

Rational Vaccination Policies - decision support

Review of International Literature for
„Rational“ Vaccination Policies



Ludwig Boltzmann Institut
Health Technology Assessment

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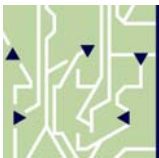
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Abbreviations

AEFI adverse events followed by immunization
DALY disability-adjusted life years
DDI Disability-Distress Index
ECDC European Centre for Disease Prevention and Control
EU European Union
EUSAFEVAC European research program for improved vaccine safety surveillance
EUVAC.NET Surveillance Community Network for Vaccine Preventable Infectious Diseases
GIVS Global Immunization Vision and Strategy
HPV Human Papilloma Virus
HUI Health Utility Index
IOM Institute of Medicine
NIP national immunization program
NNT number needed to treat
NNV number needed to vaccinate
QALY quality-adjusted life years
QWB Quality of well-being scale
U.S. United States of America
VENICE Vaccine European New Integrated Collaboration Effort
WHO World Health Organization

Summary

Background: National immunization programs differ from country to country in their vaccination schedules and decisions regarding the implementation and funding of new vaccines.

Objective: To assess the availability of decision tools, providing a standardized basis for rational decision making on vaccine introduction.

Methods: Systematic literature review, supplemented by hand-search of references, further searches on institutional websites and contact with immunization experts. Comparison of key documents and discussion of relevant criteria.

Results: Five key documents providing an analytical framework or key questions aiming at rational decision making were found. A comparison of these documents revealed an overall similarity with some differences in the approach as well as the criteria. Burden of disease and vaccine characteristics play a key role in the decision making process. The cost-effectiveness analysis is influenced by various factors and has several limitations. Therefore, the authors vary in their views on its significance. Other relevant factors also should be considered before vaccine introduction. These include, the immunization program itself as well as its conformity with other programs, its feasibility and how easily it can be evaluated. Acceptability, equity as well as ethical, legal and political considerations are discussed to highly differing extents.

Conclusion: Assuming that the most comprehensive framework possible would not provide a feasible tool for decision makers, a stepwise procedure has been suggested. Comments, examples and caveats have been given for each step to provide a basis for further discussions. The observed lack of standardized measures, defined cut-off points and comparable weighing of included criteria currently hinder rational decision making.

**objective of paper:
providing tool for
rational decisions on
new vaccinations**

**5 documents analyzed:
comparison of
similarities and
differences**

stepwise approach

Zusammenfassung

Hintergrund: Nationale Impfpläne sowie einzelne Entscheidungen, neue Impfungen in Programme aufzunehmen und diese zu finanzieren unterscheiden sich stark.

Studienziel: Die Erarbeitung einer Entscheidungshilfe, die als Basis für einen rationalen und standardisierten Entscheidungsprozess für die Aufnahme neuer Impfungen in nationale Impfprogramme dienen soll, war Ziel der Arbeit.

Methode: Systematische Literatursuche, unterstützt durch Handsuche in Referenzen und auf institutionellen Webseiten sowie durch Kontaktaufnahme mit Impfsachverständigen. Vergleich von Schlüsseldokumenten und Diskussion der relevanten Kriterien.

Ergebnisse: Fünf internationale Publikationen, die Analyseraster oder Schlüsselfragen für rationale Impfentscheidungen bieten, wurden identifiziert. Ihr Vergleich zeigt Gemeinsamkeiten, aber auch Unterschiede sowohl im Zugang als auch den Entscheidungskriterien selbst und deren Gewichtung auf.

- ✧ Die Analyse der Erkrankung, d.h. die Krankheitslast für Betroffene wie die klinische Manifestation und mögliche Ausprägungen, die Größensortierung und Public Health Relevanz des Gesundheitsproblems und ihrer Folgen,
- ✧ die Prüfung bestehender im Gesundheitssystem eingeführter Alternativen und deren Effekte,
- ✧ die Eigenschaften der verfügbaren Impfstoffe wie prognostizierte Effektivität und bekannte Nebenwirkungen, Fragen der Bereitstellung, Lagerung, Eingliederung oder gar Kombination in bestehende Impfpläne, aber auch
- ✧ die Kosten der Erkrankung durch Nutzung der Ressourcen (Hospitalisierung, Rehabilitation etc.)

nehmen in allen Arbeiten eine zentrale und prioritäre Rolle im Entscheidungsprozess ein.

- ✧ Eine Kosten-Effektivitätsanalyse wird hingegen von diversen Faktoren beeinflusst: von den Kosten des Impfstoffes sowie des zusätzlichen Aufwands für das Impfprogramm einerseits, andererseits von der realen Effektivität der Impfung basierend auf Durchimpfungsraten der Risikopopulation, unerwarteten - die Akzeptanz beeinflussenden - Nebenwirkungen, etc.

Darüber hinaus fließen Kriterien wie die Finanzierbarkeit, die Umsetzbarkeit und/oder Adaptierbarkeit einer neuen Impfung in den bestehenden Impfplan, die Möglichkeit der Überwachung der Immunantwort und -dynamiken sowie Gleichheitsgrundsätze und ethische, rechtliche und politische Überlegungen ein.

Schlussfolgerung: Zur Anwendung der Entscheidungshilfe wird ein Stufenmodell vorgeschlagen. Der aufgezeigte Mangel an standardisierten Kriterien, klar definierten Grenzen und einer vergleichbaren Gewichtung der eingeschlossenen Kriterien, erschweren aber derzeit rationale Impfentscheidungsprozesse. Eine internationale Diskussion vor aktuellen Entscheidungen unter Nachfragedruck ist notwendig und soll mit dem vorliegenden Bericht forciert werden.

**rationale
Entscheidungshilfe zur
Aufnahme neuer
Impfungen in Impfpläne**

**5 Publikationen:
Analyse von
Ähnlichkeiten und
Unterschieden**

**Entscheidungskriterien:
Krankheitslast,
Alternativen,
prognostizierte Effekte,
reale Annahmen,
Kosten**

stufenweises Vorgehen

1 Introduction

The national immunization programs of various countries differ in their vaccination schedules and decisions regarding the implementation and funding of new vaccines. One of the objectives of the Vaccine European New Integrated Collaboration Effort (VENICE) research project funded by the European public health action program is to encourage a rational approach in making decisions on vaccination policies. In one of its initial findings, VENICE discovered variations throughout Europe in the case of Human Papilloma Virus and Rotavirus vaccine recommendations¹. This, in turn, raises questions about rational decision making processes.

Vaccines are a potential preventive measure to support and increase the health status of a population. Many objectives have already been achieved. The ongoing development and commercialization of new vaccines which, on the one hand, target less severe or less widespread diseases and on the other hand are more expensive than commonly used vaccines, will challenge national health authorities worldwide. Whereas developing countries already struggle with problems involving the funding of vaccines and the extent of coverage of standard immunization programs, industrialized nations face problems involving the financing of expanded programs. From a public health perspective, limited financial resources should be distributed in a fair and effective manner that aims at achieving the best possible outcomes.

Decisions on implementing new vaccines in national immunization programs should be unbiased, comprehensive and systematic and therefore based on deliberate, rational, comprehensible and evidence based criteria.

Due to the lack of standardized national approaches, the aim of this study is twofold. First, it attempts to determine whether support for decisions concerning rational vaccine introduction exists. Second, this study attempts to determine which criteria are crucial for a rational decision making process.

This paper aims at giving decision support on the criteria for assessing new vaccines and at highlighting the main issues that have to be addressed before a decision can be made.

heterogeneity of vaccination schedules

leads to question of rational decision-making

new vaccines are targeting less severe diseases, but more costly

public health perspective: fair & rational approach to use limited resources

decisions to implement new vaccines: based on unbiased, comprehensive, systematic criteria

2 Methods

The paper is based on a systematic review. The flowchart of literature selection is given in figure 2-1.

systematic review based on systematic literature search

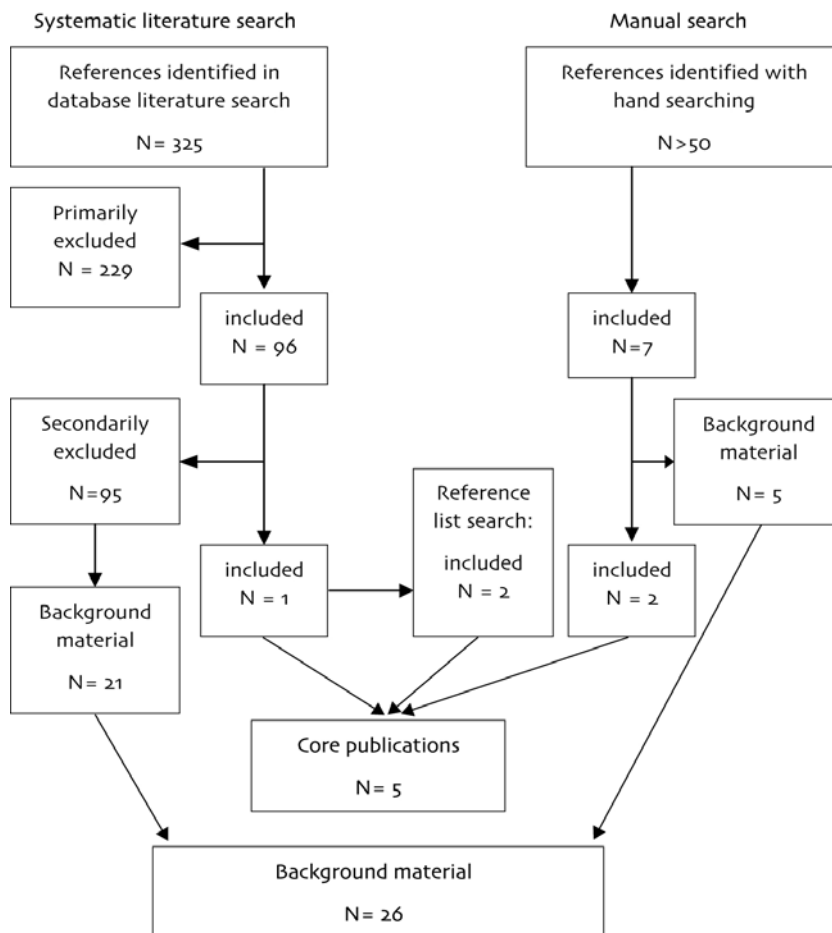


Figure 2-1: Literature selection

To gather information about rational vaccination policies a database search for relevant literature was conducted in MEDLINE, EMBASE, CCRCT, CDSR, DARE and HTA. Search terms and search strategy can be seen in table 2-1.

search terms & strategy

Table 2-1: Search terms and search strategy

1	(vaccination and (policş or strategş or programş)).ti,ab.
2	(immuni#ation and (policş or strategş or programş)).ti,ab.
3	decision making.ti,ab.
4	advisory structures.ti,ab.
5	formali#ation.ti,ab
6	designş.ti,ab.
7	assessş.ti,ab.
8	guidelineş.ti,ab.
9	national immuni#ation programş.ti,ab.
10	nnv.ti,ab.
11	qaly.ti,ab.
12	(development of vaccination and (policş or programş or strategş)).ti,ab.
13	1 or 2
14	or/4-8
15	13 and 14
16	13 and 3
17	11 and vaccination.ti,ab.
18	9 or 10 or 12 or 15 or 16 or 17
19	18
20	limit 19 to humans

**exclusion criteria:
developing countries,
basic research,
specific vaccines,
national immunization
programs**

This search resulted in 325 hits. 229 results could be excluded fulfilling primarily exclusion criteria (table 2-2). Of the remaining 96 documents only one dealt with decision making on national immunization programs in general² (95 publications were excluded according to the secondarily exclusion criteria).

Table 2-2: Exclusion criteria

Primarily exclusion criteria	Secondarily exclusion criteria
Guidelines and other recommendations for vaccine introduction and program planning in developing countries	recommendations for and studies performed with specific vaccines
scientific basic research on vaccine development	Published before 2000
description of national immunization programs	Full text in languages other than English
other meanings of NNV	

**manual search
highly effective**

Manual search proved to be much more effective: hand search for this paper resulted in the second core document³. In its reference list, the third decision making tool was found⁴. To identify papers not indexed in the databases, additional searches were conducted in Google and Google Scholar with search terms listed in table 2-1 and websites of relevant organizations were accessed (see table 2-3). Only in WHO library database search (<http://dosei.who.int/>) two additional main documents^{5,6} were found. Some public health experts or expert institutions were contacted by email or

phone. A list of contact persons who assisted in further investigations or answered specific questions on rational immunization policies is given in the annex (Table 7-1).

Table 2-3: Web-search

Organizational websites accessed	
Australian Government, Department of Health and Aging, Immunise Australia Program	http://www.immunise.health.gov.au/ ,
Bundesministerium für Gesundheit, Familie und Jugend (Austria), Impfen	http://www.bmgfj.gv.at/
Centers for Disease Control and Prevention (U.S.), Vaccines and Immunization	http://www.cdc.gov/vaccines/
European Centre for Disease Prevention and Control, Vaccines& Immunisation	http://ecdc.europa.eu/Health_topics/VI/VI.html
European Union, Directorate General Health and Consumer Protection, Public Health	http://ec.europa.eu/health/index_en.htm
Ministry of Health New Zealand, Immunisation	http://www.moh.govt.nz/immunisation
National Centre for Immunisation Research and Surveillance, Australia	http://www.ncirs.usyd.edu.au/
National Health Service (Great Britain)	http://www.nhs.uk/ , http://www.immunisation.nhs.uk/
Public Health Agency of Canada, Immunization and Vaccines	http://www.phac-aspc.gc.ca/im/index-eng.php
Robert Koch Institut (Germany), Infektionsschutz, Impfen	www.rki.de
Swedish Institute for Infectious Diseases Control	http://www.smittskyddsinstitutet.se/in-english/
The Netherlands Vaccine Institute	http://www.minvws.nl/en/organization/chart/diensten_en_instellingen/NVI/
World Health Organization (International, Regional Office for Europe and the Western Pacific Region, Pan American Health Organization ,WHO library database,)	http://www.who.int/ , http://www.euro.who.int/ , http://www.wpro.who.int/ , http://www.paho.org/ , http://dosei.who.int/

web-search: institutions concerned with immunisation

Based on the most comprehensive framework, a comparison of the five key documents was performed. All relevant criteria to be taken into consideration during a decision making process on vaccine introduction were reviewed and compiled to propose a more comprehensive framework.

Other relevant background literature aiming only at parts of the decision making process were introduced in the discussion to give explanatory examples.

identification of 5 key documents

3 Results

3.1 Central Publications on rational immunization policy

The following five key publications were included in the analysis (in order of their publication date):

1. **Stratton KR, Durch JS, Lawrence S, Editors Committee to Study Priorities for Vaccine Development. Division of Health Promotion and Disease Prevention, Institute of Medicine (2000). *Vaccines for the 21st Century: A Tool for Decisionmaking*⁴**

The Institute of Medicine released reports on “New vaccine development: Establishing priorities” for the first time in 1985. In the first part of their current publication, the authors reassess the progress and advances made as well as the barriers encountered in vaccine development. The main objective of the work is to analyze the setting of priorities for 26 preventive and therapeutic vaccines against diseases of domestic public health importance and likely to be approved within the next two decades. For vaccine ranking they chose a cost-effectiveness approach. Reasons for choosing this method as well as its limitations are outlined. Examples for hypothetical vaccines are given. Information on how the analyses have been performed is provided in great detail and issues to be addressed concerning vaccine introduction are “operationalized”. In the 300 pages appendix results of analyses of each of the 26 vaccines are presented. The model used can be accessed and used free of charge on www.iom.edu/vaccinepriorities.

IOM 2000:

tool for priority setting based on cost-effectiveness

2. **Mansoor O, Shin S, Maher C and the Immunization Focus, World Health Organization, Regional Office for the Western Pacific (2000). *Assessing new vaccines for national immunization programmes- A framework to assist decision makers*⁵**

The authors provide a set of seven questions as suggested basis of their framework (Table 7-2 in the Annex). Working through these key questions should facilitate the decision making process by providing more detailed on-going questions for each issue.

WHO 2000:

framework to facilitate decisions on the implementation of new vaccines

The detailed Asian Vaccination Initiative assessment framework is presented in an Annex. It is used to assist in initial assessments on financing issues of a NIP/national Immunization Program. It identifies key information to facilitate the analysis of current costs and cost projections. It provides a step-by-step manual on this process. Using this assessment, decision makers should be able to draw conclusions about the program and its priority needs.

3. **World Health Organization. Immunization, Vaccines and Biologicals (2005). *Introduction Guideline- Adding a vaccine to a national immunization programme: decision and implementation*⁶**

By way of a flowchart (figure 7-1 in the Annex) the authors present key issues that have to be considered before making decisions on the introduction of new vaccines. What is needed to implement the decision and monitor the impact are discussed separately.

WHO 2005:

key issues to be addressed before decisions of new vaccines

<p>Erickson et al. 2005: categories to be considered</p>	<p>4. Erickson LJ, De Wals P, Farand L (2005). <i>An analytical framework for immunization programs in Canada</i>³</p> <p>The framework consists of 13 categories and explanatory notes are given. Key questions that should be considered before making decisions on vaccination programs are listed (Table 7-3 in the Annex). The Appendix of this paper provides a complete list of all of the 58 criteria that had been grouped into the 13 categories.</p>
<p>Kimman et al. 2006: relevant issues & cost-effectiveness analysis</p>	<p>5. Kimman TG, Boot HJ, Berbers GA, Vermeer-de Bondt PE, Ardine de Wit G, de Melker HE (2006). <i>Developing a vaccination evaluation model to support evidence-based decision making on national immunization programs</i>²</p> <p>Relevant issues of consideration were grouped into three fields (Figure 7-2 in the Annex), giving the input for following cost-effectiveness analyses. Details that should be provided for each of the fields are listed in tables and further discussed.</p>
<p>purpose of publications: to analyse & discuss priorities for vaccine implementation</p>	<p>All publications aim at assisting in the making of decisions on vaccine introduction and to strengthen national immunization programs²⁻⁶. Additionally they might act as a common tool and language in analyzing and discussing priorities for vaccine development and implementation⁴, be used as a tool for consensus building or public education³ or support vaccine manufacturers in vaccine development and presentation⁴.</p>
<p>prospective audience: policy makers</p>	<p>Two analytical frameworks^{3,4}, two checklists^{2,5} and one list of key issues⁶ are presented in the analyzed papers. To collect and synthesize relevant information for the development of the decision aids, questionnaires were sent to immunization experts³ and discussions with multidisciplinary health experts on immunization were arranged². A committee to study priorities for vaccine development had been established. This group held meetings and workshops, heard presentations from NIP/National immunization program managers and contacted other experts with targeted questions⁴. The authors of two documents^{5,6} did not provide a description on the methods that led to the final approach (see table 3-1).</p>
<p>design/ methods: framework, checklists, relevant issues</p>	<p>Two analytical frameworks^{3,4}, two checklists^{2,5} and one list of key issues⁶ are presented in the analyzed papers. To collect and synthesize relevant information for the development of the decision aids, questionnaires were sent to immunization experts³ and discussions with multidisciplinary health experts on immunization were arranged². A committee to study priorities for vaccine development had been established. This group held meetings and workshops, heard presentations from NIP/National immunization program managers and contacted other experts with targeted questions⁴. The authors of two documents^{5,6} did not provide a description on the methods that led to the final approach (see table 3-1).</p>
<p>target countries: industrialised</p>	<p>All decision aids included might be used at national levels all over the world. One was originally designed for international use⁶ and therefore is the most general. The others were developed in different regions/ countries (western pacific region⁵, Netherlands², Canada³, U.S.⁴), potentially influencing their transferability due to specific domestic considerations. The extensiveness and depth of the five key publications vary widely between 7³ and up to 500⁴ pages. The reference lists contain at least 14⁵ and up to 150⁴ references.</p>

Table 3-1: Purpose and prospective clients & design/methods and target countries

	Stratton 2000	WHO 2000	WHO 2005	Erickson 2005	Kimman 2006
purpose	to develop a model for prioritizing vaccine development, that is quantitative and relatively unbiased toward a specific vaccine candidate	To support rational, logical and consistent decisions on new vaccines by clarifying the technical and operational issues through a series of technical questions	to assist an informed decision making process to add a vaccine, to ensure smooth introduction of the new vaccine, to promote further strengthening of the immunization program	for structuring program report presentation; for structuring discussion and consensus building in expert committees, for teaching and public education	to present an evaluation model in the form of a checklist, that may support decision making on a national immunization programs
prospective audience	vaccine science community, vaccine manufacturers, research and program policymakers	policy makers	country level decision-makers, national immunization program managers, consultants working on immunization	decision-makers, public education	decision-makers
design/ methods	analytical framework and quantitative model (and evaluation of 26 specific vaccines for the U.S. health system) produced by an committee of the Institute of Medicine on behalf of the National Institutes of Health;	checklist, methods not described	list of key issues to be considered before deciding to introduce a vaccine, criteria for assessing the NIP readiness for new vaccine introduction; giving examples; methods not described	analytical framework (58 different criteria, grouped into 13 categories) based on questionnaire sent to key scientific and public health experts involved in the planning of immunization programs across Canada	checklist assembled after discussions by a multidisciplinary team consisting of microbiologists, immunologists, epidemiologists, experts on vaccine safety and health economists; information assigned to one of the three fields (vaccine, disease, pathogen)
target countries	domestic US (focus on conditions of domestic public health importance); special analysis of vaccines that could be developed within the next two decades, including therapeutic vaccines)	international: Focus on Western Pacific countries	international	domestic (Canada)	International? (Europe?)

3.2 Synthesis – Criteria for rational immunization policy

Though issues to be considered before vaccine introduction are quite similar at a first glance, comparison of the frameworks and checklists is difficult. The grouping of relevant factors varies, as does their predicted weight and detailed analysis. This might be explained by different development backgrounds, methods and aims of the works.

Ericksons framework³ has been chosen as the basis for direct comparison due to its comprehensive structure of the 13 categories. To point out similarities and highlight additional concerns, issues that should be taken into consideration during the decision making process were added by informa-

criteria to consider quite similar, but weight & relevancy assigned to criteria varying

basis for synthesis here: Erickson 2005 framework

tion provided by the other publications^{2,4,6}, assigning them to these 13 categories.

Burden of disease

**main criterion:
burden of disease
described by
characteristics of
infective agent:**

All authors agree that the burden of disease is the main or one of the most crucial concerns driving vaccine development and vaccine introduction. While there is agreement on the weight given to burden of disease, the analysis of details varies:

- ✳ *Infective Agent*³: the characteristics of the infective agent can be described by their pathogenicity, transmission properties and antigenic variation² (table 3-2).

**pathogenicity,
transmission properties,
antigenic variation**

Table 3-2: Pathogen issues

Pathogenicity	Transmission properties	Antigenic variation
part of population in contact with pathogen, incidence in (sub-) population(s),	infectiveness during various stages of infection	occurrence of variation
variations in pathogenicity, interactions with other pathogens, ecological consequences after vaccine implementation (ecological niche?)	routes of transmission, importance of different transmission routes	evolutionary pressure leading to emergence of antigenic or virulence variants- consequences on vaccine's effectiveness

**clinical manifestations
of disease**

- ✳ *Clinical Manifestations*³ can be characterized by symptomatic or asymptomatic infections or carrier ship². Designing additional morbidity scenarios⁴ requires information about typical patterns of disease as well as information about variations in disease presentation, patterns or severity. The duration of each phase as well as the proportion of infected people who will experience each pattern must be considered. The consequences of infection⁴ can be outlined through complications, case fatality, relapses and sequelae as well as their duration (“short and long term”) ² and proportion. Due to variation in clinical morbidity patterns several morbidity scenarios for each pathogen are required⁴.

**epidemiology
of disease:
incidence, mortality**

- ✳ *Epidemiology*: Epidemiology addresses incidence and mortality of a disease. Incidence can be characterized in more detail by overall and age specific incidence (= rate of cases per year) of clinical/ sub clinical/ latent and chronic infections⁴. Attention should also be paid to changes in disease incidence including their reasons⁴ and time trends, as well as geographical or seasonal variations³. Epidemiologic assessment depends on reliable data². In absence of reliable surveillance data estimates have to be used based on available literature or clinical medicine and epidemiology experts' estimation⁴.

- ✧ *Risk groups/ Risk factors*: Groups at greatest risk for infection (or one of the patterns of disease, e.g. more severe forms of disease) must be highlighted^{2,3,4}. Age, sex, ethnicity, socioeconomic status, immunologic competence, geographical areas or other specific risk factors should be taken into account⁴.

risk groups &
risk factors
- ✧ *Alternative measures*: Besides the current treatment³ the availability of other preventive measures that might be in favor of vaccination should be assessed^{2,3,5}. Appropriate prevention interventions could be available for nosocomial infections (minimizing contamination risks), waterborne infections (water supply), vector-borne microbial agents infections (vector control) or infections occurring in immunocompromized hosts (e.g. minimizing behavioral risks)⁴. The “new” vaccine should also be compared with other currently available vaccines⁶. All alternative measures should be compared with a vaccination strategy in terms of effectiveness, costs and practicality^{2,4}.

alternative preventive
interventions
- ✧ *Disease as public health problem*⁵: The health impact of the disease in the population must be assessed³ to decide if the disease is of domestic health importance⁴.

importance of public
health problem
- ✧ *Social impact of disease*: The social impact can, on the one hand, be seen as the influence of intensity of suffering (quality of life reduction) and frequency of survivors with sequelae or long term disability on disturbing social structures (e.g. impact on families, caregivers)^{2,3}. The resulting stress on communities³, the public perception² (“fear of disease”³) and possible differences in real and presumed burden of disease² should be taken into account. On the other hand, the magnitude of absenteeism from school or work of infected individuals themselves and their caretakers as well as associated costs can be seen as part of the social impact of disease².

social impact
of the disease to
persons concerned,
families, communities
- ✧ *“Costs” of the disease*: Health short- and long-term care utilization/ health system cost are the main part of the economic impact of the disease^{2,6}. Additionally payments by patients and families and productivity losses should be considered. To calculate the overall costs caused by a pathogen costs of each terms (hospitalizations, procedures, medications, office visits, rehabilitation services, long-term institutional care) have to be multiplied with the proportion of patients receiving this care and finally summed up⁴. Due to the variation in health expenditures national data of “health care costs” for all services mentioned are therefore necessary⁴.

costs of disease

Vaccine

All authors include vaccine considerations in their decision making process. Issues to be considered are:

- ✧ *Vaccine characteristics³/ presentation⁶*: The nature and characteristics of the immunizing agent and the characteristics of the products (preparation, the stabilizing agents and preservatives, dosage, combination, storage, handling, conservation and product format)³ must be known. Vaccine availability and registration, as well as the target indication/ population of the vaccine should be examined².

vaccine-specifices

characteristics of
immunizing agent

producer capacities & quality	✧ <i>Vaccine supply.</i> Data of vaccine manufacturers and their production capacity must be collected ³ . Potentially arising conflicts of interest and differing quality criteria in case of national production facilities ⁴ and the impact of vaccine introduction on any local vaccine producer ⁵ should also be stated.
schedules, doses & combinations	✧ <i>Administration schedule, number of doses, combination.</i> The administration schedule ³ and possible alternatives to the optimal schedule ² should be assessed. The number of doses (number needed for complete immunization (initial series) and frequency of boosters) ⁴ and possible combinations must be taken into consideration.
immune response & duration of protection	✧ <i>Immune response.</i> Issues to be assessed in this category are the nature and characteristics of immune response ³ and (type-specific) protection afforded, the critical determinants of immune response associated with protection ² as well as the expected duration of protection, the effects of waning immunity and consequences resulting in the necessity of possible repeated vaccinations (also regarding their expected coverage) ² .
immunogenicity & failure within risk groups	✧ <i>Immunogenicity and failure.</i> The immunogenicity in different population groups ³ and the frequency of and risk groups for vaccine failure (despite optimal vaccination or when using alternative schedules) ² should be considered.
efficacy based on actual utilization	✧ <i>Efficacy and utilization.</i> Efficacy can be seen as short and long-term reduction of disease and death by the vaccine ³ or in other words as the capability to prevent a disease in immunized populations ⁶ . Availability of data has to be considered, especially if the study population is comparable with the target population and if the studies were performed in countries with similar disease epidemiology ⁶ . Efficacy could also include assumptions on licensure approval and patient acceptance ⁴ . Utilization (coverage ⁵) can be defined as the proportion of the target population that will use the vaccine ^{2,4} . The data of population that has already been vaccinated should also be collected ² .
effectiveness based on performance	✧ <i>Population effectiveness.</i> Vaccine effectiveness reflects the performance of the vaccine in the actual target population under programmatic implementation ⁶ and therefore stand for “the net impact of the vaccine” ⁵ . Vaccine effectiveness is therefore usually lower than vaccine efficacy ⁶ . Effects can be seen as reduction of burden of disease ³ and the reaching of a level of herd immunity by a sufficient vaccination rate ^{2,3} .
adverse events	✧ <i>Safety.</i> Precautions ³ and contraindications for vaccination and their proportion in the target population ² as well as the nature and frequency and consequences of short- and long term (severe ³) adverse events ² are major safety issues. Risk groups or risk factors for adverse events and differences in true and presumed burden of disease due to adverse events (perception of population) should also be considered ² . For live attenuated vaccines the chance of reversion to virulence can be added ² . Summing up, frequency, nature, severity, care required and public reaction should be assessed when safety issues are included in calculations ⁴ .

- ✳️ *“Side-Effects”*: Effects of antigen transmission of the targeted antigen (e.g. on reduction in carriage³; changes in antigenic composition, changes in virulence and transmissibility² and therefore indirect effects on reducing disease transmission⁵) and also of related antigens (e.g. replacement by other antigens³; emerge of new ecological niches²) should be considered as possible long-term effects. Shifts in age-distribution of the disease might occur and the reduced pathogen transmission under vaccine pressure might lead to enhanced vulnerability of specific sub-populations². Possible interactions/ interference with other vaccines^{2,3} should also be considered as well as the impact of the new vaccine on resistance to antibiotics/ antivirals³.

**long-term
unintended effects**

Immunization strategy

Goals of the new vaccine implementation should be expressed precisely in the decision making process.

**clear definition of goals
of implementation &
strategies to achieve
these goals**

- ✳️ *Existing recommendations/ guidelines*: To assess the immunization strategy, availability of existing recommendations or guidelines to be searched for and taken into account³.
- ✳️ *Goal of prevention/ specific program objectives*: Different goals (disease control, elimination or eradication) as well as specific program objectives (e.g. reduction of incidence or complications) should be defined³.
- ✳️ *Alternative strategies/ specific operational objectives*: Selective vaccination versus universal or catch-up vaccination and specific operational objectives (e.g. coverage for different target groups) should be weighted³.
- ✳️ *Different program delivery strategies and systems*: Public versus private vaccine delivery or vaccination in schools versus in primary care settings should be discussed for example³.

Conformity of programs

The planned program should be compared with other existing or planned programs in other countries³.

**comparison of
conformity with
other national health
programs**

Cost effectiveness

The cost effectiveness category is the most difficult to compare because all authors chose different approaches. It can be seen as one step beyond others^{3,5,6}, an intermediate result (after assessing other main factors)² or a central approach respective to the outcome⁴ of the analysis.

**different approaches:
central criterion or one
among others**

- ✳️ *Vaccine costs*: Costs to be considered are:
 - *Costs of research and development⁴*: Assessing vaccines already available on the market for implementation in national immunization programs, will allow neglecting the pre-licensure expenditures.

cost categories:

R & D costs

costs of vaccine	<ul style="list-style-type: none"> - <i>Costs of the vaccine</i>: The cost per dose of the vaccine has to be given. It should be noted that these costs depend on the number of companies distributing the vaccine and their marketing strategies³.
costs of vaccination program	<ul style="list-style-type: none"> - <i>Costs of the vaccination program</i>: In addition to the vaccine cost itself, the cost to administer the vaccine has to be added and then multiplied with the number of doses needed and the size of the target population⁴. This will reflect the annual vaccine use costs, if the “steady state” is already reached. Costs during initial use might differ (once-only versus yearly costs²): decreased costs might occur because the usage depends on how familiar a health care system and the target population are with the new vaccine. Increased costs also might result from "catch-up" usage of the new vaccine beyond the target population⁴. Additionally costs from a “societal perspective” including direct and indirect costs for families and the health system should be considered³. Further costs for implementation and running of the program³ and for monitoring safety and effectiveness of the vaccine and the program² should be taken into account.
benefits: health impact	<ul style="list-style-type: none"> ✧ <i>Effectiveness of the program</i>: Evidence of short and long-term effectiveness of the program (incl. the reduction in disease incidence, complications, sequelae and mortality) has to be analyzed³
benefits: economic & social impact	<ul style="list-style-type: none"> ✧ <i>Economic, social and other (“non-health”) benefits are</i>: <ul style="list-style-type: none"> - <i>savings on health care costs</i>²⁻⁶ - <i>improvement of life expectancy and quality of life</i> for individuals (“QALYs gained”) ²⁻⁶ - possible (positive) <i>impacts on caregivers and communities, productivity gains</i> and other indirect benefits (like reduced microbiological resistance or reduced emergency room overcrowding)³.
costs of alternative interventions	<ul style="list-style-type: none"> ✧ <i>Economic evaluation of alternative measures</i>: the cost effectiveness ratio of vaccination has to be compared with alternative preventive measures (how many infections could be prevented by other vaccines/ health care interventions and what would be the savings on costs of health care?) ²⁻⁶. For this comparison costs and health effects using current forms of prevention and treatment or vaccines have to be known⁴.
Influence of different factors on cost-effectiveness (utilization, coverage, schedules etc.)	<ul style="list-style-type: none"> ✧ <i>Testing underlying/ alternative assumptions</i>: <ul style="list-style-type: none"> - <i>Sensitivity analyses</i> testing alternative assumptions (different morbidity/ clinical scenarios, quality adjustment weights, costs of care, vaccine development, utilization,...) have to be carried out to show the robustness of the economic model^{3,4}. - Using <i>different schedules or different strategies</i> (e.g. high risk immunization) will influence cost-effectiveness analyses and therefore must not be neglected².

- The *maximum impact* of a new vaccine is the ideal vaccine benefit calculated under the assumption, that the vaccine is fully efficacious and utilized (optimal conditions)⁴. It should be *compared with the cost-effectiveness for incomplete use and efficacy*⁴. In case of vaccines under development the impact of developing time and resources has additionally being taken into account⁴.
- The results of all analyzes should be *compared with similar studies* and their pertinence for local settings should be considered³.

✳ *Time interval*: Time intervals between the age of vaccine use and the age at which health effects and related costs are experienced have to be regarded^{2,3}. Reasons for and possible ethical consequences of discounting for costs and health benefits should be discussed⁴.

best & worst case scenarios: assumptions for effectiveness of vaccination

time of effects & discounting

Acceptability

The acceptability of the new vaccine or a whole new program can be evaluated by assessing the

- ✳ *Public's perception of disease risk and severity* as well as the demand for the immunization program at target group and population at large level³, concerns about rapidly enough changing NIPs (modernization) in public's opinion²
- ✳ *Demand and acceptability* by health professionals and political authorities³
- ✳ *Time effects*: Adding a new vaccine to a NIP could increase or decrease the overall perception of the value of immunization⁵. During a vaccination program the balance between presumed adverse events and beneficial effects may shift in time².

public acceptance is influenced

by perception of severity of disease by demand

changes of perception over time: adverse events

Feasibility

Feasibility addresses practical consequences of the planned vaccine implementation and reflects the opportunity of implementing the new program³. Differences in the approach can be observed. Some authors completely neglect issues of implementation during the decision making process⁴ or first consider them after the fact^{5,6}.

Issues to be considered are the

- ✳ Assessment of the *overall NIP performance*^{5,6} and the effectiveness of the primary care system² ahead of introduction of any new vaccine

implementation is influenced by

overall performance of national immunization programs

<p>by supply, funding/coverage,</p>	<ul style="list-style-type: none"> ✿ Availability of <i>long term supply</i>³ (see vaccine) ✿ Availability of <i>funding for vaccine purchase</i>^{5,6}
<p>by integration in existing programs & schedules</p>	<ul style="list-style-type: none"> ✿ Chance of <i>integrating the new vaccine in existing immunization programs and schedules</i>³: Often average schedules for combined administration have to be chosen for practical and economic reasons (NIP is likely and perhaps necessarily a compromise)². Reducing the number of vaccines delivered to children by combination vaccines can increase the level of acceptance and utilization⁴, while the complexity of the vaccination schedule or multiple injections administered at a single visit might lower compliance². ✿ <i>Impact of the new program on existing services</i>³ is influenced by financial concerns about sustainability, concerns about potential increase or complication of the workload for the staff and the risk of reducing the credibility of the NIP⁵.
<p>by access & awareness of target groups,</p>	<ul style="list-style-type: none"> ✿ <i>Accessibility</i>: Whether or not the new vaccine is accessible for the target population has to be considered³ (access, waiting times, reminders)² and if the desired levels of coverage will therefore be reached³. Special attention should be paid to difficult-to-reach groups². Furthermore, other concerns regarding poor compliance that hindered successful vaccine implementation in the past should be considered (e.g.: lack of parental awareness, competing parental priorities, parental complacency, inappropriate interpretation of contraindications, concerns regarding adverse reactions)²
<p>by compliance</p>	
<p>by issues of operationalization:</p>	<ul style="list-style-type: none"> ✿ <i>Existence of operational planning and implementation committees</i>³, the <i>availability of human, technical and financial resources</i> for distribution, conservation and administration of the program³, the <i>availability of documentation/ consent forms</i>³, the <i>availability of recording/ registering systems</i> for vaccine administration³, because poor records keeping also minimizes compliance², and the <i>availability of resources for marketing/ communication</i> to the public and information and training of health professionals³
<p>resources for administration, documentation, communication</p>	

Surveillance

<p>monitoring & evaluating the program</p>	<p>The desirability and necessity of monitoring and evaluation of the altered program should be beyond all questions. Therefore most authors include main issues of surveillance in their decision aids^{2,3,5}, sometimes even providing a separate post-introduction evaluation checklist for the assessment of overall implementation⁶.</p>
<p>coverage, surveillance of epidemiology, adverse events, microbiology</p>	<ul style="list-style-type: none"> ✿ <i>Coverage</i>: Vaccine coverage and utilization should measure general acceptance and identify regions or groups with lower coverage². These could/ should be added by surveillance of quality of services³ and trust in the NIP². ✿ <i>Epidemiology</i>²⁻⁶: The reduction of burden of disease² can be determined by surveillance of reduction in disease incidence, complications, sequelae and mortality³. Simultaneously time trends can be detected and observed². ✿ <i>Safety</i>: The frequency and nature of adverse events has to be observed²⁻⁶.

- ❖ *Immune surveillance and surveillance of microbial population dynamics*²: markers of protection should be observed in the general population, subgroups with waning immunity and also altered circulation pathways should be identified. The microbial population dynamics must be monitored².
- ❖ *“Linking systems”*³: information systems in general⁶ and systems for linking health outcomes databases (immunization registries and population registries) must be available³

instruments for surveillance: registries

Research questions/ Uncertainties

Vaccines should be primarily excluded from analysis, if only insufficient basic scientific information is available⁴.

major uncertainties: automatic exclusion

Issues to be considered are

- ❖ uncertainties about the *nature of the infective antigen*, major contributors to a disease or other pathogenetic factors⁴
- ❖ main uncertainties concerning the *effects of the vaccine* and the impacts of program³, need for a pilot immunization program³
- ❖ ongoing/ planned *research projects* (e.g.: vaccine development, immunogenicity, efficacy, safety)³
- ❖ need for *research to assist evaluation*, planning or decision-making³

Because the information gathered during the decision making process is not stable, evaluation and updating of the program will be necessary after implementation².

updating evaluation of vaccination program

Equity

- ❖ *Universality, accessibility and gratuity* of services for the most vulnerable population groups³ are political responsibilities⁴ that cannot be addressed by cost-effectiveness approaches (e.g. allocation of resources- need for specific populations). Equal opportunities for vaccination and equal access to information are therefore challenges for governments².
- ❖ *Introduction of expensive new vaccines*²: The high costs of (new) vaccines that may prohibit universal vaccination even when the burden of disease is high will place wealthy and well-informed individuals at an advantage². Therefore small NIPs plus voluntary packages that are offered in some countries inevitably lead to inequalities in comparison with comprehensive NIPs for the whole target population².

ensuring equal access

Ethical considerations

All decisions to implement or withhold a vaccine always must be taken as seriously and discussed from a scientific as well as from an ethical point of view². Some ethical and value judgments can be built into analytical models, others have to be discussed separately⁴.

<p>ethical issues are:</p> <p>informed consent & confidentiality</p> <p>assigning value to individual's life or only to productive individual's life</p> <p>discrimination: age & disabilities, chronic disease</p> <p>discounting: the sooner the better</p> <p>inclusion of non-health benefits discriminates low-income/ women</p> <p>maximizing health benefits vs. fairness</p>	<p>Ethical considerations include:</p> <ul style="list-style-type: none"> ✳ <i>Appropriate informed consent forms and the protection of confidentiality</i>³: Particularly for vaccinations that are not mandatory, information is necessary to ensure that the population is capable of making informed choices³. ✳ <i>QALY versus DALY</i>: the question if an additional year of life should have the same value regardless of the receiver's age remains an ethical question². Under QALYs, an additional year of life of the recipient has the same value regardless of the recipient's age. In comparison, the use of DALYs would assign greater value to years of life gained during the economically productive young adult years, assuming a greater social value because old and young depend on them. Choosing QALYs might therefore be judged more appropriate if the value of extending the individual's life seems more important than the value of the individuals' lives to others⁴. ✳ <i>Adjusting for differences in average health status</i> of population at different ages, nevertheless may weigh years of life at different ages by quality⁴. ✳ <i>Value of life extension with and without disabilities</i>^{2,4}: Vaccines used to prevent (opportunistic) infections in people with predisposing conditions or preexistent disabilities that initially caused a reduction of the quality of life (chronically ill or elderly people) will not achieve the same gain in health related quality of life as preventive vaccines given to healthy people⁴. Prioritizing vaccines preventing morbidities (not mortality) according to that method of valuing health benefits potentially discriminates persons with disabilities (if disability reduces benefits from treatment/prevention or makes the treatment/prevention more costly)⁴. The value of life extension on different levels of health related quality of life therefore remains a controversial ethical issue^{2,4}. ✳ <i>Applying discount rates to costs and health benefits</i> gives a period of well-being greater value the sooner it occurs⁴, an early in life health gain is therefore assigned a greater value². This might be ethically controversial, too⁴. ✳ <i>Including non-health benefits of vaccination</i>: from a public health perspective non-health benefits that are not included in a cost-effectiveness approach pose ethical questions, but also an inclusion might lead to problems^{2,4}: For example taking lost wages due to absence from work into account, would reduce the value of prevention against diseases acquired during nonworking years of life or occurring more frequently in lower-income populations⁴. ✳ <i>Comparing total health benefits of vaccines</i>: From a public health perspective in allocating resources, this approach of looking at overall benefits is coherent⁴. Reducing the total burden of disease
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does not differentiate in disease distribution⁴. Considerations of fairness arise if a decision is only based on maximizing cost-effectiveness². Priority judgment of aggregating small benefits for many can lead to ethical questions because in many peoples' minds avoiding a disease with an extremely large burden of disease has a higher priority even if the disease is less widespread⁴. The controversy remains if the maximum aggregate benefits should be achieved by large benefits for a few or small benefits for many⁴.

- ✳ *Vaccines avoiding diseases (or treating them) in primarily sick people*⁴: There is no objective basis for determining how much health gain in overall well-being should be achieved, therefore the priority of treating the sickest remains an unsolved problem and a political responsibility⁴.
- ✳ *Setting priorities in vaccine development*⁴: Funding only one of two vaccines against diseases that result in almost the same burden of disease may seem unfair to those who end up with that disease which did not receive vaccination funding. ⁴ This argument is somewhat mitigated because vaccines are developed mainly against diseases that are not life-threatening and nobody is able to predict, which disease one will develop over the years⁴.

trade-off: prevention vs. treatment

setting priorities excludes other vaccines

Legal considerations

- ✳ *Use of a vaccine in a different schedule as originally recommended by the manufacturer*³: Even if there might be some evidence that a single-dose vaccine could be as effective as the original schedule, the lack of clinical trials' data would lead to legal actions in case of vaccine failure³.
- ✳ *Legal issues as barrier in vaccine development and licensure*⁴: Vaccine producers require legal protection from lawsuits (e.g. development of vaccines that could be administered to pregnant women in the future) that address liability concerns. A vaccine injury compensation program already successfully has encouraged the development of vaccines for children⁴.
- ✳ *The implementation of compensation for people who suffered serious adverse events from vaccinations* already exists in some countries like the U.S. ².

issues of liability in case of failure or adverse events

Political considerations

It should be stated if

- ✳ the decision will be *free of controversy*³ and if
- ✳ it will produce *immediate political benefits or risks*³.

transparency on controversy and political benefits/risks

4 Discussion - Feasibility of analytical frameworks: a stepwise approach

Gathering information on the issues to be addressed in a decision process concerning the implementation of a new vaccine as provided in the framework comparison above, results in a most comprehensive as well as detailed list of categories. However the pertinent question of whether this approach is feasible for decision makers at all arises. Some of the categories will be beyond all questioning. Others, however, should be discussed in terms of relevance and chronology.

A rational approach that could be the basis of a discussion among decision makers would be a stepwise procedure. A draft proposal is given in Figure 4-1)

for policy process:

simplifying the criteria list & prioritizing according to relevancy is proposed

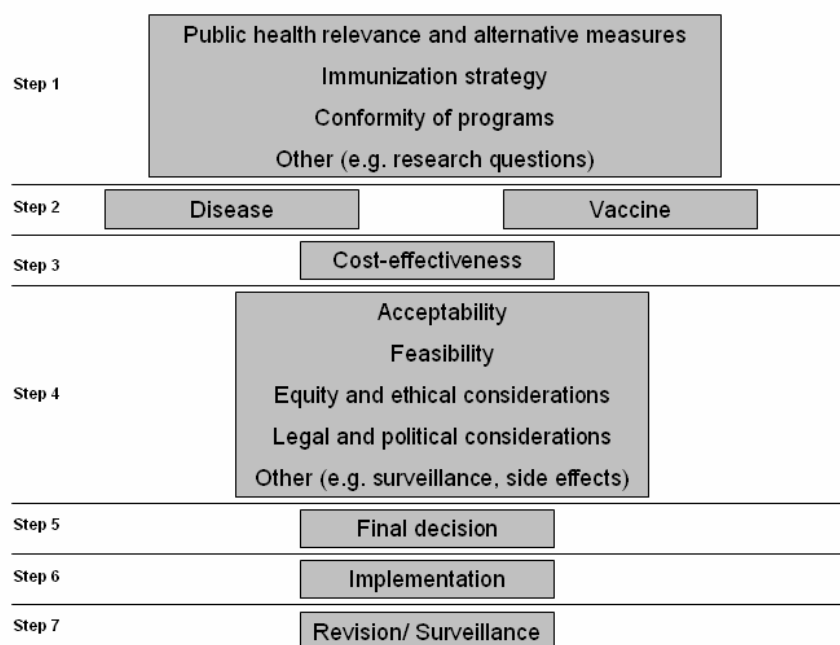


Figure 4-1: Analytical steps in the decision making process

4.1 Step 1: Public Health relevance, alternative measures, immunization strategy and conformity of programs

Some fundamental considerations concerning the disease as a public health problem, aims of the planned immunization strategy, the comparison with other programs and the availability of sufficient basic research data could be a starting point for the decision process and should be taken into account prior to further analyses.

The question of whether or not the disease is a public health problem for the country in which the adaptation of the immunization program is planned, should be considered before further analyses, though the precise answer, if

size of public health problem, existing preventive interventions & added value of vaccination

the burden of disease justifies a control program can't be given until all issues of disease burden and possible other alternative measures are weighted in step 2.

search for existing evidence & analyses:

basis for developing immunization strategy and before consideration on national policy

In a global world, international organizations play a key role in providing general recommendations on immunization strategies. In response to global immunization challenges, including the need to protect more people and introduce new vaccines, the World Health Organization and the United Nations Children's Fund, in consultation with other partners, have developed the Global Immunization Vision and Strategy/GIVS for the period 2006-2015⁷. GIVS is a framework that offers policy-makers and stakeholders a unified vision of immunization and a set of strategies from which countries can select those most suited to their specific needs.

looking across borders:

**WHO:
GIVS/ Global Immunization Vision & Strategy,**

Immunization represents a priority issue in the agenda of EU member states as well. Moreover many EU wide projects concerning vaccination – funded by European Commission - are in place at the present. The European Centre for prevention and disease control (ECDC)⁸ states that providing evidence based scientific advice on vaccine policies and strengthening surveillance of vaccine preventable diseases (VPD) in the EU in order to provide more information for scientifically sound decisions on vaccinations are VPD priority areas.

The goal of prevention (disease control, elimination or eradication) as well as specific program objectives (e.g. reduction of incidence or complications) might already be defined in international documents. Alternative immunization strategies (selective vaccination versus universal or catch-up vaccination) and specific operational objectives (e.g. coverage for different target groups) should be primarily discussed and finally weighted after the following steps.

**EU:
VENICE, EUVAC.NET**

Especially if there are no universal recommendations available, a planned program should be compared with other existing or planned programs in other regions/ countries. Looking across borders should facilitate considerations in the first planning phase. Providing updated online information about national vaccine schedules is one of the outcomes of the Surveillance Community Network for Vaccine Preventable Infectious Diseases (EU-VAC.NET)⁹ project. Facilitating the flow of information between European countries is also an objective of the Vaccine European New Integrated Collaboration Effort (VENICE)¹⁰ project.

**cautious observance of uncertainties:
long-term effects duration of protection**

Another aspect that might be considered previous to further analysis refers to scientific uncertainties concerning the vaccine. It would be a negligent act to introduce a new vaccine despite insufficient basic data. The answer to the question concerning what data should be available to be considered as sufficient cannot be given in this paper but should be discussed seriously. Due to restricted observation times during clinical trials, uncertainties on the long term effects of a vaccine will always remain. Duration of vaccine protection is one of these crucial issues directly affecting the cost-effectiveness analysis. Current literature does not shed light on the degree to which uncertainties had been accepted in the past. Also unavailable, is literature on how great the estimated benefits had to be in order for the vaccines to be introduced despite the missing information.

Promising ongoing or planned research projects in the same field of target disease could not only strengthen a decision to withhold a vaccine but also justify a postponement of analysis as does the lack of capable assistance for evaluation, planning or decision-making

**looking into the future:
research in target
disease**

4.2 Step 2: Disease and Vaccine

The two main criteria - disease and vaccine - that all authors considered as key parameters in the vaccine decision making process²⁻⁶ should be assessed in the next step.

The assessment of epidemiology, risk groups and clinical manifestations depend on reliable surveillance data. Insufficient surveillance systems, especially in diseases that are not reportable events and the lack of adequate data linkage (e.g. between physicians, health insurances and health authorities) due to considerations of privacy protection hinder conclusive argumentation. Therefore often less precise estimates have to be used based on available literature or clinical medicine and epidemiology experts' estimations⁴. To increase data quality of epidemiological surveillance and control of vaccine-preventable diseases in the European Community, the EUVAC.NET⁹ project was created. Currently only surveillance data and annual reports about measles, mumps, pertussis and varicella and diseases fact sheets and case definitions of these diseases plus rubella are available on the EUVAC.NET web site⁹.

**collection of data on
burden of disease:**

**expert estimates &
surveillance data**

A discussion on which criteria should be fulfilled by the burden of disease measure is necessary. A measurement applicable for various conditions should be used⁴. Though QALYs may have possible disadvantages as discussed, QALYs can serve as basis for disease burden measurement. In terms of quality adjustments, various instruments are available¹. To compare the burden of disease with a population not affected by the disease, basic data of these quality adjustments for average population health states (at different ages) are necessary⁴. Though published literature currently uses QALYs rather than DALYs weighing procedures in particular often remain unclear.

**effect measures as
guidance to compare
burden of disease**

Costs caused by the disease or its consequences vary in different healthcare systems⁴. The influence of the perspective from which the cost-analyses are conducted will be discussed later in conjunction with the cost-effectiveness matter.

The social impact of disease is probably the most difficult parameter to assess. While data of the extent of quality of life reduction and the frequency of survivors with sequelae or long term disability might be available, their impact on caregivers or even the community is hypothetical in the majority of cases⁴. Therefore one author⁴ excluded matters of time or costs saved by patients or their caregivers from analyses. But if sustainable time cost esti-

**costs of social impact of
target disease**

¹ Stratton⁴ chose the Health Utility Index (HUI) for weighting. HUI Mark II characterizes morbidity by using seven health attributes (sensation, mobility, emotion, cognition self-care, pain and fertility). Alternative instruments as the Disability-Distress Index (DDI), Quality of well-being scale (QWB), World Bank/ WHO disability (used for calculating DALYs) would be available.

	<p>mates are available for a disease they could and should be incorporated in the analyzing model⁴.</p>
prevalence in population or in risk-groups	<p>Published literature provides no limits (cut-off points concerning epidemiological indicators or burden of disease measures) on when a disease and its consequences should be considered a severe public health problem. In some cases general recommendations are available on the strategy (e.g. schedule and coverage) that should be followed depending on the prevalence of the disease. These disease specific immunization policy recommendations are available on the WHO Immunization, Vaccines and Biologicals website¹¹.</p>
cost-effectiveness of alternative interventions	<p>Current and alternative measures should be outlined in detail at the end of burden of disease assessments. Their effectiveness and costs must be calculated to allow comparison with the planned measure and answer whether or not the planned immunization is the best strategy to control the disease.</p>
vaccine-supply	<p>Basic analyses can be conducted on the assumption of 100% vaccine supply availability meeting the demand⁴. Nevertheless, one should keep in mind that inadequate supply has hindered extensive use of some vaccines in the past⁴.</p>
vaccine characteristics: requirements for handling, storage, combination	<p>In order to determine requirements for vaccine handling and storage or to draw conclusions on possible combinations and the immunization schedule, the vaccine characteristics must be known. If combinations are available, this might influence not only costs or effectiveness but also vaccine utilization (likely to increase)⁴. The number of doses needed for complete immunization (initial series) is suggested and approved by clinical trials. In new vaccines the frequency of boosters is mainly based on estimates and comparison with other vaccines due to the short trial observation period. All data or further estimates on immune response, including those on vaccine failure must be outlined to design different scenarios (influencing costs of the program, coverage and population effectiveness).</p>
immune response, failure & adverse events	
optimistic & realistic utilization & effectiveness scenarios	<p>Assumptions of 100 % effectiveness and utilization could be used to assess the ideal vaccine benefit (ideal population effectiveness)⁴. Setting efficacy levels at (realistic) less than 100% will influence the results of analyses by reducing health benefits and therefore also derogating expected savings in health care costs⁴. On the other hand assumptions of utilization rates lower than 100% reduce health benefits and expected savings in health care costs but also simultaneously lower costs of vaccinating⁴. Coverage levels to be reached might be given in WHO recommendations already mentioned above (e.g. for varicella immunization¹²). Ideal (100%), desired and less optimistic scenarios must be compared to point out discrepancies in the (expected) benefits, taking care of effects on herd immunity or side effects⁴.</p>
long-term safety surveillance, changes over time	<p>Because clinical trials have to prove the safety of new vaccines and possible contraindications previous to approval of the vaccine all vaccines are assumed to be safe at the time of vaccine implementation. For this reason, safety issues might play a minor role in initial vaccine assessment (presumed infrequent and usually not severe) and be excluded from basic analyses⁴. As part of the post-introduction surveillance, safety surveillance gains importance in detecting long-term negative consequences or rare adverse events over a longer time period (because pre-approval trials may not capture rare adverse events)^{5,6}. If adverse events occur they will lead to a reduction in health benefits, increase the costs of care and might limit public acceptance⁴. Also relevant is that risk-benefit ratios may vary between countries: risk of</p>

adverse events might be outweighed if the morbidity and mortality of a disease is domestically high^{5,6}.

Most side-effects will be unknown at the time of vaccine introduction, but some conclusions might be drawn from observations in countries where the vaccine already is in use or from effects that were observed after vaccine introduction of other vaccines (see surveillance). Additionally, computer simulations might be used to detect the impact of different strategies¹³.

**unknown side-effects:
conclusions from other
vaccines,
observations from other
countries**

4.3 Step 3: Cost-effectiveness

The cost-effectiveness analysis could be the third step in the decision process. Simplified answering of the question concerning whether or not the vaccine is a good investment can be given by weighing the net costs of the program (total cost of additional resources minus savings in treatment and other costs) against the net health impact (disease, disability and death avoided minus adverse events from the vaccine)⁵. In other terms a cost-effectiveness ratio is expressed as cost per unit of health benefit gained⁴. For the sake of completeness one should note that there are differences between cost-effectivenessⁱⁱ, cost-benefitⁱⁱⁱ and cost utility^{iv} analyses that are not outlined here in detail.

**weighing net costs
against net benefits**

No controversy exists about main costs and benefits that should be incorporated in the analysis (vaccine costs/ program costs, effectiveness of the program, economic benefits). No controversy exists either on the fact that time effects have to be considered and underlying assumptions must be tested (sensitivity analyses). The necessity of comparison with alternative measures should be beyond all questions as well.

**no controversy
about cost-elements
to consider**

But disagreement exists on which costs and benefits should be included. The results of cost-effectiveness analyses depend on the perspective from which they are carried out. From a societal perspective all health outcomes and costs regardless of who experiences them must be taken into account⁴. Therefore the results of selective analyses carried out by government agencies, third party payers or vaccine manufacturers usually differ from those societal perspective analyses⁴.

**but different
perspectives of
analyses:
societal,
reimbursing,
manufacturer**

Costs from a societal perspective would include direct and indirect costs for families, the community as well as those for the health system, for example co-payments, costs for transportation or productivity losses and lost wages. The main obstacle in the discussion about indirect costs could be the lack of appropriate data. The duration of care for an ill child might be possible to estimate, but the necessity for care of ill adults can not be captured un-

**in societal perspective:
inclusion of indirect &
direct costs**

ⁱⁱ Cost-effectiveness analysis (CEA) is a form of economic analysis that compares the relative expenditure (costs) and outcomes (effects) of two or more courses of action

ⁱⁱⁱ Cost-benefit analysis (CBA) is a formal discipline used to weight the total expected costs against the total expected benefits of one or more actions in order to choose the best or most profitable option.

^{iv} Cost-utility analysis (CUA) is a form of economic analysis used to guide procurement decisions (e.g. health technology assessment (HTA)).

equivocally⁴. Just to outline the diversity of included indirect costs, examples from background material papers are given in Table 4-1.

Table 4-1: Examples for indirect costs considered in cost-effectiveness analyses

indirect costs	vaccine
lost productivity (calculated based on the average production value of one hour of work per parent) due to care-giving ¹⁴	Meningococcal vaccine
medical visits, loss of earnings due to illness or mortality ¹⁵	Hepatitis B vaccine
work time lost, lost productivity resulting from premature death or severe disability (parents' s time for caregiving or because of their own disease) ¹⁶	Varicella vaccine
not included (due to "diversity") ¹⁷	Pneumococcal vaccine
not included ? ¹⁸	Human Pappiloma Vaccine
no consideration of productivity losses though statement of considering social health care costs ¹⁹	Hepatitis B vaccine

non-health benefits & benefit for others often excluded

Benefits achieved by vaccination for the vaccination recipient, e.g. improvement in life expectancy and in quality of life are included in all analyses²⁻⁶. Non-health benefits or benefits for others are not generally included in analyses, consequences of excluding those "real benefits" were already discussed from an ethical point of view.

discounting rates vary from country to country

Implications of discount rates depend on the duration of the time interval between vaccination and expected effects. Stated discounting rates for costs vary between zero and five percent in literature. If all authors also discounted benefits for the same amount (as Stratton⁴ did), cannot be answered in a brief overview and would have to be analyzed separately.

cost-effectiveness analyses are subject to various influences, cannot be transferred easily to other contexts

The given variation of key issues that might be included in an analysis and the examples for various viewpoints and approaches highlight that various factors influence cost-effectiveness analyses. Therefore comparisons of different cost-effectiveness analyses have to be conducted with caution. Beyond the variation in included criteria, the bases of the underlying assumptions should be noted (e.g. surveillance systems, published literature, expert's opinion).

Key factors that essentially influence costs per QALY gained could be summed up as⁴:

- ✿ the number of vaccination recipients vs. number of cases,
- ✿ the time between vaccination and prevented disease,
- ✿ and the differences in age groups, mortality or lengths of periods spent in a disabled state.

Keeping these factors in mind also assists in the rational comparison of different outcomes of analyses.

cost per QALY as basis for general comparison

If costs per QALY gained by the planned vaccination program are finally assessed, rational decision making then would be facilitated, if this outcome could be classified in some way. Available literature provides few informa-

tive bases for this. Stratton⁴ gives such a ranking for the USA, placing vaccines within general levels. (see Table 4-2)

Table 4-2: Favorability of vaccines ranked by costs per QALY (US)

level	favorability	costs
level 1	most favorable	saves money per QALY gained
level 2	more favorable	costs <10000\$ per QALY gained
level 3	favorable	costs >10000\$ and < 100000\$ per QALY gained
level 4	less favorable	costs >100000\$ per QALY gained

Kimman² states when vaccines are considered to be cost-effective in the Netherlands (see Table 4-3).

rankings

Table 4-3: Cost-effectiveness ranked by costs per QALY (Netherlands)

cost-effectiveness	costs
cost-effective	costs <20000€ per QALY gained
intermediate cost-effective	costs >20000€ and < 50000€ per QALY gained
not cost-effective	costs >50000€ per QALY gained

Cost-effectiveness analyses and groupings can aid rational approaches whether to implement a new vaccine or not. Making rankings used in different countries public would enable serious discussions. Nevertheless rankings cannot determine whether the health benefit is - in the end - worth the cost. Weighing remains a value judgment⁴.

comparing, ranking...
but finally a value-judgment

Corresponding to the commonly used “number needed to treat” (NNT) a measure “number needed to vaccinate” (NNV) has been introduced. The number of people (or the number of vaccine doses) to prevent one event (e.g. hospitalization or death) per year and consequently the associated vaccination costs could be defined by this measure. This procedural method could provide additional comparable and reproducible results across different vaccination strategies. A PubMed search for “number needed to vaccinate” currently^v only reveals 21 hits, reflecting that this approach is not well-established. In some cases the NNT²⁰ is given. This heterogeneity further impedes rational vaccine comparison.

NNV/ number
needed to vaccinate

^v Search term: „number needed to vaccinate“, full text search carried out on 18.1.2008 on <http://www.ncbi.nlm.nih.gov/sites/entrez>

4.4 Step 4: Acceptability, Feasibility, Equity and Ethical Considerations, Legal and Political Considerations

public demand: enforces policy decision

Acceptability of the new vaccine and the program by patients and health professionals is a key factor for the success of the program. In the past, the demand for a new program has often been a powerful argument for decision makers at the political level³. For example a meningococcal program in Canada was introduced though varicella vaccination was the most favorable from an economic point of view and a pneumococcal program would have been able to achieve the greatest disease reduction at the time of consideration³. Likewise the introduction of a meningitis C vaccine in the Netherlands was (partly) based on the judgment, that it would reduce public anxiety².

perception of disease risk can be manipulated

The public's perception of disease risk and severity causing the demand for an immunization program can be manipulated to a high degree and has to be handled with care. All lobbies that would profit from the introduction of a vaccine could outweigh other rational considerations. A health market should differ from supply and demand models of other markets, mainly because the "product health" cannot be purchased. Different indirect cash flows, stakeholders and issues of fairness and ethical considerations have to be taken into account. Therefore a rational decision remains questionable if just demand forces vaccine introduction.

public acceptance is prerequisite for successful implementation

Nevertheless acceptability is necessary for the successful implementation of a new vaccine and participation as a basic principle of health promotion will enhance positive health outcomes.

Operational issues should be considered during the decision process: Availability of funding is an important concern, especially if the new vaccine is implemented in a public financed program. Otherwise if the new vaccine is added as a voluntary extension of the regular NIP and has to be (at least partly) paid out-of-pocket by patients themselves, accessibility of target groups will be influenced and consequences on broadening the social gap have to be considered.

feasibility: funding, access, delivery aspects (schedules, documentation)

Most feasibility concerns address successful implementation. Different delivery systems, schedules and impacts on existing services (health-care "side effects") will influence costs and success of the program. If the target group of a new vaccine differs from those of commonly used vaccines, new strategies have to be developed for successful implementation (e.g. for adolescents)⁴.

The lack of instruments to enhance feasibility (e.g. documentation forms or resources for communication or registering systems) has to be discussed and resolved (necessity of establishing missing instruments and allocating additional human, technical and financial resources).

equity and ethical considerations

Value judgments concerning equity and ethical considerations have to be clarified. Most of these judgments cannot be built in cost-effectiveness models⁴. Therefore it is necessary to keep in mind that rational approaches to implement or to withhold a vaccine are on the one hand limited but on the other hand endorsed by further ethical and equity considerations.

If a vaccine will be administered in a schedule that differs from the one recommended by the manufacturer because of the need to match the existing NIP due to enhanced feasibility, legal considerations have to be taken into account³. Though decision-makers bear responsibility for their decisions, liability concerns mainly affect vaccine manufacturers⁴.

liability issues & political issues

A rational approach would be supported by including a disclosure step in the decision process. This would bring to light any potential controversies or immediate political gains that could influence or appear to influence the decisions being made.

disclosure of conflicts of interests

Including the ability to evaluate in the decision making process, highlights the need for reviewing the performance and success of a target-orientated program. Issues that surveillance systems should cover will be discussed later with regard to the revision chapter.

At the end of step 4 it could be necessary to introduce a new stand-alone criterion „side effects“ that should sum up “side-effects” according to each other criterion. Otherwise the chance of missing additional side-effects of vaccine introduction increases.

unintended side-effects are important to observe

- ❖ “vaccine side effects”: microbial population dynamics, replacement diseases, age-shifts
- ❖ “feasibility side effects”: impact on health care system, workload, credibility of the NIP
- ❖ “utilization side effects”: impact on the utilization of other preventive measures or for example on diagnostic tests themselves (e.g. introduction of HPV vaccine could result in the loss of precision in Pap test screening - false positive rate and even false negative rate increase - when the prevalence of HPV infections falls and the volume of and the time for performances stay the same).

4.5 Step 5: Decision Making

The ongoing research project VENICE (Vaccine European New Integrated Collaboration Effort)¹⁰, funded by the European public health action program, Work package 4 (Priority setting and decision making) aims at encouraging a rational approach to vaccination policy and the decision making processes in Europe. This objective is addressed by promoting the exchange of experience and expertise through

ongoing research: EU-project VENICE

research in support of information-sharing & exchange of methodology for rational decision-making

- ❖ *“sharing of information about recent and current studies performed, the methodologies used and the outcomes of the expertise for vaccination policy decisions;*
- ❖ *increasing the efficiency of work by reducing redundant analysis and sharing the tasks when the various member states are faced with similar issues such as integration of a new vaccine in the immunization schedule;*
- ❖ *increasing the level of expertise to a common high standard within the enlarged EU, including on public perception of vaccinations and techniques and methods to gauge such perceptions, e.g. by suitable questions in surveys;*

- ✿ *setting the basis for European immunization schedules through ensuring common scientific background for future vaccination decisions.”*

<p>current VENICE-activity: analyzing national rationales for/against HPV& rotavirus decisions</p>	<p>The project started almost at the same time that the approvals of HPV and Rotavirus vaccines were granted. Therefore the decision making processes of these two vaccines are used as real-time vehicles to explore how rather than why the vaccines are implemented in or withheld from the national immunization program. The questionnaires sent to the participating countries are currently analyzed. Only first results have been published, reporting the current situation about recommendations for Rotavirus and Human Papilloma Virus vaccines in each country¹. A more detailed manuscript on the decision making processes will be available in spring 2008.</p>
<p>final decision making: systematic analysis, step by step, avoidance of influence</p>	<p>After consideration of pre-analysis issues (step 1) the result of the cost-effectiveness analysis (step 3) that was mainly based on data on disease and vaccine (step 2) can be added and probably weighted by concerns reported in step 4. A systematic analysis of all outlined fields is necessary as input for the final decision to avoid major influences of other factors (like political pressure or public anxiety).</p>
<p>immunization is a public health issue: interdisciplinary teams, comprehensive analysis, pre-defined structures and processes for decision making</p>	<p>All authors agree that final decisions are a political responsibility²⁻⁶. But decisions on implementing new vaccines in national immunization programs are public health decisions. Therefore interdisciplinary teams should evaluate and discuss the previous steps in order to achieve a most comprehensive analysis and to avoid influences of single stakeholders. Organizational structures supporting the decision making, e.g. scientific boards or advisory committees and decision making routes vary in different countries. These differences as well as the unequal power to implement decisions on national, federal state or community levels likely influence not only the success of a program but also the decision itself. Neither these effects nor the possible weight of different health care systems (mainly Bismarck type health insurance system vs. tax based systems vs. private systems) have been considered as part of this study.</p>
<p>uncertainties always remain, no excuse for transparent, rational approach</p>	<p>Decision makers should notice that even the best rational approach and most comprehensive evaluation is limited by remaining uncertainties concerning long term consequences, future vaccine prices and economic circumstances for example². This fact does not impair a rational decision making process and must not be used as an excuse not to utilize.</p>
<p>transparency in the process and arguments facilitates public confidence in policy</p>	<p>At the end of this chapter on decision making it is necessary to say that comprehensible arguments for all possible decisions have to be made public. It might be easier to convince patients and health professionals of the need for a new vaccine rather than to argue on behalf of withholding it, especially if the perceived demand is high. But it might be even harder to explain a withdrawal of a previously introduced vaccine unless there are severe negative and unexpected consequences². In any case, a rational decision making approach will facilitate the public's confidence in the decision and its realization.</p>

4.6 Step 6: Implementation

Some of the concerns of successful vaccine introduction that must be considered during the decision making process have already been discussed mainly in the feasibility chapter. The implementation itself is not part of this process anymore. Therefore it will not be outlined in any more detail in this study.

implementation based on feasibility analysis

4.7 Step 7: Surveillance and Revision

The importance of discussing post-introduction surveillance in a study about decision making can be justified by the necessity of reviewing consequences of the primary decision. Also pertinent is that the process of pre-introduction decision making is not completed by the decision itself. Post-introduction surveillance does not only serve as a tool for performance measurement, it also might reveal unforeseen factors that force decision-makers to alter their new vaccination program.

post-introduction surveillance

measuring performance, revealing unforeseen factors

Coverage rates of the new vaccine in the whole population or specific groups might be lower than expected and endanger, for example, the goal of reaching herd immunity. This might lead to age-shifts of the disease (see also “other side effects” below) or influence disease severity as previously discussed.

lower coverage-rates might influence age-shift of disease, severity of disease

Besides these direct effects, the impact of the introduction of a new vaccine on the coverage rates of other vaccines must be observed. Concerns of perceived overloading of the NIP resulting in lower vaccine utilization in general must be taken seriously. Also to be looked at is whether the immunization program is still working well enough to justify the introduction of the new vaccine, aiming at the allocation of limited resources for the best possible preventive measures to protect a population.

impact on coverage rates of other vaccinations

Immunosurveillance can identify risk groups with low coverage rates due to non-compliance²¹. Recent measles outbreaks in Germany²², Switzerland²³ and other European countries reflected suboptimal coverage levels. In this case appropriate measures to increase coverage rates should be taken.

identification of non-compliant groups

Reducing the burden of disease is the primary objective of all immunization strategies. Assumptions of vaccine effectiveness are based on estimates during the decision making process. Therefore basic epidemiologic data have to be compared with data (reduction of cases, hospitalizations and deaths) collected after the implementation of national vaccine recommendations.²⁴ Particularly in cases in which the time period between vaccination and desired effects is long, only the surveillance of changes in disease incidence, complications, sequelae and mortality provides data on real impact. For example, the influence of universal varicella vaccination on the incidence of zoster later in life is currently not known²⁵.

comparison of epidemiologic data pre- & post introduction

<p>immunosurveillance:</p> <p>changes of vaccination schedules & schemes</p> <p>due to increasing number of vaccines</p>	<p>The importance of immunosurveillance and consecutive opportunities to optimize national vaccination programs were recently outlined²⁶: existing vaccine schedules are often based on historical developments rather than scientific evidence. After surveillance of immunity (and re-infections leading to the disease) over a longer time period, it would often be necessary to alter a vaccination scheme. Effects on herd immunity might be different from those primarily expected and vaccination during pregnancy or perinatal time periods could become necessary if the protection of very young children is needed. Simultaneously other vaccines might be postponed if diseases are less frequent than at the time of introduction, having the advantage that fewer injections might be needed to be effective. Altering of vaccination schedules often fails, because this optimization can lead to (legal) problems due to the lack of studies performed with the new scheme.²⁶</p> <p>Nevertheless these obstacles have to be overcome from a scientific as well as an economic point of view because of adaptations of immunization programs in changing environments and the increasing number of vaccines available²⁶.</p>
<p>safety monitoring:</p> <p>adverse events due to additional agents</p>	<p>As already discussed, data about adverse events following immunization might be incomplete at the time of vaccine introduction. Therefore the monitoring of safety performance of a vaccine should be obligatory. In the past serious adverse events due to vaccination have occurred. Even deaths²⁷ or an increased incidence of neurodevelopmental disorders²⁸ following immunization have been observed because of an increased dose of an additional agent or the added compound itself. In the case of the rotavirus vaccination, discussions about possible changes in the incidence of intussusceptions are still ongoing²⁹.</p>
<p>lack of reporting of adverse events</p> <p>EU-project 2001-2003 EUSAFEVAC for improvement of surveillance</p> <p>ongoing EU-project VENICE: national monitoring systems</p>	<p>A lack of reporting of adverse events followed by immunization (AEFI) data as well as heterogeneity of case definitions and methods for data collection, analysis and presentation of AEFI was observed in a systematic review of published articles of prospective clinical trials of vaccines in humans³⁰. Efforts to improve AEFI reporting systems were carried out in the European research program for improved vaccine safety surveillance (EUSAFEVAC)³¹ project between 2001 and 2003. As a result, tools for improved safety surveillance of immunizations were made available by providing guidelines for standardized reporting of AEFI, using standardized case definitions or examples of active surveillance tailored at specific events signaled by routine passive surveillance. The ongoing VENICE¹⁰ project will also gather information on the adverse events monitoring systems in the participating countries.</p> <p>Finally, in regards to safety monitoring issues, reliable independent safety boards are able to ensure optimal vaccine safety and would enhance public confidence in vaccines³².</p>
<p>challenges for efficacy:</p> <p>microbial population dynamics,</p> <p>replacement diseases</p>	<p>Global spread of virus strains that are not currently covered by a vaccine, challenges vaccine efficacy. This is commonly known in the case of influenza due to continuous antigenic variation, but might also occur in the case of other pathogens. Local distribution of specific antigen strains, in particular the emergence of strains that are not addressed by the currently used vaccine, may necessitate the replacement of a vaccine by a more effective one over time. For example, a change in serotype distribution recently has been observed after universal immunization of children against rotavirus³³. Replacement diseases (increase in disease caused by serotypes not included in the vaccine) might emerge and have already been observed in the case of the Prevenar (7-valent pneumococcal conjugate) vaccine³⁴ and in the case of</p>

Haemophilus influenzae type b conjugate vaccine³⁵ after routine use. Age distribution of a disease is likely to change after vaccine introduction (e.g. drift of infections towards older groups of children after mumps vaccine introduction in Poland³⁶. Additionally all other expected positive and negative “side-effects” that have been outlined in step 4 have to be observed.

5 Limitations

Challenges of vaccination strategies in special situations (e.g. immunosuppression, pregnancy or post-exposure) as well as those of therapeutic vaccines have not been addressed. Influences of organizational structures or health care systems on decision making were not analyzed. Therefore no best practice model that meets optimal conditions can be given.

References given in the discussion were used as examples only and cannot cover all relevant aspects (e.g. indirect costs or vaccine safety issues).

Due to the lack of comparable information, this study remains general and cannot provide specific advice or defined cut-off points.

The proposed stepwise approach of decision making, the order as well as the criteria themselves, are suggestions and do not claim to be the correct and fixed procedures. This approach should rather be used by advisers and decision makers on vaccination policy as a basis for further discussion. In addition to the systematic literature search and the manual search of references and other sources, a Delphi process based on the results of this study will be carried out in spring 2008 to assess the completeness of criteria and the feasibility of the step-wise approach.

**this paper gives
no information on
vaccination under
specific conditions,**

**nor on therapeutic
vaccines,**

**no specific advises or
cut-off points**

**paper is meant as a
suggestion & bases for a
Delphi process to
complete criteria and
discuss feasibility**

6 Conclusion

Observing heterogeneous immunization programs and decisions in case of new vaccines on the one hand and the recent efforts of developing standardized tools for decision making on the other hand emphasizes the demand for a higher degree of transparency in the vaccine implementation decision processes.

This study confirms the basic assumption, that vaccine introduction is currently not based on a generalized rational decision making processes. The comparison of the five key documents led to a comprehensive framework, outlining as many issues to be taken into consideration as possible. A step-wise approach could increase feasibility of decision aids. The lack of standardized measures, defined cut-off points and comparable weighing of included criteria hinder rational decision making.

**demand for
transparency in
deciding on new
vaccines**

**comprehensive
framework with key
issues for consideration
as starting point**

7 Annex

Table 7-1: List of contacted persons who answered requests

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Table 7-2: Key questions (WHO 2000)

7 key questions of the framework	Issues to be addressed (Asian Vaccination Initiative assessment framework)
Is the disease a public health problem? Is immunization the best control strategy for this disease?	Data Collection: (demographic, economic, political, health sector, immunization and vaccines legal status) Data characteristics and sources of necessary information are presented.
Is the immunization program working well enough to add a vaccine? What will be the net impact of the vaccine?	The Immunization Program: management (capacity), immunization delivery services, surveillance (of disease, coverage, adverse events), vaccine supply, logistic systems, safe injection practices, and communication
Is the vaccine a good investment? How will the vaccine be funded? How will the addition of the new vaccine be implemented?	Costs and financing requirements for the NIP: management, systems, budget, expenditure, sources

Source: Mansoor O, Shin S, Maher C and the Immunization Focus, World Health Organization Regional Office for the Western Pacific. *Assessing new vaccines for national immunization programmes- A framework to assist decision makers*; available at <http://whqlibdoc.who.int/hq/2000/9290611545.pdf>, accessed on 1.2..2008

Table 7-3: Criteria and key questions (Erickson 2005)

category	key question
Burden of disease	Does the burden of disease justify a control program?
Vaccine characteristics	Do the characteristics of the vaccine permit implementation of an effective and safe immunization program?
Immunization strategy	Is there an immunization strategy which allows goals of the control program as well as sanitary and operational objectives to be attained?
Cost-effectiveness	Is it possible to obtain funding for the program and are cost-effectiveness indices comparable to those of other health care interventions?
Acceptability	Does a high level of demand or acceptability exist for the immunization program?
Feasibility	Is program implementation feasible given existing resources?
Ability to evaluate	Can the various aspects of the program be evaluated?
Research questions	Have important research questions affecting implementation of the program been adequately addressed?
Equity	Is the program equitable in terms of accessibility of the vaccine for all target groups?
Ethical considerations	Have ethical concerns regarding implementation of the immunization program been adequately addressed?
Legal considerations	Have legal concerns regarding implementation of the immunization program been adequately addressed?
Conformity of programs	Does the planned program conform to those planned and implemented elsewhere (other regions, countries)?
Political considerations	Will the proposed program be free of controversy and/or produce some immediate political benefits?

Source: Erickson LJ, De Wals P, Farand L. An analytical framework for immunization programs in Canada. Vaccine. 2005 Mar 31;23(19):2470-6.

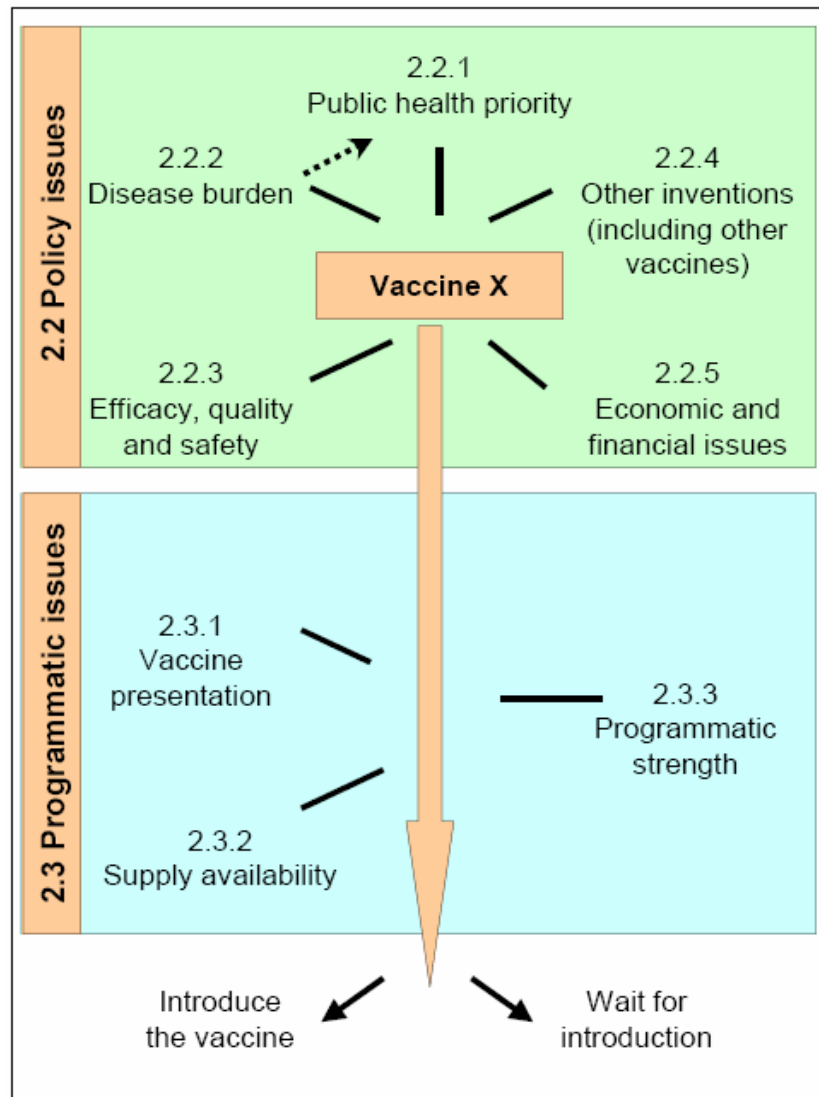


Figure 7-1: Key issues in the decision process (WHO 2005)

Source: World Health Organization. *Immunization, Vaccines and Biologicals, Introduction Guideline- Adding a vaccine to a national immunization programme: decision and implementation*. Available at http://whqlibdoc.who.int/hq/2005/WHO_IVB_05.18.pdf, accessed on 1.2.2008

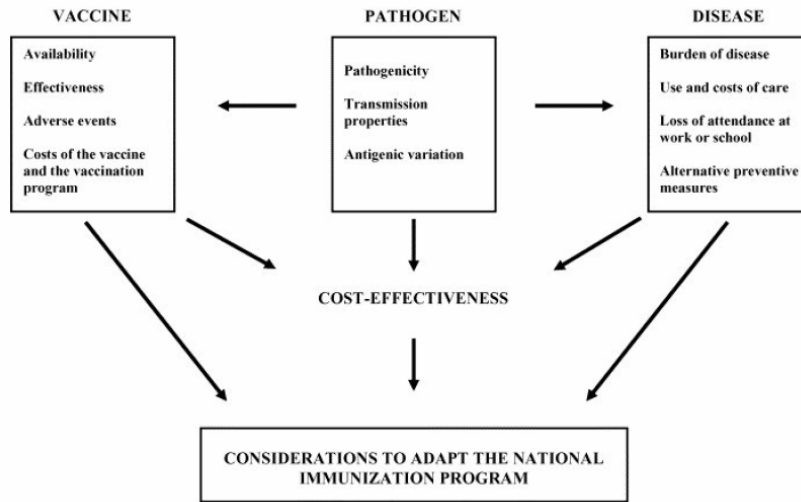


Figure 7-2: Considerations to adapt the national immunization program (Kimman 2006)

Source: Kimman TG, Boot HJ, Berbers GA, Vermeer-de Bondt PE, Ardine de Wit G, de Melker HE. Developing a vaccination evaluation model to support evidence-based decision making on national immunization programs. *Vaccine*. 2006 May 29;24(22):4769-78.

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