evident. Next, for each set of states defined by a set of cut-points, incidents within these states were counted over a specific time period and the measurement of the suitability of categorization for a set of cut-points was calculated. We performed this exercise for three and for four states, with all possible cut-points beginning with an initial cut-point of zero.

6.2.3 An Illustration of Modeling Health States Based on HRQOL

For a given state structure, individuals can be classified under one of the HRQOL-based health states at any point in time. As time passes, individuals either move to a better or worse health state or remain in the same state of health according to a set

of probabilities for a given time interval known as a Transition Probability Matrix (TPM, also called P-matrix). The TPM, along with the initial distribution of the population into various states, provides the final distribution at the end of the given interval.

The TPM can be estimated from the empirical data by capturing the state individuals are in at the beginning and at the end of the interval. The TPM can be used to measure the effectiveness of health interventions by comparing two sets of transition probabilities, one associated with an intervention group and the other associated with a control group. At the same time, the health state probabilities, which are a result of applying these TPMs on the initial state distribution, can also be used as a measure of effectiveness. However, with regard to the PAL study, the initial distribution of patients was not the same in the intervention and in the control groups. The use of health state distribution as a measure of effectiveness is difficult to compare and, hence, we used the TPMs as a measure of effectiveness. Furthermore, the interpretation of the transition probabilities is easier and makes more sense at the individual level than the health state distribution approach. We compared the transition probabilities of two TPMs by defining a (positive) effect as implicating a higher probability of transition to a better health state or as maintaining the status quo, or displaying a lower probability of transition to a poorer health state. Specific transition probabilities between two TPMs can be compared, for example, if the probability of transition from, say, a low state of health to a moderate one within a two week time period is 0.4 in the case of PAL and 0.3 in the case of STS, then the PAL strategy can be considered as being more effective than the STS strategy.

However, the comparison would remain vague unless the difference is quite profound as the number of states increases. For each TPM, a unique distribution at stability exists referring to the long-term distribution, given the TPM remains constant. Analogous to a speedometer, this stable distribution can be used to compare the effectiveness of various TPMs, hence reducing the number of factors to include in a comparison.

Further, a single measurement of effectiveness can be derived from each TPM by weighing the degree of stability in the different states of stability against the average utility of time spent in the respective states. The average utility in each state is estimated using the empirical HRQOL data. The single measurement thus obtained is the commonly used average quality adjusted life years (QALYs) lived every year by every person, in our case, the average QALYs lived by the stable population, since the distribution at stability does not change to any further extent. The average QALYs lived by the stable population ranges from a maximum value of 1 (entire population is in full health) to a minimum value of –0.59 (entire population is in worst health).

The uncertainty in the TPM due to sampling was addressed by using a bootstrap method with a 95% confidence interval with 2.5th and 97.5th percentiles of bootstrapped results. We drew 5000 bootstrapped samples repeatedly from the original sample and used STATA 8.2 and Excel for our calculation.

6.2.4 Data Source

Data used in this study was derived from a facility-based, cluster randomized trial conducted to study the cost-effectiveness of the implementation of the Practical Approach to Lung health (PAL) guidelines as compared to the Standard Treatment Schedule (STS) in the lowland district of Nawalparasi in Nepal. 42 health facilities in the Nawalparasi district of Nepal were randomly categorized into PAL (n = 22) and STS (n = 20) groups. At least one health care provider at each of the 22 health facilities was trained during the period of June–July 2002. Data were collected from 2243 patients who visited the 42 facilities throughout the period of September 2002 to September 2003 (see *Table 6.1*). Patients aged 15 years and above with at least one of the following symptoms, fever, cough, and breathing difficulties were included and interviewed at the health facility. Patients who only had a fever or cough with a duration of less than 15 days were excluded for further follow-ups, since the chances of actually having one of the target diseases (pneumonia, TB, chronic obstructive pulmonary disease, and asthma) was rather low. Patients with a chronic cough (chronic condition) that lasted more than 15 days were interviewed two months later and the remainder (acute condition) were interviewed after two weeks. All patients who completed the EQ-5D in both interviews were included in our analysis (in total, 1167 patients).

6.3 Results

We used MIT criteria to determine best cut-points for the three and four states model using data from the PAL-study (n = 1167). For the three state model, the percentage of actual transitions (with the change in utility score being greater than the MIT) and actual non-transitions (with the change in utility score being lower than the MIT) was revealed among all patients in the range of 70.9% to 81.1%. The highest value was obtained for the cut-points 0.6 and 0.9. For four states, the range was from 75.0% to 87.7%, and the highest value was obtained for the cut-points 0.4, 0.7, and 0.9.

Table 6.1 presents the results of the comparison of the effectiveness of STS (1^{st} column) and PAL (2^{nd} column) for two groups of patients, namely those 'without a chronic cough' (1^{st} row) and those 'with a chronic cough' ($2nd$ row) (see Chapter 3 for details), by using the multistate model for determining transition probabilities. In *Table 6.1*, the origin states are displayed in the rows and the destination states

are found in the columns. In each of the blocks, the numbers in the first column (in italics) represent the distribution of states at the beginning of a period, and the numbers in the first row (in italics) indicate the distribution of states at the end of the period as a result of the transition probabilities represented by the remaining numbers in the block. The transition probabilities for patients without a chronic cough are considered for a period of two weeks, and the transition probabilities for patients with a chronic cough are considered for a period of two months (see Chapter 3 for details). To illustrate, the transition probability that a patient without a chronic cough and in a severe health state, will move to a state of full health within a two week period, is 0.23 given that patients are visiting a STS health facility. The transition probability is higher at 0.29 if the patient visits a PAL facility.

We determined that all the transitions between the two states of health are possible, except the transition from a full health to a severe health state. According to the data, only few patients with respiratory symptoms at the time of their first visit to a health facility enjoyed full health, but later regressed to poorer states (mild or moderate health states), but not to a severe health state. Among patients with a chronic cough, more patients stayed in or moved to full health states in PAL than in STS.

Each transition probability matrix in the long-term leads to a unique stable distribution shown in *Table 6.2*. Among patients without a chronic cough, STS' performance was better than PAL's, since more people stayed in healthier states, while in the case of patients with a chronic condition, the PAL performed better than the STS, since more people remained in healthier states. Since the results in *Table 6.2* represent the distribution in the long-term, it should be interpreted as a theoretical consequence, since in reality a person who is cured does not stay in the system, which is not affected by the transition probabilities. Its use should be strictly limited to being implemented as a comparative tool, since the results are independent of the initial state distribution. Another advantage of the stable distribution is the interpretation of results in terms of time spent in each state by a person at stability. For example, a patient with a chronic cough who visits an STS facility will spend 38% of his/her time in a state of full health, compared to 61% full health, if he/she had visited a PAL facility.

In order to obtain a single value associated with a transition probability matrix of health states based on EQ-5D utility scores, we first estimated the utility weights for time spent in each state, along with the mid-95% range of 5000 bootstrapped samples, for comparative purposes (*Table 6.3*). The utility weight of spending time in each of the four states was estimated by calculating the mean of the EQ-5D utility scores at the time of the first visit to a health care facility for groups of patients in each distinct state of health. The QALYs lived per year at stability associated with each TPM in *Table 6.1* were calculated by weighing the time spent in each state (*Table 6.2*), by corresponding utility weights (*Table 6.3*), and finally, by adding the

Table 6.1. Transition probabilities for patients without a chronic cough (two weeks) and with a chronic cough (two months) in PAL and STS, with states defined on the utility cut-points 0.4, 0.7, and 0.9 with the state of origin displayed in rows and the destination state in columns

	STS					PAL				
		Destination States					Destination States			
Origin States		Full	Mild	Moderate	Severe		Full	Mild	Moderate	Severe
Patients Without Chronic Cough										
	State Distribution	*46%*	*27%*	*10%*	*6%*	*State Distribution*	*46%*	*31%*	*14%*	*9%*
Full	*8%*	0.83	0.13	0.04	0.00	*6%*	0.74	0.26	0.00	0.00
Mild	*39%*	0.51	0.36	0.11	0.02	*25%*	0.58	0.30	0.10	0.02
Moderate	*24%*	0.53	0.31	0.13	0.04	*35%*	0.48	0.29	0.14	0.08
Severe	*29%*	0.23	0.39	0.18	0.20	*34%*	0.29	0.34	0.20	0.17
Patients With Chronic Cough										
	State Distribution	*36%*	*32%*	*15%*	*18%*	*State Distribution*	*42%*	*23%*	*20%*	*14%*
Full	*6%*	0.33	0.58	0.08	0.00	*13%*	0.68	0.24	0.08	0.00
Mild	*31%*	0.44	0.39	0.08	0.10	*39%*	0.60	0.22	0.10	0.08
Moderate	*28%*	0.44	0.29	0.15	0.13	*50%*	0.36	0.28	0.19	0.16
Severe	*36%*	0.24	0.23	0.21	0.32	*53%*	0.28	0.20	0.32	0.20

Table 6.2. Distribution at stability: Consequence of P-matrix

	EQ-5D utility cut-points	
States	STS	PAL
Patients Without Chronic Cough		
Full	74%	68%
Mild	19%	27%
Moderate	6%	3%
Severe	1%	1%
Patients With Chronic Cough		
Full	38%	61%
Mild	44%	24%
Moderate	10%	11%
Severe	8%	4%

Table 6.3. Average EQ-5D utility weights (95% bootstrapped range) of time spent in each state

States	Average Utility Weights
Full	1.00 (–)
Mild	0.78 (0.77–0.78)
Moderate	0.62 (0.61–0.62)
Severe	0.03 (0.02–0.05)

weighted time. For example, for patients without a chronic cough who visited STS facilities, the time spent in different states at stability is illustrated in *Table 6.2* (74% of time in full health, 19% of time in moderate health, etc.) and are weighted with the state utility scores from *Table 6.3* (1 for full health, 0.78 for moderate health, etc.), to determine the QALYs lived per year of 0.93 years ($0.74*1 + 0.19* 0.78 + 0.06*0.62 + 0.01*0.03$). The final results are presented in *Table 6.4* along with the mid-95% range of 5000 bootstrapped samples. The results are similar for both state-structures. PAL performed well among patients with a chronic condition, but not among patients with an acute condition.

Table 6.4. QALYs lived per year per person at stability and 95% bootstrapped CI

Conditions	STS	PAL
Acute	0.93 (0.88–0.98)	0.92 (0.88–0.96)
Chronic	0.78 (0.73–0.85)	0.86 (0.81–0.93)

6.4 Discussion and Conclusion

We have demonstrated the method of identifying optimum categories by determining cut-points that capture most of the *true transitions* and *true non-transitions* based on individuals' responses to an HRQOL questionnaire, by maximizing the percentage of accurate identification of incidents over time. We have shown that for a four states model, the optimum cut-points for the EQ-5D utility score in patients with lung disease are 0.4, 0.7, and 0.9. For the given state-structure, we presented an algorithm to arrive at a single measurement of effectiveness as QALYs lived per year at stability, using multistate models, and compared PAL and STS' effectiveness. We presented the results for a state-structure based on the EQ-5D utility score. By modeling health states categorized on the basis of HRQOL, which is a recommended outcome measurement tool in public health, we are the first to model the evolution of patients in an HRQOL-based multistate model and used the results to compare the effectiveness of an intervention with the help of a control.

In the methods section, we described several methods for categorizing a single variable by exploring distribution and a method based on minimizing variance within each group in line with Dalenius and Hodges (1959) [2]. For cross-sectional data, these methods can be used to categorize the results of a variable (continuous or discrete with many values) into smaller groups for descriptive purposes. However, if the objective is to study a process with additional data on the process or available outcomes, the final results achieved following classification might be affected by the different choices of classification. We aimed to determine the best set of cut-points to stratify the EQ-5D-based utility. Hence, we proposed a criterion that included measures of a process at two different points in time and defined a measurement of suitability of the classification by determining *true transitions* and *true non-transitions*, captured by the classification as a percentage of total transitions. The *true transition* was defined as a change of 0.10 in EQ-5D utility scores. The choice to use 0.10 corresponds to twice the minimal important difference of 0.05, mentioned by Dolan [18], and to the change in utility, when a person in full health is confronted with 'some problem'.

The incidents considered were those that triggered transition to a different state, as well as within the same state; the measure of the suitability of classification consists of the sum of *true transitions* and *true non-transitions*. Here, we assume that the value of identifying a true transition is similar to identifying a true non-transition. Two state-structures might have the same number of identified *true transitions* and *true non-transitions*, but may differ in how they capture the *true transitions* and the *true non-transitions*. That is, if the relative significance of these incidents can be expressed as a weight, the weighted measure would indicate the improved state. In this study, we assumed the relative importance to be 1 for both transition types identified.

Lastly, the use of multistate models to model disease over time using different outcomes is common, but we did not find any literature defining health states based on health-related quality of life. In that sense, this is the first attempt to do so. HRQOL is an established measurement of individuals' health states. The definition of a few distinct states based on HRQOL will increase the use of analytical techniques such as multistate models, including Markov models. It is also convenient to scale individual's HRQOL according to a few distinct states. In this study, we have demonstrated the use of a multistate model with homogeneous Markov assumptions, to compare the effectiveness of an intervention with a control. Moreover, we used the stable proportional distribution at stability as an outcome of an intervention. Stable distribution is independent of initial distribution, which makes it more appealing. However, care should be taken in the interpretation, since the stable distribution is technically not possible in some case, and the results only imply a theoretical consequence of a transition probability matrix and should be used for comparative purposes only.

In conclusion, we presented a way to define states in lung health based on HRQOL data. We demonstrated that a uni-dimensional utility measure is needed to do so, like, for instance, the utilities attached to the EQ-5D health states. We defined a measure of suitability for the classification by determining the occurrence of true incidents or no incidents causing *transitions* and *non-transitions* and identified by the classification as a percentage of the total transitions among patients with lung disease. For a state structure with four states of EQ-5D, the best set of cut-points is 0.4, 0.7, and 0.9. Finally, using this best set of cut-points in a multistate model, we found that the PAL intervention is as effective as the STS strategy among patients without a chronic cough, whereas among patients with a chronic cough, the PAL strategy could foster a better state of health state than the STS strategy.

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7

The Health Effects and Medical Costs of the WHO's Practical Approach to Lung Health for the Nepalese Population – A Model-Based Analysis Using Cluster-Randomized Trial Data

Lung diseases are a leading cause of morbidity and mortality in developing countries. This study models the long-term cost-effectiveness of implementing the WHO's Practical Approach to Lung health (PAL) in adults in Nepal. The PAL guidelines on symptomatic case management of tuberculosis, chronic obstructive pulmonary disease, asthma, and pneumonia are compared to the current Standard Treatment Schedule (STS).

A multi-disease, multi-state projection model was used to compute the PAL-related lifetime change in the Nepalese population's lung health. Parameters for the model were largely drawn from a facility-based cluster-randomized trial involving 42 health care facilities and 2243 patients, and the impact of PAL and STS on the health-related quality of life, and patient-level costs were collected in interviews with patients with respiratory symptoms. Program level PAL implementation costs were also estimated. Costs and effects were extrapolated to scale up PAL to the whole of Nepal, with uncertainties presented on a bootstrapped cost-effectiveness plane and in acceptability curves.

When keeping to the PAL guidelines, the treatment of a lung disease episode costs US$4.40 and US$3.54 on the basis of the STS guidelines. Implementing the PAL guidelines at all first level government health facilities in Nepal would cost US$111 per quality-adjusted life years gained, compared to the STS guidelines. Using a threshold of US$150 per QALY gained, PAL's probability to be cost-effective is 54%.

For the government, the implementation of the PAL guidelines is more costly than maintaining the current STS guidelines, but patients benefit in terms of the reduction of their out-of-pocket expenses for their treatment and in terms of better health of the population. The implementation of the PAL guidelines in Nepal is, therefore, likely to be cost-effective.

7.1 Introduction

Lung diseases are a leading cause of morbidity and mortality in developing countries. Lower respiratory infection, tuberculosis, chronic obstructive pulmonary disease (COPD), and asthma together amount to 15.4% of all disability-adjusted life years (DALYs) lost in the South-East Asia Region [1, 2]. In Nepal, most people live in rural areas with primary health care available through nurses who obtain basic training in health care and some additional training on the job [3]. The common symptoms associated with various lung diseases often lead to misdiagnosis and hence, the worsening of disease severity which may lead to death. With the exception of the case management of tuberculosis, the Nepalese health system has no standard strategy for dealing with the large number of lung diseases. This translates into a low quality of health care delivery and unnecessary expenses for both the health system and the individual patient [2].

With the progress in the Integrated Management of Childhood Illness (IMCI) [4], an integrated case management strategy, a number of countries throughout the world together with the World Health Organization (WHO) have initiated a Practical Approach to Lung health (PAL), developing generic clinical practice guidelines on integrated case management of pneumonia, tuberculosis, chronic obstructive pulmonary disease, and asthma [2, 5]. The PAL strategy requires local adaptation of the WHO guidelines for the specific epidemiology, formulary, and health manpower of a country. So far, only few countries have undertaken local adaptations of PAL including Peru, Morocco, Kazakhstan, and Nepal. In Nepal, the National Tuberculosis Centre (NTC) together with the WHO convened Nepali professionals and organizations to adapt the PAL guidelines in 2000. The Nepal guidelines were designed for implementation by health care providers at health posts and sub-health posts and were accompanied by training materials. This initiative is intended to promote better lung care among adult patients at first level health facilities [2].

It is important to assess PAL's economic attractiveness to verify whether the resulting health benefits merit the use of (scarce) health care resources. In a prior study on the effectiveness of PAL, Shrestha *et al.* [6] found that the implementation of PAL is effective in promoting the rational use of drugs in select respiratory diseases. They also found that PAL was effective in patients with a chronic cough and asthma [6]. To date, no economic evaluation of PAL has been performed. Because the next decision regarding PAL would be whether to implement it in the entire country we created a simulation model of the costs and effects resulting from such a policy.

We used a multi-disease, multi-state projection model to model the changes in lung health among Nepal's adult population based on what was learned from the Nawalparasi trial. We used cost data from the trial to evaluate the cost-effectiveness of implementing PAL guidelines in all first level government health facilities in

Nepal. Such a policy would cover around 30% of all adult patients seeking care for lung diseases, with the remainder seeking care from traditional healers or private health care providers.

7.2 Methods

7.2.1 Background on Design of Field Trial of PAL Nepal

A prospective trial of the PAL-Nepal program was conducted between 2001 and 2003 during which staff at 42 health care facilities were randomized into a control group of 20 facilities, which applied the standard treatment schedule (STS) used in community practices to treat lung disease, and an intervention group of 22 facilities at which five days of training were offered by the NTC in the use of the PAL guidelines.

At least one health care provider from each of the 22 health care facilities was trained in the period of June to July 2002. Patients aged 15 years and up with at least one of the symptoms fever, cough, or breathing difficulties were included and interviewed at the health care facility. We obtained clearance from the local Committee of Ethics and written consent from the patients included in the study. Patients with only a fever or a cough lasting less than 15 days were excluded for further follow-up interviews, since the likelihood of these patients having one of the target diseases was quite low. Patients with a chronic cough lasting over 15 days were interviewed two months later, and the remainder two weeks later. A maximum of three attempts were made to schedule a follow-up interview. Data were collected from 2243 patients who visited the 42 facilities in the period from September 2002 to September 2003. The translated version of the EuroQol EQ-5D questionnaire [7, 8] was used to obtain a single preference-based utility score for each patient on a scale in which 0 represented death and 1 represented full health [9]. All patients who completed the EQ-5D during both interviews were included in our analysis (a total of 1167 patients). It was assumed that all first level government health facilities in Nepal treat around 30% of all adult patients seeking care for lung diseases, with the remainder visiting traditional healers or private health care providers.

7.2.2 A Multi-State Projection Approach

A multi-disease, multi-state projection model (*Figure 7.1*) was developed to study the lifetime health experience of closed cohorts who had reached the age of 15 years before the projection period subject to the two interventions:

i. Continuation of current STS guidelines (STS scenario)

ii. Implementation of PAL guidelines (PAL scenario)

Both interventions were implemented for 10 years following standardized WHO methodology for modeling cost-effectiveness of health interventions [10]. The model integrates four different lung diseases, namely pneumonia, tuberculosis, chronic obstructive pulmonary disease, and asthma, reflecting the nature of the PAL-guidelines. All diseases include both an acute state represented by *X-state* and a chronic state represented by *C-state* (with the exception of pneumonia which only has an acute state). Individuals at any point in time can either be in a *Susceptible* state (susceptible to different lung diseases) or in any one of the diseased states in the *X-states* or *C-states*.

The model is evaluated in a time-step of two weeks. This time-step was chosen based on the extensive review of studies on multi-state models of lungs diseases (for details, see Chapter 5). The status of an individual at the beginning and at the end of a time-step could differ due to a transition between health states. At the beginning of a time-step, an individual in the *Susceptible* state can either remain in that same state, die, or enter an acute state (*X-states*) as a result of an incidence of either tuberculosis or pneumonia, or on account of a first incidence of either asthma or chronic obstructive pulmonary disease. While in an acute state at the beginning of a time-step, individuals at the end of one can either remain in the same acute state (in the process of remission or due to the worsening of the condition) or die (lack of proper treatment, no treatment, or failure of treatment) while the patient can move to a chronic state (*C-states*) due to remission (treatment of an acute state or natural remission) or recovery (natural or owing to proper treatment), or, in case of pneumonia, to the *Susceptible* state after recovery. In our multi-state model, patients in an acute or a chronic state of disease cannot make a transition to another disease's acute or chronic state. For example, a patient in a chronic state of tuberculosis will not experience an asthma attack.

Within a time-step of two weeks, patients who are in a chronic state of tuberculosis can either move to the state *Susceptible* (after a complete recovery), die (from tuberculosis or other causes), or remain in a chronic state during the process of treatment, or because of unsuitable treatment. For example, patients not following the treatment schedule (DOTS) can remain in a chronic state of tuberculosis for extended periods and may in the worst case enter an acute state of tuberculosis due to remission.

In the case of asthma and chronic obstructive pulmonary disease, patients remain in a stable chronic state within a time-step of two weeks due to good control of asthma or appropriate management of chronic obstructive pulmonary disease. Patients in chronic states do not die as a result of the disease since the transition to the acute state precedes death-related asthma and chronic obstructive pulmonary disease. However, death could occur during a time-step of two weeks when, for

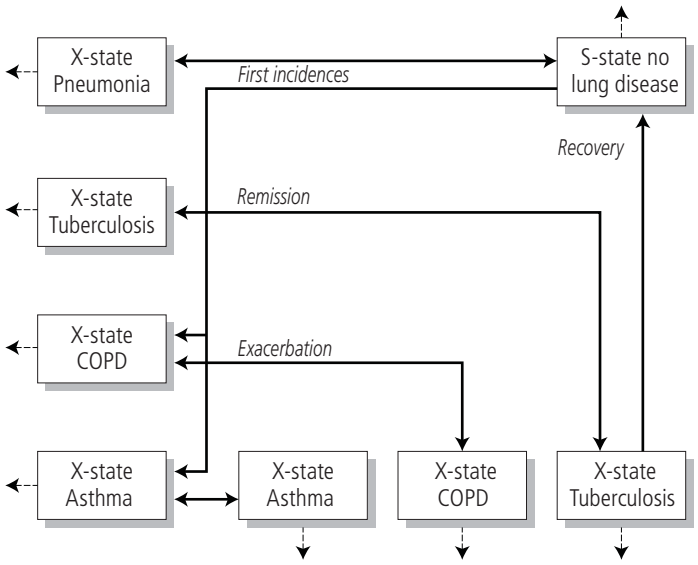

Figure 7.1. Multi-disease, multi-state model

Note: Dashed lines represent deaths due to specific lung disease or due to other causes

example, a patient in a chronic state actually makes a transition to the acute state and dies during that time period. We assume that the probability of such consecutive events is rather very low and, hence, do not include it in the model. This implies that deaths in chronic states are attributed to other causes. Patients in a chronic state of asthma or chronic obstructive pulmonary disease are always at risk of exacerbation which will change the patient's state from a chronic to an acute state.

The change in an individual's status within a state-space during a given time-step is triggered by an incident or incidents that result in a transition from one state to another. Information on transitions during a time-step can either be expressed through transition rates or transition probabilities. Transition rates during a specific time-step from one state (say, state S) to another (say, state X) are estimated by the ratio of observed number of incidents during the time-step in which the transition from state S to state X takes place, and total time spent in state S by those who already were in state S at the beginning of the given time-step. Whereas transition probability from state S to another state X during a given time-step is estimated as the proportion of individuals who were in state S at the beginning of the time-step, but are in state X by the end of the time-step. Transition rates are not duration-specific, however, transition probabilities are. In our multi-state model, we modeled the status distribution of the population in an interval of two weeks and hence, transition probabilities were easier to calculate and explain, since we

were interested in the status of individuals at the beginning and at the end of each time-step.

After defining the state-space, the next step was to fill the model with the data collected. Firstly, the baseline distribution of the study population in 2001 in various states of the multi-state, multi-disease lung model (*Figure 7.1*) was prepared. Secondly, the transition probabilities between the states were estimated and the model tested for 10 years in a time-step of two weeks. The data for estimating the initial distribution and the transition probabilities were obtained from various sources, including the national census of Nepal [11], the WHO's studies on burden of disease [12], and literature [13–16].

The initial distribution of the population in various states is needed before projecting a population's development using a multi-state model. The age-sex specific distribution of the population derived from the 2001 census [11]. Since information on the prevalence of pneumonia, tuberculosis, chronic obstructive pulmonary disease and asthma was available through the Burden of Disease study for Nepal (BoD) [12], we divided the population into five states, namely: susceptible and four states for each disease.

However, in our multi-state model (*Figure 7.1*) as already mentioned, we have more than one state of diseases for tuberculosis, chronic obstructive pulmonary disease, and asthma, namely *X-states* and *C-states*. In total, the model consists of eight states, susceptible, four acute states (X), and three chronic states (C). Hence, we had to divide the prevalence ratios of tuberculosis, chronic obstructive pulmonary disease, and asthma into *X-states* and *C-states*, for which data was not available in the BoD database. In Appendix A, we explain the method we developed to divide the diseased population into either the acute or chronic states for the initial baseline setting.

The procedure in Appendix A provides an approximation of the prevalence of chronic states of tuberculosis, chronic obstructive pulmonary disease, and asthma, and was calculated for each age and sex. Data on prevalence of disease (pr^i), rate of new incidences (m^i_{sx}), mortality rates (case fatality, background mortality, and all cause mortality) were obtained from the Burden of Disease study for Nepal [12]; the population numbers are based on the census of Nepal [11]; and the data on rate of remission/exacerbation were calculated from the frequency of exacerbations and remissions per year, obtained from various literature (see *Table 7.1*) [13–16].

In the next step, transition probabilities between the different states were calculated by sex and one-year age group, reflecting the probability of moving from one state to another or maintaining the status quo during a time-step of two weeks. (for more details, see Appendix B) [17, 18]. The transition rates for estimating the transition probabilities derived from various sources. The new incidence rates of diseases, duration of diseases (pneumonia and tuberculosis), mortality rates (case

Table 7.1. Inputs in the model for duration of disease episode and number of exacerbations per year

	Pneumonia	Tuberculosis	Chronic obstructive pulmonary disease	Asthma
Duration of disease episode (in state X)	10 days[a]	28 days[b]	7 days[c]	13 days[d]
Duration of disease (in states X and C)	–	1.6 yrs[a]	–	–
Number of exacerbations per year	–	–	2.4[c]	1.3[d]

Source: [a]Burden of Disease study; [b]Hansel(2004)[13] and Dion (2004)[14]; [c]Wilkinson (2004)[15]; [d]Dennis (2000)[16]

fatality, background mortality, and all-cause mortality), and recovery rate (tuberculosis) were obtained from the Burden of Disease estimates for Nepal [12]. Average duration of disease in an acute state of tuberculosis, chronic obstructive pulmonary disease, and asthma (see *Table 7.1*) [13–16] were used to calculate the transition rates from acute states. Transition probability from an acute state to a chronic or susceptible state is inversely proportional to the duration of the disease in an acute state. For example, if the average duration in an acute state is, say, 10 days, and assuming there are no deaths, then the rate of transition from the acute state can be approximated by 1/10 = 0.01 transitions per day of exposure, or 36.5 transitions per year of exposure. This procedure, as well as the deaths (case fatality, background mortality), are taken into consideration to estimate the transition rates from acute states. Yearly transition rates were converted to a two-weekly transition rate, reflecting a realistic timeframe for all four diseases to detect potential changes in patients' clinical status that may occur while in an acute state of health (see Chapter 5 for more details) [19]. These two-weekly rates were used to determine the two-weekly transition probabilities as explained in Appendix A [20].

The model was tested in a time-step of two weeks for 10 years, and we assumed the transition probabilities to remain constant during the projection period. Based on the two-weekly transition probabilities and the distribution of patients in different states at the beginning of each two week time-step, the model estimates the number of patients in acute and in chronic states of tuberculosis, chronic obstructive pulmonary disease, and asthma, and time spent in these states within each two week time-step, by taking the average of the number of patients in different states at the beginning and at the end of each time-step multiplied by two weeks. This corresponds to the assumption of a uniform distribution of incidents within a two week interval. Total time spent in various states weighted by health-related quality of life weights for each state are used to estimate the quality adjusted life years (QALYs) (explained below), which are then used in the calculation of cost-effectiveness analysis as a measurement of effect.

7.2.3 Utilities and QALYs

Utilities were calculated on the basis of the trial data. In the absence of disease diagnosis, utilities were not estimated in accordance with disease category but differentiated by acute and chronic state as an average across all patients. A baseline utility was estimated by taking the mean of the utility scores across all patients at the time of their first visit to a health care facility (n = 1167). Therefore, the baseline utility score represents the utility score of patients shortly after entering the acute state. Of the total number of patients (n = 1167), only those without a chronic cough (n = 658) were followed-up after two weeks (see Section 7.2.1) and the average change in utility within two weeks was estimated. Assuming that the utility of a patient changes uniformly during the two week period of undergoing treatment in an acute state, we estimated the average state utility of patients in the acute state as the sum of all patients' baseline utility and half the difference for change in the utility during the first two weeks. This method is equivalent to estimating the state utility by taking an average of the utility at the time of entering the state and at the time of exiting it. When we planned the data collection, two weeks was considered representative of the average duration of all diseases under study (ranging from seven days for pneumonia to 28 days for tuberculosis, see *Table 7.1*). Since patients with a chronic cough were followed-up only two months later, we do not have information on the utility score of these patients two weeks after their first visit to the health care facility. We assumed that the average change in utility within two weeks for patients with a chronic cough was the same as that for patients without a chronic cough: for example, if the average utility of patients without a chronic cough is 0.60 at the time of their first visit to a health care facility, and if the average change in utility within two weeks is 0.20, then the final average utility at the end of two weeks is 0.80. And if average utility of patients with a chronic cough is 0.50 at the time of their first visit, and assuming that the average change in utility is the same among both groups of patients, the final average utility will be 0.70. The utility scores for the chronic state were assumed to be equal to the average utility obtained from patients with a chronic cough two months later. The two sets of utilities for the acute and chronic states were estimated for both PAL and STS groups of patients. The utility score in a state without any of the four diseases (S in *Figure 7.1*) was assumed to equal 1. Apart from the different sets of utility scores for patients by type of facility visited, all the transition probabilities were assumed to be same, due to the unavailability of the data.

With the output from the model, quality adjusted life years (QALYs) were calculated by multiplying the total time spent in various states with the corresponding utility scores. The difference in QALYs between the STS and PAL scenarios is considered being the population's health gain following the implementation of the PAL guidelines.

7.2.4 Costs

Costs were analyzed from the societal perspective and include patient-level costs and program-level costs. Patient-level costs include the costs of facilities, personnel, equipment, materials, drugs, and laboratory investigations, and were based on trial data [21]. Program-level costs include costs of meetings, training, logistics, etc., and were calculated for the implementation of PAL in all first-level health care facilities in Nepal, assuming an initial training of all health care providers took place before the implementation of PAL and that a refresher training was offered after five years. In addition, the operating costs of implementing PAL with the assistance of a central- and district-level contact responsible for supervising the appropriate implementation during the clinical trial was included in the program costs. Data on these costs were gathered from the trial and extrapolated to the country as a whole. All costs were discounted at 3%. Because of measurement problems, productivity costs were not included. All costs are reported in the exchange rate from January 1, 2003 with US$1 equivalent to NPR 73.15.

The total costs of the STS scenario were calculated by multiplying average patient-level costs per episode and total number of incidences of acute episodes obtained from the model. The same procedure was followed to estimate the costs in the PAL scenario, but in addition, total program costs were added. The total incremental cost is the cost difference between the PAL and STS scenarios.

7.2.5 Cost-Effectiveness Analysis

The Incremental Cost Effectiveness Ratio (ICER) was calculated by dividing the difference in cost between the PAL and STS scenarios by their difference in the population's health. To deal with the uncertainty related to the costs and utilities derived from the trial, patient-level data was bootstrapped 5000 times. To measure the impact of choosing different time-steps, we ran the model with a time-step of one, three, and four weeks.

7.3 Results

Patients treated in accordance with the PAL guidelines experience higher utility weights in acute and chronic states than patients treated with the current STS (*Table 7.2*). The utility weight of being in an acute state is slightly higher for patients receiving treatment at PAL facilities than for those visiting STS facilities. We do not have any means of knowing whether there is a difference in average recovery time or rather, the average duration in an acute state between the PAL and STS scenarios. Hence, our assumption is that, irrespective of facility type, patients will spend the same amount of time in the acute state. The only difference there might

be is in the health-related quality of life reflected by the difference in state utility. The same is true for the chronic state; we do not know whether patients treated at PAL facilities will have lower rates of exacerbation or remissions, and therefore, we assumed that the outcome of the PAL and STS scenario is identical, except that the health-related quality of life might differ. The model's output indicates that individuals spent an average of 0.29% of their total lifetime in an acute state of lung disease, and 4.26% in a chronic state of lung disease. Based on these estimates, the total QALYs lived by the population is higher in the PAL scenario than in the STS scenario.

Patient-level costs per lung disease episode were lower in PAL than in STS (*Table 7.2*). Program costs did not apply to STS, and in PAL were largely related to operating costs for supervision and coordination during the 10 year period. In total, treatment of a lung disease episode costs US$6.40 in keeping to the PAL guidelines, and US$5.74 on the basis of STS, including both patient costs (health-related and non-health related) and program-level costs. Excluding non-health related costs, the treatment of lung disease is US$4.40 following the PAL guidelines, and US$3.54 applying the STS. The total costs of implementing PAL in all governmental first-level health care facilities would equal almost US$7 million, of which the bulk would be spent on program costs. Compared to STS, implementing PAL in all first-level government health care facilities in Nepal would cost US$111 per QALY gained. Results for the implementation in all first-level governmental health care facilities are presented in a cost-effectiveness plane [22] to illustrate the uncertainty in the estimate of costs and effectiveness (*Figure 7.2*).

A cost-effectiveness acceptability curve [23] shows the probability of PAL being cost-effective, taking the study's uncertainty and the maximum willingness to pay for a QALY (threshold) into account. With a threshold of US$150 per QALY gained [24], PAL has a 54% probability of being cost-effective. The maximum probability of PAL's cost-effectiveness is 69%, given the probability of occurrence of negative health effects. Sensitivity analysis by changing the model's time-step to one, three, and four weeks resulted in no change in the ICER value.

7.4 Discussion

Implementing PAL in all governmental first-level health facilities is a relatively cost-effective intervention, with a cost per QALY gained of around US$111. In comparison, benchmarks that have been suggested for assessments of whether or not a health sector intervention is cost-effective include a cost per DALY averted or life year gained of per capita income [25] (Nepal having a per capita income of around US$230 per year) [26], twice per capita income (US$460) [27], three times per capita income (US$690) [28], and US$150 [24]. The cost per QALY gained

Table 7.2. Results on Costs (US$), utilities, and cost-effectiveness

Health Outcomes	STS	PAL
Health state utility (EQ-5D utility scores)		
Acute State: Baseline utility, mean (SD)[†,i]	0.49 (0.36)	0.49(0.36)
Acute State: Change in utility at follow-up, mean (SD)[†,ii]	0.27 (0.35)	0.31 (0.38)
Acute State: Utility at follow-up, mean[†,iii]	0.63	0.65
Chronic State: Utility, mean (SD)[†,iv]	0.71 (0.36)	0.73 (0.35)
Total time spent without lung disease over 10 years ('000 years)	37,415	37,415
Total time spent in acute state over 10 years ('000 years)[v]	114	114
Total time spent in chronic state over 10 years ('000 years)[vi]	1,672	1,672
Total number of new/recurrent episodes over 10 years ('000)[vii]	3,723	3,723
Total QALYS lived during 10 years ('000)	38,746	38,774
Cost		
Non-health care costs per episode: food, travel and lodging, mean (SD)[†]	2.20 (0.31)	2.00 (0.22)
Health care costs per episode	3.54	3.36
Health care costs: drugs, registrations and laboratory, mean (SD)[†]	1.01 (1.09)	0.83 (1.00)
Health care costs: salary, rent, equipment, etc.[†]	2.53	2.53
Total program level costs	–	5,960,022
Adaptation costs		8,985
Training and refresher training		1,875,075
Operating costs (national-, district-level supervision, contact person)		4,075,962
Program-level costs per episode	–	1.04
Cost-effectiveness results		
Including non-health care costs		
Difference in costs		2,459,181
Difference in QALYs		28,749
Incremental cost-effectiveness ratio		86
Excluding non-health care costs		
Difference in costs		3,203,830.19
Difference in QALYs		28,749
Incremental cost-effectiveness ratio		11

[†]based on trial data;
[i] based on the baseline utility of all patients included in the analysis;
[ii]follow-up done after two weeks assumed to have endpoint utility of the acute episode;
[iii](baseline utility score) + (change in utility)/2, assuming that change is gradual during the episode;
[iv]measured at two months after treatment, and assumed to be the utility weight during the chronic/stable state of lung disease;
[v]pneumonia (27%), tuberculosis (6%), chronic obstructive pulmonary disease (14%), and asthma (53%);
[vi]tuberculosis (10%), chronic obstructive pulmonary disease (15%), and asthma (75%);
[vii]pneumonia (30%), tuberculosis (3%), chronic obstructive pulmonary disease (22%), asthma (45%).

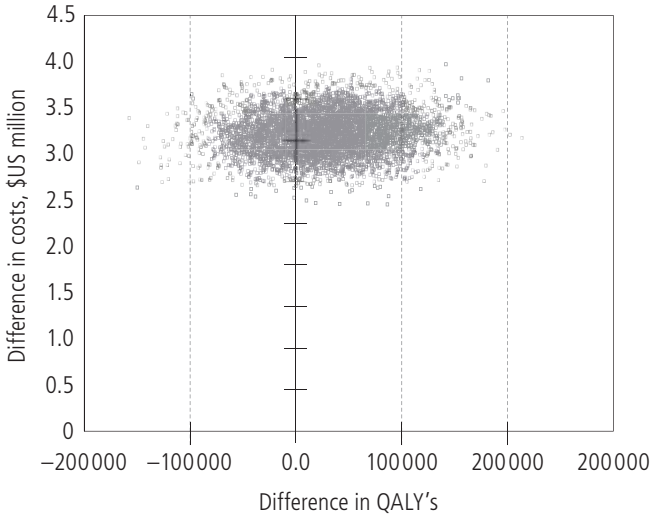

Figure 7.2. Cost-effectiveness plane with 5000 bootstrap samples of the difference in costs and QALYs generated between the PAL-scenario and the STS scenario

is less than most of these benchmarks, indicating that the PAL scenario is a cost-effective intervention. However, considering the presence of uncertainties in the study, this can only be said with a probability of around 54%. The variation in cost and effectiveness shown in Figure 7.2 could have occurred due to the variation in age, sex, marital status, or severity of the disease. These similar factors along with the distance between a patient's home and the healthcare center, which is directly related to non-health care costs (travel, food and lodging), might have contributed to the variation in the costs. Further, knowledge of the disease specific utility score for acute and chronic states would have reduced the variation in both health effects and costs. It was not possible in this study to diagnose the patient due to various constraints. For optimum use of the multi-state model, the disease specific health effects and costs would have contributed to a more detailed single disease analysis.

The model included the change in utility in acute states and the state utility of chronic states (an approximate) to estimate the health effects of PAL, and can thus be considered conservative. Other effects on, for example, case fatality, different utilities while in the chronic state, incidences, and remissions were not taken into account due to lack of data. The positive effect of the Integrated Management of Childhood Illness (IMCI) (see Chapter 1, p. 6), an integrated case management strategy, has been proven in many settings [29]. Similar expectations can be made regarding PAL. With a longer follow-up period of PAL patients, more data on the effect of PAL on mortality, incidences, and remission, and the state utility of the chronic state (for example, with utility data collected after longer periods of time

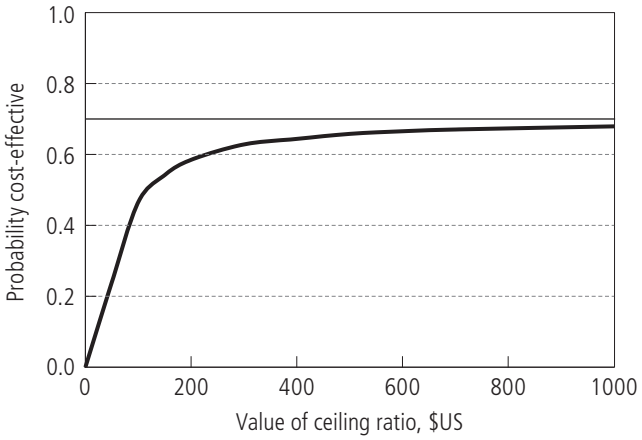

Figure 7.3. Cost-effectiveness acceptability curve based on 5000 bootstrap samples illustrating the probability of cost per QALY gained being cost-effective at different values of ceiling ratios

when patients are more stable) would become available, and PAL could appear even more cost-effective.

The implementation of PAL in all governmental first-level health facilities carries with it high program costs. Program costs per episode would decrease if a higher proportion of the population were reached. No extra health care facility costs related to the implementation of PAL were included. In practice, additional resources such as oxygen cylinders, inhalers, extra medicine, additional time, and paper work may increase the cost per episode in the PAL scenario compared to the STS scenario.

PAL guidelines target four lung diseases that are unique in their epidemiology, with a single algorithmic approach through a training of health care providers at first-level health care facilities in rural communities. Our model was specifically developed keeping in mind the nature of these guidelines. Though many disease-specific models exist for the diseases modeled here, a single model combining these four diseases does not exist, i.e. we were the first to develop one for the purpose of the economic evaluation of the PAL guidelines. This is a unique model for the purpose stated. Depending on specific diseases, more states can be added to detect transitions in disease sub-states resulting in better and more precise outcomes.

In conclusion, the implementation of PAL increases intervention costs compared to the current care received for US$1.04 per episode. Patients, on the other hand, benefit with regard to the reduction of their out-of-pocket expenses on direct medical costs (by 18%) and on non-medical costs (by 9%). The health benefit, on the other hand, is not substantive as demonstrated by the minor difference in

utility's average difference at the beginning and end of the observation period between patients receiving treatment under the PAL guidelines and those visiting STS. In general, the study reveals that the probability of a PAL intervention to be successful measured by its cost-effectiveness compared to the STS lies just over 50%. Further evidence on the impact of PAL on incidences and duration of exacerbations of lung diseases could render the intervention more cost-effective.

Appendix A

For a specific population, let $S(t)$, $X^P(t)$, $X^{TB}(t)$, $X^C(t)$, $X^A(t)$, $C^T(t)$, $C^C(t)$ and $C^A(t)$ be the number of people in the state *Susceptible* and in the respective states (P - Pneumonia, TB - Tuberculosis, C - Chronic obstructive pulmonary disease, and A - asthma) at time t, which is the sum $N(t)$, the total population.

Let $pr^i(t)$ represent the prevalence of respective diseases (i equal to P, TB, C, and A) in the population at time t.

Then,

$$X^P(t) = N(t) \cdot pr^P(t) \tag{7.1}$$

$$X^i(t) + C^i(t) = N(t) \cdot pr^i(t); \quad \text{for } i \text{ in } \{\text{TB, C and A}\} \tag{7.2}$$

$$S(t) = N(t) \cdot (1 - sum(pr^i(t)); \quad \text{for } i \text{ in } \{\text{P, TB, C and A}\} \tag{7.3}$$

Let, $v^i(t)$ be the proportion of a population with disease i in an acute state at time t.

Then,

$$X^i(t) = N(t) \cdot pr^i(t) \cdot (1 - v^i(t)) \tag{7.4}$$

$$C^i(t) = N(t) \cdot pr^i(t) \cdot v^i(t) \tag{7.5}$$

Let d^i be the average duration of disease i in an acute state.

To approximate the value of v^i, we go back in time with $t - d^i$. Assuming that the prevalence of disease, $pr^i(\cdot)$, and the proportion of diseased (with/among prevalence pr^i) in chronic states, $v^i(\cdot)$, at time t and $t - d^i$ are equal, the following equations apply:

$$X^i(t - d^i) = N(t - d^i) \cdot pr^i \cdot (1 - v^i) \tag{7.6}$$

$$C^i(t - d^i) = N(t - d^i) \cdot Pr^i \cdot v^i \tag{7.7}$$

$$S(t - d^i) = N(t - d^i) \cdot (1 - sum(pr^i)); \quad \text{for } i \text{ in } \{\text{P, TB, C and A}\} \tag{7.8}$$

Assuming that the time spent in an acute state is equal to the average duration of disease in an acute state at time t, all the patients who were initially in state X^i at time $t - d^i$ will either die or remit to state C^i from state X^i.

During time $(t - d^i, t)$, due to new incidences of disease individuals move to state X^i from state S and either die or remain in the state X^i at least until the end of the period, the number of new incidences during $(t - d^i, t)$ being:

$$sx^i(t - d^i) = S(t - d^i) \cdot p^i_{sx}(t - d^i) \tag{7.9}$$

where $p^i_{sx}(t-d^i)$ is the probability of new incidences of disease during interval $(t-d^i,t)$ for those who are in state S at the beginning of the interval. For a given incidence rate of new cases of disease (S to X^i), $m^i_{sx}(t-d^i)$, the probability of new incidences can be calculated as:

$$p^i_{sx}(t-d^i) = [m^i_{sx}(t-d^i)\cdot d^i]/[1+m^i_{sx}(t-d^i)\cdot d^i/2] \tag{7.10}$$

In addition to new incidences of disease i, prevalent cases in state C^i at time $t-d^i$ move to state X^i in time $(t-d^i,t)$, with incidences of remission or exacerbation, and either die or remain in state X^i, the number of incidences from a chronic to an acute state is described by:

$$cx^i(t-d^i) = C(t-d^i)\cdot p^i_{cx}(t-d^i) \tag{7.11}$$

where $p^i_{cx}(t-d^i)$ is the probability of remission or exacerbation of disease during a time interval $(t-d^i,t)$ for those who are in state C^i at the beginning of the interval. For an incidence rate of remission or exacerbation of disease *(C-state to X-state)*, $m^i_{cx}(t-d^i)$, the probability of remission or exacerbation can be calculated as:

$$p^i_{cx}(t-d^i) = [m^i_{cx}(t-d^i)\cdot d^i]/[1+m^i_{cx}(t-d^i)\cdot d^i/2] \tag{7.12}$$

From equations (7.9) and (7.11), the total number of patients in the *X-state* at the end of the interval is defined as:

$$X^i(t) = [sx^i(t-d^i)+cx^i(t-d^i)]\cdot cf^i \tag{7.13}$$

where cf^i is the mortality correction factor. Assuming uniform distribution of events during the interval, the correction factor is calculated as:

$$Cf^i = [1-(f^i+f^b)\cdot d^i/2]/[1+(f^i+f^b)\cdot d^i/2] \tag{7.14}$$

where f^i is the case-fatality rate (per year) in state X^i due to disease i, and f^b is the background mortality rate (per year) due to disease other than the four diseases studied here.

Hence, using the above equations, we can derive the proportion of people with disease i in a chronic state (C^i) as:

$$\begin{aligned} v^i = \quad & [(pr^i/cf^i)\cdot(N(t)/N(t-d^i)) - (1-sum(pr^i(t)))\cdot p^i_{sx}(t-d^i)]/ \\ & [pr^i\cdot p^i_{sx}(t-d^i) + (pr^i/cf^i)\cdot(N(t)/N(t-d^i))] \end{aligned} \tag{7.15}$$

where $N(t)/N(t-d^i) = (1-f\cdot d^i/2)/(1+f\cdot d^i/2)$, f is the cause for the mortality rate.

Appendix B

Obtaining a P-matrix from rates

Age and sex-specific transition probabilities are collected in a matrix known as a **P**-matrix, with the initial state in the column and final state in the row. If transition probabilities are known, the construction of the **P**-matrix is straightforward. However, epidemiological measures are often reported in rates and these rates have to be transformed into probabilities. Assuming uniform transitions within a cycle, we used a method suggested by Rogers *et al.* and Willekens *et al.* [17, 18] to obtain a **P**-matrix from the rates using the formula $\mathbf{P} = [\mathbf{I} + 1/2\mathbf{M}]^{-1}[\mathbf{I} - 1/2\mathbf{M}]$, where **I** is a unit matrix and **M** represents a matrix – known as **M**-matrix – constructed of rates. In our model, the rates depend on age and sex only. The model runs for 10 years, age-sex specific population experiences, the transition according to the age-sex specific **P**-matrix in a cycle of 2 weeks, i.e., 26 times a year. After one year, the population turns one year older and the **P**-matrix is also replaced accordingly.

Types of health care providers trained in PAL

The health care providers refer to auxiliary health care providers, ANMs, health assistants and medical officers in the facility. Other lower level health care providers are not PAL-trained.

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8
Conclusion and Discussion

8.1 Conclusion

In this study we have demonstrated that implementing the PAL guidelines increases the Nepalese government's expenditure, owing mainly to training and the supervision of health care providers. On the other hand, implementing the PAL guidelines reduces patients' out-of-pocket costs, mostly due to the lower average cost of drugs prescribed. The PAL implementation is also found to be effective in improving patients' health-related quality of life, especially in non-chronic cough patients. Finally, a multi-state integrated lung disease model was developed to analyze the cost-effectiveness of the PAL guidelines compared to the standard practice. The model outcomes show that the implementation of PAL is found to be cost-effective given standard benchmarks. Uncertainty analysis shows that the probability of the PAL program to be effective is only 54%. So, it is difficult to conclude that PAL is effective. This is discussed in detail below.

The first objective of the evaluation study was to compare the costs of implementing the PAL guidelines in governmental health care facilities with the costs of maintaining the standard range of medical services. We demonstrated in Chapter 7 that the costs for the government when implementing the PAL guidelines in terms of program-level costs is about US$6 million (spread over ten years), which comes to be an average of US$ 1.04 per episode, per patient. At the patient level, patients visiting PAL facilities pay less per episode in terms of health care costs (US$ 0.83 vs. US$ 1.01), as well as in terms of non-health care costs (US$ 2.00 vs. US$ 2.20). In Chapter 4, a reduction in patient-level cost in terms of reducing wastage drug costs (due to the prescription of drugs not needed by the patients) by NPR 2.46 (US$ 0.033) is found, however, to be statistically insignificant. Hence, in terms of costs, PAL likely reduces patients' out-of-pocket expenditures. On the other hand, it is evident that implementing PAL will incur extra costs for the government. However, this cost can be reduced once PAL is integrated in the basic and continuous training of health care providers. After PAL is adapted nationally, we expect the costs of training health care providers on how to treat lung patients using the standard schedule will cover some or all of the program costs of implementing the PAL guidelines.

The second objective of the PAL evaluation study was to compare the outcome for patients treated at PAL facilities to the outcome of those treated at facilities using the standard range of medical services. We began with a symptom-specific outcome analysis in Chapter 2. We determined a higher effectiveness of treatment at PAL facilities for patients with breathing difficulties and a non-chronic cough. These patients were suspected to have asthma. Next, in Chapter 4, we demonstrated an indirect positive health effect on patients through the change in prescription behavior of health care providers. Health care providers were more likely to adhere to the guidelines, as well as increase the rational use of drugs which resulted in lower antibiotic prescriptions, higher prescriptions of generic drugs, as well as drugs from the essential drugs list. Similarly, the use of the PAL guidelines led to fewer prescriptions of multiple drugs. These effects, though not all statistically significant, are expected to lead to better health in patients. Next, the general health effects in patients were analyzed using a generic health-related quality of life questionnaire.

We have shown that the patients treated at PAL facilities scored higher on the health-related quality-of-life questionnaire than the patients treated at non-PAL facilities, albeit only in patients with a chronic cough. Based on a preference-based utility measure, EuroQOL, the difference in the average utility gained during certain periods between those patients visiting PAL and those visiting non-PAL facilities was insignificant among patients with a non-chronic cough, whereas the difference was significant among patients with a chronic cough, with a higher utility gain being achieved among patients treated at the PAL facilities. In Chapter 6, we proposed a multistate model approach to study the evolution of patients' health-related quality of life. This reported similar results. We have used multistate models in the evaluation since they are expected to be useful for studying the evolution of diseases as defined by different disease states. Multistate models are widely used in studies on medical prognosis, as well as in studies of model-based economic evaluations and medical decision making, as the costs and effectiveness of treatment can be properly analyzed by observing the changes in disease states over time. The analysis in Chapter 6 shows that the implementation of PAL affords better health for patients with a chronic cough, who are mostly likely to have COPD or TB.

Lastly, the third objective of the PAL evaluation study was to determine the cost-effectiveness of the PAL guidelines strategy compared to other potential investments in a population's health, as well as to the existing services being provided. In Chapter 7, we estimated the cost-effectiveness of the PAL guidelines strategy as compared to the existing standard treatment schedule. Our results indicate that the PAL guidelines strategy is more likely to be cost-effective compared with the standard treatment schedule among patients other than those with a chronic cough. Overall, the cost-effectiveness of PAL is not significant for all patient groups considered, as revealed by the uncertainty analysis which showed that when the PAL implementation is likely to be (cost-)effective in little more than half

of the cases. We used an integrated multistate life table model for all four diseases to carry out the cost-effectiveness analysis of the implementation of PAL compared to standard practice. Based on the results, we concluded that the implemented PAL guidelines strategy as a whole is less likely to be cost-effective than assumed. During the follow-up we observed various problems in the implementation of PAL. We will discuss these in the following section.

8.2 Discussion

Before a new intervention or already existing intervention within a new context can be fully implemented, a pilot implementation is a necessary and an important step to study the interaction between the intervention and the local context. The pilot implementation process consists of various steps, and during each step, the intervention is continuously modified in an iterative way. We discuss each step of the pilot implementation of the PAL guidelines in Nepal.

The first step in the implementation process was to establish theoretical validity of the intervention itself on ethical grounds, as well as on scientific grounds. A well-documented, well-reviewed report on the process of the development of the PAL guidelines with state-of-the-art knowledge of science was the basis to launch the implementation process. The PAL guidelines passed this test as reported in the various documents of the World Health Organization (WHO) available on its Web site (http://www.who.int/tb/dots/pal/en/). Based on the initial face value of the guidelines and discussions at various levels, the Nepal Tuberculosis Center (NTC) under the Ministry of Health-Nepal (MoH-N), along with technical support from the WHO, planned to carry out a pilot implementation of the PAL guidelines in Nepal. The assessment of the process at this level is beyond the scope of this study and reported by Ten Asbroek *et al.*

The training of health care providers in the use of the PAL guidelines was carried out by trainers who had previously been trained by experts from the NTC and the WHO. The training of the trainers and the actual training of the health care workers by these trainers were the most important steps in the implementation process. How well the training was conducted and how the trainees received the knowledge was crucial for the success of the implementation of the PAL strategy. As far as we can recall, the actual training process was not documented. This could be important question as much of the success of the training depends on the knowledge gained by the trainers and the trainees. If the training is ineffective, health care providers will be more likely to adhere to their old ways. During the observation of patients, we included some questions (observation points) to check whether the health care providers were following the PAL guidelines but the results are inclusive. Thus, it is highly recommended to place more emphasis on evaluation of the

training of health care providers. In the case of PAL, we assumed the training to be a black-box. We continued with the cost-effectiveness analysis on the assumption that the training was successful.

Two months after the last training session was conducted, we sent out field assistants (FAs) to each of the 42 health care facilities to collect data from individual patients with lung disease-related symptoms. We waited for two months before examining the actual effect of the PAL guidelines, since we believed that the immediate effect of the training would be misleading and wanted to measure the effect in a real-life setting. An additional expectation was that the trained health care providers shared their knowledge of PAL with their co-workers. Our analyses is based on the assumption that patients treated at a PAL facility are not differentiated based on whether or not the health care was provided by a PAL-trained health care provider. In sub-health posts the same person who had received training in the use of the PAL guidelines generally also treated patients. However, in health posts and primary health care centers, non-PAL trained health care providers were included in the intervention group as well. In a one case, a PAL-trained health care provider at a sub-health post was replaced by another health care provider who had no PAL training. These are the issues related to the real-life design of the experiment and contributed to the (lower) effectiveness of the implementation of PAL as compared to an efficacy study.

During the entire period of study, a few providers who had received training in PAL were briefly monitored by higher level medical personnel with regard to the implementation of the PAL guidelines. This can be considered a serious omission on the part of implementation. In the general set-up, a series of regular monitoring is conducted by supervisors from local, regional, national, and international levels. PAL was not included in these regular supervisions in spite of the agreement with the NTC. This is the second issue (the first being the quality of training) that we observe a possible dilution of training effort and the quality of implementation. Basically, a single training session was provided and the health care providers were left to themselves to work for the rest of the period. This is a common practice, yet we believe that additional supervision and managerial activities would have contributed considerably to PAL's effectiveness.

In the evaluation we need to measure effectiveness using valid instruments. As explained in previous chapters, the remoteness and the lack of resources at the facilities restricted us using modern medical equipment to measure the health status of patients. This is also the reason why the PAL intervention is a symptom-based approach and not diagnosis-based. We could only afford to measure symptoms whose descriptions could be obtained either from the patients reporting them directly, or by using inexpensive general medical equipment. The follow-up visits to patients' homes took place mostly in remote areas with no, or only partial, public transport facilities, and it was not possible to bring along expensive equipment to

these areas. Therefore, we used different questionnaires, as well as observations by field staff, to measure the health status of patients.

The reliability and validity of the translated questionnaires was not tested in the specific Nepalese settings. A first challenge was the language, as several languages are spoken in the area. We prepared two sets of questionnaires, one in Nepali and the other in Bhojpuri, a dialect spoken by people in the Terai region of Nawalparasi. Questionnaires were translated again backwards. They were developed to make them simple and comprehensible. Still, some respondents had trouble understanding some of the questions. Many of the questions were used for the first time in Nepal. In Chapter 3, we presented the results of the validation analysis, using patient data. Apart from the questionnaire used in this analysis, additional instruments are available. We recommend that more exploration of such tools is conducted, and more validation exercises carried out in the future for these and other instruments, considering that such questionnaires are very effective, cheap, and easy to administer.

Based on the collected data, we performed an empirical analysis and developed a PAL multi-state model to study the evolution of four PAL diseases in the Nepalese population. During our review of existing models for lung diseases, we found many disease-specific models for single diseases. In most cases, disease states were defined based on measurements of health status assessed mostly in well-equipped and well-manned environments. This was not possible for the new models. Because these models are disease-specific, all disease models have different definitions. We used generic measures of health status so the model could be used to study all PAL diseases at the same time. This generic measure facilitates comparisons with other diseases as well.

Based on a review of existing multi-state models for lung health, we proposed a new multistate model in Chapter 6 for the modeling of generic health-related quality of life data. We did not find any multistate model using the HRQOL and, hence, this is the first effort to do so. Our model can be further developed to study the evolution of HRQOL in other disease processes and in other national settings.

Finally, we used the PAL model along with our empirical analysis to estimate the cost-effectiveness of PAL compared to the standard range of treatment. We did not find PAL to be particularly cost-effective. Based on the field experience during the pilot phase, we listed several reasons. We would like to emphasize that when studying cost-effectiveness analysis in developing countries, one must seriously plan the implementation of the intervention. Lack of dedication and capacity of both national and international implementers profoundly affects the process.

In conclusion, the future implementation of the PAL strategy in the primary health care facilities should consider the strengths and weaknesses at various levels of implementation as reported here in this book, to achieve better results in terms of better health returns given the budgets spent. We found that some patients at

the individual level with specific respiratory symptoms who visited PAL facilities are enjoying improved health, as well as a reduction in their out-of-pocket costs. However, the overall cost-effectiveness of the PAL program is doubtful, possibly due to either lack of real effect in the acute phase or to the small sample size of disease sub-groups. Because of the partial positive results and the existing possibilities to improve further implementation the next PAL phase should be flexible and conditional to more evaluation and monitoring.

Longaandoeningen in ruraal Nepal

Modellering van gezondheidstatus en de economische evaluatie van richtlijnen voor een geïntegreerde benadering van longaandoeningen

Mensen lopen verschillende gezondheidsrisico's. Ziekten kunnen worden voorkomen, verzacht of genezen. In arme landen lijden mensen aan ziekten die in rijke landen goed te voorkomen zijn. Kennisoverdracht van rijke naar arme landen en investeringen in de gezondheidszorg kunnen bijdragen aan de vermindering van de gezondheidsverschillen in de wereld. Om hierbij succesvol te zijn dienen interventies te zijn aangepast aan lokale omstandigheden en vooraf te worden onderworpen aan een kosten-baten analyse. Hierbij worden gezondheidseffecten gerelateerd aan de kosten van de interventie.

Dit boek presenteert de resultaten van een kosteneffectiviteitsanalyse van een door de Wereldgezondheidsorganisatie (WHO) ontwikkelde geïntegreerde aanpak van longaandoeningen, de zogenaamde Practical Approach to Lung Health (PAL). De WHO-PAL aanpak werd toegepast in ruraal Nepal waar verschillende longaandoeningen zoals longontsteking, tuberculose (TBC), chronische obstructieve longziekten (COPD) en asthma veel voorkomende kwalen zijn. Veelal ontbreken er goed uitgeruste gezondheidsvoorzieningen en goed opgeleid personeel. De PAL aanpak voor de eerstelijnsgezondheidszorg is ontwikkeld voor gezondheidswerkers met een beperkte opleiding. In 22 willekeurig gekozen centra voor basisgezondheidszorg in een ruraal district (uit een totaal van 42 centra) werd ten minste één gezondheidswerker opgeleid volgens het PAL richtlijnenprogramma. In hetzelfde district werden de 20 andere centra als controle centra meegenomen. In een vervolgonderzoek werden de gegevens gedurende een periode van een jaar verzameld van alle patiënten die deze 42 gezondheidscentra bezochten en die symptomen van longziekten vertoonden i.c. koorts, hoesten en ademhalingsproblemen. In dit boek worden de resultaten van de PAL benadering vergeleken met die van al bestaande gezondheidszorg in de controle centra, in termen van kosten, gezondheidseffecten en kosteneffectiviteit.

Het onderzoek laat zien dat introductie van PAL tot hogere kosten leidt, als gevolg van de kosten van scholing en supervisie van gezondheidswerkers. Per ziekte-episode nemen de kosten toe met US $1.04. Deze additionele kosten moeten

worden gedragen door de overheid of de internationale gemeenschap. Indien eenmaal PAL op brede schaal is geïntroduceerd en geïntegreerd in de basis- en vervolgopleidingen van gezondheidswerkers, zullen deze extra kosten aanzienlijk dalen.

Voor patiënten vermindert PAL de zelfgemaakte kosten, vooral als gevolg van de lagere kosten van medicijnen. De WHO-PAL aanpak bevordert rationeel gebruik van medicijnen: vermindering van overbodig gebruik van medicijnen en antibiotica, en toename van recepten voor generieke medicijnen en andere medicijnen van de lijst van essentiële geneesmiddelen. Patiënten die gezondheidscentra bezoeken waar de PAL aanpak wordt gevolgd, geven per ziekte-episode gemiddeld minder uit aan gezondheidszorg (US$ 0.83 versus US$ 1.01) en overige indirecte kosten (US$ 2.00 versus US$ 2.20). Dit is een belangrijk resultaat omdat de meeste patiënten die gezondheidscentra bezoeken arm zijn en iedere substantiele besparing van uitgaven een verschil maakt.

Patiënten met niet-chronische ademhalingsmoeilijkheden (met een duur van minder dan twee weken) hebben baat bij PAL. De betere gezondheidseffecten van een bezoek aan een PAL voorziening vergeleken met een bezoek aan een ander centrum zijn het resultaat van een beter voorschrijfgedrag van gezondheidswerkers, geringere kosten en een hogere effectiviteit van de behandeling. Deze effecten zijn echter niet allemaal statistisch significant.

Bij een effectmeting is van belang hoe het resultaat wordt gemeten. In ruraal Nepal kunnen de effecten van PAL interventies niet worden uitgedrukt in standaard ziekte-specifieke uitkomsten omdat meting van de gezondheidstoestand van een longpatiënt medische apparatuur vereist die in afgelegen gebieden niet beschikbaar is. De WHO-PAL aanpak is daarom gebaseerd op symptomen en niet op diagnose. In het onderzoek werden verschillende vragenlijsten gebruikt om de gezondheidstoestand van de patiënt te bepalen. De algemene gezondheidstoestand werd vastgesteld met generieke maten van kwaliteit van leven de zg. Quality-of-Life score (QoL) die aan de specifieke context waren aangepast. Ons onderzoek toont aan dat patiënten met chronische hoest die behandeld werden in gezondheidscentra die werken volgens de WHO-PAL methode een betere QoL score hadden dan patiënten die in andere centra waren behandeld.

Voor de studie van effecten van interventies is het van belang het ziektepatroon te volgen in de tijd en men kan de veranderingen beschrijven aan de hand van een ziektemodel voor longziekten. Voor het onderzoek werden twee rekenmodellen ontwikkeld die voor een specifiek longaandoening een aantal toestanden onderscheiden en het verloop van de aandoening beschrijven in termen van transities tussen toestanden (multi-state modellen). Het eerste multi-state model is een generiek model van kwaliteit-van-leven (QoL). Het tweede model geeft een geïntegreerde beschrijving van de vier longaandoeningen. Dit laatste model werd ontwikkeld op basis van een uitgebreid literatuuronderzoek. Hierbij werd een groot aantal modellen van longaandoeningen werden bestudeerd om een verantwoorde keuze te

kunnen maken van de te onderscheiden toestanden en van de tijdseenheid voor de beschrijving van het ziekteproces.

Het eerste multi-state model beschrijft de gemeten veranderingen bij patiënten in het vervolgonderzoek in termen van generieke, gezondheidsgerelateerde kwaliteit-van-leven (QoL). De gezondheidsmaten zijn gemeten met behulp van de zogenaamde EuroQoL schaal. Dit model is te gebruiken wanneer een diagnose onbekend is en men alleen de symptomen kan vaststellen en de verandering hierin door behandeling. Dit model is ook te gebruiken wanneer de symptomen worden veroorzaakt door verschillende aandoeningen zoals in het PAL onderzoek. Modelberekeningen tonen aan dat de gezondheidsgerelateerde QoL van patiënten met niet-chronische hoest meer verbeterde bij bezoek aan gezondheidscentra waar de PAL methode werd gevolgd dan aan een bezoek aan de controle centra. Dit resultaat komt overeen met de andere empirische bevindingen.

Het tweede model is ontwikkeld om de kosteneffectiviteit van de PAL richtlijnen te bepalen ten opzichte van de standaard praktijk. Bij de longpatiënten zijn hierbij de drie gezondheidstoestanden onderscheiden: gezond, ziek met acute symptomen, en ziek met chronische symptomen. Aan de hand van het model werd de verblijfsduur in iedere toestand geraamd en die verblijfsduur werd gewogen voor de ernst van de gezondheidstoestand. Tevens werden de kosten uitgerekend naar gezondheidstoestand in de acute en vervolg-fase. De modelberekeningen en de diverse economische uitkomstenmaten tonen aan dat de PAL aanpak kosteneffectief kan zijn. De onzekerheidsanalyse toont dat de kans dat WHO-PAL effectief niet hoger is dan 54 procent wanneer men alle patiëntengroepen gezamenlijk beschouwt. De conclusie dat PAL kosteneffectief is, kan daarom niet zonder meer worden getrokken omdat de kans op succes in de hele groep te gering is.

Op basis van de resultaten van dit onderzoek kan men de WHO-PAL benadering het voordeel van de twijfel geven. De resultaten zijn gedeeltelijk positief. De verdere uitbouw van het programma is reeds begonnen. De huidige studie geeft verschillende opties om de aanpak verder verbeteren.

K.C. Samir

About Lung Health in Rural Nepal

Good health is a basic human right, yet many people in developing countries suffer illness and death from causes that can be easily prevented or cured. How can we close the gap between potential benefits available from medical advances and the health of poor in a most effective way? This book addresses these basic questions in the field of health and development, providing insights from a case study in lung health, developing new analytical methods.

The book presents an economic evaluation of the World Health Organization's Practical Approach to Lung Health (PAL) in rural Nepal. The detailed picture to emerge from this study offers new perspectives on efforts to improve health in poor developing countries. In addition to the case study, the book also presents a new analytical method for studying health in similar contexts. This approach, based on a multi-state framework, offers a potentially significant step forward in the field of health status modeling in the developing world contexts.

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