Economic Evaluation of Rotavirus Vaccine

December 2018 – August 2019

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Abbreviations

Bhutan Health Trust Fund	BHTF
Disability-adjusted life years	DALY
Department of Medical Services	DMS
Essential Medicines and Technology Division	EMTD
Gross Domestic Product	GDP
Health Intervention and Technology Assessment Program	HITAP
High-Level Committee	HLC
Health technology assessment	HTA
Incremental cost-effectiveness ratio	ICER
International Decision Support Initiative	iDSI
Low- and middle-income country	LMIC
London School of Hygiene and Tropical Medicine	LSHTM
Mahidol-Oxford Tropical Research Unit	MORU
Ministry of Health, Bhutan	MoH
Pneumococcal Conjugate Vaccine	PCV
Prince Mahidol Award Conference	PMAC
Probabilistic Sensitivity Analysis	PSA
South-south knowledge exchange	SSKE
Under-five years of age	U-5
Water, health, and sanitation programmes	WASH
World Health Organization	WHO

Table of Contents

Executive Summary

Bhutan is a rapidly growing economy that is transitioning from international donor support. As such, the country is looking for ways to ensure that they continue to provide the adequate services and support for their population in a rational and sustainable manner. Bhutan has begun using health technology assessment (HTA) as one of the priority-setting tools in the realm of healthcare. Previous collaborations, such as the economic evaluation of pneumococcal conjugate vaccine (PCV) for national implementation, with the Health Intervention and Technology Assessment Program (HITAP) has helped to pave the way for the creation of a process within which evidence can be used for policymaking.

At the end of 2018, the High-Level Committee (HLC) of the Bhutanese Ministry of Health (MoH) commissioned an economic evaluation of rotavirus vaccine to explore the options for Bhutan. There is a high disease burden of diarrhea in the country, which is especially problematic for children under the age of 5 (U-5). To reduce the disease burden of diarrhea in the country, the MoH considered introducing a vaccine and commissioned an economic evaluation to assess the economic feasibility of this intervention. The study was conducted over a period of eight months with support from PATH, Seattle, and the International Decision Support Initiative (iDSI). The lead investigator was the Essential Medicines and Technology Division (EMTD) of the Department of Medical Services (DMS) with technical support from PATH, HITAP, and the Mahidol-Oxford Tropical Research Unit (MORU). Two country visits and one study visit to the HITAP offices were facilitated. With the extensive use of local data validated by stakeholders, the study found that rotavirus vaccine was cost-ineffective in the Bhutanese setting at a threshold of 0.5 Gross Domestic Product (GDP)/capita (US$ 1,537 = Nu. 111,908). However, the most promising vaccines among those assessed in terms of cost-effectiveness, ROTAVAC and ROTASIIL, were only cost-effective at a higher threshold. The study also found that human resource needs for nurses and health assistants increased while those for more specialized experts such as doctors and pediatricians decreased.

This study, along with other activities conducted, can help Bhutan to further institutionalize a systematic process for decision-making. During the study, trainings and sensitization workshops at different levels were conducted to increase stakeholders' knowledge and understanding of the use of evidence and especially HTA. This also helped to generate interest in HTA use and potentially further create demand and supply of researchers to conduct the studies. Stakeholder acceptance and buy-in are key for the growth of this process in Bhutan.

Introduction

The Kingdom of Bhutan (hereafter: 'Bhutan') provides free health care to its citizens through a system that is predominantly funded and managed by the national and local governments. The constitution of Bhutan stipulates that the government must ensure a safe and healthy environment and "provide free access to basic public health services in both modern and traditional medicines".[1] The Ministry of Health (MoH) is responsible for shaping health policy, organizing health services, ensuring quality, and providing technical support to district-level health offices.[2]

Bhutan's growing economy has led some development partners to end their support, increasing the government's financial burden and the need for financial sustainability of the health sector. While Bhutan continues to receive financial and programmatic support from foreign development partners, its transition from Gavi support in 2016 has returned the burden of vaccine funding to the government. Funding for vaccines is currently the responsibility of the Bhutan Health Trust Fund (BHTF), a government-run entity aiming to "eliminate financing uncertainties for [...] Primary Health Care Services out of the income generated from the investment of the Fund" and "achieve self-reliance in the Primary Health Care Sector" (Bhutan Health Trust Fund, 23 December 2018).

In order to improve financial sustainability of the health sector, Bhutan has been seeking to improve its capacity for conducting health technology assessments (HTA). Use of HTA ensures that health funding decisions are evidence-informed, leading to resources being used efficiently by focusing on funding interventions that offer value for money. In Bhutan, the division responsible for the use of HTA is the Essential Medicines and Technologies Division (EMTD) under the Department of Medical Services of the Bhutanese MoH.

In Thailand, HTA is a well-established practice, and is used to guide policy choices on the benefits offered in its social health insurance schemes. Thailand uses HTA to evaluate the cost-effectiveness of healthcare interventions to ensure efficient resource allocation, negotiate drug prices with companies, evaluate the feasibility of an intervention, and implement evidence-informed policies. In recent years, HTAs are also increasingly recognized globally as an essential part of the priority-setting process to ensure decisions are made fairly, efficiently, and sustainably for the health system.

[1] National Health Policy Ministry of Health Bhutan

[2] Thinley, S., et al. "The Kingdom of Bhutan health system review." (2017).

In 2016-17, HITAP[3] supported the EMTD in its first economic evaluation study, which looked at pneumococcal conjugate vaccine (PCV), and its results led to policy changes. With support from the Health Intervention and Technology Assessment Program (HITAP), the International Decision Support Initiative (iDSI), and the World Health Organization (WHO), EMTD conducted an economic evaluation of PCV in 2016-2017. Its findings deemed the vaccine to be good value for money, and resulted in the inclusion of the vaccine in the national immunization programme in 2018.[4]

In addition, HITAP provided a variety of other types of support—including training, workshops, and network strengthening—to establish HTA as a priority-setting mechanism in Bhutan. For all study-related engagements, HITAP provided technical support as a form of 'on-the-job' training; Bhutanese researchers worked side-by-side with more experienced researchers from HITAP in order to improve their understanding of and competence in the study process. These side-by-side efforts were supplemented with formal trainings on conducting economic evaluations, a key step in the conduct of HTA. Additionally, to also support the institutional uptake of HTA, HITAP delivered awareness raising workshops with various stakeholders and connected them with like-minded international partners.

In 2017, the High-Level Committee (HLC) of the Bhutanese Ministry of Health (MoH) requested for an economic evaluation of rotavirus vaccines, and a formal request for technical support from HITAP on this study was made. This is a positive development in the awareness and acceptance of the use of evidence to support decision-making. As the MoH was eager to introduce the vaccination into its benefits package, the HLC wanted to better understand its cost-effectiveness in order to make an informed decision on which vaccine variant would be the best option for Bhutan. A 'whole of society' approach meant that this decision would not be made just on price justifications, but also other considerations, such as the human resources required and their related feasibility. These developments prompted the Bhutanese government to request support from the Thai Ministry of Public Health (MoPH) for evaluating the implementation of rotavirus vaccination.

Consequently, EMTD and HITAP partnered once again in late 2018 to work on an economic evaluation of rotavirus vaccines. This project is supported by PATH, Seattle, a non-profit organization working to advance health globally through the improvement of systems and technologies, and iDSI, a global network of institutions that aims to increase the value and impact of health spending and decision-making. Encouragingly, the BHTF and the Bhutanese MoH provided matched support to the conduct of the study, showing commitment to evidence-informed decision making in health. HITAP also involved an expert from the Mahidol Oxford Tropical Medicine Research Unit (MORU), an academic unit based in Bangkok with extensive experience

[3] The Health Intervention and Technology Assessment Program (HITAP) is a semi-autonomous research unit under the Thai Ministry of Public Health and is primarily responsible for HTA-informed advice.
[4] Pneumococcal Conjugate Vaccines Now Introduced in Bhutan, 23 December 2018

in conducting clinical research and performing mathematical modelling. The complete list of members involved in this study collaboration is given in Table 1.

Table 1: Members of the study collaboration

Name	Organisation
Dr. Wanrudee Isaranuwatchai	Health Intervention and Technology Assessment Program (HITAP), Thai Ministry of Health
Dr. Pritaporn Kingkaew	Health Intervention and Technology Assessment Program (HITAP), Thai Ministry of Health
Dr. Nantasit Luangasanatip	Mahidol Oxford Tropical Medicine Research Unit (MORU)
Ms. Alia Luz	Health Intervention and Technology Assessment Program (HITAP), Thai Ministry of Health
Frederic Debellut	PATH, Seattle
Pempa Pemba	Essential Medicines and Technology Division (EMTD), Department of Medical Services, Bhutan Ministry of Health
Deepika Adhikari	Essential Medicines and Technology Division (EMTD), Department of Medical Services, Bhutan Ministry of Health

This report serves as a summary of HITAP's activities in Bhutan and with the country partners to support the study development as well as advancing HTA capacity and institutionalization in the country. The report is structured into three parts: summary of activities, details of the rotavirus study and the support for HTA development in the country. The report concludes with the next steps with supporting information in the appendices.

Summary of Activities

The study proposal was developed and presented to stakeholders to discuss the data inputs and plan for the study in December 12-14, 2018. The HITAP team, along with partners from the MORU and PATH, supported the team in developing and presenting the proposal to stakeholders. The team identified and explored the potential parameters and models for use in the study. Stakeholders from the national referral hospitals, the National Committee for Immunization Practices (NCIP), community healthcare unit, procurement division, drug regulatory authority, Vaccine Preventable Disease Program (VPDP), Health Information Management Systems (HMIS), and the Royal Center for Disease Control (RCDC) attended the meeting and provided their comments (see Appendix 2: Summary Minutes of Stakeholder Consultations for more information on the minutes of the meeting).

In January 28 to February 8, 2019, the Bhutanese colleagues came to Thailand to continue working on the study alongside a training workshop. The team from Bhutan completed the study proposal and the first iteration of the Excel model required for the economic evaluation. To facilitate this, trainings for economic evaluation overall, costing, systematic reviews, outcome measurement, and budget impact and human resource analysis were provided over the two-week period. Study parameters such as health-seeking behavior, incidence, program costs, and vaccine prices were discussed in detail. A study schedule outlining the main activities and milestones was prepared (see Appendix 3: Outputs from the Study). In addition, the team joined the annual Prince Mahidol Award Conference (PMAC) in Bangkok to participate and share their experience of setting up a priority-setting mechanism such as HTA in the country. They were able to benefit from learning about the various issues surrounding non-communicable diseases, which was the theme of the conference. The team visited the HITAP office to learn about the methods for the studies. The partners detailed their experiences in the following article: Opportunities and learning economic evaluation in Thailand.

Between February and May 2019, HITAP and MORU provided remote support on data collection for the model and facilitated a south-south knowledge exchange (SSKE) meeting. Weekly and bi-weekly calls were coordinated to discuss the progress of the study and plan next steps. During this period, the initial draft of the policy brief and the HTA report were prepared along with the completion of the parameter inputs and model improvements. HITAP also supported the Bhutanese colleagues to join the HTAsiaLink (a network of HTA agencies in Asia) annual conference in South Korea in April 2019 where they participated in a SSKE event on the challenges of institutionalizing HTA.

In May 2019, HITAP and colleagues returned to Bhutan to support the final analysis and stakeholder consultation for the rotavirus vaccine study as well as plan for the dissemination of the study findings. The study found that rotavirus vaccine is not cost-effective at the 0.5 GDP/capita threshold; however, two of the options, ROTAVAC and ROTASIIL, are cost-effective at the 1 GDP/capita threshold (see study details in the next section). In terms of the human resource requirements for introducing the vaccine, there is potential for reducing the

specialists required, though there the resources needed for less-specialized expertise like nurses and health assistants increases significantly. Administering the most promising vaccine in terms of its cost-effectiveness, ROTASIIL would also require additional training for staff since it is not sold in a liquid form at the moment. The results were accepted by the stakeholders (which included primarily the same stakeholders from the initial consultation meeting along with a representative from the BHTF) and the EMTD is now preparing the HTA report and policy brief for presentation to the HLC in September 2019.

The visit in May 2019 also supported the advancement of the HTA agenda by conducting a training and sensitization workshop. The team provided a training for technical stakeholders and an awareness-raising workshop for high-level stakeholders. Through this workshop, it is expected that more stakeholders in the Bhutan MoH will have been able to understand and support the development of HTA. High-level stakeholders expressed their support and interest in ensuring that the EMTD have the necessary resources and autonomy, both in practical and legal terms. This will pave the way for more systematic inclusion of evidence for health policymaking in Bhutan through the implementation of the HTA process. For more information, see the HTA Development section below.

Rotavirus Vaccine Study

Rotavirus infections contribute significantly to Bhutan's high diarrhoea incidence rate in U-5 children, which in turn is a significant factor in U-5 mortality. In 2017, Bhutan had a diarrhoea incidence rate of 1,448 per 10,000 children under the age of 5, which is considered high by international standards.[5] Rotavirus infections are known to be a leading cause of severe diarrhoea in young children, although vaccines that protect against these infections have been available since 2006.

Although interest in rotavirus vaccination as an additional strategy to reduce the U-5 mortality related to diarrhoea has grown in Bhutan, its sustainability has remained uncertain. Though incidence has decreased with the initiation of various public health interventions in recent years, such as health advocacy and WASH (water sanitation and hygiene) programmes, diarrhoea incidence in U-5 children has remained high. As such, the WHO, a long-term partner and advisor to the MoH, Bhutan, has recommended the introduction of rotavirus vaccines into Bhutan's national immunization programme. However, due to resource limitations, financial sustainability has been a major challenge in introducing additional vaccines into the country's immunization programme.

To determine the rotavirus vaccines' value-for-money, a cost-effectiveness study was conducted with local inputs that were validated by stakeholders. The researchers used the UNIVAC model (version 1.3.41), a deterministic static cohort model developed at the London School of Hygiene and Tropical Medicine (LSHTM), which evaluates a number of vaccines including rotavirus. Using a government perspective, ROTARIX, RotaTeq, ROTAVAC, and ROTASIIL were individually evaluated against a base case scenario of "no vaccination." Vaccine provision for ten cohorts of children under five years of age was modeled. Disability-adjusted life years (DALYs) averted along with cases, visits, and hospitalizations averted were the main health outcomes evaluated. Healthcare cost averted was also measured along with the incremental cost-effectiveness ratio (ICER) result. A threshold of 0.5xGDP/capita ($1,537 = 111,908 Nu. [2018]) was used, with 1xGDP/capita ($3,704 = 223,815 Nu. [2017]) used for sensitivity analysis. Costs and outcomes were discounted at 3%. The essential data inputs that require context-specific information, i.e. program and healthcare costs, disease burden, vaccine provision and coverage were primarily taken from local data. The vaccine efficacy, DALY weights, equity coverage and projections were taken from the UNIVAC inputs, which were based on systematic reviews of studies from low- and middle-income countries (LMICs). This information was validated in the two study visits, with the first focusing primarily on the approach and parameters and the second on the results. The approach is summarized in the table below (Table 2).

[5] Annual Health Bulletin-2018 - Ministry of Health

Table 2: Study approach

Particulars	Details
Type of analysis	Cost-utility analysis (CUA)
Analytical approach	UNIVAC model (developed at LSHTM)
Perspective	Government
Population of interest	Under-5 (U5) children
Intervention	ROTARIX (1 dose/plastic tube, liquid) RotaTeq (1 dose/plastic tube, liquid) ROTAVAC (5 dose/vial, frozen) ROTASIIL (1 dose/vial, lyophilized)
Target population	Children under 1 year of age
Birth cohort	10 (starting 2020 through 2029)
Discount rate	3% per annum for costs and outcomes
Health outcome	Disability-adjusted life years (DALYs) averted, cases/visit/hospitalization/death averted
Non-health outcomes	Incremental cost, treatment cost averted, budget & human resource impact
CE Threshold	0.5×GDP per capita (and 1×GDP per capita)
Result	Incremental cost per DALY averted
Uncertainty analysis	Deterministic (scenario analysis and threshold), probabilistic sensitivity analysis

Rotavirus vaccine is effective at averting the burden of disease (see Table 2), though the vaccine is cost-ineffective in the base case scenario, with ROTASIIL and ROTAVAC offering better value-for-money if the disease burden is high. The ICERs of ROTARIX ($9,267), RotaTeq ($11,606), ROTAVAC ($3,201), and ROTASIIL ($2,801) in the base case are above the threshold base case (0.5xGDP/capita or US$ 1,537 = Nu. 111,908, based on 1 USD = 72.8 Bhutanese ngultrum).[6] RotaTeq, ROTAVAC, and ROTASIIL avert 115 DALYs while ROTARIX averts 104 more DALYs as opposed to having no vaccine. Program cost is high, however, compared to the healthcare costs averted (see Table 3). The scenario analysis in the

[6] Royal Monetary Authority. Royal Monetary Authority [Internet]. [cited 2019 Feb 15]. Available from: https://www.rma.org.bt/

base case of 0.5xGDP/capita showed that RotaTeq is cost-ineffective, ROTARIX is cost-effective only under certain conditions (i.e. high disease burden, low vaccine price, and high healthcare cost), while ROTASIIL and ROTAVAC are cost-effective when the disease burden is high.

Table 3: Health outcome results

Results	ROTARIX (2 doses)	RotaTeq, ROTAVAC, ROTASIIL (3 doses)
Non-severe RVGE cases averted	8,973	9,876
Non-severe RVGE visits averted	5,830	6,417
Severe RVGE cases averted	1,600	1,760
Severe RVGE visits averted	300	330
Severe RVGE hospitalizations averted	739	814
Deaths averted	3	4

Note: RVGE = rotavirus gastroenteritis

Probabilistic sensitivity analysis (PSA) showed that ROTASIIL was the most cost-effective option. PSA was conducted for all vaccines compared to the base case. ROTARIX and RotaTeq have zero to low probability of cost-effectiveness at 0.5 and 1xGDP/capita (US $3,074 = Nu. 223,816). ROTAVAC and ROTASIIL have better probabilities of cost-effectiveness: 5% and 12%, respectively, at 0.5xGDP/capita, and 59% and 69%, respectively, at 1xGDP/capita. Threshold analysis was also conducted to understand at what price/dose the vaccines will be cost-effective at the 0.5xGDP/capita threshold. ROTARIX will be cost-effective at $1.02, RotaTeq is cost-effective at $0.75, ROTAVAC is cost-effective at $0.57, and ROTASIIL will be cost-effective at $0.76.

Table 4: Rotavirus vaccine results compared to a “no vaccination” scenario

Result	ROTARIX	RotaTeq	ROTAVAC	ROTASIIL
Vaccine Program Cost	1,098,000	1,477,000	512,000	467,000
Healthcare cost averted	131,000	145,000	145,000	145,000
DALYs averted	104	115	115	115

ICERs (compared to no vaccine scenario)	**9,267**	**11,606**	**3,201**	**2,803**

Costs are in USD (2018), 1 USD = 72.8 Nu.

The government will need to invest more in the program annually in terms of financial investment and reallocation of human resources. Budget impact analysis shows ROTASIIL with the lowest average annual net cost at $40,600 (see Table 4 for the yearly breakdown). Human resource calculations using the Quantity, Task, and Productivity (QTP) model showed that the vaccine displaces the full-time equivalent (FTE) from specialized task forces (i.e. doctors and pediatricians) to nurses and health assistants who administer the vaccines (an increase between 1.87 to 2.85).

Table 5: Budget impact projections

Yearly	ROTARIX	RotaTeq	ROTAVAC	ROTASIIL
Year 1	147,000	192,000	66,000	68,000
Year 2	114,000	159,000	42,000	36,000
Year 3	112,000	156,000	41,000	34,000
Year 4	109,000	151,000	40,000	33,000
Year 5	105,000	147,000	39,000	32,000
Total	587,000	805,000	228,000	203,000

The study recommends that the government consider the benefits of implementing the vaccine program in the reduction of rotavirus infection; however, significant vaccine price reduction would be needed. Though ROTASIIL and ROTAVAC are more likely to be cost-effective at the 1xGDP/capita threshold, all the vaccines are cost-ineffective at the base case compared to no vaccination. Other considerations could also strongly influence the decision for implementation e.g. ethical and social concerns and feasibility. ROTASIIL, the most promising in terms of cost-effectiveness, would require additional training for the nurses and health assistants to administer the vaccine to switch from its current lyophilized form (the costs for which were not included in the study). Though benefiting from local data and validation, the study has limitations which should also be considered. One important concern is on the parameter that influences the ICER the most: the disease burden. There could be underreporting of rotavirus-caused diarrhea cases from the surveillance system, which was the main data source. Indirect benefits of rotavirus vaccines were also excluded.

For the full study results, please visit the HITAP website (www.hitap.net).

HTA Development

During the visit on May 6-10, 2019, the EMTD, with support from HITAP, MORU, and PATH, conducted a training, a high-level sensitization meeting, and a stakeholder consultation that helped advance the institutionalization of HTA. A training for ministry staff, university professors and students, as well as managers and hospital staff was conducted to introduce a wider audience to HTA. Importance of HTA for priority-setting, its process and guidelines, as well as an introduction to economic evaluation and its components were discussed. Further, other components such as budget impact, social and ethical considerations, and communicating the results, which are integral parts of the decision-making process, were also presented. The stakeholders expressed a broader understanding of the use of evidence for policy and recognized the critical role of HTA.

In addition, on 9 May 2019, the team arranged a high-level meeting to introduce HTA to chief representatives from the different departments of the Ministry of Health, Bhutan (MoH), including the Director General of the Department of Medical Service. The aim of this meeting was to engage the high-level officers at the MoH to discuss how HTA can and will be used in their country. Mr. Dechen Choiphel, Chief Program Officer of the EMTD, which is currently tasked with the management of HTA activities, delivered an interesting session about institutional arrangement of HTA in Bhutan. He presented that they aim to ensure the availability of safe and quality health technologies and interventions for health care services. He added that EMTD is the nodal agency in the MoH for matters related to health technology assessment and strengthening HTA capability and capacity are their key institutional missions. In addition, they also plan to actively engage all key stakeholders and facilitate collaboration with academia and researchers. Some of the potential projects are developing the local HTA method guideline, reference pricing guidelines, threshold study for Bhutan, and conducting the national health care cost study.

Finally, the research team presented the key findings of the cost-effectiveness study of rotavirus vaccine study in Bhutan to stakeholders that consisted of clinicians, immunisation programme operators, epidemiologists, and policy makers. The consultation was helpful in showing the participants the importance of the evidence and its crucial role in the policy decision-making process. They were also more aware of the types of studies and context within which HTA could contribute. This study is one of the first projects that not only represents a great case study for adopting economic evaluation in the country but also shows the framework of prioritizing healthcare needs based on evidence at the institutional level.

Reflections

Bhutan's progress in using evidence for policy is promising and should be capitalized on with concrete steps and support. The rotavirus vaccine study provides a space to showcase the involvement of stakeholders in the HTA evaluation process and the benefits of using HTA for healthcare decision-making. However, there is a concern over the length of time required to generate HTA evidence for the introduction of new health technologies in Bhutan. There is a need for Bhutan's current HTA process guideline to be embedded and considered as the systematic process to identify and evaluate new technologies, given the limited HTA research capacity. It was noted that some stakeholders may oppose the use of HTA due to a delay process of HTA evidence generation.

In order to advance in Bhutan's HTA institutionalization, several types of activities are needed in order to meet the needs from all areas. These include: prioritization for HTA research topics; training to increase the knowledge and supply of HTA researchers; sensitization workshops to generate buy-in from the high-level stakeholders; capacity building through the conduct of a HTA study; and, linking said study to policy, especially with involvement from relevant stakeholders. This is crucial for long-term sustainability of institutionalization of HTA and its use in the decision-making process in Bhutan.

Appendix 1: Agendas

Visit 1: Evaluation of the Introduction of Rotavirus Vaccine in Bhutan
Date: 12-14 December 2018

Rotavirus infects almost every child by the age of 3 to 5 years and is the leading cause of acute diarrhea in children under 5 years of age. According to the World Health Organization (WHO), 453,000 children die annually from rotavirus infection. Diarrhea remains as one of the top ten morbidity among children under age five years although the morbidity report shows gradual decrease in incidence trend from 18,595 cases in 2014 to 11,721 cases in 2017. However, the mortality is very low (Annual Health Bulletin 2018). Based on rotavirus burden study conducted in 2010-2012, Group A rotavirus was detected in 32.5% and 18.8% of the stool samples from children hospitalized in the pediatric ward and OPD respectively in Jigme Dorji Wangchuck National Referral Hospital (JDWNRH). Overall, 22.3% of the stool samples were rotavirus-positive, and the majority (90.8%) of them was detected in children under 2 years of age. The estimated annual incidence of hospitalization due to rotavirus diarrhea was 2.4/1000 in the ward and 10.8/1000 in the dehydration treatment unit (DTU). The cumulative 5-year risk for rotavirus diarrhea-associated hospitalization in the ward and DTU was estimated to be 1 in 416 and 1 in 93 children, respectively.

To address this issue, the Essential Medicines and Technology Division (EMTD) will be conducting an evaluation of the rotavirus vaccine options for implementation on a national level in Bhutan. The team has requested the Health Intervention and Technology Assessment Program (HITAP) to provide technical support for the project, which HITAP will provide in partnership with the Mahidol-Oxford Research Unit (MORU). The support will be structured over a period of approximately six months throughout the completion of the study, with both parties learning from each other through in-country visits and using Bhutan's existing HTA process guideline and relevant international guidelines.

This project aims: 1) to assess whether rotavirus vaccine offers good value for money; 2) to estimate the budget impact of introducing rotavirus vaccine in the routine immunization program; and, 3) to identify conducive factors and barriers of rotavirus vaccine introduction.

Meeting Objectives:

- To discuss the methodology and determine the timeline for the project
- To present the research proposal in a consultation with relevant stakeholders
- To revise the proposal for the next stage of the study (data collection and analysis)

HITAP's assistance is funded through the International Decision Support Initiative (iDSI), the Thailand Research Fund (TRF), and PATH.

Dates: 12th – 14th December 2018

Location: Essential Medicines and Technology Division (EMTD), Department of Medical Services, Ministry of Public Health, Thimphu, Bhutan

Schedule:

Time	Session	Description	Person(s) Responsible
12th December 2018			
13:00 – 13:30	Welcome	• Introductions, background of HITAP and EMTD partners • Discuss overall objectives and strategy for technical assistance	All
13:30 – 14:30	Background of the rotavirus vaccine project	• Disease history and profile • Project history • Expected outputs and impact	EMTD
14:30 – 16:00	Project proposal presentation	• Methodology based on information from the research proposal (including available data and data collection plan) ○ Study population and setting ○ Model structure ○ Interventions (3 different types) ○ Perspective and time horizon ○ Model input parameters ▪ Epidemiological data e.g. natural progression of disease ▪ Clinical efficacy e.g. vaccine efficacy by population subgroups ▪ Health utility ▪ Resource and cost ○ Model validation ○ Analysis (cost-effectiveness analysis, sensitivity analysis) • Human resources for health analysis • Timeline	EMTD
16:00 – 18:00	Project proposal planning session 1	• Discuss methodology and data collection plan (+ timeline, feasibility): ○ Study population and setting ○ Interventions (3 different types) ○ Perspective and time horizon ○ Model input parameters	EMTD and HITAP / MORU / PATH
13th December 2018			
09:00 – 09:30	Recap	• Summary of discussion from previous day	EMTD
09:30 – 12:00	Project proposal planning session 2	• Discuss methodology and data collection plan (+ timeline, feasibility): ○ Model structure ▪ Introduce models (TSE, UNIVAC, others) ○ Model input parameters	EMTD and HITAP / MORU / PATH
Lunch			
13:00 – 16:00	Project proposal planning session 3	• Discuss methodology and data collection plan (+ timeline, feasibility): ○ Model input parameters ○ Data collection ○ Model validation ○ Analysis	EMTD and HITAP / MORU / PATH

Time	Session	Description	Person(s) Responsible
16:00 – 17:00	Project proposal planning session 4	• Finalize timeline for overall study • Discuss human resource for health analysis	EMTD and HITAP / MORU / PATH
17:00 – 18:00	Stakeholder consultation planning	• Prepare the presentation of the project proposal	EMTD and HITAP / MORU / PATH
14th December 2018			
Stakeholder consultation			
09:00 – 09:30	Welcome and Introductions		All
09:30 – 10:30	Background of the rotavirus vaccine project		EMTD
10:30 – 11:30	Project proposal presentation		EMTD
11:30 – 12:30	Discussion		EMTD and relevant partners
12:30 – 13:00	Closing		EMTD
Lunch			
14:00 – 14:30	Recap	• Review of stakeholder consultation	All
14:30 – 16:00	Revision of project plan and proposal	• Discuss comments from stakeholder consultation for each section of the economic evaluation ○ Study population and setting ○ Model structure ○ Interventions (3 different types) ○ Perspective and time horizon ○ Model input parameters ○ Model validation ○ Analysis • Discuss the human resources for health study	EMTD and HITAP / MORU / PATH
16:00 – 17:00	Next steps	• Discussion and closing of the visit	EMTD and HITAP / MORU / PATH

Visit 2: Evaluation of the Introduction of Rotavirus Vaccine in Bhutan
Bhutan Team Study Visit to Thailand
28 January – 8 February 2019

Rotavirus infects almost every child by the age of 3 to 5 years and is the leading cause of acute diarrhea in children under 5 years of age. According to the World Health Organization (WHO), 453,000 children die annually from rotavirus infection. Diarrhea remains as one of the top ten morbidity among children under age five years although the morbidity report shows gradual decrease in incidence trend from 18,595 cases in 2014 to 11,721 cases in 2017. However, the mortality is very low (Annual Health Bulletin 2018). Based on rotavirus burden study conducted in 2010-2012, Group A rotavirus was detected in 32.5% and 18.8% of the stool samples from children hospitalized in the pediatric ward and OPD respectively in Jigme Dorji Wangchuck National Referral Hospital (JDWNRH). Overall, 22.3% of the stool samples were rotavirus-positive, and the majority (90.8%) of them was detected in children under 2 years of age. The estimated annual incidence of hospitalization due to rotavirus diarrhea was 2.4/1000 in the ward and 10.8/1000 in the dehydration treatment unit (DTU). The cumulative 5-year risk for rotavirus diarrhea-associated hospitalization in the ward and DTU was estimated to be 1 in 416 and 1 in 93 children, respectively.

To address this issue, the Essential Medicines and Technology Division (EMTD) will be conducting an evaluation of the rotavirus vaccine options for implementation on a national level in Bhutan. The team has requested the Health Intervention and Technology Assessment Program (HITAP) to provide technical support for the project, which HITAP will provide in partnership with the Mahidol-Oxford Research Unit (MORU) and PATH, Seattle. The support will be structured over a period of approximately six months throughout the completion of the study, with both parties learning from each other through in-country visits and using Bhutan's existing HTA process guideline and relevant international guidelines.

This project aims: 1) to assess whether rotavirus vaccine offers good value for money; 2) to estimate the budget impact of introducing rotavirus vaccine in the routine immunization program; and, 3) to identify conducive factors and barriers of rotavirus vaccine introduction.

Study Visit Objectives:

- To share knowledge about economic evaluation and systematic review analyses (days)
- To finalize the project parameters for input in the model, including the costing methodology (days)
- To develop all parts of the economic evaluation model, including probabilistic sensitivity analysis (days)
- To develop the methodology for the human resource for health (HRH) model (days)

HITAP's assistance is funded through the International Decision Support Initiative (iDSI), the Thailand Research Fund (TRF), and PATH.

Dates: 28th January – 8th February 2019

Location: Health Intervention and Technology Assessment Program (HITAP), 6th floor, 6th building, Department of Health, Ministry of Public Health, Nonthaburi 11000, Thailand

Schedule:

Time	Session	Description	Person(s) Responsible
28th January 2019 **Team Member Lead: Alia Luz**			
09:00 – 09:30	Introductions	• Introductions and overview of the meeting objectives and schedule; discuss expectations from the study visit	HITAP / MORU + EMTD
09:30 – 10:30	PCV costing methodology	• Present the methodology used to collect data for the PCV study (conducted 2016-2017)	EMTD
10:30 – 12:00	Costing healthcare	• Concepts and approaches	Alia Luz
Lunch			
13:00 – 16:00	Costing session 1: Applying the GHCC Reference Case	• Present the concepts from the Global Health Cost Consortium (GHCC) Reference case • Utilize the concepts for the rotavirus costing component	Alia Luz + EMTD
16:00 – 17:00	Costing Session 2	• Develop the costing methodology • Review additional costs to be identified and valuation approach	EMTD
17:00 – 17:30	Reflections	• Summarize the main points and ideas from the day; discuss next sessions' goals	EMTD
29th January 2019 **Team Member Lead: Pritaporn Kingkaew**			
09:00 – 12:30	PMAC Side Meeting	Best buys, wasted buys, and controversies in NCD prevention: Discussion with knowledge users in the community *Location: Centara Grand Hotel (Bangkok)*	EMTD + HITAP
Lunch and travel to HITAP			
14:00 – 14:30	Review	• Review previous day's theories and concepts	EMTD
14:30 – 15:00	Costing Session 3	• Develop materials/tools for data collection • Finalize the timeline for data collection	EMTD
15:00 – 17:00	Project proposal review	• Which parameters require more research?	EMTD (with all advisors including Frederic Debellut)
17:00 – 17:30	Reflections	• Summarize the main points and ideas from the day; discuss next sessions' goals	EMTD

Time	Session	Description	Person(s) Responsible
30th January 2019 **Team Member Lead: Nantasit Luangasanatip**			
09:00 – 09:30	Review	• Review previous day's theories and concepts	EMTD
09:30 – 11:00	Evidence Synthesis	• Introduction to different methods for evidence synthesis: systematic review, rapid review, scoping, etc. theory and techniques	Alia Luz
11:00 – 12:00	Systematic Review	• Systematic review theory and techniques	Dr. Nantasit Luangasanatip
Lunch			
13:00 – 17:00	Practical Exercise on Systematic Review: Session 1	• Systematic review on parameters as required OR a sample problem ○ Costing sections ○ Parameters ○ PSA-specific research	EMTD
17:00 – 17:30	Reflections	• Summarize the main points and ideas from the day; discuss next sessions' goals	EMTD
31st January 2019 **Team Member Lead: Nantasit Luangasanatip**			
09:00 – 09:30	Review	• Review previous day's theories and concepts	EMTD
09:30 – 12:00	Practical Exercise on Systematic Review: Session 2	• Systematic review on parameters as required OR a sample problem ○ Costing sections ○ Parameters ○ PSA-specific research	EMTD
Lunch			
13:00 – 14:00	Costing Session 4	• Finalize methodology and timeline	EMTD
14:00 – 15:00	Review: overview of economic evaluations	• Concepts and practices for conducting economic evaluations	HITAP / EMTD
15:00 – 16:00	Useful resources for conducting economic evaluations	• Overview of resources e.g. medical databases, guidelines, costing database, GEAR, etc.	HITAP
16:00 – 17:00	HTA development in Thailand OR continue exercises	• Present the HTA development in Thailand, as well as the process and methods • Continue exercises	HITAP

Time	Session	Description	Person(s) Responsible
17:00 – 17:30	Reflections	• Summarize the main points and ideas from the day; discuss next sessions' goals	EMTD
1st February 2019 **Team Member Lead: Pritaporn Kingkaew**			
09:00 – 09:30	Review	• Review previous day's theories and concepts	EMTD
09:30 – 11:00	Measuring health outcomes	• Concepts and approaches	Alia Luz
11:00 – 12:30	Practical exercise on measuring health outcomes	• Applying the concepts and approaches to measure utility and value outcomes	Alia Luz + EMTD
Lunch			
13:30 – 14:30	Health economic modelling	• Overview of Decision Tree and Markov models	Dr. Pritaporn Kingkaew
14:30 – 15:30	Introduction to economic modelling exercises	• Exercises on economic evaluations using case study of evaluation of End-stage renal disease (ESRD) in Thailand	Dr. Pritaporn Kingkaew
15:30 – 17:00	Practical exercises	• Build a simple model and work on the ESRD study	EMTD
17:00 – 17:30	Reflections	• Summarize the main points and ideas from the day; discuss next sessions' goals	EMTD
2nd February 2019 **Team Member Lead: Alia Luz**			
09:00 – 17:00	PMAC Conference	*Location: Centara Grand Hotel (Bangkok)*	EMTD + HITAP
3rd February 2019 **Team Member Lead: Alia Luz**			
09:00 – 12:30	PMAC Conference	*Location: Centara Grand Hotel (Bangkok)*	EMTD + HITAP
4th February 2019 **Team Member Lead: Alia Luz**			
09:00 – 09:30	Review	• Review previous week's theories and concepts	EMTD
09:30 – 12:00	Practical exercises OR Thresholds	• Continue working on the ESRD study OR • Thresholds discussion and practice	EMTD
Lunch			

Time	Session	Description	Person(s) Responsible
13:00 – 14:00	Sensitivity Analysis	• Introduction to deterministic and probabilistic sensitivity analyses	Dr. Pritaporn Kingkaew
14:00 – 17:00	Rotavirus vaccine model building: Session 1	• Understand sensitivity analyses sheets for the model	HITAP / MORU + EMTD
17:00 – 17:30	Reflections	• Summarize the main points and ideas from the day; discuss next sessions' goals	EMTD
5th February 2019 **Team Member Lead: Alia Luz**			
09:00 – 09:30	Review	• Review previous day's theories and concepts	EMTD
09:30 – 12:00	Rotavirus vaccine model building: Session 2	• Understand sensitivity analyses sheets for the model	HITAP / MORU + EMTD
Lunch			
13:00 – 17:00	Rotavirus vaccine model building: Session 3	• Understand sensitivity analyses sheets for the model	HITAP / MORU + EMTD
17:00 – 17:30	Reflections	• Summarize the main points and ideas from the day; discuss next sessions' goals	EMTD
6th February 2019 **Team Member Lead: Alia Luz**			
09:00 – 09:30	Review	• Review previous day's theories and concepts	EMTD
09:30 – 12:00	Rotavirus vaccine model building: Session 4	• Input parameters for sensitivity analyses sheets for the model	HITAP / MORU + EMTD
Lunch			
13:00 – 17:00	Rotavirus vaccine model building: Session 5	• Input parameters for sensitivity analyses sheets for the model • Populate the model with available parameters and make changes to the model structure as needed	EMTD
17:00 – 17:30	Reflections	• Summarize the main points and ideas from the day; discuss next sessions' goals	EMTD
7th February 2019 **Team Member Lead: Alia Luz**			

Time	Session	Description	Person(s) Responsible
09:00 – 09:30	Review	• Review previous day's theories and concepts	EMTD
09:30 – 12:00	Rotavirus vaccine model building: Session 5	• Populate the model with available parameters and make changes to the model structure as needed • Conduct the analysis for the study	All
Lunch			
13:00 – 14:00	Human resources for health (HRH)	• Present concepts and theories on human resources for health calculation	Sarayuth Khuntha
14:00 – 17:00	HRH model formulation: Session 1	• Create the plan and the model for the HRH calculation	EMTD
17:00 – 17:30	Reflections	• Summarize the main points and ideas from the day; discuss next sessions' goals	EMTD
8th February 2019 **Team Member Lead: Alia Luz**			
09:00 – 09:30	Review	• Review previous day's theories and concepts	EMTD
09:30 – 12:00	HRH model formulation: Session 2	• Create the plan and the model for the HRH calculation	EMTD
Lunch			
13:00 – 14:30	Results presentation	• HITAP communications methods and plan for results presentation	HITAP / MORU
14:30 – 17:00	Planning for the next phase of the study	• Check progress against timeline • Plan for the data collection, model updating, and write-up schedules • Plan for next steps for the collaboration between the partners	EMTD (with all advisers including Frederic Debellut)
17:00 – 17:30	Closing		All

Visit 3 (Part 1):
Evidence-informed Decision-making: The Power of HTA
6-7 May 2019

As the WHO defines it, health technology assessments (HTA) are "the systematic evaluation of properties, effects, and/or impacts of health technology. It is a multidisciplinary process to evaluate the social, economic, organizational and ethical issues of a health intervention or health technology."[7] In recent years, the use and impact of HTAs have increased in healthcare decision-making on different levels. In Thailand, HTAs have been used to evaluate the cost-effectiveness of healthcare interventions to ensure efficient resource allocation, to negotiate drug prices with companies, to evaluate the feasibility of an intervention, and to implement evidence-informed policies. With many countries embarking on universal health coverage with HTA as one of the tools in their arsenal, the need for more understanding and awareness of HTA is apparent. But how has it been applied and what is the impact? What are its main methods? How can its results be interpreted? How do you ensure that HTA is context-specific and relevant to stakeholders and decision-makers?

The successful completion of the HTA study in 2017 on the economic evaluation of the pneumococcal conjugate vaccine (PCV) and subsequent implementation of PCV13 showed the potential for HTA in Bhutan. With the new study on the economic evaluation of the rotavirus vaccine for national implementation, this forum and training aims to address the questions above and introduce the value of HTA not just through the current studies but to the rest of the Bhutanese healthcare system.

Meeting Objectives:

- To introduce HTA to high-level policy and decision-makers
- To conduct a preliminary HTA training for technical experts and stakeholders

The Essential Medicines and Technologies Division (EMTD) conducts this training with the technical assistance of the Health Intervention and Technology Assessment Program (HITAP), which is funded through the International Decision Support Initiative (iDSI), the Thailand Research Fund (TRF), and PATH.

Dates: 6-7 May 2019

Location: Tashi Yarphel Hotel, Khuruthang Town, Punakha Region, Bhutan

[7] Health Technology Assessment, WHO. https://www.who.int/health-technology-assessment/en/. Accessed February 15, 2019.

HTA: Introduction Workshop

Time	Session	Description	Person(s) Responsible
6th May 2019			
09:00 – 09:30	Welcome	• Introductions • Organization and background/interest in HTA • What would you like to take away from this forum?	Ms. Deepika Adhikari
09:30 – 10:00	What is HTA	• Priority setting and the role of HTA • What are the different types of HTA studies? • Examples of its use and case studies in Thailand	Ms. Alia Luz
10:00 – 10:30	HTA process and topic selection	• How is HTA embedded in policy (linking HTA to existing decision-making structures) • HTA methods, guidelines, and processes • How are topics selected for evaluation	Dr. Pritaporn Kingkaew
10:30 – 10:45	**Coffee and tea break**		
10:45 – 11:30	Evidence synthesis	• Methods and principles	Dr. Nantasit Luangasanatip
11:30 – 12:00	Costing Interventions	• Methods and principles	Mr. Pempa Pemba
Lunch			
13:00 – 13:45	Health outcomes	• Methods and principles	Dr. Nantasit Luangasanatip
13:45 – 14:45	Exercise 1	• Measuring health outcomes	Ms. Alia Luz
14:45 – 15:45	Economic Evaluation	• What is economic evaluation? • Why do you need economic evaluations? • What are the methods and main components?	Dr. Pritaporn Kingkaew
15:45 – 16:00	**Coffee and tea break**		
16:00 – 17:00	Exercise 2	• Understanding economic evaluations' results	Dr. Pritaporn Kingkaew
7th May 2019			
09:00 – 09:45	Budget impact analysis	• Methods and principles	Dr. Nantasit Luangasanatip
09:45 – 10:15	Social and ethical considerations in HTA	• Aside from cost-effectiveness, what considerations do policymakers integrate in the process?	Ms. Alia Luz
10:15 – 10:30	**Coffee and tea break**		

Time	Session	Description	Person(s) Responsible
10:30 – 11:00	Communicating HTA results	• Understanding and communicating HTA results	Ms. Alia Luz
11:00 – 11:30	Institutional arrangements for HTA	• What are the necessary institutional arrangements? (e.g. staff sizes, organizational structure, budget, etc.) • Plans for the future of Bhutan's HTA system/How HTA can be used in the system • Stakeholder involvement • Discussion	Chief Dechen Choiphel
11:30 – 12:00	Closing	• Thanking partners	Ms. Deepika Adhikari
13:00 – 14:00	**Lunch**		

Evidence-informed Decision-making: The Power of HTA (Sensitization Workshop)

Time	Session	Description	Speaker
9th May 2019 in Thimpu, Bhutan			
10:00 – 10:15	Welcome	• Introduction to HTA efforts and impact in Bhutan • Goals of the meeting	Ms. Deepika Adhikari
10:15 – 11:15	What is HTA?	• Video of its use and impact • High-level overview of HTA • Priority-setting for universal healthcare coverage and the role of HTA • Incorporating HTA into policy • Brief discussion of HTA in Thailand along with case studies	Ms. Pritaporn Kingkaew and Ms. Alia Luz
11:15 – 12:00	How can HTA add value to Bhutan?	• Short presentation on the EMTD current process for HTA and plans for its development • Discussion and inputs from stakeholders	Chief Dechen Choiphel
Lunch			

Visit 3 (Part 2):
Evaluation of the Introduction of Rotavirus Vaccine in Bhutan
8-10 May 2019

Rotavirus infects almost every child by the age of 3 to 5 years and is the leading cause of acute diarrhea in children under 5 years of age. According to the World Health Organization (WHO), 453,000 children die annually from rotavirus infection. Diarrhea remains as one of the top ten morbidity among children under age five years although the morbidity report shows gradual decrease in incidence trend from 18,595 cases in 2014 to 11,721 cases in 2017. However, the mortality is very low (Annual Health Bulletin 2018). Based on rotavirus burden study conducted in 2010-2012, Group A rotavirus was detected in 32.5% and 18.8% of the stool samples from children hospitalized in the pediatric ward and OPD respectively in Jigme Dorji Wangchuck National Referral Hospital (JDWNRH). Overall, 22.3% of the stool samples were rotavirus-positive, and the majority (90.8%) of them was detected in children under 2 years of age. The estimated annual incidence of hospitalization due to rotavirus diarrhea was 2.4/1000 in the ward and 10.8/1000 in the dehydration treatment unit (DTU). The cumulative 5-year risk for rotavirus diarrhea-associated hospitalization in the ward and DTU was estimated to be 1 in 416 and 1 in 93 children, respectively.

To address this issue, the Essential Medicines and Technology Division (EMTD) will be conducting an evaluation of the rotavirus vaccine options for implementation on a national level in Bhutan. The team has requested the Health Intervention and Technology Assessment Program (HITAP) to provide technical support for the project, which HITAP will provide in partnership with the Mahidol-Oxford Research Unit (MORU). The support will be structured over a period of approximately six months throughout the completion of the study, with both parties learning from each other through in-country visits and using Bhutan's existing HTA process guideline and relevant international guidelines.

This project aims: 1) to assess whether rotavirus vaccine offers good value for money; 2) to estimate the budget impact of introducing rotavirus vaccine in the routine immunization program; and, 3) to identify conducive factors and barriers of rotavirus vaccine introduction.

Meeting Objectives:

- To finalize the model inputs and analysis
- To present the approach and results to relevant stakeholders
- To revise the first draft of the HTA report and manuscript

HITAP's assistance is funded through the International Decision Support Initiative (iDSI), the Thailand Research Fund (TRF), and PATH.

Dates: 8-10 May 2019

Location: Essential Medicines and Technology Division (EMTD), Department of Medical Services, Ministry of Public Health, Thimphu, Bhutan

Schedule:

Time	Session	Description	Person(s) Responsible
7th May 2019			
13:00 – 15:00	Return to Thimpu	• Travel time	EMTD and HITAP / MORU / PATH
15:00 – 17:30	Modelling and presentation preparation session 1	• Validation, analysis, and results presentation preparation	EMTD and HITAP / MORU / PATH
8th May 2019			
09:00 – 17:30	Modelling and presentation preparation session 2	• Validation, analysis, and results presentation preparation	EMTD and HITAP / MORU / PATH
9th May 2019			
09:00 – 12:00	High-level stakeholders sensitization workshop	• See sensitization agenda	EMTD and HITAP / MORU / PATH
12:00 – 13:00	Lunch		
13:00 – 17:00	Modelling and presentation preparation session 3 / Writing	• Validation, analysis, and results presentation preparation • Or writing sessions	EMTD and HITAP / MORU / PATH
10th May 2019			
Stakeholder Consultation			
09:00 – 09:15	Welcome	• Welcome the stakeholders • Present the project background	EMTD
09:15 – 10:00	Presentation of approach and results of the study	• Discuss the methodology and results of the study	EMTD
10:00 – 10:10	**Coffee Break**		
10:10 – 11:30	Discussion	• Validate the methodology (specifically the model and data inputs) • Discuss the results of the study	EMTD and stakeholders
11:30 – 12:00	Next steps	• Discuss the next steps, including: ○ The plan for results communication to high-level stakeholders and relevant departments, media, and the Bhutanese population	EMTD

Time	Session	Description	Person(s) Responsible
		○ The written outputs of the study and publication of the manuscript in a journal ○ Stakeholder action points ○ Thanking the stakeholders and closing the meeting	
12:00 – 13:00	**Lunch**		
13:00 – 15:00	Stakeholder consultation revision	• Discussion on stakeholder consultation points • Revise the model as needed including the results	EMTD and HITAP / MORU / PATH
15:00 – 16:00	HTA report and policy brief discussion		EMTD and HITAP / MORU / PATH
16:00 – 17:00	Manuscript discussion		EMTD and HITAP / MORU / PATH
17:00 – 17:30	Closing and next steps	• Discuss the next steps for all written outputs, the study's use in policy, and plan for this collaboration • Thank all partners	EMTD and HITAP / MORU / PATH

Appendix 2: Summary Minutes of Stakeholder Consultations

MINUTES OF THE MEETING:
Proposal Stakeholder Consultation

Subject: Stakeholder consultation meeting on the economic evaluation of rotavirus vaccine

Date: 14th December 2018, 09:30 – 13:00

Venue: Dorji Elements, Chubachu, Thimphu

Participants:

STAKEHOLDERS

1. Dr. Mimi Lhamu, Pediatrician at Jigme Dorji Wangchuck National Referral Hospital (JDWNRH) and Chairperson of the National Committee for Immunization Practices (NCIP)
2. Dr. Sophie Jullien, Pediatrician and researcher at MOH
3. Bharosa Dural, Community Health Department, JDWNRH
4. Dechen Choiphel, Chief Program Officer, Essential Medicines Technology Division (EMTD), Ministry of Health (MOH)
5. Jangchup Peljore, Pharmacist at Medical Supplies Procurement Division (MSPD), MOH
6. Kinga Jamphel, Drug Controller, Drug Regulatory Authority (DRA)
7. Sangay Phuntsho, Program Officer, VPDP
8. Kinley Dorjee, Health Information Management System (HMIS), MOH
9. Tshering Dorji, Royal Center for Disease Control (RCDC), MOH
10. Tshewang Tamang, Deputy Chief Program Officer, Vaccines Preventable Diseases Program (VPDP)
11. Yeshi Dorji, Community Health Department, JDWNRH

RESEARCH TEAM

12. Dr. Nantasit Luangasanatip, Health Economist and Mathematical Modeller, Mahidol-Oxford Tropical Medicine Research Unit (MORU) – Project Adviser
13. Dr. Wanrudee Isaranuwatchai, health economics professor at the University of Toronto and a Senior Research Fellow at HITAP – Project adviser
14. Dr. Pritaporn Kingkaew, Researcher, HITAP – Project Adviser
15. Alia Luz, Project Associate, HITAP International Unit – Project Adviser
16. Deepika Adhikari, Senior Laboratory Officer, EMTD – Project Coordinator
17. Pempa, Laboratory Officer, EMTD – Project Lead

The meeting started with the introduction of the participants and a brief overview and introduction of the project by EMTD.

EMTD then presented to the forum the details of the study including what health economic evaluation is, the research methodology, the economic evaluation model adopted, the required input (data), the expected outcome and the timeline of the study.

The presentation ended with the discussion on the way forward and key highlights of the study which are as follows:

1. Background
   Diarrhea is one of the major illnesses in Bhutan, and rotavirus accounts for 20% of all cases (Wangchuk et al). Children under five years of age are especially vulnerable to this disease. For this reason, the Bhutanese government and Ministry of Public Health decided to address the issue through the potential inclusion of the rotavirus vaccine in the national immunization program. The rotavirus vaccine has been shown to be value-for-money and is currently provided in 96 countries as of 2018.To determine the most appropriate vaccine for Bhutan, an economic evaluation will be conducted exploring the vaccine options in terms of their associated costs and outcomes, cost-effectiveness, budget impact, and human resource (HR) impact.

2. Economic model adopted for the study
   During the two-day preliminary meeting between the technical advisors and EMTD before the stakeholder meeting, the research team (referred to as 'the team' from here on) had decided to use the UNIVAC model for this economic evaluation considering that this model is highly relevant to Bhutan's context and has been used in other similar settings.

   The forum asked the team the justification for the choice of the UNIVAC model as opposed to the TRIVAC model, which too has been used in many other countries. The team informed the floor that UNIVAC is a newer and improved version of the TRIVAC model. The following is the comparison of key highlights between the two models:

UNIVAC	**TRIVAC**
Validated by WHO IVIR-AC[8]	Validated by WHO IVIR-AC
Vaccine evaluation for **5 diseases**: • rotavirus (RV) vaccine • pneumococcal conjugate vaccine (PCV) for streptococcus pneumonae • meningitis (MEN) vaccine • haemophilus influenzae type b (Hib) vaccine • human papillomavirus (HBP) vaccine	Vaccine evaluation for **3 diseases**: • rotavirus (RV) vaccine • pneumococcal conjugate vaccine (PCV) for streptococcus pneumonae • haemophilus influenzae type b (Hib) vaccine
Publication year: 2017	Publication year:2013, used at various stages and forms in Latin America, Europe, and other regions previously since the 2000s(Clark et al 2013)

[8]Immunization and Vaccine-related Implementation Research Advisory Committee

Update year: N/A	Update year: UNIVAC is the next step for TRIVAC (Sanderson 2014)
Input parameters for rotavirus vaccine: relatively unchanged parameters but updated from TRIVAC	Input parameters for rotavirus vaccine: outdated for country-specific data

3. Data collection timeline

   The presentation highlighted that the data collection for this project will take 2 months' time, i.e. from January until February 2019; however, there were questions raised on the length of time for data collection. The team responded that there are numerous data inputs (i.e. disease burden data on incidence and prevalence by population, cost data representative of the rotavirus associated costs in Bhutan) required for the study. Many of the data are inadequate or require reformatting. In some cases, visits to the health facility for data collection are required. Details can be found in the summary sheet in Appendix 1 of this document.

4. Incidence

   The stakeholder consultation participants' discussions showed that there are variations in disease burden data from two different sources, namely, the surveillance data from the RCDC and the annual reported data from the HMIS (i.e. Annual Health Bulletin or AHB). The team considered using both sources and evaluating which dataset or a combination will be used. One option is to consider taking the median from all available data as inputs for base case analysis and taking the higher value from the one data source (i.e. RCDC) and lower values (i.e. AHB) for sensitivity analyses.

   Following WHO guidelines, RCDC's surveillance on diarrheal cases covers 215 health centers (now including outreach clinics since 2016) with the highest diarrhea burden. They track acute bloody and watery diarrhea cases. Although the surveillance started in 2011, the reporting and quality of data is better for the years 2017-2018 during which they expanded from 4 geographical sites to 12 sites covering most of Bhutan. The representative from RCDC also confirmed that they can provide surveillance data in any required format. The epidemiology unit of the RCDC might have detailed information on this data.

   Salient numbers:

   - Diarrhea mortality over 5 years: 5-6 cases (AHB 2018)
   - Diarrhea cases: 10,000 (AHB 2018)
   - Dysentery cases: 70,000 (RCDC 2015)

5. Definition of severe and non-severe diarrhea

   It was unanimously decided that the study should assume that all those cases that were admitted shall be considered as 'severe' and all non-admitted cases as 'non-severe'.

6. Vaccine consideration

   The team presented that there are 4 vaccine options that can be considered for the study: Rotarix, Rotateq, RotaSIL, and RotaVAC. However, for the information of the stakeholders, the team and

the VPDP informed the floor that vaccines such as Rotarix and Rotateq have market availability issues in the coming years (at least 2). RotaSIL and Rotateq have storage issues. Rotarix is not available at GAVI price for Bhutan. Considering the birth cohort of 10 years, uncertainty and availability for the current and coming few years cannot be taken as a guiding factor, therefore, the forum decided that all 4 vaccines be considered for the study. The forum also suggested that both single and multi-doses of all the vaccines can be considered. Detailed vaccine profiles are available through: https://www.gavi.org/about/market-shaping/detailed-product-profiles/.

7. Vaccine price

   It was learnt that some vaccines are available at GAVI eligible price and some are not; therefore, this study shall consider the non-GAVI price that is offered to the program via the UNICEF procurement.

8. Vaccine program cost

   VPDP shall furnish the detailed breakdown program cost partly based on the past years' cost information and include human resource training cost, wastage, storage, freight charges (given that the Bhutanese government may pay for the delivery), as well as other relevant parameters for each vaccine. The cost shall also explore the difference in price for freight charges by flight and by road. The VPDP program also mentioned about buying a truck to transport the vaccines; if so, this must be accounted under the program cost. Increased or additional volume for storage was not considered to be an issue given current storage capacity. Though the VPDP has information on the cost and budget of new vaccine introduction, they are requested to provide not only this but the cost for each vaccine as all will vary according to their attributes and what they entail. The team will work closely with the VPDP to gather information needed.

9. Vaccine timeliness and coverage

   It was decided that the timeliness shall be tagged along with the DTP3 vaccines. For coverage, there is a Joint Reporting Form (JRP) that shall provide information to guide the team in deciding on this matter. A guideline for the rotavirus vaccine that was used by the VPDP to train the health workers says that if the clients come after 14 weeks, the health workers are not supposed to give the vaccine; however, the forum discussed that the timeliness is acceptable within 1 year after the child birth. A confirmation on these contradicting statements must be obtained by EMTD in consultation with the NCIP, community health department, and VPDP.

   Comments from NCIP Chairperson:

   Dosing of the vaccine will depend on the vaccine that we choose to purchase.

   Rotarix - product pamphlet says not later than 24 weeks
   Rotateq - says no later than 32 weeks.
   Rotavac - says complete course by 8 months (34 weeks)
   Rotasil - does not give the upper age limit.

   The WHO paper states that "in low and middle income countries the additional lives saved by removing the age restrictions would by far outnumber the vaccine associated intussusceptions deaths"

   Comments from VPDP Program:

When the guideline was developed, they referred WHO recommendation and took the 6 weeks, 10 weeks and 14 weeks schedule.
Since the schedules mentioned by the program falls under the individual limits of each of the vaccines, the programs schedule could be followed, however, those who avail the services even after 14 weeks can still be entertained without too much restriction considering point no 2 mentioned by Dr. Mimi.

Salient numbers:

- 96% coverage for DTP3 vaccine may be used for rotavirus vaccine as well

10. Vaccine wastage
    The forum suggested that we should use the default wastage data available in the literature. GAVI also has a detailed product report and it can be used for obtaining the vaccine information.

11. Cost (direct/indirect)
    There is a document available on "the cost of healthcare in Bhutan" but it was developed by the Policy and Planning Division (PPD) in 2009-2010; most of the information might be irrelevant to the current date given improvements in the healthcare system since. Therefore, the team is directed to reach out to the authors of this report and find out if there has been any update or published similar study.

    Another option is to calculate the treatment cost by collecting data from a number of health facilities from each health level of health facilities:
    a. Regional Referral Hospitals
    b. District Hospital
    c. Basic Health Unit I
    d. Basic Health Unit II

    The methodology will follow the PCV vaccine economic evaluation costing conducted from 2016-2017, with a focus on service costs, cost of admission and delivery, as well as other direct costs. Post-survey or data collection, the information will be verified with experts to confirm the treatment and prescription patters as well as health-seeking behavior.

    A final option is to use the UNIVAC default inputs on costs collected through systematic reviews and extrapolated from the WHO-CHOICE cost parameters. However, the forum decided against this.

    The forum also discussed the variation in costs between two sources: UNIVAC costs ($66) is lower compared to local data ($84 average across hospitals, from the PPD costing study of 2009/2010). However, the latter includes capital costs. If data is confirmed for the PPD study and cost components are standardized, the same technique of applying the average between the data collection and the PPD costing data as the base case and using the lower and higher costs for sensitivity analysis.

12. Study timeline

Although urgency to complete the study early to be included in the decision-making before the new fiscal year was brought up, the team decided to try to move quickly but follow the timeline of end of May 2019 considering the numerous inadequate data requirement.

Activities	**Study Timeline**					
	December	**January**	**February**	**March**	**April**	**May**
Stakeholder Consultation meeting	✓				✓	
Data collection		✓	✓			
Data analysis & validation				✓	✓	
Report writing					✓	
Report dissemination						✓
Draft Manuscript & Policy brief						✓

13. Study Output

The main outputs of this study shall be as follows:

1. The research report
2. The policy brief to inform the decision makers
3. A manuscript for possible publication

The team from HITAP also informed the forum that they intend to do a blog and other communications materials on their visit to Bhutan and asked if anyone had and reservations and the forum had none.

The team also decided that short notes for the appraisal of the new Health Minister shall be developed.

14. Study perspective

The presentation touched upon the study perspective options (namely government, societal, or health system perspective) but it got left out of the discussion points. The team has currently decided on the government perspective with the option of doing societal perspective if data is collected and available. Therefore, EMTD is to circulate this issue via email with the stakeholders and ask for their opinion while circulating the draft minutes.

Perspectives:

- Government: includes direct and indirect medical costs(e.g. travel costs from home to health center/hospital)
- Societal: includes direct and indirect medical and non-medical costs (e.g. productivity loss from parents' absence from work due to caring for their sick children)
- Health System: includes direct medical costs

Since no one commented on the perspective in the circulated email, EMTD would like to stick to what is written in the proposal that we would go for Government perspective, however, we would also like to explore the possibility of doing societal perspective if it is possible to do so with available data.

15. HR Impact component of the study

    Data needs to be collected on this from the selected sites. Two models can be used: the FTE calculation (used in the PCV study) and the quality, task, and productivity (QTP) model. The FTE calculation identifies hours spent on activities related to the prevention and treatment of the disease, which are then estimated as a percentage of the no. of work days per year and the total hours spent on the disease per person/type of health profession per year. The QTP model was "developed under the concept of functional job analysis whereby the skill requirements tocomplete a certain task are assessed. There are four main key features of this model: (1) it includes a set of priority interventions, (2) it estimates HRH by calculating the number of casesneeded for a service (service quantity), (3) it identifies the tasksand estimates the time needed to deliver a service, and (4) itincludes the productivity by combining staff productivity and serviceproductivity. This model has been developed for low-income countries that want to scale up their priority interventions. A study conducted by Kurowski et al. showed that the QTP method was robust in estimating the required human resources (Chootipongchaivat et al 2016)."

16. Second stakeholder consultation

    The forum also asked the team to explore the possibility to develop the capacity of the technical resources such as the NCIP members and the high-level policy makers in health economic evaluation and health technology assessment. The forum also suggested the HITAP team to explore possibilities of collaboration with the Khesar Gyalpo University of Medical Sciences of Bhutan for such capacity building activities. The chief of EMTD will coordinate.

    A two-three-day training can be conducted during the next study visit for the stakeholder consultation on model and results validation (with the same group of stakeholders during the proposal stakeholder consultation). This training can cover introduction to HTA and its uses and economic evaluation results interpretation, which HITAP has provided to other partner countries. HITAP also came to train medical universities' representatives in Bhutan in 2015-2016.

17. Next steps:
    1. The team will send the meeting minutes to the stakeholders by December 21, 2018.
    2. The stakeholders will respond with comments by December 28, 2018.

Appendix 1: Parameters Summary

Point	Decision/comments	Sources	Contact person
Model	Descriptions on the different characteristic of TRIVAC and UNIVAC		Frederic Debellut, PATH Health Economist, Project Adviser
Vaccine types	Rotarix, Rotateq, ROTAVAC, ROTASIL and consider single-dose and multi-doses	GAVI product details	
Vaccine price	Non-GAVI price from UNICEF price	UNICEF	
Vaccine program cost	Detail break-down for the vaccine introduction (unit costing) International handling and transportation - By road - By flight	Collect from VPDP	VPDP programme manager
Incidence	Bhutan age-specific incidence rate per 100,000 population - Severity (hospitalized & admitted HMIS) - Non- severe (non-admitted) - Assumption: Admitted cases would be the severe diarrhea Food-bound diseases lab-based surveillance data from acute diarrhea cases (all country, including outreach clinic) - Better reported data from 2017-2018, 215 centers The incidence from HMIS might be under-reported so the data from HMIS can be used in the lower bound value.	Health Management Information System (HMIS), Surveillance data	
Vaccine coverage	The same percentage as DTP3	Joint Reporting Form (JRF)	
Vaccine timeliness	No issue regarding timeliness, but follow the DTP *Clarify the time interval of the rotavirus vaccination vs the guideline of rotavirus vaccine training	Joint Reporting Form (JRF)	
Vaccine wastage	Waste depends on the vaccine	GAVI detailed product profiles	
Treatment cost for diarrhea cases	The unit cost study (2009/2010) is outdated. The first option is to ask Policy and Planning Division (PPD) for any updated data.	PPD, MoH or	

Point	Decision/comments	Sources	Contact person
	The second option is to collect unit cost for treatment for diarrhea. - Unit cost from PCV - Collect service delivery cost (like PCV), use the template from the PCV study - Sample hospitals from all region: referral hospital/ district hospital/ BHU grade1/ BHU grade 2 (outreach clinic). - 3 sites for each level = 12 sites	Local data collection	
HR impact	- PCV or QTP model	Local data collection	
Research outputs	Communication materials - Research report - Policy brief - Manuscript - In-house capacity development/ Training of the trainers o HTA & EE training o National Committee for Immunization Practices (NCIP) members/ high-level committee and policy members - Short note for the Health Minister		

Appendix 2: References

Wangchuk et al. Prospective Surveillance Study to Determine the Burden of Diarrhea in Bhutan. 2017.

Chootipongchaivat et al. Vaccination program in a resource-limited setting: A case study in thePhilippines. Vaccine2016.

Dorji et al. Towards the introduction of pneumococcal conjugate vaccines inBhutan: A cost-utility analysis to determine the optimal policy option.Vaccine 2018.

Sanderson. The ProVac initiative and evolving decision support. Vaccine 2014.

Clark et al. TRIVAC decision-support model for evaluating the cost-effectiveness of Haemophilus influenzae type b, pneumococcal and rotavirus vaccination. Vaccine 2013.

MINUTES OF THE MEETING:
Results Stakeholder Consultation

Subject: Stakeholder consultation meeting on the economic evaluation of rotavirus vaccine study results

Date: 10th May 2019, 09:30 – 13:00

Venue: Dorji Elements, Chubachu, Thimphu

Participants:

STAKEHOLDERS

18. Dr. Mimi Lhamu, Pediatrician at Jigme Dorji Wangchuck National Referral Hospital (JDWNRH) and Chairperson of the National Committee for Immunization Practices (NCIP)
19. Dechen Choiphel, Chief Program Officer, Essential Medicines Technology Division (EMTD), Ministry of Health (MOH)
20. Tshewang Tamang, Deputy Chief Program Officer, Vaccines Preventable Diseases Program (VPDP), Department of Public Health (DOPH), MOH
21. Bharosa Dural, Community Health Department, JDWNRH
22. Dr. Sonam Wangchuk, Specialist, Royal Center for Disease Control, DOPH, MOH
23. Sonam Dorji, Reigstrar General, Bhutan Medical Health Council
24. Sonam Phuntsho, Director, Bhutan Health Trust Fund
25. Sonam Dhendup, Bhutan Health Trust Fund
26. Jigme Tenzin, Seniro Pharmaicst, Drug Regulatory Authority
27. Ugyen Penjore, Medical Records Unit, JDWNRH

RESEARCH TEAM

28. Dr. Nantasit Luangasanatip, Health Economist and Mathematical Modeller, Mahidol-Oxford Tropical Medicine Research Unit (MORU) – Project Adviser
29. Frederic Debellut, health economist from PATH – Project adviser
30. Dr. Pritaporn Kingkaew, Researcher, HITAP – Project Adviser
31. Alia Luz, Project Associate, HITAP International Unit – Project Adviser
32. Deepika Adhikari, Senior Laboratory Officer, EMTD – Project Coordinator
33. Pempa, Laboratory Officer, EMTD – Project Lead

The meeting started with the introduction of the participants and a brief overview and introduction of the project by EMTD.

EMTD then presented to the forum the details of the study including the type of health economic evaluation, the research methodology, the model adopted, the inputs (data) used, and the results. These included the health outcomes (e.g. disability adjusted life years or DALYs, cases, deaths, and hospitalizations averted), the incremental cost-effectiveness ratio, cost outcome including vaccination program cost and cost of treatment averted, the deterministic and probabilistic sensitivity analyses, the threshold analysis, and the budget and human resource impact analyses.

The presentation ended with the discussion on the way forward and key highlights of the study, which are as follows:

18. Background

    Diarrhea is one of the major illnesses in Bhutan, and rotavirus accounts for 20% of all cases (Wangchuk et al). Children under five years of age are especially vulnerable to this disease. For this reason, the Bhutanese government and Ministry of Public Health decided to address the issue through the potential inclusion of the rotavirus vaccine in the national immunization program. The policy was announced, with Rotarix determined to be the most efficacious; however, it is currently unavailable until 2020 and even then may be prioritized only for countries with very high burden of diarrhea. To determine the most appropriate vaccine in terms of value-for-money for Bhutan, an economic evaluation was conducted through the request of the High Level Committee (HLC).

19. Summary of results

    The four vaccines evaluated with UNIVAC (Rotarix, RotaTeq, ROTAVAC, and ROTASIIL) were found to be cost-ineffective at the threshold of 0.5 GDP/capita ($1,537 = 111,908 Nu.). However, ROTAVAC and ROTASIIL have approximately 60% and 70% chance, respectively, of being cost-effective at the threshold of 1 GDP/capita, especially if the disease burden is high (as the scenario analysis shows). Disease burden and price of the vaccine are the primary drivers of the cost-effectiveness of a rotavirus vaccine program.On average, the vaccine program cost for ROTASIIL or ROTAVAC is 58,000 or 63,000 USD per year, respectively. On average, the net budget impact is 40,600 (ROTASIIL), 45,600 (ROTAVAC) USD per year. Specialized workforce (e.g. doctor, dietician, etc.) would be less needed, however, there will be increase in need of nurse and health assistant FTE with vaccination.

20. Limitations

    - Many vaccine-specific details aren't accounted for or uncertain, e.g. ROTAVAC is modelled with a 30% wastage rate due to a 5-dose presentation though this may not be the case in Bhutan. ROTASIIL requires an additional reconstitution step before being administered, which may require more training.
    - As per the HISM reporting system, all diarrhea cases are reported based on ICD 10 coding. Although RCDC has conducted rotavirus surveillance in the past years, there is high probability of underreporting rotavirus diarrhea cases because the surveillance was limited to few sentinel sites. Further, the numbers of stool samples collected for rotavirus testing are low which could have attributed to low rotavirus positivity rate hampering validity of the results.
    - Further, all diarrhoea deaths included as rotavirus deaths is not laboratory confirmed and a may not be true rotavirus death case. However, the researchers assume that the rotavirus is more severe than diarrhoea only so all the deaths are likely to be from rotavirus. Currently, other than RCDC, no hospitals have testing facilities to determine the aetiology gents for diarrheal cases. Possible causes of deaths may sometimes go unreported as well. Further, JDWNRH has recorded 2 diarrhoeal deaths in children in 2019 till Maycompare with only 1 death in the previous year (2018?), which was use as the basis for data input in the study.
    - Increase in human resource for vaccination (higher FTE requirement) after the first year is not accounted for in the model.

21. Efficacy

Given the assumption in the model that efficacy is similar for all 4 vaccines, a question was raised on the efficacy of ROTASIIL and ROTAVAC, which are still undergoing clinical trials in African countries and showing lower efficacy than the older vaccines RotaTeq and Rotarix. Given that ROTASIIL and ROTAVAC are relatively newer vaccines, there is limited information of their efficacy. Vaccine efficacy levels and waning included in the model were taken from a systematic review and meta-analysis of all published randomized control trials (RCTs) and were shown to be similar for all the vaccines (Clark et al, Lancet Infectious Diseases 2019, forthcoming).

It was mentioned that there is only data from India and Niger for ROTAVAC and ROTASIIL, which may or may not be applicable to Bhutan. In this case, the researchers will continue with the current assumption of using a similar efficacy across vaccines. Further, the UNIVAC data uses these efficacy estimates, which methods used to develop have been validated by the IVRAC and WHO.

22. IPD and OPD data

    Researchers assumed that diarrhea cases admitted in IPD are severe cases and OPD are moderate cases of rotavirus. However, it is likely that only the most severe cases of diarrhea will be admitted and the rest, including severe cases would be managed in OPD. Total referral of IPD from OPD is 6% in all diarrhoeal cases, which is similar to the researcher's calculations.

23. Threshold

    The threshold is a tricky subject and one that the country needs to decide on. The WHO has now stepped away from the use of the 1 GDP/capita (with interventions falling below this threshold as highly cost-effective, and those falling under 3 time GDP/capita as cost-effective) and some studies show that LMIC thresholds could be lower, e.g. 1-50% of GDP/capita (Woods et al). Thailand uses a threshold that is based on a willingness-to-pay study that informed policymakers decision-making (Thavorncharoensap et al). The Committee recommended keeping the 0.5 GDP/capita threshold. It is up to the policymakers to decide on this issue and whether they will use the 0.5 or 1 GDP/capita in considering the results of this study. They could also consider and potentially use the results of the threshold analysis, which shows the price at which rotavirus vaccine can be cost-effective, for price negotiation to ensure the vaccine is cost-effective. There is also a planned study in the EMTD 5-year pipeline aiming at determining the CE threshold for Bhutan. The committee also recommended exploring the Gross National Happiness (GNH) values in the threshold study.

24. Budget impact

    The budget impact per year is around 1.2% of the total amount (350 million Nu.) that Bhutan Trust Fund provides to the MOH to purchase vaccines and essential medicines annually. The government can use the information from this study for allocation of their resources, especially accounting for the priorities of the Bhutan Trust Fund as well, which are: vaccines, essential drugs, and reproductive health.

25. Other concerns

    Cold storage in the country will be sufficient for the vaccine. All health centers in the country has refrigerator at 2 to 8°Celsius. Freezers are available at central and district levels as they are used to store oral polio vaccine and space is sufficient to accommodate ROTAVAC. The study did not use a societal perspective for the analysis, which underestimates the costs of the illness on the child and his/her family and caregivers in terms of indirect costs and productivity loss. There are other health effects that weren't included in the study. Diarrhea contributes to stunting and malnutrition, which

means that reduction in the cases by introducing rotavirus vaccine would have an indirect impact. There are also studies that show rotavirus vaccine has a protective effect against febrile seizures. Finally, the indirect impact of less specialized staff used hasn't been accounted for as well as indirect and herd effects.

26. Consultation meeting conclusion
    Although the study had limitations, stakeholders appreciated that the study was well designed and professionally conducted and recommended EMTD to present to HLC for policy decision and further directive. The EMTD should ensure that the results are clear and easily understandable for decision makers.

27. Next steps:
    1. The team will send the meeting minutes to the stakeholders by May 22, 2019.
    2. The stakeholders will respond with comments by May 29, 2019.
    3. EMTD will prepare the HTA report and policy brief to be shared by May 24, 2019.
    4. The results will be presented to the HLC by end of May 2019.

References:

1. Wangchuk, Sonam, et al. "A prospective hospital based surveillance to estimate rotavirus disease burden in Bhutanese children under 5 years of age." *Tropical medicine and health* (2014).
2. Woods, Beth, et al. "Country-level cost-effectiveness thresholds: initial estimates and the need for further research." *Value in Health* 19.8 (2016): 929-935.
3. Thavorncharoensap, Montarat, et al. "Estimating the willingness to pay for a quality-adjusted life year in Thailand: does the context of health gain matter?." *ClinicoEconomics and outcomes research: CEOR* 5 (2013): 29.

Stakeholder Comments:

Stakeholder 1:

Please remove the comment on 2 cases this year - as I am not exactly sure whether the first case was in December or this year.

Will need to check the records before making this comment in the minute

In addition the comments on –

1. the importance of other measures for diarrhea control is not reflected (hand hygiene, sanitation and safe drinking water)

2. Lack of proper surveillance data on Rotavirus is not mentioned. The data we have is that from 2012 which is not relevant in the current scenario.

3. We need to do proper surveillance data / disease burden in the current age

Another comment that I made was regarding the lower efficacy of the vaccines that are currently available for Bhutan (Rotasil and Rotavac).

Responses:

Agree to remove comment on 2 cases

Point 1 – agree to add under Limitations section.

Point 2 – addressed in the second bullet point of the Limitations section, but we can mention that we extrapolate the information from the previous years.

Point 3 – We can add this in the second bullet point of the Limitations section.

Point 4 – already mentioned under Efficacy section.

Stakeholder 2:

Suggest to remove: However, the researchers assume that the rotavirus is more severe than diarrhoea only so all the deaths are likely to be from rotavirus

Response: This is an assumption made. We can highlight in the minutes that it is a limitation of the model.

Suggest to remove: Possible causes of deaths may sometimes go unreported as well.

Response: This was mentioned during the meeting. Suggest to keep and incorporate the comment in the study.

Appendix 3: Outputs from the Study

The study materials can be found in the following links:

1. Study Schedule
2. Report
3. Policy Brief
4. Photos from the Study

Acknowledgements:

This report benefited from the inputs of Drs. Pritaporn Kingkaew and Nantasit Luangasanatip and Ms. Saudamini Dabak.