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**Introduction of a handbook on health economic evaluation, as a tool to support
decision-making, in the Venezuelan Ministry of Health:**

A feasibility study applied to vaccines

Master Thesis

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Preface

As an economist with experience working in the Venezuelan Ministry of Health (VMH), and of course in my position as a Venezuelan citizen I have a great interest in health policy, it's design, and implementation. During 9 years in the planning department of this institution I witnessed the implementation of new policies, like the strengthening of the public Primary Health Care (PHC) network and in general a reinforcement of a National Public Health System (NPHS) with the aim of ensuring access to health to a broader population.

There are a wide range of policies which appear positive in terms of health improvement: an expansion of the physical capacity; abolishing charging patients in public health (PH) facilities; incorporating a new vaccine to the national immunization programme (NIP); and even establishing agreements to treat patients from other countries free of charge. However a reoccurring concern –probably due my academic background in Economical Sciences– arises from a reduction of the annual public budget since 2009 due to a severe oil price drop. Therefore the VMH needs to incorporate evidence-based decision making in its processes.

For this reason this thesis to obtain my Master Degree in Public Health intends to be a contribution on the use of health economics evaluation (HEE) to support policy makers' decisions. It proposes a hand book on HEE, with a broad abridgement of major concepts related to the topic. Then it narrows the perspective to vaccines evaluation as an example of how to translate theory to practice; identifying information –input needs, stakeholders, and processes, to actually carry on HEE.

I would like to express my sincere gratitude to *Fundación Gran Mariscal de Ayacucho* (Fundayacucho), a Venezuelan institution that supports my studies in the Hamburg University of Applied Sciences, under its agreement with the German Academic Exchange Service (DAAD).

Abstract

Background: Health expenditure has undoubtedly an upward trend. Scarcity of resources and uncertainty will be always present, and under this scenario there is a real need to boost health economic evaluation (HEE) within the Venezuela Ministry of Health (VMH) with the aim to improve efficiency on resources allocation, and therefore in health. **Objectives:** To develop a proposal of a handbook on HEE to be used by the Venezuelan Ministry of Health. To analyse the feasibility of cost-effectiveness analysis applied to vaccines in the context of the VMH. To present a summary of relevant health economic concepts to help with a better understanding of the tool and in general of HEE within the VMH. **Methods:** Pertinent literature was searched in electronic databases: PubMed, SciELO; also Google search engine and Google Scholar were used to identify other possible sources of information. Data related with the VMH was retrieved from its official website. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement checklist was considered to design the handbook proposal. **Target – Scope:** Public health experts; head of projects, programmes and departments; as well as planning professionals who act as a support for policy makers within the VMH. This handbook intends to provide useful guidance to initiate HEE studies in the VMH, and also to aid comprehension of HEE literature.

Results: Current theory and studies indicate that HEE cannot always be transferred from country to country. Therefore a national effort is needed to generate valid evidence to strengthen decision making processes. International standards to develop guidelines were considered to develop this handbook. It is expected that after initial attempts to gain experience in the field within the VMH, this document would be considered and put in place.

Conclusions: Venezuela has meagre experience in HEE; however it could benefit from international and especially regional know-how. This handbook could potentially support the challenge of implementing HEE in the VMH. It is considered that implementing a handbook on HEE applied to vaccines would be feasible. **Limitations:** The Venezuelan health's legal framework; defragmentation of the health sector; and a lack of professionals with a health economics background, represent obstacles to implementing this handbook.

Key words: Cost-effectiveness analysis, Health economics, Health economics evaluation, Health policy, Vaccines, and Venezuela.

Table of Contents

Preface	2
Abstract.....	3
Table of Contents.....	4
List of tables and figures	6
List of acronyms and abbreviations	7
1. Introduction	9
1.1. Problem Definition.....	9
1.2. Research question.....	10
1.3. Background	11
1.3.1. Some basics and concepts for understanding HE, HEE and the relevance of economical appraisal on health.....	11
1.3.2. Why is the public intervention in health justified from an economical perspective? Health, public goods and economical principles failures.....	14
1.3.3. Use of HE worldwide and in Latin America	16
1.3.4. The role of HE and HEE in the decision-making process	17
1.3.5. Transferability of HEE for LA.....	17
1.4. Objectives of the study	18
1.5. Study relevance and justification	18
1.6. Target – Scope.....	20
2. Methods.....	21
2.1. Relevant aspects for developing a handbook on HEE	21
2.1.1. A brief overview of some guideline development tools	22
2.1.2. Comparing LA guidelines.....	23
2.1.3. Scoring according to the CHEERS adapted-checklist.....	26
2.2. HEE applied on vaccines. Which data is relevant for the evaluation according to HEE evaluations published?.....	27
3. Results. Elements for a Health Economic Evaluation.....	30
3.1. Types of HEE	30
3.1.1. Cost-minimisation analysis.....	31
3.1.2. Cost-benefit analysis	31
3.1.3. Cost-effectiveness analysis	31
3.1.4. Cost-utility analysis	32
3.2. The cost-effectiveness plane and the threshold decision point	33
3.3. What to measure: Costs and outcomes. The role of analysis perspective, time, and prices on HEE.....	35
3.3.1. Perspective of evaluation	35

3.3.2.	Time horizon and discount.....	36
3.3.3.	Currency, prices, and conversion.....	37
3.3.4.	Visualising costs for HEE.....	37
3.3.5.	Visualising benefits for HEE.....	38
3.3.5.1.	Measuring health gain in utility units. QALY.....	39
3.3.6.	Modelling in HEE: How to structure decisions.....	39
3.3.6.1.	Decision tree models.....	41
3.3.6.2.	Markov models.....	42
3.3.7.	Sensitivity analysis. Dealing with uncertainty.....	44
4.	Discussion.....	46
4.1.	Handbook proposal.....	46
4.1.1.	Handbook on HEE layout.....	47
4.1.2.	Objectives of the handbook on HEE for the VMH.....	48
4.1.3.	Target and scope of the handbook.....	49
4.1.4.	Developing recommendations.....	49
4.1.5.	Handbook-introduction route map. Using AGREE as a step mark for conducting the process.....	51
4.1.5.1.	Steps to introduce the handbook on HEE.....	51
4.1.6.	Special considerations applied to vaccines.....	52
4.2.	Feasibility study applied to vaccines: From theory to practice. How to implement such analysis in the VMH.....	53
4.2.1.	The VMH institutional structure to provide information. Stakeholders analysis.....	54
4.2.2.	Inputs need for CEA applied to vaccines.....	56
5.	Conclusion.....	59
5.1.	Limitations.....	60
5.2.	Further Research.....	60
	References.....	62
	Statutory declaration.....	67
	Appendix.....	68

List of tables and figures

Table 1: Scoring of selected HHE guidelines according to the CHEERS checklist	25
Table 2: HEE applied to vaccines considered in this research	27
Table 3: Review of main data included in HEE on vaccines	29
Table 4: Characteristics of the different HEE analysis types	32
Table 5: Summary of recommendations based on 'WHO guide to cost-effectiveness analysis' and VMH experience	50
Table 6: Unites potentially involve in HEE.....	55
Table 7: Specific data for HEE applied to vaccines	57
Figure 1: Graphic representation of CEA analysis results	34
Figure 2: Decision model selection flowchart.....	40
Figure 3: Decision tree basic model	41
Figure 4: Basic Markov stage diagram.....	44

List of acronyms and abbreviations

ACER	Average Cost-Effectiveness Ratio
BCV	<i>Banco Central de Venezuela</i>
CASE	<i>Comisión Andina de Salud y Economía</i> (Health Economics Andean Commission)
CBA	Cost-Benefit Analysis
CEA	Cost-Effectiveness Analysis
CER	Cost-Effective Ratio
CMA	Cost-Minimisation Analysis
CUA	Cost-Utility Analysis
DALY	Disability-Adjusted Life Years
GDP	Gross Domestic Product
HE	Health Economics
HEE	Health Economics Evaluation ¹
HTA	Health Technology Assessment
HS	Health System
ICER	Incremental Cost-Effectiveness Ratio
INE	<i>Instituto Nacional de Estadísticas</i> National Statistics Institute
LA	Latin America – Latin American
MPD	<i>Ministerio de Planificación y Desarrollo</i> Ministry of Planning and Development
MS	Ministry of Health
NICE	National Institute for Health and Clinical Excellence
NIP	National Immunization Programme
INH	<i>Instituto Nacional de Higiene</i> National Hygiene Institute
NHS	National Health System
NPHS	National Public Health System
PAHO	Pan American Health Organisation
PPP	Purchasing Power Parity
PH	Public Health

¹ HEE would be used as well in this research to refer to Economic Evaluation in general.

PHC	Primary Health Care
QALY	Quality-Adjusted Life Years
UHC	Universal Health Coverage
VMH	Venezuelan Ministry of Health
WHO	World Health Organisation
WHR	World Health Report
YLD	Years of Life with a Disability
YLL	Years of Life Lost
YLS	Years of Life Saved

1. Introduction

1.1. Problem Definition

Going top-down from the international context to the national one, discussions about health have always been a major topic. Perhaps two remarkable milestones are the Universal Declaration of Human Rights which was established in 1948 and stated that ‘everyone has the right to a standard of living adequate for the health and wellbeing of himself and of his family, including food, clothing, housing and medical care and necessary social services.’ (1). Later in 1978, Alma-Ata Declaration signatories noted that ‘Health for All’ would contribute both to a better quality of life and also to global peace and security (2).

Consistent with those declarations the health sector in Venezuela has undergone significant changes. The new Venezuelan Constitution (1999) sets new rights to health for the entire population, especially low-income individuals; it also asserts that it is the duty of the state to finance the system (3).

But recognising the relevance of health in modern society guides the discussion to a different level - how to achieve the concept of ‘Health for All’? For the World Health Organisation (WHO) the strategy is the access to Universal Health Coverage (UHC) (4), and it is clear that among other perspectives considering economical aspects is unavoidable.

In 2010 the WHO took into account the notorious gap in health access, and recognised in its World Health Report (WHR) the need to develop a health financing system that would allow its members to guarantee the health of the population being protected against financial risk. Later its 2013 WHR was focused on research as the way to move the UHC (5, 6) forward.

In the context of resources scarcity and rises in the cost of health something has to be done. The international answer to tackle this matter has been the establishment of health economic evaluation (HEE) as a requisite for health authorities, or health payers, when assessing introduction of new projects, programmes, new technologies, equipments, or drugs (7–10).

In the Venezuelan context progress in this direction has been slight. Despite the evidence of vulnerability that PH funding faces from unexpected economical changes, such as

reducing the VMH budget during 2009 following the drop of oil prices (11), the institution has not incorporated any formal criterion related to resources allocation additionally to the legal requirements for all governmental agencies. Iglesias CP *et al.* 2005 noticed that there is no HEE related to decision-making processes or planning routines in the institution, either by a established criteria or regular use of HEE studies. They assess four different aspects: resources allocation in general; provision of PH interventions; reimbursement of new drugs; and inclusion of services in health insurance packages² (12).

However, it has to be highlighted that through ensuing Pan American Health Organization (PAHO), and the Health Economics Andean Commission (CASE by its Spanish acronym) agreements a HE unit has been introduced within the Planning Department. It's first project focuses on an 'estimation of costs associated with maternal care, during antenatal care, labour, and postpartum' (13). Also four project drafts were developed following a HE training during 2012 but it is not clear if they have been finished (14).

Considering these facts it seems that the introduction of a handbook on HEE would be an initiative consistent with recent local experiences, and may also create a foundation to adequately conduct research in this field.

1.2. Research question

Although different projects and programmes, and in general healthcare facilities under the rule of the VMH, are in place providing all range of services (health promotion and prevention strategies; screening; treatment; and rehabilitation) to the population³, during the annual planning process I worked on there was a recurring debate point: Beside political decisions is there any criterion in place to incorporate new projects or to allocate additional funding?

From a personal perspective I considered that having an explicit benchmark would contribute to an open and transparent planning process, and therefore achieve greater

² The Venezuelan PNHS do not have reimbursement of new drugs. Inclusion of services in health insurance packages would refer to private insurance, nevertheless the situation is similar for services included by the VMH or other public institutions.

³ Due to the socio political panorama it may be necessary to clarify that this research does not pretend to assess services, not quality, neither its coverage.

participation from all actors involved to improve the quality of projects and programmes, but especially to increase efficiency in the institution.

How would this be achieved in the best possible way? In carrying out this research I hope to determine how to establish an effective guidance tool; to decide what kind of information would be needed; and moreover to assess the feasibility of performing HEE for vaccines in the VMH.

Another important factor to clarify is whether or not HEE is actually incorporated into the decision-making process in reality, and to identify key factors that may adversely affect this goal. Because one would expect that the use of HEE by the VMH's would subsequently improve efficiency within the institution.

In order to design an effective handbook it would also be important to determine the best way to structure and deliver the information, for which a review of the contextual situation will be summarised.

1.3. Background

Without attempting to cover all economical aspects regarding health in order to contextualise the develop of the handbook on HEE it is of utmost importance to present some basic concepts and terms related with Health Economics (HE), especially considering that some potential users of this research do not have necessarily knowledge on economical sciences or HE. The information presented below covers what was considered to be more relevant for HEE, and immunization policies due to the feasibility approach.

1.3.1. Some basics and concepts for understanding HE, HEE and the relevance of economical appraisal on health

First of all it is necessary to define HE and HEE. HE is a sub-discipline of economy, which in simple words means the scientific focus on study rational choices facing scarcity of resources, thus HE could be described as the study of 'rational choices' in terms of the scarcity of resources available to invest in health. HE studies among others aspects: health spending form a macro perspective and its impact on development; resource (budget)

allocation decisions; behaviour of actors (general population, healthcare providers, and workers) to establish payment strategies or introduce policies for behavioural change; and Health Technology Assessment (HTA) of which HEE is part.

HTA covers four different aspects: Safety, efficacy, quality, and cost-effectiveness (15). The aim of HTA in a way is to answer the questions: Is the technology in question safe for human beings? This is normally determined on clinical trials. Is it the technology effective to address the issue for what is being developed? This means for example that a new drug actually improves the specific conditions in question. Is it the technology produced for an entity following certain standards? And finally, is the technology cost-effective? This last question is address by HEE and will be covered next.

Under this discipline HEE defines the way of comparing different choices (health interventions), considering its costs and health effects (8,16–18), and determining which one is a better option. HEE could have different modes of analysis, cost-minimisation analysis (CMA); cost-benefit-analysis (CBA); cost-utility analysis (CUA); and cost-effectiveness analysis (CEA). They will be covered in section 3.1. HEE is among other aspects based on the micro economical concept of marginal benefit or marginal cost, and for its performance it integrates economic tools with epidemiologic and statistics ones.

To summarise in a simple way HEE could be understood as a tool to tackle a somewhat basic issue: the increase on health expenditure and the discrepancy in services access (19,20). The aim therefore would be to present evidence of the best possible choice from the available alternatives with the focus of getting the best health outcome, to support decision-making (17).

Before continuing it is important to emphasise that concepts covered next are those that are considered to be necessary for understanding HEE; they will later help to conceptualise particular characteristic of health. Important aspects regarding equity, transactions costs, and asymmetric information will not be explained.

Scarcity: The concept of scarcity in this context is related to availability of resources. As in any other situation resources in health are limited. There are a certain number of healthcare workers, health facilities, health technologies, and in general a fixed budget to allocate. On the other hand there could be some situations or problems to be addressed, and because health is particularly essential, these situations may demand more than what the

current resources are able to cover, this is known as budget constraint (21). Therefore a need to choose between options (health interventions for our concern) is present.

Opportunity Cost: In economic terms the opportunity costs of a certain good is defined by what you give up in order to obtain it (21). Thinking about health, the opportunity cost of implementing a scanning programme would be what we need to give up, if it was not possible to have a health promotion campaign or introduce a new vaccine due to the scarcity of resources. This cost should be considered when deciding resources allocation.

Benefit, marginal benefit, marginal cost, and maximisation: Economic theory establishes that people perceive benefit from using or consuming goods, but this benefit is lower when more is consumed (decreasing marginal benefit principle). Then the extra benefit from an extra unit consumed represents its marginal benefit. At the same time it is a necessary a trade-off, in order to consume a cost that has to be assumed; and again every extra unit would have a marginal cost (21).

The theory indicates that one will consume something until the point when the marginal benefit is equal to the marginal cost; then someone would 'maximise' his-her benefit. To better picture this concept someone would for instance go to the cinema once, pay the ticket, and spend what is necessary to do it. Whilst you keep attending the benefit of an extra picture would be lower, but yet you still have to pay and spend the time. Someone would do it until the point that attending one more picture would add less 'pleasure' than the extra cost the action implies. This concept could be applied to 'public health' interventions, but probably it is less clear from a personal perspective.

Efficiency: At this point opportunity cost, budget constraint, and maximisation could be seen as an interaction. A person would choose from alternatives and consume to maximise his/her benefit, according to the budget constraint in place. In the same way a health authority would choose from different health interventions, trying to get the higher benefit, within a given budget (17). Under this circumstance it is possible to say that it has reached an efficiency point.

Equity: In basic terms equity could be understand as a proper distribution of goods, in this case health and healthcare. This could be seen from two perspectives, horizontal equity, and vertical equity. Horizontal equity refers to an equal distribution between 'equals', in terms of health same healthcare access for people with similar needs. On the other hand,

vertical equity refers to a differentiated healthcare access for those with different needs. Yet the point would be how to assess those situations (16).

Trade-off between efficiency and equity: In spite of being both, efficiency and equity desirable, there is a trade-off between them. It is perceived that facing a given mix of resources it would be necessary to give up efficiency to be more equitable, and vice versa. For instance although allocating resources to implement a surgery programme in rural areas would enhance equity; allocating the same resources in an urban area could be more efficient, in terms of what outcomes we would get for the same budget.

Choices: From an economical point of view people continuously take decisions among different alternatives available. There is a trade-off between resources and potential benefits, and it is expected that those choices pursue maximisation of benefits, therefore efficiency (21).

The concepts covered until this point are economical principles, those that define how 'economics' works. But those principles are not always present, especially for the health sector (21). So, what is known as the market tends to fail regulating supply and demand of health. The following points will give a better idea of why.

The relevance on all concepts commented above regarding health and healthcare are clearly define by Gray et al. 2011:

“The concepts of scarcity and choice will have resonance for anyone involved in the planning and provision of health care: the available resources are never sufficient to allow all available health interventions to be provided, and so choices have to be made, which sometimes involve very difficult decisions.” (22) p.1

Other aspects specifically related with HEE will be covered in section 3 where results are presented.

1.3.2. Why is the public intervention in health justified from an economical perspective? Health, public goods and economical principles failures.

The previous section mentioned some of the basic principles of economics, but clearly not all of them, or not all the times they are present when the analysis is focused on health. And on top of that some health interventions could be characterised as public goods by economic science.

Public goods: In economics public goods are defined as those that fulfil two characteristics, non-rivalry and non-excludability. Non-rivalry means that when someone consumes this good, it does not affect someone else to access the same good. Non-excludability means that when a good is provided to someone, it is not possible to avoid someone else to enjoy the good; this situation causes a dilemma, no one would pay for the costs of this good if everybody could access it, and consequently there would be no good. This paradox is known as free-rider in the literature. A good health example would be an awareness campaign of promotion of safe-sex practices for instance, also epidemiological surveillance systems (17,21).

For these goods it is clear that the government needs to intervene, if not no private entity would produce this good, because no one would pay for it.

Some principle failures: Beside public goods, some characteristics of health itself and other factors such as externalities affect efficiency, and also HEE; justifying governmental intervention at some grade⁴.

Personal choices that achieve maximisation of benefit from a private perspective could be perceived negative from a PH point of view. For instance the so called modern-lifestyle (lack of physical activity and less than favourable eating behaviour), or smoking and alcohol consumption for instance would clearly affect health status; but it affects society as well, via increasing morbidity-mortality rates, and also healthcare services demands. This scenario could lead health authorities to intervene implementing awareness campaigns, or introducing taxation for example (21). This is more obvious in countries like Canada, the UK, and also Venezuela where the Health System (HS) is primary based on general taxation; so health expenditure is a direct concern of health authorities.

Another important aspect to mention is the externalities. Some health interventions would have positive effects on the general population when just a group accesses the intervention. Immunization is a clear example, when a segment of the population is immunised against certain disease, non-immunised people also would benefit by reducing the chance of getting sick. Under this scenario it would be necessary to consider positive external effects of the intervention when performing a HEE (16,17,21).

⁴ Regardless of political view the government does clearly play a role in PH. The degree of intervention that different people perceive as appropriate would naturally depend on his own point of view.

Finally it would be worth to mention that health is especially relevant for the well-being, it affects personal behaviour in terms of 'economical choices'. As mentioned earlier there is an assumption of decreasing marginal benefit, but in case of health this principle does not always apply. Also when there is not a visual cost (price)⁵ for the person who accesses the service, it could be even more common that consumption behaviour does not follow economical principles. This situation is notable in cases where people expect to prolong life after a treatment, or relieve acute pain.

Those cases warrant governmental intervention, and this could be done by defining what services are provided based on HEE.

1.3.3. Use of HE worldwide and in Latin America

HE has being mainly developed in industrialised countries and is less common among Latin American (LA) ones (7,9,16,23). Probably the best known example is the United Kingdom (UK) where there is a National Institute for health and Clinical Excellence (NICE) which sets criteria for HEE to be used by the National Health Service (NHS). Some of them have developed mandatory guidelines (e.g. Australia; Brazil; Canada; Colombia; Mexico; the Netherlands; and the UK) with some of those guidelines released as recommendations (e.g. Chile); and some others have experiences in performing studies on HE without formal guideline (for instance Argentina where is there is a Institute for Clinical Effectiveness and Health Policy (23)). This matter will be mention again in section 2.1.

Probably a common characteristic of countries where HE and HEE is more common is based on the fact that there are separate institutions for funding; policy-making; provision of services, in addition to other actors such as manufacturers and of course users of services.

⁵ Price may not be perceived as a constrain in presence of a general taxation-based HS, or by being insured.

1.3.4. The role of HE and HEE in the decision-making process

It has been mentioned that the aim of HE and HEE is to support policy makers by providing them with understandable, transparent evidence to support their decisions. In fact studies are often performed with this final objective.

To assess if evidence is really considered and impacts upon policy development some studies use different approaches, either focusing on one country, or with a wider perspective. With variable results it seems like at least in the United Kingdom (UK) policymakers consider indeed evidence produced by HEE when taking their decision.

An evaluation of the UK NHS Health HTA programme shows that the two thirds of its projects had an impact on policy design (24,25), although it should be expected because its studies are prepared to be delivered to other NHS dependant bodies such as NICE. A previous study from HTA showed some contrasts, while at a national level the NHS incorporated HEE in its policy decision, on a local level cost implications and clinical benefit were mainly the base of decisions. Nevertheless, it shows a integration of HEE into policy action (26).

On the other hand a systematic review that considered 43 studies from the UK; Australia; Canada; and the United States concluded that evidence of the use of HEE to support decision-making was limited and irregular. However 30 studies found evidence indicating that HEE impacted policy (27).

From this brief review it seems that evidence is not conclusive. Nevertheless when HEE is performed by an agency related with the health authority it tends to be incorporated into the decision-making process.

1.3.5. Transferability of HEE for LA

Due of the disparity in HEE expertise worldwide, it could seem productive to use evidence produced by a different country but this may not be entirely possible. It may be tempting to start by applying the findings of one research to another setting but this should not be done. Basic inputs for such a study (demographic data; socioeconomic characteristics; burden of diseases; or cultural behaviour) are expected to differ, making inconsistent any generalisations of its findings (28).

As regard of transferability of HEE from one Latin American country to another one, understood as the potential of such HEE to adapted for a new setting according to Drummond *et al.* 2009 -cited by (9), evidence indicates that beside major recent improvements on HEE in the region some challenges are still present. In general HEE methodology in LA has weaknesses related for instance with specification of decision problems or standards of studies use by those HEE that in consequence restraint its transferability.

Those findings are important to highlight taking into account that some stakeholders (advocacy groups) could intend to make pressure to get a different treatment based on HEE for a different setting. Alternatively policy makers could decide to implement a new intervention based on evidence of a different country.

1.4. Objectives of the study

- To develop a proposal of handbook on health economic evaluation to be used by the Venezuelan Ministry of Health.
- To analyse the feasibility of cost-effectiveness analysis applied to vaccines in the context of the Venezuelan Ministry of Health.
- To present a summary of relevant health economic topics to support and help with a better understanding of the discipline within the Venezuelan Ministry of Health.

1.5. Study relevance and justification

As previously mentioned there have been some attempts to do some work in the field of HE in the VMH, partially because of regional agreements between CASE and PAHO members, and also due to the perceived budgetary constraints.

The country has established NPHS financed via general taxation as a model for the health sector, focusing on Universal Health Coverage (UHC). According to the WHO, actions to improve health financing are essential to improve UHC (5,6,29), consequently research focusing on understanding -and later improving- the way resources are allocated in the NPHS would represent a great contribution. This is the role of HEE, to help decision

makers in the process of identifying interventions that would provide the best outcome-health status for the investment (30).

This project could be helpful to orientate the introduction of academic-based health policies to ensure a sustainable NPHS that could eventually support the development of regulations that remain regardless of governmental changes.

For the specific case of HEE applied to vaccines it is important to mention a couple of aspects.

First of all it is worthy to mention that the NIP is one of the best structured in the country, it counts with regular budget allocation since 1997; the surveillance system is in place for most communicable diseases; and well qualified personnel is dedicated exclusively to the programme (31).

The country also participates in the PAHO's Revolving Fund for Vaccine Procurement, which helps to get access to vaccines with considerable savings. But despite the continuous contact with PAHO, Venezuela has not joined its ProVac initiative, the regional WHO programme focused on support evidence-based decision making related with vaccines (32).

Also it is necessary to highlight that there is not in place a formal National Immunization Technical Advisory Group (NITAG). In fact is, beside Guyana, it is the only country in South America where there is no NITAG (33); even though literature indicates that well established decision-processes are necessary to ensure transparency and reliability of decision-making related with vaccines introduction (34).

Another factor to consider when deciding to perform the feasibility applied to vaccines was the pressure that the author witnessed from patients advocacy-groups, and pharmaceutical companies to introduce an specific vaccine to the NIP.

Those facts support the idea that a national action may be more effective in terms of involving policymakers. Considering that it is expected to be a sufficient capacity to perform such assessments applied to vaccines.

1.6. Target – Scope

The Handbook presented as a result of the Master Thesis research intends to be a useful tool for public health experts, head of projects, programmes and departments; as well for planning and managerial professional who act as a support for policy makers within the VMH. It is a compilation of pertinent concepts and basic methodology aspects to create the base of HEE in the setting.

We hope that users from academic institutions have access to this material, to use it and eventually contribute to its improvements when need it.

The handbook also aims to lay the foundations for a more systematic, regulated, and organised way to establish the use of HE techniques in Venezuela. Without question this would be a first step from where more actors are expected to be involved and broaden the scope of the handbook.

It is relevant as well to mention that this handbook is a first approximation of a formal introduction of HEE in a systematic way. It does not pretend to be a fully comprehensive tool to cover all aspects regarding HE or HEE; it neither intends to be a sufficient source of information to train personnel. Other sources and references need to be reviewed to understand all details of modelling and estimations. Without question this would be a first step from where more actors are expected to be involved and the scope of the handbook would be wider.

2. Methods

In order to find pertinent literature a search was performed in electronic databases: PubMed, SciELO. Also Google search engine and Google Scholar were used to identify other possible sources of information, and to find organisations related with the topic. Search terms such as: ‘health economics’, ‘health economics techniques’, ‘guideline’, ‘handbook’, ‘cost-effectiveness analysis’, ‘vaccines cost-effectiveness analysis’, ‘policy’, ‘public policy’, ‘public health’, ‘Latin America’, and ‘Venezuela’ (either by themselves or combined, and with synonymous). The data searching conducted was not a systematic review.

Because of the country of interest some papers and sources in Spanish were incorporated and referenced accordingly. In addition published bibliography was reviewed, and information related with the VMH was retrieved from its official website.

The objectives and layout of this research was discussed with former colleagues from the VMH, who worked on the previous experiences.

The process to develop the handbook on HEE was conceived as an integration of three different perspectives. First of all, it considered a review of relevant theory concerning HE, and HEE; second, a review of existent guidelines, and recommendations for HEE; and finally a special consideration about the setting for which the handbook is designed to assess feasibility of such intervention.

It has to be clearly established that for this handbook there is a major relevance of information from LA experiences, specifically for countries comprising the CASE –those are: Bolivia, Chile, Colombia, Ecuador, Peru, and Venezuela. This is under the assumption that those institutions may have regional similarities that require an equal strategy for data collection, and would allow easy transferability of the methodological development.

2.1. Relevant aspects for developing a handbook on HEE

To face the challenge of developing a handbook on HEE it seems obvious to start by reviewing experiences on the topic. The literature indicates that just four countries in the LA region have an approved instrument regarding HHE under the figure of guideline (9,10,23); namely Brazil, Colombia, Cuba and Mexico. On top of that Chile has recently

released a document as a recommendation because it has still not been established as a mandatory requirement (35). As it was mentioned in section 1.3.3, this is clearly a field mainly developed in industrialised countries from Europe; Canada; United States of America; Australia; New Zealand; and China (7,23).

But because of the differences in setting, aim, or the process of developing those guidelines they may have differences with their structure and methodology; whereby it would be necessary to scrutinise them to determine what is generally incorporated it.

Also, because of the increasing amount of literature regarding guidelines on HEE, authors have performed assessments to compare their structure, develop different approaches to evaluate the quality of the evaluations they contain, or simply compare different appraisal instruments (7,30,36,37). All of them with the ultimate goal of improving HEE, guiding research reporting, and moreover making life easier for the policy makers and decision-making bodies with the process of assessing published researches.

Under this panorama it seems necessary to look at them to sustain the design of the handbook on HEE for the VMH. As assessing those methodologies is not the main objective of the present research they are considered as a model for the handbook structuring.

2.1.1. A brief overview of some guideline development tools

The study of Hjelmgren *et al.* 2001 (7) compared guidelines available at the time using 15 items of observation derived from theoretical framework, in the form of qualitative analysis focusing in the existent or not of those items. The study of Joshua *et al.* 2003 (30) creates an quantitative instrument assigning value points to 16 item questioner that covers a similar range of levels as the Hjelmgren *et al.* 2001 study.

Meanwhile Langer 2012 (36) focused her work on assessing other instruments designed to evaluate HEE guidelines. A review of its methodology revealed that beside minor differences it is quite similar to the ‘appraisal of guidelines for research and evaluation instrument’ known by its acronym AGREE (38) –commented below. It contents seven dimensions from which five are equivalent to those incorporated in by AGREE.

Finally we comment on Husereau *et al.* 2013 (37) work, named ‘Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement’, it presents a 24 item checklist structured in six domains that could lead researchers to release their work in a well-framed and understandable way. The CHEERS checklist also includes a brief recommendation for each item, making it easy to follow and implement.

The CHEERS checklist is presented on Appendix 1 and would be used as a benchmark for the layout of the handbook. The idea is to identify what aspects are recommended to be reported along a HHE, and therefore it may be ideal to cover them in the handbook.

Beside contributions specifically focusing on guidelines on HEE, other methodologies for general guidelines development and appraisal have been released. With respect to guideline development, WHO handbook (39) presents a fully comprehensive process, including recommendations regarding the need for a guideline, to its implementation and publication. On the other hand, regarding guidelines evaluation, an exhaustive instrument was collected as an international effort with the aim to tackle the existing heterogeneity present on guidelines - the ‘appraisal of guidelines for research and evaluation instrument’ known by its acronym AGREE (38). One of the best attributes for the AGREE instrument is that it provides the user with a complete on-line access to training resources, templates to download and print, and it is available in different languages, including Spanish, which corresponds with the future implementation settings of the present research.

A common aspect of those documents is that they propose a checklist to easily perform a guideline assessment. For this research this would be examined in a retrospective way in order to contribute with design of the handbook.

Because of its free accessibility on-line, and being available in Spanish the AGREE tool will be considered to guide the further discussion, and aid in the final development and implementation of the present handbook.

2.1.2. Comparing LA guidelines

The primary scanning of information regarding HHE was focused on CASE member countries, and therefore for the process of defining the handbook a comparison of the regional available experience was considered necessary. From the five published

guidelines on HEE just two of them are from CASE region, the one corresponding to Brazil was been excluded for linguistic reasons, leaving Chile; Colombia; Cuba; and Mexico (35,40–42).

To have an idea of the final four guidelines considered a brief synthesis is presented next, and an overall comparison of them using a modified CHEERS checklist can be read below in **Error! Reference source not found.** The scoring of the checklist was performed considering the explicit recommendations incorporated in each guideline for HEE reports.

Chile: The guideline on HEE is called *Guía metodológica para la evaluación económica de intervenciones de salud en Chile* (35). It was released on March 2013 and prepared by the Ministry of Health. It has the purpose of acting as a recommendation, and until its publication there was not binding regulation in place. The guideline seems to be the result of a long term process and incorporated previous research outcomes, some of them the product of contracted consulting with third party actors –mainly academic institutions. These facts support what was stated in this thesis handbook. Guidelines on HHE development in our case hand book, tend to be a medium term action.

Colombia: The guideline name is *Manual para la elaboración de evaluaciones económicas en salud* (40), released in 2014 by the *Instituto de Evaluación Tecnológica en Salud*, which is the Colombian institute for health technology assessment created in 2012 with the clear aim of contributing to the sector providing evidence-based information. The publishing body is integrated in the health authority, and other research, scientific, and academic agencies. The institute considers reviewing the guideline annually to ensure its continued applicability. The document incorporates the CHEERS check list as criteria to proceed with HEE.

Cuba: The *Guía metodológica para la evaluación económica en salud* (41) from Cuba was officially published in 2003, its development started as part of a project financed by the European Union and it was lead by the MH of the country. Different institutions participated in the process and international consulting was considered.

Mexico: The new edition guideline from Mexico was released on February 2015 by a Governmental agency that gathers all public institutions related with health, and healthcare. It is called *Guía para la Conducción de Estudios de Evaluación Económica para la Actualización del Cuadro Básico y Catálogo de Insumos del Sector Salud en México* (42).

Table 1: Scoring of selected HHE guidelines according to the CHEERS checklist

Section/item	Item No	Chile	Colombia	Cuba	Mexico	Total
Title and abstract						
Title	1	X	X	X	X	4
Abstract	2	X		X	X	3
Introduction						
Background and objectives	3	X			X	2
Methods						
Target population and subgroups	4	X	X		X	3
Setting and location	5		X			1
Study perspective	6	X	X	X	X	4
Comparators	7	X	X	X	X	4
Time horizon	8	X	X	X	X	4
Discount rate	9	X	X	X	X	4
Choice of health outcomes	10	X	X	X	X	4
Measurement of effectiveness	11a	X	X	X	X	4
	11b	X	X	X	X	4
Measurement and valuation of preference based outcome	12	X	X		X	3
Estimating resources and costs	13a	X	X		X	3
	13b					0
Currency, price date, and conversion	14		X			1
Choice of model	15	X	X	X	X	4
Assumptions	16	X	X	X		3
Analytical methods	17	X	X			2
Results						
Study parameters	18	X	X	X	X	4
Incremental costs and outcomes	19	X	X	X	X	4
Characterising uncertainty	20a	X	X	X	X	4
	20b		X			1
Characterising heterogeneity	21				X	1
Discussion						
Study findings, limitations, generalisability, and current knowledge	22	X	X	X	X	4
Other						
Source of funding	23	X		X		2
Conflicts of interest	24	X	X		X	3
Total	27	22	22	16	20	

Source: Checklist adapted from Huserau *et al.* 2013 (37) to assess guidelines. Items selected are highlighted.

The guideline presents the legal framework for its implementation being mandatory in Mexico, a HEE to justify financing of new technologies. One particular attribute is that it contains a section on the transferability of HEE.

Overall it is important to highlight that all guidelines share some core objectives: They help to individuals carry out research with limited background in the field; they aid better comprehension of HEE literature by non trained personnel; they enhance validity, transparency, and credibility of HEE research; and finally they support decision-making processes by providing evidence-based information.

Additionally they provide a list of concepts and terminology to help novice users to understand HE, and a layout for HEE presentation is provided as well. Chile, Colombia, and Mexico incorporated an extended appendix for HEE reporting.

2.1.3. Scoring according to the CHEERS adapted-checklist

The guidelines from Chile and Colombia scored 22 out of 27 (three of the 24 items consider two values), Mexico 20, and Cuba 16. From the point of view of items 13 (48.15%) were present in all guidelines; six (22.22%) were present for three countries, three (11.11%) are covered by two countries –Chile as a common for the three items, four (14.81%) items are presented in just one guideline; while the one remaining (13b) was not mentioned at all.

This result will help to structure the handbook, for its content and recommendations. From this scores the item that was not present in the guidelines will not be consider; two out four items mentioned once will be take into consideration: No 14: ‘Currency, price date, and conversion’ because of the relevance in the Venezuelan high inflation economy; and No 5: ‘Setting and location’, because of the defragmentation of the health sector.

In section 3 are presented all relevant aspects to fulfil the handbook sections derived from this scoring.

2.2. HEE applied on vaccines. Which data is relevant for the evaluation according to HEE evaluations published?

To determine which data is relevant for HEE applied to vaccines, the scanning of information was focused on published research from CASE member's countries. The idea is to assess their content to later use the result as criteria for the feasibility study.

Using the terms ((cost effectiveness[Title]) AND vaccine[Title]) AND country name [Title]) on PubMed for all CASE member's countries retrieved just three studies, one from Chile, and two from Colombia. Therefore the term Latin American was used instead of country name, retrieving two studies.

Because of the limited available literature a second search was performed, this time focusing on possible Spanish articles using SciELO database with the following criteria(((costo [Title words]) and efectividad [Title words]) and vacuna [Title words]). It retrieved a total of 37 articles, of which 8 of them were duplications, resulting in 29 different articles specifically on CEA on vaccines. From there it was possible to incorporate one study from Venezuela and one from the two available from Peru. This was considered to have a more broad perspective from the CASE member's countries. In total six studies presented in Table No 2 were considered.

Table 2: HEE applied to vaccines considered in this research

Country / Region	Study name	Year of publication
Chile (43)	Potential cost effectiveness of a rotavirus vaccine in Chile	2006
Colombia (44)	Cost-effectiveness analysis of pneumococcal conjugate vaccine 13-valent in older adults in Colombia	2014
Peru (45)	Health and economic impact of human papillomavirus 16 and 18 vaccination of preadolescent girls and cervical cancer screening of adult women in Peru	2012
Venezuela (46)	Assessment of the economic impact of the antiretroviral vaccine in Venezuela	2006
LA (47) (Argentina, Brazil, Chile, Mexico, and Peru)	Cost-effectiveness analysis of a cervical cancer vaccine in five Latin American countries	2009
LA (48) (Argentina, Brazil, Chile, Colombia, Mexico and Peru)	A cost-effectiveness analysis of a 10-valent pneumococcal conjugate vaccine in children in six Latin American countries	2013

Source: Self designed.

A general observation review was performed and the basic data necessary for a HEE applied to vaccines identified in those studies is summarised in Table No 3. It was constructed using a self-designed checklist. The items were checked when the inclusion of information regarding the item was explicit, and then reported in the research method, results or discussion.

The inputs generally used could be summarised in: 1) Demographic data; 2) Clinical data for case definition and background; 3) Epidemiological data (incidence; mortality; burden of disease, actual vaccination coverage when in place); 4) Healthcare facilities statistics (to determine services used); 5) Clinical information about vaccine efficacy; 6) Economical data (costs estimation, discount rate). Depending on the disease for which the vaccine is used a Markov Model may be needed to consider different estimates; or a Monte Carlo simulation model, information regarding this two last points will be presented on section 3.3.6.

Three of the inputs were present just in the study from Venezuela and those covering more than one country from the LA region. The inputs in question are: Setting information and infrastructure in place, direct non medical costs, and indirect costs.

The common items retrieved from this review could be used for the feasibility assessment applied to vaccines presented in section 4.2.

Table 3: Review of main data included in HEE on vaccines

Input / Country	Chile	Colombia	Peru	Venezuela	LA (47)	LA (48)
Background - Case definition and comparators.	X	X	X	X	X	X
Setting information, infrastructure in place.	X				X	X
Demographic information	X	X		X	X	
Epidemiological data from surveillance system	X	X	X	X	X	X
CEA / Method	DALY ⁶	Cost saving	YLS ⁷	DALY	CEA / CUA ⁸	QUALY ⁹ gained
Modelling		MM ¹⁰	MCSM ¹¹		MM	Dec. Tree
Healthcare statistics	X	X	X	X		X
Vaccine efficacy and vaccination coverage	X	X	X	X	X	X
Costs either direct or by estimations						
Vaccination costs	X	X	X	X	X	X
Direct medical-care costs	X	X	X	X	X	X
Direct non medical costs - indirect				X		X
Sensibility analysis		X	X	X	X	X
Discount rate (3% in general)	X	X	X	X	X	3.5%

Source: Self designed.⁶ Disability-adjusted life year⁷ Year of Life Saved⁸ Cost-utility analysis⁹ Quality-adjusted life- years¹⁰ Markov Model¹¹ Monte Carlo Simulation Model

3. Results. Elements for a Health Economic Evaluation

In section 2.1 aspects to be included in the handbook were identified from a comparison of experiences in LA based on the CHEERS adapted checklist. The items selected go from those covering general aspects about the desirable outline of a HEE, to those more technical regarding methodology. They are meant to be part of a HEE report itself.

General aspects items: Title; Abstract; Background and objectives; Target population and subgroups; Setting and location; Study parameters; Study findings, limitations, generalisability, and current knowledge; Source of funding; and Conflicts of interest.

Methodological items: Study perspective; Comparators; Time horizon; Discount rate; Choice of health outcomes; Measurement of effectiveness; Estimating resources and costs; Currency, price date, and conversion; Choice of model; Assumptions; Analytical methods; Study parameters; Incremental costs and outcomes; and Characterising uncertainty.

Now it is necessary to go through all basic concepts to perform and understand HEE. They will not be organised as they normally appear in HEE reports, but in a logical way to better understand the idea behind the analysis. The logic is to have the necessary knowledge to fulfil all items when structuring a HEE. Also it must be clarified that the next points do not pretend to be a fully descriptive explanation of HEE different methods, they rather intend to illustrate key notions to guide the reader of the handbook. More in depth information could be found in the specialised literature (8,16–18,21,22). Aspects about general items will be presented in section 4.1 where the HEE outline is summarised.

3.1. Types of HEE

It was already explained that HEE is the analysis used to compare a range of alternatives (e.g. vaccines; drugs; screening programme; or promotion campaign), combining an assessment of its costs and benefits. It was also mentioned that there are four forms of HEE: CMA; CBA; CUA; and CEA. They differ in their means of analysing benefits/outcomes of health interventions, while assessing cost in monetary units.

3.1.1. Cost-minimisation analysis

In this analysis the alternatives under study have similar outcomes. They don't differ in terms of their health benefit, so the analysis is focused on comparing their costs. This analysis could be used on drugs with similar effectiveness. The idea is to find the best option in terms of a lower associated cost (15,37).

3.1.2. Cost-benefit analysis

This type of evaluation assesses and compares all benefits and costs related with the interventions under study. For that reason they have to be in the same units. So, benefits are measured in natural units and then represented in monetary ones to perform the CBA. The transformation into monetary units could lead to some difficulties, and also some controversy. For instance how can one value in monetary units an improvement in health status? (15,17). Therefore it would not be recommended for HEE, not being common to find this kind of evaluation in literature related with health. Nonetheless it has uses for cross-sector assessment (49).

3.1.3. Cost-effectiveness analysis

Cost-effectiveness analysis measures health outcomes in their 'natural' unit, depending on the intervention. Those units could be case detected, hospital days prevented, laboratory test performed, and even clinical units such as blood pressure. The evaluation between alternatives is done in relative terms, meaning how much it costs to prevent a case, or to perform a test, this is known as cost-effective ratios CER; $CER = C/B$. Then, to compare the alternatives, the differences between costs and benefits give us the incremental CER, or ICER (8,17,22). Where $ICER = (C_2 - C_1) / (B_2 - B_1)$.

This evaluation has an important disadvantage. It would not be possible to use CEA to compare interventions for which benefits are measured in different units (15,22). It would be also unsuitable to evaluate interventions with multiple outcomes (15).

3.1.4. Cost-utility analysis

The CUA is similar to the CEA, in the way that it assesses incremental ratios but they differ on how to measure health outcomes. CUA uses a utility measure. In the field of health this corresponds to a quality of life unit. The concept commonly used is defined as Quality Adjusted Life Year (QALY); a QALY combines life expectancy and quality of life itself. This conception would be explained with more detail in section 3.3.

This analysis has two important uses on HEE. First, it allows comparing interventions with dissimilar health measures, for example a breast cancer screening program or an environmental interventions to reduce malaria incidence. In this case measuring health consequences with QALYs would be convenient. And secondly, it becomes possible to evaluate interventions that have multiple health impacts, because an intervention could prolong life and improve health conditions at the same time (15,18,22,49). On the other hand, it is important to recognise the difficulties related with assessing quality of life, itself a subjective task.

A summary of the different types of HEE analysis and its characteristics is shown below.

Table 4: Characteristics of the different HEE analysis types

Characteristic	Type of HEE			
	CMA	CEA	CUA	CBA
What is evaluated?	Alternatives with similar effectiveness	Alternatives with outputs are in the same unit.	Alternatives for which benefits are expressed in utility units	Evaluating between programs with important non health-related benefits or between sectors
How are costs expressed?	Monetary units	Monetary units	Monetary units	Monetary units
How are benefit expressed?	Not consider for being equivalents.	Natural or clinical units	Utility values (QALYs)	In natural units and then transform into monetary units

Source: Self designed.

Some considerations about CEA and CUA: This mathematical construction has the quality to provide information to guide decisions regarding resources allocations especially in those cases where the ‘price’ is not visible for the person who receives or uses the resource. As healthcare tends to be covered by healthcare insurances or financed by the

government the decision about which option to take is more complicated (20). This is the analysis commonly use for HEE.

Despite the CEA being of use in general for prospective studies, it has a wider application to assess a group of different interventions to determine the mix that would provide the best possible outcome (50,51). The problem with this approach is that first an incredible amount of information, time and resources would be required. Secondly it would be difficult to incorporate social inequalities (20,51). In other words, it helps to allocate new resources, but also to re-allocate them from a possible 'less' cost-effective intervention to a better one (50).

It is also important to add that the term CEA is commonly used to refer to both cost-effectiveness and cost-utility analysis because it is assumed that CUA is a CEA with a particular outcome measure. Hereafter information will be focused on CEA, being the one typically use for HEE.

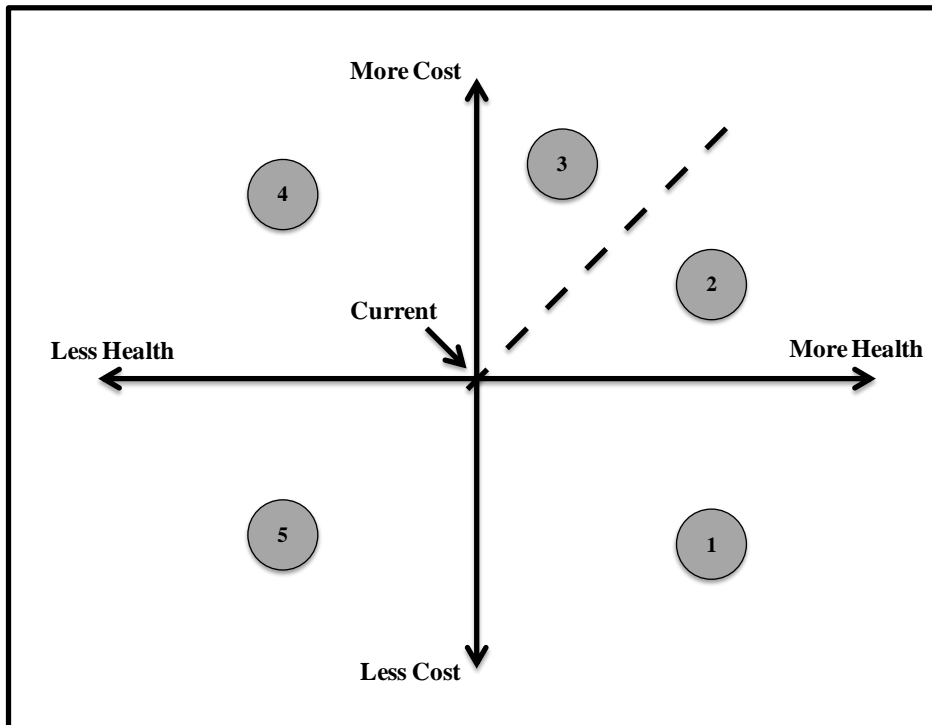
3.2. The cost-effectiveness plane and the threshold decision point

At this point it is possible to have an idea about the forms of HEE, but a decision criterion is needed in order to know when an intervention would be better, or in HEE terms, more cost-effective (8,22). A graphic interpretation of CEA results could be seen in Figure 1. There are five possible scenarios:

- 1) The intervention evaluated is cheaper and more effective. In this case the new intervention is cost-effective. The new treatment is clearly dominant.
- 2) The new intervention is more expensive, but more effective as well. The intervention would be technically cost-effective.
- 3) The new intervention is more expensive but without extra advantages. The new intervention is not cost-effective.
- 4) The new intervention is more expensive, without extra advantages. The new intervention is not cost-effective. The current treatment is clearly dominant.

5) The new intervention is cheaper, but gives fewer health benefits as well. The new intervention is not cost-effective. The decision at this point is about how much ‘benefit’ would be exchange for saving money.

Figure 1: Graphic representation of CEA analysis results



Source: Self designed based on Annemans (2008) and Gray A *et al.* (2011)

To answer this question another factor has to be considered, a threshold until the point where there is willing to ‘buy’ cost-effectiveness, but this should come from countries in a consensus. WHO for its part suggested in 2001 a new intervention ‘very cost-effective’ when the cost of gain a QALY is less than 1 Gross Domestic Product (GDP) per capita. On the other hand an intervention should be considered ‘non cost-effective’ when gaining a QALY costs more than 3 GDP per capita (35,40). But again, this decision depends on the particularities of each HS; they differs from country to country (8).

3.3. What to measure: Costs and outcomes. The role of analysis perspective, time, and prices on HEE

In order to perform the HEE it is necessary to identify and collect the costs and benefits related with the health interventions. The data could sometimes be available in administrative records, but mostly it may be necessary to calculate it, or get approximations. Ways to obtain data could be synthesise in three methods: obtained directly through database review, inferred through observation using questionnaires or interviews; or by empirical analysis (8,49).

But when calculating resources and outcomes from the intervention it is important to keep in mind that some factors involved would probably change depending on the perspective of analysis, the time horizon, and be affected by economic factors such a inflation or currency exchange. In understanding the costs and benefits involved some questions have to be answered: Are we considering resources afforded by a specific healthcare provider; by the health system; by patients and families? Are those resources direct or indirect? Are we going to measure the benefits of people involved directly with the interventions, or externalities as well? The analysis looks at a point on time. Therefore how are costs/benefits are distributed over time?

All this has to be clarified because affects HEE results.

3.3.1. Perspective of evaluation

The perspective of the study may change the result of the analysis; and by perspective HEE refers to the consideration of the different ‘actors’ that could be covering costs associated with the intervention in question, and also those benefiting. The literature suggests that a ‘societal perspective’ should be considered (8,15,16,18), but this point of view could be narrowed, taking into account just a healthcare facility, health authority (for instance the VMH), or the HS. The broader perspective is theoretically preferred but it leaves many difficulties to measure (8).

In practice the first experience from the VMH mentioned earlier was conceived as a two-step analysis. First, from the VMH point of view; then a patient-family perspective would be added (13).

The perspective also has a second view. What kind of cost and benefit is being considered on the HEE? Direct medical costs/benefits, indirect costs/benefits associated with the health interventions; or also costs/benefits others affecting other sectors (e.g. productivity at work, education).

Perspective and HEE applied to vaccines: The evaluation of vaccine interventions is particularly sensitive regarding how wide the perspective in place is. Bloom DE, and Madhavan G (2015) (52) mention for example how current evaluation models (specifically studies applied on vaccines) tend to incorporate medical benefits of immunization, but exclude collateral benefits such as school attendance, that in future may affect socio-economical development; but again the key factor is how to value those inputs in a valid model? A research by Bärnighausen T *et al.* (2014) (53) covers studies focusing on a broader analysis applied to vaccines.

3.3.2. Time horizon and discount

Time is incorporated in HEE evaluation for different reasons. Health status may change over time, affecting variables associated with the analysis. Incidence of a disease for example, people could get infected with a virus, present symptoms of sickness, but also recovery; all these situations would affect need for healthcare (18). Also prevention and promotion interventions would provide benefits with time. If the HEE considers only factors in the present time it would be impossible to evaluate such kind of interventions (50).

Discounting basically incorporates preferences about time, this concept is associated with price inflation but even in an hypothetical scenario of no inflation people would prefer to have a benefit now, rather than later (49). Time, and therefore discount is applied because the future is uncertain (50).

To discount costs and benefits a rate is needed, but there are discussions about its application for health effects. Nonetheless it is commonly applied. It is also possible to use a different discount rate for costs and benefits. In general every country adopts its own discount rate, literature suggests using 3% or 5% (8,54). According to the LA guidelines and LA HEE applied on vaccines, the dominant practice in the region is 3%.

Time horizon-discount applied to vaccines: It is important to keep in mind that discount would affect evaluations that involve prevention intervention and healthcare services, but in an unequal way. Considering that prevention programmes would ‘payback’ with benefits in the future, discount would make them look less cost-effective after discount (50).

3.3.3. Currency, prices, and conversion

Cost valuation is affected by prices, and they tend to vary over time (50). This reality is particularly relevant for the Venezuelan context. The same apply for resources that need to be imported and paid for with international currency. Exchanges rates may change drastically. Under this scenario it would be essential to include a clear identification of time. Information collecting data and purchasing goods dates, and conversation rates applied have to be specified. All those aspects related with the economical environment in the setting will affect the discount rate.

By conversion it is also important to have in mind studies covering different countries. Market currency exchange may not be adequate in this case, it may my better to use the ‘international dollars’ based on the purchasing power parity (PPP) (54).

Now it is necessary to go back to the costs and benefits identification to perform a HEE.

3.3.4. Visualising costs for HEE

The costs associated with HEE will always be considered in monetary units.

In HEE costs are determine by adding all resources needed to provide the service or intervention. In order to do so it is be necessary to identify, measure, and value resources. And of course, what is going to be identified as cost associated with the intervention depends on the perspective, and time horizon (8,18,22,54).

One way to perform the cost evaluation is the ingredient method, one should identify all factors involve in the intervention and then value each one (49). Typically resources on HEE from the health provider perspective are personnel, healthcare facilities, equipment and material, other inputs (for instance services). Costs associated with users could be either in monetary units (e.g. out-of pocket payments, co-payments, or extra-care) or in

terms of time (e.g. time consume in waiting rooms, transportation, or providing care to family members) (21,49).

An easy way to visualise costs is to classify them by category, activity, or organizational unit as suggested by WHO (2003) (54).

Costs may also be estimated by ‘top-down’ procedures. Meaning, if an intervention requires a certain procedure, and the costs of all the procedures are known, then the unitary value is estimated (total cost / # of procedures = unitary cost) (17). But when costs demand use of resources such as infrastructure another technique must be used to estimate them.

When costs are estimated it is important to keep in mind this fact for further use of results. For instance, if estimation was based in one healthcare facility, HEE results could be helpful to have an idea of the evaluation, but would affect generalisability (16). Of course this may be addressed by sensitivity analysis; this would be presented later in section 3.3.7. This procedure would require specific techniques that are covered in literature (18,22).

3.3.5. Visualising benefits for HEE

In section 3.1 types of HEE were covered, it was established that the present research was going to focus on CUA and CEA. Benefits have to be in ‘natural units, or ‘utility units’. The key factor is that benefits from all alternatives under analysis must be expressed in the same unit in order to perform a HEE. If natural units are available only interventions with similar results could be assessed (18,54).

Benefits, regardless of type as well as costs have to be identified, and then measured. They could be intermediate indicators, closely related with the intervention itself, such as: cases for a screening programme; people immunised for a vaccination campaign; # of cases averted for a prevention programme; blood pressure level reduced for a treatment; and so on. And there are ‘final’ indicators, normally related with survival rates for an intervention such as: death averted, or year of life saved (YLS) (18).

Alternatively there are utility benefit measures, in HEE the commonly used is QALY, or disability adjusted life years (DALY), in this case it would be DALY averted because we want to avoid it. A brief explanation about the concept of QALY is presented next.

Before covering the QALY measure concept it is important to comment on the measurement of health effects. While some data could be available from patient records and epidemiological surveillance systems, if the HEE is for example assessing a new treatment, drug, or vaccine; data to be integrated has to come from a source of the HEE – assuming that the HEE is not part of a clinical trial. Other sources of information could be used but if a literature review, and clinical studies are used they should be high standard (18).

3.3.5.1. Measuring health gain in utility units. QALY

Perhaps one of the best characteristics of QALY is that it integrates impacts on life expectancy and quality of life (8,18,22,50). It therefore suits interventions which extend the lives of patients and improve health conditions at the same time. A QALY is a weighted measure. It ponders life extended, and ‘quality’ of life.

QALYs construction is based on life expectancy, and then incorporates its changes on ‘health status’ over time because of an intervention. The assumption is that an intervention would extend someone’s life, and affect quality of life from now on. It could also compare two interventions in this sense. This is a positive impact due of a health intervention (8,18).

Conversely there is DALY, which assesses life of years lost (LYL) because of a health event, and the disability associated with it. In this sense DALY is a negative measure that would be preferable to avoid (17,18).

It is important to clarify that utility measures, such as QALY, are also discounted because they are uneven over time (49).

Finally it has to be recognised that the use of DALY has been criticised due its methodology, which for example weighted different changes in health according to the age when they occur (17).

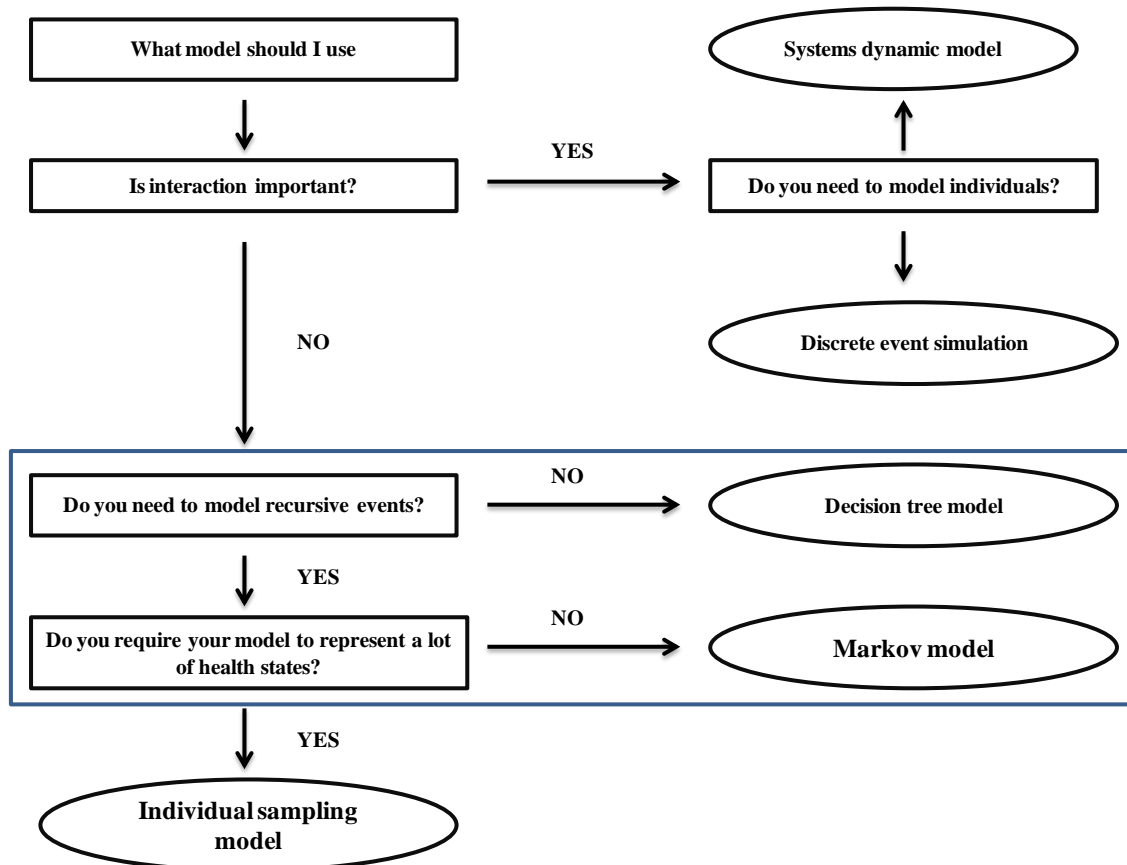
3.3.6. Modelling in HEE: How to structure decisions

HEE is a discipline that involves economic theory and techniques with epidemiology and statistics, among other factors and data sources, therefore it needs a way to integrate all the

elements to perform the evaluation. The way to do it is by creating a model which represents the inputs of analysis, in a mathematical construction. Models are also allowed to incorporate uncertainty, because some values may not be as certain as it considered (8,17,18). They summarise alternatives under analysis, the uncertainty involved, and quantify outcomes (22). The idea is to represent simply a complex perspective which is normally the case in health interventions.

To decide which model would suit the HEE it is important to consider several aspects such as: characteristics of the interventions (that involves the health condition in question); the target population; and setting, and location (22). While in the next sections just the most common models will be cover (Decision tree model and Markov model), the flowchart below shows how to decide between them, based on basic questions. The decision models are first classified according to the relevance of interaction (22).

Figure 2: Decision model selection flowchart



Source: Barron *et al.* (2004) en Gray A *et al.* (2011) (22)

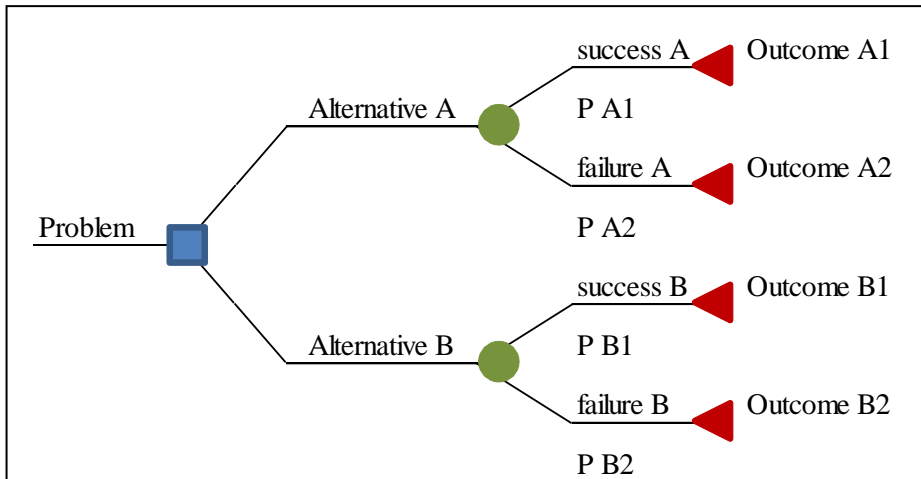
It is important to keep in mind that whichever model is used to perform a HHE, the reasons of its use should be clearly specified and the model explained in the methods.

3.3.6.1. Decision tree models

This model may be the most common use in HEE. It is based on a health situation to be addressed, and at least two alternatives of interventions that will be assessed (e.g. treatment, surgery). The construction is designed with branches. Each one represents an event that may occur in the future. To start with the tree alternatives have to be identified; then their consequences; the probability that they will take place in the future; their outcomes (e.g. QALY, survival); and their costs (18).

It has decision nodes (represented by a square). In this node decisions between alternatives are made; chance nodes (represented by a circle), symbolising probabilities; and terminal node (represented by a triangle), outcome point. The decision tree is normally constructed from left to right, and then calculated backwards (17,22). A graphic representation is presented next:

Figure 3: Decision tree basic model



Source: Self designed based on Annemans (2008) and Gray A *et al.* (2011) (8,22)

In this case:

Alternative A = success A x P A1 + failure A x P2A, while

Alternative A = success B x P B1 + failure B x P2B

The alternatives or comparators as it was said could be two or more, and it is possible to represent the alternative to no changes, or in other words, no intervention. To organise events the easiest way is to do it according to how they occur over time.

The decision tree represented above is a basic form. Chances nodes, and consequences could be added for different situations. Decision trees are normally used to represent health events that occur at one point in time, without follow-up, following the Barron *et al.* 2004 flowchart. Decision makers hold trust in their simplicity. However to use them to represent long term conditions that may not be the best option, because the model does not allow one to incorporate changes in health status along time. For this reason other models need to be put in place (18,22).

3.3.6.2. Markov models

The Markov decision model is normally used to represent chronic diseases, or health situations that could re-occur in time (17,18). For example some chronic conditions have stages, each of them requiring different treatment; or be evaluated differently according to DALYs/QALYs effects; and some associated consequences may occur –death for instance, then relive, or reapers. Those situations could be represented in a Markov model (17).

As well as decision trees models, the Markov model incorporates consequences; valuation of states; probabilities of occurrence; and costs. The particularity is the change of situations over time, the lapse between stages is called ‘Markov cycle’, those cycles could be infinitive (8). The probability to change from one ‘stage’ to another in every cycle is called transition probability (18).

Markov models is a common tool to predict evolution of chronic health conditions, during a set period of time; and to compare accordingly different alternatives (8). While the graphic representation in Figure 4 may seem simple, stages are represented in tables with calculations that may be not easier to understand.

To understand how they are built up it may be helpful to follow Gray et al. (2011) (22) steps:

1 Structure the model defining states and possible transitions between them > **2** identify starting probabilities > **3** set transition probabilities > **4** set cycle length > **5** establish a stopping rule > **6** determine costs and outcomes.

States and transitions: They should be defined accordingly clinical information, considering important health and economical events. They should be mutually exclusive.

Starting probabilities: Define how population under evaluation (cohort) is distributed among possible stages.

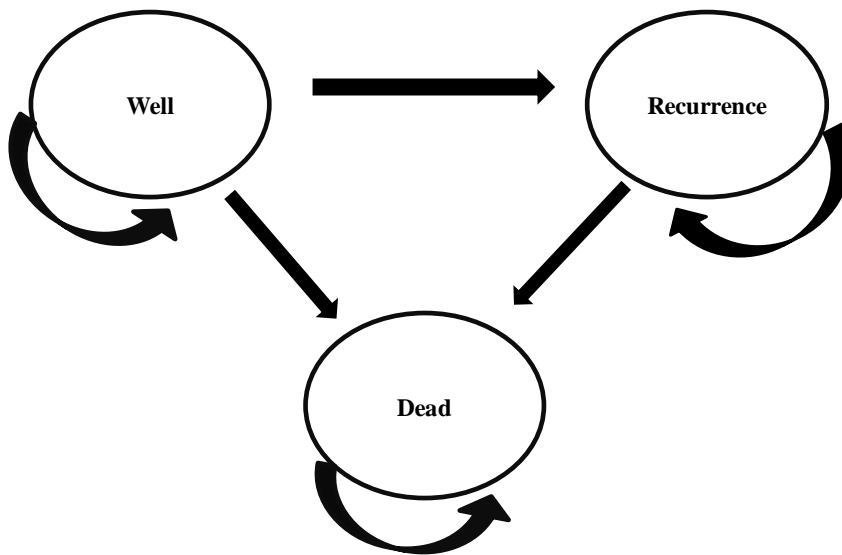
Transition probabilities: Determine the chance to move from one state to another one, they as expected have to sum 1. They could be determined from clinical trials, epidemiological data, or administrative data.

Cycle length: Length of time between cycles has to be equal, could be days, weeks, months, etc. It would depend on the natural evolution of the clinical condition.

Stopping rule: It indicates the point where calculations may stop, in some cases depending on the transition rules, that would happen when all subjects are in a absorbing state (healthy for instance). Some models would be infinitive, so it is necessary to establish, probably when proportion of subjects changing between states is very low.

Costs and outcomes: For each estate cost, outcomes associated have to be incorporated; it is necessary to fully assess all resources needed to face those previous stages defined at the start of the design (therapies, clinical procedures); and of course outcomes values (e.g. QALYs).

Figure 4: Basic Markov stage diagram



Source: Gray A *et al.* (2011) (22)

3.3.7. Sensitivity analysis. Dealing with uncertainty

HEE integrates modelling, estimations, assumptions, all of them affecting the analysis by adding uncertainty. It is possible that some factors considered may not be accurate, and therefore the result of evaluation may vary in response of alterations in assumptions. Different techniques addressing this fact have been developed (18).

The idea behind sensitivity analysis is to perform the HEE considering possible scenarios to address the probability of an parameter included not being the one it was used, for example, the effectiveness of a treatment; incidence of a diseases; and also estimation of costs associated with the HEE (8).

When just one parameter is changed, it is called *one-way analysis*. But also more than one input could be modified at the same time, so there are *two-way analysis* and *multi-way analysis*, where a few inputs are changed at once. Finally, there is the *probabilistic sensitivity analysis*; in this case instead of varying inputs to different values, it is assumed that inputs are uncertain, assuming in general normal probabilistic distributions with standard error of 0.05. This is also known as a *Monte Carlos analysis* in the literature (8,18). The sensitivity analysis could also be performed to segment the target population, or modifying a group of parameters, showing results by scenarios (49).

The use of sensitivity analysis is to present possible scenarios, and compare them with the threshold decision point –assuming that there is one established (17); this is done by presenting a ‘ceiling’ point until where the intervention is still cost-effective (for one-way analysis), or by indicating for which combinations of inputs it would be still cost-effective (for two-ways or multi-way analysis). On the other hand when probabilistic sensitivity analysis is applied, by statistics methods its result provide a ‘confidence interval’ of the intervention still being cost-effective.

It is not the intention to present an extended explanation of the different types of sensitivity analysis of its construction because it is out of the scope of this research. A more in deep detail could be consulted in Gray *et al.* (2001) (22). However, as uncertainty is harder to avoid HEE must include a sensitivity analysis. To help choose the right model for a specific research it could be helpful to review similar experiences in the literature. In addition should be added that extra comments on this matter would be incorporated in section 4.

4. Discussion

Until this point basic economical principles have been presented. Some knowledge of HEE focusing on CEA and CBA has been summarised; international and above all Latin American experiences in HEE and guideline development have been considered; also specific HEE applied to vaccines in Latin America. The idea was to build up the necessary know-how to develop a handbook on HEE for the VMH, and subsequently perform feasibility assessment applied to vaccines.

It is also necessary to mention that although specialised literature covered methodological aspects regarding HEE in a very detailed way; it is still important to include in the handbook proposal a summarise section covering the topic. This decision is based on the fact that the present research intends to provide the target population within the VMH with essential tools for introducing HEE in the institution providing enough information to be understandable by itself.

The next step is to present the handbook on HEE proposal, with its tentative layout based on the review of LA experiences, and consider guideline appraisal tools and recommendations from literature; a brief draft of recommendations to be included in the handbook; and a route-map to guide the process of handbook consensus and introduction after the academic revision. Later aspects regarding a feasibility study of implementing this handbook applied to vaccines will be brought up.

4.1. Handbook proposal

Following international guidelines and the assessment presented in section 2.1 the handbook draft presented in this section will follow a systematic structure intending to be practical, comprehensive and useful for potential users. The supportive tool of ‘AGREE II for Practice Guideline Development’ was considered (55). Some sub-parts of the layout will provide a brief comment when considered necessary; some others covered in section 3 will be just subheadings in order to avoid duplication. The handbook layout includes a specification of how to structure a HEE report, matching the scoring from section 2.1, description of its items from Husereau *et al.* 2013 (37) are used along the layout.

4.1.1. Handbook on HEE layout

To better follow the structure presented below, extra comments were kept as brief as possible, however some sections particular to this handbook such as objectives, scope, target public, and brief recommendations, will be added later.

- **Introduction and background**
- **Objectives**
- **Target and Scope**
- **Key concepts and theory about HEE**
 - Types of HEE: CMA, CUA, CEA, and CBA
 - Threshold and decision point
 - Perspective of study
 - Time and discount in HEE
 - Currency, prices date and conversion
 - Costs and Benefits in HEE
 - Modelling in HEE
 - Sensitivity analysis
- **Methodological aspects to perform and present a HEE**
 - Background and objectives of the HE: Include the research question; its relevance in the setting context for policy or academia has to be explicit. Studies have to present a clear title and an abstract to be easily identify.
 - **Methods to be incorporated and reported**
 - Target population of the HEE: Describe the population; include any important data about subgroups when available.
 - Setting and location: Clarify geographical location and institutional setting relevant for costs and decisions.
 - Comparators: Describe interventions under assessment; be explicit why they were chosen.
 - Study perspective
 - Time horizon
 - Discount: Clarify use of rate, for costs and outcomes
 - Currency, prices date, and conversion
 - Health outcomes: Describe type of outcome used to measure benefit.

- Efficacy and effectiveness: Describe source of any data regarding efficacy and effectiveness used in the study
- Measurement and valuation of preference based outcomes: Describe methods of calculation if apply.
- Estimating resources and costs: Include all data related with calculation, source, method used, and etcetera.
- Currency, price date, conversion
- Choice of model
- Assumptions: Describe assumptions regardless the decision model selected.
- Analytical methods: Describe all methods used for the evaluation.
- **Result of the HEE**
- Study parameters: Report the values used in calculations.
- Incremental costs and outcomes: Report mean values for costs and autcomes.
- Characterising uncertainty: Report effects of sensitivity analysis.
- Discussion
- Study findings, limitations, generalisability, and current knowledge
- Other
- Report: Source of funding; authors of the study and affiliation; and conflict of interest.

Additional comments: All information used has to be clear regarding, sources, date of collection and methodology. Any data base has to be presented along with the studies.

4.1.2. Objectives of the handbook on HEE for the VMH

The handbook has the aim to present a summary of relevant health economic topics to support and help with a better understanding of the discipline within the Venezuelan Ministry of Health.

To contribute with the use of HEE in a systematic way and establish a standard to perform them, at first in the VMH and lately in the NPHS HHE and thereby incorporate transparency, and comparability of such studies.

It also has the purpose of promoting discussions about the role of HEE in the decision-making process within the institution, and encourages academic debate about the topic.

4.1.3. Target and scope of the handbook

Target: The handbook on HH is intended primarily for technical staff from the VMH and its subordinated institutes who collaborate in the design of projects and programmes. It could also be useful for policy makers to help them understand HEE evaluations. Finally the handbook targets universities and researchers, to bring them into the discussion about the convenience of HEE in the Venezuelan context.

Scope: Although this handbook purportss to establish the first steps to initiate HEE to support decision making, it could not be seen as a legally binding document. It is intended as reference for further development and improvement of HEE in the VMH.

4.1.4. Developing recommendations

In order to fully achieve its objective the final version of the handbook on HH for the VMH needs to go through a discussion process after its academic revision; and therefore count on local validated consensus. Meanwhile, recommendations regarding some standards are presented next to better support the performance of HEE based on this handbook. All of them are based on Adam T et al (2003) (54), unless another source is mentioned. For some recommendations extra information is added to make it more specific for Venezuela, based on cost-estimation associated with maternal care experience (13).

Recommendations are presented in a summarised way, to make information visually-friendly helping potential users to identify key aspects and track them in their HEE.

Table 5: Summary of recommendations based on ‘WHO guide to cost-effectiveness analysis’ and VMH experience

Component	Recommendation.
Time horizon	Interventions should assume to be implemented over 10 years length, costs and benefits related with the intervention according lifetime.
Perspective	It should be preferred a societal perspective.
	VMH: Considered a institutional perspective with a further extension to include patient-family perspective.
Efficacy-efficiency	<p>Could be use relative risks rates. It should be adjusted considering coverage, quality of care, adherence, and so on.</p> <p>Regarding parameters assumed for efficacy, efficiency and modelling it is vital to obtain them from the best possible source; when primary data is not available information could comes from systematic reviews of studies.</p>
Estimating costs	<p>Micro-costing should be applied when possible. It is recommended to provided data regarding quantities and prices, along with total expenditure. Capital investments could be base on rental market, or by annualise values (using account purchase value; resale value; interest rate; and working life).</p> <p>VMH: Experience indicates that records of costs are difficult to track, making difficult to apply micro-costing. Also, despite the free access to health care interviews or questionnaires for patients may be needed to assess out of pocket payments (for drugs, or tests generally).</p>
Estimating health effects	DALYs and QALYs measures should be preferred. If an intervention impact life expectancy use YLS.
Health status valuations	Should be used information from the global burden of diseases study by regional specification when possible (incorporated age-weighting apart).
Discount	Apply an annual rate of 3% for costs and effect.
Sensibility analysis	<u>For costs</u> : Sensitivity using an annual rate of 6%.
	<u>For effects</u> : 0% discount.
	<u>Related to variables</u> : Subject to one-way or multi-way analysis. Add stochastic league tables to help with decision-making process.
Threshold	<p>Cost/QALY < 1 GDP per capita ‘very cost-effective’</p> <p>Cost/QALY > 3 GDP per capita ‘non cost-effective’</p>

Source:Self designed

Special mention needs to be given to the discount rate. Although literature shows consensus about WHO recommendations to use 3% for costs may not be convenient in the Venezuelan context due the high inflation economy. Perhaps a multi-disciplinary team is needed in order to set a more realistic criterion, this could included the Central Bank (BCV by its Spanish acronym), Ministry of Planning and Development (MPD), and the National Statistics Institute (INE by its Spanish acronym); those governmental agencies coordinate together the National Statistics System on economy and other social variables.

4.1.5. Handbook-introduction route map. Using AGREE as a step mark for conducting the process

As a primary product of this master thesis was to develop a proposal handbook, in order to implement it in the setting for which it was considered some steps have to be accomplished. In this brief section some considerations regarding this future process are considered. Although the AGREE (38) tool was developed to assess guidelines, now it provides some resources to orientate the process of developing such kind of documents; inputs and recommendations considered useful were incorporated.

4.1.5.1. Steps to introduce the handbook on HEE

An abbreviation of main steps from the present document to its full implementation could be seems ass:

Academic validation > Presentation for discussion with stake holders > Establish a working group > Obtain and consider feedback > Incorporate new inputs to adapt the tool > Validate with a HEE on vaccine

In general methodologies for developing these kind of documents imply a set of more descriptive and comprehensive levels that may be useful to look at, regardless of the order or its final consideration. The Canadian Partnership against Cancer suggests in its methodology 17 steps (56), an adaptation of those considered more relevant, and are presented next with a brief comment when needed especially adapted for the VMH, and extra steps. The starting point of this process would be after academic feedback and necessary translation into Spanish.

- **Assembling a panel:** Members should be from a different backgrounds, methodological experts, members institutions and agencies involve (VMH from different levels, National Hygiene Institute (INH by its Spanish acronym); *Instituto de Altos Estudios en Salud Pública* (IAES by its Spanish acronym, public health academic institution; BCV; INE; PAHO local representation). The experience of a technical group on HE could be follow (13).
- **Planning the handbook development as a project:** Establish components of the process; deadlines; rules for development recommendations and consensus; external validation; internal-practical validation; release of the handbook.
- **Developing recommendations:** All recommendations to be incorporated in the handbook have to be product of consensus, it is important to present extra documents that support those recommendations as appendix on the final version.
- **External review of handbook draft:** It would be necessary to select a group of experts outside the working groups to review and give feedback on the handbook.
- **Internal validation:** Implement the handbook with a HEE on vaccine to assess its methodology and document all details that could help to improve the handbook.
- **Edit report and release:** Always when possible incorporate visual information and provide with useful guide to collecting and reporting data. Make it fully available on line.

Further steps would consider:

- **Implementation:** It would be important to release the document after a Ministerial resolution to support its use.
- **Monitor and evaluate use of handbook:** Promote a tool assessment using AGREE II methodology after a two of its release. Perform a study to determine its actual use.
- **Updating:** The handbook needs to be update according any change on regulation, for instance, re organisation of the VMH or the NPHS.

In addition to this tentative step mark material regarding all six AGREE II Tool domains would be provided to facilitate tracking different standards accomplishment.

4.1.6. Special considerations applied to vaccines

In the light of the intention of validating the handbook, and performing a HEE on vaccine cost-effectiveness it is worthy to highlight again a couple of things.

First, the role of HEE as part of the HTA (and in consequence within policy-design and decision-making processes) has to be clear. HEE would provided essential information to established an evidence-based decision making culture but it has to be recognise the interaction with political and social factors. However the inputs that HEE could provide in terms of its specificity could be of great help, especially in the case of vaccines.

Also, as pointed by Ricciardi GW et al. 2015 (34), well established evaluation criterion for vaccines introduction are crucial for the NIP success in terms of adherence to standards and trustiness among the general public. Therefore it could be stated that performing HEE on vaccines by the VMH could help improve the NIP general goals in terms of coverage by improving population perception about benefits of immunization. It is expected that if HEE are established at least by the NIP, it would strengthen the programme and possible be the first step in establishing a NITAG.

This gives reason to pursuit with future implementation of the handbook on HEE.

4.2. Feasibility study applied to vaccines: From theory to practice. How to implement such analysis in the VMH

An essential step when considering a new policy is assessing its feasibility in the setting of application. This feasibility should be seen first from a technical-organisational perspective. The point is to determine whether or not it would be possible to carry out HEE taking into account the current structure of the VMH. In other words, it is essential to figure it out if there is technical knowledge, personnel, and availability of resources (57). The question to answer is simple, is it possible fully accomplish this kind of evaluation, specifically applied to vaccines- by the VMH? This analysis needs to consider as well the information needed as input for HEE.

In addition a brief analysis of the contextual setting is presented to help better understand which factors would be supportive or negative forces, when introducing this handbook, and therefore HEE in general. For this purpose an adaptation of the contextual factors presented by Leichter (1979) (as cited by (57)). This author considered situational; structural; cultural; and international or exogenous factors.

It is implied that this evaluation must take into consideration the necessary information to plan and perform a HEE applied to vaccines.

4.2.1. The VMH institutional structure to provide information. Stakeholders analysis

The setting: Administrative units involve

The VMH is by law the governing body in the sector (3), however since 1999 the Health Act has not been yet adapted to fulfil all aspects required by the Constitution, therefore any attempt to introduce regulation regarding HEE would also be applicable within the units and facilities under VMH' rule. Yet, this reality would not have counterproductive effects on HEE applied to vaccines because this programme is fully covered and financed on a national level by the VMH.

The structure of the VMH is established in code known as '*Reglamento Orgánico*'(58), an organizational regulatory code that outlines in a general level the competences for all high level departments, it also defines institutions depending on the VMH. A more comprehensive code should be developed to describe in detail competences and responsibilities of every unit based on process, but it has not been published.

However, the organizational chart allowed having a perspective of the functionality inside the institution. To help understand which units would be involved in a HEE considering the existent scenarios the information is shown in the Table 6.

Despite the lack of an in depth description of responsibilities and processes of each administrative unit, the organisational regulatory code allows the reader to identify key actors inside the structure. According to the organizational regulatory code 5 units seem to have a certain degree of responsibility on HEE: planning, organisation, and budget office; administrative office; epidemiology direction; health programmes direction; and National Hygiene Institute (INH). Also public policy office may play a role.

Some actors different to the VMH, namely BCV, INE, and MPD for their potential role in guide regarding the appropriate discount rate, were also considered.

Some key responsibilities according the organizational regulatory code:

The planning, organisation, and budget office has the duty of participating in the design, follow up, and evaluation of any programme or project to be implemented.

Table 6: Unites potentially involve in HEE

Input - field	Organisational scenarios according to available codes and charts ¹²		
	Organisational regulatory code	Structural organisation chart ¹³	Functional organisation chart ¹⁴
Economical information and analysis	- POB Office ¹ - A Office ² - BCV / INE / MPD	- POB Office - A Office - BCV / INE / MPD	- POB Office - A Office - EM in health Department ⁵ - BCV / INE / MPD
Epidemiological information	- Epi Department ³	- Epi Department	- Epi Department
Clinical information	- Epi Department - HP Department ⁴ - INH	- Epi Department - HP Department - INH	- Epi Department - H projects Department ⁶ - INH
Technology available	- Epi Direction - HP Department - INH	- Epi Department - HP Department - INH	- I Direction ⁷ - HP Department - INH

¹ Planning, organisation, and budget office

² Administrative office

³ Epidemiology department

⁴ Health programmes department

⁵ Economic management in health department

⁶ Health projects department

⁷ Immunization direction

Source: Self designed based on available information on the Venezuelan Ministry of Health official site:

www.mpps.gob.ve

The epidemiology department has the duty of coordinating and developing the National Epidemiologic Surveillance System; defining priorities for health interventions; and guarding the systematic data collection, process and analysis to generate epidemiologic profiles.

The health programmes direction has the duty of establishing guidelines and standards for healthcare; and to participate in the process of defining action plans to be implemented in healthcare facilities.

The public policy office has the duty of developing technical reports on trends and possible scenarios, with the aim of supporting decision making processes. It has also the function of

¹² Consider a self-translated terminology of the structure. Organisational charts in Spanish are listed in appendix 2 and 3

¹³ It represents the organization chart develop from the Organizational regulatory code, including some changes.

¹⁴ It considers a new structure propose on 2014 but still not enacted.

leading health-sector forecast analysis, evaluating scenarios, and defining strategic objectives to be implemented by programmes and projects.

The Contextual factors

The factors that may affect the implementation of a handbook on HEE, and more precisely perform a cost-effectiveness evaluation applied to vaccine will be summarised next. They could have a positive or negative impact, the relevance of appointing them is to be aware of scenarios and act accordingly to succeed with the aims of performing the HEE.

Situational factors: The undergoing crisis in the health sector due to a lack of supplies could act as a negative factor; authorities and technical groups would be expected to focus their response capabilities to address immediate problems. Nonetheless despite the negative situation it could be used as a reason to introduce tools such as the handbook to strengthen the decision-making process in the future.

Structural factors: The undergoing transformation could affect identification of key actors. However, the fact that a unit called ‘Economic management in health department’ has been proposed indicates that HE is being considered an important aspect of the VMH.

Cultural factors: Hierarchies are important in Venezuelan culture; it would be positive to count on support of high authorities to guarantee a successful experience. Also access of information it is difficult due the distrust of political use of data.

Exogenous factors: In general they could act as positive forces. The VMH used to participate in regional meetings addressing HE topics, all of them support the idea of introducing some kind of HE research in national institutions.

After reviewing structural and organizational aspects it is necessary to go through the data needed to perform the HEE applied to vaccines in a more detail way,

4.2.2. Inputs need for CEA applied to vaccines

In addition of the general inputs of any HEE, for the specific case of vaccination data regardless incidence of diseases to be covered by the vaccine need to be available. Also

data of costs associated with the vaccine introduction, its application, and of course costs associated with the alternative as well. In general it would be easier to think about the possibility of immunise against no intervention. In this case data about cost of treatment needs to be established accordingly. Data needed for the HEE in detail was retrieved from the review of LA experiences in section 2.2. It will be summarised next, matching units and stakeholders who should be involved.

Table 7: Specific data for HEE applied to vaccines

Input	Unit - Stakeholder
Background - Case definition and comparators.	Epi Department ¹
Setting information, infrastructure in place.	Epi Department
Demographic information	Epi Department
Epidemiological data from surveillance system	Epi Department
CEA / Method	POB Office ²
Modelling	POB Office
Healthcare statistics	Epi Department
Vaccine efficacy and vaccination coverage	Epi Department - INH
Costs either direct or by estimations	
Vaccination costs	Epi Department
	POB Office
	Healthcare facilities Departments ³
Direct medical-care costs	HP Department ⁴
	Estimations - POB Office ²
	Healthcare facilities Departments
Sensibility analysis	POB Office
	POB Office
Discount rate	BCV/INE/MPD

¹ Epidemiology department

² Planning, organisation, and budget office

³ Healthcare facilities national Offices according to level of care

⁴ Health programmes department (depending on the vaccine)

Source: Self designed

According to knowledge from the institution, some considerations have to be added, as it was pointed out the NIP is well structured, the epidemiology department manages a comprehensive set of statistics especially for communicable diseases. However, despite the fact that there is software in place to manage healthcare statistics, this module is not used for all centres. Consequently data has to be collected locally (perhaps with a sample).

Perhaps the biggest challenge will be to work with the costing estimation because of the fragmentation of the sector. Resources come from multiple places and there is no real track of how much was spent for each programme, service, or even healthcare facility. But there is experience on building up the data from interviews of healthcare managers and inputs from head of specific programmes (13).

Also it is to be considered to consult with BCV, INE, and MPD regarding the appropriate discount rate. However, meanwhile WHO recommendation would fit the intention of perform a HEE.

The fact that there is a NIP in place would help to track major costs associated, perhaps micro-costing would be necessary to incorporated resources as personnel and infrastructure, information indicates that even the cold chain is financed by the national programme.

Finally, it is important to consider actors involved in special immunizations campaigns as it would affect considerations about cost-estimation.

In conclusion it could be said that despite obstacles mentioned and the existence of some situational and structural factors impacting negatively on the project it would be feasible to perform a HEE applied to vaccines without major problems.

5. Conclusion

Institutional changes are always a challenge, perhaps in the Venezuelan public sector this reality is even more visible but as it was pointed by Oliveira *et al.* 2013 (31), political commitment is compelling for the decision-making process. In the other hand technical effort and research to provide evidence could not be enough by itself but they both combine are absolutely decisive for a more effective and transparent policy.

If the introduction of the present handbook on HEE in the VMH is perceived as a process; to achieve a positive result it may be necessary to start by small steps. Performing a HEE to assess the introduction of a new vaccine, or compare between two different drugs could lay the proper foundations to later on perform HEE to other kind of interventions, and hopefully incentivised other HE areas such as techniques for resources allocation to health care facilities, or for a more macro perspective, develop a system of health accounts.

In order to really achieve the goal of performing HEE evaluations, it would be necessary to establish a multidisciplinary working group focusing on validate this handbook; this should be done in two levels. First, discuss the handbook as working paper; and then work on recommendations adapted to the Venezuelan context. Aspects like inflation, currency exchange controls, prices control, and special details of administrative steps for public procurements, governmental supplies, and contract with private entities all have to be considered. It should be reviewed periodically considering the socio-economic factors that may affect recommendations regarding discount rates.

A positive side of this process lay in the fact that my experience working in the VMH allowed me to understand the dynamic inside the institution. It may perhaps validate the position of being a third party involve in the process. At the same time not being involved in the day by day routines and problem-solving tasks, that in fact consume considerable amount of time, reinforce the idea of introducing the present handbook –and its future adaptation, under a project management vision.

Regarding the feasibility study it could be affirmed that the Venezuelan NIP has the strength needed to supply with quality information for the HEE.

As a didactic measure it is recommended for the final handbook to incorporate graphics and visual representation to help understanding and following the handbook. It is also important to provide formats, and guidance to collect and present data.

5.1. Limitations

Without doubt the most relevant limitations for further progress in the field of HE within the VMH rely on the outdated legal framework. The 1999 Venezuelan Constitution introduced new aspects regarding health, however the Health Act (59) has not been adapted to the Constitution, and as a result the public health providers are not yet organised in a system. This reality creates a counterproductive environment to a future introduction of a binding handbook or guideline on HEE, considering that multiple buyers, payers and providers do not follow VMH regulation.

This affects how the health sector is organised. In Venezuela, unlike other countries, the health authority (VMH) plays the role of regulator, financier-payer, and provider. This situation could be affecting how a handbook on HEE and therefore any guidance regarding it is perceived by authorities, understanding that one of the main reasons a guidance on HEE is developed is to help deciding about new health services to be covered, or reimbursement of drugs for example (7).

Also an ongoing institutional transformation of the VMH makes it difficult to perform a stakeholder analysis considering that there are three different pictures of how the institution is organised. However when any indication regarding administrative unites' responsibilities to contribute to a theoretical research has been shown in this handbook, an assumption of transferability to the equivalent one for a different scenario was implicit.

From the HR perspective there is an important obstacle considering the lack of professionals with an academic training on HE. Nevertheless, there is room for improving this reality by designing a postgraduate programme backed by the VMH research and education department.

5.2. Further Research

It would be positive to incentive carry out HEE, but not just by the VMH, incorporate academics and universities would definitely maximise any attempt to create the basis of evidence-based decision making in health by having more researches available.

There is the intention to bring the present research under discussion at a national level, to introduce considerations of potential users of this handbook, and furthermore get an official approval by the health authority.

Adapt the present handbook to perform HEE assessment within the recent process of regulating private health insurance policies it would be also positive to strength technical capacities.

References

1. The Universal Declaration of Human Rights [Internet]. [cited 2014 Mar 16]. Available from: <http://www.un.org/en/documents/udhr/>
2. WHO | WHO called to return to the Declaration of Alma-Ata [Internet]. WHO. [cited 2014 Mar 16]. Available from: http://www.who.int/social_determinants/tools/multimedia/alma_ata/en/
3. Asamblea Nacional Constituyente. Constitución de la República Bolivariana de Venezuela [Internet]. Sect. Capítulo V: De los Derechos Sociales y de las Familias 1999. Available from: http://www.inpsasel.gob.ve/moo_doc/ConstitucionRBV1999-ES.pdf
4. World Health Organization. WHO Universal health coverage (UHC) [Internet]. WHO. 2014 [cited 2015 Jul 1]. Available from: <http://www.who.int/mediacentre/factsheets/fs395/en/>
5. WHO | The world health report - Health systems financing: the path to universal coverage [Internet]. WHO. [cited 2013 Dec 6]. Available from: <http://www.who.int/whr/2010/en/>
6. WHO | Research for universal health coverage: World health report 2013 [Internet]. WHO. [cited 2015 Jun 23]. Available from: <http://www.who.int/whr/2013/report/en/>
7. Hjelmgren J, Berggren F, Andersson F. Health economic guidelines--similarities, differences and some implications. *Value Health J Int Soc Pharmacoeconomics Outcomes Res.* 2001 Jun;4(3):225–50.
8. Annemans L. *Health economics for non-economists*. Gent: Academia Press; 2008. 106 p.
9. Augustovski F, Iglesias C, Manca A, Drummond M, Rubinstein A, Martí SG. Barriers to generalizability of health economic evaluations in Latin America and the Caribbean region. *Pharmacoeconomics.* 2009;27(11):919–29.
10. Augustovski F, Garay OU, Pichon-Riviere A, Rubinstein A, Caporale JE. Economic evaluation guidelines in Latin America: a current snapshot. *Expert Rev Pharmacoecon Outcomes Res.* 2010 Oct;10(5):525–37.
11. Ley de reforma parcial de la ley de Presupuesto para el ejercicio fiscal 2009 [Internet]. 39.147 Mar 26, 2009 p. 368.191–368.200. Available from: <http://virtual.urbe.edu/gacetitas/39147.pdf>
12. Iglesias CP, Drummond MF, Rovira J, NEVALAT Project Group. Health-care decision-making processes in Latin America: problems and prospects for the use of economic evaluation. *Int J Technol Assess Health Care.* 2005;21(1):1–14.

13. Grupo Técnico de Economía de la Salud - Ministerio de Salud. Costo del Manejo del Embarazo en el Sistema Público de Salud en Venezuela. Unpublished; 2012.
14. Entrega de certificados en Evaluación Económica de Intervenciones Sanitarias, OPS/OMS - IAES [Internet]. 2015 [cited 2015 Jul 10]. Available from: http://www.paho.org/ven/index.php?option=com_content&view=article&id=136%3AEntrega-de-certificados-en-evaluacion-economica-de-intervenciones-sanitarias-opsoms-iaes&catid=645%3Aven.04-gestin-de-la-cooperacin-tnica&Itemid=215
15. ProVac Initiative. Introduction to Economic Evaluation [Internet]. PAHO; [cited 2015 May 11]. Available from: http://www.paho.org/provac/index.php?option=com_content&view=article&id=1654&Itemid=1619&lang=en
16. McPake B, Normand C. Health Economics: An international perspective. 2nd ed. United Kingdom: Routledge; 2008. 292 p.
17. Morris S, Devlin N, Parkin D. Economic Analysis in Health Care. England: John Wiley & Sons, Inc; 2007. 400 p.
18. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for the Economic Evaluation of Health Care programmes. 3rd ed. Oxford: Oxford University Press; 2005. 396 p.
19. Eccles M, Mason J, Freemantle N. Developing valid cost effectiveness guidelines: a methodological report from the North of England evidence based guideline development project. Qual Health Care QHC. 2000 Jun;9(2):127–32.
20. Detsky AS, Laupacis A. Relevance of cost-effectiveness analysis to clinicians and policy makers. JAMA. 2007 Jul 11;298(2):221–4.
21. Getzen T. Health Economics and Financing. 4th ed. US: John Wiley & Sons, Inc; 2010. 470 p.
22. Gray A, Clarke P, Wolstenholme J, Wordsworth S. Applied Methods of Cost-effectiveness Analysis in Health Care. 1st ed. United Kingdom: Oxford University Press; 2011. 313 p.
23. Augustovski F. Issue Panel: Outsider Perspectives on the US Comparative Effectiveness Research Movement: Real Progress or Real Disappointment? ISPOR Meeting; 2012; Washington (DC).
24. Hanney S, Buxton M, Green C, Coulson D, Raftery J. An assessment of the impact of the NHS Health Technology Assessment Programme. Health Technol Assess Winch Engl. 2007 Dec;11(53):iii – iv, ix – xi, 1–180.
25. Williams I, Bryan S, McIver S. How should cost-effectiveness analysis be used in health technology coverage decisions? Evidence from the National Institute for Health and Clinical Excellence approach. J Health Serv Res Policy. 2007 Apr;12(2):73–9.

26. Williams I, McIver S, Moore D, Bryan S. The use of economic evaluations in NHS decision-making: a review and empirical investigation. *Health Technol Assess Winch Engl.* 2008 Apr;12(7):iii, ix – x, 1–175.
27. Niessen LW, Bridges J, Lau BD, Wilson RF, Sharma R, Walker DG, et al. Assessing the Impact of Economic Evidence on Policymakers in Health Care—A Systematic Review [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012 [cited 2015 May 22]. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK114636/>
28. Yothasamut J, Tantivess S, Teerawattananon Y. Using economic evaluation in policy decision-making in Asian countries: mission impossible or mission probable? *Value Health J Int Soc Pharmacoeconomics Outcomes Res.* 2009 Dec;12 Suppl 3:S26–30.
29. WHO | Health systems service delivery [Internet]. WHO. [cited 2013 Aug 21]. Available from: <http://www.who.int/healthsystems/topics/delivery/en/>
30. Ofman JJ, Sullivan SD, Neumann PJ, Chiou C-F, Henning JM, Wade SW, et al. Examining the value and quality of health economic analyses: implications of utilizing the QHES. *J Manag Care Pharm JMCP.* 2003 Feb;9(1):53–61.
31. de Oliveira LH, Toscano CM, Sanwogou NJ, Ruiz-Matus C, Tambini G, Roses-Periago M, et al. Systematic documentation of new vaccine introduction in selected countries of the Latin American Region. *Vaccine.* 2013 Jun 2;31, Supplement 3:C114–22.
32. Activities in countries [Internet]. 2014 [cited 2015 Jun 22]. Available from: http://www.paho.org/provac/index.php?option=com_content&view=article&id=1637&Itemid=1610&lang=en
33. Who We Are [Internet]. OMS - NiTAGS Ressources Center. [cited 2015 Jun 22]. Available from: <http://www.nitag-resource.org/who-we-are>
34. Ricciardi GW, Toumi M, Weil-Olivier C, Ruitenber EJ, Dankó D, Duru G, et al. Comparison of NITAG policies and working processes in selected developed countries. *Vaccine.* 2015 Jan 1;33(1):3–11.
35. Ministerio de Salud de Chile. Guía metodológica para le evaluación económica de intervenciones en salud en Chile [Internet]. Ministerio de Salud de Chile-MinSal; 2013 [cited 2015 Feb 9]. Available from: http://desal.minsal.cl/wp-content/uploads/2013/09/EE_FINAL_web.pdf
36. Langer A. A framework for assessing Health Economic Evaluation (HEE) quality appraisal instruments. *BMC Health Serv Res.* 2012;12:253.
37. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *BMC Med.* 2013 Mar 25;11:80.

38. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. Development of the AGREE II, part 1: performance, usefulness and areas for improvement. *Can Med Assoc J.* 2010 Jul 13;182(10):1045–52.
39. World Health Organization. Handbook for Guideline Development [Internet]. 2nd ed. Geneva: World Health Organization; 2014 [cited 2015 Apr 7]. 167 p. Available from: http://www.who.int/kms/handbook_2nd_ed.pdf?ua=1
40. Instituto de Evaluación Tecnológica en Salud. Manual para la elaboración de evaluaciones económicas en salud [Internet]. Instituto de Evaluación Tecnológica en Salud; 2014 [cited 2015 Feb 9]. Available from: <http://www.iets.org.co/Manuales/Manuales/Manual%20evaluacio%CC%81n%20econo%CC%81mica%20web%2030%20sep.pdf>
41. Gálvez González AM. Guía metodológica para la evaluación económica en salud: Cuba, 2003. *Rev Cuba Salud Pública.* 2004 Mar;30(1):0–0.
42. Consejo de Salubridad General. Guía para la Conducción de Estudios de Evaluación Económica para la Actualización del Cuadro Básico y Catálogo de Insumos del Sector Salud en México. [Internet]. Consejo de Salubridad General; 2015 [cited 2015 Apr 14]. Available from: http://www.canifarma.org.mx/descargables/Docs_interes_paps/Gu%C3%ADa%20de%20Conducci%C3%B3n%20de%20Estudios%20de%20Evaluaci%C3%B3n%20Econ%C3%B3mica%202015%20-%20CSG.pdf
43. Constenla D, O’Ryan M, Navarrete MS, Antil L, Rheingans RD. Potential cost effectiveness of a rotavirus vaccine in Chile. *Rev Médica Chile.* 2006 Jun;134(6):679–88.
44. Ordóñez JE, Orozco JJ. Cost-effectiveness analysis of pneumococcal conjugate vaccine 13-valent in older adults in Colombia. *BMC Infect Dis.* 2014;14:172.
45. Goldie SJ, Levin C, Mosqueira-Lovón NR, Ortendahl J, Kim J, O’Shea M, et al. Health and economic impact of human papillomavirus 16 and 18 vaccination of preadolescent girls and cervical cancer screening of adult women in Peru. *Rev Panam Salud Pública.* 2012 Dec;32(6):426–34.
46. Constenla D, Pérez-Schael I, Rheingans RD, Antil L, Salas H, Yarzabal JP. Assessment of the economic impact of the antiretroviral vaccine in Venezuela. *Rev Panam Salud Pública.* 2006 Oct;20(4):213–22.
47. Colantonio L, Gómez JA, Demarteau N, Standaert B, Pichón-Rivière A, Augustovski F. Cost-effectiveness analysis of a cervical cancer vaccine in five Latin American countries. *Vaccine.* 2009 Sep 4;27(40):5519–29.
48. Martí SG, Colantonio L, Bardach A, Galante J, Lopez A, Caporale J, et al. A cost-effectiveness analysis of a 10-valent pneumococcal conjugate vaccine in children in six Latin American countries. *Cost Eff Resour Alloc CE.* 2013;11(1):21.

49. McEwan PJ. Cost-effectiveness analysis of education and health interventions in developing countries. *J Dev Eff.* 2012 Jun 1;4(2):189–213.
50. Jamison DT, Breman JG, Measham AR, Alleyne G, Claeson M, Evans DB, et al. Cost-Effectiveness Analysis. 2006 [cited 2014 Sep 24]; Available from: <http://www.ncbi.nlm.nih.gov/books/NBK10253/>
51. Murray CJ, Evans DB, Acharya A, Baltussen RM. Development of WHO guidelines on generalized cost-effectiveness analysis. *Health Econ.* 2000 Apr;9(3):235–51.
52. Bloom DE, Madhavan G. Vaccines: From valuation to resource allocation. *Vaccine.* 2015 Jun 8;33, Supplement 2:B52–4.
53. Bärnighausen T, Bloom DE, Cafiero-Fonseca ET, O'Brien JC. Valuing vaccination. *Proc Natl Acad Sci U S A.* 2014 Aug 26;111(34):12313–9.
54. Adam T, Edejer TT-T, Baltussen RM, Hutubessy R, Acharya A, Evans DB, et al. WHO Guide to Costo-effectiveness analysis [Internet]. World Health Organization; 2003 [cited 2015 Jun 20]. Available from: http://www.who.int/choice/publications/p_2003_generalised_cea.pdf
55. Using AGREE II for Practice Guideline Development - AGREE Enterprise website [Internet]. [cited 2015 Jun 22]. Available from: <http://www.agreetrust.org/resource-centre/agree-ii-as-a-practice-guideline-development-framework/>
56. Canadian Partnership Against Cancer. Cancer View Canada - Guideline Resource Center [Internet]. [cited 2015 Jun 16]. Available from: http://www.cancerview.ca/cv/portal/Home/TreatmentAndSupport/TSPProfessionals/ClinicalGuidelines/GRCMain?_afLoop=10950829486754000&lang=en&_afWindowMode=0&_adf.ctrl-state=fn15a5aon_584
57. Buse K, Mays N, Walt G. *Making Health Policy.* 1st ed. United Kingdom: Open University Press - McGraw-Hill; 2005. 206 p.
58. Asamblea Nacional de Venezuela. Reglamento Orgánico del Ministerio de Salud [Internet]. GO 38.591 Dec 26th 2006, 5.077 Dec 22, 2006. Available from: http://www.mpps.gob.ve/index.php?option=com_content&view=article&id=419&Itemid=807
59. Congreso de la República de Venezuela. Ley Orgánica de Salud [Internet]. GO 36.579 Nov 11, 1998. Available from: <http://www.fundaribas.gob.ve/paginaweb/pdf/salud.pdf>

Statutory declaration

I hereby confirm that I am the author of the thesis presented. I have written the thesis as applied for previously unassisted by others; using only the sources and references stated in the text.

Date:

Appendix

Appendix 1: CHEERS checklist

Table 1 CHEERS checklist—Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No
Title and abstract		Recommendation	
Title	1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared.	
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	
Measurement of effectiveness	11a	Single study-based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	
	11b	Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference based outcome	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	

Table 1 CHEERS checklist—Items to include when reporting economic evaluations of health interventions

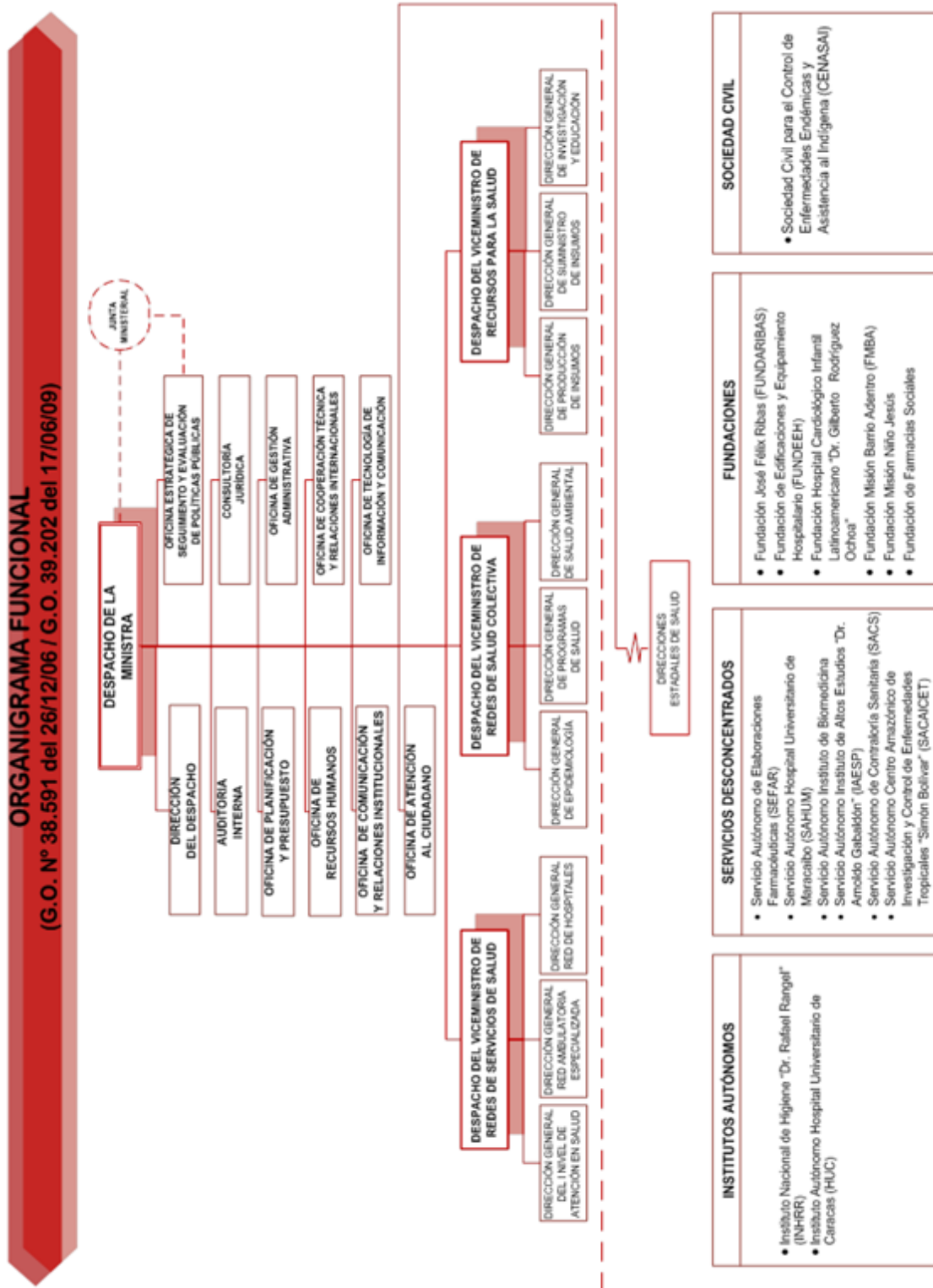
Section/item	Item No	Recommendation	Cont. Reported on page No
Estimating resources and costs	13a	Single study-based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	
Characterising uncertainty	20a	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	
	20b	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	

Table 1 CHEERS checklist—Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Cont. Reported on page No
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	
<hr/>			
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other nonmonetary sources of support.	
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	

Source: Husereau D. *et al.* 2013. (37).

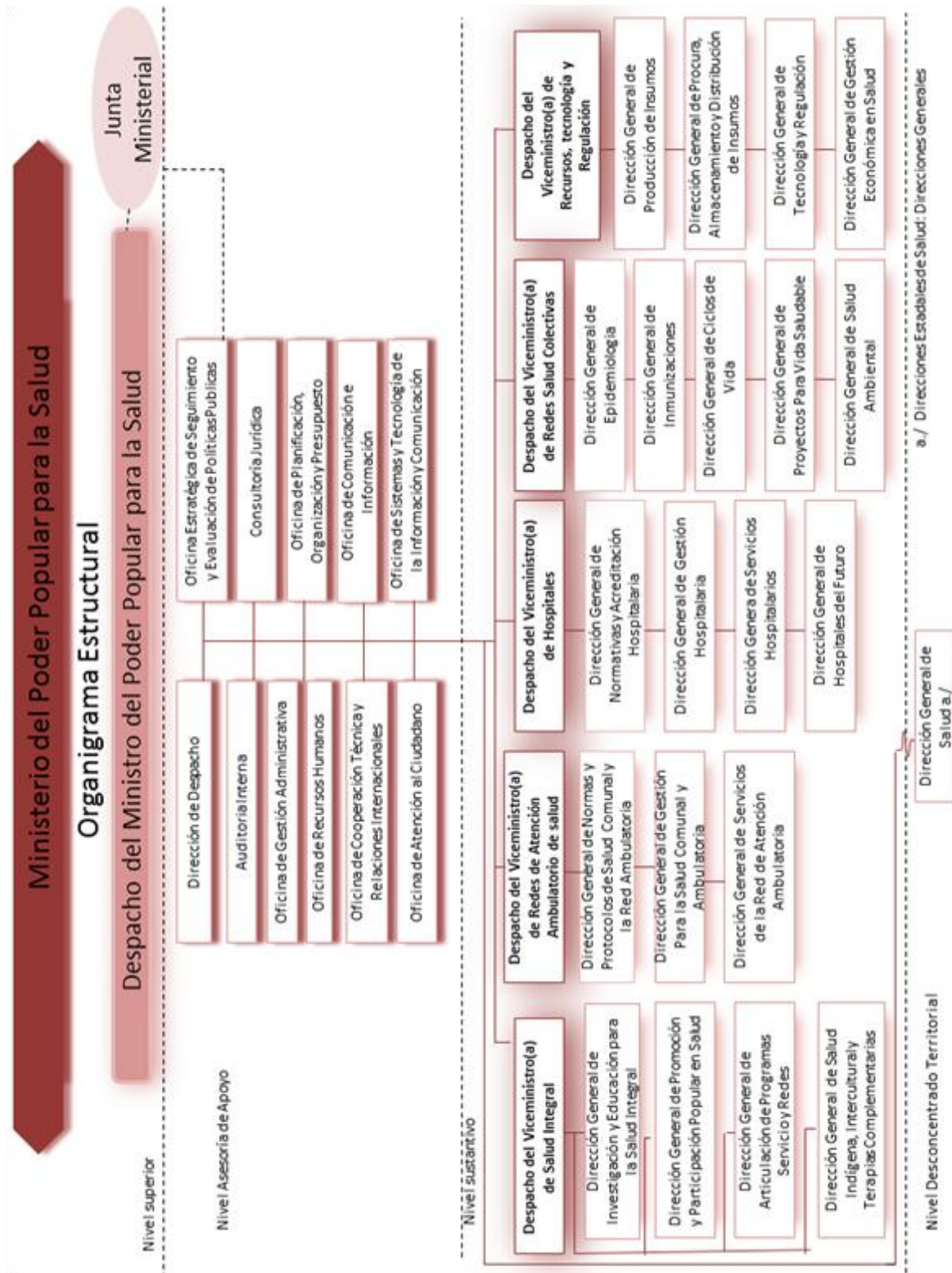
Appendix 2: Structural organisation chart



Despite the name of the chart it is based on the Organisational code as the reference and date indicate.

Source: Venezuelan Ministry of Health official site: www.mpps.gob.ve

Appendix 3: Functional organisation chart



Despite the name of the chart it is the current proposal, therefore functional instead of structural.

Source: Venezuelan Ministry of Health official site: www.mpps.gob.ve