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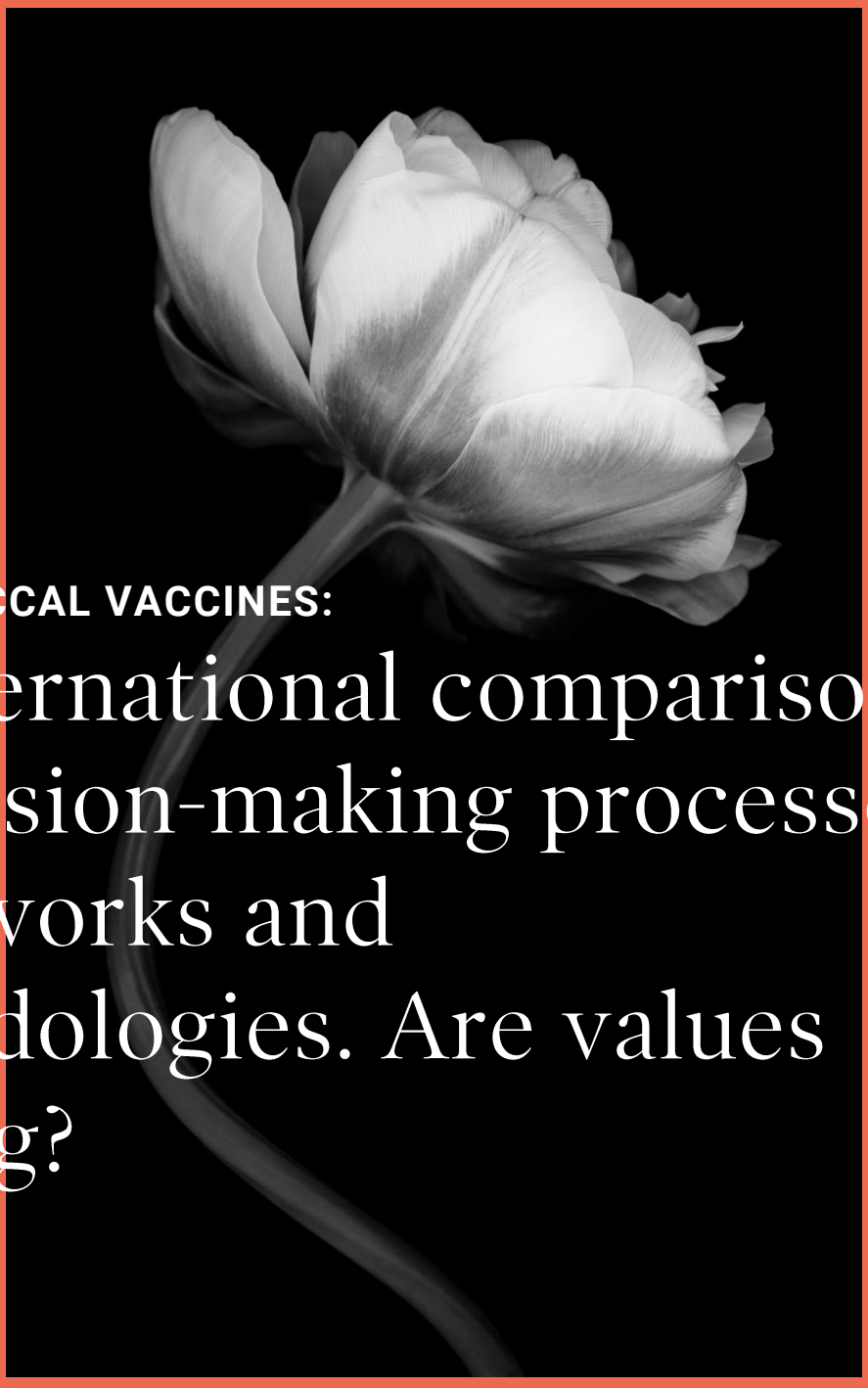

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MENINGOCOCCAL VACCINES:

An international comparison of decision-making processes, frameworks and methodologies. Are values missing?

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Karla Hernandez-Villafuerte

Koonal Shah

Mike Herdman

Paula Lorgelly

Office of Health Economics, London

OFFICE OF HEALTH ECONOMICS **CONSULTING**

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Corresponding Author:
Paula Lorgelly
Email Paula.Lorgelly@ucl.ac.uk

For further information please contact:

OHE Consulting Ltd
(a registered company number 09853113)
Southside, 7th Floor
105 Victoria Street
London SW1E 6QT
Tel: 0207 747 8850

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Executive Summary

Meningococcal disease is a **life-threatening infection** and can result in severe sequelae. Recent scientific and technical advances have led to the discovery and implementation of **novel meningococcal vaccines** which have resulted in a **substantial reduction in the burden of disease worldwide**, representing a major public health achievement (Crum-Cianflone and Sullivan, 2016).

In Europe, serogroup C meningococcal disease infection has markedly decreased after the introduction of a conjugate vaccine into a number of National Immunisation Plans (Pelton, 2016). Now **serogroup B meningococcal infection (Men B)** is dominant (Pelton, 2016). The development of a Men B vaccine proved to be difficult, requiring a high level of investment and many years of intensive research (Green et al., 2016). There remains **uncertainty** surrounding some elements of the vaccine, particularly the **indirect effect of herd immunity**.

The **adoption of a new health technology** often requires an assessment as to whether it represents an effective use of public resources, i.e. whether it **offers value-for-money**. This is commonly assessed by comparing the cost-effectiveness of the new intervention with alternative options. For vaccines the **evaluation of cost-effectiveness** hinges on whether all effects (outcomes) have been identified and valued appropriately, particularly given the benefits can be accrued wider than just the individual vaccinated and the benefits tend to occur far into the future.

Study Objectives

- To **document the current evidence base** that is available to inform adoption decisions of meningococcal vaccines
- To summarise the **specific decision making criteria** for vaccine reimbursement in a number of countries, as well as the methodology used to inform decisions about adopting meningococcal vaccines
- To **suggest new criteria and improvements in methodologies** given the nature of the benefit derived from meningococcal vaccines

Methodology

Rapid evidence assessment (REA) of the economic evaluation literature with respect to meningococcal vaccines: Review of abstracts identified from the NHS Economic Evaluation Database (NHS EED), MEDLINE and Google Scholar. Data extraction from selected studies according to key characteristics of economic evaluations of vaccines, including: health outcomes and sources of value, discount rate employed, nature of the modelling, perspective of the study.

Country comparison: Semi-structured interviews with experts from a selected group of countries: France, Germany, Italy, Netherlands, Australia, New Zealand and Japan, to identify and document country-specific decision making criteria. Supplemented with a review of country-specific publications and the reference case for each of the selected countries.

Literature review: A review of the literature of the wider benefits of vaccination and public preferences for vaccination, and a discussion of the appropriateness of currently available quality of life instruments.

Rapid Evidence Assessment

The literature search identified 31 articles (papers and conference abstracts) published between January 2005 and November 2016 that comprise information pertaining to the economic evaluation of one or more meningococcal vaccine strategies. Twenty six are full economic evaluations (comparative analyses comparing costs and consequences) of which 12 articles correspond to evaluations of Men B vaccines. The majority of these papers refer to the adoption and implementation of a Men B vaccine in high income countries. The main conclusions of the articles (cost-effectiveness of the vaccine strategy under evaluation) are summarised in Table A.

TABLE A. ECONOMIC EVALUATIONS OF MENINGOCOCCAL VACCINES – MAIN CONCLUSION

	Total	Men B	Men C	Men ACYW
Cost-effective	7	1	4	2
Not cost-effective	5	4	0	1
Mixed results†	11	7	1	3
Unclear	3	0	0	3
Total number of articles	**26**	**12**	**5**	**9**

† Mixed results: Conclusion depends on particular factors. Those articles whose results indicate that vaccination is cost-effective only under a certain price level per dose are included in this category.

Our review found that recommendations regarding the cost-effectiveness of a meningococcal vaccine schedule are **dependent on particular model assumptions; herd protection and the cost of the vaccine dose are decisive factors.** A large majority of the studies (77%) used no vaccination as main comparator, while 61% included more than one vaccination schedule. This appropriately reflects the non-binary decision faced by decision-makers.

Most evaluations (85%) considered the **vaccine schedules of children** (≤ 4 years old). This reflects the burden of disease being high in this age group (Sadarangani and Pollard, 2016). The evaluation of vaccination including one or more doses during adolescence was also common (69%), again reflecting a high incidence rate in 15 and 24 year olds (Sadarangani and Pollard, 2016) as well as the high carriage rate in this age group and consequent potential for vaccination to provide herd protection.

Health utility losses were considered in 77% of papers. All of these used the outcome measure of **quality adjusted life years (QALYs)**. Some papers (46%) only evaluated QALY losses from sequelae related to meningococcal infection; 19% considered both acute episodes and survivors with sequelae.

A third of papers specified **the health utility losses by type of sequelae.** Among this group of studies, we observed differences in the type of sequelae considered. For instance, the list of sequelae considered by Pouwels et al. (2013) (hearing loss, motor deficits and neurological sequelae) differs from that of Lecocq et al. (2016) (severe and mild hearing loss, blindness, epilepsy, attention deficit hyperactivity disorder and amputation).

Variation was observed in the sources of information used to extract the relevant values of QALY losses by sequelae. Welte et al. (2005) noted that country-specific QALY or DALY (disability adjusted life year) weights are rarely available for all complications and sequelae related to meningococcal disease. Because of this, and the lack of high-quality data, quality of life weights included in most of the studies are estimates of health state values. Three studies (Christensen et al., 2016; Christensen et al., 2014; Hanquet et al., 2014a) estimated health utility losses based on a single study (MOSAIC)

(Viner et al., 2012). Only 23% of the economic evaluations included mention the instrument used to estimate QALYs, and even these provide insufficient levels of detail.

Meningococcal disease (like many other childhood infectious diseases) has a number of features that make the assessment of the validity of QALY values used particularly important. Such features include difficulties in correctly capturing QALY losses for the most vulnerable age groups (children and adolescents) and the insensitivity of the health-related quality of life instrument in assessing the quality of life impact of hearing loss and some neurological sequelae.

The UK Joint Committee on Vaccination and Immunisation (JCVI) recognised that these particular features of meningococcal disease can hinder the estimation of the cost-effectiveness of Men B vaccination strategies. Therefore, the JCVI agreed to apply a **QALY adjustment factor (QAF)** of three (x3) to all long term sequelae (Joint Committee on Vaccination and Immunisation, 2016), in an attempt to address any underestimate of the QALY effects.

The JCVI is the first agency to consider a QAF, although the National Institute for Health and Care Excellence (NICE) has used alternative thresholds in the past to account for potential underestimates of QALY gains in other health conditions.

Economic theory implies that both costs and outcomes need to be discounted to present values if they occur in the future. As the health benefits derived from a vaccination strategy, or any preventative health programme, are observed in a time period that is posterior to the initial expenditure (this excludes potential 'utility in anticipation' benefits that occur from the point of vaccination; see below), **health benefits are more heavily discounted than costs** (Jit and Mibei, 2015). There is debate as to whether this discount rates for costs and benefits need to be the same.

Thirty eight per cent of economic evaluations included more than one discount rate; either as alternative discount rates in the **sensitivity analysis** (5 studies), or **differential discount rates** (3 studies), or a **non-constant discount rate** over time (2 studies). Table B shows a substantial effect on the incremental cost-effectiveness ratios (ICERs) of increasing the discount rate.

TABLE B. EFFECT OF THE SELECTED DISCOUNT RATE ON THE ICER VALUE – MEN B STUDIES

Article	Increase in discount rate (%)	Increase in ICER (%)
Tu et al. (2014)	0 to 5	301.5
Tirani, Meregaglia and Melegaro (2015)	0 to 3	216.0
Hanquet et al. (2014b)	3 costs/1.5 benefits to 3 both	177.5
Tu et al. (2014)	0 to 3	162.4
Tirani et al. (2015)	0 to 1.5	92.6
Tirani et al. (2015)	1.5 to 3	64.1
Tu et al. (2014)	3 to 5	53.0

Note that the majority of countries' economic evaluations guidelines require the use of a single discount rate (Jit and Mibei, 2015), with few exceptions, e.g. the Netherlands, Belgium and Poland (Hanquet et al., 2014b; Jit and Mibei, 2015; Zorginstituut Nederland, 2016).

Dynamic models can intrinsically count for herd protection. However, model calibration and probabilistic sensitivity analysis are extremely complex and computationally intensive. Moreover, the required data sources may not be easily accessible (Ultsch et al., 2016). Given the complexity of the dynamic models, common practice in the identified economic evaluations is to use a simple static model. We found that **static models are the most commonly used mathematical models (38%)**.

Herd protection has proved to be an important element in reducing disease incidence as a result of the Men C vaccine implementation. It could be expected that the vaccination against other meningococcal serogroups would also affect carriage probability. However, **only 27% of the economic evaluations include a dynamic model**.

Herd protection is particularly important for evaluations of adolescence strategies since carriage prevalence is higher in this age group. Therefore, it is not surprising that a number of sensitivity analyses in the studies reviewed indicated that **the impact of a routine adolescent programme is affected by how much the vaccine affects carriage**.

In order to demonstrate that a vaccine strategy represents an effective use of public resources, it is key to consider all relevant economic savings. An intervention that is not cost-effective based only on direct medical costs could be an effective use of public resources when all related economic effects that would improve the well-being of the population are considered. In this regard, it is likely that **indirect costs could be key to demonstrating the value of a preventive intervention such as vaccination implementation**.

A **societal perspective** for costs is common practice in economic evaluations of meningococcal vaccination strategies (61%). Five articles that considered productivity losses include both **patients' and carers' productivity losses** (Christensen et al., 2016; Gasparini et al., 2016; Ginsberg, Block and Stein-Zamir, 2016; Hepkema et al., 2013; Pouwels et al., 2013).

MAPPING THE METHODOLOGY FOR HTA OF VACCINES

	In **Australia** the National Immunisation Committee (NIC) is responsible for the implementation, delivery and overseeing of the immunisation programme. The Pharmaceutical Benefits Advisory Committee (PBAC) undertakes the health technology assessment (HTA). Additionally, the Australian Technical Advisory Group on Immunisation (ATAGI) provides advice to the Department of Health and the PBAC on existing, new and emerging vaccines. The Department of Health cannot fund a vaccine without a positive recommendation from the PBAC, but it can decide not to fund a new intervention despite a positive recommendation.
	The Technical Vaccination Committee (CTV) is the National Committee on Immunisations that evaluates scientific information in **France**. It develops vaccination strategies, conducts risk-benefit analyses and health economics studies and makes recommendations for immunisation schedule updates. CTV and HAS (Haute Autorité de Santé) undertake the HTA. The outcome of this assessment is a non-binding recommendation.
	The Standing Committee on Vaccination (STIKO) is the National Committee on Immunisations in **Germany** and develops the national immunisation schedule. Normally the HTA is led by scientific researchers at Robert Koch Institute (RKI), advised by STIKO members. A STIKO recommendation needs to be approved by the Federal Joint Committee (G-BA) for the vaccine to be reimbursed.
	In **Italy** the Istituto Superiore di Sanità is the National Committee on Immunisations that assesses new vaccines and elaborates recommendations that are considered by the regions for their particular immunisation plans. HTA is undertaken at the national level by Agenas (The National Agency for Regional Health Services) while at the regional level each region must undertake its own HTA. The HTA analysis in all regions is mandatory, but is not binding.

	The Health Sciences Council for **Japan** (the national immunisation committee) takes responsibility for vaccines approved by the Pharmaceuticals and Medical Devices Agency (PMDA). HTA takes the form of an assessment of safety, quality and efficacy by the PMDA. Cost-effectiveness is considered by the Health Sciences Council only; PMDA do not formally require an economic evaluation. The outcome of the HTA is a binding recommendation.
	In **New Zealand** the Immunisation Advisory Centre is responsible for advising the Ministry of Health on the risks and benefits of immunisation, while the Pharmaceutical Management Agency (PHARMAC) is responsible for undertaking HTAs of vaccines. PHARMAC considers the affordability of a vaccine (or health technology) compared to other vaccines and pharmaceuticals; when funding is made available within PHARMAC's capped budget this is a binding recommendation to the Ministry of Health.
	The sub-committee of the Health Council is the National Committee on Immunisation in **the Netherlands**. The drug committee makes recommendations on vaccines to be included in the positive list. Under a new initiative, two HTAs will be required: (1) National Institution for Public Health and Environment (RIVM), and (2) one prepared by the manufacturer. The Council makes a non-binding recommendation.

Note that **Men C** vaccination is part of the National Immunisation Programmes of the Netherlands, Italy, France and Germany. In Australia, it was substituted by a combination vaccine against meningococcal serogroup C and Haemophilus influenzae type b. The Italian national plan includes **Men B** for new-borns and Men ACYW for adolescents; however, it has not been adopted in all regions. **Men B** vaccine has been used in France and New Zealand to control specific outbreaks and it is used in Germany and New Zealand for immunocompromised individuals.

Mapping Decision Criteria

Note information in this section is reflective of the knowledge of the experts interviewed.

Experts were asked to classify a number of decision criteria (from clinical outcomes to herd protection to disease burden to budget impact) in terms of whether within their national programme they are: (1) '*formally considered*' – criteria that the guidelines specified must be included in the decision; (2) '*commonly and informally considered*' – criteria that are part of the decision in most cases, but that are not required in the guidelines; (3) *'uncommonly and informally considered'* – criteria that have been considered in particular cases, but that are normally not part of the analysis; and (4) '*It could be considered, but the information is unclear*' – criteria about which the experts are not completely certain.

Of the criteria related specifically to the intervention, only **clinical outcomes** are 'formally considered' in all countries. **Disease burden** is a main criterion in six of the seven countries. **Equity** is a key criterion in Australia, Japan and New Zealand, although it is not formally considered in any of these three countries.

Of the financially related criteria **cost-effectiveness analysis** and **budget impact** are the two most commonly identified by experts as key criteria. Cost-effectiveness analysis is (either formally or informally) part of the decision making process of every country.

National health system priorities is a key criterion in six out of the seven countries. Moreover, in Australia service delivery settings are particular important.

Public preferences for vaccines relative to other health technologies do not formally feature in any national guidelines, although conversely in the Netherlands there is an anti-vaccine lobby which

has raised concerns about the safety of vaccination and possible adverse effects. This has affected population trust on the national immunisation programme, such that it has become more difficult for new vaccines to be introduced into the national programme. A similar anti-vaccine lobby exists in New Zealand.

'Peace of mind' and 'utility in anticipation' benefits (see below) are 'uncommonly and informally considered' in most countries, and no expert was able to provide a specific example in which this criterion was considered in the decision making process. It has been argued that peace of mind is an important element that should be given consideration during the decision making process (see below). Therefore, it would be advisable to make use of the existing evidence base in order to bring peace of mind benefits into the decision making paradigm.

When using **cost-effectiveness** as a decision making criterion, what is considered 'cost effective' often requires an **explicit or implicit threshold**. NICE uses a threshold of £20,000-£30,000 per QALY gained. NICE's Citizens' Council has listed circumstances that could support the use of an alternative (higher) cost-effectiveness threshold (NICE, 2008a):

- the patients are children;
- the illness is rare, extremely severe and could be a result of NHS negligence;
- treatment is life-saving, prevents harm in the future, has a major impact on the patients' family, and encourages scientific and technical innovation.

Given the nature of meningococcal disease infection, the case could be made for a **different threshold/decision rule** since several of these circumstances can be shown to apply. However, the same criteria would need to be applied to other health interventions, including existing services that would be given up in order to fund any new vaccine strategy.

Consideration Of Other Criteria

Vaccines are often described as offering **peace of mind** benefits to patients and their caregivers (Beutels et al., 2003). This is based on the notion that individuals benefit from knowing that they or their family members have a reduced risk of illness, and benefit from reduced anxiety linked to disruptions to normal daily life.

A related concept – **'utility in anticipation'** – acknowledges the fact that vaccinated individuals and their caregivers benefit immediately from the moment of vaccination because of the reassurance that the illness has been prevented (Cohen and Henderson, 1991). This immediate benefit is not considered in standard economic evaluation methodologies as the benefit would be measured from the point of the illness occurring (should it occur).

Peace of mind benefits and utility in anticipation are difficult to measure and therefore tend to be ignored in economic evaluations. There may be scope for using **stated preference research** to understand the value that people place on these kinds of intangible benefits. The existing evidence in the stated preference literature suggests that the general public would place considerable value on the availability of a vaccine for meningococcal disease. On the whole, the evidence suggests that people would place greater value on preventive interventions compared to curative treatments; on preventing severe or life-threatening illness compared to mild illness; and on the health and survival of younger people compared to older people.

As noted in the mapping of criteria, most countries do not formally consider these factors in their decision making processes. This may result in an underestimation of vaccines' value to society.

Quality And Appropriateness Of Quality Of Life And Utility Measurement In Vaccines

The quality and appropriateness of quality of life and utility measurement in the area of vaccines is poor, and utility weight assessment in this area is somewhat haphazard and not built on a strong evidence base.

The use of the EQ-5D (a commonly used health-related quality of life instrument that allows for an estimation of QALYs) to measure and value health in this context is potentially questionable, given that:

- no version exists for children under 5 years of age;
- no value set is currently available for use with the youth version (EQ-5D-Y), i.e. for children aged 8 to 15 years;
- there are legitimate doubts about its ability to adequately capture the impact on health status of a number of the sequelae of meningococcal infection; and
- it is not clear that EQ-5D is well-suited to assess the impact on family members of living with a survivor of meningococcal infection.

Therefore, the **accuracy with which the impact of meningococcal disease (and other childhood infectious diseases) and the benefits of prevention are measured and valued for use in economic models can be called into question**. This includes accurate estimations of the burden of sequalae. A number of avenues are available to help better understand the implications of the current approach to the HTA of meningococcal vaccines, and to improve that approach:

- further testing and use of EQ-5D and EQ-5D-Y in meningococcal survivors, alongside other quality of life and preference-based measures;
- further quantitative and qualitative research in family members to investigate the extent to which EQ-5D adequately captures the impact of living with a survivor;
- the development of tools to enable better assessment and valuation, via the use of utility weights, of the impact of meningococcal disease in younger populations, particularly in those under 5 years.

Conclusion

Cost-effectiveness of the vaccine schedule depends principally on herd protection and vaccine price. The price can be explained by the novelty of the Men B vaccine and the investment required to develop it.

Given the variation in sources and tools used for generating the QALY estimates used in economic evaluations of Men B vaccines, **there is a need for a rigorous assessment of the quality of the information used to estimate QALY losses**. Such an analysis should explore the transferability of estimates across different contexts as well as the suitability of the estimations to reflect the health utility losses of each particular sequela.

QALY losses for caregiver of survivors with sequelae are not commonly considered. This is in part explained by the lack of adequate tools to estimate how living with and caring for survivors with sequelae affects family members and other caregivers.

The **QAF** (QALY adjustment factor) has been introduced by the JCVI to correct for the underestimation of health benefit derived from a vaccination programme. The possibility of applying

QAF in other contexts should be evaluated as well as alternative possible tools that would improve the health benefits estimation of meningococcal vaccination programmes.

Multiple and variable discount rates are uncommon in the published literature and further exploration is required to examine the extent to which the discount rate influences health benefits estimations more than costs.

According to our country experts the **main criteria for adoption of a vaccine** into their health system are the **clinical outcomes and disease burden**, followed by national health system priorities. Other peripheral but potentially important criteria with respect to meningococcal vaccination, like peace of mind benefits, are not formally considered in any HTA system reviewed.

Therefore, **there is a discrepancy between the particular factors that characterised the benefits of implementing a new vaccination programme and the methodologies and criteria considered to evaluate the programme**. This is particularly true in the case of the vaccines for meningococcal disease, where health benefits are not fully captured in the evaluations.

Experts did report a number of changes and developments in the last 15 years to the methodology and in the decision making processes: the implementation of more rigorous and transparent practices to inform adoption decisions for new meningococcal vaccines. This offers optimism but further research quantifying the wider benefits of vaccination would be useful.

Foreword

The United Kingdom (UK) was the first country to introduce a Men B vaccine into the national immunisation programme. This occurred despite the fact that the UK Joint Committee on Vaccination and Immunisation (JCVI) originally produced an interim statement concluding that it would not be cost effective to implement the Men B vaccine at any price.

Following a call from the JCVI, Meningitis Research Foundation (MRF) among other stakeholders, submitted evidence outlining why the cost effectiveness analysis had underestimated the burden of disease.1 Following this, the cost effectiveness of the vaccine in the UK was re-evaluated and it was recommended for use as long as the vaccine could be procured at a low enough price, which led to the introduction of the Men B vaccine for infants in the UK in 2015.

During the process the JCVI raised concerns regarding the difficulty in adequately assessing vaccines that prevent rare but severe childhood illness, calling for a working group to be set up to specifically address this. In parallel, MRF have been publicly questioning whether values are missing from the framework,2-4 which may lead to underuse of the vaccine.

As a result of these concerns MRF has worked with Pfizer and OHE Consulting Ltd to outline the scope for this desk research which compares international decision making processes, frameworks and methodologies and asks whether values are missing. Given the JCVI decision for the UK this project explicitly considers decision making in other countries, specifically France, Germany, Italy, Netherlands, Australia, New Zealand and Japan. Readers interested in the JCVI decision are directed to read the MRF response.1

1. Meningitis Research Foundation, 2013. Response to the JCVI Interim position statement on the use of Bexsero meningococcal B vaccine in the UK. Available from: http://www.meningitis.org/JCVI-response

2. Wright, C., 2014. Vaccine cost system lets harm from meningitis B continue. Nursing Times, 110 (11), 11.

3. Glennie, L., Wright, C., Head, C., 2014. Winter is coming: vaccine negotiations should be concluded swiftly. BMJ Letter, 349, g6748.

4. Meningitis Research Foundation, 2016. Petition on Meningitis B Vaccine. Written evidence from Meningitis Research Foundation; Available from: http://data.parliament.uk/writtenevidence/committeeevidence.svc/evidencedocument/petitions-committee/petition-on-the-meningitis-b-vaccine/written/32086.pdf.

Abbreviations

Agenas	National Agency for Regional Health Services, Italy
ASR	Agenzia Sanitaria Regionale, Italy
AQoL-8D	Assessment of Quality of Life (8 Dimensions)
ATAGI	Australian Technical Advisory Group on Immunisation
CADTH	Canadian Agency for Drugs and Technologies in Health
CSMT	Committee for Transmissible Diseases, France
CTV	Technical Vaccination Committee, France
DALY	Disability-adjusted life year
DCE	Discrete choice experiment
EMA	European Medicines Agency
EQ-5D	EuroQol five dimensions questionnaire
ESC	Economic Sub-Committee, Australia
G-BA	Federal Joint Committee, German
GKV	Mandatory service of statutory health insurances, Germany
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAS	High Authority of Health, France
HCSP	High Council for Public Health, France
HPV	Human Papillomavirus
HRQL	Health-related quality of life
HTA	Health technology appraisal
HU	Health utility
HUI	Health Utilities Index
ICER	Incremental cost-effectiveness ratio

iDSI	International Decision Support Initiative
IQWiG	Institute for Quality and Efficiency in Health Care, Germany
JCVI	Joint Committee on Vaccination and Immunisation, England
LEA	Basic Benefit Package (Livelli Essenziali di Assistenza), Italy
LY	Life Years
Men ACWY	Serogroups ACWY meningococcal disease infections
Men B	Serogroup B meningococcal disease infection
Men C	Serogroup C meningococcal disease infection
MenCCV	Meningococcal C conjugate vaccine
MeSH	Medical Subject Headings
MHLW	Ministry of Health, Labor, and Welfare, Japan
MIUR	Ministry of University and Research, Italy
NHS EED	NHS Economic Evaluation Database
NIC	National Immunisation Committee, Australia
NICE	National Institute for Health and Care Excellence, England
NIHR	National Institute for Health Research, UK
NITAG	National Immunization Technical Advisory Groups
NLM	National Library of Medicine
PBAC	Pharmaceutical Benefits Advisory Committee, Australia
PBS	Pharmaceutical Benefits Scheme, Australia
PBM	Preference-based measure
PHARMAC	Pharmaceutical Management Agency, New Zealand
PMDA	Pharmaceuticals and Medical Devices Agency, Japan
PNPV	National Vaccine Prevention Plan, Italy
QAF	QALY adjustment factor
QALY	Quality adjusted life years
REA	Rapid evidence assessment
RIVM	National Institution for Public Health and Environment, The Netherlands
RKI	Robert Koch Institute, Germany
SIGN	Scottish Intercollegiate Guidelines Network
STIKO	Standing Committee on Vaccination, Germany
VAS	Visual Analogue Scal

1 Introduction

Meningococcal disease is life-threatening infection and can result in severe sequelae. Endemic disease occurs worldwide, although there are no reliable estimates of global meningococcal disease burden due to inadequate surveillance (Jafri et al., 2013).

Invasive meningococcal disease can be fatal, whilst those that do survive have a high probability of developing long term sequelae. Individuals most at risk are non-immunised infants and toddlers, although a second peak occurs in adolescents and young adults. Meningococcal infection begins as bacteraemia which can progress to meningitis or to septicaemia, with serious septic shock and/or purpura fulminans. It is fatal in more than 50% of the cases if untreated (WHO, 2017). The fatality rate is around 5% to 10% for treated cases, but can vary depending on the types of bacteria causing the disease, the age of the patient and whether the clinical picture is of blood poisoning (septicaemia) or meningitis (infection of the lining of the brain) (Public Health England, 2016). Sequelae include cerebral lesions, hearing loss, learning difficulties, deafness severe cognitive deficits, cerebral palsy or epilepsy in rare cases (Bénard et al., 2016). Ten to 30% of children who survive purpura fulminans present with skin necrosis and limb ischemia that will require orthopaedic surgical management that could include limb amputation (Nectoux et al., 2010).

Meningococcal disease is caused by the bacterium *Neisseria meningitidis*. There are 12 types of bacterium or serogroups, where the most disease-associated serogroups are A, B, C, W, X and Y. Since about 10% of the population are symptom-free carriers of the disease, eradication is not a viable option. By far the most effective measure to combat the disease is vaccination (Ladhani et al., 2016; Towse et al., 2012). Polysaccharide meningococcal vaccines have been available for more than 40 years, however, these suffer from a number of constraints such as limited capacity to produce immunologic memory responses, poor immunogenicity in infants and lack of efficacy against nasopharyngeal carriage (Crum-Cianflone and Sullivan, 2016). Recent scientific and technical advances have led to the discovery and implementation of novel meningococcal vaccines which have resulted in a substantial decrease in the burden of disease worldwide representing a major public health achievement (Crum-Cianflone and Sullivan, 2016). The introduction of the first meningococcal conjugate vaccines in 1999, which overcame the majority of limitations presented in the polysaccharide vaccines, represented a break point in the management of the disease. The conjugate vaccines not only have superior direct effects, but also showed clear and strong positive indirect effects (herd protection).

In Europe, serogroup C meningococcal infections (hereafter Men C) markedly decreased after the introduction in a number of National Immunisation Plans of a conjugate vaccine (Pelton, 2016). For example, within the first 18 months of the immunisation programme in the UK, the Men C vaccine achieved coverage of over 80% in the targeted age groups and reduced the incidence in these groups of serogroup C by over 80% (Miller, Salisbury and Ramsay, 2001). Similarly, in Canada the incidence of Men C has been dramatically reduced (around 14% per year) with the conjugate vaccine (Sadarangani et al., 2014). A key factor responsible for this marked reduction is herd protection brought about by Men C vaccine implementation. Additionally, in the USA the introduction of the quadrivalent meningococcal conjugate vaccine against serogroups ACWY (hereafter Men ACWY) has facilitated a reduction in the incidence of meningococcal meningitis decreasing from 0.61 per 100,000 habitants in 2003 to 0.18 in 2013 (Pelton, 2016). Currently, in Europe serogroup B meningococcal infection (hereafter Men B) dominates, although cases of serogroup Y have been increasing in recent years (Pelton, 2016) and a rapid rise in serogroup W in the UK led to the introduction of MenACWY vaccine in teenagers in 2015 (Campbell et al., 2015), and other countries including the Netherlands and Australia are also experiencing a rise in MenW. For instance, in the UK

the decline of Men C since 1999 means that Men B is responsible for around 70% of cases. Similarly, in the USA and Canada Men B is now the most common cause of outbreak associated disease (Pelton, 2016).

Progressive advances in vaccinology have led to the recent licensure of two effective vaccines against serogroup B: MenB-4C and MenB-FHbp (Crum-Cianflone and Sullivan, 2016). The development of a Men B vaccine proved to be difficult, it required considerable investment in its research and development and took a number of years of intensive research (Green et al., 2016). The similarity between the serogroup B capsule and the human antigen neural-cell adhesion molecules hindered the immune response to those vaccines based on inducing antibodies to the meningococcus capsular polysaccharide (Murphy, 2013). In the case of one of the licensed Men B vaccines a new approach to vaccine development was applied: reverse vaccinology. This is based on a whole-genome sequencing of bacteria and the identification of proteins that provoke an immunological response (Green et al., 2016). These efforts made possible the development of a vaccine predicted to protect against 73% of the strains that cause the serogroup B meningococcal disease in the UK (Murphy, 2013).

Due to the novelty of Men B vaccines, there exists some uncertainty with respect to their effectiveness, particularly the indirect effects of the vaccine. National healthcare systems globally are faced with making evidence-based decisions regarding the Men B vaccine with high levels of uncertainty. There is mounting real-world evidence of the efficacy of Men B vaccination from its use in the UK against an expensive lethal disease (Parikh et al., 2016), but currently only the UK, Ireland and Italy have implemented the meningococcal vaccine against serogroup B in their National Immunisation Plans.

Vaccination adoption decisions are often made using the same or similar criteria used for the adoption of other new health technologies. However, the evaluation of immunisation and vaccination programmes differ from that of other health-related activities using public resources. This is mainly because the health benefits occur in a period that is posterior to the expenditures, they can take place over many years and impacts both the inoculated person and their family. A common criteria used in a number of countries to inform adoption/inclusion decisions is whether the implementation of a new health technology represents an effective use of public resources. This is generally informed by assessing the cost-effectiveness of the new treatment in comparison with alternatives possibilities. A common concern with respect to vaccines is whether such cost effectiveness analyses and guidelines for economic evaluation identify and value all possible health benefits.

This has fuelled a debate around the validity of the assumptions used in economic evaluations general and for vaccines, as well as the criteria used to decide on vaccine adoption. The question that arises is how to evaluate a novel prevention treatment, like the Men B vaccine, such that the effect of uncertainty on the decision is minimised but the decision is informed by public preferences with respect to the benefits of the vaccination. Therefore, it is necessary to understand how health is valued and whether these reflect society's preferences.

The purpose of this study is to document the decision making criteria for meningococcal vaccine reimbursement and the methodology used to inform decisions about adopting vaccines as well as suggest new criteria that, given the nature of the benefits derived from vaccines, could be considered in adoption decisions. We analyse whether there is a gap between the health outcomes considered in the decision making frameworks and the wider benefits of implementing a Men B vaccine. We also examine whether values and preferences of the society are considered in the decision making process of vaccine inclusion. The key research questions explored are:

- What is the current status of the literature available for decision makers and health technology assessment (HTA) agencies to support recommendations and decisions on the inclusion and reimbursement of meningococcal vaccines?
- What are the decision making criteria that are considered by decision makers for the reimbursement and inclusion of new vaccines?
- What are the methodologies that HTA agencies use to inform decisions about adopting vaccines?
- Given the nature of benefits derived from vaccination strategies, what additional criteria could be considered to appropriately evaluate vaccines' benefits?

To address these questions we used a mixed methods approach. We first undertook a review of studies that evaluated the cost-effectiveness of any meningococcal vaccine. To allow us to map the methodologies for HTA of vaccines employed by formal HTA agencies and to document the criteria used in previous decisions regarding the reimbursement of vaccines we collected key documents and conducted interviews with country experts. Lastly, we defined and discussed additional criteria that could be considered in the decision making process to improve the link between public preferences and decision making.

2 Methods

2.1 Literature review

We conducted a review of the literature to identify the methodologies and assumptions currently being applied in the economic evaluation of meningococcal vaccines. The approach employed was a rapid evidence assessment (REA). A REA is a systematic process of gathering and reviewing evidence (Grant and Booth, 2009, Thomas et al., 2013). A REA is similar to a systematic literature review but is commonly constrained by time availability and usually captures the key points reflected in the evidence rather than being entirely exhaustive.

The search for articles was based on:

1. NHS Economic Evaluation Database (NHS EED) (CRD, 2016): This comprehensive database includes over 16,000 economic evaluations of health care interventions. The Department of Health and the National Institute for Health Research (NIHR), through a constant search of articles in MEDLINE, EMBASE, CINAHL, PsycINFO and PubMed, has collected in the NHS EED those articles that compare the costs and outcomes of two or more health interventions and that apply cost-benefit, cost-utility or cost-effectiveness analysis. It is worth noting that the NHS EED does not include systematic literature reviews. Since NHS EED includes only economic evaluations, the search criteria do not include words related to cost-effectiveness, HTA or economic evaluation. The following are the search criteria used in this part of the analysis (192 hits):

    - Meningococcal
    - Meningitidis
    - Meningitis
    - "Heptavalent Pneumococcal" and "Conjugate Vaccine"
    - Septicemia
    - Septicaemia
    - "Sepsis" and "vaccine"

2. MEDLINE: The National Library of Medicine (NLM) journal citation database. The MEDLINE database is directly searchable from the PubMed database, which mainly includes MEDLINE citations. An important advantage of MEDLINE is the use of Medical Subject Headings (MeSH) to index citations (U.S. National Library of Medicine, 2016). This is a classification tool used to index journal articles and books in the life sciences literature. We used PubMed searches to conduct the review. The PubMed tool allows searches according to MeSH criteria in which the article is classified. MeSH controlled vocabulary or the MEDLINE subset allow us to extract only MEDLINE citations from the search. The following is the list of MeSh criteria used related to meningococcal disease (407 hits):

    - Heptavalent Pneumococcal Conjugate Vaccine
    - Meningitis, Meningococcal
    - Meningococcal Infections
    - Infections, Meningococcal
    - Meningococcal Vaccines
    - Waterhouse-Friderichsen Syndrome
    - Capsular polysaccharide, meningococcal group B
    - lpdA protein, Neisseria meningitidis
    - P64k meningococcal protein, Neisseria meningitidis
    - Meningococcal group A polysaccharide
    - Meningococcal group C polysaccharide
    - Meningococcal group C polysaccharide-tetanus toxoid conjugate
    - Meningococcal type B conjugate vaccine
    - N-propyl group B meningococcal polysaccharide
    - PncOMPC vaccine

- Porin protein, Neisseria
- Serogroup C meningococcal conjugate vaccine
- Tetravalent meningococcal serogroups A, C, W-135 and Y tetanus toxoid conjugate vaccine
- Hemorrhagic Septicemia
- Hemorrhagic Septicemia, Viral
- Sepsis

In addition, we included specific title/abstract search terms that allow the identification of economic evaluations:

- Economic evaluation
- Economic model
- Health Technology Assessment
- HTA
- Cost-effectiveness
- Cost-benefit
- Cost-utility
- Cost-consequence
- Cost-minimisation
- Cost per QALY
- Incremental cost-effectiveness ratio
- ICER

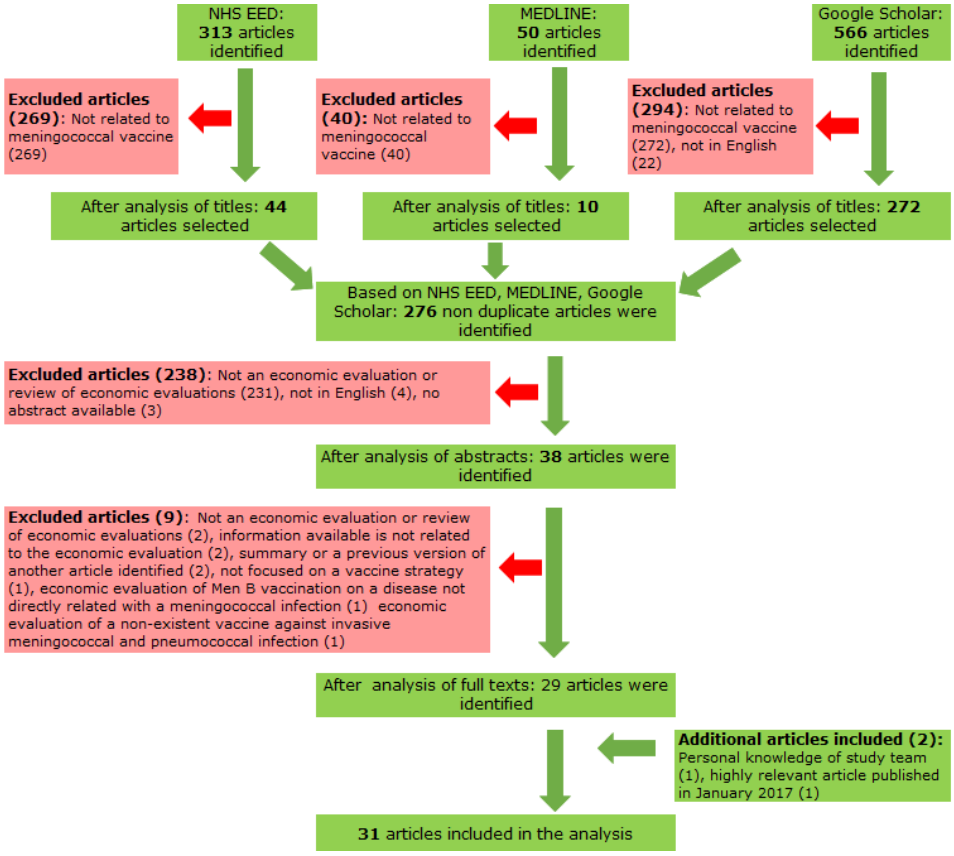
3. Google Scholar: We conducted a search using the Google Scholar search tools. We combined the search criteria applied in the NHS EED database search with the non-MeSH criteria applied in the MEDLINE search.

The search was limited to documents published between January 2005 and November 2016. In the case of the NHS EED database only those that were included before February 2015 were included.

We reviewed the abstracts of 276 articles that fulfilled the above criteria and excluded editorials, comments, letters, responses and PhD/Masters theses. During the abstract analysis, we applied an additional selection criterion: we included only those articles whose abstract indicated that the analysis reported an economic evaluation or a review of previous economic evaluations of meningococcal vaccines. In addition, we excluded those articles for which no abstract was available. The full texts of 38 documents were reviewed. This includes abstracts presented at conferences for which a full article has not (yet) been published. Four articles that did not fulfil the above criteria were excluded, while a further two were not focused and therefore excluded. Two more articles were excluded as they were duplicates of studies included in other articles. Additionally, given the scope of the analysis, we excluded an economic evaluation of the indirect effect of meningococcal vaccination on Neisseria gonorrhoeae (Régnier and Huels, 2014) and a possible but non-existent combination vaccine against invasive meningococcal B and pneumococcal infection (Bos et al., 2006). Outside of the literature review the research team identified an additional article that fulfilled all the inclusion criteria (Hanquet et al., 2014b). A further article that fulfilled all the criteria but was published in early 2017 (thus outside of the review window) was included on the basis that it was deemed to be highly relevant for the objectives of this review (Christensen and Trotter, 2017). The final analysis included 31 articles (**FIGURE 1**).

During the review of studies we extracted the following information in order to evaluate economic evaluations of meningococcal vaccination, and understand the evidence based available to inform adoption decisions: vaccination schedules (i.e. comparators), health outcomes and sources of value, discount rate employed, nature of the modelling approach employed, the perspective of the study and the affiliation of the authors and the source of funding.

FIGURE 1. PRISMA DIAGRAM OF LITERATURE SEARCH AND SELECTION OF ARTICLES



2.2 HTA agencies and decision making criteria

In order to identify the methodologies used by the HTA agencies as well as the main criteria applied by decision makers when evaluating a new vaccines, we conducted seven semi-structured interviews with experts from a selected group of countries: France, Germany, Italy, Netherlands, Australia, New Zealand and Japan. The experts were deemed to have deep knowledge of the national process for the adoption of new vaccines and/or have a direct experience of formulary development or reimbursement decisions related to vaccines (see Interview protocol, Appendix 1).

In addition, we identified key documents, guidelines and/or reference cases for each of the selected countries in order to validate and complete the information collected in the interviews. These articles were analysed together with any publications and relevant documents provided by the experts.

2.3 Broader criteria and the appropriateness of quality of life measurement

The discussion of broader criteria particularly focuses on issues of peace of mind and issues around public preferences for different dimensions of health specific to meningitis. This discussion is informed by a review of the literature. We also review the literature on the appropriateness of quality of life measurement specific to both patients with meningococcal disease and their broader network. A summary of the current state of play allows us to identify areas where future research should be focused.

3 Results

3.1 Assessing the evidence base: literature review

The literature review identified 31 documents published between 2005 and 2016 that comprise information about at least one economic evaluation of one or more meningococcal vaccine strategies. Of the 31 documents, 25 are full-length articles (24 journal articles and one report) of which 12 correspond to economic evaluations of Men B vaccines. In addition, six abstracts were identified, the majority of which are related to the quadrivalent vaccine against Men ACYW (TABLE 1).

TABLE 1. INCLUDED ARTICLES: TYPE OF PUBLICATION AND TYPE OF STUDY

		Total	Men B	Men C	Men A	Men ACYW	Serogroup unspecified
Total		**31**	**12**	**6**	**1**	**9**	**3**
Type of publication	Journal article	**24**	11	5	1	5	2
	Abstract	**6**	0	1	0	4	1
	Report	**1**	1	0	0	0	0
Type of study	*Full economic evaluations: costs and outcomes*	***26***	*12*	*5*	*0*	*9*	*0*
	Cost-effectiveness analysis	**25**	12	5	0	8	0
	Cost-consequence analysis	**1**	0	0	0	1	0
	Others approaches	***5***	*0*	*1*	*1*	*0*	*3*
	Cost-of-illness	**1**	0	0	1	0	0
	Review of cost-effectiveness analysis of Men vaccines	**4**	0	1	0	0	3

The majority of the identified studies are full economic evaluations (26/31) (TABLE 1), these correspond to comparative analysis of health treatments that consider both related costs and consequences (health outcomes). Additionally, four literature reviews of previous cost-effectiveness analyses of meningococcal vaccines were found (Kauf, 2010; Miller and Shahab, 2005; Welte et al., 2005; Zakzuk, Bess and Guzman, 2016). One cost-of-illness study examining the impact of implementing a vaccine strategy against serogroup A in Burkina Faso was identified (Colombini et al., 2015). Serogroup A was once a common cause of meningococcal disease worldwide, it is now a problem that affects mainly the so-called "meningitis belt", countries in sub-Saharan Africa where there are recurrent epidemics. The Colombini et al. (2015) study is the only article identified that refers to serogroup A.

Given that our objective to analyse the methodologies used to inform decisions about adopting vaccines we focus our attention on the 26 full economic evaluations. The aim is to examine the methods applied and assumptions considered in assessing whether a vaccine strategy represents an effective use of public resources.

3.1.1 Full economic evaluations

The literature review indicates that recent published economic evaluations of meningococcal vaccines relate mostly to developed countries (TABLE 2). In this sense, the results presented in this

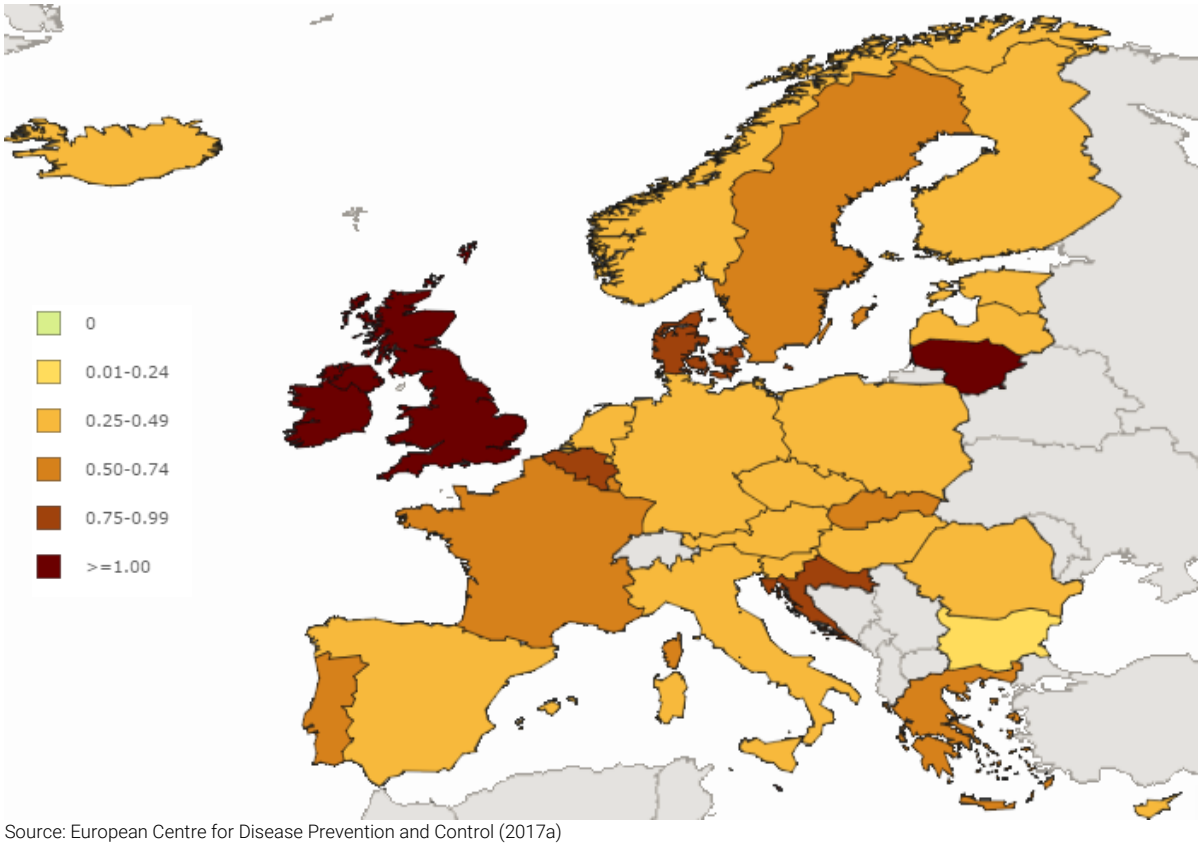
section mainly refer to the current situation of the economic evaluation analysis for meningococcal vaccine implementation in developed countries.

TABLE 2. FULL ECONOMIC EVALUATIONS OF MENINGOCOCCAL VACCINES BY COUNTRY AND SEROGROUP

	Total	Men B	Men C	Men ACYW
Belgium	1	1	0	0
Brazil	1	0	1	0
Canada	3	1	0	2
Chile	1	1	0	0
Colombia	1	0	0	1
England (only)	3	3	0	0
England and Wales	2	0	2	0
France	1	1	0	0
Germany	2	1	1	0
Israel	1	1	0	0
Italy	2	2	0	0
New Zealand	1	0	1	0
Netherlands	2	1	0	1
USA	5	0	0	5
Total	**26**	**12**	**5**	**9**

Out of the 26 full economic evaluations, five articles analyse vaccination schedules against serogroup C, one related to Brazil and four related to a European country (TABLE 2). In contrast, a previous review by Welte et al. (2005) found 12 economic evaluations of vaccines against Men C related to developed countries. The decline in the number of publications related to Men C over the previous decade and a half can in part be explained by the fact that the Men C vaccine is now included in the National Immunisation Plans for the majority of developed countries, such as France, Germany Italy, Netherlands and the UK. However, 14 out of 31 countries in Europe do not have a Men C vaccine in the recommended immunisation schedule against meningococcal disease (Bulgaria, Croatia, Denmark, Estonia, Finland, Hungary, Latvia, Lithuania, Malta, Norway, Romania, Slovakia, Slovenia and Sweden) (European Centre for Disease Prevention and Control, 2017b). Welte et al. (2005) suggest that the incidence of the disease and the linked anxiety of the population are more important factors in decisions than the economic evaluation. Of the studies included in Welte et al. (2005), countries that have implemented meningococcal serogroup C vaccination campaigns show the highest incidence levels. In fact, the results suggest that, in the case of Men C, economic evaluation had an influence in the selection of the most efficient vaccination strategy but not so much in the decision about inclusion. Nonetheless, the role of the incidence needs to be further investigated. For instance, countries such as Denmark, Croatia and Lithuania – which have relatively high rates of meningococcal cases (FIGURE 2) – have not included the Men C vaccine in their immunisation programmes.

FIGURE 2. INVASIVE MENINGOCOCCAL DISEASE - ALL CASES - NOTIFICATION RATE PER 100,000 POPULATION



Source: European Centre for Disease Prevention and Control (2017a)

Additionally, we identified nine economic evaluations of the quadrivalent vaccine against Men ACYW. Seven of these studies are based in North America, two in Canada and five in the USA (TABLE 2). USA is the country with the (equal) largest number of observations (5/26), as can be expected given its epidemiological profile; all five US studies are evaluations of vaccines for Men ACYW.

The majority of the full economic evaluations identified correspond to vaccines against serogroup B (12/26) (TABLE 2). To our knowledge, no previous literature review of economic evaluations of the implementation of a Men B vaccine has been undertaken. However, in an analysis of the epidemiology of the meningococcal disease and related vaccination strategies, Sadarangani and Pollard (2016) mention six cost-effectiveness models for the introduction of 4CMen B into vaccine programmes (Christensen et al., 2014; Christensen et al., 2013; Izquierdo et al., 2015; Pouwels et al., 2013; Tirani et al., 2015; Tu et al., 2014) (all of which are identified in our search). Sadarangani and Pollard (2016) highlight that approaches to cost-effectiveness analysis and its importance varies in different countries. Regarding effectiveness, they conclude that the duration of protection and the impact on carriage have the greatest impact on overall effectiveness.

Two economic evaluations of vaccinations strategies against Men B were identified for Italy (TABLE 2). The first publication indicates that the vaccine is not cost-effective under the Italian health service perspective (Tirani et al., 2015). The second publication, which includes a societal perspective, concludes that Men B vaccination could be cost-effective if the possibility of an underestimation of disease incidence is considered. Two economic evaluations for Men B vaccine were also identified for the Netherlands. Pouwels et al. (2013) conclude that if Men B disease incidence increases or the vaccine price is substantially lowered, routine infant vaccination has the potential to be cost-effective.

England has five economic evaluations, most of which consider Men B vaccination strategies. All five English economic evaluations indicate that Men B vaccination could be cost-effective under a certain price level.

Among the full economic evaluation related to Men B vaccine, Izquierdo et al. (2015) study is the only one that refers to a low or middle income country. They consider the implementation of a 4CMenB vaccine in the context of a hypothetical epidemic outbreak in Chile.

Main conclusions regarding cost-effectiveness

Based on the article authors' own conclusions TABLE 3 shows the main results of the full economic evaluation studies. Our results indicate that the general recommendation regarding the cost-effectiveness of the vaccine schedule depends on particular model assumptions (11/26). Herd protection is a decisive factor mentioned particularly in the conclusions of those articles focused on vaccine schedules for adolescents or young adults (Hepkema et al., 2013; Simon et al., 2016; Ortega-Sanchez et al., 2008). Additionally, the cost of the vaccine dose has also a key influence on the final recommendation – six (out of 11) articles mentioned a price above which the strategy is not cost-effective (TABLE 3) (Christensen et al., 2013; Christensen et al., 2014; Christensen and Trotter, 2017; Gravatt, 2013; Izquierdo et al., 2015; Pouwels et al., 2013).

TABLE 3. FULL ECONOMIC EVALUATIONS OF MENINGOCOCCAL VACCINES MAIN CONCLUSION BY SEROGROUP TYPE

	Total	Men B	Men C	Men ACYW
Cost-effective	7	1	4	2
Not cost-effective	5	4	0	1
Mixed results†	11	7	1	3
Unclear	3	0	0	3
Total number of articles	**26**	**12**	**5**	**9**

† Mixed results: Conclusion depends on particular factors. Those articles whose results indicate that vaccination is cost-effective only under a certain price level per dose are included in this category.

We identified seven articles whose conclusions indicate that the meningococcal vaccination strategy considered is cost-effective, one is related to the serogroup B (TABLE 3). Ginsberg et al. (2016) analyse the implementation of Men B vaccine in the Israeli context. They tested two strategies (three dose vaccine schedule - 2, 4, 12 months - and additional two dose catch-up programmes vaccinating children in cohorts aged 1–2 to 1–13 years old) against having no vaccination programme. Although a price of $19.44 per dose is mentioned as the maximum level that allows the strategies to be classified as cost-effective for the health system in general, their conclusions suggest that for high risk areas both strategies would be cost-effective and could be recommended for use.

Incidence

Notably the review did not highlight incidence as an influential factor, but it is important to note that an analysis that considers a narrow, hyperendemic time period when incidence is high would likely look very different from an analysis that considers a longer time period when incidence is low. In general, the studies reviewed do not account for the unpredictability and associated uncertainty of disease burden. There is a need to better understand whether the kinds of models currently being used are suitable for stochastic events and unpredictable diseases such as meningococcal disease.

Vaccination schedules considered

In order for an economic evaluation to be informative an appropriate comparator is required. The selection of comparator can have a considerable influence on the study conclusions. Of those

selected twenty studies use no-vaccination as main comparator. This is in agreement with recommendations by Kauf (2010) to avoid the selection of a cost-ineffective comparator, which could bias the results. In the reference case proposed by the International Decision Support Initiative (iDSI), a comparator should correctly reflect the decision problem facing policy makers (Wilkinson et al., 2016). Among the 26 economic evaluations included here, six consider the main comparator to be the vaccine schedule strategy currently applied (Christensen and Trotter, 2017; Cognet et al., 2012; de Soarez et al., 2011; De Wals et al., 2007; Hepkema et al., 2013; Trotter et al., 2006). In response to recent popular pressure to extend the Men B vaccination to all children until the age of 11 years, Christensen and Trotter (2017) conducted an economic evaluation to measure the cost-effectiveness of extending the current vaccination schedule to children aged 1, 2 or 3–4 years, that is comparing these schedules to a programme of vaccinating the under 1 year olds. Similarly, Cognet et al. (2012) and De Wals et al. (2007) consider the costs and benefits of extending the current strategy to include a booster between 1 to 15 years of age.

As shown in TABLE 4, 16 of the 26 economic evaluations include more than one vaccination schedule, and 11 out of these 16 articles include non-vaccination as main comparator. This has two advantages. First, as mentioned above, by including more than one comparator authors are reducing the probability of selecting a non-cost-effective comparator. Second, it reflects the fact that policy makers' decisions on vaccine inclusion in the immunisation schedule are normally not binary, but require the selection of the most appropriate vaccine schedule out of the list of plausible choices.

TABLE 4. FULL ECONOMIC EVALUATIONS OF MENINGOCOCCAL VACCINES VACCINATION SCHEDULES CONSIDERED BY SEROGROUP TYPE

		Total	Men B	Men C	Men ACYW
Number of vaccination schedules (vaccination strategies)	One	**10**	4	2	4
	Two to three	**11**	4	2	5
	More than three	**5**	4	1	0
Adolescents vaccination schedules (11 to 18 years old)	Catch-up vaccine programmes for adolescents	**6**	4	2	0
	Infant programmes followed by booster during adolescence	**9**	5	1	3
	Routine adolescent immunisation programs	**10**	5	1	4
	Only infant programs	**7**	4	2	1

With respect to age group, the fact that infants under 1 year old, followed by children between 1 and 4 years old, are the populations most prone to suffer from a meningococcal infection (Sadarangani and Pollard, 2016) is reflected on the number of full economic evaluations that considered vaccine schedules for children in these age groups. There are only four full economic evaluations that do not include doses applied to infants or toddlers as part of the vaccination strategy. Moreover, 27% (7/26) of the sample considers only children in the vaccination strategies (TABLE 4).

Meningococcal disease incidence rate is also relatively high between 15 and 24 years old (Sadarangani and Pollard, 2016); adolescents have the highest rates of meningococcal carriage and transmission, therefore, vaccination programmes targeted at adolescents could considerably reduce meningococcal disease at a population level (Vetter et al., 2016). Consequently, the assessment of meningococcal vaccination including one or more doses during adolescence is common among the economic evaluations. Out of the 18 articles that consider doses applied during adolescence, 10 include routine adolescent immunisation programmes. Five of these 18 articles (TABLE 4) are related to Men B vaccine doses applied between the ages of 12 and 15 years (Christensen et al., 2013;

Christensen et al., 2016; Christensen et al., 2014; Hanquet et al., 2014b; Lecocq et al., 2016). In comparison with other economic evaluations Christensen et al. (2013; 2014; 2016) consider a relatively high number of vaccine immunisation strategies (more than seven) among which two routine adolescent programmes are included in each case.

Health utility losses

Regarding outcomes included in the economic evaluations, 20 articles consider health utility (HU) losses (TABLE 5), all of them using quality adjusted life years (QALYs). Four out of the six cases that do not consider HU losses apply life-years saved (LYs) and/or the disability-adjusted life-year (DALY) as outcome measure (Carroll et al., 2006; Castañeda-Orjuela et al., 2013; de Soarez et al., 2011; Ginsberg et al., 2016).

TABLE 5 displays how HU losses are considered in the literature. The majority of articles (12/20) evaluate only QALY losses from sequelae related to meningococcal infection. Only five articles include HU losses for both acute episode and survivors with sequelae, all of which are evaluations of Men B vaccination strategies. Among these five, three also include QALY losses for caregivers.

Christensen and Trotter (2017) and Christensen et al. (2016) consider in their sensitivity analyses QALY losses for carers of a person with sequelae using estimations from Al-Janabi et al. (2015). Based on data from families in which a member has suffered from a meningococcal infection, Al-Janabi et al. (2015) found that long-term health losses to survivors' family members who report particularly anxiety and depression. Al-Janabi et al. (2015) results suggest that a meningococcal vaccine has significant health benefits not just to those that might have contracted the disease but also to their family and carers, and that these health benefits could be considered in the economic evaluations.

Additionally, Tu et al. (2014) consider HU losses for caregivers in all Men B cases of individuals experiencing major sequelae regardless of age using the data from Poley et al. (2012). Poley et al. (2012) measure the effects on the health-related quality of life (HRQL) of informal caregivers using a population of parents of children with major congenital anomalies. Similar to Al-Janabi et al. (2015), Poley et al. (2012) find significant differences between parents caring for children with congenital anomalies and the general population. However, sensitivity analyses suggest that accounting for caregivers' HU losses does not significantly affect the cost-effectiveness of the meningococcal vaccination strategy: including HU losses for caregivers decreases the incremental cost-effectiveness ratio (ICER) by 3.5% (Tu et al., 2014).

TABLE 5. CONSIDERATION OF HEALTH UTILITY LOSSES IN FULL ECONOMIC EVALUATIONS

Health utility loss considered?	Total	Men B	Men C	Men ACYW
Survivors with sequelae (Utility loss value for survivors with sequelae)	**5**	2	2	1
Survivors with sequelae (QALYs for specific diseases/disabilities)	**7**	3	1	3
For the acute episode and for survivors with sequelae (Utility loss value for survivors with sequelae)	**4**	4	0	0
For the acute episode and for survivors with sequelae (QALYs for specific diseases/disabilities)	**1**	1	0	0
Included, category unclear	**3**	0	0	3
Not included	**6**	2	2	2

Additionally, some of the literature specified the HU losses by type of sequelae (8/26) (see QALYs for specific diseases/disabilities, TABLE 5). For example, Lecocq et al. (2016) include QALY losses using EQ-5D for the following sequelae: severe and mild hearing loss, blindness, epilepsy, attention deficit

hyperactivity disorder and amputation. Among the group of selected studies, we observed differences in the type of sequelae considered. For instance, the list of sequelae considered by Pouwels et al. (2013) differs from that of Lecocq et al. (2016). Pouwels et al. (2013) consider at the reduction in QALYs related to hearing loss (different QALY losses are assigned depending on the treatment, e.g. cochlear implantation and cochlear device), motor deficits and neurological sequelae (with and without institutional care). Shepard et al. (2005) use HU values for conditions closely resembling the main related sequelae. They approach QALY losses related to single or multiple amputations by using HU values of trauma patients after undergoing amputation of an extremity, and QALY losses for patients with neurologic disability by using data relating to severe Alzheimer's disease patients.

Variation was observed in the sources of information used to extract the relevant values of QALY loss by sequelae. The eight articles that consider QALY losses for survivors with sequelae cited between one and 17 publications reporting QALY values (see QALYs for specific diseases/disabilities, TABLE 5). In total 29 different references were cited in these eight articles, TABLE 6 shows those references that are mentioned in at least two of the eight articles. Economic evaluations related for the Italian context include a noticeably different set of references than those for the Netherlands and France. Stouthard et al. (1997) is the source reference that appears in the greatest number of articles (5/8). They derived a coherent set of disability weights for a sizable number of diseases for the Netherlands contexts.

Welte et al. (2005) suggests that country specific QALY or DALY weights are rarely available for all complications and sequelae related to the serogroup C meningococcal disease. Because of this, and the lack of high-quality data, quality of life weights included in most of the studies are rough estimates of actual countries' values (Welte et al., 2005). Given the Stouthard et al. (1997) study which collected information specifically for the Netherlands is used to estimate QALY losses for Italy and France reflects the lack of country data (TABLE 6).

TABLE 6. REFERENCES THAT APPEAR AT LEAST ONCE AMONG THE STUDIES THAT ESTIMATE QALY LOSS FOR SPECIFIC DISEASES/DISABILITIES†

References	Studies that estimate QALY losses for specific diseases/disabilities						
	Men B				**Men ACYW**		
	Pouwels et al. (2013)	Tirani et al. (2015)	Gasparini et al. (2016)	Lecocq et al. (2016)	Shepard et al. (2005)	Ortega-Sanchez et al. (2008)	Hepkema et al. (2013)
	Nether-lands	Italy	Italy	France	USA	USA	Nether-lands
Stouthard et al. (1997)	x	x	x	x			x
Oostenbrink, Moll and Essink-Bot (2002)	x	x	x	x			
Krabbe, Hinderink and van den Broek (2000)	x				x	x	
Brown et al. (2001)		x	x				
Caban-Martinez et al. (2011)	x				x		
Donev et al. (2010)		x	x				
Saarni et al. (2007)		x	x				
Thein et al. (2010)		x	x				
Wyld et al. (2012)		x	x				
Xu et al. (2011)		x	x				
Yfantopoulos (2001)		x	x				

†‡Only six of the seven articles are included since the references used by Gravatt (2013) (Men C) are not quoted in any other study.

A second group of studies (9/26) consider HU losses by applying a utility loss value to all survivors with sequelae, or two utility loss values – one for mild sequelae and another for severe sequelae (see utility loss value for survivors with sequelae, TABLE 5). Christensen et al. (2013) (Men B), De Wals et al. (2007) (Men ACYW) and Trotter and Edmunds (2006) (Men C) apply an average utility loss for survivors with sequelae of between 0.2 and 0.29. Tu et al. (2014) reported that the weights used are derived from Kuppermann et al. (2000), but they do not report the actual value for the utility loss. Three economic evaluations of the cost-effectiveness of Men B vaccination strategies, Christensen et al. (2016), Christensen et al. (2014) and Hanquet et al. (2014b), approach HU losses for survivors with sequelae based on a single study (MOSAIC) (Viner et al., 2012), which is a case–control study of Men B survivors in the UK. Hanquet et al. (2014b) mention that the decrease in utility estimated in the MOSAIC study is on average 0.074 for survivors of Men B disease with any sequelae.

The MOSAIC study (Viner et al., 2012) reports that serogroup B meningococcal disease results in a range of objectively measured cognitive, psychological, quality of life, hearing, vision, and motor deficits. Around 10% of children with meningococcal disease had a major sequelae resulting in major physical or neurological disability, including major amputations, very low IQ, seizures, moderately severe bilateral hearing loss, and major hearing loss. Additionally, the MOSAIC results suggest that more that 33% of children had minor deficits, such as psychological disorders, borderline IQ, digit amputations, minor or unilateral hearing loss, and minor communication deficits (Viner et al., 2012).

In addition to the methodological weaknesses to measure HU losses common to most studies, such as the validity of the tools used to capture children's QALYs, the MOSAIC study has a series of limitations. For instance, the Meningitis Research Foundation (MRF) records of survivors with sequelae show that, when considering the same cohort than MOSAIC (children who had meningitis between July 2004 and December 2006 and who were aged 1 month to 13 years at the time of the MOSAIC study) the data suggest that the MOSAIC study underestimates the probability of amputation, and may be more generally biased towards less severe outcome (MRF, 2013). This is supported by Hanquet et al. (2014b) who identified 17 primary studies valuing the long term quality of life impact of meningococcal diseases, the utility loss value for survivor with any sequelae identified by MOSAIC study (0.074) were lower than that of other studies (range between 0.2 and 0.4). Additionally, in the MOSAIC study unrecruited children with meningococcal disease were more likely than recruited cases to be in the most deprived quintile of the population which could bias the results (Viner et al., 2012). The estimations behind the average loss value for survivors with sequelae are not stated in any of the articles, therefore, it is out of the scope of this study to compare their suitability to measure HU losses.

The selection and measurement of health outcomes to be considered in an economic evaluation can have an enormous influence on the results. Oostenbrink et al. (2002) suggest that QALY weights of sequelae after meningitis depend on the applied classification method. They evaluate the quality weights for permanent sequelae after childhood bacterial meningitis using two classification instruments: EQ-5D and Health Utilities Index (HUI). They conclude that there are significant differences in quality weight estimations between the two instruments, particularly for "deafness" and "mental retardation". Furthermore, there are criticisms regarding the suitability of current available instrument to assess the HU losses for young children (Griebsch, Coast and Brown, 2005; Raat et al., 2002). This is the most vulnerable age group, the tool selected for measuring the HU losses in children affected by meningococcal disease would have a considerable effect on the cost-effectiveness results. For these reasons, the methodologies used and assumptions made in the estimation of QALYs should be assessed in terms of their quality and suitability.

Only a few of the economic evaluations included in our analysis mention the instrument used to estimate QALYs (6/26), and even those that do tend to provide insufficient detail. Therefore, it is difficult to derive any conclusions regarding the relevance of the selected QALY estimations used to measure HU losses in the case of the meningococcal disease.

Meningococcal disease has an important number of features that make the assessment of the validity of QALY values used particularly important. Such features include, for instance, difficulties in correctly capturing QALYs losses for the most vulnerable age groups (children and adolescents) and the insensitivity of this tool for capturing the quality of life impact of hearing loss and some neurological sequelae. Significant diversity with regards to type and severity of sequelae also makes capturing HU losses for meningitis patients particularly challenging. The Joint Committee on Vaccination and Immunisation (JCVI) has recognised that these particular features of meningococcal disease can hinder the estimation of the cost-effectiveness of Men B vaccination strategies. During the discussion and deliberations by the Committee, concerns were raised around the suitability of the EQ-5D to reflect HU losses of patients that suffer from sequelae as a consequence of a meningococcal infection. Moreover, the JCVI recognised that the 'incremental innovation' value of the Men B vaccine and the difference on the value that society assign to QALY losses for severe and relatively mild disease were poorly captured by existing methodologies for assessing the cost-effectiveness of the vaccination strategy. Therefore, the JCVI agreed to apply a QALY adjustment factor (QAF) of three (x3) to all long term sequelae, which was described as being equivalent to comparing the ICER of the vaccine against a threshold of around £45,000 per QALY (Joint Committee on Vaccination and Immunisation, 2016) – three times greater than standard threshold. Confusingly, the QAF is sometimes referred to as a 'QALY adjustment factor' (implying that the factor involves an adjustment to the denominator of the ICER) and sometimes as a 'quality of life adjustment factor' (implying an adjustment to the HU losses underpinning the QALY calculations).

The concept of the QAF was first introduced by the JCVI in 2013, when it established in its code of practice that 'where there is good reason to believe that the modelled health benefits over or underestimate the true benefits, the basis for the concern should be recorded and a QALY adjustment factor (QAF) should be estimated' (Joint Committee on Vaccination and Immunisation, 2013). To our knowledge, the JCVI was the first agency to have considered the use of a QAF (or any weighting factor) to partially offset the uncertainty surrounding a cost-effectiveness assessment. Therefore, it is unsurprising that only two articles (both originating in the UK) from our sample include a QAF in their estimations: Christensen et al. (2014) and Christensen and Trotter (2017). By including a QAF equal to three (as recommended by the JCVI), the authors recognise that HU losses associated with meningococcal disease are substantial and greater than what is possible to capture using standard methods. Given that the sub-estimation of the HU losses will considerably affect the cost-effectiveness of the meningococcal vaccination programs, it is expected that QAFs or similar HU adjustments will be more frequently incorporated in future economic evaluations of meningococcal vaccines.

The HU adjustments values are important to robustly evaluate not only with respect to the effect of a meningococcal vaccination programme, but also for other preventive health interventions. QAFs are an important first step in this direction, however, there is almost no information available on how the QAF value was arrived at by JCVI. Policy makers should be aware of the difficulties in measuring HU losses for particular health interventions and propose adjustment values whose estimation is transparent and clearly reflects how the methodology limitations have been overcome.

Although the JCVI are the first to consider a QAF, NICE have used alternative thresholds in the past to account for potential underestimates of QALY gains from an intervention within the cost-effectiveness analysis. During the NICE Citizens Council meeting of 2008, a series of circumstances in which it could be justifiable for NICE appraisal committees to depart from the established threshold were discussed.[1] The Council's recommendations and conclusions are incorporated into a document called Social Value Judgements and, where appropriate, into NICE's methodology. The

[1] *NICE Citizens Council is a panel of 30 members of the public which reflect the demographic characteristics of the UK. The Council provides a public perspective on primary moral and ethical issues that NICE has to take into account to produce guidance (NICE, 2017). The Council is reflecting the public preferences of the UK population.*

following list corresponds to those circumstances that were supported by at least 65% of the Council members (NICE, 2008a):

- the treatment in question is life-saving
- the illness is a result of NHS negligence
- the intervention would prevent more harm in the future
- the patients are children
- the intervention will have a major impact on the patients family
- the illness under consideration is extremely severe
- the intervention will encourage more scientific and technical innovation
- the illness is rare

Discount rate

An additional factor that affects cost-effectiveness estimations is the selection of the discount rate. Previous analyses suggest that in general most economic evaluations apply a single, constant discount rate for future health benefits and costs (Brouwer et al., 2005; Jit and Mibei, 2015). In fact, the majority of countries' economic evaluations guidelines require the use of a single discount rate (Jit and Mibei, 2015). There are a few exceptions, such as the Netherlands, Belgium and Poland (Hanquet et al., 2014b; Jit and Mibei, 2015; Zorginstituut Nederland, 2016).

The use of a single discount rate has been challenged in the case of vaccines. The health benefits derived from a vaccination strategy are observed in a time period that is posterior to the initial expenditure (i.e. the vaccination itself). This means that health benefits are more heavily discounted than costs (Jit and Mibei, 2015). Moreover, for preventive interventions such as vaccinations, the time lag between the initial expenditure and the health benefits tends to be much longer than for other health technologies (though other benefits, such as 'utility in anticipation', may occur from the point of vaccination; see 0). Generally, a constant discount rate applied to health benefits leads to an exponential decline in the value of the benefits over time. This means that the total benefits attributed to preventive health interventions where the benefits occur well into the future are particularly affected. The time gap between health benefits and the expenditures observed in public health interventions have been recognised by NICE in its reference case for the development of public health guidance (NICE, 2012). A discount rate of 1.5% for all costs and benefits is required in economic evaluation. They recognise that to include this discount rate will give approximately the same result as a 3.5% discount rate on costs and a 1.5% rate on benefits used by the Department of Health. Moreover, a single discount rate of 3.5% is required in the sensitivity analysis (NICE, 2012).

Economic evaluations of vaccination strategies have adopted different approaches to address these concerns. This can be observed among the economic evaluations of meningococcal vaccines identified (TABLE 7). Although several studies consider only a single discount rate (10/26), 12 articles considered other options. Five studies tested alternative discount rates during the sensitivity analysis (Christensen et al., 2014; de Soarez et al., 2011; De Wals et al., 2007; Tirani et al., 2015; Tu et al., 2014). All but one of these five articles tested values between 0% and 5%, only de Soarez et al. (2011), in their analysis of a Men C vaccination, tested a 10% discount rate for both costs and health benefits.

In addition, three articles consider differential discount rates in the base case and/or sensitivity analysis. Two of these studies related to the Netherlands (Hepkema et al., 2013; Pouwels et al., 2013) and to for Belgium (Hanquet et al., 2014b), which is in accordance with the requirements of those countries. Similarly, Cognet et al. (2012) and Izquierdo et al. (2015) apply a discount rate for cost (5% and 6% respectively) but not for health benefits. The remaining two articles apply a non-constant discount rate over time. Lecocq et al. (2016) use a 4% single discount rate during the first 30 years, with a progressive reduction to 2% thereafter. Christensen et al. (2013) use a single discount rate of 3.5% for the first 30 years, which falls to 3.0% in years 31 to 75 and to 2.5% in years 76 to 99. This schedule is consistent with the recommendations of the UK Treasury to all public sector bodies (Treasury HM, 2011), which suggests the use of a stepwise discount rate given uncertainty about the future.

TABLE 7. DISCOUNT RATE USED IN FULL ECONOMIC EVALUATIONS

		Total	Men B	Men C	Men ACYW
Discount rate	Single discount rate	10	4	2	4
	Discount rate tested in sensitivity analysis†	5	3	1	1
	Differential discount rate††	3	2	0	1
	Discount rate stated only for costs	2	1	0	1
	Non-constant discount rate over time	2	2	0	0
	NA	4	0	2	2
Discount rate for health benefits†††	No discount reported	2	1	0	1
	0% to 1.5%	4	2	1	1
	1.6% to 3%	10	4	1	5
	3.1% to 5%	6	5	1	0
	NA	4	0	2	2

† Same discount rate for cost and health outcomes in both base case scenario and sensitivity analysis
†† Differential discount rates in the base case and/or the sensitivity analysis
††† Based on the discount rate used in the base case scenario

With regard to the level of discount, the most common discount rate applied to health benefits in base case scenarios is 3%. No economic evaluations were identified that used a health benefit discount rate of over 5%. Based on the data reported in the literature, TABLE 8 shows the effect on the ICER value of increasing the discount rate. The highest effect was reported by De Wals et al. (2007) in its economic evaluation of implementing a vaccination strategy to protect adolescents against meningococcal disease serogroup ACYW. de Soarez et al. (2011) when evaluating a universal vaccination strategy against meningococcal serogroup C reported the lowest effects of a decrease in the discount rate. In the middle are the studies related to Men B vaccine. A 2% increase in the discount rate varies the ICER values by at least 53%. Hanquet et al. (2014b) reported that an increase on only the discount rate value for benefit increase the ICER by 177.5%.

TABLE 8. EFFECT OF THE SELECTED DISCOUNT RATE ON THE ICER VALUE

Serogroup	ICER	Article	Increase in discount rate (%)	Increase in ICER (%)
Men ACYW	Cost per QALY gain	De Wals et al. (2007)	0 to 5	418.9
Men B	Cost per QALY gain	Tu et al. (2014)	0 to 5	301.5
		Tirani et al. (2015)	0 to 3	216.0
		Hanquet et al. (2014b)	3 costs/1.5 benefits to 3 both	177.5

		Tu et al. (2014)	0 to 3	162.4
		Tirani et al. (2015)	0 to 1.5	92.6
		Tirani et al. (2015)	1.5% to 3	64.1
		Tu et al. (2014)	3 to 5	53.0
Men C	Cost per case avoided	de Soarez et al. (2011)	0 to 5	17.2
	Cost per death avoided		0 to 5	15.7
	Cost per LYS avoided		0 to 5	14.7

Mathematical model and herd protection

The selection of the appropriate mathematical model for the economic evaluation of vaccines is key to the analysis. There are a number of options that can be divided into two main categories (Ultsch et al., 2016):

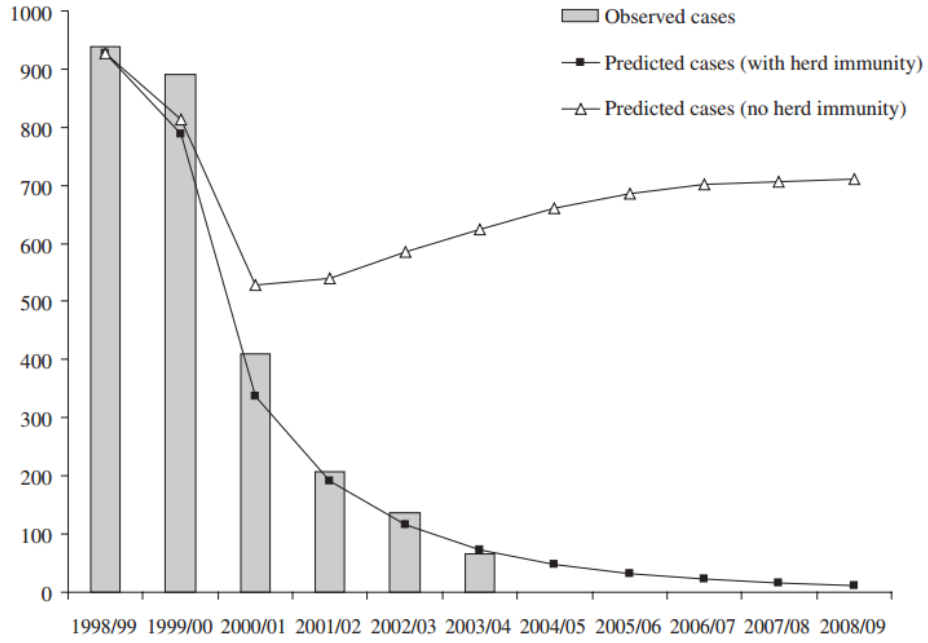
- Dynamic models - population models
  - Compartmental transmission dynamic models
  - Agent-based models
  - Discrete-event models
- Static models
  - Cohort models: decision trees and Markov models
  - Population static models

In general, cost-effectiveness analyses normally include static models. Static models indirectly assume that the probability of disease exposure is constant over time and unaffected by interventions. This is unrealistic in transmissible infectious diseases like the meningococcal infection. This is due, in part, to the fact that a treatment to control an infectious diseases is commonly linked to externalities, such as mitigating the risks of infection in others member of the population (herd protection). Given that static models do not allow for interactions among individuals in the population, these are not considered the most appropriate models to analyse the effect of a new health treatment on the prevalence rate of an infection disease. This is the case when a vaccination of one individual can lower the risk of disease transmission to other unvaccinated or untreated persons. Therefore, a different class of models is more appropriated. In this regard dynamic models have the capacity to incorporate the externalities resulting from the intervention as well as demographic and biologic characteristics that may change over time.

Dynamic models can intrinsically count for herd protection which influences the disease transmission and is the ideal methodology to assess health benefits of a new vaccine. The drawback is that dynamic models' calibration and related probabilistic sensitivity analysis are extremely complex and computationally intensive. In addition, the required data sources may not be easily accessible (Ultsch et al., 2016). In spite of this limitations, the estimation of a dynamic model to correctly consider herd protection is a valuable investment of time and effort since it substantial improves the accuracy of the results. The importance of herd protection was clearly illustrated by Trotter and Edmunds (2006) in their prediction of the effect of a Men C vaccine on the number of meningococcal disease cases thorough a dynamic model with and a dynamic model without herd protection (FIGURE 3). The herd protection model predictions are closed to the actual number of

cases observed after including the Men C vaccine. While ignoring herd protection leads to around 700 additional meningococcal infections predicted in comparison with the actual number observed (see FIGURE 3). This could considerably affect the cost-effectiveness of meningococcal vaccination.

FIGURE 3. COMPARISON OF THE NUMBER OF CASES PREDICTED BY THE DYNAMIC MODEL WITH THE NUMBER OF CASES OF SEROGROUP C DISEASE



Source: Trotter and Edmunds (2006), Figure 1

In instances in which herd protection could be a decisive factor, as in the case of the meningococcal disease, experts agree on the need for more sophisticated mathematical models (Ultsch et al. (2016) and findings from interviews with experts). As showed above, in the case of the meningococcal vaccination against Men C, herd protection has proved to be an important element in reducing the incidence. In spite of the lack of empirical data, it would be expected that vaccination against other meningococcal serogroups would also affect carriage probability, and therefore the disease incidence.

Despite the importance of dynamic models to measure herd protection, common practice in economic evaluations of meningococcal vaccines is to use a simple static model. This can be clearly observed in the selected sample, where 15 out of 26 economic evaluation use only static models (TABLE 9). Among the 26 economic evaluations, only seven include a dynamic model: two for Men C (Trotter and Edmunds, 2006; Trotter et al., 2006) and five for Men B (Christensen et al., 2013; Christensen et al., 2016; Christensen and Trotter, 2017; Christensen et al., 2014; Hanquet et al., 2014b). Notably only one of these articles concludes that vaccination would *not* be cost-effective: Christensen et al. (2016). However, the authors mention that if the vaccine has an effect on carriage, the number of cases and deaths decrease significantly for those strategies that involve doses for adolescents.

TABLE 9. FULL ECONOMIC EVALUATIONS OF MENINGOCOCCAL VACCINES, BY TYPE OF MATHEMATICAL MODEL APPLIED

	Dynamic	Static	Both	NA/Unclear	Total
Conclusion					
Cost-effective	2	5	0	0	**7**
Not cost-effective	0	4	1	0	**5**
Mixed results†	2	5	2	2	**11**
Unclear	0	1	0	2	**3**
Herd protection					
Considered only in the base case scenario	1	0	2	0	**3**
Tested in the sensitivity analysis	3	7	1	1	**12**
Not considered	0	5	0	1	**6**
NA	0	3	0	2	**5**
Total	**4**	**15**	**3**	**4**	**26**

† Mixed results: Conclusion depends on particular factors. Those articles whose results indicate that vaccination is cost-effective only under a certain price level per dose are included in this category

Herd protection is particularly important for those economic evaluations that include adolescent strategies since carriage prevalence is higher in this age group than in children. Therefore, it is not surprising that a number of sensitivity analyses indicate that the impact of a routine adolescent programme is influenced by how much the vaccine affects carriage (Christensen et al., 2014; Coudeville, 2006; De Wals et al., 2007; Ortega-Sanchez et al., 2008). Nevertheless, herd protection assumptions are also included in economic evaluations that do not include adolescents. Four out of the 15 studies that considered herd protection in the base case scenario or the sensitivity analysis include only doses of meningococcal vaccine to be applied to children. However, among these four studies, only the results of Trotter et al. (2006) are sensitive to changes in the duration of protection against carriage. Trotter et al. (2006) analyse the implementation of three different strategies against serogroup C while the other three studies are related to Men B vaccine (Christensen and Trotter, 2017; Ginsberg et al., 2016; Tu et al., 2014).

Even if the static model does not allow the direct modelling of herd protection, some authors consider herd protection by assuming different values in the sensitivity analysis. Seven economic evaluations include herd effects in their sensitivity analyses (TABLE 9). For instance, Lecocq et al. (2016) adjust the attack rate of those unprotected by vaccination with a herd protection factor that reduces age-specific attack rates. They use evidence, based on UK data, of a 67% reduction of Men C incidence among unvaccinated individuals.

Given that there exists high levels of uncertainty surrounding the novel vaccines recently introduced, carriage protection data available for Men C are used in articles that are based on dynamic as well as those based on static models to approach herd effects. Evaluations of the data collected from the UK immunisation campaign and related to indirect protection (i.e. herd protection) are the most commonly sources of information (De Wals et al., 2007; Ginsberg et al., 2016; Miller and Shahab, 2005; Ortega-Sanchez et al., 2008; Simon et al., 2016; Trotter and Edmunds, 2006). This campaign introduced routine meningococcal serogroup C conjugate vaccination for infants and a catch-up for everyone aged under 18 years (Maiden, Stuart and Group, 2002; Ramsay et al., 2003).

Societal perspective

TABLE 10 reports that a societal perspective for costs is common practice in economic evaluations of meningococcal vaccination strategies (16/26). This means that in addition to the direct medical costs, the economic burden of meningococcal disease on families and patients are taken into consideration, these are referred to as productivity losses (for both patient and family members) and other indirect costs falling on families. The inclusion of such costs in the economic evaluation takes into consideration society needs and preferences during the decision making process.

TABLE 10. CHARACTERISTICS OF THE FULL ECONOMIC EVALUATIONS OF MENINGOCOCCAL VACCINES, BY SEROGROUP TYPE

		Total	Men B	Men C	Men ACYW
Societal perspective included (costs)	Yes	16	9	1	6
	No	6	3	2	1
	NA	4	0	2	2
Productivity losses	Articles that include productivity losses	11	5	1	5
	Patient	4	1	0	3
	Carer/Parent	1	0	1	0
	Both	5	4	0	1
	NA	1	0	0	1

NA: Not available/not reported

In order to demonstrate that a vaccine strategy represents an effective use of public resources, it is key to consider all relevant economic savings (NICE, 2012). An intervention that is not cost-effective based only on medical direct costs could be an effective use of public resources when all related economic benefits that improve the well-being of the population are considered. In this regard, indirect costs are key to demonstrate the value of a preventive intervention such as a new vaccination implementation. Since meningococcal vaccine strategies commonly focus on children or adolescents, indirect costs associated with productivity losses due to care-giving are generally included and calculated using average wage rates (Kauf, 2010). It has been estimated that the indirect costs related to patient productivity losses could be twice the value of direct medical costs when calculated using the human capital approach (Kauf, 2010).

Five out of the 11 articles that considered productivity losses include both patients' and carers' productivity losses (Christensen et al., 2016; Gasparini et al., 2016; Ginsberg et al., 2016; Hepkema et al., 2013; Pouwels et al., 2013). However, the definition of productivity losses varies among the articles. For instance, Pouwels et al. (2013) assume that productivity losses are related to one of the parents taking time off during half the period that the child is in the hospital, while Gasparini et al. (2016) take into account the productivity losses of parents of children with severe sequelae only. de Soarez et al. (2011) include productivity losses for family and carers.

External funders and authors' affiliation

It is of interest to consider the affiliation of authors and sources of funding when critiquing economic evaluations. In TABLE 11 the affiliation of all authors listed is summarised into four categories. It can be seen that research by academics affiliated to universities is central in the development and elaboration of the economic evaluations of meningococcal vaccines. Eleven out of 26 studies have only university-affiliated authors. All articles that assess Men B vaccines have at least one university-affiliated author. There are only five cases without university-affiliated authors, four of which are linked to Men C and one to Men ACYW. These five studies were written by public institutions or

pharmaceutical companies' affiliates, all but one of these five articles were published between 2005 and 2006. This summary should be considered with caution, as it could be the case that not all economic evaluations undertaken by private companies are indexed in the databases used to identify articles (MEDLINE, PubMed and Google Scholar).

Regarding the external funder, 38% of the articles have been supported by public institutions (TABLE 11) such as relevant country's Ministry of Health, the Robert Koch Institute in Germany, Department of Health and the National Institute for Health Research (NIHR) in the UK, the Italian Ministry of University and Research (MIUR) and the Netherlands Vaccine Institute, among others. However, in 14 articles external funders are not reported (14/26). Given the dominance of university academic authors in the literature, this could be explained by academics' time spent on the assessment of vaccines being supported by universities' core funding arrangements. In this regard, nine out of 14 studies include at least one university-affiliated author, four of which have only university-affiliated authors.

TABLE 11. FULL ECONOMIC EVALUATIONS OF MENINGOCOCCAL VACCINES EXTERNAL FUNDERS AND AUTHORS AFFILIATION, BY SEROGROUP TYPE

		Total	Men B	Men C	Men ACYW
Author affiliation†	Pharmaceutical industry	5	1	2	2
	University	20	12	1	7
	Public institution or international organisation	8	4	2	2
	HTA agency	3	2	0	1
External funder	Public funder	10	9	1	0
	Pharmaceutical industry	2	0	0	2
	No funder or not reported	14	3	4	7
	Total number of articles	**26**	**12**	**5**	**9**

† Refers to the affiliation of all authors listed. For instance, an article whose authors have two different affiliation will be counted twice.

TABLE 12 reports further details related to the 31 articles selected, including the 26 economic evaluations.

TABLE 12. CHARACTERISTICS AND MAIN ASSUMPTIONS RELATED TO THE STUDIES IDENTIFIED

Article	Serogroup	Type of article	Country	Cost-effect. Analysis	Cost-effective?	Static/ dynamic	Time horiz. (yrs)	Discount rate*	Are productivity loses considered (no or describe)	Work losses only	Are health utility losses considered	Tools used for estimation of health utility losses
Christensen et al. (2013)	Men B	Journal article	England	yes	Mixed results	Both	100	3.5% years 1-30 / 3% years 31–75 / 2.5% years 76–99	No		Survivors with sequelae (Utility loss value for survivors with sequelae)	Those with sequelae were assumed to have a reduced quality of life (0.2 utility reduction compared to susceptible individuals, and survivors of disease without sequelae.
Pouwels et al. (2013)	Men B	Journal article	Netherlands	yes	Mixed results	Static	Lifetime	4% costs 1.5% health benefits	Work loss: For children less than 15 years of age, it is assumed that one parent took time off during half of the period that the child is in hospital. For patients older than 15 years it is assumed they would miss the total duration of hospitalisation plus one day.	Yes	Survivors with sequelae (QALYs for specific diseases/ disabilities)	Specific QALY losses were assigned to each health state on a scale ranging from 0 (immediate death) to 1 (a state of perfect health). QALY losses associated with acute forms of disease or minor vaccine-related adverse events excluded
Christensen et al. (2014)	Men B	Journal article	England	yes	Mixed results	Dynamic	100	3.5% (Sc. 1.5%)	No		Acute episode and survivors with sequelae (Utility loss value for survivors with sequelae)	QALY losses during the acute disease episode estimated from a recent Public Health England study using EQ-5D-Y in children up to a year after the illness. Long term reductions in quality of life for survivors with sequelae.
Hanquet et al. (2014b)	Men B	Report	Belgium	yes	Mixed results	Both	Lifetime	3% costs and 1.5% health benefits (Sc. 3% for both)	No		Survivors with sequelae (Utility loss value for survivors with sequelae)	Evidence on quality of life measures based on a systematic review of the literature. Following criteria applied to the 17 studies identified: (1) Health states described with a generic descriptive instrument (EQ-5D strongly recommended). (2) Health state description made by patients as much as possible (no possible for small children). (3) HU losses specific to Men B diseases. Only one suitable study (MOSAIC) that reports utility decrement of 0.074, which is used for survivors with any sequelae.
Tu et al. (2014)	Men B	Journal article	Canada	yes	no	Static	Lifetime	5% and 3%	No		Acute episode and survivors with sequelae (Utility loss value for survivors with sequelae+ HU losses for caregivers included)	QALYs: Utility weights for acute meningococcal infection and long-term sequelae. Death was assigned a utility score of 0. Scenario analysis: quality of life loss of caregivers was applied to all Men B cases experiencing major sequelae regardless of age.

Article	Serogroup	Type of article	Country	Cost-effect. Analysis	Cost-effective?	Static/ dynamic	Time horiz. (yrs)	Discount rate*	Are productivity loses considered (no or describe)	Work losses only	Are health utility losses considered	Tools used for estimation of health utility losses
Izquierdo et al. (2015)	Men B	Journal article	Chile	yes	Mixed results		NA	6%	Productive years lost due to mortality multiplied by the average annual salary accounted for a mean indirect cost due to early MD associated death	No	Not included	
Tirani et al. (2015)	Men B	Journal article	Italy	yes	no	Static	100	3% (Sc. 0% and 1.5%)	No		Survivors with sequelae (QALYs for specific diseases/ disabilities)	
Christensen et al. (2016)	Men B	Journal article	Germany	yes	no	Both	100	3%	Costs due to loss of work considered in the scenarios. Cases with an amputation would result in a 50% work loss over their lifetime.	Yes	Acute episode and survivors with sequelae (Utility loss value for survivors with sequelae + HU losses for caregivers included)	Upon disease, QALY losses for the acute episode were included. Losses for carers of a person with sequelae were also considered.
Gasparini et al. (2016)	Men B	Journal article	Italy	yes	Mixed results	Static	Lifetime	3%	Productivity loss of the patient's parents or relatives. Patient: only considered cases during working age. Additional cost for parent in cases of severe complications: mental retardation, severe neurological disability, severe speech or communication problems, epilepsy, blindness, motor deficit, severe amputations and hearing loss.	No	Survivors with sequelae (QALYs for specific diseases/ disabilities)	QALYs loss of survivors with long-term sequelae. Sometimes quality of life evaluations for sequelae or pathologies similar to those caused by meningitis are used.
Ginsberg et al. (2016)	Men B	Journal article	Israel	yes	yes	Static	100	3%	Work losses are considered for the acute episode and for survivors with sequelae	Yes	Not included	
Lecocq et al. (2016)	Men B	Journal article	France	yes	no	Static	100	4% first 30 years, and 2% progressive decrease	No		Acute episode and survivors with sequelae (QALYs for specific diseases/ disabilities)	QALYs related to acute bacterial meningitides and acute septicaemia. QALYs estimated using EQ-5D in accordance with French guidelines.
Christensen and Trotter (2017)	Men B	Journal article	England	yes	Mixed results	Dynamic	100	3.5% (Sc. 1.5%)	No		Acute episode and survivors with sequelae (Utility loss value for survivors with sequelae + HU losses for caregivers included)	Not reported, but assumed to be equal to the previous version of the model: QALY losses during the acute disease episode estimated from a recent Public Health England study using EQ-5D-Y in children up to a year after the illness. Long term reductions in quality of life for survivors with sequelae.

Article	Serogroup	Type of article	Country	Cost-effect. Analysis	Cost-effective?	Static/ dynamic	Time horiz. (yrs)	Discount rate*	Are productivity loses considered (no or describe)	Work losses only	Are health utility losses considered	Tools used for estimation of health utility losses
Welte et al. (2005)	Men C	Journal article		Review								
Carroll et al. (2006)	Serogroup unspecified	Poster	Germany	yes	yes	Static	NA				Not included	
Trotter and Edmunds (2006)	Men C	Journal article	England and Wales	yes	yes	Dynamic	NA	3%	No		Survivors with sequelae (Utility loss value for survivors with sequelae)	QALY gain estimated using previously published health-related quality-of-life reductions of 0.282 for survivors with sequelae
Trotter et al. (2006)	Men C	Journal article	England and Wales	yes	yes	Dynamic	NA	3.50%	No		Survivors with sequelae (Utility loss value for survivors with sequelae)	
de Soarez et al. (2011)	Men C	Journal article	Brazil	yes	yes	Static	10	0% (Sec.5% to 10%)	Work time lost by mothers of children acutely ill with MD or with neurological sequelae. The analysis followed children from 0 to 10 years old and added the costs of lost productivity by parents caring for their children with sequelae until 10 years of age. Costs of lost productivity of patients with sequelae in adulthood were not included.	No	Not included	
Gravatt (2013)	Men C	Journal article	New Zealand	yes	Mixed results	Unclear	NA				Survivors with sequelae (QALYs for specific diseases/ disabilities)	
Colombini et al. (2015)	Men A	Journal article	Burkina Faso	cost-of-illness	cost-saving	Dynamic	26	0% (Sc. 3% both and 3% for costs)	Loss of income due to a temporary work interruption, calculated by multiplying the average number of days of illness by the daily per capita GDP (1 adult per case affected)	Yes	Not included	
Shepard et al. (2005)	Men ACYW	Journal article	USA	yes	Unclear	Static	Lifetime	3%	Age-specific estimates of productivity losses due to death based on average wages and the value of unpaid labour to calculate the economic value of life lost. For survivors with neurologic disability: productivity losses equivalent to the projected	No	Survivors with sequelae (QALYs for specific diseases/ disabilities)	QALYs survivors with long-term sequelae. QALYs lost: multiplying the years of life remaining with each long-term sequela by the sequela-specific health-utility rate. Health-utility rates for conditions closely resembling each of the 5 long-term sequelae in the model are used.

Article	Serogroup	Type of article	Country	Cost-effect. Analysis	Cost-effective?	Static/ dynamic	Time horiz. (yrs)	Discount rate*	Are productivity loses considered (no or describe)	Work losses only	Are health utility losses considered	Tools used for estimation of health utility losses
									labour market earnings only. Persons with multiple amputations 30% lost of lifetime labour market earnings, persons with hearing loss 33%			
Coudeville (2006)	Men ACYW	News	USA	yes	unclear						Included, category unclear	
De Wals et al. (2007)	Men ACYW	Journal article	Canada	yes	yes	Static	Lifetime	3% (Sc. 0% and 5%)	Sick leave of working adults developing meningitis, assumed to last on average 18.6 days. Sequelae impact on productivity and other long-term indirect costs related to productivity losses in case of death	No	Survivors with sequelae (Utility loss value for survivors with sequelae)	Age-specific health utilities in the absence of long-term sequelae based on reported EQ-5D preference scores. Average utility loss for adults affected by long-term sequelae was estimated to be 0.263. Individuals under the age of 18 years: a large study on outcomes of invasive disease in children was combined with complication-matched utility losses for each type of complication giving an average loss of 0.280.
Suh and Hay (2007)	Men ACYW	Poster	USA	yes	yes	Static		3%			Included, category unclear	
Ortega-Sanchez et al. (2008)	Men ACYW	Journal article	USA	yes	Mixed results	Static	Lifetime	3%	Value of work time lost for invasive meningococcal disease	Yes	Survivors with sequelae (QALYs for specific diseases/ disabilities)	QALYs among survivors with long-term sequelae. Outcome-related QALY saved is based on EQ-5D (skin scarring/upper-bound amputation), HUI (lower-bound amputations/hearing loss for death children), SF-36. HUI-2 (post-cochlear implant), and HUI-3 (neurologic disability)
Cognet et al. (2012)	Men ACYW	Poster	Canada	cost-consequence	unclear			5% costs	Accounts for the productivity lost from IMD and its sequelae	Unclear	Not included	
Castañeda-Orjuela et al. (2013)	Men ACYW	Poster	Colombia	yes	no	Static	Lifetime				Not included	
Hepkema et al. (2013)	Men ACYW	Journal article	Netherlands	yes	Mixed results	Static	Lifetime	4% costs 1.5% health benefits	Productivity losses due to vaccination and side effects are included	Unclear	Survivors with sequelae (QALYs for specific diseases /disabilities)	Losses due to permanent sequelae. QALY losses associated with acute disease or minor vaccine-related adverse events not considered.
Simon et al. (2016)	Men ACYW	Journal article	USA	yes	Mixed results	Static	Lifetime	3%	No		Included, category unclear	
Miller and Shahab (2005)	Serogroup unspecified	Journal article		Review								
Kauf (2010)	Serogroup unspecified	Journal article	Developed countries	Review								
Zakzuk et al. (2016)	Serogroup unspecified	Poster		Review								

†Sc. = Studies tested alternative discount rates during the sensitivity analysis

3.2 Mapping the methodology for HTA of vaccines

In the previous section, we analysed the methodologies and assumptions considered in the recent literature on economic evaluations of meningococcal vaccines. In this section, we explore whether those findings reflect the current methodologies and processes followed by agencies responsible for issuing recommendations regarding the inclusion of a new vaccine on their countries' positive list and/or on the national immunisation plan.

We selected a group of countries of interest (as agreed with Pfizer) to further explore the current decision making processes for vaccines and the factors driving the recommendations of committees and agencies based on HTA studies. One of the most recent vaccine against meningococcal infection approved by the European Medicines Agency (EMA) is the Men B vaccine (EMA, 2013). The novelty of the Men B vaccine is reflected in the high levels of uncertainty surrounding a number of parameters that are central to the economic evaluation, such as the effect on carriage, duration of the protection and strain coverage. Consequently, the methodology and assumptions used could have a considerable impact on the recommendations based on the HTA evaluation. Therefore, we are particularly interested in analysing those countries for which economic evaluations of meningococcal vaccines against serogroup B exist. With this in mind, a group of countries were selected: France, Germany, Italy, New Zealand and the Netherlands. In addition, we also included two countries whose evidence base and decision making processes are known to have been rapidly evolving: Australia and Japan.

Sub-section **Error! Reference source not found.** compares the various countries' decision making p rocesses for the approval of new vaccines, and the methodologies and assumptions commonly applied. Note that most of the information presented in sub-section **Error! Reference source not f ound.** were collected during interviews with experts. Additional information extracted from publication to support the experts' views include the relevant reference.

3.2.1 Main characteristics of the decision process for the inclusion of new health treatment, particularly vaccines, by country

Australia

The State Governments are responsible for ensuring the provision of health care in their regions, including vaccines. However, the responsibility of purchasing the vaccines included in the National Immunisation Program is of the Department of Health (Sussex, Shah and Butler, 2010).

When preparing a submission for consideration manufacturers (or sponsors) must indicate whether they want their product to be included in the National Immunisation Program or in the Pharmaceutical Benefits Scheme (PBS). The Pharmaceutical Benefits Advisory Committee (PBAC) is responsible for assessing the manufacturer submission and advises the Department of Health on whether to list the vaccine in the PBS or to include the vaccine in the National Immunisation Schedule (Sussex et al., 2010).

Vaccines considered for inclusion in the National Immunisation Program are expected to offer an additional health benefit to society beyond the individuals vaccinated. Specific criteria considered for inclusion in the National Immunisation Program are: (1) the individual-level risk factor assessment is straightforward; (2) there is good reason for maximising population coverage of the vaccine reduction (e.g. disease burden); (3) the vaccine protects against a new infection or reactivation of an existing infection; (4) there are likely to be advantages of increasing herd protection (Nolan, 2010).

PBS listing, on the other hand, might be favoured in cases where the vaccine is considered discretionary for the majority of the population, or where the assessment of risk factors is less straightforward (Sussex et al., 2010).

The same PBAC guideline applies to all pharmaceutical products, including vaccines. The guideline includes a specific subsection for vaccines (Australian Department of Health 2016). Some of the required information includes:

- Proposed schedule of administration of the vaccine and any consequential programmatic requirements for administration
- Information about funding, restrictions and catch-up programmes
- Economic Evaluation:
    - To explain whether herd activity or community activity influence the time horizon of the model. Detail whether the model is static or dynamic, and whether joint analysis is relevant.
    - Define the relevant Australian population(s) for the model.
    - Present a systematic review to support key variables associated with effectiveness, such as waning and the duration of vaccine effectiveness, and any herd protection implications.
    - Transform immunogenicity outcomes to patient-relevant outcomes. Include any regulatory standards for immunogenicity outcomes that would inform the transformation of these surrogate outcomes.
    - Include additional vaccine programme resource use and costs.
    - Ensure that the model validation process has attempted to validate the duration of vaccine effectiveness and any herd protection assumptions.
    - Include sensitivity analyses of alternative discounting approaches and scenario analyses of potential vaccination catch-up programmes.

During the interview, we collected information in whether the decision-makers are usually aware of the uncertainty surrounding the economic evaluation results. In the case of Australia, uncertainty is clearly considered in the final decision. The quality of the evidence is carefully assessed and uncertainty is required to be characterised and presented in the evaluation process.

TABLE 13. AUSTRALIA MAIN CHARACTERISTICS

Variable	Characteristic
National Committee on Immunisations	The National Immunisation Committee (NIC)
Role	It is responsible for the implementation, delivery and overseeing of the immunisation programme. Although the vaccines in the National Immunisation Plan are the main focus and priority of the NIC, this does not preclude consideration of implementation issues for other vaccines. The NIC consults and collaborates with stakeholders and other committees in the development of national immunisation priorities, strategies and service delivery.
Where does it sit?	The NIC works together with, but is independent from the Department of Health.
HTA	Required by the Pharmaceutical Benefits Advisory Committee (PBAC)
Who undertakes the HTA for vaccines?	The assessment is undertaken by PBAC, who make a recommendation for the Department of Health. The PBAC is an independent expert body appointed by the Australian Government. No new medicine can be listed unless the committee makes a positive recommendation. There is an additional PBAC committee the Economic Sub-Committee (ESC) that reviews and interprets economic analyses of technologies submitted to the PBAC. PBAC sends the manufacturer submission to an independent group (such as academic health economics departments) who assess the dossier. These groups prepare comments and recommendations for the PBAC and the ESC. Additionally, the Australian Technical Advisory Group on Immunisation (ATAGI) provides advice to the Department of Health on the National Immunisation Program and other related issues. Their membership comprises mainly medical and public health experts. This committee advises the PBAC on existing, new and emerging vaccines in relation to their effectiveness and use in Australian populations. ATAGI provides pre-PBAC advice to companies on their applications, and clinical advice to PBAC, in particular relating the suitability of including a particular vaccine in the National Immunisation Program and the appropriateness of implementing catch-up programmes.
Final decision-maker for vaccine reimbursement	Department of Health
Final decision national or regional level?	National
What is the ultimate outcome of the assessment of a new vaccine?	The Department of Health could decide not to recommend a new drug that has a positive recommendation from the PBAC, meaning that the recommendations are not binding. However, the government cannot fund a vaccine without a positive recommendation from the PBAC.

Source: Experts interviews

France

Vaccination policy is developed by the Ministry of Health who establishes the immunisation conditions, sets forth necessary guidelines, and publishes immunisation schedules after a recommendation from the Technical Vaccination Committee (CTV) (Chevreul et al., 2015). The main tasks of the CTV are to develop the immunisation strategy and advise on new vaccines.

The CTV select the vaccines that are going to be considered based on suggestions from different stakeholders, such as the Ministry of Health and pharmaceutical companies. The manufacturer can submit a dossier to the CTV of any vaccine that has market authorisation. The CTV can also suggest recommendations on issues that they considered relevant (Floret and Deutsch, 2010).

Currently, most CTV investigations consist of pharmaco-epidemiological studies, disease modelling and assessing of vaccination strategies. Although it is not required that CTV takes into account vaccine cost, programme cost, affordability and/or financial sustainability, if the CTV considers necessary, it can contract experts to conduct full economic analyses (Floret and Deutsch, 2010). Economic analyses were taken for the recommendations of vaccinations against rotavirus, human papilloma virus (HPV) and meningococcus C. In each case a cost-benefit analysis was carried out using high and low price estimates of the vaccines. The cost-effectiveness of a vaccine is considered in decision making but only to inform price negotiations (so its impact is marginal), not to determine whether a technology is reimbursed. Note that before 2013, economic evaluations in France were conducted for vaccines but not for pharmaceuticals.

Previously the CTV was part of the Haut Conseil de la Santé Publique (High Council for Public Health or HCSP). Recently, the Minister of Social Affairs and Health decided to transfer the CTV from the HCSP to the High Authority of Health (HAS). In this context, and at the request of the Minister, the HCSP has set up a working group to make proposals on the evolution of CTV within the framework of the High Authority for Health (HAS). Some of the recommendations of the working group are: (1) the CTV remains a permanent and well-identified structure within the HAS with specific missions; (2) a multidisciplinary composition in order to take into account all the necessary dimensions and involving the other institutions; (3) an organisation to respond to urgent referrals; (4) linkage with the other HAS structures involved in vaccine evaluation; (5) maintaining the possibility of self-referral in order to anticipate and respond to possible public health issues; (6) the improvement of the quality of expertise; (7) the transparency of the work and the links with pharmaceutical companies; (8) the structuring of procedures enabling the conduct of economic evaluations (HCSP, 2016).

TABLE 14. FRANCE MAIN CHARACTERISTICS

Variable	Characteristic
National Committee on Immunisations	Technical Vaccination Committee (CTV) (Comité Technique des Vaccinations)
Role	The committee functions as an independent expert advisory committee. Its role includes: evaluating scientific information on advances and perspectives in vaccination; developing vaccination strategies based on applicable epidemiological data; conducting risk-benefit analyses (individual and population) and health economics studies on measures under consideration; and proposing changes to vaccine guidelines and making recommendations for immunisation schedule updates.
Where does it sit?	It was part of the Committee for Transmissible Diseases (CSMT) (Commission spécialisée des Maladies Transmissibles) which is part of the HCSP. Currently, it is in the process to be transfer to HAS.
HTA	Requested for the recommendations
Who undertakes the HTA for vaccines?	- Technical Vaccination Committee (CTV): When a submission o referral is received, the CTV establishes a working group to assess the topic. Certain working groups, such as those working on meningococcus and influenza, are permanent. The working group synthesises the data collected, elaborates a report and drafts the recommendations. These recommendations are discussed by the wider CTV that decides on the final recommendation. - HAS (Haute Autorité de Santé): After CTV recommends a new vaccine, the Commission for Transparency, which is a part of HAS, evaluates the impact of its administration on public health services. This evaluation will be used to negotiate vaccine's price and to determine the level of reimbursement, which is normally 65%. After this, the Ministry of Health decides whether or not the

	recommended vaccine will be integrated into the national immunisation schedule.
Final decision-maker for vaccine reimbursement	Ministry of Health
Final decision national or regional level?	National level
What is the ultimate outcome of the assessment of a new vaccine?	No binding recommendations

Source: Experts interviews

Germany

The organisation of immunisation is under the responsibility of the individual social health insurances and the state ministries of health and municipality health authorities. The decision to include a vaccination in the mandatory service of statutory health insurances (GKV) is the concern of the Federal Joint Committee (G-BA). Since 2007 vaccinations have been part of the GKV, previously there had only been a voluntary service according to the optional benefit package of the particular health insurance funds (Droeschel et al., 2015).

The inclusion of a vaccinations in the positive list is a two-tier process distinguishing between the appraisal at a national level and the proof of eligibility for reimbursement at a regional level. Standing Committee on Vaccination (STIKO) conducts the appraisal and makes a recommendations. Based on this recommendation the G-BA updates and includes the vaccination directive by specifying the details of the GKV's obligation to render service details of the type and scope of the vaccination. On the basis of the G-BA statement, the regional health insurances negotiate and contract prices based on the manufacturers price less discounts and rebates and including the agreements with different health authorities on state and municipality level (Droeschel et al., 2015; STIKO, 2016c).

The inclusion of a vaccination in the GKV service catalogue requires a STIKO's recommendation. STIKO considers mainly the risk-benefit assessment to development a vaccination recommendation. It evaluates individual risks and benefits, risks and benefits at the population level (e.g. herd protection, the possibility of eliminating a disease if high vaccination coverage is achieved, potential pathogen replacement phenomena, or likely shifts in the age distribution of cases acquiring the targeted disease if a vaccination programme is implemented). Economic evaluations are currently not routinely required for vaccine inclusion, but can be economic considerations can be taken into account in the decision-making process (Droeschel et al., 2015; STIKO, 2016a; c).

In 2016 a guideline to define the minimum requirements for an economic evaluation to be considered in decision-making process of STIKO was published (STIKO, 2016b). The guidelines states that, because there is not a willingness-to-pay threshold for ICERs in Germany, the economic evaluation results are considered in an 'informal assessment'. When the risk-benefit assessment (which may consider results from the epidemiological-mathematical models) is positive regarding the inclusion of the new vaccine, the most efficient vaccination strategy could be identified based on the results from the economic evaluation where the ICER indicates the most efficient vaccination strategy. Nevertheless, STIKO decisions give priority to the risk-benefit assessment that includes number needed to vaccinate, the total number of health outcomes that can be prevented, or adverse effects of the vaccination (STIKO, 2016a; b).

During the interview, we collected information in whether the decision-makers are usually aware of the uncertainty surrounding the economic evaluation results. In the case of Germany, STIKO is fully aware of parameter uncertainty and their report includes details of meta-analyses, one-way sensitivity analyses, probabilistic sensitivity analyses and scenario analyses. However, the G-BA is generally not aware of uncertainty in the estimation of the economic evaluation findings.

TABLE 15. GERMANY MAIN CHARACTERISTICS

Variable	Characteristic
National Committee on Immunisations	Standing Committee on Vaccination (STIKO)
Role	STIKO develops the national immunisation schedule and presents an updated version usually once a year in the Epidemiological Bulletin of the Robert Koch Institute. STIKO also recommends vaccinations for specific indications or target groups. The inclusion of a vaccination in the GKV service catalogue requires a recommendation by STIKO. It is a group of experts, mainly physicians and epidemiologists. There are currently 17 members, appointed on three-year terms. The STIKO meets between two and four times per year.
Where does it sit?	It is located at the Robert Koch Institute (RKI) in Berlin – this is the government's central scientific institution in the field of biomedicine.
HTA	New vaccines undergo a risk-benefit assessment. It is not formally called HTA but includes several elements similar to HTA – e.g. systematic review, meta-analysis and mathematical modelling of long-term consequences.
Who undertakes the HTA for vaccines?	It is not conducted by typical HTA organisations in Germany. Normally the assessment is led by scientific researchers at RKI, advised by STIKO members. Sometimes external organisations – e.g. universities – are commissioned to contribute modelling work. Manufacturers not usually invited to contribute analyses, but they occasionally have the opportunity to present new data on their vaccines to the RKI (but not directly to STIKO members).
Final decision-maker for vaccine reimbursement	G-BA is the final decision-maker, but in reality it tends to approve STIKO recommendations without changes.
Final decision national or regional level?	National
What is the ultimate outcome of the assessment of a new vaccine?	Outcome is often described as binding but in fact is a recommendation – the first step to getting reimbursed. After the STIKO has published its recommendation, the G-BA needs to approve the recommendation in order for the vaccine to be covered by the health insurance funds. Only then does it become binding.

Source: Experts interviews

Italy

Italy has a national health service that is highly decentralised. The local authorities are responsible for the organisation of the health care system. The national government retains only limited coordinating and supervisory powers. While responsibility for the elaboration of the main guidelines is at the national level, the main decisions are taken regionally by each federal state. National Ministry of Health decisions can be seen as non-binding recommendations to the local authorities. Therefore, decisions on the inclusion of health technologies could differ among regions not only because of epidemiological factors, but also because differences in budget constraints.

In this context, HTA activities have been expanding, and are untargeted and uncoordinated, and without priorities. However, the regional governments have become more sensitive to the need to apply clinical- and cost-effectiveness criteria and to be more rigorous in deciding which services to guarantee (France, 2000; Favaretti et al., 2009).

Regarding the decision making process for vaccines, the National Vaccine Prevention Plan (PNPV) is the guidance document issued by the Ministry of Health that establishes immunisation recommendations at the national level and sets national coverage targets with the overall aim of harmonising immunisation strategies among Italian regions (Consiglio Superiore di Sanità, 2015). However, given that service delivery and management are the responsibility of the regional institutions, the final decisions for vaccine inclusion are the responsibility of the local health authorities, which analyses the possibility of inclusion of a recommended vaccine. This leads to differences in reimbursement levels and specific vaccines offered between regions. For instance, among those regions that have adopted Men B vaccine, some offer the vaccine free of charge while others offer the vaccine with a co-payment. In addition, there is variation between regions in terms of coverage level – a number of regions have not achieved the uptake objectives proposed by the PNPV (Curto, Duranti and Garattini, 2013).

The most recent PNPV for the period 2017-19 will soon be subjected to a vote in the 'State-Regions conference'. This new plan introduces vaccines for meningococcal B for children in their first year of life (three months old) (Bocci, 2017).

TABLE 16. ITALY MAIN CHARACTERISTICS

Variable	Characteristic
National Committee on Immunisations	Istituto Superiore di Sanità
Role	- Assesses new vaccines and elaborates recommendations that are considered by the regions for their particular immunisation plan. - Provides certification for the chemical and biological purity of drugs and vaccines.
Where does it sit?	A technical research institute under the control of the Ministry of Health
HTA	HTA is mandatory for each new health technology to be introduced. Results of the HTA are not binding.
Who undertakes the HTA for vaccines?	National level: Agenas (The National Agency for Regional Health Services). - Agenas has only a limited number of professionals. Therefore, in many cases HTA is undertaken by academic departments. - Assessments from the industry could also be considered. Regional level: Each region must develop its own HTA, This is normally a short report and not a full analysis that considers the work done at the national level.
Final decision-maker for vaccine reimbursement	Ministry of Health through the Istituto Superiore di Sanità. The Ministry decides on the inclusion of vaccines in the National Plan of Vaccination.
Final decision national or regional level?	Regional
What is the ultimate outcome of the assessment of a new vaccine?	The HTA analysis in all regions is mandatory, but is not binding.

Source: Experts interviews

Despite these differences, the PNPV determines the ages at which the vaccines are offered to the Italian population. Moreover, since 2012 some vaccines are included in the Livelli Essenziali di Assistenza (LEA). The LEA is a list that defines the essential levels of care and is established by the Ministry of Health. The 21 regional health agencies (Agenzia Sanitaria Regionale (ASR)) must guarantee the provision of treatments listed in the LEA free of charge or with cost sharing, using the resources collected through general taxation.

The Italian guidelines identifies cost-effectiveness analysis and QALYs as the main elements to form the basis for the economic evaluation. Economic evaluations should be based on the principles of methodological rigor, feasibility (given methodological rigor, not all programmes are feasible in terms of time and investment) and utility to public bodies (Fattore, 2009). In order to ensure comparability across regions and countries, economic evaluations should follow the reference case, similar to that of NICE in England. The guidelines also points out that currently there is no range of acceptance for cost-effectiveness (Fattore, 2009).

Note that in July 2017 the national authority in Italy became the main decision maker.

Japan

The Ministry of Health, Labor, and Welfare (MHLW), in coordination with the Pharmaceuticals and Medical Devices Agency (PMDA), is responsible for the regulation of pharmaceutical products, including vaccines. The immunisation system have two standard categories: routine recommended (also called regular vaccines) and voluntary vaccination. According to current policy, local governments receive annual allocations from the central government to provide health care services to their residents, including the purchasing and administrating of the routine vaccines which are offered at no or a negligible cost (Doshi and Akabayashi, 2010). However, while routine vaccination was once mandatory in Japan, since 1994 citizens are obliged to make efforts to vaccinate, vaccination itself is no longer mandatory. Moreover, mass vaccination was replaced in 1994 by private vaccination, because of the idea that it is better that vaccinations are performed by children's family doctors who are familiar with their health conditions (Nakayama, 2013).

The main difference between voluntary vaccination and routine recommended vaccination is that routine recommended vaccines are principally covered by the regional government and patients have to take the vaccine at a timing specified by the government (Nakayama, 2013). In the case of voluntary vaccination, the person can take the vaccine on a voluntary basis (e.g. meningococcal) and the full cost must be borne by the recipient.

In the past the MHLW policy was to use only domestically manufactured vaccines to protect domestic manufacturers from international competitors. This policy resulted in a significant vaccine lag (Tanimoto, 2015). For instance, Shimazawa and Ikeda (2012) analysed approval and immunisation programme data from Japan and the UK for 20 common vaccines, all were approved in the English NHS but only four vaccines were approved by the MHLW. This problem was addressed in 2013 throughout a partial amendment of Japan's Immunisation Law. Before 2013, the only vaccines covered by the routine vaccination programme were diphtheria, pertussis, polio, measles, rubella, Japanese encephalitis, tetanus, tuberculosis, and influenza for the elderly. After 2013, the coverage were extended to a number of other vaccines such as Haemophilus influenzae type B, child pneumococcus, HPV, varicella, and adult pneumococcus vaccines (Akazawa et al., 2014).

An additional important change in the Japan policy-making process occurred in 2009, after the recommendations of the Infectious Disease Sectional Committee, with a governmental decision to commission economic evaluations for vaccine inclusion (Akazawa et al., 2014). It began in August 2010 with the appointment of eight working groups comprised of infectious disease specialists, clinicians, epidemiologists and health economists to conduct assessments of the two routine (pertussis and polio) and seven voluntary vaccines (Hib, PCV for children and adults, HPV, varicella, mumps, and hepatitis B).

According to Akazawa et al. (2014), in the decision making process for vaccine inclusion in Japan there is still a need to address topics such as the high influence of external pressures on the adoption decision, the choice of evaluation methods and the formalisation of the use of cost-effectiveness analyses.

TABLE 17. JAPAN MAIN CHARACTERISTICS

Variable	Characteristic
National Committee on Immunisations	The immunisation committee is the Health Sciences Council
Role	Most national-level decisions are made by a committee in the Pharmaceuticals and Medical Devices Agency (PMDA) (a government-associated body similar to NICE). It plays a role in approval and pricing decisions. The immunisation committee takes responsibility for vaccines approved by the PMDA. PMDA activities include the assessment of side effects, efficacy, post-marketing approval assessments and cost-effectiveness analysis.
Where does it sit?	Sits within the Ministry of Health, Labour and Welfare (MHLW)
HTA	PMDA and the Health Science Council consider HTA in the decision making process. PMDA uses two categories when industry applies for approval – routine/regular and voluntary vaccination
Who undertakes the HTA for vaccines?	If HTA refers to assessment of safety, quality and efficacy, then the PMDA can be said to be the first body to conduct HTA for vaccines. Cost-effectiveness is considered by the Health Sciences Council only.
Final decision-maker for vaccine reimbursement	For regular vaccines, local government/insurance officers make decisions about reimbursement but there is no inclusion on the national programme. For voluntary vaccines, the price is freely determined by the industry with no public reimbursement (though local government can occasionally provide financial support). Industry consults PMDA and agrees a price based on informal negotiation.
Final decision national or regional level?	National
What is the ultimate outcome of the assessment of a new vaccine?	The outcome is a binding recommendation to the Minister of Health, Labour and Welfare (who is the final decision maker). So the committees ultimately work for the minister.

Source: Experts interviews

New Zealand

The Pharmaceutical Management Agency (PHARMAC) is the New Zealand government agency that decides which pharmaceuticals to publicly fund in New Zealand. PHARMAC has grouped the criteria that are considered in the decision into four main dimensions: (1) need, (2) health benefits, (3) costs and savings and (4) suitability. There are also three levels of impact that are taken into account: (1) to the person, (2) to the wider health sector, and (3) to family/whanau/wider society.[2] The factors are not weighted or applied rigidly, and not every factor is relevant for every funding decision. This is because the situation for one assessment may require quite different considerations compared with another. Funding decisions are made relative to other options, and the context within which decisions are made is constantly changing.

The guidelines for conducting cost-utility analysis also apply to the case of vaccine. However, there is a particular chapter in the guidelines that states the additional information that should be considered as well as adjustments to apply when modelling vaccine efficacy (PHARMAC, 2015). Some of the considerations mentioned for vaccines are: (1) degree of protection and length of protection, (2) age at administration, (3) adherence with the vaccination schedule (compliance and time between

[2] *A whanau is an extended family or community of related families who live together in the same area.*

doses), (4) adverse reactions, (5) potential loss of potency (e.g. due to heat and cold exposure) which only needs to be considered if relevant data are available, and (6) herd protection.

TABLE 18. NEW ZEALAND MAIN CHARACTERISTICS

Variable	Characteristic
National Committee on Immunisations	Immunisation Advisory Centre
Role	Advisory and educational, not operational
Where does it sit?	Independent of the Ministry of Health.
HTA	
Who undertakes the HTA for vaccines?	The manufacturer (and/or their consultant) presents the clinical and economic case to PHARMAC, which reports directly to the Minister of Health. After a positive decision, the Ministry of Health operationalises the immunisation programmes
Final decision-maker for vaccine reimbursement	National level
Final decision national or regional level?	The Minister of Health, advised by PHARMAC
What is the ultimate outcome of the assessment of a new vaccine?	Consideration of affordability compared to other vaccines and pharmaceuticals; when funding is made available from PHARMAC's capped budget, a binding recommendation to the Ministry of Health, which operationalises the immunisation programme.

Source: Experts interviews

The Netherlands

The Ministry of Health is the institution that decides on the final inclusion of a new vaccine on the national immunisation plan and/or the positive list. A sub-committee of the Health Council makes recommendations regarding the inclusion a new vaccines on the national immunisation plan. Regarding the inclusion in the positive list, the recommendation and analysis is undertaken by the drug committee, which is responsible for the assessment of all new medicines. It is possible for a vaccine rejected by the Health Council to be submitted to the drug committee (e.g. rotavirus vaccine). However, there has not yet been a case in which the decisions of the two committees differ from each other. Currently, a new initiative has just been put in place for vaccines to have a joint assessment and recommendation from both committees, the Health Council and the drug committee.

The prioritisation of the vaccines to be assessed by the Health Council is conducted by the Ministry of Health based on the priorities of the country. Factors such as disease burden and severity are the main factors in defining the health priorities. However, pressure from stakeholders also have a significant influence. Opinions from the parliament, lobbyists and the media are considered by the Ministry in determining the priorities. Regarding the positive list, the drugs committee evaluates all dossiers submitted by the manufacturers, meaning that there is no prioritisation.

Concerning the decision making process, it is worth highlighting that the recommendations of the drug committee and the Health Council include a statement on the level of uncertainty of the results of the HTA. This is based on the results of the sensitivity analyses (deterministic and probabilistic sensitivity analysis) and the scenario analyses. They conclude on how parameter uncertainty, that are

always present, translate to important uncertainties on the outcomes or whether the outcome is robust with respect to changes in the parameters. If there is uncertainty the vaccine is not introduce.

Notably vaccine evaluations follow the same guidelines as drugs, including the recent broadening of the societal perspective: previously productivity effects and costs of travel to hospitals were included, now it also covers caregiver impacts and unrelated future costs.

TABLE 19. THE NETHERLANDS MAIN CHARACTERISTICS

Variable	Characteristic
National Committee on Immunisations	- Sub-committee of the Health Council advises the Ministry of Health on the National Immunisation Plan - The drug committee makes recommendations on vaccines to be included in the positive list
Role	The Health Council provides the Ministry of Health with independent 'state of the art' advice regarding the National Immunisation Plan
Where does it sit?	The Health Council is sited in the Ministry of Health, but it is independent
HTA	HTA analysis is used by the Health Council and the drugs committee to inform recommendations on vaccine reimbursement
Who undertakes the HTA for vaccines?	National Immunisation Plan: The Health Council requires two separate independent HTAs: - The first is undertaken by the National Institution for Public Health and Environment (RIVM), which is a research institute independent of the Ministry of Health. RIVM informs Health Council and Ministry of Health on the possible impact of a vaccine through surveillance, modelling, scenario analysis, cost-effectiveness studies - The second assessment is normally undertaken by a university. Ideally the Health Council looks for an independent assessment. However, the assessment is in a number of cases founded by a pharmaceutical company Drug committee: One HTA, which is prepared by the manufacturer. Under the new initiative, with a single joint assessment from the Health Council and the drug committee, only two HTAs will be required: (1) National Institution of Public Health and Environment, and (2) manufacturer
Final decision-maker for vaccine reimbursement	Ministry of Health decides on both the vaccines that are going to be included in the immunisation programme and those that will be in the positive list
Final decision national or regional level?	National
What is the ultimate outcome of the assessment of a new vaccine?	The recommendations from the Health Council and the drug committee are both non-binding.

Source: Experts interviews

3.2.2 Methodologies country comparison

TABLE 20 summarises the information collected in relation to the methodology and assumptions applied in the economic evaluations for the selected countries. According to the interviewed experts, a systematic review of the clinical evidence is required in all countries. In the case of New Zealand, it is also recommended to conduct a literature review for health utility losses. The inclusion of unpublished literature is common, particularly for those vaccines for which there is limited

information available. Moreover, the quality of the clinical evidence in France, Germany and The Netherlands is assessed by using the GRADE approached while in New Zealand the SIGN approach is applied.

Regarding mathematical modelling, dynamic models are recommended when herd protection is a key factor. Otherwise, the static model are considered adequate. For instance, PHARMAC guidelines states that static models may be appropriate if herd protection does not play an important role, meaning that the additional effectiveness per additional person vaccinated is constant (PHARMAC, 2015). Similarly, the German STIKO indicates that the use of static models is legitimate for the evaluation of vaccinations and vaccination strategies that do not lead to indirect effects (STIKO, 2016b).

In Germany and Japan no formal statement exists for the requirement of economic evaluations results for vaccine inclusion. Nevertheless, the interviewed experts reported that economic evaluation results are considered alongside other criteria. The type of economic evaluation normally used is cost-effectiveness analysis. In every case health utility losses are considered, usually by estimating QALY losses.

Regarding the type of cost considered, our Australian expert reported that indirect cost, such as productivity losses, are normally not considered. On the contrary, indirect cost are required in the guidelines of economic evaluations of the Netherlands, Germany and France. In Japan, indirect costs are considered for voluntary vaccines, but not for those seeking inclusion in the positive list. In New Zealand and Italy, indirect costs are not required but are commonly included.

The highest discount rate for health benefits was reported by the Australian expert (5%). The Netherlands requires the lowest discount rate for health benefits (1.5%). This is the only country in the sample that applied a differential discount rate. In general, guidelines require the evaluation of the impact of the discount rate by considering different values in the sensitivity analysis. It is worth noting that when we observed the discount rates required in both, base case and the sensitivity analysis, 3% and 3.5% are the most common values. Understanding the variation in discount rates across countries is beyond the scope of this analysis.
In general, the changes in the methodology and in the decision making process reported by the experts suggests that most updates have been directed towards developing a more rigorous and transparent process to decide on the inclusion of new vaccines. Australia and Germany have introduced guidelines that also affect vaccine assessment, while France and New Zealand have passed the responsibility of new vaccine evaluation to the country HTA agency.

TABLE 20. HTA FOR VACCINES: METHODOLOGY (COUNTRY COMPARISON)

	Australia	France	Germany	Italy	Japan	New Zealand	The Netherlands
Systematic review required?	In the submission the company must include a comprehensive systematic review. It is also required to provide a systematic review of economic evaluations from other jurisdictions.	Of clinical and economic studies, respecting good practices in terms of literature search, selection and critical analysis.	A systematic review of efficacy, effectiveness and safety is always required.	For clinical evidence. Literature from other countries and regions could be included. Model parameters taken from different studies, but not from systematic review.	For clinical evidence.	For the clinical evidence a literature review is required. PHARMAC analysis also include an investigation into health-related quality of life scores, including a systematic review of the literature.	Required by both committees. The Health Council does a systematic review in addition to those provided in the two separate independent HTAs.
Unpublished data included?	Yes	No. normally data source is only peer reviewed.	Uncommon to include unpublished data from manufacturer. Data on other aspects often collected using non-systematic methods.	The guidelines states that effectiveness must be assessed given its utility to the public Italian NHS, based on solid data from randomised trials, quasi-experimental or observational studies.	If the vaccine is new and evidence is limited.	Key studies if submitted for publication.	Only posters, e.g. information on QALYs could be extracted from posters that have not been published. Manufacturer dossier: information from clinical trial.
Is the quality of the evidence normally assessed?	Yes. It is rigorously assessed, particularly for the risk of bias. There is a section in the guidelines related to the risk of bias in the systematic literature review.	Yes. They use the approach of the GRADE (Grading of Recommendations Assessment, Development and Evaluation) to evaluate the quality of the evidence.	Formal quality assessment is limited to efficacy, effectiveness and safety (GRADE tool).	NA	Implicitly but not (normally) explicitly.	Quality of the clinical evidence is analysis by the checklist developed by the Scottish Intercollegiate Guidelines Network (SIGN).	The systematic review of the literature should proof to be of sufficient quality. If this is not the case, the evidence should be evaluated using the GRADE approach.
Mathematical modelling: What is the model most commonly used?	PBAC prefers the use of dynamic transition models in order to properly consider herd protection, so these are normally used. Static models can be used if they can correctly answer the question.	Yes. Developed by NITAG or outsourced.	Normally dynamic models. It depends on the vaccine.	Depends on the experience of the local HTA committee (commonly consists of physicians who are not familiar with modelling). Markov models are sometimes used.	A Markov model is most commonly used. Transmission models and dynamic compartment models also used.	Markov model or decision analysis; normally not formal transmission modelling.	Decision trees are most commonly used. More complex models required in cases where herd protection or age shift are important and/or could affect the results.
Are health economic evaluations required?	Yes	It was not required for CTV analysis when it was part of the HCSP.	Grey area – health economic evaluations are not required but	All regional health authorities must	These are not required but can be considered (implicitly rather than	Yes	It is a main criteria for the Health Council. Drug committee

	Australia	France	Germany	Italy	Japan	New Zealand	The Netherlands
		However, now CTV is part of HAS and HAS required health economic evaluations.	can be included. Cost-effectiveness is not a 'fourth hurdle'.	consider economic evaluations.	explicitly). Pharmacoeconomic guidelines for vaccines not mandatory but are becoming influential.		requires that the manufacturer presents a cost-effectiveness analysis.
What type of economic evaluation?	PBAC prefers cost-utility analysis. However, cost-effectiveness analysis (e.g. will clinical endpoints) can be accepted.	If an important impact on health-related quality of life (HRQL) is expected then cost-utility analysis. This is always accompanied by a cost-effectiveness analysis which uses length of life as health outcome.		Cost-effectiveness analysis.		Cost-effectiveness analysis.	Cost-effectiveness analysis.
Are budget impact or cost analyses required?	Budget impact analysis is required. Manufacturer submission should include budget impact.		Not really considered – the overall cost impact is sometimes mentioned in one chapter of the economic model report.	Exclusively considered at the regional level.	These are not required but can be considered (implicitly rather than explicitly).	Yes	Health Council: budget impact not considered Drug committee considers budget impact.
Principal outcomes considered	QALYs	The primary vaccine-preventable outcomes that the CTV uses to generate recommendations are, in order of importance: overall morbidity, mortality, and hospitalisations, as well as epidemic potential HAS required patient's length of life weighted by a valuation of the HRQL.	Cost-per-QALY Other outcomes can include cost-per-presented case, cost-per-prevented hospitalisation.	QALYs and years of life lost. DALY are sometimes also considered. The guidelines identify the cost-effectiveness analysis and the QALY as the main elements in the economic evaluation.	Safety, quality, efficacy, adverse events.	Clinical, quality of life and economic.	Incidence, cases of symptomatic infections, complications, hospitalisations, QALYs and cost-effectiveness.
In the economic evaluation: are health utility losses considered?	Yes. Note no preference for one instrument over another.	Yes. If an important impact on HRQL is expected. HRQL is described using EQ-5D or HUI 3.	Germany doesn't have much primary data on health utilities – models normally rely on published data from other countries.	Yes	Yes	Yes. Published NZ EQ-5D tariffs (weights) or NZ disability weights or global burden of disease weights and NZ mortality.	Yes

	Australia	France	Germany	Italy	Japan	New Zealand	The Netherlands
Are QALYs considered an important outcome?	Given that cost-utility analysis is used, QALYs are included most of the time.	Important, but not as important as other factors.	Yes, but many STIKO members have a critical attitude towards the use of QALYs.	Yes. QALYs should be calculated, mainly by means of the ED-5Q.	The guidelines recommend the use of QALYs.	Yes, critical	Yes, QALYs must be measured using EQ-5D applied to the Netherlands. In the case of children, it is common to use proxies from parents.
Types of costs	Direct cost (e.g. vaccine costs, clinical services, hospitalisation, diagnosis). For vaccines, factors such as cost of the implementation logistics (e.g. storage). Healthcare system perspective is used, therefore, indirect cost are not normally included.	Collective perspective: Cost must reflect all resources consumed, whatever the source of funding (patients, compulsory and supplementary health insurance schemes, the central government, etc.).	Direct medical costs, indirect costs (in Germany, this refers to production losses). Sometimes (rarely) transfer payments are considered.	The national guideline states that national health system costs must be included (health care system perspective). In the case of vaccine is common to consider the social perspective.	Direct costs (medical, non-medical) and indirect costs (production loss). Regular vaccines are listed on the national health insurance formulary and are treated like other interventions (such as drugs): assessed using a government perspective – considering direct costs only. Indirect costs often included in voluntary vaccines assessments.	Direct medical costs only; indirect costs and non-medical costs will be considered but are not required.	Societal perspective must be used: direct medical cost (vaccine costs), direct non-medical cost (transport costs), indirect non-medical costs (production losses) and medical indirect cost (people living longer will suffer from other diseases). Indirect costs estimated using friction approach.
What discount rate is used for vaccines?	5%. Normally, a sensitivity analysis is presented that includes values from 0%, 3.5% to 7%.	4%. A sensitivity analysis is included that varies form 0% to 6% and normally includes 3%. No constant discount rate is also used.	3%, in accordance with IQWiG's methodological guidelines. In sensitivity analyses, differential discounting applied.	3%	3%. 0 to 5% in sensitivity analysis.†	3.5% per annum. Sensitivity analysis required: 0% and 5% for health benefits.	4% for costs and 1.5% for health benefits. An uncertainty analysis with different discount rates must be performed.
same for costs and outcomes?	Yes	Yes	Yes	Yes	Yes	Yes	No
same for other health technologies?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Over the past few years have there been any changes in the way that new vaccines have been assessed for	Before 2006 vaccines were not evaluated by the PBAC's rigorous process.	CTV has just be transferred to HAS.	Standard operating procedure for STIKO was introduced and published in 2012. 2014: vaccine acceptance was	Since 2012 some vaccines have been included in the LEA.	Pharmacoeconomic guidelines were introduced and accepted by the MHLW five years ago, but they	Jurisdiction passed from an advisory committee of the MoH to PHARMAC that evaluates the clinical	There is a new initiative to start conducting a joint assessment for vaccines between the sub-committee of the

	Australia	France	Germany	Italy	Japan	New Zealand	The Netherlands
reimbursement purposes?			included as a secondary criterion.		are not used by the PBMA.	and economic case presented by suppliers.	Health Council and the drug committee.
Reference case or guidelines for the evaluation of the new vaccines	There are general PBAC guidelines. These include a section related to additional requirements for vaccines (Australian Department of Health 2016)	HAS guidelines for economic evaluations (HAS, 2013).	Yes – the STIKO guidelines (standard operating procedure) (STIKO, 2016b; c).	The guidelines for economic evaluations also applied to vaccines (Fattore, 2009).	Yes, interviewee reported a cost-effectiveness analysis as a case study (Shiroiwa et al., 2016).	No reference case, but general guidelines for all pharmaceuticals apply to vaccines (PHARMAC, 2015).	The guidelines for economic evaluations also apply to vaccines. (Zorginstituut Nederland, 2016).

†The value reported by the Japan's expert coincide with the discount rate applied in a number of the cost-effectiveness analysis for vaccines founded in the literature (e.g. Konno et al. (2010); Sato, Nakagomi and Nakagomi (2011), and Shiragami et al. (2015)). However, the guidelines published in 2013 (Fukuda, 2013) and 2016 (Shiroiwa et al., 2016) mentioned a discount rate of 2% for both health benefits and cost.
Source: Experts interviews and clinical guidelines

3.3 Mapping decision criteria

TABLE 21 summarised the information elicited from experts as to whether various decision criteria are considered in each country, and if so, how important they perceive they are. The criteria were organised into four categories.

- *Formally considered:* refers to those criteria that the guidelines specified must be included in the decision.
- *Commonly and informally considered:* are those criteria that are part of the decision in most cases, but that are not required in the guidelines.
- *Uncommonly and informally considered:* criteria refers to those that have been considered in particular cases, but that are normally not part of the analysis.
- *It could be considered, but the information is unclear:* refers to the criteria that the experts are not completely certain (in terms of whether they have been considered in any previous decisions).

Experts also selected from the list of possible criteria those that they considered to be particular important for decisions about the introduction of a new vaccine. These key criteria are marked with '✓' in TABLE 21.

Among the 'intervention specific' group of criteria, the only criterion that is 'formally considered' in all countries is clinical outcomes. In addition to clinical outcomes, treatment side effects profile was noted as an important criterion in at least three countries: Germany, Japan and New Zealand. Additionally, patient HU losses, measured using QALYs, is a key criterion in Italy and New Zealand and is formally considered in all countries except Japan.

The three criteria listed in the 'disease related' category are required in the majority of the countries. Disease burden is the most important criterion in this category. Although in Japan consideration of the severity of the condition and sequelae is not formally required, these factors are key drivers of decisions and are commonly considered.

Two are the criteria related to particular features of the target population that were included in the analysis (see 'characteristics of the target population', TABLE 21). First, age group which is formally considered in every country, and second, equity which is a key criterion for decisions in Australia, Japan and New Zealand (TABLE 21).

Vaccination programmes have been considered as a factor to reduce inequalities in developed and developing countries (Lennon et al., 2012; Hinman and McKinlay, 2015). (Jimenez, 2001). Although important, equity is not formally considered. In Australia equity is implicitly considered – the committees operate under the premise that equity should always guide the decision. According to the Japanese expert, the committee members state that equity is important and should always be part of the decision, but it is unclear whether and how it is formally considered. In New Zealand the meaning of equity is defined by the Ministry of Health, and is primarily related to ethnicity (Maori/Pacific) and socioeconomic status, which are correlated. In Germany, although not listed as a criterion, equity plays a role in the modelling. In the Netherlands, equity is an overall consideration for including a new vaccine in the immunisation programme. However, it is not contemplated for decisions about inclusions in the positive list. This because for vaccines listed only in the positive list, the patients pay a co-payment, while vaccines in the national immunisation plan are given free of charge. Although not a formal criterion, in Italy the improvement of equity has been considered for listing vaccines in the LEA.

TABLE 21. CRITERIA CONSIDERED DURING THE DECISION OF INCLUSION OF A NEW VACCINE

Factors	Criteria	Australia	France	Germany	Italy	Japan	New Zealand	Netherlands
Intervention specific	Clinical outcomes	✓	✓	✓	✓	✓	✓	
	Health effects - patient health utility losses measured through QALYs			*	✓		✓	
	Health effects - patient health utility losses measured through other measures				✓			
	Health effects - family / caregivers health utility losses			*				
	Treatment side effects profile			✓		✓	✓	
	Impact on existing processes of care or care pathways		✓					
	Patient convenience							✓
	Average duration of the vaccine protection							**✓
	Herd protection			✓		✓		
	Other 1			Suitability				
	Other 2			Co-administration with other vaccines				
Disease-related	Severity of health condition			✓	✓	✓		✓
	Sequelae			✓	✓	✓		
	Disease burden	✓	✓	✓	✓		✓	✓
	Other			Perception of the target disease in the population				
Characteristics of the target population	Equity (e.g. socioeconomic status, gender, stigma)	✓				✓	✓	
	Age group							
Financial	Cost-effectiveness analysis	✓		** ✓	✓			✓
	Cost offset (per patient) to the health care system			*	✓			**

Factors	Criteria	Australia	France	Germany	Italy	Japan	New Zealand	Netherlands
	Indirect costs - impact on non-health public sectors							
	Indirect costs - impact on individuals/households			*				
	Productivity losses - patients			*				
	Productivity losses - family / caregivers			*				
	Catastrophic effect/financial risk on individuals for not funding certain interventions							
	Total budget impact		✓	*	✓	✓	✓	Drug committee Health council
Macro-level	National health system priorities; political considerations / objectives	✓	✓		✓	✓	✓	✓
	Service delivery setting/health care system "readiness" to provide the vaccine							✓
	Existence of legal process to get access to interventions if they are not included							
Additional Criteria	Incremental innovation (aids development)							
	Potential of peace of mind							
	Public preferences							
	Other 1	Impact on the immunisation programmes on other vaccination programmes		Acceptance				
	Other 2			Recommendation in other countries				

✓ Key criteria
* Only as part of the economic evaluation
** Often formally evaluated but not considered in every case
Formally considered
Commonly and informally considered
Uncommonly and informally considered
It could be considered, but the information is unclear Source: Expert interviews

In relation to the 'financial factors', cost-effectiveness analysis and budget impact were the two most commonly mentioned key factors (TABLE 21). Cost-effectiveness analysis is (either formally or informally) part of the decision making process of every country in the sample.

It is important to highlight that decisions about whether to augment an immunisation programme with an additional component are typically informed by the cost effectiveness of the additional component rather than by the cost effectiveness of the entire, augmented programme. This focus on 'marginal' cost effectiveness is consistent with the principles of economic evaluation. It is also reflected, for example, in NICE's reference case approach to economic evaluation, which requires a 'fully incremental analysis' (NICE, 2013) and assumes that the primary objective of the health care system is to maximise population health using available resources. From a public health perspective, however, other objectives may also be important, such as disease control and/or eradication. The incremental approach is well suited for achieving the best overall outcomes (across diseases) using a given budget, but may not always achieve the best outcomes within a specific disease area. Indeed, it was it was acknowledged in a recent JCVI meeting that the incremental analysis approach may not adequately value control of disease (Joint Committee on Vaccination and Immunisation, 2016).

In Australia and Italy, cost-effectiveness analysis is an important criterion for determining the inclusion of all pharmaceutical products, including vaccines. Likewise, in New Zealand vaccines compete on the same criteria as other pharmaceuticals and for the same capped annual budget. Equally, in Japan cost-effectiveness has the same level of importance regardless of the medical technology being assessed, but there is a new policy whereby pharmaceuticals, excluding vaccines, will get repriced every two years, and this process will be guided by cost-effectiveness analysis. In the case of Germany, cost-effectiveness is not considered for the reimbursement of any other type of health intervention. It is therefore a unique feature of vaccines that economic value is considered. Similarly, in the Netherlands according to the local expert cost-effectiveness is more important for vaccines than for other drugs.

Among the 'macro-level factors', national health system priorities is a key criterion in six out of the seven countries (TABLE 21). Moreover, in Australia service delivery settings are particular important. The logistic surrounded the implementation of the new vaccine and how this will affect the national immunisation plan are significant factors in the decision. An important question is whether the vaccine can be included in the current schedule or whether it is necessary to stablish a new vaccination programme.

The three 'additional criteria' listed were not formally considered in any system (TABLE 21). Although public preferences are not directly considered in Germany, the STIKO considers that there is a particular public interest if at least one of the following three criteria are met: (1) severe outcomes (e.g. death or long-term sequelae) can be prevented as a result of direct vaccination effects, (2) there is need for herd protection, (3) the vaccine is able to reduce the of risk or intensity of an epidemic that can significantly disrupt public life. With respect to peace of mind effects, while some of the experts said that this is 'uncommonly and informally considered', none were able to provide any specific examples in which this criterion was considered in the decision making process. Peace of mind effects are further discussed in the next section.

We also collected information on whether adoption decisions in the selected countries are influenced by the decisions made in other countries. In New Zealand, PHARMAC considers during its deliberations the analyses and decisions taken by NICE, PBAC and the Canadian Agency for Drugs and Technologies in Health (CADTH). However, this information is not as important as other criteria, such as clinical and economic evidence, local need, budget impact, security of supply and product quality. In Germany, the STIKO considers NICE analyses and decisions, as the decision making process in the UK is (implicitly) thought to be clearer than in other countries. Although in Japan a cost-effectiveness threshold approach has not yet been implemented, the government is also influenced by NICE and its cost per QALY threshold approach. While other countries' decisions do not influence Italian decisions, in regional Italian HTA reports information from other countries is normally included, for instance in determining the parameters used in the HTA. Moreover, NICE assessment guidelines are in some cases followed in conducting the HTA. The experts from the Netherlands, France and Australia were of the opinion that economic evaluations conducted in other

countries may be taken into account but are not usually considered to constitute sufficient evidence upon which to base a decision.

An additional criteria highlighted by the Australian expert is the need to prevent an epidemic. As Australia has high levels of migration, if there is a certain epidemic in a country from which Australia receives immigrants, the vaccine used to protect against the outbreak could be considered for inclusion to avoid a similar epidemic in Australia.
It is noteworthy to highlight that in the Netherlands there is an anti-vaccine lobby which has raised concerns about the safety of vaccines and possible adverse effects. This has influenced the public's trust in the national immunisation programme. For instance, as a consequence of this anti-vaccine lobby the HPV vaccine generated significant attention in the media, which resulted in low uptake at the beginning of the programme. As a result of this the Netherlands government is proceeding with caution, which means that it is even more difficult for new vaccines to be introduced into the national programme. A similar anti-vaccine lobby exists in New Zealand, this is addressed by an 'immunisation advisory centre', independent of the reimbursement process.

3.3.1 Meningococcal vaccine country comparison

TABLE 22 shows the status of meningococcal vaccines in the selected countries as well as the criteria used to decide on their inclusion. Experts reported that the first meningococcal vaccine were introduced after 2000. Currently, Men C vaccine is part of the National Immunisation Programmes of Italy, France and Germany. In Australia Men C vaccine has been substituted in the national plan by a combination vaccine against meningococcal serogroup C and Haemophilus influenzae type b. In addition to Men C vaccine, the Italian national plan includes Men B for new-born and Men ACYW for adolescents, however, it has not been adopted in all regions. New Zealand does not have a meningococcal vaccine as part of its immunisation plan, however, in 2002 Men B vaccine was used during an outbreak. Similarly, in Japan meningococcal vaccine is voluntary, meaning that it is not part of the routine immunisation programme. However, it is worth noticing that in Japan meningococcal disease infections are less common than in other developed countries (Pelton, 2016).

TABLE 22. MENINGOCOCCAL VACCINES (COUNTRY COMPARISON)

	Australia	France	Germany	Italy	Japan	New Zealand	Netherlands
Men vaccine included in national immunisation schedule?	Yes	Yes	Yes	Yes	No	No	Yes
When was the vaccine approved?	Men C: In 2003 Men C conjugate vaccine added to childhood vaccination schedule at 12 months of age. 2013: A combination vaccine containing meningococcal serogroup C and Haemophilus influenzae type b antigens (Hib-MenCCV) has been used in the national immunisation plan since July 2013 (one dose at 12 months of age). Men B: It is available only via purchase on the private market.	Men C: recommended in 2009 and reimbursed since January 2010. 12 months and one additional dose for children older than 2 years. Men B: has been considered to control local serogroup B outbreaks.	Men C: late 2006/early 2007 for children aged 2 years. Men B: 2014 'indication recommendation' - not routinely given to all children; only indicated for very specific immune system related chronic diseases.	Tetravalent vaccines Men ACYW: Before 2000, included in the national immunisation plan. Men C: Included in the 2012-2014 immunisation plan. Currently included in the immunisation programme for children under 2 years of age. Men B: Currently, recommended in the immunisation programme for new-born children. Adoption of the vaccine differs among regions.	Men ACYW: In 2015, meningococcal vaccination with a meningococcal conjugate vaccine (Menactra® or Menveo®) was approved as a 'voluntary' vaccine.	Men C: not funded because the incidence is relatively low. Men B: Introduced briefly in 2002/3 to combat an epidemic.	Men C: Included in 2000 together with a catch up programme until 18 years. There are discussions ongoing regarding revaccination at 12 years.
Main criteria that supported the decision to include or not to include the meningococcal vaccine	Combination vaccine Hib-MenCCV: -Cost-minimisation analysis: it was cost saving. The PBAC recommended inclusion of this new presentation of Hib–Men C vaccine under the same conditions as the existing single antigen Hib and Men C vaccines, at the price	Men C: -Epidemiological findings played an important role. -Economic evaluation to select the strategy (infants from 12 to 24 months of age, and catch up vaccination up to 25 years of age) -Promotes herd protection.	Men C: High efficacy in Western European countries, severity of the disease, favourable cost-effectiveness. Men B: STIKO discussed the use of the Men B vaccine – high priced vaccine for a rare albeit very severe disease; highly cost-ineffective.	Tetravalent vaccines for Men ACYW: adopted because of the high rate of the disease and the high cost of the sequelae for the health system (the latter being particularly important).	Interviewee had no information – suggested that there may be concerns about high price, but was not aware of any cost-effectiveness analyses that had been conducted and presented to the Health Sciences Council.	Men B: Epidemic of Men B which peaked in 2001 Men C: doesn't meet the 'clinical need' criterion, although a special case could probably be made for immunocompromised individuals.	-An outbreak that brought a lot of media attention. -Cost-effectiveness: selection of the number of doses - three doses would be better, but one dose at 12 months was the most cost-effective strategy. -Severity also a very important criterion.

	Australia	France	Germany	Italy	Japan	New Zealand	Netherlands
	proposed in the submission.						

Source: Experts' interviews

A vaccine against meningococcal serogroup B is included just in the Italian National Immunisation plan (TABLE 22). It is only used in France and New Zealand to control specific outbreaks. Additionally, Men B vaccine is used in Germany for patients with particular immune system diseases. Similarly, the New Zealand's expert mentioned that it could be the case that for immunocompromised individuals the health system would pay for the Men B vaccination.

Regarding the main criteria that supported the decision to include or not to include the meningococcal vaccine, cost-effectiveness is the most commonly mentioned by the experts (TABLE 22). The German expert indicates that a favourable ICER tipped the scale in favour of the vaccine implementation for Men C. Similarly, in Australia the Hib-MenCCV vaccine was included mainly because it was found to be cost-saving (the price of the vaccine is similar but the administration of the dual vaccine is cheaper). Dutch and French experts reported that vaccine schedule were selected based on a cost-effectiveness analysis that compare different schedules.

As mentioned in section 0, during a NICE Citizens Council meeting in 2008 the majority of Council members selected a set of circumstances that could support the use of an alternative cost-effectiveness threshold (NICE, 2008a):

- the patients are children;
- the illness is rare, extremely severe and could be a result of NHS negligence;
- treatment is life-saving, prevent more harm in the future, have a major impact on the patients family, and will encourage more scientific and technical innovation.

Given the nature of meningococcal disease infection, most of these circumstances apply to the meningococcal vaccine. Meningococcal infection is characterised for being a severe disease, with a high probability of resulting in a severe long-lasting sequelae. It is a disease that affects principally infants and toddlers with a considerable negative impact on the well-being of the families, particularly for patients with long-lasting sequelae. Furthermore, it is difficult to diagnose since its symptoms can be easily confused with those of a common flu.

Although UK NICE Citizens Council's list of circumstances reflects the particular preferences of the UK population, it primarily considers moral and ethical value issues which should not be too divergent from those of other countries. Of the main criteria reported by the experts, few reflect the meningococcal disease features that the NICE Citizens Council would argue should relax the cost-effectiveness criteria (TABLE 22). The French expert mentioned the effect of the Men C vaccine on the probability of carriage. Herd protection reflects the capacity of the meningococcal vaccination to prevent harm in the future. In Italy a key criteria was the high cost of the sequelae which could also be related to the capacity of the vaccine to prevent more harm in the future. Moreover, given that in Italy a societal perspective is normally employed for vaccines, this criteria can be seen as related to the capacity of the vaccine to have a major impact on the patients' family. Finally, the severity of the meningococcal disease played a main role in German and Dutch decisions of implementing a meningococcal vaccination programme.

It is important to highlight that the criteria listed in TABLE 22 are based on the information collected during the interviews with the experts. Therefore, this cannot be seen as a robust list of criterion endorsed by the HTA agencies.

3.4 Consideration of other criteria

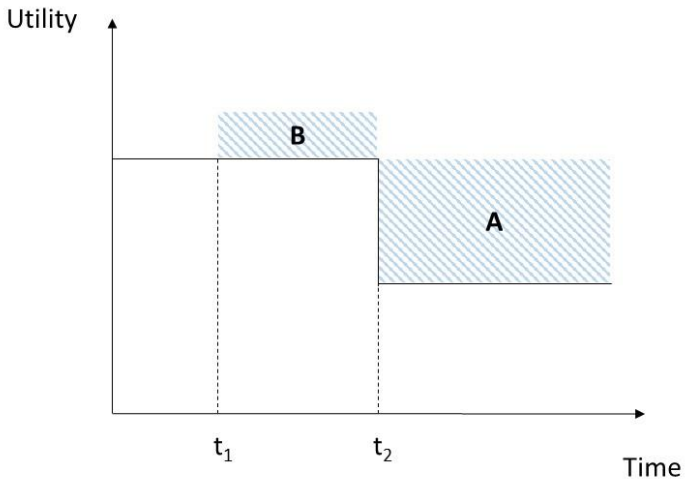
3.4.1 Peace of mind benefits and utility in anticipation

The concept of vaccines offering 'peace of mind' benefits was discussed in a paper by Beutels et al. (2003), who suggested that individuals benefit not only from knowing that they or their children have a reduced risk of illness, but also from reduced anxiety linked to disruptions to normal daily life, such as having to take time off work to care for a sick child. Such anxiety costs will be particularly large for high-profile conditions. On the other hand, the vaccination procedure itself may cause short-term anxiety effects for some individuals. Such intangible costs and benefits are difficult to measure and therefore tend to be ignored in economic evaluations.

Jit and Hutubessy (2016) argue that vaccines are associated with peace of mind benefits for patients and their caregivers. They note that such benefits are not captured by the standard methods used to provide estimates for health measures such as the QALY. Alternative techniques, such as willingness-to-pay, may be better suited to assessing peace of mind benefits and providing evidence that can be considered in economic evaluations. The authors refer to a study of US mothers' preferences for vaccinating their daughters against HPV, which found that respondents' stated choices were significantly associated with concerns about HPV risks (Brown et al., 2010). However, spending on health care other than vaccines also provides peace of mind benefits – for example, investment leading to improvements in end of life care may offer peace of mind benefits for individuals who are healthy today but anticipate needing such care in the future (Jit and Hutubessy, 2016). Displacement of activities at the margin in order to fund a new vaccine may therefore result in the loss of potential peace of mind benefits offered by other types of health intervention.

A related concept – 'utility in anticipation' – was introduced by Cohen and Henderson (1991) and discussed in relation to vaccines by Drummond, Chevat and Lothgren (2007). The standard approach in the economic evaluation of vaccines is to consider only the utility that would be lost if the illness were to occur, from the point at which it would occur. The utility in anticipation concept further acknowledges the fact that individuals gain utility immediately from the moment of vaccination until the time that the illness was expected to occur, *because of the reassurance that the illness has been prevented*. The higher the perceived risk of infection and the perceived effectiveness of the vaccine in reducing that risk, the higher this utility gain will be. See FIGURE 4 for a conceptual illustration. The solid black line shows the utility curve for an unvaccinated individual who is infected at t_2, resulting in health loss *A*. If the individual is vaccinated at t_1 and therefore avoids the infection at t_2, they benefit not only from avoiding health loss *A*, but between t_1 (the time of vaccination) and t_2 they also benefit from utility in anticipation (*B*). The total value of the vaccine is therefore *A+B*. An unvaccinated individual who is aware of the possibility that they may get infected in the future would suffer a lower utility prior to the point of infection than would a vaccinated (and therefore reassured) individual. Drummond et al. (2007) suggest that preventive interventions are generally undervalued under the standard approach, which would only count *A*. Ignoring *B* results in an underestimation of QALY gains and therefore an overestimation of the ICER. *B* may be particularly substantial in cases where there is a long lag between t_1 and t_2 – e.g. when individuals are vaccinated at a relatively young age to protect against an infection that typically occurs later in life.

FIGURE 4. UTILITY IN ANTICIPATION



Source: Adapted from Drummond et al. (2007)

In the consensus framework paper for the health economic evaluation of vaccines to support the development of national guidelines in Europe, Ultsch et al. (2016) also mention utility in anticipation, noting that vaccinated individuals and their families benefit from improved quality of life due to feeling 'protected' after vaccination. They also refer to the possibility of short-term quality of life effects due to fear of adverse events. Although both types of effect can in principle be captured by the QALY and should be considered in uncertainty analyses, the authors acknowledge in their consensus statement that relevant data are likely to be scarce.

While the potential for peace of mind and related benefits is acknowledged by researchers and those involved in working groups set up to advise on vaccine evaluation methods (Gosden, 2016; Joint Committee on Vaccination and Immunisation, 2013; Staine, 2016), the evidence base remains limited at present. Given that such effects may be substantial for infectious diseases and immunisation programmes, future research should seek to fill this gap in the evidence in order to enable their consideration in reimbursement decisions. One avenue of research – suggested by Beutels et al. (2003) – would be to conduct a discrete choice experiment (DCE) to elicit the preferences of potential beneficiaries. DCE is a stated preference technique that produces quantitative trade-offs between different factors based on hypothetical choices. DCEs are typically implemented in surveys comprising several 'choice sets', each containing competing alternative 'profiles' described using 'attributes' and a range of attribute 'levels'. Respondents are asked to choose between these alternative profiles, and the resulting choices are analysed to estimate the relative contribution of each of the attribute levels to overall utility (Lancsar and Louviere, 2008). In this case, the alternative profiles could be two different vaccines, and one of the attributes could be designed so as to represent peace of mind-type benefits. This would be one of several attributes representing important features of the vaccines, such as the severity of the condition against which they protect, the expected health gains from vaccination, and the nature and likelihood of side effects. By asking survey respondents to make a series of choices between competing vaccines described in terms of these attributes, preference data could be collected that can be analysed to determine the extent to which their choices are being driven by peace of mind benefits, relative to other factors.

A drawback of such an approach is that there is conceptual overlap between the expected health gains of a vaccine and the peace of mind benefits associated with vaccination. It is difficult to present choices that involve a realistic trade-off between health gains and peace of mind benefits – the latter is presumably derived from knowledge of the former. A further issue is that explicitly including a peace of mind attribute in the study design may result in a focusing effect whereby respondents place more importance on the attribute than they otherwise might have done. This is a well-known phenomenon in the behavioural science literature, where evidence has been reported that

people attend to and focus on things they are being asked about to a degree than exceeds how much those things matter in the actual experiences of their lives (Dolan, 2014).

An alternative avenue of research would be to conduct a willingness-to-pay exercise whereby survey respondents are asked how much they would pay, out of their own pocket, for hypothetical vaccines with different attributes of interest. This technique also has limitations, not least in countries with tax-funded health systems where most people are not used to the idea of paying for health care. Nevertheless, it has the potential to provide data on the extent to which respondents would be willing to pay amounts that are above and beyond what would be predicted for the expected health benefits on offer (the values could be compared to how much the respondents would pay for a curative treatment offering similar expected benefits). Peace of mind would not necessarily need to be mentioned explicitly in the exercise, but respondents could be asked debriefing questions to understand the reasons for their choices and the extent to which they were paying to achieve a sense of reassurance.

Research on this topic could also seek to understand what drives people's perceptions and fears about different diseases of interest. A carefully designed study may be able to assess the impact on peace of mind of information provision and/or changes in perceptions over time.

3.4.2 Public preferences

Severity

Jit and Hutubessy (2016) suggest that people may place greater weight on the health gains from preventing severe or life-threatening illness than on that from preventing mild illness. This claim is supported by empirical reviews of priority-setting preference studies (Gu et al., 2015; Shah, 2009; Whitty et al., 2014). Based on a review of literature on severity-related preferences, Shah (2009) found that "the empirical evidence suggests that people are, on the whole, willing to sacrifice aggregate health in order to give priority to the severely ill" (p.77). In spite of the evidence in favour of prioritising interventions to treat or prevent severe illness, QALY weighting based on equity and related factors remains controversial and an appropriate weighting system has yet to be developed (Paulden et al., 2014; Wailoo, Tsuchiya and McCabe, 2009).

In a paper authored by NICE's Chairman (at the time of publication) and the Chairs of the NICE Appraisal Committees, Rawlins, Barnett and Stevens (2010) acknowledge that the Institute's advisory bodies have "often given more generous consideration to the acceptability of an ICER in serious conditions" (p.348), based on the view that society would prefer to give priority to the relief of very serious conditions.

Age

A review of the literature on cost-effectiveness and ageism suggests that in many cases, health losses in childhood are valued more highly than health losses at other times (Edlin et al., 2008). More recent studies reporting evidence of giving priority to the young include Olsen (2013) and Skedgel, Wailoo and Akehurst (2015). Evidence to the contrary has also been reported by Linley and Hughes (2013). Some studies (e.g. Baker et al. (2010)) have found that although there appears to be a general preference for placing greater weight on the health and survival of younger people, the relationship is not necessarily linear – children, adolescents and young adults may be prioritised over babies, for example.

The benefits of vaccinations for infants and children may be underestimated if parent or caregiver preferences are not taken into account. For example, Prosser et al. (2004) report that routine pneumococcal conjugate vaccination for children is found to be more economically favourable when the values of parents are considered. This was based on a US stated preference study in which respondents were asked how much of their own lifetime and money they would be willing to give up

in order to prevent or reduce the risk of illness in their children (it seems likely that at least some of the value parents placed on preventing/reducing the risk of health in children were driven by peace of mind effects). Similar results were reported based on the preferences of general public respondents in the same study, which indicates a general societal preference for giving greater weight to health gains for children.

Decision makers in the UK are required to respect anti-discrimination legislation that states that access to health care cannot be denied or restricted on the basis of age or other protected characteristics. NICE's general principle is that its guidance should not result in denying patients access to treatment based solely on their age, unless it is clinically relevant to do so (e.g. if there is good evidence that patients of different ages will respond differently to a given intervention (NICE, 2008b)). However, the aforementioned paper by Rawlins et al. (2010) states that "NICE understands that society would generally favour 'the benefit of the doubt' being afforded to sick children", based on a recognition that the "assessment of improvements in the quality of life in children are methodologically challenging" (p.349). A recent review has shown that NICE is far more likely to report evidence of differential effectiveness and cost-effectiveness by age in its public health guidelines than in its technology appraisals (Forrest et al., 2016).

Prevention

An early person trade-off study of preferences for prevention versus cure in Sweden found that the majority of respondents expressed a slight preference for saving lives through prevention. However, the authors conclude that the sizes of the health benefits are more important than whether those benefits are achieved through prevention or cure (Johannesson and Johansson, 1997).

In a study of the preferences of the US general public, Ubel et al. (1998) found that respondents slightly preferred prevention over cure, holding constant the magnitude of benefit for both types of intervention. However, the most common response was to indicate that prevention and cure were of equal importance. In both the preventive and curative scenarios, an overall preference for directing resources towards the severely ill was observed.

In a DCE administered to members of the Australian general public, Mortimer and Segal (2008) found that preventive interventions were preferred to curative treatments, controlling for other attributes. The same study also reported an overall preference for prioritising interventions for young children over interventions for other age groups (young adults, working age adults, and the elderly).

Based on a DCE examining the views of the US general public, Bosworth, Cameron and DeShazo (2010) report that respondents valued marginal lives saved via prevention about twice as much as equivalent marginal lives saved via treatment policies.

A recent DCE examining the views of the general public in Belgium Luyten et al. (2015) found that although prevention was not necessarily preferred to cure overall (the relevant coefficient was not statistically significant), preventive treatments were greatly valued for more severe, long-lasting and life-threatening diseases. Conversely, curative treatments were valued more for milder, temporary health losses. An age effect was also observed, with prevention valued more for younger patients than for older patients.

In a willingness-to-pay study administered to members of the US general public, Corso et al. (2002) found significantly higher values for treatment than for prevention. The authors note that the results are in contrast to public opinion polls and choice-based empirical studies, which "have consistently found that prevention is preferred to treatment when the two are directly compared" (p.S97). They conjecture that the results may be explained by the study design: it has previously been found that willingness-to-pay asked ex post (e.g. the condition is described as one that the respondent already has and might die from – as used for the treatment question) is typically greater than willingness-to-pay asked ex ante (e.g. the condition is described as one that the respondent might contract and might die from – as used for the prevention question). This suggests that the willingness-to-pay

technique may underestimate the value of vaccines and other preventive interventions compared to other methods.

An overall preference for curative treatments over preventive interventions was also reported by Schwappach (2002), based on a survey of the German general public using multiple methods (person trade-off, standard gamble, ranking exercise).

On the whole, the empirical literature suggests that society places greater value on preventive treatments than on curative treatments, though there are some studies reporting the opposite finding and limited evidence of preferences relating to vaccines specifically.

Dispersion Of Benefits

In the UK Government's (now scrapped) proposals for the value-based pricing of medicines (Department of Health, 2010), it was suggested that treatments that lead to 'significant' improvements in health ought to be given a premium, based on the view that society prefers to concentrate sizeable QALY gains amongst a few people rather than to distribute smaller QALY gains to a larger number of people. Similarly, Christensen et al. (2014) suggest that society places greater value on preventing rare cases of severe disease rather than frequent instances of mild disease, citing a US study of preferences and willingness-to-pay for different health outcomes (of varying severity) prevented by pneumococcal conjugate vaccine (Prosser et al., 2004).

A recent review of the empirical literature (Gu et al., 2015) identified 23 studies that elicited preferences for the size or distribution of health gains. The evidence suggests that large gains are universally preferred over small gains, though several studies report diminishing preferences for larger gains as the size of gain increases. More often than not, studies investigating the issue of concentration versus dispersion have reported that people prefer to give small gains to many rather than large gains to a few (in contrast to the view underpinning the value-based pricing proposals). However, some studies (e.g. Olsen (2000)) find that this preference is observed only when the size of gain is greater than a certain threshold. Further, Bosworth et al. (2010) report findings that utility is not linear in the numbers of avoided deaths, with evidence of diminishing marginal utility in the numbers of prevented or treated illnesses. This means, for example, that the value (in terms of utility) of avoiding 5,000 deaths would be worth less than 10 times the value of avoid 500 deaths. The authors suggest that this may be linked to a psychological phenomenon known as 'psychophysical numbing' (Fetherstomhaugh et al., 1997). The results of the Bosworth et al. (2010) study lend weight to the argument that people would place greater weight on the prevention of a small number of deaths or a small number of serious sequelae or disabilities than on preventing/treating a large number of mild health problems.

Other Aspects Of Preferences

Christensen et al. (2014) point out that demand for the meningococcal vaccine is driven by a combination of the aforementioned factors: it is used to prevent a severe disease, and it is children that are at greatest risk. There is evidence that the public would place considerable value on the availability of the vaccine based on these characteristics.

The notion of 'dread diseases' is also relevant here. In the Bosworth et al. (2010) study mentioned above, it was suggested that society may be willing to prioritise the reduction of cancer risks over the reduction of risks of other conditions, independent of the severity of the conditions, based on the fear that cancer provokes relative to other conditions. Other research also suggests that cancer is a dread disease that generates fears that are "greater than would be justified by its objective risk probabilities" (Shah, 2017; Viscusi, Huber and Bell, 2014).

Meningococcal disease may similarly be described as a dread disease; Department of Health surveys of parents have consistently found that meningitis is the illness that they fear most (Yarwood et al., 2005). It is not just parents and members of the public who dread meningococcal disease, there is evidence that health professionals also dread it, that is they dread misdiagnosing it due to the serious

consequences of failing to treat it early: "Meningococcal disease is devastating—a disease that every family doctor, emergency department doctor and paediatrician who encounters a febrile child dreads to miss" (Sarfatti, Martinón-Torres and Nadel, 2015, p.516).

This offers further evidence that investments in preventing meningococcal disease are more socially valuable than is assumed based on standard methodologies; current approaches tend not to take social preferences (including those of different stakeholders like health professionals) and the psychological effects of the disease into account.

3.5 Quality and appropriateness of quality of life and utility measurement in vaccine

In this section of the report we consider how present evaluation strategies might fail to adequately estimate the value of vaccines for individuals and society and how those failings might be addressed. In particular, we examine whether and to what extent the tools most commonly used to measure health loss in economic evaluations of vaccines are fit for purpose. We focus largely on the EQ-5D because it is the most widely-used preference-based measure (PBM) of health in economic evaluations of health technologies and because it is the measure recommended for this purpose by NICE and therefore, by extension, by the JCVI. We also examine the breadth and robustness of the quality of life information currently available to inform and populate economic models of meningococcal vaccines and discuss some of the potential ways in which the measurement of health losses and gains in this space could be improved. In addition to assessing how well tools such as the EQ-5D and others identified in previous sections measure psychological impact, we expand the assessment beyond just psychological impairment, as there are other areas of health relevant to meningitis in which the performance of the EQ-5D can be questioned.

3.5.1 Overall view of utility elicitation and the use of utility weights in meningitis economic models

A useful starting point to this section are the conclusions of a recent systematic literature review from the Office of Health Economics (Herdman et al., 2016) which looked at the sources and characteristics of utility weights used in economic evaluation of paediatric vaccines.[3] In the case of meningitis, findings from the review indicated:

- A wide range of approaches to the estimation of utilities, from the application of a, sometimes arbitrary, percentage reduction (e.g. utility decrement for moderate sequelae = 20% reduction in quality of life) to utility estimates based on a wide range of sources in the same study.
- The use of different PBMs to assign utilities to the sequelae of meningitis, as if weights obtained from the EQ-5D and HUI (two different utility instruments) were directly comparable, without adjustment.
- Lack of clarity or non-reporting of the source of utilities.
- Use of non-standard PBMs, such as the EQ-5D+ (an expanded version of the EQ-5D with add-on dimensions).
- Wide variations in the utility losses attributed to the same sequelae, e.g. amputations or scars assigned a utility of 0.83 in Bos et al. (2001) compared to utility weights of 1 for scarring and 0.70 for a single amputation in a study by Ortega-Sanchez et al. (2008).

[3] *Paediatric populations were defined in the search criteria as < 18 years.*

- No consideration given to the possibility that utility weights for the same condition, e.g. amputation, might vary across age groups, for instance between children and adults.

The authors found that, in economic modelling studies of paediatric vaccines in general, the source for the utilities used was often unclear, poorly reported, or based on weak underlying evidence. Additionally, at the time of the review, only one study was identified which directly elicited utilities for meningitis-related health states. Koomen et al. (2005) studied the health problems of school-age survivors of bacterial meningitis, using school-age siblings or friends as a reference group. The final cohort was quite large, but consisted of only 42% of the original cohort so it was likely prone to selection bias. The instrument used was the HUI and although the study was conducted in the Netherlands, the weights assigned to the resulting health states were derived from the Canadian value set, i.e. the preferences of the Canadian general population were applied to health states experienced by Dutch children. Similar issues are present in more recent evaluations of meningitis vaccines (Tirani et al., 2015) and a recent framework document on the economic evaluation of vaccines made very little mention of standards or sources for utility weights used in economic models (Ultsch et al., 2016).

3.5.2 Use and usefulness of EQ-5D in assessing the impact of meningitis

As discussed above, the EQ-5D is currently the most widely used PBM and is the instrument that NICE recommends for use in economic evaluations. However, the ability of the EQ-5D to accurately assess the impact of meningitis and the value of treatments to avoid the disease can be questioned, for a number of reasons.

One issue is that there is currently no version of the EQ-5D available for use in very young children and infants, i.e. children under the age of about 5 years. As babies and children under 5 are particularly susceptible to contracting meningitis, the lack of a suitable version of the EQ-5D for use in that age group is an obvious limitation. One possibility might be to use the 'youth' version of the EQ-5D (EQ-5D-Y). However, that version was designed for use in children aged from approximately 5 years to 15 years and recent unpublished discussions between EuroQol Group members (which includes report authors Koonal Shah and Mike Herdman) and paediatricians and child psychologists indicated that the content (i.e. the questionnaire dimensions) is not suitable for a young age group. The lack of a version for use in this population makes it impossible to obtain utility weights for meningitis-related health states in these children, at least when using the EQ-5D. In fact, according to a recent review, there are no PBMs currently available for use in children under the age of about 5 years, though one appears to be in development (Chen and Ratcliffe, 2015). Therefore, it is not clear how utility assessment could be reliably and validly carried out in the youngest age groups or how weights representing quality of life decrements or gains could reasonably be assigned in an economic model.

A further concern with the EQ-5D-Y, even in the age range in which it was designed to be used, is that the content was based on the existing adult version, with some changes to the wording to make it more amenable to children and adolescents. However, the same dimensions were used as in the adult version, so it is possible to question whether the content is entirely appropriate even for older children; for example, there are no specific dimensions on school life or relationships with friends, peers, and family, aspects of quality of life which have been found to be important in this age group (though some of these elements are mentioned in the usual activities dimension). On the other hand, the EQ-5D-Y has been quite widely used and has been validated in the relevant age group (Ravens-Sieberer et al., 2010) though not in children with sequelae of meningitis.

It should also be noted that no value sets are currently available for use with the EQ-5D-Y, though work is on-going within the EuroQol Research Foundation to rectify that. For the time being, however, the lack of a value set means that results collected using the EQ-5D-Y cannot be converted into utility values for incorporation into economic models.

Some of the problems noted are not just specific to the EQ-5D. In general, it is fair to say that measurement of public preferences and values in relation to health states for paediatric populations is an under-researched area, in which aspects such as who should value the health states and how, are still not as well defined as in the valuation of health states in adults. The inclusion of health state values in economic models for paediatric age groups is therefore fraught with difficulties.
A final concern regarding the EQ-5D is that it may not be sensitive to the type of health problems most frequently shown by survivors of bacterial infection with meningitis and not just in younger age groups. Typical sequelae of meningitis include cognitive problems, seizures, hearing loss, motor limitations, amputations, vision problems, and behavioural problems (Al-Janabi et al., 2015). With respect to cognitive problems, the evidence is somewhat contradictory; some studies have shown that the EQ-5D can be useful in diverse groups with cognitive problems, such as patients with multiple sclerosis (Campbell et al., 2017) those with post-stroke cognitive impairment (Park et al., 2013), or elderly patients (Wolfs et al., 2007), although at least one study has found no impact of cognitive impairment on EQ-5D scores (Buanes et al., 2015). Most studies of EQ-5D in the area of cognitive impairment have been carried out in elderly subjects, however, and it is not clear that the results are transferable to meningitis survivors, who may have different types of problems with cognition. Further investigation of the performance of EQ-5D in this area is therefore warranted.

In the areas of hearing and vision, a recent review indicated that the EQ-5D showed a poor performance in the former and a mixed performance in the latter (Longworth et al., 2014). The authors identified 18 studies which used a PBM in individuals with hearing impairment, with the Health Utilities Index version 3 (HUI3) being the most commonly used measure, followed by the EQ-5D. In the six studies which used HUI3, the measure showed a good performance and was able to distinguish between groups defined by their severity as well as detecting change in most cases after an intervention. On the other hand, the EQ-5D showed poor sensitivity to change over time and only a weak ability to discriminate between groups defined by the severity of their hearing problems. In the case of vision, almost all of the studies showed that the EQ-5D could discriminate between patients with vision problems and those without, though when comparing EQ-5D scores across groups defined by severity of visual impairment most studies found there was little or no difference between groups. Evidence on responsiveness and convergent validity was weak or indicated that the EQ-5D performed poorly. The HUI3 generally demonstrated good validity in patients with the visual impairments.

In a direct comparison of the EQ-5D and the HUI to estimate values for permanent sequelae of meningitis, Oostenbrink et al. (2002) indicated that each instrument resulted in different absolute quality weights, in particular for states associated with "deafness" and "mental retardation". They suggested that, due to differences in performance, the HUI might be preferable to EQ-5D in studies focused on "sensation" (hearing, vision, speech) or "cognition". They also noted that the differences were not relevant in a cost-utility study of diagnostic strategies to rule out bacterial meningitis but that they may be relevant in cost-utility analysis of therapeutic strategies and recommended that sensitivity analysis of quality weights be carried out. It should be noted, however, that health states were generated by a panel of paediatricians and were not derived from patient self-assessment or proxy evaluation.

In regard to the type of behavioural problems which may be associated with acquired brain injuries stemming from meningitis, little evidence is available on the performance of the EQ-5D. More work has been done to assess its performance in the area of anxiety and depression with the evidence indicating that it functions relatively well. Sapin et al. (2004) found that it was a useful measure in major depressive disorder while Whynes (2009) found that there was a significant association between the Hospital Anxiety and Depression Scale (HADS) identified anxiety and/or depression and the EQ-5D Index and visual analogue scores (VAS). They also found that EQ-5D scores improved over time as anxiety and/or depression decreased. A recent analysis of data from several data sets indicated that there was evidence for the construct validity and responsiveness of EQ-5D in common mental health and personality disorders, including depression (Mulhern et al., 2014), while a literature review also supported the use of the EQ-5D in depression and, possibly to a lesser extent, in anxiety (Brazier et al., 2014).

3.5.3 Possible biases associated with proxy responses

In some situations, it may not be possible to obtain EQ-5D responses directly from patients or from the individuals of interest, for example, if they are cognitively impaired. In that case, proxy reports may be used, i.e. someone who knows the patients well, such as a caregiver or family member, is asked to assess the patient's health status. However, a risk with that approach is that there can be discrepancies between the caregiver perception of the subject's health state and the perception of the subject him/herself (Kunz, 2010). One of the few studies to have used EQ-5D directly in meningitis found substantial discrepancies between proxy and self-assessments, with caregivers rating the subjects' health substantially worse than the subjects themselves (Kulpeng et al., 2013). The use of proxy respondents can therefore be a source of bias in economic models if their assessments of the subject's health are then used to generate utility weights. Notably, in the Kulpeng et al study, meningitis was associated with much lower EQ-5D scores than any of the other conditions assessed (bacteremia, pneumonia, hearing loss, epilepsy, and MMR, among others), though the study, which was performed in Thailand, only included a small number of proxy-subject pairs in the meningitis group.

3.5.4 Using EQ-5D to assess the impact of meningitis on family members of survivors

The health and well-being impact of illness of a patient's wider network, that is their family, carers and friends, is an under-researched area. An exception to this is the research of Hareth Al-Janabi, see Al-Janabi, Nicholls and Oyebode (2016a); Al-Janabi et al. (2016b); Al-Janabi, McCaffrey and Ratcliffe (2013). Notably some of this work has focused specifically on meningococcal disease. Al-Janabi et al. (2015) used the EQ-5D to investigate whether and to what extent the health-related quality of life of family members of survivors of invasive meningococcal disease was affected. The study found evidence of an effect, the estimated impact is 0.041 points on the utility index. This is an important study, particularly given its focus, and its application could be replicated more broadly. It is not clear, however, whether the EQ-5D is a sensitive instrument in this context (for the reasons discussed above) or whether other PBMs would better reflect how living with and caring for survivors of bacterial meningitis affects family members. Further research is therefore required in this area.

One avenue for additional research could be to compare the performance of the EQ-5D against other PBMs to investigate whether alternative measures show a greater effect on families/carers than the EQ-5D. One instrument that would be worth considering is the Assessment of Quality of Life (AQoL-8D) instrument (Richardson et al., 2014). This instrument includes the dimensions of Independent Living, Happiness, Mental Health, Coping, Relationships, Self Worth, Pain, and Senses. A further avenue of research would be to investigate the content validity of EQ-5D in this context (Keeley et al., 2013; Matza et al., 2015). Qualitative research could explore family members' opinions as to how well the EQ-5D captures the impact of living with survivors of invasive meningococcal disease and whether important aspects of their experience are missing from the instrument.

4 Conclusions

The individual, societal, and economic benefits of disease prevention resulting from childhood and adult immunisation programmes are without question. The Men C immunisation programme offers an example of this. This vaccine has been found to be cost-effective and has significantly decreased the probability of carriage. Although Men C vaccine has proved to be effective, a number of countries with relatively high rates of meningococcal cases do not include it in their national immunisation schedules (e.g. Denmark, Croatia and Lithuania). Similarly, Men B vaccine has proved to be key in the fight against meningococcal serogroup B infection, but is currently only in the National Immunisation Plans of a limited number of countries. The reasons for the non-implementation/non-adoption of the Men C and/or Men B vaccine in countries with a relatively high number of cases are unclear. This lack of transparency has resulted in reimbursement and adoption decisions for vaccines, and the validity of the economic evaluations and their assumptions which inform such decisions, being scrutinised.

In order to select those immunisation programmes that represent an efficient use of public resources, the decision making process should consider a set of assumptions and criteria that reflect the particularities of this group of preventive interventions. In this respect, the first step to improve the decision making process for vaccine is to understand how health benefits are currently valued, how these are compare with the related expenditures, and the importance of both in the final decision. The objective of this report was to document the decision making criteria for meningococcal vaccine reimbursement and the methodologies used to inform decisions about adopting vaccines as well as to suggest new criteria that, given the nature of the benefits derived from vaccines, could be considered.

4.1 The current evidence base

We conducted a literature review of recent economic evaluations of meningococcal vaccination strategies. The articles identified mostly relate to high-income countries. Our review found that the most common assessed vaccine in the economic literature is Men B; however, articles related to Men C and Men ACYW vaccines were also identified. The literature review suggests that the cost-effectiveness of the vaccine schedule depends on particular model assumptions, principally herd protection, the discount rate(s), the perspective of the evaluation and the vaccine price.

A key factor to extract meaningful conclusions in economic evaluations is the appropriate selection of the comparator. The literature review suggests that recent economic evaluations of meningococcal vaccines satisfied two requirements: (1) to include the non-vaccination strategy as comparator, and (2) to assess more than one strategy. These two requirements reduce the probability of selecting a non-cost-effective comparator and reflect the fact that policy makers' decisions require the selection of the most appropriate vaccine schedule out of the list of plausible choices.

When quantifying benefit in the economic evaluations QALY losses related to survivors with sequelae is the most common approach. Meningococcal B disease has a number of important features that make the assessment of the validity of QALY values used a key determinant. Our review identified differences in the type of sequelae considered as well as differences in the sources used to extract QALY weights. Given the variation in sources and tools used to estimate HU loss, there is a need for a rigorous assessment of the quality of the information used in this estimation. Such an analysis should explore the transferability of information among different context as well as the suitability of the estimations to reflect the HU losses from particular sequelae. Further research that critically appraises tools used to estimate HU values may reveal why few countries have implemented

meningococcal vaccination programmes. It could also indicate areas where methodological improvement effort should be focused.

The literature review also reveals that QALY losses for caregivers of survivors with sequelae are not commonly considered. This is in part explained by the lack of adequate tools to estimate how living with and caring for survivors with sequelae affects family members and other caregivers.

Acknowledging these potential underestimates of health gain the JCVI has suggested a QALY adjustment factor or QAF. The use of QAFs in economic evaluations of meningococcal vaccination strategies recognises that HU losses associated with the disease are substantial and greater than what it is possible to capture using standard methods. While the QAF is a welcome adjustment it is unclear how the dimensions that the JCVI sought to capture in the case of the meningococcal B vaccine (e.g. incremental innovation value, estimation of HU losses for children, etc.) are weighted in order to derive the QAF value current recommended by JCVI (x3). Further research should investigate the assumptions and methods behind the QAF factor proposed by JCVI and to what extent the difficulties in estimating the cost-effectiveness of a meningococcal vaccine are alleviated by the use of this factor. Our analysis did not reveal any other similar attempt to consider the complexities surrounding the estimation of QALYs in the case of survivors of meningococcal infections. The possibility of applying QAF in other contexts should be evaluated as well as alternative possible tools or adjustments that would improve the estimation of the health benefits of meningococcal vaccination programmes.

Given the health benefits derived from a vaccination strategy are observed in a time period that is posterior to the initial expenditure when a single discount rate is used (that is the same rate for costs and outcomes) health benefits are more heavily discounted than costs. 41% of the full economic evaluations reviewed applied only a single discount rate, effectively ignoring the lag between health benefits and expenditures. The country comparison suggests that it is common practice for HTA agencies to recommend in the base case scenario a single discount rate for both health benefits and costs. Therefore, further research is required to examine the extent to which the evaluation of a new vaccine is affected by the fact that a single discount rate influences health benefits estimations more than costs. We did identify examples where different discount rates were used. For instance, the Netherlands recommends a differential discount rate for costs and health benefits. In the majority of articles reviewed three approach to testing the sensitivity of the discount rate were common: (1) alternative discount rates during the sensitivity analysis, (2) differential discount rates in the base case and/or sensitivity analysis, and (3) non-constant discount rate over time. Our analysis of the literature found significant changes in ICERs as a result of variations in the discount rate which could lead to conflicting conclusions.

An additional source of uncertainty is structural uncertainty in the modelling of ICERs. Even though herd protection is key feature, static models were the most commonly employed mathematical models (59%). This likely due to a lack of information to populate a dynamic model and the additional cost of estimating a more complex model.

In order to demonstrate that a vaccine strategy represents an effective use of public resources, it is important to consider all relevant economic savings. In this regard, indirect costs demonstrate the value of a preventive intervention such as a new vaccination implementation to the broader society. The literature review found that a societal perspective, which includes indirect cost, is common practice. The majority of articles that considered indirect cost include productivity losses. The information collected during the interviews suggests that the HTA agencies in all selected countries, except for Australia, recommend the estimation of productivity losses in the assessment.

4.2 Current adoption criteria and alternative criteria

The majority of our country experts identified the clinical outcomes and disease burden as the main criteria required to inform a decision at a national level, followed by national health system priorities.

The clinical outcomes and disease burden were classified as being formally required in the guidelines of all included countries. Of the financial factors, cost-effectiveness analysis and budget impact were the two most commonly mentioned as key factors. Notably the experts reported that cost-effectiveness analysis is (either formally or informally) part of the decision making process of every country in our sample.

During the interviews information relating to three possible additional novel criteria: incremental innovation, potential of peace of mind, and public preferences, were collected. Incremental innovation is only commonly considered in Japan. In relation to public preferences, the experts from the Netherlands and New Zealand reported a negative effect on the probability of inclusion of a new vaccine in the national immunisation plan when the anti-vaccine lobby raised concerns about the safety of vaccination and possible adverse effects. These concerns could affect the population's trust in a national immunisation programme and negatively impact the overall uptake of vaccines, therefore, the governments should be cautious when seeking to include a new vaccine that might provoke such pressure.

Of the criteria that the experts regarded as important for informing decision makers few reflect the meningococcal disease characteristics that are in line with the NICE Citizens Council's list (a list of criteria where the Citizens' Council thought it was acceptable to depart from established cost effectiveness thresholds). Examples include the importance of herd protection and the high cost of the sequelae which are related to the capacity of the vaccine to prevent more harm in the future. With respect to peace of mind benefits, none of the experts were able to provide an example in which peace of mind was considered in the decision making process. This can be in part be explained by the lack of an evidence base regarding peace of mind, which is likely to hinder the consideration of such effects in reimbursement decisions. New instruments and/or measures of peace of mind and posterior testing of the concept will be needed before this criterion can be formally incorporated in the decision making process.

The existing evidence in the stated preference literature suggests that members of the public consider factors other than QALY gains and cost-effectiveness to be important in determining health care priorities. On the whole, the literature suggests that people would place a greater value on preventive interventions compared to curative treatments; on preventing severe or life-threatening illness compared to mild illness; and on the health and survival of younger people compared to older people. Despite these public preferences such factors are rarely considered formally in the various countries' decision making processes. Failure to take public preferences into account may result in an underestimation of the true value of vaccines to society.

4.3 Improving the measurement of value of health

Recent research has shown that there is considerable room for improving the quality and appropriateness of quality of life and utility measurement in the area of vaccines; utility weight assessment and assignation in this area is haphazard and it is not built on a strong evidence base. Another area of concern is the use of EQ-5D to measure and value health in this context, when a) no version exists for children under 5 years of age, b) no value set is currently available for use with the youth version (EQ-5D-Y), i.e. for children aged 5 to 15 years, c) there are legitimate doubts about its ability to adequately capture the impact on health status of a number of the sequelae of meningococcal infection, d) it is not clear whether EQ-5D is well-suited to assess the impact on family members of living with a survivor of meningococcal infection.

Given these issues, the accuracy with which the impact of meningitis and the benefits of prevention are measured and valued, and then incorporated into economic models, can be called into question. A number of avenues are available to improve the current situation. In particular, further testing of EQ-5D and EQ-5D-Y in meningitis survivors, alongside alternative PBMs and/or other quality of life measures, would help to increase knowledge of how well the instrument works in that population and

the extent to which it may fail to capture important effects of infection. Similarly, while we have some evidence on the effect of sequelae on family members and their quality of life, further research is required to investigate the extent to which standard HRQL instruments (like the EQ-5D that has been used in carers research to date) adequately captures the impact of living with a meningitis survivor. Such research could include both quantitative and qualitative approaches. Finally, tools are needed to better assess and value, via the use of utility weights, the impact of meningitis in children and infants. On-going developmental work within the EuroQol Research Foundation focusing on children could prove beneficial in this regard.

4.4 Final thoughts

There is discrepancy between the factors that characterise the potential benefits of implementing a new vaccination programme and the methodologies and criteria considered to evaluate the programme. This is particularly true in the case of the vaccines against the meningococcal B disease. Meningococcal B infection is a lethal disease where a significant percentage of the patients are children, among those who survive a large proportion suffer from severe long-lasting sequelae whose negative effects on well-being are extended to the family. The methodologies currently in place do not fully reflect this complex panorama, therefore, the health benefits of avoiding meningococcal B disease have not been fully considered in any decision making process.
Despite the current limitations, we can be optimistic about the future as there have been a number of important steps to improve the decision making process. There have been a number of reported changes in the last 15 years in both the economic evaluation methodology and in the decision making process that have strengthened the processes towards more rigorous and transparent practices. These improvements require continued support from governments and other relevant stakeholders, such an environment will foster further improvements in the valuation of health benefits and changes in the decision making process.

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- Appendix 1 – Interview protocol

This project aims to understand current health technology assessment (HTA) methodologies that inform decision making for the inclusion of vaccines in the reimbursement list globally. We aim to document the methodology employed by HTA agencies (often referred to as the reference case) as well as the main criteria considered during the decision making process. As part of this work, we are conducting a series of interviews with experts from seven countries.

We break down the decision-making process into:

(1) Nomination and prioritisation: First stage in the decision making process where, from the list of vaccines that have a market authorisation, the group of vaccines that will be evaluated for possible inclusion in the positive list is selected.

(2) Assessment of selected interventions: The process of assessing and interpreting research results by systematically analysing their validity, clinical and statistical significance, and clinical relevance. Given the fact that HTA is a concept that is understood differently in each country, we refer to HTA as any systematic process where a health agency (private/ public) makes evidence-based decisions or recommendations on the reimbursement status or use within the National Health System regarding health interventions.

(3) Decision on the inclusion of a new vaccine: The institution or committee responsible makes a final decision on the inclusion of the vaccine in the positive list.

The interview should take no longer than an hour. If you are willing we would like to record the interview, to help us write up and verify our notes. We will not quote you directly without your permission, and we will delete the recordings once the project is finished.

Establishing your expertise

1. Can you please give us a brief outline of your involvement in HTA and/or the decision making process for vaccines in your country?

General question

2. Is there a National Committee on Immunisations in your country? What is the role of this institution? Where does it sit in relation to your Department or Ministry of Health?

Nomination and Prioritisation

3. Are all vaccines that have gained market authorisation evaluated for possible inclusion in the positive list, or is there a process for selecting which vaccines are evaluated?
    a. Which institution decides on the prioritisation plan for the selection of the vaccines to be evaluated?
    b. Which criteria are considered for the prioritisation of the vaccines?

Assessment of the new vaccine

4. What, if any, is the role of HTA in deciding which vaccines to offer?
    a. Who undertakes the HTA for vaccines, if desired? e.g. is it an external organisation, the manufacturer or the Department/Ministry of Health?
5. Methodology

a. Does the assessment of a new vaccine require a systematic review of the clinical evidence, or any other type of systematic literature review?

    i. Is it common to include unpublished data in the literature review?

    ii. Is the quality of the evidence normally assessed?

b. Does the assessment of a vaccine include consideration of results from mathematical modelling (e.g. transmission modelling)? What is the model most commonly used?

c. Are health economic evaluations (e.g. cost-effectiveness studies) required? Are budget impact or cost analyses required?

d. Outcomes

    i. What are the principal outcomes considered?

    ii. If an economic evaluation is undertaken, are health utility losses considered in the analysis? How? Are QALYs considered an important outcome?

e. What types of costs are included?

f. Assumptions: What discount rate is used for vaccines? Is it the same for costs and outcomes? Is this the same for other health technologies?

g. Are there differences in the type of outcome or in the type of costs included in the analysis depending on the age group? e.g. for children, teenagers, adults, elderly.

6. Over the past few years have there been any changes in the way that new vaccines have been assessed for reimbursement purposes?

7. Is there a reference case or guidelines for the evaluation of the new vaccines?

8. What is the ultimate outcome of the assessment of a new vaccine: a binding recommendation, a non-binding recommendation, or something else?

Decision on the inclusion of a new vaccine

9. Who is the final decision-maker for vaccine reimbursement and inclusion on the national programme?

10. If HTA informs the decision process for vaccines in your country, are decision-makers usually aware of the uncertainty surrounding the parameters?

11. Criteria

    a. A list of possible criteria is presented in TABLE 23. In the 'Considered' column, could you please indicate the extent to which these criteria are:

        - FC: Formally considered
        - CIC: Commonly and informally considered
        - UIC: Uncommonly and informally considered
        - NAC: You do not have information on whether it is formally or informally considered

12. What do you regard as the five main criteria considered when making a decision to reimburse a new vaccine in your country? Could you please number them from one to five in TABLE 23 according to the importance that the final decision-maker assigns to them?

13. Additional comments regarding the decision criteria:

    a. How important is cost-effectiveness analysis in decisions about the introduction of vaccines in comparison with the decision about the introduction of other types of health intervention?

    b. If public preferences are a criterion for the decision, how are they considered?

    c. If equity is a factor in the decision, how is equity defined by policy makers? (e.g. socioeconomic, gender)

    d. Is there any consideration of the 'peace of mind' benefits of vaccination?

    e. Are different criteria applied to different age groups?

    f. Are there any other criteria that you would like comment on?

14. Are HTA decisions regarding vaccines in your country influenced by other countries? How?

15. Over the past few years have there been changes to the way HTA decisions have been made over time? e.g. differences in criteria and/or differences in the importance of the criteria?

Meningococcal Vaccines

16. Is there a meningococcal vaccine included in the national routine immunisation schedule? When was the vaccine approved?

17. Do you know the main criteria that supported the decision of included or not the meningococcal vaccine in the national routine immunisation schedule?

18. Are you able to share with us any documents relating to this decision?

Thank you for your time and input.

As noted above, we won't quote you directly in either reporting format without asking your permission.

TABLE 23. CRITERIA CONSIDERED IN THE DECISION PROCESS FOR THE INCLUSION OF VACCINES

Factors	Criteria	Considered	Ranking 1 to 5
Intervention specific	Clinical outcomes		
	Health effects - patient health utility losses measured through QALYs		
	Health effects - patient health utility losses measured through _____		
	Health effects - family / caregivers health utility losses		
	Treatment side effects profile		
	Impact on existing processes of care or care pathways		
	Patient convenience		
	Average duration of the vaccine protection		
	Herd immunity/protection		
	Other_____		
Disease-related	Severity of health condition		
	Sequelae		
	Disease burden		
	Other_____		
Charac. of the target population	Equity (e.g. socioeconomic status, gender, ethnicity, stigma)		
	Age group		
	Other_____		
Financial	Cost-effectiveness analysis		
	Cost offset (per patient) to the health care system		
	Indirect costs - impact on non-health public sectors		
	Indirect costs - impact on individuals/households		
	Productivity losses - patients		
	Productivity losses - family / caregivers		
	Catastrophic effect/financial risk on individuals for not funding certain interventions		
	Total budget impact		
	Other_____		
Macro-level	National health system priorities; political considerations / objectives		
	Current service delivery setting/health care system "readiness" to provide the vaccine		
	Existence of a legal process to get access to interventions if they are not included		
	Other_____		
Additional Criteria	Incremental innovation (aids development of new vaccines)		
	Potential of peace of mind		
	Public preferences		
	Other_____		

1. Office of the Federal Register. Fraud and Abuse; Removal of Safe Harbor Protection for Rebates Involving Prescription Pharmaceuticals and Creation of New Safe Harbor Protection for Certain Point-of-Sale Reductions in Price on Prescription Pharmaceuticals and Certain Pharmacy Benefit Manager Service Fees. Federal Register. Published February 6, 2019. Accessed February 15, 2019. healthaffairs.org

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- Evaluation of health care policy
- The economics of health care systems
- Health technology assessment (HTA) methodology and approaches
- HTA's impact on decision making, health care spending and the delivery of care
- Pricing and reimbursement for biologics and pharmaceuticals, including value-based pricing, risk sharing and biosimilars market competition
- The costs of treating, or failing to treat, specific diseases and conditions
- Drivers of, and incentives for, the uptake of pharmaceuticals and prescription medicines
- Competition and incentives for improving the quality and efficiency of health care
- Incentives, disincentives, regulation and the costs of R&D for pharmaceuticals and innovation in medicine
- Capturing preferences using patient-reported outcomes measures (PROMs) and time trade-off (TTO) methodology
- Roles of the private and charity sectors in health care and research
- Health and health care statistics

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