Introduction of Pneumococcal Conjugate Vaccine (PCV) in Bhutan

MISSION REPORT

Thimphu, 22-24 November 2016

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Abbreviations

CBA	Cost Benefit Analysis
CEA	Cost Effectiveness Analysis
CMA	Cost Minimization Analysis
CPI	Consumer Price Index
CUA	Cost Utility Analysis
DALY	Disability Adjusted Life Year
EE	Economic Evaluation
EMTD	Essential Medicines and Technology Division
EPI	Expanded program on Immunization
GAVI	Global Alliance for Vaccines and Immunization
HITAP	Health Intervention and Technology Assessment Program
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
LMIC	Low Middle Income Country
MOH	Ministry of Health
NCIP	National Committee for Immunization Practices
NLEM	National List of Essential Medicines
PCV	Pneumococcal Conjugate Vaccine
PSA	Probabilistic Sensitivity Analysis
QALY	Quality Adjusted Life Year
REBH	Research Ethics Board of Health
UHC	Universal Health Coverage
WHO PEN	WHO Package of Essential Non communicable disease
WHO	World Health Organization

Introduction

Since 2008, Bhutan has taken a step further in its attempt to develop HTA capacity in the country in the light of sustaining UHC by establishing an official HTA unit called EMTD under MOH. The transitional economy of the country has upgraded itself to becoming LMIC with Universal Healthcare Services Coverage of more than 90%. Total expenditure on health as % of GDP is 3.1. Bhutan has achieved Universal Child Immunization in 1991 and has quite high immunization coverage over the past decades. While Bhutan government remains the major funding source for Expanded Program on Immunization (EPI) in Bhutan, GAVI was a major international contributor. But since Bhutan is not GAVI eligible to receive support for vaccine, Bhutan government needs to allocate money by itself to introduce PCV in the country which would impose substantial financial burden to the government. Therefore, informed decisions needs to be made in terms of providing evidences about the cost-effectiveness of PCV introduction in Bhutan.

In low and middle-income countries, *Streptococcus pneumoniae* is the leading cause of most deaths from cases of severe pneumonia. It is a major cause of morbidity and mortality of children under five years of age responsible for almost about 1.3 million deaths in a year. Pneumococcal Conjugate Vaccine-7 (PCV-7), Pneumococcal Conjugate Vaccine-10 (PCV-10) and Pneumococcal Conjugate Vaccine-13 (PCV-13) are three different vaccines to protect against different *Streptococcus pneumoniae* serotypes[1]. In Bhutan, it is the 7th most common cause of deaths. Although World Health Organization (WHO) recommends PCV to be included in WHO's routine immunization schedule, PCV is not included in National Immunization Program in Bhutan due to substantial financial burden for the government in PCV introduction and implementation in the country. Since, Bhutan has been upgraded to become low-middle income country, it is no longer eligible for GAVI support for PCV. So it becomes important for Bhutan government to carefully consider introducing PCV in the country and to evaluate if it is good value for money or not. This policy study was recommended from high level committee meeting and National Committee for Immunization Practices (NCIP) in Bhutan in order to provide evidences to the Bhutanese decision makers to make informed decision which would not only reduce child mortality and morbidity but also identify value for money and budget implications for PCV implementation. Therefore HITAP was requested by the WHO to conduct an Economic Evaluation (EE) study of introducing PCV in Bhutan.

1. Bonner K, Welch E, Elder K, Cohn J. Impact of Pneumococcal Conjugate Vaccine Administration in Pediatric Older Age Groups in Low and Middle Income Countries: A Systematic Review. PloS one. 2015;10(8):e0135270. PubMed PMID: 26332848. Pubmed Central PMCID: 4557974.

Health Intervention and Technology Assessment Program (HITAP) has worked with several local and international partners to support Health Technology Assessment (HTA) developments in many Low-Middle-Income Countries (LMICs) through various initiatives. In terms of collaborative works, HITAP has been able to build projects in particularly areas such as building technical capacity and providing support, conducting economic evaluation studies and Health Technology Assessment (HTA) institutionalization through the support from local partners in those countries. In Thailand, HITAP has an important role in supporting decision making by generating key HTA evidences for Universal Health Coverage (UHC) and the National List of Essential Medicines (NLEM). Like many other transitional LMIC, Bhutan has also achieved UHC and has been striving to sustain the coverage. In 2008, Bhutan has officially established a Essential Medicine and Technology Division (EMTD) under Ministry of Health (MOH) which is the only HTA unit in the country responsible for providing evidences to the decision makers in Bhutan by assessing health technologies or interventions. This current EE study would be the second collaborative work between HITAP and MOH in Bhutan. The first visit was in 2013 to conduct another project titled EE of WHO Package of Essential Non communicable disease (WHO PEN).

This is first visit for the introduction of PCV in Bhutan and the main scope of the visit was to build technical capacity for the Bhutanese research team conducting this study. The objectives were to come up with a clear proposal for the study, drafting methodology including clear data collection plan and finalizing the timeline for the study. It was also decided during this visit that there will be second visit in which Bhutanese research team will come to HITAP for the data analysis tentatively around end of March 2017. And finally the third visit was decided to be held on tentatively May-June 2017 to conduct stakeholder consultation meeting and to discuss the final report and publication.

Summary of the visit

The list of participants can be found in *Appendix 1* while the agenda of the visit can be found in *Appendix 2*.

Details of daily activities can be found in *Appendix 3* and the activities for the next steps can be found in *Appendix 4*.

This 3-day workshop was our first visit and it was to strengthen the technical capacity for the Bhutanese research team on PCV model, fine-tuning the proposal, methodology and clear data collection plan. There were altogether 16 participants for the workshop; 12 from Bhutanese research team and 4 from HITAP as mentioned in Appendix 1. The first day was to get a general idea from the Bhutanese team about the rationale for this study, why is it being conducted, where the policy question came from, current vaccination scenarios in the country. Apart from this, it was also focused on sharing the background of EE on PCV, to introduce markov model and probabilistic sensitivity analysis. An exercise on Thai PCV model was performed, so that the participants could understand the economic evaluation model and its parameters and also help identify which parameters can be transferred from Thai PCV model into this study based on Bhutanese context. The discussion session also helped HITAP to understand the current situation in Bhutan and feasibility of this study. Issues regarding the choice of perspectives were raised in the first day and it was decided that government perspective will be followed for this study. To move ahead with the plan for this visit, the discussion on the number of researchers was done. There were six Bhutan researchers and had not conducted this model before so there were concerns on the feasibility of the study. However, the agreement was such that HITAP research team with local researchers would come up with a clear plan to conduct this study before leaving. Moreover, the first was to give the Bhutan research team a general idea on conducting EE study and help move forward with finalizing methodology of the study.

The second day was focused on costing methods involved in EE studies and to introduce cost components for PCV introduction after which it would be easier for research team to identify potential costs that needs to be incorporated in the study. HITAP also gave an idea on data transferability from Thai PCV model through experience sharing from Thailand and Philippines. It was to guide the Bhutan researchers about scoping down the methodology and identify parameters (from Thai PCV model) that can be transferred for this study which are context specific and feasible to collect in Bhutan. The discussion session was able to raise a lot of pressing issues in terms of data availability and transferability. The Bhutanese research teams brainstormed together to analyze if this study is going to be using government perspective or societal perspective, and it was decided that this study will use

government perspective since the policy question actually came from the national level policy makers. For the brainstorming session the participants were divided into 3 groups to list out the parameters, those that can be used in this study in terms of Bhutanese context. Following that, the next step was to identify the sources from which those parameters will be extracted, i.e. either from transferring data from Thai PCV model, primary data collection or conducting meta-analysis through systematic review and literature reviews. Finally, the agreement was reached and decided that this study would use cost-utility analysis and PICO was finalized. Population would be infants, intervention will be PCV- 10 or PCV – 13 (3 doses), Comparator will be no vaccination and health outcome will be Quality-Adjusted Life Year (QALY). It will use government perspective and the result will be in terms of Incremental Cost Effectiveness Ratio (ICER). One way and Probabilistic Sensitivity Analysis (PSA) method will be used for this study.

The last day was focused on finalizing a clear data collection plan including identifying the list of data enumerators responsible for conducting this study, discussing the challenges and barriers that may arise during data collection process and coming up with solutions to overcome the challenges. It was discussed that there's a lack of access to hospital data since hospitals in Bhutan use paper based records (no online database) so it becomes difficult to get access to relevant healthcare costs. Also another challenge was to get access to online databases to conduct meta-analysis including systematic reviews or literature reviews.

It was agreed that parameters like Incidence and Death rate, Vaccine Efficacy, Herd Protection, Serotype coverage, Duration of vaccine protection, Vaccine coverage, Treatment cost and Vaccination program will be used in this study for both data collection and systematic and literature review.

The next steps following this visit were also discussed including a clear stakeholder consultation meeting plan and identifying the list of stakeholders to be involved which was decided to be held on the last visit tentatively around May-June, 2017. The second visit will be made by Bhutanese research team to HITAP around the end of March, 2017 for the purpose of data analysis after the researchers finish collecting data in Bhutan.

Appendices

Appendix 1: List of participants

#	Name	Designation	Office
1	Sonam Phuntsho	Planning Officer	Policy and Planning Division
2	Tshering Wangdi	Planning Officer	Policy and Planning Division
3	Tshewang Dorji	Information and Media Officer	Bhutan Medical and Health Council
4	Dopo	Statistician	Health Information Management System
5	Sangay Phuntsho	Program Officer	Vaccines Preventable Disease Program
6	Kinley Wangchuk	Program Officer	Quality Assurance and Standards Division
7	Dechen Choiphel	Chief Program Officer	Essential Medicines and Technology Division (EMTD)
8	Kinley Dorji	Deputy Chief Program Officer	Health Technology Assessment Section, EMTD
9	Deepika Adhikari	Senior Program Officer	Health Technology Assessment Section, EMTD
10	Pempa	Program Officer	Health Technology Assessment Section, EMTD
11	Mongol Singh Gurung	Research Officer	Health Research and Epidemiology Unit
12	Rixin Jamtsho	Deputy Chief	Quality Assurance and Standardization Division
13	Wantanee Kulpeng	Researcher	Health Intervention and Technology Assessment Program (HITAP)
14	Suthasinee Kumluang	Researcher	Health Intervention and Technology Assessment Program (HITAP)
15	Sarayuth Khuntha	Researcher	Health Intervention and Technology Assessment Program (HITAP)
16	Sneha Rajbhandari	Project Associate	Health Intervention and Technology Assessment Program (HITAP)

Appendix 2: Agenda of the workshop

22nd November, 2016		
Time	**Scheduled Activity**	**Responsible person**
9.00-9.15	Introduction of workshop and participants	Bhutanese delegates and All participants
9.15-9.40	Brief Presentation on: • Background and burden of disease • Current situation of PCV in Bhutan • Policy questions • Expected outcomes from this workshop • Result generalizability	Bhutanese team
9.40-10.00	Q&A	All
10.00-11.00	• Concept of Economic Evaluation • Economic Evaluation on PCV	Wantanee Kulpeng
11.00-11.15	Coffee break	All
11.15-12.00	Demonstration of model structure (Markov Model)	Wantanee Kulpeng
12.00-13.00	Lunch	All
13.00-16.00	• Probabilistic model • Exercise on Markov Model	Wantanee Kulpeng (Facilitator: Sneha and Sarayuth)
23rd November, 2016		
9.00-10.30	Cost component of vaccine introduction	Suthasinee Kumluang
10.30-10.45	Q&A	All
10.45-11.00	Coffee break	
11.00-12.00	Data transferability: experience from Thailand and Philippines	Wantanee Kulpeng
12.00-13.00	Lunch	Lunch

13.00-15.00	• Scope of methods for Economic Evaluation of PCV • Identify parameters used in the model - Parameters that can be transferred from Thailand - Parameters specified to Bhutan	Participants divided into 3 groups (Brainstorming session)
15.00-15.30	• Presenting the methods and parameters of EE of PCV (by both groups)	Bhutanese team
15.30-16.00	Discussion on methods and parameters	All
24th November, 2016		
9.00-11.00	Data collection plan • Name of parameter • Source of parameter i.e. Lit. review, primary data collection, analysis of database, expert opinion • Identify responsible person	Bhutanese team
11.00-12.00	• Discussion on research barriers • Discussion on overcoming research limitations	All
12.00-13.00	Lunch	
13.00-14.00	Finalize data collection plan	All
14.00-15.00	Planning for expert consultation meeting	All
15.00-16.00	Next steps • Revised proposal • Activities for 2nd and 3rd visits • Discuss on TOR	All

Appendix 3: Daily Summaries

Day 1: Tuesday November 22, 2016

Chief program officer of EMTD, Mr. Dechen Choiphel welcomed the HITAP team and offered an opportunity for all participants to introduce themselves. The participants came from different department such as Essential Medicines and Technology Division (EMTD), Policy and Planning Division (PPD), and Vaccine Preventable Diseases Program (VPDP). Mr. Kinley Dorji, Deputy Chief Program Officer from EMTD, gave a background for this study, purpose and expected outcomes of this workshop which was to strengthen the technical capacity of research team to conduct economic evaluation of PCV in Bhutan. Mr. Dorji highlighted that this study will be very significant since there hasn't been an EE study in Bhutan so far. EMTD was proposed to conduct this PCV study for which the recommendation came from high level committee meeting as well as NCIP in MOH in order to provide evidences to national level policy makers to make informed decision on introduction of PCV. To give a more clear rationale of the study, current scenario of PCV in Bhutan, and why this study is necessary, Mr. Sangay Phuntsho, from department of Vaccines Preventable Disease Program, presented on pneumococcal disease burden and overview of health system in Bhutan. Pneumonia is the 7th most common cause of death in Bhutan, but no study has been done in Bhutan to ascertain the disease burden. Bhutan achieved Universal Child Immunization in 1991 and it's the first country in region that implemented HPV program.). Since WHO has recommended to include PCV in all national immunization programs (NIP), introducing new vaccines has become a key priority area for national immunization policy in the country. Bhutan is not eligible for GAVI Alliance, therefore it becomes important for Bhutan government to carefully consider introducing PCV in the country and to evaluate whether it represents good value for money or not. Mr. Sangay presented the policy questions of the study mentioned below:

1. Will it be cost-effective to introduce PCV into routine immunization program in Bhutan?
2. What could be the:
    a. Potential treatment costs averted by the vaccine due to pneumococcal disease?
    b. An incremental cost to the immunization system/program?
    c. ICERs for per QALY gained?

Following the presentation, discussion were raised and HITAP asked if Bhutan has it's own cost-effectiveness threshold for determining the cost-effectiveness of introducing new vaccines. It was discussed that since Bhutan doesn't have their own threshold, , the best alternative would be to use 1 to 3 times GDP per capita as WHO recommendation.

There is the market price list of PCV in Bhutan that PCV 10 costs Nu1399 (USD20) and PCV 13 costs NU3800 (USD56). Continuing the workshop, Ms. Wantanee Kulpeng gave presentation on the concept of economic evaluation on PCV. In order to introduce new drugs/vaccines in resource limited countries, HTA is an important tool to provide evidences in terms of cost-effectiveness of innovative and new health technology. She also provided the overview of economic evaluation which is to compare cost and health outcomes. A typical EE study is based on two criteria i.e. if there a comparison of two or more alternatives and if both costs and health outcomes are examined. There are four types of economic evaluation including cost-minimization analysis (CMA), cost-effective analysis (CEA), cost-utility analysis (CUA), and cost-benefit analysis (CBA). The most common methods are CEA and CUA, however, CUA allows to compare across disease because health outcomes can be transferred into QALY or Disability-Adjusted Life Year (DALY), whereas CEA requires very specific health outcomes in terms of natural units such as mmHg, and µL.

The participants wanted to know which methods is applicable while comparing the laboratory tests in Bhutan and outside, to which HITAP clarified that the selection of methods depends upon the outcome measured. And since there is no different outcomes for this above mentioned scenario, only cost-cost comparison, CMA would be the preferred choice of method. The Bhutan research team also concerned on how to convert the sequelae into costs, to which HITAP advised to use life-time cost because squealae e.g., epilepsy and mental retardation are chronic disease. For the cost of infectious disease, it will be calculated as cost per episode. Regarding the perspective chosen for this study, it was decided that since the policy question came from the national level decision makers, government perspective will be chosen.

Moving on, Ms. Wantanee Kulpeng gave a presentation on economic evaluation of PCV 10 and 13 in Thailand, introducing that PCV is developed to prevent the common *S. Pneumonia* serotypes among young children. Moreover, she presented the benefits of PCV including direct (vaccine efficacy) and indirect (herd) effects. There are three PCV regimens: 3+1, 3+0 and 2+1. The Bhutan team expressed their preference for 3 doses, may be 2+1 or 3+0.

The analysis for CUA is demonstrated as:

- QALYs = utility score (1-0: 1-full health, 0-death) * life years gained
- ICER = incremental costs/incremental outcomes
- Accept the new technologies (vaccines) if ICER <= cost-effectiveness threshold
- Sensitivity analysis is required when conducting the CUA, in order to deal with the uncertainty of parameters.
    - One-way sensitivity analysis

- Threshold analysis
- Probabilistic sensitivity analysis (PSA)

It was decided that PSA will be used for this study. While presenting the Markov Model that was used in Thai PCV study, she emphasized on three main parameters: transitional probabilities (epidemiological data i.e. incidence, mortality, and the occurrence of sequelae, and vaccine benefits), cost parameters (direct medical/non-medical costs) and utility parameters (QALY). Similarly she also shared the methodology, results, discussion and conclusion for Thai study as well as policy recommendations. She suggested the Bhutan research team to consult with stakeholders such as those who work in hospitals or NIP as they might encounter complicated issues along the way.

In addition, she talked about vaccine efficacy and the herd immunization. Bhutan team wanted to know if they have to study the whole population or only children under 5 years of age. HITAP clarified that although infants are vaccine recipient, we cannot ignore the effect of the vaccine as herd protection, therefore, we should consider the most relevant population.

In the afternoon, Bhutan team expressed their concern regarding the lack of enough researchers for this study and expertise on EE study. It was decided by the end of this visit, there must be a clear methodology and data collection plan so that we can identify number of researchers. All analysis of EE will be performed in the next visit, with the technical support of HITAP. Another concern raised was about conducting data collection from EQ-5D as there is no version in Bhutanese language. Since majority of people in Bhutan can speak and understand English, the team wanted to know if they can use the English version of EQ-5D. HITAP advised that if it's feasible and relevant to conduct utility score using EQ-5D English version; however, it requires permission from EuroQoL. Later in the afternoon, the participants were led to conduct an exercise on PCV model in Thailand. Ms. Wantanee presented the principle of probabilistic model before doing an exercise which included preparing the model input parameters, performing a probabilistic sensitivity analysis, and calculating ICERs consisting of six steps:

1. Specifying the variable distributions
2. Preparing the variables for calculation
3. Calculation of mean and standard error (SE), or alpha (α) and beta (β)
4. To generate a random draw from the selected distribution
5. Running and analyzing simulations by Macro function
6. Calculating ICERs using probabilistic values

Day 2: Wednesday November 23, 2016

In the morning, Ms. Suthasinee Kumluang gave a presentation on costing in health economic evaluation and an overview of types of cost i.e. direct medical costs (diagnosis, treatment, rehabilitation), direct non-medical costs (transportation, foods, informal cares), and indirect costs (productivity losses due to illness). In addition, she demonstrated perspectives used in the EE, description of costs classified by study perspectives, how to calculate discounting cost that is a method used to adjust future cost and benefits to the present market value. Ms. Suthasinee's presentation was basically to help understand the cost components so as to identify what potential healthcare relevant costs needs to be incorporated in this study. She introduced discount rate and Consumer Price Index (CPI) to the research team following which the participants wanted to know the difference between CPI and inflation rate. HITAP clarified that CPI is a measure of the average change over time in the prices paid by urban consumers for a market basket of consumer goods and services. Whereas inflation is overall general upward price movement of goods and services in an economy. For instance,

Inflation Rate in Year 2 = ((CPI in Year 2 - CPI in Year 1)/CPI in Year 1) x 100

CPI is in fact used to calculate the actual inflation rate. Moving on, the research team wanted to know the recommended exact percentage of discount rate, to which HITAP advised that the rate is different among nations, however WHO recommends for 3.5%. It needs to be in consensus within the country while it's also important to discuss on the perspective that would lead to the cost components. As in Thailand, societal perspective was used based on the THAI HTA guideline, while the Philippine used government perspective. Since it was decided within Bhutan team that this study will use government perspective, direct medical costs and other costs will be included for this study. It was clarified that in order to see 1) how much cost will be increased due to introducing PCV into NIP, and 2) how much treatment cost will be reduced as a result of introducing PCV program, Budget Impact Analysis needs to be conducted.

After discussion on cost components, Ms. Wantanee presented the examination of the utility of data transferability between countries across Asia. She gave the concepts of data transferability, and different factors involved in different county settings for the participants to better understand the challenges of conducting CUA in different settings. In addition, she showed the case study from Thailand and the Philippines. It was to make the participants clear regarding what data to transfer from another PCV model in terms of country context. In case of Bhutan, the time duration is six months, thus, it could be one of the methodological challenges so there should be a clear data collection plan. The transferable data, moreover, was discussed in detail whether they can be transferable or not. It was decided following the discussion that, baseline risk, treatment effect, utilities, and Markov model can be transferable, whereas resource use, unit costs, and cost-effectiveness cannot be transferable. This result needs to be upon the consensus in the country. The approach of data transferability depends on the nature of the data available and decision-makers'

requirements and needs in the country. However, transferring data has the potential to save time and resources.

The research team were then divided into three groups in order to discuss the scope of method and identify the parameters used in the model as well as considering the transferability of data from Thailand into this study given the relevancy of Bhutan context. During this brainstorming session, all three groups were given to read the articles (Kulpeng and Haasis), after which the groups had to discuss which parameters can be transferred into Bhutan with supporting reasons.

Before the afternoon session there were some concerns raised regarding data collection using EQ-5D and Bhutan team expressed their decision to use this tool for getting utilities score. HITAP suggested to use EQ-5D-Y English version which is practical for children aged 8-12. Although, meningitis and bacteremia mostly occur among children aged lower than 5, no utility instrument available for those who aged below 5 years. It is necessary to interview children aged >= 8 years or proxy (i.e. parents of children aged >= 8 years); by the way, it is hard to find cases aged 8 years and above. For the cost data collection, proper training for data enumerators is required and questionnaire needs to be developed.

Shortly before the afternoon session, HITAP had a chance to speak with Director General of Department of Public Health, Dr. Pandup Tshering. He expressed the importance of this study in Bhutan as a good initiative for a nationwide impact and also appreciated the collaborative works between MOH Bhutan and HITAP.

In the afternoon three research groups presented the list of transferrable parameters. After a series of intensive discussion and brainstorming, it was decided that sequelae and utilities are transferable, whereas incidence/death rates, treatment effects and all costs cannot be transferred.

Furthermore, HITAP summarized the tentative approach as listed in Table 1.

Table 1: A tentative approach for economic evaluation of PCV in Bhutan

Type of Economic evaluation	Cost-utility analysis (CUA)
Interventions	PCV10 or PCV13, 3 doses
Comparator	No vaccination
Target population	Infant
Perspective	Government perspective
Analytical approach	Markov model with 1 year length of cycle
Time horizon	Lifetime (Max. 100 years)
Discount rate	3.5% per annum both cost and outcome (Sensitivity Analysis=0%,6%)
Health outcome	Quality-Adjusted Life Years (QALYs)
Costs	Ngultrum year 2016
Results	Incremental cost-effectiveness ratio (ICER)
Uncertainty analysis	One-way and probabilistic sensitivity analyses

In addition, a clear data collection plan was also developed as mentioned below:

Data collection plan

- Epidemiological data
  - Incidence/Death rates will be collected from national database for EPI program, Health Management Information Service (HMIS) and three referral hospitals. If each source presents different data, the HMIS will be first considered.
  - Sequelae will be transferred from elsewhere.
- Treatment effects

  - Vaccine efficacy will be conducted as systematic review/meta-analysis if there are more than one research.
  - Herd protection (reduction in prevalence in unvaccinated population) will be done through systematic review.
  - Serotype coverage will be collected from Royal Center for Disease Control (RCDC)/ National Referral hospital
  - Duration of vaccine protection will be done through systematic review.
  - Vaccine coverage will be gathered from EPI program
- Direct medical costs
  - Treatment costs will be collected from medical record or asked physicians from three referral hospitals (primary data) (Jigme Dorji Wangchuck National Referral Hospital – JDWNRH – one of referral hospitals) and Department of Medical Supplies and Health Infrastructure (DMSHI)
  - Vaccination program (vaccine price, supply cost, setup cost etc.) will be gathered from EPI program.
- Utility will be transferred from other studies.

Day 3: Thursday November 24, 2016

The morning session was focused on developing the list of responsible person for each data collection method, and fixing the timeline for each methods. Each responsible person were then asked to list down the source for collecting costs/data from main parameters including epidemiological data, treatment effects, direct medical cost that cannot be transferred from other models. In addition, barriers and limitations were discussed based on data collection method. It was discussed that if some data like vaccine efficacy or herd protection are not retrievable or if not available in the country, it is possible to conduct systematic review. The result of the discussion is shown on Table 2.

Table 2: Timeline and data collection plan for each data collection method

Activities	Responsible person	Timeline in Month			
		Dec	Jan	Feb	Mar
Incidence and Death rate	Mr. Pemba (Team Leader), Mr. Sangay Phuntsho, Mr. Mongal Singh Gurung, Mr. Dopo, Mr. Kinley Dorji	Seek ethical clearance	Data Collection		Data analysis
Vaccine Efficacy	Mr. Kinley Dorji (TL), Mr. Kinley Wangchuk, Mrs. Deepika Adhekari	Systematic review			
Herd Protection	Mr. Pemba (TL), Mr. Sangay Phuntsho, Mrs. Deepika Adhikari		Literature review		
Serotype coverage	Mr. Rixin Jamtsho (TL), Mr. Tshewang Dorji	Seek ethical clearance	Data collection		Data analysis
Duration of vaccine protection	Mr. Kinley Dorji (TL), Mr. Rixin Jamtsho	Literature review			
Vaccine coverage	Mr. Sangay Phuntsho (TL), Mr. Dopo		Literature review		
Treatment cost	Mr. Kinley Dorji (TL), Mr. Tshering Wangdi, Mr. Sonam Phuntsho	Data Collection		Data analysis	
Vaccination program	Mr. Sangay Phuntsho (TL), Mr. Mongal Singh Gurung, Mr. Dopo		Literature review		

In the afternoon, each researcher team drafted the methodology for each parameter of data collection plan. The summary of the methodologies is listed in Table 3.

Table 3. List of parameters and methodology to collect data

Parameters	Data collection and review methods
Treatment cost	• Salary of health worker (Doctor and Nurses) • List out the time and activities of each hospital wards • Drugs and medical supplies • ICU cost • Laboratory • Average length of stay and IPD admission costs • OPD cost per visit • Use existing cost for pneumonia (convert from 2010 to current time) • Collect separate cost for each sequelae
Herd Protection	• Literature review • Keywords: PCV, herd, protection • Inclusion criteria: Countries that have already included PCV, at least 1 year of implementation • Database: Hinary and Pubmed through Hinary, Google Scholar • Question: % of reduction in unvaccinated population, from which PCV?

Vaccine efficacy	• Systematic review
	• PICO
	  ○ P: Infants
	  ○ I: PCV 10 and 13
	  ○ C: No vaccine
	  ○ O: Vaccine efficacy
	• Key terms: PCV, efficacy, infant*, Terms from PICO
	• Database: Hinary and Pubmed through Hinary, Google Scholar
	• Critical appraisal: CONSORT, SIGN (Standard checklist)
	• Inclusion criteria: PCV 10 and PCV 13
	• Exclusion criteria: disease specific population

While discussing throughout the workshop, some of the challenges and barriers of conducting this study in Bhutan are the lack of access to hospital data since hospitals in Bhutan use paper-based records (no online database) so it becomes difficult to get access to relevant healthcare costs. Moreover, some epidemiological data such as S.pneumonia isolates, pneumococcal meningitis incidence, and sequalae are not available. In this case, HITAP advised that Bhutan research team might consider transferring data from a similar setting or using expert opinion in case of unavailability of data. Also, it was suggest to conduct expert consultation meeting to check whether the methods and parameters used in the model are valid. Another challenge is to get access to online databases to conduct systematic reviews or literature reviews. In this case it was agreed that HITAP will help retrieve the full papers once the Bhutan research team has the list of inaccessible papers. The other challenge is the lack of technical expertise in conducting analysis for which it was discussed that HITAP will help guide the research team during analysis and throughout the conduct the study.

Moving ahead, Ms. Wantanee presented on how to conduct an expert consultation meeting in order to obtain unavailable data as well as to conduct stakeholder's consultation meeting, how to approach them and when to conduct. The list of stakeholders identified for this project are as follows:

- General practitioner
- Specialists (pediatric infectious disease, neurology)
- Epidemiologist
- EPI representative
- Health economic
- Policy maker
- WHO/UNICEF representative
- Bhutan Health Trust Fund

The research team would send letter/emails to identified stakeholders and would be conducted on the third visit to MOH Bhutan tentatively around May-June.

During the end, there was discussion between MOH, WHO and HITAP on Terms of Reference (TOR). The deliverables will be explicitly mentioned in the final proposal but there won't be any contract in the form of TOR. Some of the deliverables were revised and will be incorporated in the proposal.

Appendix 4: Next steps

After the workshop had been finished, the next step was discussed including the 2nd and 3rd visits

S. No	Activities	Remarks	Tentative deadline
1.	Prepare final proposal	Mr. Kinley Dorji (Focal person)	29th Nov
2.	HITAP submits the revised proposal to research team	Comments from HITAP	2nd Dec
3.	Research submits the proposal to WHO	Finalize the proposal	5th Dec
4.	Research Ethics Board of Health (REBH) Clearance	Getting the ethical clearance	1st week of January
5.	Data analysis	Research team to conduct data analysis for treatment cost	1st week of March
6.	Submit the list of parameters (model) to HITAP		2nd week of March
7.	Second visit to HITAP by the research team (5 days) • Presentation of the results • Policy brief	Conduct data analysis	Third week of March
8.	Third visit including stakeholder consultation meeting and finalizing	To be confirmed	Tentatively May-June