KCE REPORT 231

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

A QUADRIVALENT VACCINE AGAINST SEROGROUP B MENINGOCOCCAL DISEASE: A COST-EFFECTIVENESS STUDY

KCE REPORT 231
HEALTH TECHNOLOGY ASSESSMENT

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

A QUADRIVALENT VACCINE AGAINST SEROGROUP B MENINGOCOCCAL DISEASE: A COST-EFFECTIVENESS STUDY

GERMAINE HANQUET, HANNAH CHRISTENSEN, EMILY AGNEW, CAROLINE TROTTER, JO ROBAYS, CECILE DUBOIS, STEPHAN DEVRIESE, STEFAAN VAN DE SANDE, NANCY THIRY

2014 www.kce.fgov.be

COLOPHON

Title:	A quadrivalent vaccine against serogroup B meningococcal disease: a cost-effectiveness study
Authors:	Germaine Hanquet (KCE), Hannah Christensen (University of Bristol), Emily Agnew (University of Bristol), Caroline Trotter (University of Cambridge), Jo Robays (KCE), Cécile Dubois (KCE), Stephan Devriese (KCE), Stefaan Van De Sande (KCE), Nancy Thiry (KCE)
Project coordinator:	Kristel De Gauquier (KCE)
Reviewers:	Irina Cleemput (KCE), Frank Hulstaert (KCE), Raf Mertens (KCE)
External experts:	Nele Berthels (FAGG – AFMPS), Sophie Bertrand (ISP – WIV), Joke Bilcke (Universiteit Antwerpen), Nathalie Bossuyt (WIV – ISP), Daniel Brasseur (Hôpital Universitaire des Enfants Reine Fabiola), Pierre Chevalier (INAMI – RIZIV), Tine Grammens (WIV – ISP), Wesley Mattheus (WIV – ISP), Carole Schirvel (Fédération Wallonie Bruxelles), Béatrice Swennen (Université Libre de Bruxelles), Geert Top (Vlaams Agentschap Zorg en Gezondheid), David Tuerlinckx (Cliniques Universitaires de Mont Godinne), Erwin Van Kerschaver (Kind & Gezin), Yves van Laethem (Centre Hospitalier Universitaire Saint-Pierre), Anne Vergison (Université Libre de Bruxelles then Mutualités Socialistes)
External validators:	Philippe Beutels (Universiteit Antwerpen), Daniel Lévy-Bruhl (Institut de veille sanitaire – InVS, France), Isabelle Parent (Institut de veille sanitaire – InVS, France), Pierre Philippet (Centre Hospitalier Chrétien - Clinique de l'espérance, Liège)
Acknowledgements:	We thank Sophie Bertrand and Wesley Mattheus from the National Reference Centre for *Neisseria meningitidis* at the WIV-ISP for providing data on invasive meningococcal disease in Belgium, and Yves Parmentier (Technical Cell, RIZIV-INAMI) for the hospital data. We also thank Novartis for providing internal data that were necessary for our analysis, and the Vaccine working group of the Superior Health Council (CSS-HGR) for defining the vaccine schedules to be simulated and for providing advices. We also thank Niel Hens (Hasselt University), Mary Ramsay (PHE, UK), Helen Campbell (PHE, UK), Ray Borrow (PHE, UK), Helen Johnson (LSHTM, UK), John Edmunds (LSHTM, UK), Matthew Hickman (University of Bristol, UK), Laura Clark (University of Bristol, UK) and Bridget King (MHRA, UK) for providing data and for helpful discussions on previous versions of the models. We also thank Marijke Eyssen (KCE) and Genevieve Veereman (KCE) for their critical review of the description of the health care resources consumed to treat the sequelae after meningococcal disease. The model analysis performed by the University of Bristol builds upon independent research arising from personal fellowships [RDA/03/07/014 and PDF-2012-05-245 to Hannah Christensen, PDA/02/06/088 to Caroline Trotter] supported by the National Institute for Health Research (United Kingdom).
Other reported interests:	All authors declare to have no conflict of interest specific to the subject; Caroline Trotter has received consultant fees from GSK for a critical review of a meningococcal vaccine health economic model (March 2013) but this vaccine was targeting other serogroups.

All validators and external experts declare to have no conflict of interest specific to the subject of this study, except for the participation to a Meningococcal B Symposium sponsored by Novartis in 2013 (A. Vergison). David Tuerlinckx participated as co-investigator (Community-acquired pneumonia in children from Pfizer) and principal investigator (Measure of pneumococcal antibodies from Multigam) in two sponsored studies that were not related to this study, and received a travel grant from GSK to participate to the ESPID 2012 and ESPID 2013 conferences. The funds for research and grants were directly paid to his hospital and he received no personal remuneration for his work. Beatrice Swennen received a travel grant from GSK to participate to the ESPID 2013 and ESPID 2014 conferences. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health, United Kingdom.

Layout: Ine Verhulst

Cover picture: Left picture: http://www.medicalfacts.nl/2013/08/12/clusters-van-meningokokken-bij-msm-in-enkele-steden-in-europa-en-de-vs/

Disclaimer:

- **The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.**
- **Subsequently, a (final) version was submitted to the validators. The validation of the report results from a consensus or a voting process between the validators. The validators did not co-author the scientific report and did not necessarily all three agree with its content.**
- **Finally, this report has been approved by common assent by the Executive Board.**
- **Only the KCE is responsible for errors or omissions that could persist. The policy recommendations are also under the full responsibility of the KCE.**

Publication date: 14 October 2014

Domain: Health Technology Assessment (HTA)

MeSH: Meningococcal Vaccines; Neisseria meningitidis, Serogroup B; Infant; Adolescent; Cost-Benefit analysis; Costs and Cost Analysis

NLM Classification: WC 245

Language: English

Format: Adobe® PDF™ (A4)

Legal depot: D/2014/10.273/77

How to refer to this document?

Hanquet G, Christensen H, Agnew E, Trotter C, Robays J, Dubois C, Devriese S, Van De Sande S, Thiry N. A quadrivalent vaccine against serogroup B meningococcal disease: a cost-effectiveness study. Health Technology Assessment (HTA) Brussels: Belgian Health Care Knowledge Centre (KCE). 2014. KCE Reports 231. D/2014/10.273/77.

This document is available on the website of the Belgian Health Care Knowledge Centre.

TABLE OF CONTENTS

LIST OF FIGURES **5**
LIST OF TABLES **8**
LIST OF ABBREVIATIONS **11**
■ **SCIENTIFIC REPORT** **13**
1 BACKGROUND **13**
1.1 INVASIVE MENINGOCOCCAL DISEASE 13
1.2 MENINGOCOCCAL CARRIAGE 14
1.3 VACCINES AGAINST MENINGOCOCCAL DISEASE 14
1.4 RESEARCH QUESTIONS 14
2 BELGIAN DATABASES AND MATCHING **16**
2.1 DATABASE SOURCES 16
2.2 MATCHING OF THE MZG-RHM AND NRC DATABASES 17
3 BURDEN OF SEROGROUP B MENINGOCOCCAL DISEASE **18**
3.1 MEDICAL BURDEN 18
3.1.1 Incidence and age distribution 18
3.1.2 Temporal trends 19
3.1.3 Distribution of vaccine-preventable strains 21
3.1.4 Regional variations 21
3.1.5 Clinical picture 23
3.1.6 Mortality and case fatality ratio 23
3.1.7 Long-term complications and sequelae 24
3.2 QUALITY OF LIFE BURDEN 28
3.2.1 Methods 28
3.2.2 Results 28
4 VACCINE EFFICACY AND SAFETY **34**
4.1 VACCINE EFFICACY AGAINST DISEASE 34
4.1.1 SBA responses against the four vaccine components 34
4.1.2 Persistence of hSBA responses 36

4.1.3 Correlation between SBA and clinical protection 37
4.1.4 Predicted strain coverage of the 4CMenB vaccine 38
4.1.5 Relation between MATS and SBA 39
4.2 VACCINE EFFICACY AGAINST CARRIAGE 39
4.3 VACCINE ADVERSE EVENTS 40
5 ANALYTICAL CHOICES FOR THE ECONOMIC EVALUATION OF 4CMENB IN BELGIUM 42
5.1 MODELS STRUCTURE 42
5.1.1 Model structure - details common to both models 42
5.1.2 Model structure – static specific details 42
5.1.3 Model structure – dynamic specific details 42
5.2 OUTCOMES AND COMPARATOR 44
5.3 PERSPECTIVE 44
5.4 TIME HORIZON 44
5.5 DISCOUNTING 44
5.6 DEMOGRAPHICS 44
5.7 INTERPRETATION OF THE COST-EFFECTIVENESS RESULTS 45
6 INPUT FOR THE MODELS 45
6.1 VACCINATION STRATEGIES 45
6.1.1 Vaccination schedules 45
6.1.2 Vaccine uptakes to be simulated 47
6.2 CLINICAL / EPIDEMIOLOGICAL PARAMETERS 48
6.2.1 Age-specific incidence rates 48
6.2.2 4CMenB preventable disease 48
6.2.3 Case fatality ratio 49
6.2.4 Frequency of sequelae 49
6.3 VACCINE-RELATED PARAMETERS 50
6.3.1 Vaccine efficacy 50
6.3.2 Vaccine waning rate 50
6.3.3 Efficacy against transmission 52
6.3.4 Vaccine side-effects 52

6.4 QUALITY OF LIFE 53
6.5 ECONOMIC PARAMETERS 54
6.5.1 Acute care hospitalization costs 54
6.5.2 Cost of follow-up care for those with no sequelae 59
6.5.3 Cost of follow-up care for those with sequelae 59
6.5.4 Cost of public health interventions targeting contacts of a case 64
6.5.5 Vaccination programme costs 65
6.6 PARAMETERS SPECIFIC TO THE DYNAMIC MODEL 70
6.6.1 Meningococcal carriage 70
6.6.2 Mixing patterns 70
6.7 UNCERTAINTY 70
6.7.1 Probabilistic sensitivity analysis in the static model 70
6.7.2 Scenario analyses 73
6.8 SUMMARY OF INPUT PARAMETERS VALUES 76
7 MODEL VALIDATION 80
7.1 POPULATION 80
7.2 CASES PREDICTED 80
8 RESULTS FROM THE STATIC MODEL 81
8.1 CLINICAL IMPACT OF DIFFERENT VACCINATION POLICIES 81
8.2 COST-EFFECTIVENESS OF DIFFERENT VACCINATION POLICIES 81
8.3 FINANCIAL IMPACT OF DIFFERENT VACCINATION POLICIES 85
8.4 SCENARIO ANALYSIS 86
8.5 ANALYSIS OF COVARIANCE 89
9 RESULTS FROM THE DYNAMIC MODEL 90
9.1 CLINICAL IMPACT OF DIFFERENT VACCINATION STRATEGIES 90
9.2 COST-EFFECTIVENESS OF DIFFERENT VACCINATION STRATEGIES 96
9.3 SCENARIO ANALYSIS 97
10 USE OF 4CMENB IN OUTBREAKS OR CLUSTERS 102
11 DISCUSSION 103
11.1 4CMENB VACCINATION 103

11.1.1 If 4CMenB has no effect on transmission (base case) ... 103
11.1.2 If 4CMenB may prevent transmission ... 104
11.1.3 Use of 4CMenB in control of clusters and outbreaks ... 105
11.2 STRENGTHS AND LIMITATIONS ... 106
11.3 IMPLICATIONS FOR PRACTICE ... 108
11.4 FUTURE PERSPECTIVE ... 109
12 CONCLUSIONS ... 110
■ **APPENDICES ... 111**
APPENDIX 1. REVIEW OF THE LITERATURE ON QUALITY OF LIFE ... 111
APPENDIX 1.1. SEARCH STRATEGIES ... 111
APPENDIX 1.2. SELECTION OF THE STUDIES ... 114
APPENDIX 2. ICD-9-CM CODES ... 115
APPENDIX 3. COSTS OF IMD PATIENTS WITH SEQUELAE ... 116
APPENDIX 3.1. SEROGROUP B ... 116
APPENDIX 3.2. ALL SEROGROUPS ... 119
APPENDIX 4. INFANT VACCINE CALENDAR IN BELGIUM ... 122
APPENDIX 5. DYNAMIC MODEL EQUATIONS, POPULATION MIXING AND RISK OF DISEASE GIVEN INFECTION ... 123
APPENDIX 5.1. TRANSMISSION DYNAMIC MODEL EQUATIONS ... 123
APPENDIX 5.2. MIXING PATTERNS – SIMPLE PREFERENTIAL MIXING ... 123
APPENDIX 5.3. TRANSMISSION DYNAMIC MODEL PARAMETER FITTING ... 124
APPENDIX 6. COST OF PUBLIC HEALTH INTERVENTIONS FOR CONTACTS OF AN IMD CASE ... 126
APPENDIX 7. INCREMENTAL COST-EFFECTIVENESS ANALYSIS, DYNAMIC MODEL WITH 0% VACCINE EFFICACY AGAINST CARRIAGE ... 127
APPENDIX 8. MONTE CARLO SIMULATION RESULTS ON THE COST-EFFECTIVENESS PLANE FOR THE SCENARIO ANALYSES OF THE STATIC MODEL ... 128
■ **REFERENCES ... 133**

LIST OF FIGURES

Figure 1 – Matching algorithm of the MZG-RHM and NRC databases 17
Figure 2 – Incidence of serogroup B cases by year of age, average 2009-10 19
Figure 3 – Annual numbers of reported invasive meningococcal cases by serogroup, 1950-2012 20
Figure 4 – Serogroup B strains with Por1.4 referred to NRC over time, 1990-2012 21
Figure 5 – Regional incidences of IMD by data source 22
Figure 6 – Case fatality ratio of all serogroups and serogroup B cases in 2004-10, cases confirmed by the NRC 23
Figure 7 – Proportion of subjects with hSBA above threshold at various time points after a booster dose at 12 months 37
Figure 8 – Simplified structures of the static (A) and dynamic (B) models (Reprinted with permission from Elsevier for Christensen *et al.*[81]) 43
Figure 9 – Decline in antibodies against the 4CMenB antigens over time after three infant doses (at 2, 4 and 6 months) in study P13 52
Figure 10 – Age-specific total hospitalisation costs for an acute IMD, per serogroup (Health care payer costs, €2012 values) 58
Figure 11 – Comparison of population figures from the baseline static model (single birth cohort) and the Belgian population in 2011 80
Figure 12 – Comparison of the average annual number of serogroup B meningococcal disease cases in Belgium without vaccination against MenB and those predicted in the base case static and dynamic models, by age group 80
Figure 13 – Serogroup B meningococcal cases averted by age with infant vaccination at 3, 5, 6 and 12 months for different immunisation policies, routine vaccine free of charge (base case), partly reimbursed or private market 81
Figure 14 – Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for infant vaccination at 3, 5, 6 and 12 months 82
Figure 15 – Cost-effectiveness acceptability curves for the base case static model (3, 5, 6 + 12 months vaccination) for the three vaccination policies 82
Figure 16 – Cost-effectiveness acceptability curves for infant vaccination (3, 5, 6 + 12 months) with different assumptions about incidence and case fatality and comparing all serogroup to a serogroup B only model, vaccination free of charge (FoC) or partly reimbursed (PR) 86
Figure 17 – Serogroup B meningococcal cases averted by age, infant vaccination at 3, 5, 6 + 12 months for different assumptions of vaccine strain coverage, vaccine free of charge policy 87

Figure 18 – Cost-effectiveness acceptability curves for infant vaccination (3, 5, 6 + 12 months vaccination) with different assumptions about the proportion of people with sequelae, quality of life loss in those with sequelae and adverse reaction from vaccination, vaccination free of charge policy 88
Figure 19 – ANCOVA analysis of proportion of sum of squares for discounted incremental costs (left) and discounted incremental benefits (right) explained by uncertainty in the stochastic parameters for the base case static model (3, 5, 6 + 12 months schedule) 89
Figure 20 – Effect on annual disease cases of 3, 5, 6 + 12 month vaccination with varying assumptions about the vaccine effect against carriage acquisition for different immunisation policies 90
Figure 21 – Effect on annual disease cases of 14 year old vaccination with varying assumptions about the vaccine effect against carriage acquisition for different immunisation policies 91
Figure 22 – Effect on annual disease cases of 3, 5, 6 + 12 months and 14 year olds vaccination with varying assumptions about the vaccine effect against carriage acquisition for different immunisation policies 91
Figure 23 – Cases averted by age at selected time points since the start of vaccination from the dynamic model, infant vaccination at 3, 5, 6 and 12 months assuming the vaccine is in the routine schedule 92
Figure 24 – Cases averted by age at selected time points since the start of vaccination from the dynamic model, adolescent vaccination at 14 years assuming the vaccine is in the routine schedule 93
Figure 25 – Cases averted by age at selected time points since the start of vaccination from the dynamic model, vaccination at 3, 5, 6 + 12 months and 14 years assuming the vaccine is in the routine schedule 94
Figure 26 – Effect on annual disease cases of vaccination assuming 30% vaccine efficacy against carriage under different assumptions for population mixing, routine vaccination policy 100
Figure 27 – Flowchart of the QoL literature selection process 114
Figure 28 – Infant routine vaccine calendar, Superior Health Council, 2009 122
Figure 29 – Case-carrier ratio 'observed' and fitted values for those aged under 2 years (base case dynamic model) 125
Figure 30 – Case-carrier ratio 'observed' and fitted values for those aged 2 years and over (base case dynamic model) 125
Figure 31 – Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the static model all meningococcal serogroups, vaccine free of charge scenario 128
Figure 32 – Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the static model high incidence, vaccine free of charge scenario 128

Figure 33 – Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the static model low vaccine strain coverage, vaccine free of charge scenario 129
Figure 34 – Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the static model high vaccine strain coverage, vaccine free of charge scenario 129
Figure 35 – Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the static model low uptake of vaccine, vaccine free of charge scenario 130
Figure 36 – Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the static model high vaccine uptake, vaccine free of charge scenario 130
Figure 37 – Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the static model low duration of protection, vaccine free of charge scenario 131
Figure 38 – Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the static model high duration of protection, vaccine free of charge scenario 131
Figure 39 – Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the static model 20 year time horizon, vaccine free of charge scenario 132

LIST OF TABLES

Table 1 – Proposed vaccination scenarios and schedules....15
Table 2 – Number of cases and incidence of IMD and serogroup B by age, average 2009-10....19
Table 3 – Frequency of sequelae among serogroup B IMD survivors in published studies, all ages....25
Table 4 – Frequency of sequelae among serogroup B IMD cases in published studies, children <20 years of age....26
Table 5 – Frequency of sequelae among all serogroup IMD in published studies, different age groups....27
Table 6 – Health-related quality of studies of meningococcal diseases: summary of methods....30
Table 7 – Health-related quality of studies of meningococcal diseases: summary of results....32
Table 8 – hSBA (% >1:4 or 1:5) one month following 3 doses administered at 2, 4, 6 months of age....35
Table 9 – hSBA (% >1:4 or 1:5) before and one month following booster dose at 12-14 months of age....36
Table 10 – hSBA (% >1:4 or 1:5) one month following two doses at 11-17 years of age....36
Table 11 – Summary of the findings on the relation between SBA and effectiveness of OMV vaccines against specific strain of meningitis B[71]....38
Table 12 – Predicted strain coverage in European countries in 2007-08 according to MATS[19]....39
Table 13 – Positive predictive value for the 3 antigens based on killing by sera from children immunised with 3+1 doses (2, 4, 6, and 12 months of age)[75]....39
Table 14 – Vaccine efficacy against serogroup B carriage[78]....40
Table 15 – Selected adverse events following immunization, by study and schedule....41
Table 16 – Vaccination strategies simulated in the models....46
Table 17 – Expected vaccine uptake per schedule....47
Table 18 – Age-specific incidence rates of serogroup B IMD for different scenarios (per 100 000 per year)....48
Table 19 – Case fatality ratio of confirmed IMD cases (serogroup B and all serogroups), 2004-10....49
Table 20 – Estimated proportion of IMD cases with ≥1 sequelae, based on published studies....49
Table 21 – Estimated efficacy based on hSBA data above threshold, 1 month after last dose....50
Table 22 – Estimated average duration (in months) of vaccine protection after the immune response to the last dose[a]....51
Table 23 – Frequency of adverse events attributable to 4CMenB extrapolated from clinical trials and Belgian surveys....53
Table 24 – Age-specific hospitalisation costs for an acute IMD, per serogroup (Health care payer costs, €2012 values)....57
Table 25 – Cost of a consultation to a specialist in internal medicine....59

Table 26 – Cost per type of sequelae following IMD (Health care payer costs, €2012 values) 59
Table 27 – Cost of a consultation to an otorhinolaryngologist 60
Table 28 – Cost of a neurological consultation 61
Table 29 – Proportions of IMD survivors developing sequelae (overall and per type of sequelae), per serogroup 63
Table 30 – Cost of public health management of contacts of an IMD case 64
Table 31 – Estimated vaccine administration costs per dose for the “routine” and “partially reimbursed” vaccination policies 66
Table 32 – Main vaccine administrators in infants, “routine” and “partially reimbursed” vaccination policies 66
Table 33 – Main vaccine administrators in adolescents, “routine” and “partially reimbursed” vaccination policies 67
Table 34 – Estimated vaccine administration costs per dose for the “private market” vaccination policy 67
Table 35 – Main vaccine administrators in infants, “private” vaccination policy 68
Table 36 – Vaccine administration costs of the priming course per vaccination policy, base case 68
Table 37 – Cost of a consultation to a GP and to a paediatrician 69
Table 38 – Distribution and parameters for the cost and QoL loss inputs used in the probabilistic static model (Costs in €2012 values, health care payer perspective) 72
Table 39 – Parameters varied in the univariate scenario analyses 73
Table 40 – Parameters varied in the “All serogroups” scenario analysis 74
Table 41 – Parameters combined for the best and worst case scenarios 75
Table 42 – Summary of input parameter values 76
Table 43 – Results from the static model, comparison of vaccination strategies and scenarios (vaccination vs. no vaccination) 83
Table 44 – Financial impact (undiscounted costs) of different vaccination strategies over the lifetime of a single birth cohort, health care payer costs including the patients share 85
Table 45 – Results from the dynamic model, comparison of vaccination strategies (vaccination vs. no vaccination)[a] 95
Table 46 – Incremental costs and benefits of alternative vaccination strategies, ranked by discounted total cost of the strategies, 30% vaccine efficacy against carriage acquisition 96
Table 47 – Results from the dynamic model, scenario analyses of vaccination at 3, 5, 6 + 12 months and 14 years assuming 30% vaccine efficacy against carriage acquisition and vaccine free of charge policy (vaccination vs. no vaccination) 98

Table 48 – Results from the dynamic model, scenario analyses of vaccination at 3, 5, 6 + 12 months and 14 years assuming 30% vaccine efficacy against carriage acquisition and vaccine partly reimbursed policy (vaccination vs. no vaccination) 99
Table 49 – Results from the dynamic model, scenario analysis on mixing patterns (vaccination vs. no vaccination) 101
Table 50 – QoL search strategies for CRD HTA and CRD NHS EED 111
Table 51 – QoL search strategy for Medline (OVID) 111
Table 52 – QoL search strategy for “Pre” Medline (OVID) 112
Table 53 – QoL search strategy for PsycINFO (OVID) 112
Table 54 – QoL search strategy for Econlit (OVID) 113
Table 55 – QoL search strategy for Embase 113
Table 56 – QoL references identified by the electronic searches 114
Table 57 – ICD-9-CM codes used to select the Hospital Clinical Records 115
Table 58 – Average age-specific cost of care per IMD patient with sequelae, serogroup B, base case (Health care payer costs, €2012 values) 116
Table 59 – Average age-specific cost of care per IMD patient with sequelae, all serogroups, scenario analysis (Health care payer costs, €2012 values) 119
Table 60 – Parameters for the risk of disease given infection (Φi and θi) for the baseline dynamic model (using mixing based on POLYMOD leisure contacts), estimated using disease incidence data from 2009-2010, and a carriage duration of 6 months 124
Table 61 – Incremental costs and benefits of alternative vaccination strategies, ranked by discounted total cost of the strategies, 0% vaccine efficacy against carriage acquisition 127

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse event
AEFI	Adverse event following immunization
AZV-SHA	Anoniem Ziekenhuis Verblijf - Séjour Hospitalier Anonyme
BCFI-CBIP	Belgisch Centrum voor Farmacotherapeutische Informatie - Centre Belge d'Information Pharmacothérapeutique
CDC	Center for Disease Control and Prevention
CFR	Case fatality ratio
CLB-PMS	Centra voor LeerlingenBegeleiding - Centre Psycho-Médico-Social
CSF	Cerebrospinal fluid
CTG-CRM	Commissie Tegemoetkoming Geneesmiddelen - Commission de Remboursement des Médicaments
EMA	European Medicine Agency
EPAR	European public assessment report
EQ-5D	EuroQol 5 dimensions
fHBP	Factor H binding protein
HBD	Hospital billing data (AZV-SHA)
HRQoL	Health-related quality of life
hSBA	Serum bactericidal antibody using human complement
HUI	Health utilities index
HBV	Hepatitis B Virus
HPV	Human Papilloma Virus
ICER	Incremental cost-effectiveness analysis
ICD	International classification of disease
IMA-AIM	InterMutualistisch Agentschap - Agence InterMutualiste
IMD	Invasive meningococcal disease
LSHTM	London School of Hygiene and Tropical Medicine
RIZIV-INAMI	Rijksinstituut voor ziekte- en invaliditeitsverzekering - Institut national d'assurance maladie-invalidité

MATS	Meningococcal antigen typing system
MZG-RHM	Minimale Ziekenhuisgegevens - Résumé Hospitalier Minimum
MMR	Measles-mumps-rubella
NadA	Neisseria adhesin A
NHBA	Neisserial heparin binding antigen
NRC	National Reference Centre
OMV	Outer membrane vesicles
K&G-ONE	Kind en Gezin - Office de la Naissance et de l'Enfance
PCV7	Pneumococcal conjugate vaccine 7-valent
QALY	Quality-adjusted life year
QoL	Quality of life
SBA	Serum bactericidal assay
SF-36	Short-form 36
SF-6D	Short-form 6 dimensions
SG	Standard gamble
SPMA	Standardized procedures for mortality analysis
TCT	Technische Cel voor de verwerking van de gegevens met betrekking tot de ziekenhuizen - Cellule Technique de traitement de données relatives aux hôpitaux
TTO	Time trade-off
VAS	Visual analogue scale
VE	Vaccine efficacy
WHO	World health organization
WIV-ISP	Wetenschappelijk Instituut Volksgezondheid - Institut Scientifique de Santé Publique

SCIENTIFIC REPORT

1 BACKGROUND

1.1 Invasive meningococcal disease

Invasive meningococcal disease (IMD) is caused by the bacteria *Neisseria meningitidis*, a common commensal of the upper respiratory tract for which human carriers are the only reservoir. IMD is defined as the isolation or detection of *N. meningitidis* from a normally sterile site. Although IMD is not frequent - its incidence is estimated at around 1/100 000 persons per year in Europe - it is a severe disease affecting mainly young children and adolescents.[1] IMD clinically presents as meningitis, septicemia or both, sometimes leading to septic shock, and in a minority of cases as arthritis or pericarditis. In industrialized countries, IMD is fatal in around 5-10% of cases and may lead to sequelae in another 10-20% of cases.[1-4]

In spite of its relatively low incidence, meningococcal disease is considered as a public health priority due to its mortality, severity and epidemic potential. Although most IMD occur as sporadic cases, a proportion of cases are secondary to another case, and this was estimated in Belgium at 4.4% during a high incidence period (1971-76).[5] This study estimated secondary attacks rates at 4-7/1000 among contacts of IMD cases sharing the same household or day-care nursery. The prevention of these secondary cases is mostly done by antibiotic prophylaxis of close contacts of each case, aiming to eradicate carriage among contacts. This implies that the occurrence of a single case may have important public health implications, which include tracing of contacts and administration of antibiotic prophylaxis. IMD is also a source of public concern as it may kill young children and clusters of meningococcal disease among e.g. schools generate significant amounts of anxiety.

Serogroups of *N. meningitidis* are determined based on capsular components and six pathogenic serogroups principally cause disease worldwide: A, B, C, X, Y and W135. In Europe, serogroup B has been the most prevalent serogroup, with the exception of a peak of serogroup C around 2001 in some countries including Belgium, and accounted for 74% of all invasive meningococcal strains in 2011.[1] A number of studies have shown that serogroups differ in terms of severity, case fatality ratio, clinical picture and age distribution.[1-4]

1.2 Meningococcal carriage

Most of meningococcal transmission occurs through asymptomatic carriage of *N. meningitidis*. Carriage may lead to invasive disease in a proportion of subjects, usually within a few days of acquisition.[6] There is however a complex relationship between meningococcal carriage and disease. While disease incidence is highest among young children, prevalence of carriage is low among this group (<5%) but is higher in adolescents and young adults, with peaks at 20–30%.[6, 7]

1.3 Vaccines against meningococcal disease

A number of vaccines against meningococcal serogroups A, C, W-135 and Y are available today and the capsule polysaccharides of these serogroups are highly immunogenic. After a substantial rise in serogroup C incidence, a conjugate vaccine against meningococcal serogroup C (MenC vaccine) was introduced into the Belgian infant vaccine schedule in 2002, together with large catch-up campaigns implemented in 2001-04 among children (age range varying by region). Following this campaign, the incidence of serogroup C has dramatically declined, by 88% from 2001 to 2004 and in all age groups.[8] Widespread MenC vaccination programmes generated important herd effects as seen by high reductions in incidence in unvaccinated individuals and significant reduction in serogroup C carriage.[9,10] In England, incidence declined by 67% among unvaccinated children from the age groups targeted for catch-up immunisation.[11] Serogroup C carriage declined significantly by 66% among young adults after one year of widespread vaccination,[12] and MenC vaccine efficacy against carriage was estimated at 75% by a multicenter study.[13] This herd effect was shown to be a very influential factor in cost-effectiveness analyses.[14] Quadrivalent vaccines against the A, C, W-135 and Y serogroups are also available in Belgium, whether conjugated or not, and are advised for travellers to endemic areas.[15]

In contrast, development for a vaccine against serogroup B meningococcal disease has been difficult because its capsular components share similarities with components of human neurones – with potential risk of autoimmunity - and are poorly immunogenic.[16] Several serogroup B vaccines have been developed, derived from "outer membrane vesicles" (OMV) of *N. meningitidis* to control clonal MenB outbreaks in Cuba, Norway, New Zealand and France.[17] Although these vaccines are very effective at controlling epidemics due to the same subtype (PorA) of the pathogen, effectiveness is too low against endemic or epidemic disease due to a number of different strains.[17] These serogroup B vaccines are not available to date in Belgium.

4CMenB the first multicomponent MenB vaccine produced by Novartis under the name Bexsero, has been approved by the European Medicines Agency (EMA) and received its market authorization by the European Commission in January 2013.[18] Bexsero is the first vaccine produced by the "reverse vaccinology" technique and is based on proteins: the analysis of the serogroup B genome has allowed to identify a number of proteins that are expressed at the surface of the pathogen and are important for pathogenicity and elicitation of antibodies. Ultimately, three proteins were identified, fHbp (factor H finding protein), NadA (Neisseria adhesin A) and NHBA (Neisserial Heparin Binding Antigen), and are contained in the 4CMenB vaccine. A fourth component has been later added, an OMV derived from a specific epidemic New Zealand strain.[18]

These four components are expressed in a high proportion of European strains. A multi-country European study found that around 78% of 1052 European strains would be covered by 4CMenB.[19] There are no Belgian data of this coverage.

1.4 Research questions

4CMenB has been authorised in Europe and Belgian decision-makers need to decide on its potential utilisation. Three different vaccination policies are considered:

1. The vaccine would be included in the routine vaccine schedule, free of charge. This decision is taken by the Communities, in consultation with Federal authorities in inter-ministerial decisions. Generally, they follow a positive recommendation from the Superior Health Council (Vaccination group).
2. The vaccine would be partly reimbursed by the RIZIV-INAMI for specific age groups, as it is currently the case for rotavirus vaccines or hepatitis B vaccines for risk groups. Novartis has submitted a reimbursement file to the Commissie Tegemoetkoming Geneesmiddelen - Commission de Remboursement des Médicaments (CTG-CRM) in 2013 and retrieved it

at the end of 2013 waiting for additional data, and no decision has thus be taken.

3. The vaccine is only available in pharmacies, at full charge, as it is the case for e.g. the varicella vaccine.

The research questions are thus the following:

1. What would be the cost-effectiveness of introducing the meningococcal B vaccine in Belgium, according to these three vaccination policies:
   - In the routine vaccine schedule, free of charge?
   - As vaccine reimbursed by the RIZIV-INAMI?
   - As vaccine marketed and not funded?
2. What would be the cost-effectiveness of introducing the meningococcal B vaccine in Belgium, according to different vaccination schedules and target groups?

These analyses must take into account the potential effects on transmission if these are demonstrated. The vaccination scenarios and schedules to be simulated in the cost-effectiveness analysis have been selected in deliberation with experts and stakeholders (Communities) and the Health Council Vaccination Working Group (10 October 2013) and are described in Table 1. Basically, selected scenarios and schedules represent a compromise between age-specific disease burden, immune response to the possible schedules, current vaccine calendar, risk of adverse events when given concomitantly and population acceptability of injections per visit. In particular, it was decided to limit the co-administration with other vaccines to avoid the high reactogenicity seen in clinical trials on co-administration (see 4.3), and not to administer more than two injections per visit in line with recent research on vaccination acceptability.[20] 4CMenB could thus not be started at 2 months as usually indicated because two injections are already scheduled at that age (see Vaccine calendar in Appendix 4), but a first administration at 3 months was considered as possible because only one other injectable vaccine (hexavalent) is given at that age. Other infant doses are scheduled separately from other vaccines. Adolescent doses are provided at the same time as HPV vaccination in girls. Catch up vaccination in other age groups is not considered due to the low burden and high number of doses required. Further details are provided under 6.1.1.

Vaccination limited to risk groups has not been included, in the absence of vaccine efficacy and safety data in these groups.

Table 1 – Proposed vaccination scenarios and schedules

Schedule	Number doses	Age at doses
Infants alone	3+1	3, 5, 6 months, booster at 14 months
Adolescents alone	2	Around 13 years (2 doses 2 months apart, together with HPV vaccination for girls)[a]
Infants + adolescents	As above	As above

Note: in order to avoid a long recoding process of the model that would delay the study, the schedules presented in Table 1 vary slightly with those applied in the models (see 6.1.1). a This occurs in the second year of the secondary school in Wallonia (i.e. 13-14 years of age, see http://www.sante.cfwb.be/index.php?id=4295) and in the first year in Flanders (i.e. 12-13 years, see http://www.zorg-en-gezondheid.be/hpv/).

The use of 4CMenB to control clusters and outbreaks has also been considered. As it has not been included as a full research question, no formal analysis has been conducted, but the relevance of this strategy in a Belgian setting is discussed under section 10.

2 BELGIAN DATABASES AND MATCHING

The 4CMenB vaccine has been authorized in the prevention of invasive meningococcal disease (IMD) due to serogroup B only. We thus only collected burden data on IMD. As serogroup B disease differs from other serogroups in disease severity and age distribution, we intended to derive data that are specific to serogroup B to the largest extent possible for the main analyses. Additionally, because 4CMenB is a protein based vaccine not targeted at the meningococcal capsule and may therefore provide protection against non-MenB serogroups, we extracted as well burden data on all serogroups for scenario analyses.

2.1 Database sources

Among the various data sources with information on IMD in Belgium, the three most relevant data sources were selected:

1. The National Reference Centre (NRC) at the Scientific Institute of Public Health (WIV-ISP) receives data on each IMD case for which an isolate was referred for typing. Demographical data and diagnosis are received and the NRC determines serogroup, sub-type, sero-subtype and clonal complexes (as well as antimicrobial resistance, not dealt with in this study). As the sampling date was not always complete, the date of sample reception at the NRC has been used as proxy for the date of onset.
2. Hospital Clinical Records (MZG-RHM: Minimale Ziekenhuisgegevens - Résumé Hospitalier Minimum) were collected on the period 2004-2010. The registration of MZG-RHM is mandatory for every hospital in Belgium. For each record of hospital stay, information such as year of birth, sex, postal code of domicile, length of hospital stay, diagnostic and therapeutic procedures performed etc. has to be recorded, along with ICD-9-CM codes encoding relevant diagnoses. Records with an ICD-9-CM code “036” were extracted from the database (see Appendix 2 for a description of the codes). Due to the severity of IMD, we assume that all cases are hospitalised.
3. The Mandatory Notification systems for communicable diseases from the three federated entities (la Fédération Wallonie-Bruxelles, de Vlaamse Gemeenschap and l’Observatoire de la Santé et du Social de Bruxelles-Capitale – Observatorium voor Gezondheid en Welzijn van Brussel-Hoofdstad Brussels) have also been requested as these data are more comprehensive and may contain additional information, e.g. on control measures and treated contacts. Clinicians and laboratories are obliged by law to report all cases of IMD in these three entities, confirmed as well as probable cases, together with a number of demographic and clinical data. However, the completeness of these registration systems varies across entities with reported low completeness in Wallonia before 2013 and in the Brussels region. This source was thus not used to calculate incidence rates but was exploited as a complementary source of data on trends, chemoprophylaxis and to evaluate the completeness of other data sources (see 3).

Other data sources include the sentinel laboratory network and data on causes of death, but these datasets are either less representative or their etiological coding may involve more errors and completeness of data may differ across regions.

The only serogroup-specific data in Belgium come from the NRC. However, this source does not include all IMD cases of the country and the proportion of referred samples varies over time. Its sensitivity has only been evaluated in 1980-82, at 70% of confirmed cases.[21] For that reason, our estimates of cases and deaths were based on the MZG-RHM dataset (as it includes all hospitalised cases) complemented by NRC serogroup data to derive B-specific parameters. We also matched cases from MZG-RHM and NRC to derive serogroup B case fatality rate.

To collect information on the cost of a hospitalisation due to IMD in Belgium, a fourth database was selected, used in coupling with the MZG-RHM and NRC databases in order to select IMD stays coded with ICD-9-CM “036” as principal or any diagnosis:

1. The Hospital Billing Records database (AZV-SHA: Anoniem Ziekenhuis Verblijf - Séjour Hospitalier Anonyme) records the health care costs (public and the patients' share to some extent) of each hospital stay in Belgium. Registration of the AZV-SHA database is mandatory for all national health insurance companies. Since 1997, the MZG-RHM records are linked to the AZV-SHA records. Linkage is performed by the legally instituted "Technical cell" and the process takes about 2 years to completion and full validation. Linked MZG-RHM/AZV-SHA data were collected on the period 2004-2010, 2010 being the most recent dataset available at the time of the current analysis.

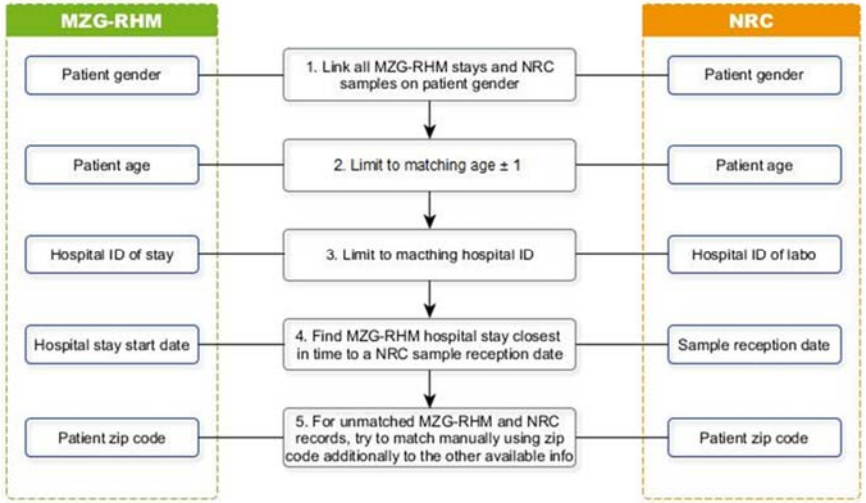
Coupling the MZG-RHM/AZV-SHA data to the NRC data allows calculation of average acute hospitalization costs separately for all IMD cases (i.e. any serogroup) and for serogroup B IMD cases only, the latter being used in the base case cost-effectiveness analysis. Costs were not stratified by clinical picture because there are no clear case definitions or criteria to distinguish between e.g. bacteraemia, septicemia and sepsis. Additionally, clinical pictures are often associated; indeed 20-40% of IMD cases present as meningitis and septicemia in studies from other EU countries.[1, 3, 4, 22]

2.2 Matching of the MZG-RHM and NRC databases

Permission to match the MZG-RHM/AZV-SHA data to the NRC data and to analyse the matched data was asked of the Belgian Commission for the Protection of Privacy. A positive answer was received on October 2013. A description of the matching is provided below.

For the years 2004 up to 2010, we tried to match all MZG-RHM hospital stays to the NRC typing data. The matching algorithm is shown in Figure 1. To allow the matching, both datasets required standardization of several fields. In addition to the algorithm, we excluded matched cases with a time difference above 40 days between the closest date of hospital stay and the NRC sample reception date. A maximum time lag of 40 days was selected because the date of sampling was not available for all cases in the NRC database (missing for 13%), the date of NRC sample reception was used as a proxy and the time lag between sampling and NRC reception ranged from 0-31 days among the 87% cases with both variables known. To account for an additional delay between NRC reception and the first day of the closest hospital stay, we set the maximum at 40 days. In the period 2004-07, the day of the month is not known for admission and the first day of the month is then used in the database; for those records, a period up to 69 days was considered, if the difference between the last day of the admission month and the sampling date was below 15 days, because admission in the same month could occur up to 29 days after the first day of the month (based on an average month of 30 days). Only one hospital record per patient was kept.

Figure 1 – Matching algorithm of the MZG-RHM and NRC databases



MZG-RHM: Minimale Ziekenhuisgegevens - Résumé Hospitalier Minimum; NRC: National Reference Centre at the WIV-ISP.

3 BURDEN OF SEROGROUP B MENINGOCOCCAL DISEASE

3.1 Medical burden

Data on medical burden were extracted from Belgian databases on IMD, with the exception of sequelae parameters for which we reviewed the literature.

3.1.1 Incidence and age distribution

Annual numbers of IMD per year and age group were obtained by extracting the number of new episodes from the MZG-RHM, defined as a ICD-9 code 036 as principal or any diagnosis, assuming that MZG-RHM new stays with ICD-9 code 036 represent all meningococcal cases.[a] The annual number of serogroup B IMD (MenB) per age and year was calculated by applying the proportions of serogroup B cases from the NRC data by year and age to the MZG-RHM numbers of cases. This assumed that NRC cases represent an unbiased sample of all IMD cases, and thus follow the same serogroup and age distributions than all IMD cases. Incidence rates by age and year were computed by using age-specific population data from Standardized Procedures for Mortality Analysis (SPMA on https://spma.wiv-isp.be/).

The number of new IMD amounted to 179 cases in 2009-10 with an incidence of 1.7 per 100 000 (Table 2). Meningococcal disease coded as principal diagnosis was found in 81% of hospital stays with ICD 036 in one of the diagnoses. In 2010, the NRC received 96 strains from peripheral laboratories, including 76 (79%) serogroup B strains.

After linking MZG-RHM and NRC databases, 82% of the NRC cases were matched to MZG-RHM stays and 47% of MZG-RHM new stays were matched to NRC cases over 2004-10. Several factors may explain the high proportion (53%) of MZG-RHM cases that were not matched: some hospitals never refer strains to the NRC, participating hospitals do not always send 100% of their strains, cases diagnosed by PCR at peripheral level often do not have sufficient fluid to send to the NRC, sample from cases with rapid death are not always referred to NRC, some cases may be diagnosed by antigen testing or not be laboratory confirmed while being clinically highly suggestive of IMD (e.g. Waterhouse–Friderichsen syndrome), and incomplete information did not allow matching of cases.

Unmatched cases from both data sources were reviewed to identify possible false positive and false negative cases. The MZG-RHM unmatched cases showed the same age distribution and mortality profile as the matched cases, but the 036 ICD code was less frequently reported as principal diagnosis (in 69% vs. 90% in matched cases). Among the 178 unmatched cases with 036 as associated diagnosis, the principal diagnosis of these cases was suggestive of meningococcal complication in 35% of them, of other – unrelated – infection in 24% cases including suggestive hospital acquired complications in at least 9%, of a risk factor for meningococcal disease in 22% of them, such as HIV, alcoholism, diabetes and neoplasms likely under immunosuppressant drugs. However 12 cases (7% of unmatched cases) had a meningitis coded as unspecified or due to other causes as principal diagnosis, and it is unclear whether the 036 code was only added (as associated diagnosis) after laboratory confirmation or whether 036 coding is incorrect and these cases are not true IMD (i.e. false positive). The diagnoses of other cases did not suggest that meningococcal disease was unlikely. The 163 unmatched NRC cases (18% of NRC cases) were more likely to be from large Brussels hospitals (22% vs. 6% in linked cases) or from large hospital consortium from big towns, which often serve as referral laboratories for smaller hospitals. Additionally, 21% of these cases had no date of birth. These cases include a higher proportion of elderly (18% were ≥65 years of age compared to 7% in linked cases) and of fatal cases (12% compared to 6% in linked cases), especially among young people, which may be explained by the concentration of cases from large university hospitals. It is thus plausible that matching these cases was less successful because hospital of stay may differ from laboratory hospital and age was less accurate. But it is also possible that some of these (true) cases had a hospital stay coded on their potential co-morbidities exclusively and would thus be false negative as they are not included in the RHM-MZG cases kept for further analyses. We made the assumption that these potential false negative are approximatively compensated by the potential false positive cases, also taking into account that the largest uncertainty is

[a] New episode defined according to patient ID.

related to the prediction of future incidences (as opposed to accurate data on recent years). Under the assumption that NRC cases are included in MZG-RHM cases and that MZG-RHM cases represent all IMD cases, the under-reporting of the NRC database is estimated at 56% overall, and vary across ages (range 44-77%).

Assuming that the serogroup distribution is similar among unmatched hospitalized cases, the incidence of serogroup B is estimated at 1.3 per 100 000 in 2009-10 (Table 2).

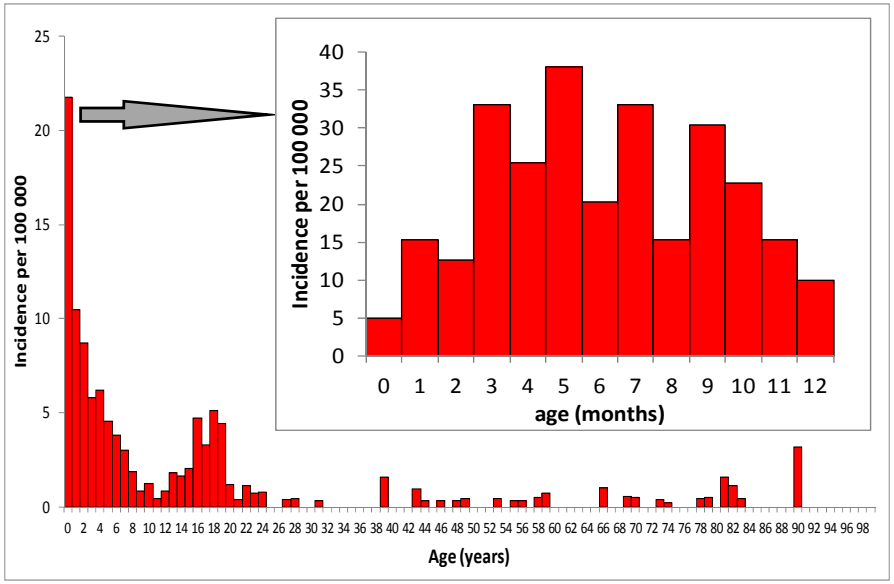
The age distribution of IMD cases among children <5 years is based on NRC data because only the year of birth is available in the MZG-RHM dataset (this inaccuracy does not affect older ages) but the age-specific incidence is based on MZG-RHM data. Incidence of serogroup B is highest in infants <1 year of age (22 per 100 000), peaking around 5 months, then declines with age up to 8-10 years and a new peak is observed in adolescents aged 15-19 years, Figure 2 and Table 2. Children <5 years and adolescents 15-19 years account for 48% and 18% of all serogroup B cases, respectively. In adults >20 years, incidence is low.

Table 2 – Number of cases and incidence of IMD and serogroup B by age, average 2009-10

	Number of IMD cases	Incidence IMD per 100 000	Number of serogroup B cases	Incidence serogroup B per 100 000
<1 year	31	24.1	28	21.8
1-4 years	42	8.5	39	7.9
5-9 years	18	3.0	17	2.8
10-19 years	37	2.9	33	2.6
20-64 years	35	0.5	17	0.3
≥65 years	16	0.9	6	0.3
Total	179	1.7	139	1.3

Source: MZG-RHM new stays with ICD-9 code 036; NRC database for proportions of serogroup B and for age distribution among children <5 years.

Figure 2 – Incidence of serogroup B cases by year of age, average 2009-10



Source: MZG-RHM new stays with ICD-9 code 036; NRC database for proportions of serogroup B and for age distribution among children <5 years.

3.1.2 Temporal trends

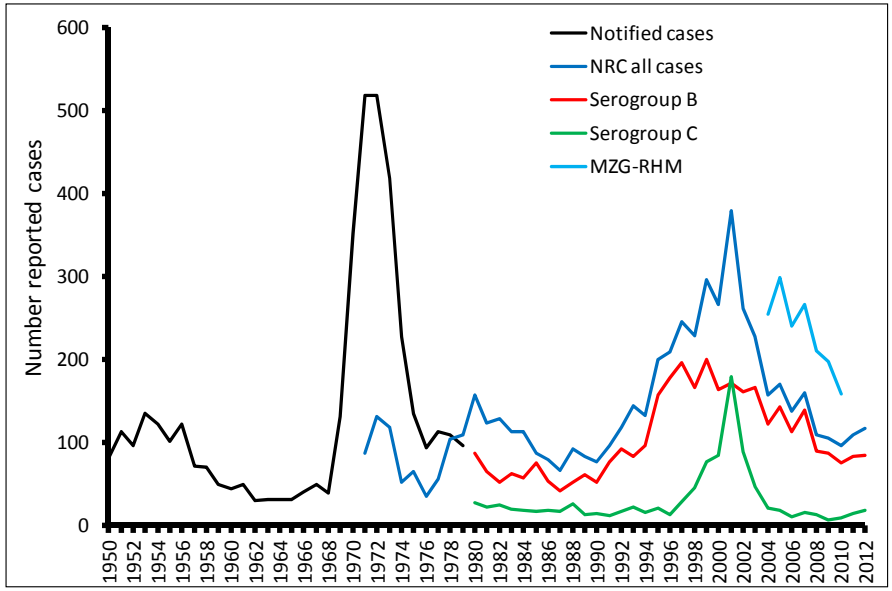
Assuming that the NRC sensitivity in capturing IMD cases is stable over time, the number of reported IMD cases – and serogroup B in particular – shows large fluctuations over time, with two sudden increases of serogroup B related to the expansion of specific clones (Figure 3). The first peak in 1970-75 corresponds to an epidemic of serogroup B:2b:P1.2, reaching a peak incidence of IMD at 5.3 cases per 100 000 in 1970-71.[21, 23] Incidence then came back to normal inter-epidemic values (around 1 per 100 000) and rose again in the nineties due to the migration from the Netherlands and the expansion of a B:4:P1.4 clone.[24] Serogroup C IMD also peaked in 2001 and declined markedly after large meningococcal C vaccination campaigns (Figure 3).

In 2004-10, serogroup B incidence showed a progressive and marked decline, which was observed in all age groups and in all data sources (Figure 3). The factors influencing these changes are still unknown. Changes in surveillance sensitivity cannot be discarded but similar trends were observed in most other EU countries, suggesting the role of secular trends.[22] The different data sources show similar temporal patterns in IMD incidence, as seen in Figure 3 for NRC and MZG-RHM in Figure 5 for regional notification systems, especially in Flanders where the time trends are totally parallel for the three sources. This suggests that these time trends are real but unpredictable.

In the Federation Wallonie Bruxelles, NRC and notification data suggests a slight increase in IMD cases (Figure 5) in 2011-12, but this is not observed for serogroup B cases in Flanders. This can be influenced by the increasing efforts from the Federation to improve notification of cases and referral of strains to the NRC (Figure 5), in addition to a slight rise in serogroup C cases. A possible rising trend should be confirmed with additional data.

Incidences are higher in winter (January-March) and lower in summer (June-September).

Figure 3 – Annual numbers of reported invasive meningococcal cases by serogroup, 1950-2012

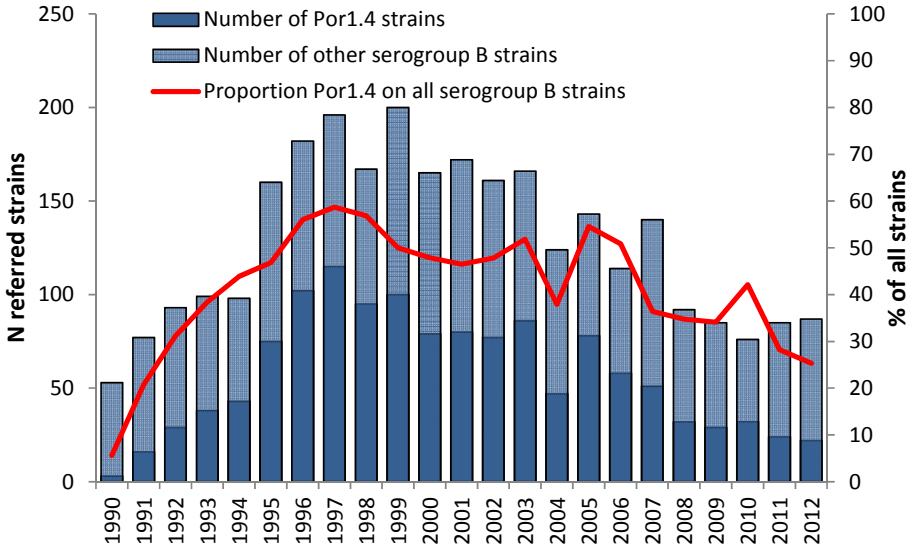


Based on WIV-ISP National Reference Centre (NRC) for Neisseria meningitidis, De Maeyer et al. J of Infection 1981,[23] Carion et al. Eurosurveillance 1997.[24] NRC activities started in 1971 and the national notification system ended around 1980 (caution: case definitions differ).

3.1.3 Distribution of vaccine-preventable strains

As previously said, specific data on the expression of antigens contained in the 4CMenB vaccine were not available from Belgium (as of 2014). However, the presence of one antigen, the PorA P1.4, is assessed routinely by the NRC. NRC data show that in 2012 25% of B strains were from sero-subtype P1.4 (included in the vaccine), but this proportion showed large fluctuations in the last 20 years, decreasing since 1997 when it represented 59% of B strains (Figure 4). The rise and decline of P1.4 strains between 1997 and 2012 is parallel to the fluctuations of serogroup B strains, suggesting that it substantially contributed to the overall changes in serogroup B incidence in recent years. The proportion of P1.4 did not show wide variations across ages but was lower in adults 50-64 years.

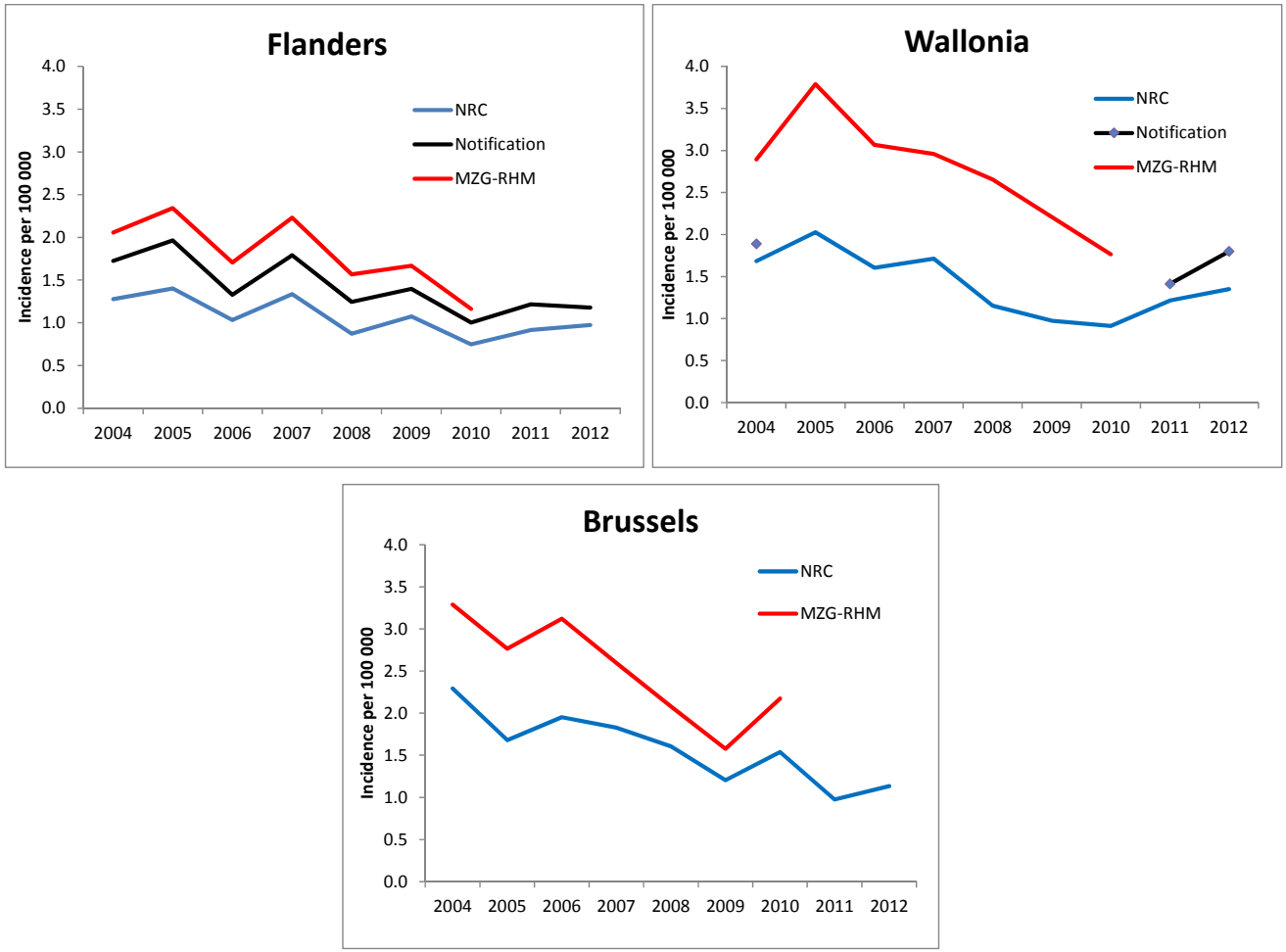
Figure 4 – Serogroup B strains with Por1.4 referred to NRC over time, 1990-2012



3.1.4 Regional variations

Regional patterns of overall IMD incidence show different levels by year but an overall similar pattern over the last decade (Figure 5). Surprisingly, IMD incidence (as estimated by MZG- RHM, see above 3.1.1) seems higher in Wallonia and Brussels compared to Flanders, but this can be due to the near elimination of serogroup C in Flanders. Indeed, the proportion of serogroup B cases is higher in Flanders (76% vs. 65% in Wallonia in 2012), likely due to a more extensive vaccination campaign against serogroup C in 2001-2004. In Flanders where notification efforts are relatively stable, above 80% of IMD cases (as estimated by MZG- RHM) are notified and this proportion tends to increase over time (86% in 2010). In Wallonia and Brussels, this comparison could not be done (no overlapping period with data).

Figure 5 – Regional incidences of IMD by data source



IMD: Invasive meningococcal disease; MZG-RHM: Minimale Ziekenhuisgegevens – Résumé Hospitalier Minimum; NRC: National Reference Centre for Neisseria meningitidis.

3.1.5 Clinical picture

No reliable data on clinical presentation of IMD was available in Belgium. NRC data on clinical syndrome are most often based on the sample fluid (blood or cerebro-spinal fluid) that tested positive. MZG-RHM data are based on the ICD codes, which are not based on case definition: 80% of cases have as a principal diagnosis “meningococcal meningitis” (036.0) or “Meningococcemia” (036.2) that are not very specific. It is also known that a substantial proportion IMD cases present as meningitis and septicemia (up to 40-50% in published studies).[2, 25, 26] We thus grouped all meningococcal clinical syndromes together in further analyses.

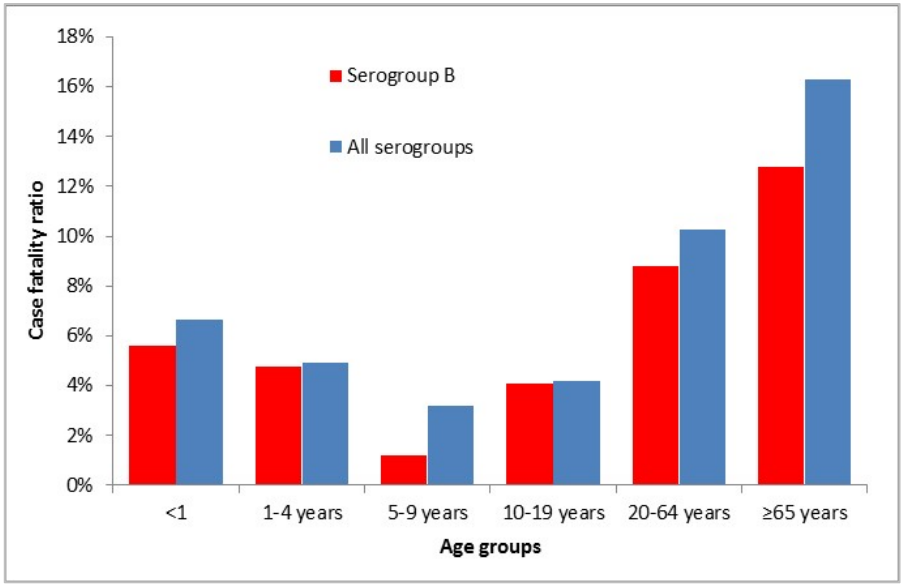
3.1.6 Mortality and case fatality ratio

The NRC data contain incomplete data on outcome (known in around 50% of the cases) but the MZG-RHM provides complete data on death during admission. To allow to estimate case fatality ratio (CFR) estimates by serogroup, we restricted the CFR computation to NRC confirmed cases, but data on outcome were completed with those from MZG-RHM on matched NRC/MZG-RHM cases. Overall CFR is estimated in 2004-10 at 7.0% (95%CI 5.5-8.8) for all serogroups, 5.4% (95%CI 4.1-7.3) for serogroup B and 15.6% (95%CI 9.7-24.2) for serogroup C, respectively, based on 932 NRC cases matched to MZG-RHM to complete outcome information. These data highlight the higher CFR of serogroup C compared to serogroup B (risk ratio 2.8, 95%CI 1.6-4.94); however age is a confounding factor as serogroup C affects older ages (and increasingly since MenC vaccine is implemented among children) and CFR increases with age. Figure 6 also shows the higher CFR for all serogroups compared to serogroup B, in each age group, though serogroup C only represents around 20% of all cases. This highlights again the need to compute model parameters on serogroup B only.

These data are in line with other Belgian and European data. CFR of non-linked MZG-RHM cases was similar, at 6.5%. Similar CFR values and differences across serogroups were found in other EU data. Overall CFR from recent studies on EU countries (average), the Netherlands, France and England & Wales amounted to 7.4%, 6.7%, 7.0% and 5.3%, respectively.[22, 27-29] However, the number of meningococcal deaths as reported by death certificates is lower (67% of those recorded in MZG-RHM), probably because these are limited to deaths for which the “initial cause” was considered to be meningococcal disease; IMD as associated cause of death is not included in death statistics.

CFR is higher among infants, lower among older children and very high in the elderly (Figure 6 and Table 19 below). CFR also varied by year, ranging 0.9-11.5% for serogroup B over 2004-10.

Figure 6 – Case fatality ratio of all serogroups and serogroup B cases in 2004-10, cases confirmed by the NRC



3.1.7 Long-term complications and sequelae

Belgian hospital databases do not capture long-term complications and sequelae of IMD. The frequency of sequelae by type was thus extracted from literature reviews of studies from comparable settings. We focused on serogroup B disease, as most studies show that serogroup C result in more frequent and severe sequelae compared to serogroup B.[2-4, 30] We performed a rapid systematic review by searching for the most recent systematic reviews and updating it with primary studies after the date of last search. We included only studies published after 1995 and providing sequelae frequency for serogroup B IMD in similar settings (Europe or North America) for the base case (Table 3), and excluded studies limited to specific population groups, to specific clinical forms of IMD (e.g. septic shock or meningitis only), narrow age groups or studies limited to non-confirmed IMD cases. No systematic reviews provided data on serogroup B sequelae and the last systematic review on IMD retrieved was from a NICE clinical guideline (June 2010) including studies published between 1994 and July 2009. Only two primary studies described in this review (most studies were limited to septic shock or meningitis) and four additional primary studies were eligible and retrieved.[2-4, 25, 31, 32] For the scenario analysis involving all serogroups, we used the same selection criteria but also included studies that did not specify serogroups. The systematic review from Edmond was also used to identify additional studies, but the meta-analysis per sequelae was not used because it pooled all settings.[33, 34] Only five primary studies providing data on all serogroups fitted with the selection criteria.[2-4, 25, 35]

The studies used different time points for description of outcome: at hospital discharge or retrospectively after a delay of 1-6 years after discharge (Table 3). However, a meta-analysis of 35 studies assessing outcome of IMD in all settings found that median risks of sequelae were similar among patients assessed at hospital discharge compared to those assessed in the post-discharge follow-up period.[33] A study in Iceland interviewed IMD survivors in average 20 years after disease, and physical examination showed that a number of self-reported sequelae were due to other (subsequent) causes.[3] We thus included sequelae at or after discharge, regardless of time points.

The proportion of serogroup B cases presenting at least one sequelae was found in 3-19% of the cases (Table 3). The most frequent sequelae include hearing loss (range 1.9-7.2%, criteria differing across studies), scar and/or necrosis (1.2-6.4%), amputation (0.3-8%), epilepsy or seizures (1.6-3.3%) and renal failure (2%). Other sequelae involved neurological consequences such as speech and communication disabilities. Permanent joint damage following arthritis was rarely described for serogroup B, as opposed to serogroup C.[2, 3] In addition, a high proportion of subjects showed psychological disorders when assessed (16% excess compared to controls in Viner *et al.*).[32] Children show a higher frequency of hearing loss, severe amputations, skin necrosis and epilepsy and a lower rate of renal failures compared to adults (Table 4). A Canadian study on serogroup B confirms these age patterns and shows an overall lower frequency of sequelae in adolescents.[31]

Frequencies of sequelae among all serogroups in Table 5, are relatively similar to those of serogroup B (Table 3 and Table 4). This might be surprising because studies comparing sequelae per serogroup showed that serogroup C causes a higher frequency of severe sequelae due to septicemia such as amputation and multiple system failure.[2-4, 25] But two factors may explain the similar frequencies: the two studies limited to serogroup B (Bettinger and Viner) showed a higher frequency of sequelae than other studies for serogroup B,[31, 32] and one of them included only cases from tertiary referral hospitals;[31] and a high proportion of serogroup B cases was found in most studies involving all serogroups.

Overall, robust proxies for the frequency of sequelae in the Belgian context are difficult to establish due to different settings, case recruitment, follow-up period, sequelae definitions and measures in published studies. Furthermore, phenotypes and clones widely differ across geographical areas, and they may be associated with different risk of death and sequelae.[25, 26, 36] In addition, the frequencies of specific sequelae do not take into account the risk of sequelae that were caused by other diseases. A case-control study in the UK compared these frequencies to those in controls;[32] for instance, hearing loss was found in 1% of the controls due other causes such as e.g. otitis media.

Table 3 – Frequency of sequelae among serogroup B IMD survivors in published studies, all ages

Studies and outcomes	Denmark, Howitz[25]	Iceland, Gottfredsson[3]	Canada, Bettinger[31]	Quebec, Erickson[2]
Design, period	*Linking of registries, ICD-10, 1992-2005*	*Retrospective study linking databases, 1975-2004*	*Active surveillance in 12 tertiary (referral) hospitals, 2002-2011*	*Retrospective survey, 1990-1994*
Time after discharge	*At discharge*	*Not stated*	*At discharge*	*Mean 38 months (range 9-72)*
Age group	*All*	*All*	*All*	*All*
Median age at onset	*8 years*	*NA*	*12 years*	*2 years*
N cases assessed	*1313*	*261*	*391*	*158*
N cases with any sequelae (%)	NA	NA	74 (18.9%)	5 physical (3.2%) 20% psycho-social consequences
N sequelae	NA	40	100	10
Hearing loss (any)	2.5% (33/1313)	3.1% (8/261)	7.2% (28/391)	1.9% (3/158), all <70db
- Needing hearing aid	NA	NA	NA	0.6% (1/158)
- Needing cochlear implant	NA	NA	NA	0% (0/158)
Amputation	NA	0%	3.8% (15/391)	0.6% (1/158)
- Minor (toe, finger)	NA	0%	2.6% (10/381)	0.6% (1/158)
- Involving limb	NA	0%	1.0% (2/158)	0%
Epilepsy/seizures	1.6% (22/1367)	NA (0.6% overall)	3.3% (13/391)	NA
- With anti-convulsant at discharge	NA	NA	2.6% (10/391)	NA
Scars/necrosis	NA	1.5% (4/261)	6.4% (25/391)	1.2% (2/158) scars only
- Requiring grafts	NA	NA	NA	0%
Renal failure at discharge	NA	1.9% (5/261)	2.1% (8/391)	0%
- Requiring dialysis	NA	NA	0.3% (1/391)	0%
Communication/speech disability	NA	NA	NA	1.9% (3/158)
Other neurological	Palsy/plegia ≥1 limb: 0.4% (5/1362)	NA	Any type: 3.6% (14/391)	Partial sensory nerve loss (foot): 0.6% (1/158)

NA: not available.

Table 4 – Frequency of sequelae among serogroup B IMD cases in published studies, children <20 years of age

Studies and outcomes	Canada, Bettinger[31]	England & Wales, Viner[32]	Ireland, Healy[4]
Design, period	*Active surveillance in 12 hospitals, 2002-2011*	*Retrospective case control study based on NRC, 2009-10*	*Retrospective survey in NRC and 2 tertiary hospitals, 1995-2000*
Time after discharge	*At discharge*	*Follow-up 2.6-7.6 years, median 3 years*	*2 months – 5 years*
N cases assessed	*266*	*245*	*303*
Age group	*<20 years*	*<14 years*	*3 months – 12.5 years*
Median age at onset	*2.5 years*	*1.6 years*	*1.5 years*
Cases with any sequelae	21% (56/266)	21%[a]	10% (31/303)
Hearing loss	7.9% (21/266)	6.5% (15/232)[c]	3.0% (9/303)
- Needing hearing aid	NA	2.2% (6/232)[b, c]	NA
Amputation	3.8% (10/266)	2.1% (5/239)	0.3% (1/303)
- Minor (toe, finger)	3.0% (8/266)	1.3% (3/239)	NA
- Involving limb	0.8% (2/266)	0.8% (2/239)	NA
Epilepsy/seizures	NA	2.1% (5/239)	NA
- With anti-convulsant at discharge	3.8% (10/266)	NA	NA
Scars/necrosis	7.5% (20/266)	NA	3.0% (9/303) scars only
- Requiring grafts	NA	NA	NA
Renal failure at discharge	0.8% (2/266)	NA	0%
- Requiring dialysis	NA	NA	0%
Communication/speech disability	NA	4.2% (10/239)	NA
Other neurological (any type)	3.4% (9/266)	NA	3.6% (11/303)

a: includes low intellectual quotient (IQ); represents difference from controls. b: defined as severe hearing loss. c: audiology results only available in 232 cases. NA: not available; NRC: National Reference Centre.

Table 5 – Frequency of sequelae among all serogroup IMD in published studies, different age groups

Studies and outcomes	Denmark, Howitz[25]	Iceland, Gottfredsson[3]	Quebec, Erickson[2]	Ireland, Healy[4]	US, Kaplan[35]
Design, period	*Linking of registries, ICD-10, 1992-2005*	*Retrospective study linking databases, 1975-2004*	*Retrospective survey, 1990-1994*	*Retrospective survey in NRC and 2 tertiary hospitals, 1995-2000*	*Retrospective study in 10 paediatric hospitals, 2001-05*
Time after discharge	*At discharge*	*Not stated*	*Mean 38 months (range 9-72)*	*2 months – 5 years*	*At discharge*
N cases assessed	*2367*	*541*	*420*	*407*	*146*
Age group	*All*	*All*	*All*	*3 months – 12.5 years*	*<20 years*
Median age at onset	*10 years*	*NA*	*14-17 years*	*3 years*	*NA*
Cases with any sequelae	NA	NA	10.7% (45/420)[a]	10.8% (44/407)	NA
Hearing loss	1.9% (44/2286)	2.6% (14/541)	1.9% (8/420)	3.2% (13/407)	9.6% (14/146)
- Needing hearing aid	NA	NA	0.5%(2/420)	NA	NA
- Needing cochlear implant	NA	NA	0%	NA	NA
Amputation	NA	0%	3.1% (13/420)	0.3% (1/407)	1.4% (2/146)
- Minor (toe, finger)	NA	0%	2.1% (9/420)	NA	0.7% (1/146)
- Involving limb	NA	0%	1.0% (4/420)	NA	0.7% (1/146)
Epilepsy/seizures	1.4% (33/2367)	0.6% (3/541)	NA	NA	6.2% (9/146)
- With anti-convulsant at discharge	NA	NA	NA	NA	NA
Scars/necrosis	NA	2.4% (13/541)	7.6% (32/420)	3.9% (16/407) scars	8.9% (13/146)
- Requiring grafts	NA	NA	2.6% (11/420)	NA	2.7% (4/146)
Renal failure at discharge	NA	2.8% (15/541)	0.7% (3/420)	0%	NA
- Requiring dialysis	NA	NA	0.7% (3/420)[b]	0.5% (2/407)	NA
Communication/speech disability	NA	NA	1.4% (6/420)	NA	NA
Other neurological (any type)	0.3% (7/2367)[c]	2.0% (11/541)[d]	0.7% (3/420)	4.4% (18/407)	4.8% (7/146)

a: physical sequelae only. b: 2 cases required temporary dialysis and 1 required long term dialysis. c: cerebral palsy and plegia. d: 8 cognitive disabilities and 3 migraines.

3.2 Quality of life burden

3.2.1 Methods

Evidence on health-related quality of life (HRQoL) measures associated with invasive meningococcal diseases (IMD) was summarized based on a systematic review of the literature. This review builds on a previous HRQoL review of meningococcal diseases that covered the literature up to September 2009.[37]

The following databases were searched from 2009 up to September 2013: CRD HTA, CRD NHS EED, Medline(Ovid), Medline(Ovid) in-process and other non-indexed citations, PsycInfo(Ovid), Econli(Ovid) and Embase. Identified citations were assessed in a two-step procedure: initial assessment of the title, abstract and keywords; followed by full-text assessment of the selected citations. Reference lists of the selected studies were scrutinized for additional relevant citations. The following inclusion criteria were used:

- Population: Patients who suffered from meningococcal diseases in general as well as sub-groups of patients experiencing a particular sequelae following meningococcal infection. Patients suffering from any bacterial meningitis or septicaemia (not only meningococcal) were also considered in order to check if quality of life (QoL) values were reported for meningococcal infection separately. All serogroups of *Neisseria meningitis* were considered at this stage and information on serogroup distribution was collected, if available.
- Outcome: Papers must report utility measures, i.e. measures that lead to a single score for the HRQoL of a particular health state and that are obtained using preference- or choice-based methods. Profile measures, i.e. giving separate scores for each dimension of a particular health state, are excluded as they cannot be directly converted into quality-adjusted life-years (QALYs) to be used in cost-utility analyses. Papers must value HRQoL utility indexes based on a generic descriptive instrument (EQ-5D, HUI, SF-6D, SF-36[b]) or directly from the patient (TTO, SG, VAS)[c].
- Design: Only original primary studies are considered. Reviews and methodological papers were excluded.
- Geographical coverage: Studies performed in countries with comparable epidemiology of meningococcus and culture were considered, i.e. Western Europe, North America, Australia and New Zealand.

The search strategies (including the MeSH and EMTREE terms, and the text words used) and the flow chart of the selection process can be found in the appendix.

3.2.2 Results

The review of the literature identified 17 primary studies (14 studies from the previous review[37] plus 3 new studies from the review update) valuing the long term quality of life impact of meningococcal diseases. None of the studies identified examined the short term quality of life impact of IMD, during the acute phase of the disease. The main characteristics of the studies are presented in Table 6 and their results in Table 7.

All studies varied considerably in terms of the instrument used for the valuation (i.e. VAS, PTO, SG, EQ-5D, HUI, SF-36), type of respondent (i.e. patients themselves, parents of patients, proxies such as physicians or lay people) and the disease considered (i.e. from as large as any bacterial meningitis to the more specific meningococcal diseases, sometimes per serogroup). As a consequence, the utility values reported per health state varied widely.

For the health state survivor with any sequelae, utility decrements ranged from 0.07 with EQ-5D (MOSAIC data[32] courtesy of Helen Johnson, London School of Hygiene and Tropical Medicine - LSHTM) to 0.4[38] (assuming all reductions are from 1). The highest reduction (0.4) is reported by Ruedin for patients with severe sequelae following meningococcal or pneumococcal disease.[38] Two studies report comparable reductions in quality of life for

[b] Although generating profile health status measures, SF-36 instruments were still considered as they may have been converted into SF-6D health states and a corresponding single utility score.

[c] TTO: time trade-off, SG: standard gamble, VAS: visual analogue scale, EQ-5D: EuroQol 5 dimensions, HUI: health utilities index, SF-36: short-form 36, SF-6D: short-form 6 dimensions.

patients with sequelae following meningococcal serogroup C disease, i.e. utility losses of 0.28[39] and 0.31.[2] Utility losses for meningococcal serogroup B disease survivors with sequelae were investigated in two studies that report lower decreases in quality of life than for serogroup C, i.e. utility loss of 0.07 with EQ-5D (MOSAIC data) and 0.2 with an ad-hoc questionnaire.[2] Similar reductions in the long term quality of life were found in Buysse for patients surviving meningococcal septic shock (mostly from serogroup B, 79%), i.e. 0.12 with HUI-2 and 0.18 with HUI-3.[40]

Values reported for specific sequelae also varied considerably. Utilities for the health state 'mild hearing loss' ranged from 0.49 with VAS[41] to 0.91 with EQ-5D;[42] while those for 'severe hearing loss' (i.e. bilateral hearing loss or deafness) ranged 0.28 with HUI-3[42] to 0.86 with SG.[43] Utilities for the health state 'mild cognitive impairment' ranged 0.24 with HUI-3[42] to 0.74 with SG[43] while those for 'severe cognitive impairment ranged 0.22 with VAS[41] to 0.39 with SG.[43] None of those studies were specific to meningococcal serogroup B disease.

Despite using different methodologies, two papers report similar values for bacterial meningitis with recovery (without any severe sequelae): using the HUI-2 Koomen reports a utility of 0.93, while Bennet reports a utility of 0.98 (compared to 1).[43]

Table 6 – Health-related quality of studies of meningococcal diseases: summary of methods

Studies	Instrument	Respondent	n	Age (years)	Disease period	Follow-up period (years)	Disease
Kramer, 1994 Canada[41]	Hypothetical ill-child scenarios valued with VAS	Parents Physicians	208	Hypothetical 3-24 months	NA	NA	Bacterial meningitis
Stouthard, 1997 The Netherlands[44]	Hypothetical ill scenarios valued with PTO and VAS	Physicians Lay people	38	All	NA	NA	Bacterial meningitis
Erickson, 1998 Canada[2]	Ad-hoc questionnaire from which an impairment score is derived	Patients or their parents	231	All	1990-1994	NS	Meningococcal disease serogroup B Meningococcal disease serogroup C
Bennet, 2000 USA[43]	Hypothetical ill-child scenarios valued with SG	Parents	94	3-36 months	NA	NA	Occult bacteraemia
Erickson, 2001 USA[45]	EQ-5D	Patients	4	College student	1990-1999	NS	Meningococcal disease (no serogroup B cases)
De wals, 2002 Canada[39]	EQ-5D	Patients or their parents	NS	All	1990-1994	NS	Meningococcal disease serogroup C
Oostenbrink, 2002 The Netherlands[42]	Hypothetical ill-child scenarios classified with EQ-5D, HUI-2, HUI-3A and HUI-3B	Physicians	28	Hypothetical 6 year old	NA	NA	Bacterial meningitis
Van de Beek, 2002 The Netherlands[46]	SF-36	Patients	25	16-65 years	1998-2000	0.5-2	Meningococcal meningitis
Ruedin, 2003 Switzerland[38]	Multi-attribute utility model and expert panel	Expert panel	NS	All	NA	None	Meningococcal and pneumococcal disease
Koomen, 2005 The Netherlands[47]	HUI-2 Child Health Questionnaire	Parents	182	0.1-9.5 years at disease onset	NS	5-10	Bacterial meningitis (78% *N. meningitidis*, 16.2% *S. pneumoniae*, 3.4% *S. agalactiae*, 1.8% *E. coli* and 0.6% *L. monocytogenes*)
Buysse, 2007 The Netherlands[48]	SF-36 Child Health Questionnaire	Patients if aged 18+ Parents for those <18	140	5-31 years 1 month - 18 at disease onset	1988-2001	3.7-17.4	Meningococcal septic shock
Allport, 2008 UK[49]	SF-36 Child Health Questionnaire	Patients if aged 16+ Parents for those <16	9	5-22 years 9 months - 17 at disease onset	NS	3-6	Meningococcal septicaemia (with amputation)
Buysse, 2008 The Netherlands[50]	Infant & Toddler QoL questionnaire Child Health Questionnaire	Parents	47	0-17 years 1 month - 18 at disease onset	2001-2005	0.8-2.3	Meningococcal septic shock Serogroup distribution (n=40), B: 65%, C: 33%, undetermined: 2%

Studies	Instrument	Respondent	n	Age (years)	Disease period	Follow-up period (years)	Disease
Buysse, 2008 The Netherlands[40]	HUI-2 HUI-3 VAS	Patients if aged 18+ Parents for those <18	120	5-31 years 1 month - 18 at disease onset	1988-2001	3.7-17.4	Meningococcal septic shock Serogroup distribution (n=100), B: 79%, C: 13%, undetermined: 8%
Borg, 2009 UK[30]	SF-36 Likert scale to assess global QoL	Patients	101	16-22 years 15-19 at disease onset	1999-2000	1.5-3	Meningococcal disease Serogroup distribution (n=84), B: 56%, C: 39%, Y: 1%, undetermined: 4%
Schmand, 2010 The Netherlands[51]	SF-36	Patients	11	Mean: 41.6 years 16-65 at disease onset	1998-2000	9.3	Meningococcal meningitis
MOSAIC study, 2014, UK[a, 32]	EQ-5D	Parents	221	1 month – 13 years at disease onset	2004-2006	3.75	Meningococcal disease serogroup B

N: sample size; VAS: visual analogue scale; TTO: time trade-off; SG: standard gamble; EQ-5D: EuroQol 5 dimensions; HUI: health utilities index; QoL: quality of life; SF-36: short-form 36; NS: not stated; NA: not applicable. a: MOSAIC data courtesy of Helen Johnson, LSHTM.

Table 7 – Health-related quality of studies of meningococcal diseases: summary of results

Studies	Instrument	Disease	Dimension / Health state	Mean utility (standard deviation)
Kramer, 1994 Canada[41]	Hypothetical ill-child scenarios valued with VAS	Bacterial meningitis	Bacterial meningitis with (range):	
			• unilateral hearing loss	0.492-0.652
			• learning/behaviour problem	0.516-0.615
			• hypertension	0.451-0.543
			• bilateral hearing loss	0.379-0.451
			• major neurological defect	0.220-0.241
Stouthard, 1997 The Netherlands[44]	Hypothetical ill scenarios valued with PTO and VAS	Bacterial meningitis	Bacterial meningitis with (mean, 95% CI):	
			• permanent locomotor impairment	0.83 (0.702-0.964)
			• permanent cognitive impairment	0.75 (0.616-0.881)
			• permanent locomotor and cognitive impairment	0.24 (0.139-0.348)
Erickson, 1998 Canada[2]	Ad-hoc questionnaire	Meningococcal disease serogroups B and C	% reduction in quality of life for psychosocial sequelae after:	
			• meningococcal disease from serogroup B	20%[e]
			• meningococcal disease from serogroup C	31%[e]
Bennet, 2000 USA[43]	Hypothetical ill-child scenarios valued with SG	Occult bacteraemia	Meningitis with recovery	0.9768 (0.08)
			Meningitis with deafness	0.8611 (0.22)
			Meningitis with minor brain damage	0.7393 (0.29)
			Meningitis with major brain damage	0.3903 (0.37)
Erickson, 2001 USA[45]	EQ-5D	Meningococcal disease (no serogroup B case)	Amputation of fingers in both hands and bilateral amputation forefeet	0.69
			Amputation of fingers in both hands	0.80
			Bilateral amputation forefeet	0.73
			Hearing loss and decreased knee mobility	0.73
De wals, 2002 Canada[39]	EQ-5D	Meningococcal disease serogroup C	Utility decrement for meningococcal disease survivor with sequelae (mainly skin scars and amputation)	0.282[e]
Oostenbrink, 2002 The Netherlands[42]	Hypothetical ill-child scenarios classified with EQ-5D, HUI-2, HUI-3A[a] and HUI-3B[b]	Bacterial meningitis		EQ-5D / HUI-2 / HUI-3A / HUI-3B
			Deafness	0.81 / 0.79 / 0.47 / 0.28
			Mild hearing loss	0.91 / 0.84 / 0.74 / 0.65
			Epilepsy	0.83 / 0.88 / 0.78 / 0.70
			Mild mental retardation	0.62 / 0.55 / 0.44 / 0.24
			Severe mental retardation with tetraplegia	-0.15 / 0.12 / 0.02 / -0.33
			Leg paresis	0.67 / 0.80 / 0.64 / 0.51
			Epilepsy, mild mental retardation and leg paresis	0.47 / 0.46 / 0.28 / 0.02
Van de Beek, 2002 The Netherlands[46]	SF-36	Meningococcal meningitis	-	No utility index

Studies	Instrument	Disease	Dimension / Health state	Mean utility (standard deviation)
Ruedin, 2003 Switzerland[38]	Multi-attribute utility model and expert panel	Meningococcal and pneumococcal disease	% reduction in quality of life for moderate sequelae	20%[e]
			% reduction in quality of life for severe sequelae	40%[e]
Koomen, 2005 The Netherlands[47]	HUI-2 CHQ	Bacterial meningitis	Meningitis without severe sequelae:	
			• HUI-2	0.93 (0.18)
			• Reference population[c]	0.92 (0.08)
Buysse, 2007 The Netherlands[48]	SF-36 CHQ	Meningococcal septic shock	-	No utility index
Allport, 2008 UK[49]	SF-36 CHQ	Meningococcal septicaemia (with amputation)	-	No utility index
Buysse, 2008 The Netherlands[50]	ITQoL CHQ	Meningococcal septic shock	-	No utility index
Buysse, 2008 The Netherlands[40]	HUI-2 HUI-3 VAS	Meningococcal septic shock Serogroup distribution (n=100): B: 79%, C: 13%, Not determined: 8%	Meningococcal septic shock:	
			• HUI-2	0.88 (0.16)
			• HUI-3	0.82 (0.25)
			• VAS	85.4 (15.3)
			Reference population[d]:	
			• HUI-2	0.94 (0.09)
			• HUI-3	0.93 (0.12)
			• VAS	92.7 (9.2)
Borg, 2009 UK[30]	SF-36 Likert scale	Meningococcal disease	-	No utility index
Schmand, 2010 The Netherlands[51]	SF-36	Meningococcal meningitis	-	No utility index
MOSAIC study, 2014 UK[f, 32]	EQ-5D	Meningococcal disease serogroup B	Utility decrement for meningococcal serogroup B disease survivor with any sequelae	0.074[e]

a: HUI-3A with anchor points 1=healthy and 0=the worst health state; 'Death' is thus valued in between (here at 0.22). b: HUI-3B with anchor points 1=healthy and 0=death. c: reference population scores for HUI-2 come from representative sample of 353 Dutch schoolchildren aged 5 to 13 years. d: reference population scores for HUI2 and HUI3 come from a representative sample of 1435 Dutch schoolchildren aged 5 to 13 years. e: % reduction in utility or utility decrement. f: MOSAIC data courtesy of Helen Johnson, LSHTM. VAS: visual analogue scale; TTO: time trade-off; SG: standard gamble; EQ-5D: EuroQol 5 dimensions; HUI: health utilities index; SF-36: short-form 36; CHQ: child health questionnaire; ITQoL: Infant & Toddler quality of life questionnaire.

4 VACCINE EFFICACY AND SAFETY

Data on efficacy and safety were extracted from reviews of the literature and the European Medicines Agency assessment report (EPAR). We listed all clinical trials that were registered for this product (based on clinicalTrials.gov), and searched for published results of these trials. For trials whose results were not published, we contacted the vaccine manufacturer to receive unpublished data. As this vaccine had not yet been implemented in any country and no data had been generated on the clinical protection of this vaccine, we did not perform further literature reviews on efficacy and/or effectiveness, but reviewed related editorial, narrative reviews and commentary papers for the interpretation of data. We did not perform literature reviews on vaccine effectiveness of other meningococcal vaccines as their mechanism of action is different from this protein vaccine, with the exception of OMV vaccines which include one component of 4CMenB. Studies on the efficacy and effectiveness of OMV vaccines are described later for the validation of SBA correlates (see 4.1.3).

No efficacy data involving clinical endpoints were generated before licensure of this vaccine, due to the low incidence of meningococcal disease. 4CMenB has thus been licensed based on a serological correlate of clinical protection, the serum bactericidal antibody using human complement (hSBA).[18] This assay has been shown to correlate to protection against meningococcal disease in studies on other meningococcal vaccines, and has been validated by regulators for former meningococcal vaccine licensures.[18, 52, 53]

We describe below hSBA responses against the four vaccine antigens (fHbp, NadA, OMV PorA1.4 and NHBA). However, hSBA responses are based on highly selected strains and are therefore not sufficient to estimate the clinical protection that the vaccine can provide to a population. In addition, data on the distribution and expression of the four vaccine components are required to estimate the potential strain coverage of the vaccine.[53] We also retrieved information on how hSBA relates to clinical protection, and how hSBA against specific meningococcal antigens translate into clinical protection against the meningococcal strains circulating in a given country. We also retrieved unpublished efficacy data on carriage.

We limit the description of efficacy and safety data to the three schedules related to the simulations of this study (described in 1.4): infant primary series of three doses at 2, 4 and 6 months (for the simulated 3, 5 and 6 month schedule); booster around 13 months of age; and two doses in adolescents. The rationale for the selection of these schedules is further described under 6.1.1.

4.1 Vaccine efficacy against disease

The manufacturer has studied several vaccine schedules. Schedules that received authorization are:[54]

- Infant schedule, 3 primary doses and a booster: normal schedule at 2,4,6 months or accelerated at 2,3,4 months, booster at 12-13 months of age.
- Delayed infant schedule: 2 doses between 6 and 11 months of age and a booster.
- Catch-up: 2 doses at 12 to 23 months and a booster, or 2 doses at 2 to 10 years (need for booster not established).
- Adolescents and adults: 2 doses from 11 years of age (need for a booster not established).

Most of these schedules have been studied as given concomitantly or alone ("intercalated" with the routine schedule). Data on a 2+1 schedule, i.e. a schedule replacing the three classical primary doses by two primary doses, were not available at the time of this study (see further under 6.1.1).

4.1.1 SBA responses against the four vaccine components

A multicomponent vaccine must show serum bactericidal activity against its target antigens independently of others.[55] The hSBA measures the level of antibodies that recognize bacterial surface antigens and are capable of directing bacterial lysis, the main mechanism by which *N. meningitidis* serogroup B strains are killed in natural infection.[18] The primary endpoint of most studies was the proportion of subjects with hSBA titers ≥1:4 (or ≥1:5, depending on the study) against each of the reference meningococcal serogroup B strains. The use of this threshold is based on previous work described under 4.1.3.

Immunogenicity studies mainly provide data on fHbp, NadA and OMV as a reference strain for NHBA has only been recently identified and limited data have been provided later by the manufacturer.

4.1.1.1 Infant primary series at 2, 4 and 6 months

Three clinical trials provided data on this schedule, involving a total of 2562 subjects for three antigens (fHbp, NadA and OMV) but only 118 subjects for NHBA. hSBA responses to fHbp and NadA antigens were high in all studies, while responses to OMV and NHBA ranged 79-86% (Table 8). Proportions of hSBA above the threshold among controls were very low (<10%) in the two studies providing it. A substantial proportion of subjects had hSBA levels against NHBA above the threshold before vaccination at baseline (range 33-53% at 2 months), probably reflecting residual maternal antibodies.[18, 56]

Table 8 – hSBA (% >1:4 or 1:5) one month following 3 doses administered at 2, 4, 6 months of age

Study and design	Vaccines	ITT/PP	N subjects	fHbp	NadA	OMV	NHBA
Gossger 2012 (V72P12) and EPAR[18, 57]							
Multicentre RCT in Belgium, UK, Czech Rep., Germany, Italy and Spain. Open label (no blinding of subjects nor study staff).	4CMenB, PCV7/ hexa[a]	mITT	520-528	99%	99%	79%	NA
	4CMenB[b]	mITT	517-531	99%	99%	86%	NA
	PCV7/ hexa (controls)	mITT PP for NHBA	226-250 18 NHBA	4%	5%	4%	6%
Vesikari 2013 (V72P13) and EPAR[18, 56]							
Multicentre RCT in Finland and Czech Rep. Subjects evaluated randomized from study subjects. Observer blind.	4CMenB, PCV7/ hexa[a]	mITT PP for NHBA	1149-1183 100 NHBA	100%	100%	84%	84%
	PCV7/ hexa (controls)	mITT	116-120	3%	2%	2%	NA
Findlow 2010 (V72P6)[58]							
RCT in UK, open label (no blinding described).[c]	4CMenB, PCV7/ hexa[a]	PP only	34-40	87%	95%	85%	NA

a: hexavalent vaccines and PCV7 given concomitantly at 2, 4 and 6 months of age. b: called intercalated schedule: routine vaccines are given separately at 3, 5 and 7 months of age. c: data in controls not provided. mITT: modified intention-to-treat analysis, i.e. all infants from the sub-study who provided serum samples for immune testing; PP: per protocol.

4.1.1.2 Booster doses at 13 months

Immunity data suggest a rapid waning before the booster dose compared to immunity one month after the primary series, especially for OMV (Table 9 and see 4.1.2). hSBA responses to the booster 4CMenB dose were high and similar in children receiving concomitant MMRV or not.

Table 9 – hSBA (% >1:4 or 1:5) before and one month following booster dose at 12-14 months of age

Timing	Vaccines	ITT / PP	N subjects	fHbp	NadA	OMV	NHBA
Vesikari 2013 (V72P13) and EPAR[18, 56]							
Multicentre clinical trial in Finland and Czech Rep. No controls, observer blind.							
Before booster	4CMenB as primary series	mITT	434-437 100 NHBA	81%	99%	22%	61%
One month post-booster	4CMenB, with MMRV or not	mITT	421-424 100 NHBA	100%	100%	95%	98%
Findlow 2010 (V72P6)[58]							
Clinical trial in UK, open label (no blinding described)							
Before booster	4CMenB primary	PP	27-30	63%	89%	34%	NA
One month post-booster	4CMenB, routine	PP	27-30	100%	96%	93%	NA

mITT: modifed intention-to-treat analysis, i.e. all infants from the sub-study who provided serum samples for immune testing; PP: per protocol; MMRV: measles mumps rubella varicella given at 12 months of age.

4.1.1.3 Adolescent vaccination

Only one clinical trial provided hSBA data among adolescents.[59] The proportion of subjects above the threshold was high at baseline, ranging 36-88%, probably reflecting acquired immunity. Proportion of immune individuals was nearly 100% after 2 doses for each antigen.

Table 10 – hSBA (% >1:4 or 1:5) one month following two doses at 11-17 years of age

Timing	Vaccines	ITT / PP	N subjects	fHbp	NadA	OMV	NHBA
Santaloya 2012 (V72P10) and EPAR[18, 59]							
Randomized placebo-controlled trial at 12 sites in Chili. Observer blind.							
At baseline (pooled arms)	None		667-668 92 for NHBA	44%	36%	36%	88%
1 month after 2 doses	4CMenB 2 doses 1 month apart	PP	330 46 for NHBA	100%	100%	100%	100%
1 month after 2 doses	4CMenB 2 doses 2 months apart	PP	330 46 for NHBA	100%	99%	100%	100%

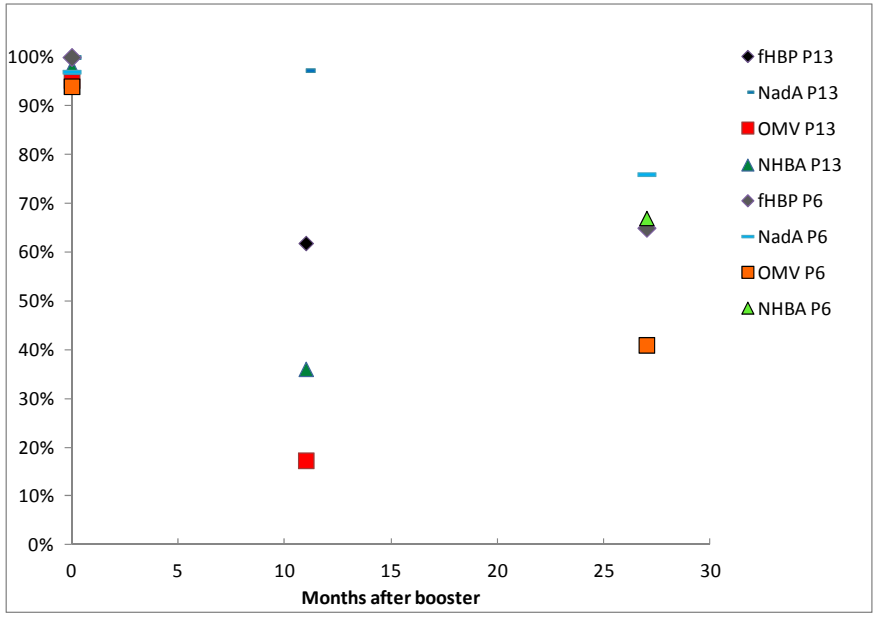
PP: per protocol.

4.1.2 Persistence of hSBA responses

The four components of 4CMenB show variable rates of antibody waning.[60]

In general, immune responses to NadA remain high, showing limited decline after vaccination (e.g. 76% at 28 months after the 12-month booster dose).[61] But for the other antigens, the proportions of infants with hSBA titers above the threshold decreased rapidly after the primary series, as shown in the pre-booster SBA levels (Table 9).[18, 56-58] Titres increase after the booster dose at 12-months but then decrease rapidly again, especially for NHBA and OMV (Figure 7).[61] For NHBA, the proportions of subjects above the threshold at 12 months after the booster are similar between vaccinated and controls.[18] At 28 months after the booster in a smaller follow-up study, these proportions seem to be constant for fHbp and even rise for antigens OMV and NHBA, but become similar to those of unvaccinated controls for fHbp and NHBA, suggesting a role of natural immunity in this rise: 65% and 63% for fHbp and 67% and 68% for NHBA in vaccinated and unvaccinated subjects, respectively.[61] This suggests that vaccination does not provide additional antibody level in children >3 years of age for these two most frequent antigens, unless a further booster is administered.

Figure 7 – Proportion of subjects with hSBA above threshold at various time points after a booster dose at 12 months



P13 is the follow-up of the Vesikari study, data published in the EPAR;[18, 56] P6 is the follow up of the Findlow study published by Snape et al.[61]

In adolescents, follow-up data of the two-dose schedule suggests relatively good persistence, with proportions above threshold ranging 75-95% at 22-23 months after the second dose, but no data were available for NHBA.[18, 62] However, it should be noted that the proportion above the threshold ranged from 25-50% among unvaccinated controls of the same study, suggesting again a level of protection from natural immunity.[18]

Some authors note that the significance of waning of antibody levels in relation to efficacy and effectiveness is currently unknown.[63, 64] However, declines in effectiveness of OMV vaccines over time after vaccination were reported in several studies,[65, 66] and corresponded with waning of bactericidal antibodies.[66] The same pattern was observed with meningococcal C vaccine.[10]

4.1.3 Correlation between SBA and clinical protection

An association between the age-related increase in the prevalence of SBA activity and a corresponding decrease in the incidence of meningococcal disease, including serogroup B, was demonstrated in the 1960s by Goldschneider *et al*.[67] However, further studies showed that SBA activity following infection is age-dependent, with children <10 years having a lower level of activity compared to those older.[68] SBA requirements have been defined by the WHO in 1976 to support meningococcal polysaccharide vaccine licensure.[69] High SBA activity was later proposed as a correlate for efficacy of serogroup B vaccines in a 2005 international consensus meeting.[70]

The relationship between SBA and meningococcal vaccine efficacy has been described in several reviews.[52, 53, 71] It was first determined for conjugate meningococcal C vaccines.[72, 73] For serogroup B, the only evidence is the relationship between SBA and efficacy/effectiveness for OMV vaccines against outbreak specific strains in Brazil, Chile, Norway and New Zealand (Table 11).[66, 70, 71] In a case-control disease efficacy trial in Brazil, vaccine efficacy was estimated to be 74% in subjects greater than 4 years of age, while SBA response rates in this population were greater than 50% (Table 11). In the same study, immunization of children under 24 months of age with 3 doses of vaccine showed no disease efficacy and only a 13% response rate in SBA. In a randomized double-blind study in 14–16-years-old in Norway, administration of two doses resulted in 87% efficacy at 10 months post-immunization and 57% efficacy at 29 months with an SBA response rate (% ≥4) of 97% 1.5 months after immunization and 42% at 24 months. Data on efficacy and SBA responses from other OMV vaccine studies are in Table 11. Based on these data, Frash *et al*. suggested that SBA could serve not only as a correlate but also as a surrogate of protection.[71, d]

[d] Correlate is defined as a variable correlated with the true clinical outcome. Surrogate endpoint is defined as a replacement for true clinical outcome.[71]

Table 11 – Summary of the findings on the relation between SBA and effectiveness of OMV vaccines against specific strain of meningitis B[71]

Country (year)	Design, age	Efficacy/effectiveness (subject age)	% with 4-fold rise in SBA	% with SBA >= 4 post-vaccination
Brazil (1990–1991)	Case control	-37% (3–23 months)	22%	13%
		47% (24–47 months)	45%	43%
		74% (>48 months)	52%	52%
Chile (1995)	RCT	0% (1–4 years) 70% (5–21 years)	12% 65%	Not reported
Norway (1988–1991)[66]	RCT, 13–14 years	87% (10 months post)	80% (1.5 months post)	97% (1.5 months post)
		57% (29 months post)	26% (24 months post)	42% (24 months post)
New Zealand (2004–2007)	Cohort studies	80% (6 months–<5 years)	92% (>6 months at 1st dose) 82% (post 4th if <6 months at 1st dose)	

Vipond *et al*. consider however that important questions are left unanswered. The major issue is that the evidence is based upon experience with one protein, PorA.[53] It is uncertain whether such an approach is broadly applicable to the other three antigens in the vaccine, and the proof that the level of SBA is a valid correlate of protection for the other antigens awaits confirmation through effectiveness studies. First, the majority of meningococcal isolates express PorA at a high level making it a good target for bactericidal antibodies, while other vaccine antigens, in particular fHbp, are expressed at lower levels. Second, other factors influencing antigen gene expression in the human host against meningococcal isolates may not be reflected in the way bacteria are grown in vitro for e.g. SBA assays. For instance, the conditions of iron load and oxygen in the human body are very different from those used to grow strains, and may suppress the expression of certain antigens in vivo. Vipond *et al*. consider that this may lead to an overestimation of the effectiveness for fHbp and to an underestimation of the effectiveness of NadA, but uncertainty is high.

4.1.4 Predicted strain coverage of the 4CMenB vaccine

A problem with vaccines based on proteins is that the binding of antibodies elicited by vaccine antigens cannot be predicted and the presence and level of expression of these proteins may vary between isolates.[74] This means that not all invasive meningococcal serogroup B strains will be covered by this vaccine. Therefore, the determination of whether an isolate is targeted by 4CMenB induced antibodies has to rely on specific tests. The gold standard test for this purpose is the serum bactericidal assay (SBA) described before, but this test is difficult to standardize and is only available in a limited number of laboratories.[74] In addition, the use of SBA for this purpose would require performing it on many strains in each geographic region.[75]

To address this problem, the meningococcal antigen typing system (MATS) has been developed to estimate the extent of 4CMenB clinical protection against meningococcal isolates. As of June 2014, MATS is the sole validated and reliable instrument to obtain expression data for the four 4CMenB components.[74-76] However, MATS is provided by the vaccine manufacturer and its availability in Europe is restricted to a few laboratories determined by the vaccine manufacturer.

MATS is applied on clinical specimens with the use of a modified ELISA, which measures the expression and antigenic cross-reactivity of fHbp, NadA and NHBA and combines these data with PorA data. MATS measures the binding of carefully selected antibodies against each of these three antigens from invasive isolates grown in laboratories, and antibody binding correlates with killing of the same strains in the SBA.[74] MATS is therefore a surrogate assay which measures properties of the bacteria, while SBA provides a functional measure of antibodies in a vaccinated person.[74] Inter-laboratory reproducibility and comparability of this test have been demonstrated in a study involving seven laboratories.[76]

Unfortunately, Belgian strains could not be tested by MATS for this study. The MATS distribution of neighbouring countries and a European average in the epidemiological year 2007-08 are presented in Table 12.[19]

Table 12 – Predicted strain coverage in European countries in 2007-08 according to MATS[19]

Countries	Number strains tested	% strain covered by MATS	95% CI
England and Wales	535	73%	57-87%
France	200	85%	69-93%
Germany	222	82%	69-92%
EU average*	1011	78%	63-90%

**: pooled estimates based on tested strains from England and Wales, France, Germany, Italy and Norway.*

4.1.5 Relation between MATS and SBA

Data on the relationship between MATS/SBA are rather sparse. A first study established the Elisa threshold values to predict the probability that strains are killed by immune sera in the SBA.[75] In that study, a non-representative sample of 57 serogroup B strains from varying geographic regions were tested by MATS as well as by SBA, using pooled sera from 141 vaccinated infants (13-month-olds, vaccinated 2, 4, 6 and 12 months of age),Table 13. Among the strains with MATS titres above the threshold for at least one antigen, 89% (i.e. positive predictive value) were killed in the SBA, while 77% strains with MATS below the threshold (i.e. predictive negative value) for all antigens were not killed (Table 13). Positive and negative predictive values were 83% and 73% respectively when pooled serum of infants vaccinated with 3 doses was used. As the numbers by antigen are very small, 95% confidence intervals are expected to be wide, especially for individual antigens, but these are not provided in the article.

Table 13 – Positive predictive value for the 3 antigens based on killing by sera from children immunised with 3+1 doses (2, 4, 6, and 12 months of age)[75]

Vaccine	Antigen positive predictive value	% positive MATS killed in SBA	Negative predictive value	% negative MATS not killed in SBA
NHBA	82%	9/11		
NadA	83%	5/6		
fHbp	100%	7/7	77%	10/13
Any antigen or combination	89%	39/44		

A second study aimed to validate the accuracy of MATS predictions against strains that are representative of a specific epidemiologic setting.[77] A representative sample of 40 strains selected from all 535 isolates collected in England & Wales in 2007-08, was tested in SBA based on pooled sera from infants and adolescents following vaccination and results were compared with those from MATS. The positive predictive value of MATS was 96% (27/28) and the negative predictive value was only 33% (4/12). As MATS-predicted coverage was lower than the coverage measured by hSBA using pooled sera from infants and adolescents – though not statistically significantly, the authors concluded that MATS may underestimate strain coverage.[77]

However, caution should be used in interpreting a surrogate (MATS) of a correlate (hSBA).[63] Details on how these data are interpreted to derive model parameters are provided later under 6.2.2.

4.2 Vaccine efficacy against carriage

The only study on 4CMenB effect on carriage was conducted among British university students in 2010 (Table 14). It was not published at the time of writing this report but data were presented at various conferences.[78] Crude vaccine efficacy values were not provided but have been calculated based on available data: VE is computed as 1-RR, RR being the rate ratio between the prevalence of carriage in vaccinated children and in placebo. The huge difference between crude and adjusted efficacy values is difficult to understand in a randomized clinical trial, as only small differences among both vaccinated and placebo groups in baseline characteristics are expected

unless randomization was not successful. Despite various questions to the manufacturer, this issue is still unclear.

Overall, efficacy estimates against carriage of virulent serogroup B strains at 1 month after 2 doses (primary endpoint), against serogroup B carriage at any later sampling point and against new acquisition of serogroup B strains were not significant (Table 14).

Table 14 – Vaccine efficacy against serogroup B carriage[78]

Endpoint	Carriage in vaccinees	Carriage in placebo	Crude VE[a]	Adjusted VE[b] (95% CI)
Primary: carriage of virulent serogroup B strains at 1 month after 2 doses	9.5%	8.1%	-17.3%	-18.2% (-73.3 to 19.4)
Secondary: carriage of any *N. meningitidis* at cumulative later sampling points	32.0%	34.4%	7.0%	18.2% (3.4-30.8)
Carriage of serogroup B *N. meningitidis* at cumulative later sampling points	NA	NA	NA	15.6% (p=0.225)
New acquisition of serogroup B strains[c]	5.4%	7.4%	27%	29% (-12 to 54)

a: calculated based on provided data, as 1-rate ratio. b: adjusted for baseline carriage, treatment group, centre and significant risk factors as identified within a multivariate model. c: acquisition of any serogroup B strains among subjects negative at visits 1, 2 or 3. VE: vaccine efficacy.

4.3 Vaccine adverse events

We extracted data on adverse event following immunization (AEFI) per dose from clinical trials that administered the selected schedules.[56, 57, 59] Severe effects and those related to fever are described by schedule. Other mild effects (i.e. local pain, induration, etc.) are not described here as they are not included in the models (see also 6.3.4). Endpoints vary per study, even for fever (i.e. >38°C and 39°C in Gossger and >38.5°C and 40°C in Vesikari) and are thus presented per study in Table 15. Severe AE presented in Table 16 are severe conditions that are possibly, probably or definitely related to the vaccine. Frequency are presented for all doses together as no substantial variations are observed across doses; however, a slight trend is observed with lower frequencies after the third primary dose. The Vesikari study pooled adverse events from the two sub-studies (an RCT and an open label randomized observer-blind).[56]

Studies show that 4CMenB vaccination is followed by a high frequency of fever and side effects, especially when co-administered with routine vaccines (Table 15):[56, 57] rates of fever were systematically more frequent in infants receiving a concomitant primary schedule compared to those receiving routine vaccination only.[56, 57] Fever >38°C was observed in 80% of children receiving three doses of concomitant 4CMenB and routine vaccines (58% of all doses) in one study,[57] and fever >38.5°C in 65% of subjects in the other study (22% of all doses).[56] When 4CMenB is given alone, high fever and serious adverse events were also more frequent compared to those in control subjects receiving routine vaccine only (Table 15).[56] We included in Table 16 the Kawasaki disease cases that were considered as possibly or probably related to 4CMenB in the trials. It should be noted that the EMA assessment report states that these cases do not allow a definitive assessment of the causal relationship between 4CMenB and the disease.[18]

Among children receiving the booster dose at 12 months, mild adverse events (such as fever >38°C, antipyretic use and medically attended fever) were more frequent per dose compared to those in the primary schedule, while serious adverse events such as fever >40°C and seizures were rare.[56] Adverse events were overall infrequent in adolescents, and no vaccine related serious adverse event was reported.[59]

Table 15 – Selected adverse events following immunization, by study and schedule

Study and schedule	Outcome[c]	Total doses	% vacciness with AE	% doses with AE in vaccinees	% doses with AE in controls
Primary series (2, 4 and 6 months)					
Gossger, primary series, concomittant[a,57]	Fever >38°C	1841	80%[b]	58%	30%
	Fever >39°C	1841	NA	12%	3%
	Any vaccine-related serious AE	1841	NA	0.5%	0.1%
	Vaccine-related seizures	1841	NA	0%	0%
Gossger, primary series, 4CMenB alone[57]	Fever >38°C	1836	NA	35%	NA
	Fever >39°C	1841	NA	6%	NA
	Any 4CMenB-related serious AE	1836	NA	0.38%	NA
	Vaccine related seizures	1836	NA	0.11%	NA
Gossger, all primary schedules[57]	Kawasaki disease, confirmed and possibly/probably related to 4CMenB	4615	NA	0.02%	NR
	Hospital observation for fever post-4CMenB	4615	0.5%	0.13%	NR
Vesikari, primary series, concomitant. RCT + open label study[a,56]	Fever >38.5°C	7293	65%	22%	11%
	Fever >40°C	7293	1.2%	0.4%	0%
	Medically-attended fever	7293	2.3%	0.78%	0.61%
	Anti-pyretic use	7293	93%	32%	24%
	Seizures probably / possibly related to 4CMenB	7293	0.16%	0.05%	NR
	Kawasaki disease, confirmed and possibly/probably related to 4CMenB	7293	0.08%	0.03%	NR
	Other serious vaccine-related AE	7293	NA	0.22%	0.15%
Booster at 12 months					
Vesikari, booster, alone[56]	Fever >38°C	783	32%	32%	NA
	Fever >40°C	761	0%	0%	NA
	Medically-attended fever	765	1.1%	1.1%	NA
	Anti-pyretic use	765	57%	57%	NA
	Possibly 4CMenB-related seizures	765	0.13%	0.13%	NR
	Kawasaki disease, confirmed and possibly/probably related to 4CMenB	765	0%	0%	NR
Adolescents, 2 or 3 doses at 11-17 years, one or two months apart					
Santaloya, 2 or 3 doses[59]	Fever >38°C	3329	NA	3.7%	1.6%
	Fever >39°C	2738	NA	0.7%	0.3%
	Medically attended fever	1480	NA	0.27%	0.16%
	Anti-pyretic use	1461	NA	4.2%	3.2%
	Serious vaccine-related AE for 2 doses	NA	NA	0%	0%

a: concomitant with hexavalent and PCV7 vaccines; controls are hexavalent and PCV7 vaccines. b: this takes into account that the same subjects could experience fever once, twice or three times; in average, each subject experienced 1.7 episode of fever >38°C in this arm. c: vaccine-related or related includes events that were possibly, probably or definitely related to 4CMenB after assessment. AE: adverse event; NR: non relevant (i.e. events related to 4CMenB alone and no placebo control group); NA: not available.

5 ANALYTICAL CHOICES FOR THE ECONOMIC EVALUATION OF 4CMENB IN BELGIUM

5.1 Models structure

Two types of model were developed using Berkley Madonna software[79] to predict the impact of vaccination: a single cohort static model, which assumes direct protection only and a transmission dynamic model, which also allows the potential effect of the vaccine on carriage, and thus wider herd protection effects, to be estimated.[80]

As the study on carriage failed to show a significant effect of 4CMenB on carriage of serogroup B strains,[78] and since the point estimate for the primary endpoint was even negative, we assumed no effect on carriage in the base case analysis. However, we considered an efficacy on carriage in a scenario analysis, using the dynamic model (see 4.2 and 6.3.3).

The models used to assess the potential impact of 4CMenB in England have previously been described.[81] In the text below the structures are briefly described, and differences from the England model and key points to aid interpretation of results are highlighted.

5.1.1 Model structure - details common to both models

The models are structured into 100 single year of age classes. After disease individuals may survive with sequelae, survive without sequelae, or die due to the disease. Survivors with sequelae are assumed to have a reduced quality of life; quality of life losses were not included for the acute phase of the illness, for survivors without sequelae or for vaccine-related adverse reactions. Those dying from the disease were assumed to lose the average life expectancy for the age at which they died. The base-case models considered serogroup B meningococci only, as the vaccine has received EMA authorization for immunization against serogroup B only. In an alternative scenario all serogroup meningococci were modelled. Disease incidence was modelled by month of age for young children (<2 years), and by years of age thereafter. Individuals may die due to causes other than meningococcal disease; published mortality rates were adjusted to remove deaths due to meningococcal disease as these are explicitly modelled. Based on the available literature, vaccinated individuals were assumed to acquire immunity one month following their second dose of vaccine and have a reduced risk of disease. Immunity can wane over time, in which case individuals then have the same risks of infection as unvaccinated individuals.

Infant strategies are simulated in both the static (base case) and the dynamic models. Adolescent strategies are simulated in the dynamic model only as these were a priori considered relevant only under the assumption of an indirect effect.

5.1.2 Model structure – static specific details

The static model is constructed using a Markov model, with monthly time steps (Figure 8, A). Individuals are born susceptible and cases arise by multiplying the age-specific probability of disease by the susceptible population. We assumed individuals only have disease once and are removed from the susceptible pool. Years of life are weighted by the age-specific quality of life. The cohort size was based upon population figures for 2011. For infant vaccination a single birth cohort (128 605 individuals) was considered.

5.1.3 Model structure – dynamic specific details

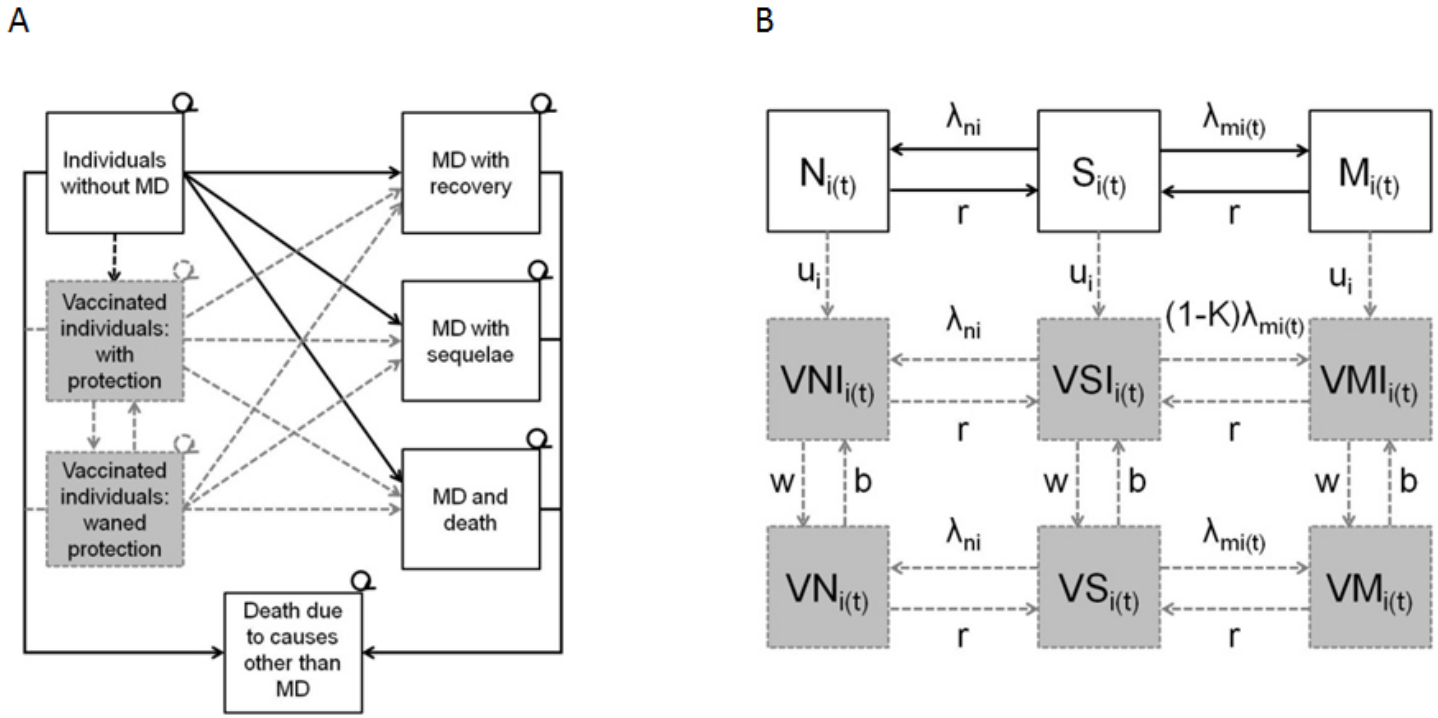
A Susceptible-Infected-Susceptible (SIS) model[e] was used to represent the transmission of meningococcal carriage (Figure 8, B), with a daily time step. Model equations are presented in Appendix 5.1. This structure was chosen because individuals are expected to have multiple episodes of asymptomatic carriage of meningococci in their lifetimes.[6] Current evidence suggests carriage of multiple meningococcal strains is rare,[82] thus the model does not consider co-infection. Individuals are born susceptible, may become carriers of a meningococcal strain which is vaccine preventable, or non-vaccine preventable, and after a period of time (average of 6 months)

[e] The SIS structure of the dynamic model implies that individuals can be carriers and therefore have disease more than once. By contrast in the static model individuals may only have disease once. Although the impact of such a difference would be very low due to the rarity of the disease, is it a true theoretical difference in the underlying assumptions of the two models.

clear carriage to return to the susceptible state. Population mixing is based on mixing patterns from self-reported leisure contacts in Belgium (POLYMOD, see 6.6.2). Cases are generated by applying an age-specific case-carrier ratio to the number of new carriage acquisitions (Appendix 5.3).

Vaccinated individuals with immunity may have protection against carriage acquisition (if any) as well as disease. The demographics (single year of age population) were based on the living population from the static model, to aid comparisons between the static and dynamic results.

Figure 8 – Simplified structures of the static (A) and dynamic (B) models (Reprinted with permission from Elsevier for Christensen *et al.*[81])



The 'no vaccination' model consists of white boxes and solid arrows; the 'with vaccination' model includes shaded boxes and dashes arrows in addition. (A) Static model structure. MD: meningococcal disease. (B) Dynamic model structure. Once individuals acquire carriage they have a chance of developing disease, with the same outcomes as shown in (A). S: susceptible non-vaccinated; M: infected carrier of a vaccine preventable meningococcal strain; N: infected carrier of a non-vaccine preventable meningococcal strain; VSI: susceptible vaccinated and immune; VMI: infected carrier of a vaccine preventable meningococcal strain, vaccinated and immune; VNI: infected carrier of a non-vaccine preventable meningococcal strain, vaccinated and immune; VS: susceptible vaccinated not immune; VM: infected carrier of a vaccine preventable meningococcal strain, vaccinated not immune; VN: infected carrier of a non-vaccine preventable meningococcal strain, vaccinated not immune; λm: force of infection for vaccine preventable meningococcal strains; λn: force of infection for non-vaccine preventable meningococcal strains; r: recovery rate; κ: vaccine efficacy against carriage acquisition; u: vaccine uptake; w: waning vaccine protection; b: vaccination booster; i: age; t: time.

5.2 Outcomes and comparator

Key outputs of the models include: cases, cases with sequelae and deaths averted, life years saved, quality adjusted life years gained and cost-effectiveness. The main outcome for the cost-effectiveness analysis is the incremental cost per QALY gained, although other ratios are reported (cost per case averted, per death averted and per life year saved).

Several vaccination scenarios are modelled, in each case the model results are compared to the situation without vaccination (i.e. the current situation where there is no vaccination against MenB, and cases are treated as they arise), and to the next best alternative when relevant (i.e. in the dynamic model where adolescent strategies are modelled on top of infant strategies, thus where different vaccination options can be opted for within each vaccination policy).

The next best alternative for a vaccination option was identified through application of the concepts of dominance and extended dominance to the incremental direct costs and QALYs. Options were ranked by increasing discounted total cost of vaccination. Options were excluded if they cost more and prevent fewer QALYs than another option (i.e. “excluded by dominance”), or if they had a higher incremental cost-effectiveness ratio (ICER) and were less effective in gaining QALYs than the option that precedes them (i.e. “excluded by extended dominance”).

5.3 Perspective

The economic evaluation was undertaken under the perspective of the health care payer, as recommended by the Belgian guidelines on economic evaluations.[83] Costs included were direct medical costs paid out of the health care budget (be it the federal government or the three federated entities) and the patients’ out-of-pocket expenses for health care. Societal costs such as productivity losses and direct non-health care costs such as personal travel expenses were not accounted for. All costs are expressed in Euro 2012. Costs from previous years were updated to 2012 using health consumer price indices if needed.[84]

5.4 Time horizon

The base case time horizon of the models was 100 years. In scenario analysis a 20 year time horizon was further considered.

In situations where there is continuous vaccination of multiple cohorts (i.e. in the dynamic model), not all cohorts are followed for their whole lives (i.e. babies vaccinated in the last year of the model will only be followed up for one year). This is a limitation of this method, but unlikely to have much practical effect when discounting is applied in the 100 year time horizon models.

5.5 Discounting

Future costs and benefits were discounted back to their present value in order to calculate the net present value. In the base case a discount rate of 3% was applied to costs and 1.5% was applied to benefits, as recommended by the Belgian guidelines on economic evaluations.[83] Applying equal discount rate (3%) for both costs and benefits was also explored in the sensitivity analysis.

5.6 Demographics

Population figures, natural death probabilities and life expectancies expressed by single year of age were taken from the 2011 estimates for Belgium, published by the Belgian statistical authority “Statistical Belgium”.[85]

In order to obtain monthly data, annual probabilities of death were transformed using the density method,[86] assuming a constant rate over time:

- from annual probabilities to monthly rates: - [ln (1 - annual probability of death)] / 12;
- from monthly rates to monthly probabilities: 1 - exp (-monthly mortality rate).

Given the distribution of the infant deaths reported by the WIV-ISP for 2009,[87] where 67% of the deaths occur in those aged 0 months, 22% in those 1-5 months and 11% in those 6-11 months, the assumption of a constant rate of death overtime in infants <12 months does not hold. Probabilities in the first 11 months of life were thus adjusted to account for the true distribution of deaths in those age groups. Monthly values for the Belgian population and the life expectancy were further derived based on the monthly probabilities of death.

5.7 Interpretation of the cost-effectiveness results

The ICER alone does not allow conclusions to be made about the cost-effectiveness of an intervention. Such conclusions require a comparison with a reference ("threshold") value for the ICER, above which an intervention would be considered not cost-effective (because the additional cost for an additional unit of effect is considered too high) and below which it would be considered cost-effective. However Belgium does not use such a threshold.[88]

As a guide to interpret the results we provide here ICER estimates from past KCE reports for recently implemented routine vaccinations in Belgium. The introduction of childhood pneumococcal conjugate vaccination (PCV) was estimated at €10 000 per QALY gained for 2+1 doses assuming no replacement disease.[90] Human Papillomavirus (HPV) vaccination of 12 year-old girls was estimated at €33 000 per QALY gained for 3 doses at €0 marginal administration costs, and a booster dose every 10 years administered by GPs.[89, 90]

By contrast, with an ICER estimated at >€85 000 per QALY gained depending on the modelled time horizon and assuming exogenous boosting (i.e. exposure to chickenpox reduces the risk for herpes zoster), varicella-zoster-virus vaccination with two doses in children was not included in the Belgian routine vaccination calendar, nor reimbursed.[91] Universal childhood hepatitis A vaccination (2 doses) was estimated at €262 000 per QALY gained and was not approved for inclusion in the routine vaccination calendar, nor for reimbursement.[92]

ICERs reported in the current study will be appraised as compared to the ICERs of the introduced routine PCV and HPV vaccinations reported above. However caution should be taken when comparing the results of the current study with other (non-)introduced interventions. Decisions are rarely made on the basis of cost-effectiveness considerations alone and it is thus not clear whether economic or other arguments (e.g. therapeutic value, ethical and organisational issues, etc.) have been considered or played a decisive role in the decision-making process. Moreover comparisons with ICERs calculated in the past is only warranted if the ICERs are obtained in the same way, i.e. using the same methodology and under the same conditions (costs, existing technologies, experience, etc.).

6 INPUT FOR THE MODELS

This section presents the inputs used to populate the static and the dynamic models. It also presents the rationale for variations around the input parameters used in scenario analyses. A summary of the input parameters can be found in Table 42.

The parameters related to IMD are described for serogroup B (base case analysis) as well as for all serogroups (scenario analysis).

6.1 Vaccination strategies

6.1.1 Vaccination schedules

The selected vaccination schedules and scenarios presented in Table 1 were slightly adapted to fit with the existing model structure and avoid a long recoding process that would delay the study (Table 16). The models simulated the booster dose at 12 months instead of 13-15 months, and the adolescent vaccination at 14 years instead of around 13 years (concomitant to HPV in girls, in the first or in the second year of the secondary school, in Flanders and Wallonia respectively). The adolescent strategy is simulated in the dynamic model only. The infant strategy is simulated in both the static and the dynamic model (Table 16). Two main schedules are considered: one in infants with primary series at 3, 5 and 6 months and a booster at 12 months of age (3+1 doses); another one in adolescents of 14 years of age, with two doses separated by two months.

Table 16 – Vaccination strategies simulated in the models

Target group	Model	N doses	Age at doses
Infants alone	Static and dynamic	3+1	3, 5, 6 months, booster at 12 months - 3 months: co-administration with hexavalent vaccine - 5 months: alone - 6 months: alone - 12 months: alone
Adolescents alone	Dynamic	2	At 14 years, co-administration with 2 doses HPV (2 months apart)
Infants + adolescents	Dynamic	As above	As above

It should be noted that the need for further boosters after those schedules has not been determined yet by the manufacturer and the EMA. The EMA assessment report concludes "the responses to NHBA and OMV had decreased to very low levels, suggesting the need for a further booster dose from 12 months to 23 months after the primary series".[18] This second booster (5th dose) is however not mentioned in the Summary of Product Characteristics (SPC) and thus not considered in our scenarios.

The following considerations have guided the choice of vaccine scenarios and schedules described in Table 1:

- The age groups with higher incidence and/or higher potential for disease transmission should be targeted, and these are the infants <1 year of age and the adolescents.
- The co-administration with other vaccines should be limited to avoid high reactogenicity.
- When co-administration cannot be avoided, not more than two injections can be administered, in line with recent research on acceptability of vaccination in Flanders.[20] This implies that a first administration at 2 months of age was not possible due to the two already scheduled injections but a first administration at 3 months was considered as possible because only one other injectable vaccine (hexavalent) is given at that age (see current calendar in Appendix 4).
- A second dose could be administered at 5 months, alone, because medical visits are usually scheduled at that age, but would require extra-cost for administration.
- A third dose could be administered at 6-7 months.
- A booster could be administered around 14 months, separately from other vaccines to avoid again three injections.

Accelerated (2, 3 and 4 months and booster) and delayed (2 doses between 6 and 11 months) schedules were discarded for the following reasons:

- The 2, 3 and 4 month schedule shows a much lower response to the NHBA antigen, which is among the most frequent antigens. Overall, SBA titers do not decline more rapidly compared to the 2, 4 and 6 month schedule but the proportion of protected subjects is much lower before the booster dose at 12 months, due to a longer delay after the 3rd dose.[18] Pre-booster, SBA titers to NHBA in vaccinees become similar to those of unvaccinated controls of the same age (24%).[18] According to the Bexsero EPAR, the need for further booster doses after the booster at 12-15 months is currently unclear.[18]
- Routine vaccines are given at a 2, 3 and 4 month schedule in Belgium and concomitant administration is to be avoided.
- The delayed schedule (2 doses between 6 and 11 months and a booster at 12 months) would provide protection later in life, after the highest disease burden and should thus not be considered as a routine immunization schedule.[63] In addition, SBA levels against fHbp and OMV decline rapidly and represent 36% and 14% (>1:4), respectively, two years after the 3rd dose i.e. at 3.5 years of age.[63] This would imply that an additional booster (4th dose) must be given after the delayed schedule.[61, 63] This does not present any advantage over the 3+1 schedule, in which SBA levels above 1:4 are 65% and 41%, respectively, at the same age.

Catch-up schedules (targeting children above one year) were not considered because they present the same disadvantages overall: lower burden of disease and need for three doses <2 years and at least two doses for children above 2 years of age (need for a 3rd dose-booster not established).

There are no data available at the time of this study on a 2+1 schedule. Such a schedule, based on administration at 3, 5 and 11 months of age, is being investigated by the manufacturer in 2011-2014 but will only be completed by December 2014.[f] Given the rapid decline of immunogenicity after a 3-dose primary series, we expect that such schedule may not provide sufficient protection before booster, unless widespread vaccination may provide sufficient indirect effect to protect these infants. This schedule is also likely to provide lower protection at an age with high incidence (<12 months). A 2+1 schedule has however been selected for future introduction of 4CMenB in England and Wales, and effectiveness data might become available in the coming years.

6.1.2 Vaccine uptakes to be simulated

The vaccine uptakes per schedule and vaccination strategy that could be expected have been determined in consultation with experts and based on Belgian data on similar vaccines or similar situations. We mostly used Belgian uptake data on vaccines recently introduced against comparable diseases (e.g. invasive bacterial diseases), and/or administered at comparable visit time (e.g. adolescence) and following similar policy (i.e. free, partly reimbursed or fully charged), as well as drop-out rates between doses of other vaccines (Table 17). For 4CMenB infant doses to be given separately from other vaccines, we used the proportion of regular medical visits at under 5 clinics (ONE or K&G) or to a physician. All these values were based on past regional surveys and estimated by weighted pooling of region estimates.[93-98] Other uptakes were based on expert advices, especially those for high and low scenarios. For instance, the expected uptake for the 1st 4CMenB dose is estimated at 90% because this dose is administered together with scheduled vaccines; we estimated a lower expected uptake for the following doses because no other vaccine is given at those ages and we based the uptake on the proportion of children regularly attending child clinics (ONE or K&G).

Table 17 – Expected vaccine uptake per schedule

Doses	Basis for estimation of base case[a]	Base case	High	Low
For routine vaccination, vaccine free of charge				
1st dose	PCV7 2nd dose (at 3 months) and MenC 1st dose	90%	NR	NR
2nd dose	Rotavirus 2nd dose and % regular visits	60%[b]	93%	49%
3rd dose	% regular visits at child clinics (K&G-ONE)	55%	93%	49%
Booster	% regular visits and drop-out hexavalent for booster	50%	91%	43%
Adolescents	MenC at 10-19 years in 2002-04 and HPV 3rd dose	60%	82%	42%
Vaccine recommended and reimbursed by RIZIV-INAMI				
1st dose	Hep B 1st dose in 1999 (when only reimbursed)	60%	NR	NR
2nd dose	Rotavirus 2nd dose and % regular visits	55%[b]	65%	34%
3rd dose	2nd dose Hep B in 1999 (reimbursed) and drop-out	50%	65%	34%
Booster	3rd dose Hep B in 1999 (reimbursed) and drop-out	40%	50%	25%
Adolescents	Value for routine adjusted for reimbursement	30%	39%	21%
Marketed only, full charge				
1st dose	PCV7, 1st dose in 2004-06 (when full charge)	40%	NR	NR
2nd dose	PCV7, 2nd dose in 2004-06 (when full charge)	30%[b]	30%	10%
3rd dose	PCV7, 3rd dose in 2004-06 (when full charge)	20%	30%	10%
Booster	PCV7, 4th dose in 2004-06 (when full charge)	10%	30%	10%
Adolescents	Hep B and MenC adolescents before introduction	10%	30%	10%

a: estimated based on weighted pooled estimates from the three regional vaccine coverage surveys. Basis for high and low estimates are mostly based on expert opinion. b: the uptake value of the third dose is used for vaccine benefit of the 2nd dose due to the model structure. K&G-ONE: Kind en Gezin - Office de la Naissance et de l'Enfance; NR: non relevant (uptake for first dose are not taken into account in benefits, as no protection is assumed from 1st dose).

[f] According to http://www.clinicaltrials.gov/ct2/show/NCT01339923?cond=Meningococcal&rank=12. Accessed on 1st August 2014.

6.2 Clinical / epidemiological parameters

6.2.1 Age-specific incidence rates

For the base case, serogroup B incidence rates were derived for the most recent period, i.e. 2009-10 (see 3.1.1). To account for temporal variations in incidence, the high case was based on historical data on the last serogroup B peak (1999-2001) reported by the NRC (see Figure 3). The low case could not be based on historical data due to lack of information on age specific incidences, and was based on the number of cases that would be predicted if the current declining trend observed in NRC data over 2004-12 would be prolonged in 2013 (0.93 per 100 000), based on a Poisson regression model. Age-specific serogroup B incidences (Table 18) were estimated from NRC and RHM-MZG data, as explained under 3.1.1, for the 2009-10 base case. Because MZG-RHM data were not available for the scenarios (older period or hypothetical low incidence), we used observed or projected NRC data, adjusted for under-reporting by using under-reporting factors by age described under 3.1.1, assuming the same under-reporting per age group as observed in 2007-10.

All serogroup incidence was estimated on the same 2009-10 period, directly based on the number of new hospital admissions, by age (Table 18).

Table 18 – Age-specific incidence rates of serogroup B IMD for different scenarios (per 100 000 per year)

Cases/100 000	Base case 2009-10	High 1999-2001	Low modelled	All serogroups 2009-10
<1 year	21.8	47.4	15.3	24.1
1-4 years	7.9	20.3	5.6	8.5
5-9 years	2.8	7.9	1.9	3.0
10-19 years	2.6	6.3	1.8	2.9
20-64 years	0.3	0.8	0.3	0.5
65+ years	0.3	0.3	0.2	0.9
Total	1.3	3.1	0.9	1.7

6.2.2 4CMenB preventable disease

To estimate the proportion of Belgian strains preventable by the 4CMenB vaccine, we did not identify a given country with MATS information that had a distribution of invasive meningococcal strains that was comparable to the one found in Belgium, according to PorA and clonal complex distributions.[19] Due to the absence of Belgian data on MATS, the base case parameters for the proportion of vaccine preventable strains were thus derived from the average European proportions of the 2007-08 MATS study, which amounted to 78% (95%CI 63-90%) of serogroup B strains (822/1052 strains).[19] For the static model, we used age-specific MATS estimates (internal data Novartis).

We did not adjust the MATS estimates for the positive and negative predictive values (described under 4.1.4) to derive the model parameters for three reasons: first, we assumed that the number of false MATS positive would be approximately compensated by the number of false negative, as suggested by the Donnelly study on 57 strains from various geographic regions (5 MATS false positive and 3 MATS false negative according to killing in SBA, with predicted MATS coverage of 77%);[75] second, a more recent study on a sample of 40 English and Wales strains indicated a higher positive predictive value (96%) and a lower negative predictive value (33%), suggesting a high variation of these values according to region;[77] and third, the highest uncertainty resides in the prediction of future incidence of IMD and vaccine preventable strains, as illustrated in 3.1.3 by the temporal fluctuations of Por1.4 in Belgium, rather than in the accuracy of the testing instrument. These substantial PorA 1:4 variations over time and probable variations in the other three antigens were accounted for by scenario analyses: a high scenario for the proportion of vaccine preventable strains was based on 2007-08 MATS data from France (the most favourable in the EU panel), i.e. 85% overall. Likewise a low scenario was based on the assumption that the presence of at least two antigens is required in a meningococcal invasive strain to provide protection from the vaccine, i.e. 50% overall.[19]

Similar proportions of vaccine preventable strains have been assumed in the scenario involving all serogroups, when we hypothesize that 4CMenB would be effective against all serogroups.

6.2.3 Case fatality ratio

The 2004-10 average CFR for serogroup B, described under 3.1.6 and in Figure 6, is used for the base case. Periods with higher (2008-10) and lower (2001 and 2006) CFR were selected for high and low scenarios (Table 19), by age group. CFR for all serogroup IMD is based on the same 2004-10 period (Table 19).

Table 19 – Case fatality ratio of confirmed IMD cases (serogroup B and all serogroups), 2004-10

	Base 2004-10	High 2008-10	Low 2001 and 2006	All serogroups 2004-10
<1 year	5.6%	6.5%	4.3%	6.7%
1-4 years	4.7%	4.7%	2.6%	4.9%
5-9 years	1.2%	1.2%	0.0%	3.2%
10-19 years	4.1%	9.8%	0.0%	4.2%
20-64 years	8.8%	11.4%	0.0%	10.3%
65+	12.8%	22.2%	0.0%	16.3%
Total	5.4%	7.1%	1.5%	7.0%

6.2.4 Frequency of sequelae

Table 3 and Table 4 show that selected studies report different estimates of sequelae frequencies, likely due to different settings, sequelae definitions, case recruitment and strain virulence. We thus used weighted pooled estimates from these studies to derive parameters for serogroup B and all serogroups. Overall, 15.3% of all serogroup B case survivors presented at least one sequelae. This estimate is higher than the median estimate from a meta-analysis of 24 older European studies (9.4% for Europe),[33] used in a UK model published in 2013.[37g] Frequency is highest in children, with a pooled estimate at 16.9% among <20 years old.

Risk of sequelae per age group could not be directly derived as only few studies presented age-specific risk. The only study providing age-stratified analysis across all ages was conducted in tertiary reference hospitals in Canada (Bettinger *et al.*) and thus presents higher estimates.[31] We thus applied the age gradient from Bettinger *et al*. to the <20 years (for the <5 and 5-19 years) and to the all-age frequencies (for the ≥ 20 years) to derive age-specific parameters for the base case. Table 20 presents the overall proportions of IMD cases with ≥1 sequelae, per age group and for each scenario. The same method was used to derive the frequency of each specific sequelae. Frequencies of the nine most frequent sequelae that were costed are presented in Table 29 under cost estimates (see 6.5.3).

Table 20 – Estimated proportion of IMD cases with ≥1 sequelae, based on published studies

	Base case[a]	High[b]	Low	All serogroups
<5 years	21.5%	26.7%	10.2%	21.5%
5-19 years	8.6%	10.6%	6.6%	8.6%
≥20 years	11.6%	14.4%	8.9%	11.6%

a: estimates of base case are pooled frequencies of published studies on serogroup B using the age distribution of Bettinger et al.[3, 4, 31, 32] Other studies did not provide an overall frequency of all sequelae. b: high case is directly based on Bettinger frequencies.[31] c: low case is based on Healy in <5 years,[4] and base case estimate reduced by 30% for other age groups.

Estimates for a high scenario were based on the higher frequencies from Bettinger (Table 20).[31] The low scenario in children <5 years was based on the Healy study from Ireland;[4] for other age groups, the frequencies of the base case were reduced by 30% by lack of specific data on these ages. For all serogroup parameters, no reliable data were found on the overall frequency by age group (Table 5). Considering that these are relatively similar to those of serogroup B (see 3.1.7, Table 5, Table 3 and Table 4) and that a high proportion of all IMD cases are due to serogroup B, we used the same frequency as for serogroup B (Table 20).

g An update of this study was conducted in 2013-14 but was unpublished at the time of writing this report.

6.3 Vaccine-related parameters

6.3.1 Vaccine efficacy

To derive estimates of efficacy against MATS positive strains, we took into account the natural protection against meningococcal disease by accounting for the proportion of control subjects with protective hSBA titers, according to the formula developed by Andrews *et al*:[72]

$$VE = 1 - \frac{P(SBA_V < CO)}{P(SBA_U < CO)}$$

$P(SBA_V < CO)$ and $P(SBA_U < CO)$: probabilities that vaccinated (V) and unvaccinated (U) individuals have SBA titers less than the protective cutoff (CO).

The proportions of subjects with protective hSBA titer (Table 8) were adjusted for the protection in controls and pooled per antigen and schedule (primary, booster and adolescent), whenever relevant. As hSBA data are only provided by antigen, the proportion of vaccinees with protective SBA levels against circulating strains needs to account for the combination of antigens in circulating strains. This was estimated by a weighted pooling of each antigen data, and the weight given to each antigen data was the proportion that this antigen represent among MATS positive strains, based on the MATS 2007-08 EU study.[19] As these antigens are also found in combination, the "leading" antigen of each combination was determined, i.e. the antigen against which the vaccine has the highest efficacy, and only this antigen was considered in the estimates of proportion. This assumes that the presence of other antigens in a circulating strain does not translate into higher efficacy among vaccinees compared to the efficacy against the leading antigen alone.

Table 21 presents efficacy estimates per schedule, based on studies described in Table 8 and the adjustments above described. To simplify the model and take into account the uncertainty of protection against clinical disease, a value of 95% vaccine efficacy was selected as base case for the primary series (similar for 2 and 3 doses) and booster doses. The low case was estimated by reducing the efficacy values of the base case by 20%, to account for reduced efficacy under field conditions and the uncertainty of the relation between SBA and clinical efficacy. In adolescents, a RCT of OMV vaccines in Norway showed that 97% of subjects with SBA above threshold translated into an efficacy of 87% against the specific strain (Table 11),[66] and efficacy values were also adjusted for that factor (97/87). No high case is estimated as efficacy estimates in the base case are close to 100%. It should be noted that other modelling studies assumed similar values of efficacy against MATS positive strains in the base case (e.g. 92% and 98% for primary series and booster in France, 95% in England & Wales).[37, 99]

Similar vaccine efficacy has been assumed against all serogroups in the scenario assuming an efficacy of 4CMenB against all serogroups.

Table 21 – Estimated efficacy based on hSBA data above threshold, 1 month after last dose

Antigen	Infants 2 doses	Infants 3 doses	Booster at 12 months	Adolescents
fHbp	95%	99%	99%	100%
NadA	100%	100%	100%	99.7%
OMV	74%	83%	95%	99.8%
NHBA	NA	84%	98%	100%
Pooled (all antigens)	94%	96%	99%	100%
Base case	**95%**	**95%**	**95%**	**100%**
Low case	**77%**	**77%**	**79%**	**73%**

6.3.2 Vaccine waning rate

The average durations of vaccine protection were based on persistence data of hSBA responses among vaccinated subjects after the last dose of each schedule (see 4.1.2). We also corrected the proportion of subjects above threshold for the protective titres in controls (see formula above) but did not pool study results due to high heterogeneity in time points after vaccination and in duration results. We assumed an exponential decline of immunity after vaccination to model the proportion of hSBA above threshold over time, using the following formula:

$$VE_t = VE_0 \times e^{-\beta t}$$

VE_t: vaccine efficacy at time t; VE_0: vaccine efficacy at time 0 (i.e. 1 month after vaccination); β: waning rate (1/mean duration); t: time.

We thus fitted separate exponential models by schedule, antigen and study to estimate average durations of vaccine protection; an example showing observed and fitted data for waning after the primary schedule (2, 4 and 6 months) is presented in Figure 10, based on the two major studies, P12 (Novartis internal data and [57]) and P13.[56]

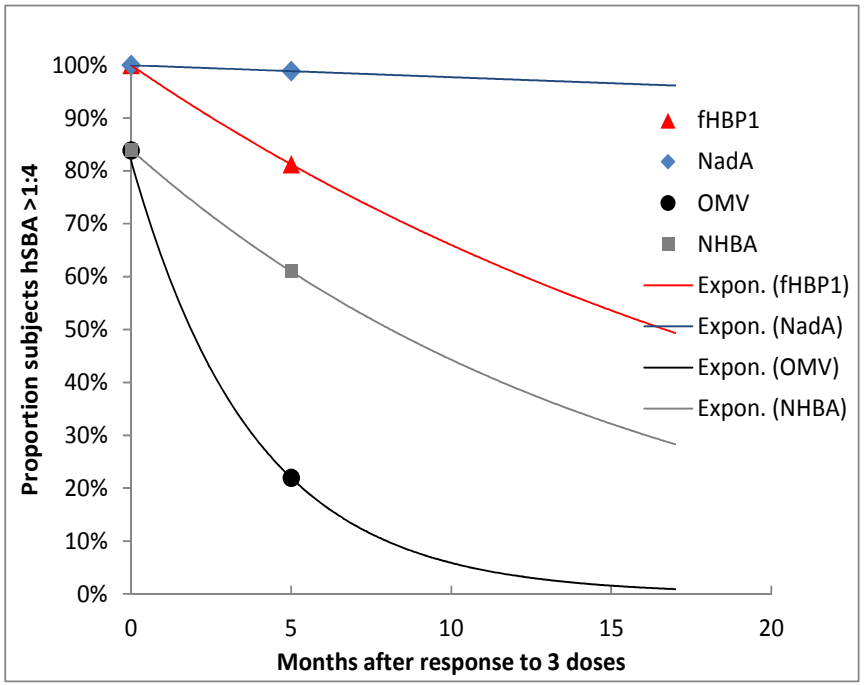
As data on hSBA persistence for NHBA was missing for some time points in several studies, we worked with a number of assumptions for NHBA waning. As for efficacy estimates, we estimated the overall duration of protection of each schedule, by pooling the durations of protection estimated for each antigen and taking into account the "weight" of each antigen in circulating strains (weighted pooling). The weight given to each antigen was the proportion that this antigen represent among MATS positive strain, based on the MATS 2007-08 EU study, as explained under 6.3.1 for vaccine efficacy.[19] To account for combinations of antigens, we determine a "leading" antigen in each combination on the basis of the longer duration of protection. This assumes that the presence of a second or third antigen in a strain does not translate into a longer protection among vaccinees compared to the duration against the leading antigen. The estimated duration of protection per antigen and overall is presented below, per schedule. As estimates after an infant schedule differed among the two studies, we took the average of the two study estimates for the base case, and estimates of each study for high and low case. Parameters used for vaccine waning rates are summarized in Table 22.

Table 22 – Estimated average duration (in months) of vaccine protection after the immune response to the last dose[a]

Study / antigen	fHbp	NadA	OMV	NHBA	Base case	High	Low
After infant 3 doses, study P13 E1 and E2[18, 56]	23	413	4	11	26		
After infant 3 doses, study P12 E1	16	204	4	NA	16[a]		
After infant 3 doses (average P12 and P13)	20	308	4	11	**22**	**26**	**16**
After booster (P13E1 and E2)	22	400	6	6	**27**	**36**	**17**
Adolescents, base (P10 E1)	67	318	57	NA	**73**	**105**	**69**

a: assuming that the (unknown) protection against NHBA antigen is similar to the one against OMV. Using other assumptions would minimally change the overall estimate, e.g. using NHBA duration of study P13, the overall estimate would be 18 months.

Figure 9 – Decline in antibodies against the 4CMenB antigens over time after three infant doses (at 2, 4 and 6 months) in study P13[h]



Note: month 0 corresponds to the time at which the mounting of immune response is measured, i.e. around one month after the last dose.

6.3.3 *Efficacy against transmission*

Efficacy data on carriage were used to estimate the vaccine efficacy against transmission/infectiousness for the dynamic transmission model (scenario analysis). This parameter was based on unpublished data on the 4CMenB efficacy against new acquisition of serogroup B strains, see Table 14.[78]

Although not statistically significant in that study, we estimated vaccine efficacy against transmission at 30% in the scenario analysis assuming an effect on transmission (dynamic model).

6.3.4 *Vaccine side-effects*

As the risk of adverse event (AE) is substantially different when 4CMenB is given concomitantly to routine vaccines or alone, we used several methods to calculate the frequency of AE per dose administered:

- For the first dose of infant schedule (i.e. concomitant administration in our model), the risk of AE attributable to Bexsero was computed as a difference of the AE risk between 4CMenB vaccinees and those receiving routine vaccination only (controls). For all other doses (4CMenB administered alone), the risk of AE attributable to Bexsero was the risk difference between 4CMenB vaccinees and placebo - when data on placebo arms was available.
- The frequency of outpatient visits for AE per dose was based on the proportion of doses leading to “medically attended fever” attributable to 4CMenB, as defined in the trials, assuming that the same subjects would present other higher reactogenicity symptoms (medically attended AE were not available for other symptoms). When the proportion of medically attended fever per dose was not available from trials, we used the proportions of medical visits following vaccination-related AE for routine vaccines measured in two Belgian surveys and applied a ratio of the proportion of doses resulting in high fever (>39°C) in recipients of 4CMenB on the same proportion for routine vaccines (i.e. hexavalent and pneumococcal vaccines), from the same trials.

h Data on study P12 are not shown here, as they are unpublished, but were used for the determination of parameters (based on Novartis internal data).

- Frequencies of mild AE calculated on this basis did not show substantial differences between the primary schedule (0.84% doses for outpatient) and the booster dose (1.05% doses) and 95%CI (calculated) overlapped. Because the model was not structured to account separately for each dose and these frequencies in a Belgian setting are still uncertain, we selected an average 1% as frequency of mild AE per dose for both primary and booster doses. Similar averages were used for severe AE leading to hospitalisations. This limitation of the model structure is expected to have limited impact on results as the majority of children receiving the primary series are also expected to receive the booster dose.
- We only considered severe AE that were possibly, probably or definitely related to 4CMenB after assessment, or resulting from the difference in rates between 4CMenB and routine vaccination when relevant.
- As very few data were available on hospital admissions following AE of 4CMenB, we estimated the proportion of 4CMenB doses that would likely lead to a hospital admission in Belgium based on the type and frequency of severe AE (e.g. febrile seizures, hydrocephaly, apnea, etc.). We assumed that children who were "observed in the hospital" for fever according to Gossger *et al.* would be hospitalized (short term) in the Belgian setting.[57]
- Estimations of proportions of doses leading to an outpatient visit or to hospitalisation took into account the proportion of doses that would be concomitant to routine vaccines and those that would be administered alone, as defined in the vaccination scenarios.

Frequency of AE following vaccination is described in Table 15. Surveys in Belgium indicate that 1.2% of routine vaccine doses (range 0.7-2.6% according to the vaccine) will lead to an outpatient visit for AE after vaccination,[98] or 5% of vaccinated children for combination vaccines.[94, 96] These proportions are similar to those found in the 4CMenB trials for similar routine vaccines (e.g. hexavalent/PCV7, 0.7% measured in Belgium and 0.6% in the trial reporting it).[56, 98] High and low proportions were mostly based on upper and lower bounds of 95%CI of AE frequency, calculated on trial data.[56, 57, 59] In some instances, Belgian data were used, e.g. high and low estimates for infant doses are the frequencies of outpatient visits after MenC-RRO and hexavalent-PCV7 vaccines, respectively, measured in Wallonia and Brussels in 2006.[98] For hospitalisations in adolescents, no severe event was observed in the only trial and we used the rate of hospitalisation for serious AE (anaphylaxis) reported for another MenB vaccine in adolescents (bivalent vaccine, 1/1208) for the high scenario. [59 100]

Table 23 – Frequency of adverse events attributable to 4CMenB extrapolated from clinical trials and Belgian surveys

% of doses with AE	Outpatient visit (mild)			Hospitalisation (severe)		
	Base case	High	Low	Base case	High	Low
Infant 3 doses and booster	1.00%	2.6%	0.44%	0.35%	0.85%	0.16%
Adolescents	0.12%	0.27%	0.07%	0.00%	0.08%	0.00%

AE: adverse events.

6.4 Quality of life

Utility values used for quality-adjusted life-year (QALY) computations in the cost-effectiveness analysis were selected by applying the following criteria (conforming to the Belgian guidelines on economic evaluations[83]) to the 17 studies identified in the literature review (see section 3.2):

- Health states should be described with a generic descriptive instrument and, in order to increase the comparability across studies, it is strongly recommended to use the EQ-5D.
- The health state description should be made by patients. The use of proxies, such as medical professionals or family, should be avoided as much as possible but is acceptable only if the patient cannot contribute him/herself (e.g. small children).

In addition, because serogroup B disease differs from other serogroups in disease severity and age distribution, the following criteria was added:

- Utility values should be specific to meningococcal serogroup B diseases. Utility values associated with any bacterial meningitis (caused e.g. by *S. pneumoniae*) or *meningococci* of other serogroups (e.g. C) are thus not relevant.

Applying those criteria to the 17 quality of life (QoL) studies from the literature review allowed the identification of one suitable study (MOSAIC data[32] courtesy of Helen Johnson, LSHTM). The UK MOSAIC study valued the long-term QoL of 221 patients who survived meningococcal serogroup B disease in childhood with the EQ-5D questionnaire, which is a generic descriptive instruments. Parents were used as proxy to complete the EQ-5D questionnaire on behalf of their child. A utility decrement of 0.074 is reported and is used as base case for survivors of meningococcal serogroup B disease with any sequelae. This QoL loss was not significantly associated with age or gender. In a univariate scenario analysis, utility loss in survivors of meningococcal serogroup B disease with sequelae is assumed to be high and equals the loss for survivors of meningococcal serogroup C disease with sequelae, i.e. on average 0.30 as reported by DeWals (0.28[39]) and Erickson (0.31[2]) (see section 3.2).

None of the studies from the literature review valued the quality of life lost during the acute phase of the meningococcal (serogroup B) disease. Although the impact on QoL loss is likely to be considerable during the acute phase of the disease, because of its short duration compared to the time horizon of the model, its overall impact on the total QoL is likely to be small. QoL losses during the acute IMD phase were thus not accounted for in the base case.

Quality of life losses for vaccine-related adverse reactions were not included.

As per the Belgian guidelines on economic evaluations,[83] QoL losses for caregivers (e.g. the parents) of sick patients were not considered in the base case.

Quality of life utilities for susceptible individuals and survivors of meningococcal disease without sequelae for use in the cohort model were obtained from UK population norms obtained with EQ-5D.[101] This is in line with the recent Belgian guidelines that recommend that (1) in the absence of Belgian data, population norms from another country should be used and (2) when quality of life data from another country are used, baseline population norm data should also originate from that country.

6.5 Economic parameters

This section presents the cost input parameters used to populate the static and the dynamic models. Values used to describe the uncertainty around those parameters in a probabilistic analysis are presented in a separate section, see 6.7.

6.5.1 Acute care hospitalization costs

6.5.1.1 Data selection

The costs of a stay in hospital due to acute IMD were obtained by coupling the MZG-RHM/AZV-SHA data to the database of the National Reference Centre (NRC) at the Scientific Institute of Public Health (WIV-ISP) (see section 2). Data were collected for the period 2004-2010. Records were selected based on ICD-9-CM diagnostic code “036” as principal or any diagnosis, indicating IMD. Based on the NRC database, average acute hospitalization costs were computed separately for all IMD cases (i.e. any serogroup) and for serogroup B IMD cases only, the latter being used in the base case analysis.

Several rules and processes were applied on the matched MZG-RHM/AZV-SHA/NRC data in order to obtain the final database on which hospital cost analyses could be performed:

- Selection of the records effectively containing both clinical and cost information. A few stays recorded clinical information, but no cost data. Those stays were excluded.
- Aggregation of the hospital stays belonging to the same episode. Typically if an IMD patient is transferred from one hospital to another, this is recorded as 2 separate stays in the MZG-RHM/AZV-SHA database although both stays are clearly linked to the same IMD episode. Consecutive stays for the same patient were thus aggregated as one single IMD episode if the stays were apart for maximum 1 day.
- Clinical review of cases recording the ICD-9-CM code 036 as secondary diagnosis only and exclusion of the cases unrelated to IMD. Most hospital episodes identified through coupling of the MZG-RHM/AZV-SHA/NRC data recorded the ICD-9 code 036 as a principal diagnosis (see 3.1.1). The few episodes with 036 coded as secondary diagnosis only (mostly unspecified meningococcal infections) were reviewed by a

clinical expert in order to exclude episodes not directly related to IMD, e.g. patients whose main cause of hospitalisation would not be due to IMD according to the listed clinical symptoms.

- Exclusion of episodes containing long-term treatment costs of IMD sequelae. Hospital episodes presenting diagnostic (ICD-9) or procedure (nomenclature) codes for amputation were excluded (i.e. 7 episodes). Costs for treating this sequelae were computed separately (see below) and therefore were not included in the treatment costs of the acute phase of an IMD. However, amputations caused by IMD would mostly be performed during the index IMD hospitalisation in real practice, such that computing amputation costs separately may add an extra hospitalisation cost. However, the rationale for separating the costs of acute IMD from the costs of sequelae is to avoid an overestimation of the average costs of an acute IMD that are also applied to patients with no sequelae.

The coupling and processing of the MZG-RHM/AZV-SHA/NRC data resulted in 597 hospital stays due to serogroup B meningococci and 698 hospital stays due to meningococci of any serogroup available for the cost analysis.

6.5.1.2 Costs computations

Costs were adjusted to 2012 values using the health consumer price index.[84] Before aggregating the costs recorded in each IMD stays the following adjustments were performed.

Extrapolation to 100% per diem costs

Conforming to the KCE guidelines, for each IMD stay the total per diem costs (i.e. "hotel" costs) reported in the MZG-RHM/AZV-SHA database were removed and replaced by their 100% equivalent cost (per type of stay and per year) multiplied by the length of stay (KCE guidelines p. 28).[83] This is because hospital per diem costs in Belgium are financed by a dual system and the MZG-RHM/AZV-SHA database only records one system, which represents about 20% of the total per diem costs.

Extrapolating the lump-sums for laboratory testing, medical imaging and drug

Laboratory testing (clinical biology) and medical imaging acts performed during a classical hospitalization in a general hospital are financed through a mixed system of fee-for-service (per act) and lump-sum (per inpatient day or per admission) payments. Both types of payments are recorded in the MZG-RHM/AZV-SHA. However, only the RIZIV-INAMI costs are recorded, not the patient out-of-pocket share. Although there is no link with actual consumption, as the lump-sums are paid to the hospital irrespective of the actual service delivered, all medical imaging and laboratory testing costs recorded in the database were aggregated and included as such in the cost analysis. This is in line with the procedure recommended by the KCE guidelines (for the IMA-AIM database).[83] As the patients' share is not recorded in the MZG-RHM/AZV-SHA database, these costs have further been added, i.e. the lump-sums of €7.44 and €6.20 per admission to cover any laboratory tests and medical imaging acts, respectively. Note that the patients' lump-sums are constant since 2004[i] and were thus not indexed.

Since July 2006, costs (RIZIV-INAMI perspective) of pharmaceutical products recorded in the MZG-RHM/AZV-SHA database include the lump-sum and the fee-for-service payments received for the "forfaitised" drugs, together with the fee-for-service reimbursements of the "non-forfaitised" drugs (drugs on the exclusion list). In order to account for real consumption, the prospective lump-sum payments received to cover the "forfaitised" drugs were identified and removed from the cost computation; and the recorded fee-for-service parts (i.e. 25% of the drugs reimbursement bases) were multiplied by the extrapolation factor[83] of the corresponding year to obtain the total real expenses of the "forfaitised" drugs. The recorded fee-for-service costs of the "non-forfaitised" drugs were kept as is (KCE guidelines, p.29).[83] From the patient side, the MZG-RHM/AZV-SHA database records the "theoretical" patient share for the drugs on the exclusion list (i.e. the non-forfaitised B, C, Cs, Cx, Fa, Fb drugs). However, the patient does not

[i] Historical costs (honorarium – history) to be found on the RIZIV-INAMI website with the nomenclature codes 591102 and 591603 for clinical biology, and 460703 and 460821 for medical imaging.

actually pay this cost as their contribution is limited to a lump-sum of €0.62 per hospital day, irrespective of their actual drug consumption. The theoretical costs were therefore discarded. The database further records the costs paid by the patients for the Class D drugs (0% reimbursement class). Those costs being real costs to the patient, they were kept. Finally, as the daily lump-sum paid by the patient is not recorded in the database, the cost of €0.62 multiplied by the length of stay was added. Pharmaceutical costs recorded in the MZG-RHM/AZV-SHA database previous to July 2006 were simply aggregated, as the system of lump-sum payments was not in force yet.

6.5.1.3 Results

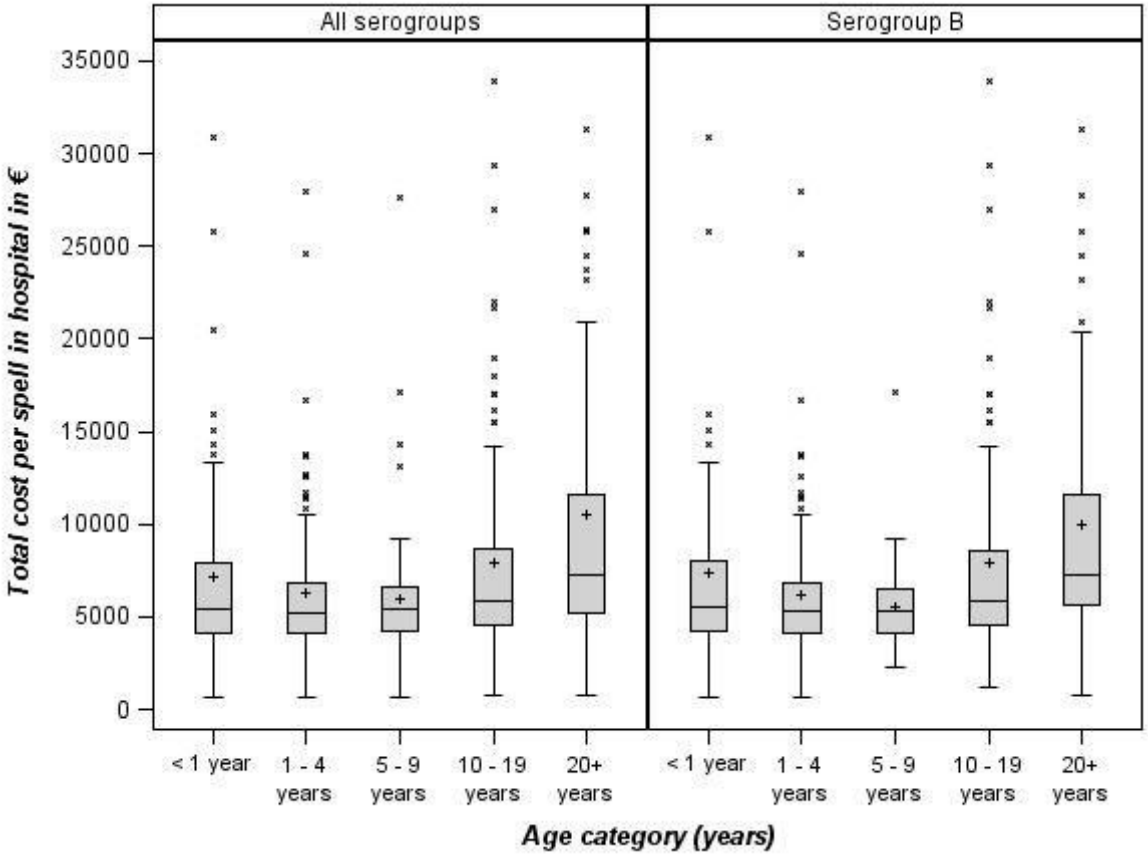
Mean age-specific health care payer costs of a stay in hospital for serogroup B meningococci (base case) and for any serogroup (scenario analysis) are presented in Table 24, together with some other descriptive statistics and the stratification of the total costs per type of payer (i.e. the patients and the health care budget from the federal government/the communities).

Figure 10 below illustrates the u-shape association between the total direct medical costs and the age of disease onset, with higher total average cost per hospital stay in the lower and higher age groups and lower hospitalization costs in intermediate age groups.

Table 24 – Age-specific hospitalisation costs for an acute IMD, per serogroup (Health care payer costs, €2012 values)

Age - years	Number of episodes	Mean total cost	Standard deviation	Min	1rst quartile	Median	3rd quartile	Max	Patient share	Health care budget
Serogroup B (base case)										
< 1	100	7320	8293	702	4254	5491	8067	77 095	199	7121
1-4	162	6228	4931	622	4163	5259	6814	51 274	165	6063
5-9	70	5511	2077	2229	4162	5280	6498	17 169	150	5361
10-19	153	7934	6858	1211	4562	5838	8608	42 595	179	7755
20+	112	9989	8033	741	5660	7246	11 642	42 258	220	9769
All	597	7470	6680	622	4375	5705	8085	77 095	183	7287
Any serogroup										
< 1	117	7195	7863	702	4068	5453	7873	77 095	195	7001
1-4	169	6243	4895	622	4146	5216	6814	51 274	166	6077
5-9	77	5960	3502	659	4230	5370	6613	27 679	163	5797
10-19	165	7918	6702	732	4568	5838	8623	42 595	179	7739
20+	170	10 516	11 099	741	5240	7246	11 615	89 024	230	10 286
All	698	7808	7789	622	4325	5740	8416	89 024	189	7619

Figure 10 – Age-specific total hospitalisation costs for an acute IMD, per serogroup (Health care payer costs, €2012 values)



The bottom and top of the boxes are the first and third quartiles. The band inside the box is the second quartile (the median). The crosses are the means. The ends are the lowest data still within 1.5 IQR of the lower quartile, and the highest data still within 1.5 IQR of the upper quartile. Y-axis truncated at €35 000. IQR: interquartile range.

6.5.2 Cost of follow-up care for those with no sequelae

Follow-up care costs occurring after hospital discharge were estimated from the Belgian reimbursement scheme (the so-called "nomenclature", which contains the unit costs of all health care services reimbursed by the Belgian health care insurance)[102, 103] and from an assumed frequency of consultation.

Following hospital discharge, survivors of meningococcal disease that do not develop sequelae are attributed the cost of 2 to 3 control visits with a specialist in internal medicine[j] (i.e. 2.5 * €38.85 = €97.14 in the base case). Accounting for the proportion of accredited versus non accredited specialists,[103] the cost of 1 consultation to a specialist in internal medicine is valued at €38.85, Table 25.[102]

Table 25 – Cost of a consultation to a specialist in internal medicine

Nomenclature code	Nomenclature label	Cost
102034	Consultation au cabinet par un médecin spécialiste en médecine interne, y compris un rapport écrit éventuel	€36.84
102550	Consultation au cabinet par un médecin spécialiste en médecine interne accrédité, y compris un rapport écrit éventuel	€40.05
Proportion of accredited specialists		62.75%
Average cost of a neurological consultation to a specialist in internal medicine		**€38.85**

6.5.3 Cost of follow-up care for those with sequelae

Table 26 – Cost per type of sequelae following IMD (Health care payer costs, €2012 values)

Sequelae following invasive meningococcal disease (IMD)	Age at IMD onset (years)	One-off acute cost (year 1)	Lifetime annual cost (year 1 on)
Severe hearing loss requiring hearing aid	0-17	€1059	€565
	18+	€529	€339
Neurological sequelae requiring institutional care	All ages	-	€41 640
Skin graft	All ages	€2262	-
Epilepsy with anti-convulsant at discharge	0-17	-	€243
	18+	-	€476
Renal failure with dysfunction at discharge	All ages	€5149	-
Renal failure requiring dialysis / renal transplantation	All ages	-	€56 637
Minor amputation (finger, toe)	0-13	€4094	€1361
	14-20	€4094	€680
	21+	€4094	€272
Major amputation (limb) - unilateral	0-17	€25 456	€3647
	18+	€25 456	€1042
Major amputation (limb) - bilateral	0-17	€25 456	€7294
	18+	€25 456	€2084
All other remaining sequelae	All ages	-	€78

[j] Note that the cost of a consultation to a specialist in internal medicine is roughly the same as that for a paediatrician (€35.17, Table 37) such that children may be assumed to be followed by any of both specialists without affecting the results of the current study. Assuming that a proportion of IMD survivors with no sequelae may consult a GP (€23.05 per consultation, Table 37) instead of a specialist would only have a limited impact on the study results as vaccination would avoid less expensive treatment costs.

The coupled MZG-RHM/AZV-SHA/NRC data allowed the identification of hospital stays treating acute IMD cases. Treatments of IMD sequelae/complications persisting after this acute stay (either ambulatory or during subsequent hospital stays) could not be retrieved from the same coupled database and were thus estimated from the Belgian literature,[103] former KCE reports,[104-107] the Belgian reimbursement scheme,[102] the database of drug prices in Belgium[15] and the publicly available data from the Belgian Technical Cell (TCT)[108] which hosts and analyses the coupled MZG-RHM/AZV-SHA database and publishes among others average total costs per hospital stay for 355 All Patient Refined-Diagnosis Related Groups (APR-DRG). The type and frequency of the resource consumed to treat each sequelae were reviewed by two independent medical experts.

The costs of treatment and support care for the most frequent sequelae of IMD survivors are presented in Table 26. Costs are split between one-off acute treatment costs, and long-term annual treatment costs incurred each year over the lifetime of the patient. All costs are valued for the year 2012 (using the health consumer price index[84] if needed). Sources and methods used to derive those costs are detailed below.

Severe hearing loss requiring hearing aid

The cost of providing a (non-implantable) hearing aid to a patient with severe hearing deficit post-IMD was taken from a former KCE report.[104] In this study, the average cost of a non-implantable hearing aid was valued at €1650 based on a survey from the main Belgian importers of hearing aid devices. The cost of 2 otorhinolaryngology (ORL) visits, one for prescribing an hearing test and one for discussing the results and obtaining the reimbursement of the device, is added (2 * €22.82 = €45.64). Taking into account the proportion of accredited versus non accredited professionals,[103] the costs of 1 ORL consultation is presented in Table 27.[102] The hearing aid is further assumed to be replaced every 3 years in children and every 5 years in adults, following the RIZIV-INAMI nomenclature that allows reimbursement at this replacement frequency. The average lifetime annual cost of a severe hearing loss requiring a hearing aid is thus:

- Children (0-17): (€1650 + €45.64) / 3 = €565
- Adults (18+): (€1650 + €45.64) / 5 = €339

Table 27 – Cost of a consultation to an otorhinolaryngologist

Nomenclature code	Nomenclature label	Cost
102012	Consultation au cabinet par un médecin spécialiste	€20.58
102535	Consultation au cabinet par un médecin spécialiste accrédité	€24.15
Proportion of accredited specialists		62.75%
Average cost of a consultation to an otorhinolaryngologist		**€22.82**

According to our experts, we further assumed that logopedic rehabilitation would be needed at a frequency of 2 consultations per week during 12 weeks for children and 6 weeks for adults.[109] The cost of a consultation (60 minutes) is valued at €44.11 (Nomenclature codes 712611, 712633, 712670, 712681).[102] The mean one-off cost of logopedic rehabilitation is thus:

- Children (0-17): 2 * 12 * €44.11 = €1059
- Adults (18+): 2 * 6 * €44.11 = €529

Severe neurological sequelae requiring institutional care

The cost of IMD patients who develop neurological sequelae severe enough to require lifelong institutional care was estimated from a previous KCE report.[107] This report calculated the annual health care payer cost (RIZIV-INAMI and patients shares) for adults (18-65 years) with acquired brain injury residing in Belgian nursing homes (RVT-MRS: rust en verzorgingstehuizen – maison de repos et de soin) (€30 174), in institutions for disabled persons (€67 000) and in psychiatric institutions (€34 614). For patients with "injuries following meningitis", it was estimated that 50% would stay in RVT-MRS, 29% in institution for disabled persons and 21% in paediatric institution. Based on those figures, the average lifetime annual cost for institutional care is estimated at €41 640. Due to lack of data this cost was also applied to patients <18 years.

Skin graft

Patients with IMD may develop skin scars or necroses that are severe enough to require a skin graft. The one-off cost of a hospital stay due to skin graft was attributed to those patients (€2262).

This cost is estimated from the data of the Belgian Technical Cell. In 2010, 2945 hospital stays with APR-DRG code 361 "Skin graft and wound debridement except for skin ulcer and cellulitis" were recorded, generating mean and median hospitalization costs of €4447 and €2262, respectively (costs in 2012 values). Due to the highly skewed nature of those data where the mean appears to be particularly influenced by a few high costs outliers, we used the median over the mean.

Epilepsy with a-convulsants at discharge

Based on experts' opinion, IMD patients with severe residual epilepsy requiring long-term treatment were assumed to consult a neurologist once every year, to undergo an electroencephalogram (EEG) every 2 year and to receive lifelong medication (i.e. 30 mg valproate per kg per day in children or 750 mg daily assuming an average child weights 25 kg; and 1200 mg carbamazépine or oxcarbazépine per day in adults).

The costs of 1 neurological consultation is calculated in Table 28.[102, 103] The cost of an EEG is valued at €69.55 (RIZIV-INAMI nomenclature code 477610-477621).[102] In children the cost of a daily dose of valproate (750 mg) is calculated as €0.43 per day or €156.60 per year. This is based on the generic cost of €8.58 for 100 tablets of valproate 150 mg (€8.58 / 100 * 5 = €0.43) reported by the Belgisch Centrum voor Farmacotherapeutische Informatie - Centre Belge d'Information Pharmacothérapeutique (BCFI-CBIP).[15] In adults the cost of a daily dose of carbamazépine/ oxcarbazépine (1200 mg) is calculated as €1.07 per day or €389.35 per year, based on the average of the generic costs reported for this drug by the BCFI-CBIP. The average lifetime annual cost for severe residual epilepsy is thus:

- Children (0-17): €51.75 + (€69.55 / 2) + €156.60 = €243
- Adults (18+): €51.75 + (€69.55 / 2) + €389.35 = €476

Table 28 – Cost of a neurological consultation

Nomenclature code	Nomenclature label	Cost
102174	Consultation au cabinet par un médecin spécialiste en neurologie ou un médecin spécialiste en pédiatrie, porteur du titre professionnel particulier en neurologie pédiatrique, y compris un rapport écrit éventuel	€49.60
102675	Consultation au cabinet par un médecin spécialiste en neurologie accrédité ou un médecin spécialiste en pédiatrie, porteur du titre professionnel particulier en neurologie pédiatrique et accrédité, y compris un rapport écrit éventuel	€53.03
Proportion of accredited specialists		62.75%
Average cost of a neurological consultation to a neurologist		**€51.75**

Renal failure with dysfunction at discharge

Patients with short-term renal dysfunction at IMD discharge were attributed the one-off cost of a hospital stay due to renal insufficiency (€5149) in the year following their acute IMD hospitalization.

In the 2010 TCT database, 4650 hospital stays with APR-DRG code 460 "Renal insufficiency" were recorded, generating mean and median hospitalization costs of €7634 and €5149, respectively (costs in 2012 values).[108] Due to the highly skewed nature of those data where the mean appears to be particularly influenced by a few high costs outliers, we used the median over the mean.

Renal failure requiring dialysis / renal transplantation

Patients with long-term chronic renal dysfunction at IMD discharge were assumed to require life-long dialysis and a kidney transplantation in some cases, according to a recent KCE report.[105]

In this study, the long-term annual health care payer (RIZIV-INAMI and patients' share) cost of adults (>18 years) with chronic renal disease requiring renal replacement therapy was estimated from an analysis of the Belgian administrative data (InterMutualistisch Agentschap - Agence InterMutualiste database, "IMA-AIM") for the period 2003-2006. This

database records inpatient and outpatient health care resource consumptions for the Belgian population. Based on reimbursement codes for chronic dialysis treatment, patients were selected and their costs collected if they had at least 7 consecutive weeks of chronic dialysis treatment. Kidney transplant was considered as indicating the end of dialysis treatment and was included in the cost analysis. It was estimated that each year, 4% of chronic dialysis patients would receive a renal transplantation.[105] The costs of different dialysis modalities are reported but given the typical young age of most IMD patients, we assumed that only peritoneal dialysis (thus no hospital dialysis) would be delivered. Based on this report, the lifetime annual cost of renal failure requiring dialysis / renal transplantation is estimated at €56 637 per patient (2012 values).

Minor amputation (finger, toe)

IMD patients with minor amputations were attributed the one-off cost of a hospital stay for the surgical procedure (€4094). In the 2010 TCT database, 405 hospital stays with APR-DRG code 178 "Upper limb and toe amputation for circulatory system disorders" were recorded, generating mean and median hospitalization costs of €7425 and €4094, respectively (costs in 2012 values).[108] Due to the highly skewed nature of those data where the mean appears to be influenced by a few high costs outliers, we used the median.

A finger/toe prosthesis is further assumed to be fitted and replaced every 1, 2 or 5 years in patients aged 0-13, 14-20 or over 20 years, respectively, following the RIZIV-INAMI nomenclature that allows reimbursement at this replacement frequency (Article 29 §4 of the RIZIV-INAMI nomenclature). The average cost of the finger/toe prostheses listed in Article 29 §1 E F of the RIZIV-INAMI nomenclature is €1361.[102] The average lifetime annual cost of minor amputations is thus:

- Patients aged 0-13 years: €1361
- Patients aged 14-20 years: €1361 / 2 = €680
- Patients aged 21+ years: €1361 / 5 = €272

Major amputation (limb) – unilateral

IMD patients with major amputations of one limb (e.g. a leg) were attributed the cost of one hospital stay for the surgical procedure (€19 458). In the most recent 2010 TCT database, 722 hospital stays with APR-DRG code 172 "Amputation for circulatory system disorders except upper limb and toe" were recorded, generating mean and median hospitalization costs of €25 196 and €19 458, respectively (costs in 2012 values).[108] Due to the highly skewed nature of those data where the mean appears to be influenced by a few high costs outliers, median values were used.

IMD patients with major unilateral amputation were further attributed the cost of prosthetic training. This cost was derived from a former KCE report[106] studying multidisciplinary rehabilitation for patients with lower extremity amputation (transtibial or transfemoral) and a prosthesis. Rehabilitation for lower extremity amputation is described to last 4 to 10 weeks. Using micro-costing techniques applied to a typical rehabilitation protocol for an average patient with lower extremity amputation, rehabilitation costs (including the RIZIV-INAMI and patients shares) were valued at €3190 following an amputation below the knee and €9580 above the knee. It is further documented that 56% of the amputations are transtibial and 44% transfemoral, resulting in an average cost of rehabilitation following limb amputation of €5998.

The total one-off costs for IMD patients with major unilateral amputation, covering the hospital stay and the prosthetic rehabilitation, are thus valued at €25 456 (€19 458 + €5998). This is in line with a former Belgian prospective observational study that recorded the health care required by 16 diabetic patients hospitalized for lower extremity amputation. Using micro costing, the total costs of amputation surgery, artificial limb and rehabilitation post-amputation ranged €19 700 to €44 700 (1993 dollars converted to 2012 euros).[110]

A limb prosthesis is further assumed to be fitted and replaced every year in patients aged 0-17 years and every 3 to 4 years in patients aged above 18 years, following the RIZIV-INAMI nomenclature that allows reimbursement at this replacement frequency (Article 29 §13 of the RIZIV-INAMI nomenclature). The average cost of the limb prostheses listed in Article 29 §1 E F of the RIZIV-INAMI nomenclature is €3647.[102] The average lifetime annual cost of major unilateral amputations is thus:

- Children (0-17): €3647
- Adults (18+): €3647 / 3.5 = €1042

Major amputation (limb) – bilateral

IMD patients with major bilateral amputation were attributed the same one-off acute costs as for patients with unilateral major amputation, i.e. €25 456 for surgery and rehabilitation. However, the lifetime annual costs of the artificial limb and its replacement were counted twice:

- Children (0-17): 2 * €3647 = €7294
- Adults (18+): 2 * €3647 / 3.5 = €2084

Other remaining sequelae

All remaining sequelae, other than those explicitly described and valued in the above sections, were attributed the lifetime annual cost of 2 consultations with a specialist in internal medicine (i.e. 2 * €38.85 = €77.70, Table 25).[102, 103]

Transformation of the costs per type of sequelae to fit the model structure

For each sequelae, the proportions of IMD survivors developing a particular sequelae/complication was divided by the overall proportion of IMD survivors with at least one sequelae/complication (see 6.2.4 above and Table 29), in order to obtain the proportions of each type of sequelae among IMD survivors with sequelae. Those frequencies were multiplied by the costs of each sequelae (Table 26) to compute average age-specific (one-off and lifelong annual) costs per patient with sequelae, with age expressed as age at disease onset (i.e. the age at which the patient developed IMD). The model being structured per age of the cohort (i.e. current age of the patient), the lifelong annual costs were further transformed accordingly.

Appendix 3 lists the average age-specific (by current age of the patient) cost of care per IMD patient with sequelae used in the base case (serogroup B) and in scenario analysis (all serogroups).

Table 29 – Proportions of IMD survivors developing sequelae (overall and per type of sequelae), per serogroup

	Serogroup B			All serogroups		
Age (years):	**<5**	**5-19**	**≥20**	**<5**	**5-19**	**≥20**
% IMD survivors with at least one sequelae	21.5	8.6	11.6	21.5	8.6	11.6
Average number of sequelae per case with sequelae	1.29	0.94	1.61	1.50	1.50	1.61
% IMD survivor developing a particular sequelae :						
- Significant hearing loss needing hearing aid	2.41	0.74	0.88	0.78	0.78	0.37
- Neurological sequelae requiring long-term care	1.16	1.06	0.52	1.13	1.13	0.52
- Scar/necrosis requiring skin grafts	0.00	0.00	0.00	1.61	1.61	3.65
- Epilepsy/seizures with a-convulsants at discharge	5.46	0.00	0.00	4.74	4.74	0.00
- Amputation toes, fingers	2.46	0.00	0.83	0.27	0.27	0.99
- Amputation limb, unilateral	0.31	0.00	0.42	0.00	0.00	0.00
- Amputation limb, bilateral	0.31	0.00	0.42	0.27	0.27	0.44
- Renal failure with renal dysfunction at discharge	0.51	0.00	2.91	0.40	0.40	3.74
- Renal chronic failure requiring dialysis	0.00	0.00	0.42	0.09	0.09	0.54
Sum % of individual sequelae (a)	12.62	1.80	6.39	9.29	9.29	10.24
Total % of sequelae expected (b)[§]	27.86	8.09	18.69	32.29	12.85	18.73
- All other remaining sequelae (b - a)	15.24	6.29	12.30	23.00	3.55	8.49

*§: total % of sequelae expected = % IMD survivors with at least one sequelae * average number of sequelae per case with sequelae. IMD: invasive meningococcal disease.*

6.5.4 *Cost of public health interventions targeting contacts of a case*

The cost of public health interventions targeting contacts of an IMD case varies across Belgian regions due to the use of different guidelines. The costs of managing contacts of a IMD case were thus estimated by region, based on available data, literature and information from regional public health officers, as well as the price of drugs in Belgium.[15] We did not compute specific costs for the management of IMD outbreaks as only small clusters were reported in the last 10 years and these did not involve specific costs besides the management of contacts.

For Flanders, the costs of chemoprophylaxis to IMD contacts was computed by assuming that 7.2 IMD contacts on average would be treated with azithromycin. The average number of treated contacts was taken from an English study, used as a proxy for the average number of treated contacts in Flanders as guidelines on which type of contact should receive prophylaxis are similar between these two regions; this number was also considered as acceptable by a responsible for disease control in Flanders (personal communication Geert Top). For Wallonia, the costs of chemoprophylaxis to IMD contacts was based on notification data describing the number of contacts having received chemoprophylaxis in the period January-September 2013, and was computed by assuming that 23 IMD contacts on average (Table 30 for age-specific numbers) would be treated with ciprofloxacin. Guidelines from Wallonia consider that all children in the same day-care and all kindergarten classmates of a IMD case are close contacts and should be treated, which results in a much higher average number of treated contacts than in Flanders. The age-specific costs of chemoprophylaxis in Flanders and Wallonia are presented in Table 30.

Average cost of chemoprophylaxis for Belgium was computed by weighting the respective costs of the Walloon and Flemish regions by their total population (Brussels population proportionally distributed across Wallonia and Flanders as no information on chemoprophylaxis is available).[111]

Two hours of public health professional time (1 hour for a nurse and 1 hour for a doctor) were further included per IMD case for managing the case, i.e. for contacts tracing and arranging prophylaxis, based on the annual salary grids published on the website of the federal personnel.[112]

The base case total public health management costs per IMD case, including prophylaxis and staff costs, are presented in Table 30. Details of the costs computations can be found in Appendix 6.

Table 30 – Cost of public health management of contacts of an IMD case

Age (years)	Average number of treated contact per case		Cost of drug (chemo-prophylaxis) per IMD case			Cost of personnel per IMD case		Total cost public health management per IMD case§
	Flanders	Wallonia	Flanders	Wallonia	Belgium	Doctor	Nurse	
<1	7.20	10.00	€29.95	€21.95	€27.09	€36.71	€20.46	€84.26
1-4	7.20	43.50	€29.95	€39.51	€33.38	€36.71	€20.46	€90.55
5-9	7.20	40.00	€29.95	€57.07	€39.67	€36.71	€20.46	€96.84
10-19	7.20	13.20	€29.95	€30.73	€30.23	€36.71	€20.46	€87.40
20-64	7.20	7.00	€29.95	€15.37	€24.73	€36.71	€20.46	€81.90
65+	7.20	7.00	€29.95	€15.37	€24.73	€36.71	€20.46	€81.90

*§: total cost public health management = cost of doctor + cost of nurse + cost of drug Belgium. Cost of drug Belgium = cost of drugs Flanders * % Flanders population in 2013 (64.17%) + costs of drugs Wallonia * % Wallonia population in 2013 (35.83%). IMD: invasive meningococcal disease. Mean costs for treating a contact were estimated at €4.16 for azithromycin and €2.19 for ciprofloxacin. Detail of computations to be found in Appendix 6.*

6.5.5 Vaccination programme costs

The cost of the vaccine, its administration, the cost of treating vaccine-related adverse events and the cost of post-vaccination surveillance were estimated from Belgian reports about the type of vaccinators,[93-96] caregivers (GP versus paediatrician),[113] and negotiated vaccine price reductions obtained in Belgium in the past.[114] Other sources are the Belgian literature, databases on the prices of drugs/vaccines[15] and on the costs of (partially) reimbursed procedures in Belgium,[102] and the database of the Technical Cell.[108]

6.5.5.1 Cost per vaccine dose

The pharmacy retail and the ex-factory prices for 1 dose of the 4CMenB vaccine are the prices set at the Federal Public Service Economy. These prices are not explicitly reported here as they are not yet public at the time of writing the report. The retail price is used in the base case for the "partially reimbursed" (i.e. the patients bears part of the cost of the vaccine) and the "private market" (i.e. the patient bears the total cost of the vaccine) vaccination policies. If the vaccine is included in the routine vaccination calendar free of charge to the patient (i.e. the "routine" vaccination policy), its price will be negotiated. The same negotiated reduction as the one obtained in the past by the French Community for Prevenar was applied to the ex-factory price of Bexsero (Prevenar: Ex-factory price €51.67, negotiated price €33.76, negotiated reduction 34.66%).[114]

In scenario analyses for the "routine" vaccination policy, the negotiated reduction obtained for the Meningococcal C vaccine (roughly 50% of the ex-factory price) was used for the low vaccination cost scenario.[114] For the high vaccination cost scenario, an assumption was made (+28% of the ex-factory price).

A low vaccination cost scenario was also explored for the "partially reimbursed" vaccination policy, where the reduction obtained over time (2008 to 2014) on the pharmacy retail price of the human papilloma virus vaccine Cervarix (50%) was applied to the public price of Bexsero.[15]

6.5.5.2 Vaccine administration costs

"Routine" and "partially reimbursed" vaccination policies

Vaccine administration costs used for the "routine" vaccination policy are listed in Table 31. The same costs were used for the administration of the vaccine under the "partially reimbursed" vaccination policy. Vaccine coverage surveys from the three communities report similar proportions of children vaccinated by the Belgian under-5 clinics (K&G-ONE: Kind en Gezin - Office de la Naissance et de l'Enfance) whether the vaccine administered was included in the routine vaccination calendar or was recommended but only partially reimbursed.[94-96]

The first dose of the vaccine at 3-month of age is assumed to be co-administered with the existing Hexavalent vaccine. Although in theory no additional financial payment would be required to include the new vaccine, an opportunity cost approach is adopted and a €5 administration cost per dose is used to value the extra time vaccinators will need to take to explain and make the injection.

For the second, the third and the booster doses of the vaccine, we calculated that 73% of the children would be vaccinated by K&G-ONE, 23% by a paediatrician and the remaining 4% by a GP. Those percentages were derived by weighting the reported vaccine administration rates per vaccinator type in the 3 communities (for all paediatric vaccines in the Flemish Community; for the measles-mumps-rubella (MMR) and the first dose of the Hexavalent vaccine in the French and Brussels Communities respectively)[94-96] by the paediatric 2008 population in each community, Table 32.[111] Additionally, for the second and third doses of the vaccine, administered at 5 and 6 months respectively, we assumed that 50% of doses would be administered during a new GP or paediatrician consultation while the other 50% would be administered within an already planned visit to the GP/paediatrician. This is in line with a report from the French Community documenting that a clinical visit is planned for infants aged 5 months.[93] Administration of Bexsero during an already planned visit is attributed an opportunity cost of €5 (i.e. similar to the cost of a vaccine co-administration). Administration cost by K&G-ONE was assumed to be €10 on average, whether the vaccine is administered within a new or an existing K&G-ONE consultation. The cost of 1 GP consultation is valued at €23.05 and the cost of a consultation to the paediatrician at €35.17 (Table 37).

Table 31 – Estimated vaccine administration costs per dose for the "routine" and "partially reimbursed" vaccination policies

Doses	Type of vaccine administration	%	Unit cost	Administration cost per dose
1st dose	Co-administration with Hexavalent vaccine	100%	€5.00	**€5.00**
2nd dose	Vaccination by K&G-ONE	73%	€10.00	**€12.45**
	Vaccination by a paediatrician	23%		
	New consultation (50%)		€35.17	
	Existing consultation (50%)		€5.00	
	Vaccination by a GP	4%		
	New consultation (50%)		€23.05	
	Existing consultation (50%)		€5.00	
3rd dose	Vaccination by K&G-ONE	73%	€10.00	**€12.45**
	Vaccination by a paediatrician	23%		
	New consultation (50%)		€35.17	
	Existing consultation (50%)		€5.00	
	Vaccination by a GP	4%		
	New consultation (50%)		€23.05	
	Existing consultation (50%)		€5.00	
Booster	Vaccination by K&G-ONE	73%	€10.00	**€16.26**
	Vaccination by a paediatrician	23%	€35.17	
	Vaccination by a GP	4%	€23.05	
Ado – dose 1	Co-administration with HPV vaccine (girls)	50%	€5.00	**€9.58**
	Vaccination within school (CLB-PMS)	34%	€10.00	
	Vaccination by a GP	16%	€23.05	
Ado – dose 2	Co-administration with HPV vaccine (girls)	50%	€5.00	**€9.58**
	Vaccination within school (CLB-PMS)	34%	€10.00	
	Vaccination by a GP	16%	€23.05	

K&G-ONE: Kind en Gezin - Office de la Naissance et de l'Enfance; GP: general practitioner; HPV: human papillomavirus; CLB-PMS: Centra voor LeerlingenBegeleiding - centre Psycho-Médico-Social.

Table 32 – Main vaccine administrators in infants, "routine" and "partially reimbursed" vaccination policies

	% vaccinators per community			Population of children aged 0-4 years in 2008	% population of children aged 0-4 years	% vaccinator weighted per community		
	Paedia-trician	GP	K&G-ONE			Paedia-trician	GP	K&G-ONE
Flanders	12%	4%	84%	325 972	54.26%	6.49%	2.31%	45.47%
Wallonia	39%	5%	56%	199 069	33.14%	13.06%	1.63%	18.45%
Brussels	24%	4%	72%	75 687	12.60%	3.02%	0.52%	9.06%
Total	-	-	-	600 728	100.00%	**22.56%**	**4.46%**	**72.98%**

GP: general practitioner; K&G-ONE: Kind en Gezin - Office National de l'Enfance. Main vaccinators reported for all pediatric vaccines in the Flemish Community;[96] vaccinators reported for the MMR and the first dose of the Hexavalent vaccine in the French[94] and Brussels[95] Communities, respectively.

Vaccination of adolescents is assumed to occur concomitantly to HPV vaccination for half of the adolescents receiving 4CMenB and is attributed the opportunity cost of €5 per dose administered. The remaining half of adolescents receiving 4CMenB would be vaccinated within their school (68%) – via the "centra voor leerlingenbegeleiding - centre psycho-médico-social" (CLB-PMS) – or by their GP (32%). Those percentages were calculated by weighting the reported adolescent vaccine administration rates per vaccinator type in the 3 communities (for the first dose of the HPV vaccine in the Flemish Community;[96] for the HPV and HBV vaccines in the French Community,[93] French Community values attributed to the Brussels Community as no information available for Brussels) by the adolescent 2008 population in each community, Table 33.[111] Vaccine administration within the school was assumed to cost €10.

Table 33 – Main vaccine administrators in adolescents, "routine" and "partially reimbursed" vaccination policies

	% vaccinator per community		Population of adolescents aged 10-14 years in 2008	% population of adolescents aged 10-14 years	% of vaccinator weighted per community	
	GP	School			GP	School
Flanders	13%	88%	345 065	56.60%	7.08%	49.53%
Wallonia	57%	43%	207 469	34.03%	19.40%	14.63%
Brussels	57%	43%	57 085	9.36%	5.34%	4.03%
Total	-	-	609 619	100.00%	**31.81%**	**68.19%**

GP: general practitioner. Vaccinators reported for the first dose of the HPV vaccine in the Flemish Community;[96] for the HPV and HBV vaccines in the French Community;[93] French Community values attributed to the Brussels Community as no information available for Brussels.

"Private market" vaccination policy

Vaccine administration costs used for the private market vaccination policy are listed in Table 34. The same methodology was adopted as for the "routine" and "partially reimbursed" vaccination policies but the distribution across the different types of vaccinators considerably changed, hence the different administration costs.

For the second, the third and the booster doses of the vaccine, we calculated that 41% of the children would be vaccinated by K&G-ONE, 48% by a paediatrician and the remaining 12% by a GP (Table 35). Rates per type of vaccinator for the PCV7 vaccine before its introduction into the routine calendar were found in a former report of the French Community.[93] Compared to routine vaccination, the proportion of children vaccinated by K&G-ONE with PCV7 in the private market decreased by 44% (i.e. a drop from 56% to 31% in the current study). In the absence of data for the private market vaccination for the two other communities, the K&G-ONE rates of routine vaccination for Flanders and Brussels were decreased proportionally to the rates reported for the French Community. Repartition of remaining patients between GP/paediatricians follows the routine vaccination paediatrician to GP vaccinator ratio for each region, i.e. 2.81 in Flanders (12%/4%) and 5.77 (24%/4%) in Brussels.

Table 34 – Estimated vaccine administration costs per dose for the "private market" vaccination policy

Doses	Type of vaccine administration	%	Unit cost	Administrat° cost per dose
1st dose	Co-administration with Hexavalent vaccine	100%	€5.00	**€5.00**
2nd dose	Vaccination by K&G-ONE	41%	€10.00	**€15.28**
	Vaccination by a paediatrician	48%		
	New consultation (50%)		€35.17	
	Existing consultation (50%)		€5.00	
	Vaccination by a GP	12%		
	New consultation (50%)		€23.05	
	Existing consultation (50%)		€5.00	
3rd dose	Vaccination by K&G-ONE	41%	€10.00	**€15.28**
	Vaccination by a paediatrician	48%		
	New consultation (50%)		€35.17	
	Existing consultation (50%)		€5.00	
	Vaccination by a GP	12%		
	New consultation (50%)		€23.05	
	Existing consultation (50%)		€5.00	
Booster	Vaccination by K&G-ONE	41%	€10.00	**€23.53**
	Vaccination by a paediatrician	48%	€35.17	
	Vaccination by a GP	12%	€23.05	
Ado – dose 1	Vaccination by a GP	100%	€23.05	**€23.05**
Ado – dose 2	Vaccination by a GP	100%	€23.05	**€23.05**

K&G-ONE: Kind en Gezin - Office de la Naissance et de l'Enfance; GP: general practitioner.

Vaccination of adolescents in the private market is attributed the cost of 1 GP consultation for its administration per dose.

Table 35 – Main vaccine administrators in infants, "private" vaccination policy

	% vaccinator per community			Population of children aged 0-4 years in 2008	% population of children aged 0-4 years	% vaccinator weighted per community		
	Paedia-trician	GP	K&G-ONE			Paedia-trician	GP	K&G-ONE
Flanders	39%	14%	47%	325 972	54%	21.35%	7.60%	25.32%
Wallonia	60%	9%	31%	199 069	33%	19.88%	2.98%	10.27%
Brussels	51%	9%	40%	75 687	13%	6.44%	1.12%	5.04%
Total				600 728	100%	**47.67%**	**11.69%**	**40.63%**

GP: general practitioner; K&G-ONE: Kind en Gezin - Office National de l'Enfance. Main vaccinators reported for the PCV7 vaccine before its inclusion in the routine calendar,[93] vaccinator rates for the Brussel and Flemish community derived indirectly from Table 32.

Accounting for different vaccine uptakes in the priming course

As stated under 6.1.2, vaccine uptake declines along the three first 4CMenB doses of the priming course. For the first (at 3 months), second (at 5 months) and third (at 6 months) doses of the vaccine, vaccine uptake was 90%, 60% and 55% for routine vaccination; 60%, 55%, 50% for the recommended but partially reimbursed vaccination; and 40%, 30% and 20% for the private market vaccination.

For simplicity within the model, the costs of vaccine administration were assumed to be equal for each priming dose and based on a third of the administration costs for the whole priming course. The administration costs for a priming course were derived by attributing the total administration costs of all doses administered (taking into account the uptake for each dose) to the population receiving the third dose. This different allocation does not change the results and was done to avoid delaying the project by having to recode the existing model. Vaccine administration costs are presented in Table 36 and are used in the base case.

Table 36 – Vaccine administration costs of the priming course per vaccination policy, base case

Doses	Vaccine uptake	Population vaccinated	Administration cost per dose	Total vaccine administration costs
"Routine" vaccination policy				
1st dose	90%	115 745	€5.00	€578 722
2nd dose	60%	77 163	€12.45	€961 054
3rd dose	55%	70 733	€12.45	€880 966
Total administration costs of all doses administered				€2 420 743
Administration costs of the priming course, three dose total (all costs imputed to the 3rd dose)				**€34.22**
"Partially reimbursed" vaccination policy				
1st dose	60%	77 163	€5.00	€385 815
2nd dose	55%	70 733	€12.45	€880 966
3rd dose	50%	64 303	€12.45	€800 878
Total administration costs of all doses administered				€2 067 659
Administration costs of the priming course, three dose total (all costs imputed to the 3rd dose)				**€32.16**
"Private" vaccination policy				
1st dose	40%	51 442	€5.00	€257 210
2nd dose	30%	38 582	€15.28	€589 464
3rd dose	20%	25 721	€15.28	€392 976
Total administration costs of all doses administered				€1 239 650
Administration costs of the priming course, three dose total (all costs imputed to the 3rd dose)				**€48.20**

First, second and third doses of the vaccine administered at 3, 5 and 6 months of age. Size of a birth cohort (2011): 128 605.[85] Administration costs of the priming dose = total administration costs / population receiving the third vaccine dose.

6.5.5.3 *Vaccine adverse event costs*

Mild vaccine adverse event

Patients with mild reactions attributable to the vaccine were attributed the cost of one consultation to the GP or to the paediatrician, depending on their age.

The 2008 Health Interview Survey reports that only 0.9% of adolescents aged 10-13 years consult a paediatrician in case of disease.[113] We thus assumed that 100% of adolescents would consult a GP in case of mild vaccine adverse reaction. In children aged <2 years in the Flemish Community, consultations in case of disease most often occur with the GP (55%) and only 45% to the paediatrician.[96] Consultation with the paediatrician is more frequent in the two other communities with rates increased by 41% (i.e. consultation rate paediatrician 64%) and 98% (consultation rate paediatrician 89%) in the French and Brussels Communities, respectively, compared to the rate in the Flemish Community.[113] Based on the consultation rates to the paediatrician in the three communities and on the distribution of the 2008 Belgian population across the three communities[111] (children aged 0-4 years: Flanders: 54%, Brussels: 13%, Wallonia: 33%), the percentage of children aged 0-2 years consulting a paediatrician in case of disease was estimated at 57%.

Table 37 – Cost of a consultation to a GP and to a paediatrician

Nomenclature code	Nomenclature label	Cost
General practitioner		
101032	Consultation au cabinet par un médecin généraliste	€20.63
101076	Consultation au cabinet par un médecin généraliste accrédité	€24.15
Proportion of accredited general practitioner		69%
Average cost of a GP consultation		**€23.05**
Paediatricians		
102071	Consultation au cabinet par un médecin spécialiste en pédiatrie	€33.34
102572	Consultation au cabinet par un médecin spécialiste en pédiatrie accrédité	€36.25
Proportion of accredited specialists		63%
Average cost of a paediatrician consultation		**€35.17**

Taking into account the proportion of accredited versus non accredited professionals,[103] the costs of 1 GP/paediatrician consultation are presented in Table 37.[102]

In the base case, the cost of 1 consultation for a vaccine related mild adverse reaction is thus valued at €29.96 (43% * €23.05 + 57% * €35.17) in a 0-2 year-old child and at €23.05 (100% * €23.05 + 0% * €35.17) in a 10-13 year-old adolescent.

Severe vaccine adverse event

Patients with severe reactions attributable to the vaccine were assumed to be hospitalized and were attributed the average cost of a stay due to febrile convulsions, i.e. base case cost of €2136.

Total costs of all stays with the following criteria were requested of the Belgian Technical Cell which hosts and analyses the coupled MZG-RHM/AZV-SHA database:

- ICD-9-CM code 78031 (Febrile convulsions (simple), unspecified) as principal diagnosis.
- Low degree of severity (≤ class 2 out of 4 classes of severity).
- Patients aged 0 to 18 years.
- Covered period: 2007-2010.

One thousand and two (1002) hospital stays fulfilled those criteria. Costs were inflated to 2012 values using the Belgian Health consumer price indices and the base case mean (€2136), the median (€1940) and the standard deviation (€1054) were calculated directly from the data.

6.5.5.4 *Cost of post-vaccination surveillance*

In the base case, a fixed cost of €25 000 per year was assumed for the additional activities required for post-vaccination laboratory surveillance. This could involve the introduction of a new testing technique, such as the MATS or other method to identify the presence and expression of meningococcal proteins targeted by the vaccine. This cost is based on an estimation by the WIV-ISP estimating a minimum budget for the financing of the Belgian reference laboratories, i.e. the cost of minimal activities for a rare pathogen. The lump-sum is assumed to cover the introduction of a new technique, materials and reagents, costs for accreditation and quality control

of the new technique, the presence of a minimum of staff (one person working quarter time), its continued education, depreciation of equipment, etc.

6.6 Parameters specific to the dynamic model

6.6.1 Meningococcal carriage

As the only Belgian study on carriage dates from 1975-76,[115] we used the age-specific carriage prevalence estimated by the meta-analysis of a systematic review including 82 studies (all countries model).[7] This meta-analysis showed that carriage by age was non-linear, increasing through childhood from 4.5% in infants to 7.7% in 10-year olds and peaking at 23.7% in 19-year olds before decreasing into older adulthood (13.1% in 30-year olds and 7.8% in 50-year olds).[7] Data from the Belgian carriage study were used to derive the proportion of serogroup B in carried strains (0.32), as this was measured in a period with similar incidence and proportion of serogroup B.[115] This study was however limited to small numbers of subjects (92 carriers), in a single year and among 3-14 year-old children. In an alternative scenario, higher serogroup B carriage prevalence (0.47 proportion applied) was assumed, based on a study in Germany.[116]

6.6.2 Mixing patterns

A simple assumption of random mixing is inappropriate for meningococcal disease because the force of infection is age-dependent.[117] Due to the uncertainty on the type of contact that leads to effective transmission of virulent meningococcal strains, we explored the effects of two preferential mixing structures:

1. In the base-case analysis, we opted for Belgian data collected by survey, and population mixing is based on self-reported leisure contacts in Belgium (POLYMOD).[118] Survey data on self-reported contacts can be used to generate transmission parameters under the social contact hypothesis, where the number of potentially infectious contacts is assumed to be proportional to the self-reported age-specific number of social contacts.[119] The method presented by Wallinga *et al*.[119] was used to derive the social contact matrix using unpublished smoothed POLYMOD data for Belgian respondents reporting leisure contacts.[119-121] We chose leisure contacts because these data provided the best fit to the carriage data of the contact types reported in POLYMOD, as assessed by visual inspection of Belgium Polymod data and carriage (data not shown). Social contacts that belong to leisure (attendance to youth clubs, pub, discotheque, party and sport activities) were also among important risk factors associated to meningococcal carriage in several European studies,[122-125] including carriage of epidemic strains during outbreaks.[123, 124] These risk behaviours are also frequently reported modes of transmission in outbreaks.[126-129]
2. We also explored an alternative scenario because contact surveys have their limitations, and assumed a simple and theoretical preferential mixing: individuals are assumed to be more likely to mix with individuals within one year of their own age, according to a mixing pattern based upon Trotter *et al*. (see formulas in Appendix 5.2).[117]

6.7 Uncertainty

Uncertainty around the input parameters was handled by making the static model (partially) probabilistic. Furthermore as probabilistic analyses were not always possible or appropriate, e.g. because of less informative data or because uncertainty was too large to inform a plausible probability distribution, the static model was run under a series of univariate and multivariate (including best and worst-case) scenarios. The most likely scenarios were determined based on expert opinion.

Uncertainty in the dynamic model was only handled by scenario analyses (univariate and multivariate, including best and worst case), but not probabilistically due to the complexity of the model.

6.7.1 Probabilistic sensitivity analysis in the static model

In the static model, probabilistic sensitivity analysis was used to characterise the uncertainty around the quality of life (QoL) loss and all the cost parameters, with the exception of the vaccine costs per dose that are varied in scenario analyses. Distributions were used to represent QoL and cost input parameters instead of point estimates; 1000 simple random samples of these distributions were then propagated through the model to provide a distribution in the output parameters. Results are presented on cost-effectiveness planes - illustrating the joint distribution of incremental costs and quality adjusted life years (QALY) gained from the 1000 probabilistic simulations - and using cost-effectiveness acceptability curves. An analysis

of covariance (ANCOVA) was performed to indicate the proportion of the variance in the output parameters (the incremental costs and the incremental QALY gained) 'explained' by variations in the stochastic input parameters, or in other words which input parameters are most important for explaining the uncertainty of the outcome.

6.7.1.1 Type of distribution

For the acute care hospitalization costs, age-specific distributions were fitted to the cost data (Table 24) by minimizing the absolute difference between fitted and observed costs.

Other cost inputs not generated by a database were modelled as gamma distributions. Gamma distributions are constrained on the interval 0 to positive infinity and are thus suitable to represent skewed data such as costs. The gamma distribution is parameterised as (α, β). Alpha and beta parameters for each gamma distribution were generated using the methods of moments approach setting the sample mean (μ) and variance (s^2) to the mean and variance of the gamma distribution and rearranging the expressions.

$$\mu = \alpha \beta$$
$$s^2 = \alpha \beta^2$$

Quality of life loss for IMD survivors with any sequelae was also modelled as a gamma distribution. A gamma distribution was chosen to constrain the utility loss to 0 at one end. The EQ-5D utility range being not constrained to 0-1, a gamma rather than a beta distribution was used.

6.7.1.2 Parameterisation of the distributions

Standard deviations[k] were calculated directly from the data for the severe vaccine adverse event costs (€1054, see 6.5.5.3).

For other cost parameters, details of the values used to parameterise the distributions are provided below. Uncertainty in those cost parameters was handled by setting a distribution around the total cost of each parameter (e.g. the total cost of treating mild adverse events), instead of around each component (e.g. a frequency and a unit cost) of the total cost. This was done due to the complexity in the computation of some cost parameters (e.g. vaccine administration costs and costs of sequelae) and because the variability around the estimated components of the costs parameters could not be described properly.

For the cost of follow-up care for survivors of IMD without sequelae, standard deviation was chosen such that the 95% confidence interval is approximately €78-117, which represents the cost of 2 (lower limit = 2 * €38.85) to 3 (upper limit = 3 * €38.85) control visits with a specialist in internal medicine.

The standard deviations for the age-specific costs of IMD patients with sequelae (both one-off acute and lifelong annual costs) were chosen in order to produce +/- 30% variation around the means. These age-specific costs are presented in Appendix 3, together with the parameters of the gamma distributions and the 95% confidence intervals.

The standard deviations for the age-specific costs of public health management of contacts of a case were chosen in order to produce +/- 30% variation around the means.

For the administration costs of the priming course, the booster and the adolescent vaccines, standard deviations were chosen in order to produce variations of about +/- 30% around the means for the "routine" and "partially reimbursed" vaccination policies. For "private" vaccination, we assumed no uncertainty around the administration costs of adolescent vaccination (e.g. fixed GP consultation). Standard deviations for the priming course and booster "private" vaccination were chosen in order to produce variations of about +/- 20% around the means.

For the costs of consultations resulting from mild adverse reactions to the vaccine, standard deviations were chosen such that the upper 95% confidence intervals are approximately €60 (infants) or €46 (adolescents), which represents the cost of treating mild vaccine adverse reactions if 2 (instead of 1) consultations are required, i.e. 2 * €29.96 for infants and 2 * €23.05 for adolescents.

[k] Standard deviations, instead of standard error, have been used to calculate the uncertainty around those parameters as it was not possible to obtain estimates of the standard errors due to the nature of the data (e.g. data obtained from the literature or based on expert opinion).

The standard deviation around the mean cost of post-vaccine surveillance was chosen in order to produce a wide distribution because robust data are not available in the literature.

For the quality of life loss, the mean and 95%CI were taken from the MOSAIC study and alpha and beta values were generated by selecting the gamma distribution which minimized the sum of square difference between the mean and 95%CIs.

The mean values, 95%CI, distribution and alpha and beta parameters of the cost and quality of life inputs used to make the static model probabilistic can be found in the table below.

Table 38 – Distribution and parameters for the cost and QoL loss inputs used in the probabilistic static model (Costs in €2012 values, health care payer perspective)

Parameter	Base case	95% CI	Distribution
Acute care hospitalization costs – Serogroup B			
– **< 1 year**	7320	1059 – 19 504	Gamma (2.25, 3247.07)
– **1-4 years**	6228	1454 – 14 410	Gamma (3.38, 1842.24)
– **5-9 years**	5511	2570 – 9555	Gamma (9.39, 586.88)
– **10-19 years**	7934	1321 – 20 353	Gamma (2.50, 3169.29)
– **20+ years**	9989	1449 – 26 597	Gamma (2.26, 4422.53)
*Acute care hospitalization costs – All serogroups**			
– **< 1 year**	7195	1055 – 19 104	Gamma (2.28, 3161.41)
– **1-4 years**	6243	1449 – 14 470	Gamma (3.36, 1856.83)
– **5-9 years**	5960	1869 – 12 382	Gamma (4.77, 1250.40)
– **10-19 years**	7918	1318 – 20 312	Gamma (2.50, 3163.16)
– **20+ years**	10 516	1032 – 30 741	Gamma (1.76, 5962.90)
Cost of follow-up care in those without sequelae	97.14	79.03 – 117.08	Gamma (100, 0.97)
Sequelae treatment costs			
– **Cost of care for IMD sequelae, one-off, serogroup B**			Varies by age (Appendix 3)
– **Cost of care for IMD sequelae, annual, serogroup B**			Varies by age (Appendix 3)
– **Cost of care for IMD sequelae, one-off, all serogroups***			Varies by age (Appendix 3)
– **Cost of care for IMD sequelae, annual, all serogroups***			Varies by age (Appendix 3)
Cost of public health management of contacts of an IMD case			
– **<1 year**	84.26	61.33 – 110.77	Gamma (44.44, 1.90)
– **1-4 years**	90.55	65.91 – 119.04	Gamma (44.44, 2.04)
– **5-9 years**	96.84	70.49 – 127.31	Gamma (44.44, 2.18)
– **10-19 years**	87.40	63.62 – 114.91	Gamma (44.44, 1.97)
– **20-64 years**	81.90	59.61 – 107.67	Gamma (44.44, 1.84)
– **65+ years**	81.90	59.61 – 107.67	Gamma (44.44, 1.84)
Vaccination costs			
Administration costs - Routine			
– **Priming course**	34.22	24.91 – 44.99	Gamma (44.44, 0.77)
– **Booster**	16.26	11.84 – 21.38	Gamma (44.44, 0.37)
– **Adolescent**	9.58	6.97 – 12.59	Gamma (44.44, 0.22)
Administration costs - Partially reimbursed			
– **Priming course**	32.16	23.40 – 42.27	Gamma (44.44, 0.72)
– **Booster**	16.26	11.84 – 21.38	Gamma (44.44, 0.37)
– **Adolescent**	9.58	6.97 – 12.59	Gamma (44.44, 0.22)
Administration costs - Private market			
– **Priming course**	48.20	39.21 – 58.09	Gamma (100.00, 0.48)
– **Booster**	23.53	19.14 – 28.35	Gamma (100.00, 0.24)
– **Adolescent**	23.05	-	Assumed to be fixed
Mild VAE - Infants	29.96	10.30 – 59.92	Gamma (5.43, 5.52)
Mild VAE - Adolescents	23.05	7.93 – 46.10	Gamma (5.43, 4.24)
Severe vaccine adverse event	2136	595.14 – 4642	Gamma (4.11, 519.92)
Post-vaccination surveillance	25 000	18 196 – 32 867	Gamma (44.44, 562.50)

** Used in the "all serogroups" scenario analysis, see below. VAE: vaccine adverse event.*

6.7.2 Scenario analyses

6.7.2.1 Univariate scenario analyses

In addition to the probabilistic sensitivity analyses performed on all costs (except the vaccine cost per dose) and QoL parameters in the static model, the following parameters were varied in univariate scenario analyses: disease incidence, case fatality rate, vaccination uptake, vaccine strain coverage, duration of protection, proportions with sequelae, quality of life loss for survivors with sequelae, vaccine efficacy against disease, rate of adverse reactions, vaccine cost per dose, time horizon and discount rates.

In the dynamic model assuming a 30% vaccine efficacy against carriage acquisition (see 6.3.3), the same univariate scenario analyses as those described above for the static model were run. Moreover the following parameters were also varied in univariate scenario analyses: proportion of meningococci of serogroup B in carried strains, population mixing structure, vaccine efficacy against disease and cost of vaccine administration. The dynamic model being deterministic, low estimates for the costs of vaccine administration were set to the lower 95%CI of their probability distribution, as defined for the probabilistic static model (Table 38).

Low and high values of the parameters used in univariate scenario analyses are reported in Table 39, together with the section where the rationale for selecting the estimates is described.

Table 39 – Parameters varied in the univariate scenario analyses

Parameter	Base case	Low scenario	High scenario	Section
Disease incidence (per 100 000) - serogroup B				6.2.1
– **<1 year**	21.8	15.3	47.4	
– **1-4 years**	7.9	5.6	20.3	
– **5-9 years**	2.8	1.9	7.9	
– **10-19 years**	2.6	1.8	6.3	
– **20-64 years**	0.3	0.3	0.8	
– **65+ years**	0.3	0.2	0.3	
Case fatality rate (%) - serogroup B				6.2.3
– **<1 year**	5.6	4.3	6.5	
– **1-4 years**	4.7	2.6	4.7	
– **5-9 years**	1.2	0.0	1.2	
– **10-19 years**	4.1	0.0	9.8	
– **20-64 years**	8.8	0.0	11.4	
– **65+ years**	12.8	0.0	22.2	
Proportion of survivors with sequelae				6.2.4
– **≤4 years**	0.215	0.102	0.267	
– **5-19 years**	0.086	0.066	0.106	
– **20+ years**	0.116	0.089	0.144	
QALY utilities				6.4
– **QALY loss for survivors with sequelae**	0.074	-	0.30	
Vaccination uptake (%)				6.1.2
– **Routine vaccination: infant priming course**	55	49	93	
– **Routine vaccination: infant booster**	50	43	91	
– **Routine vaccination: adolescent**	60	42	82	
– **Partly reimbursed: infant priming course**	50	34	65	
– **Partly reimbursed: infant booster**	40	25	52	
– **Partly reimbursed: adolescent**	30	21	39	
– **Private market: infant priming course**	20	10	30	
– **Private market: infant booster**	10	10	30	
– **Private market: adolescent**	10	10	30	
Vaccine strain coverage (%)				6.2.2
– **<1 year**	71	38	90	
– **1 year**	74	43	63	
– **2-5 years**	79	59	82	
– **>5 years**	82	54	86	
– **In the dynamic model, all ages**	78	50	85	
Vaccine efficacy against disease (%)				6.3.1
– **Infant**	95	77	-	
– **Adolescent**	100	73	-	
Average duration of vaccine protection (months)				6.3.2
– **Infant immunisation after primary doses**	22	16	26	

Parameter	Base case	Low scenario	High scenario	Section
– **Infant immunisation after booster**	27	17	36	
– **Adolescent immunisation**	73	69	105	
Frequency of adverse events (# of vaccine doses resulting in 1 reaction)				6.3.4
– **Mild adverse reactions, infants**	100	225	38	
– **Mild adverse reactions, adolescents**	868	1429	370	
– **Serious adverse reactions, infants**	282	643	118	
– **Serious adverse reactions, adolescents**	719 790	0	1208	
Cost per vaccine dose (€)				6.5.5.1
– **Routine vaccination**	†	†	†	
– **Partly reimbursed**	†	†	-	
– **Private market**	†	-	-	
Discount rate (% for costs, % for outcomes)	3, 1.5	-	3, 3	5.5
Time horizon (years)	100	20	-	5.4
In the dynamic model only:				
– **Cost of vaccine administration**	Varies per dose	Low 95%CI	-	6.7.1.2
– **Proportion MenB in carried strain**	0.32	-	0.47	6.6.1
– **Vaccine efficacy against disease, infants**	95	-	77	6.3.1
– **Vaccine efficacy against disease, ados**	100	-	73	6.3.1
– **Mixing patterns**	Polymod	Preferential mixing		6.6.2

† Prices set at the Federal Public Service Economy, which are not published yet.

6.7.2.2 *"All serogroups" scenario analysis*

In the base case analyses of the static and the dynamic models, 4CMenB is assumed to be effective against serogroup B IMD only. An alternative scenario explores the possibility that the vaccine might also be effective against other serogroups of IMD. The values of the following parameters were simultaneously modified in the base static and in the dynamic models to run this "all serogroups" scenario: disease incidence, case fatality rate, acute care hospitalization costs and costs of follow-up care for those with sequelae Table 40. Other parameters remained unchanged.

Table 40 – Parameters varied in the "All serogroups" scenario analysis

Parameter	Serogroup B	All serogroups	Section
Disease incidence (per 100 000)			6.2.1
– **<1 year**	21.8	24.1	
– **1-4 years**	7.9	8.5	
– **5-9 years**	2.8	3.0	
– **10-19 years**	2.6	2.9	
– **20-64 years**	0.3	0.5	
– **65+ years**	0.3	0.9	
Case fatality rate (%)			6.2.3
– **<1 year**	5.6	6.7	
– **1-4 years**	4.7	4.9	
– **5-9 years**	1.2	3.2	
– **10-19 years**	4.1	4.2	
– **20-64 years**	8.8	10.3	
– **65+ years**	12.8	16.3	
Acute care hospitalization costs (€)			6.5.1.3
– **<1 year**	7320	7195	
– **1-4 years**	6228	6243	
– **5-9 years**	5511	5960	
– **10-19 years**	7934	7918	
– **20+ years**	9989	10 516	
Cost of care for IMD sequelae (€)			6.5.3 and Appendix 3
– **One-off**	Varies by age	Varies by age	
– **Annual**	Varies by age	Varies by age	

Values of all parameters modified simultaneously.

6.7.2.3 Best and worst case scenario analyses

Best and worst case scenarios were run on the base case analyses of the static model and on the dynamic model by combining the low and high univariate scenarios presented in section 6.7.2.1 and in Table 39 above. The combinations of parameters used for the best (favouring vaccination) and worst (against vaccination) cases are presented in Table 41.

In the dynamic model, which is deterministic, low and high estimates for the costs parameters (except for the vaccine costs per dose) were set to the lower and upper 95%CI from their probability distributions (or to their 25th and 75th percentiles), as defined for the probabilistic static model (Table 38).

Table 41 – Parameters combined for the best and worst case scenarios

Parameter	Static model		Dynamic model		Section in report
	Best case	Worst case	Best case	Worst case	
Disease incidence - serogroup B	High	Low	High	Low	6.2.1
Case fatality rate - serogroup B	High	Low	High	Low	6.2.3
Proportion of survivors with sequelae	High	Low	High	Low	6.2.4
Vaccination uptake	High	Low	High	Low	6.1.2
Vaccine strain coverage	High	Low	High	Low	6.2.2
Average duration of vaccine protection	High	Low	High	Low	6.3.2
Cost of follow-up care in those with no sequelae	Probabilistic		High 95%CI	Low 95%CI	6.7.1.2
Sequelae treatment costs – serogroup B	Probabilistic		High 95%CI	Low 95%CI	6.7.1.2[a]
Cost of public health management of contacts	Probabilistic		High 95%CI	Low 95%CI	6.7.1.2
Acute care hospitalization costs – serogroup B	Probabilistic		75th perc	25th perc	6.5.1.3
Frequency vaccine adverse event (mild and serious)	Low	High	Low	High	6.3.4
Cost per vaccine dose	Low	High	Low	High	6.5.5.1
Costs of vaccine administration	Probabilistic		Low 95%CI	High 95%CI	6.7.1.2
Costs vaccine adverse event (mild and serious)	Probabilistic		Low 95%CI	High 95%CI	6.7.1.2

Best case: favours vaccination; Worst case: against vaccination; Perc: percentile; CI: confidence interval. Values for low and high estimates to be found in Table 39. Values for low and high 95%CI to be found in Table 38. Values for 25th and 75th percentiles to be found in Table 24. a: see also Appendix 3.

6.8 Summary of input parameters values

The parameters used in the base case analysis and in scenarios analyses in the static and dynamic models are summarized in the table below.

Table 42 – Summary of input parameter values

Parameter	Base case	Uncertainty	Low scenario	High scenario	References, sources and notes
Epidemiological and demographical parameters					
Carriage prevalence	Variable by age	High scenario	-	Variable by age	Overall prevalence from systematic review (all countries model).[7] MenB proportion (0.32) from Belgian study.[115] Alternative serogroup B proportion (0.47) based on a German study.[116] See 6.6.1. Used in the dynamic model only.
Disease incidence (per 100 000) - all serogroups	1.7 (variable by age)	-	-	-	Hospital databases (MZG-RHM) ICD-9 036 (any diagnosis) See 3.1.1 and 6.2.1. Used in "all serogroups" scenario only.
Disease incidence (per 100 000) - serogroup B	1.3 (variable by age)	High and low scenarios	0.9 (Variable by age)	3.2 (Variable by age)	NRC % serogroup B applied to overall incidence. High: NRC 1999-2001 incidence corrected for under-reporting. Low: modeling current decrease in recent years (2003-2012). See 6.2.1.
Case fatality rate (%) - all serogroups	7.0 (Variable by age)	-	-	-	NRC data linked to MZG-RHM in 2004-10. See 6.2.3. Used in "all serogroups" scenario only.
Case fatality rate (%) - serogroup B	5.4 (Variable by age)	High and low scenarios	1.5 (Variable by age)	6.1 (Variable by age)	High: 2008-10 NRC data linked to MZG-RHM (base case CFR in 1-9 years). Low: 2001 and 2006. See 6.2.3.
Mixing patterns	Polymod	Alternative scenario	Preferential mixing		Population mixing based on Polymod self-reported leisure contacts in Belgium. Alternative scenario assuming preferential mixing. Used in dynamic model only. See 6.6.2.
Years of life lost	Variable by age	-	-	-	Statistics Belgium, natural deaths, 2011. See 5.6.
Natural mortality rates	Variable by age	-	-	-	Statistics Belgium, natural deaths, 2011. See 5.6.
Population birth cohort	128 605	-	-	-	Statistics Belgium, 2011. See 5.6.
Proportion of IMD survivors with sequelae (serogroup B and all serogroups)					Published studies, applying age distribution of Bettinger.[3, 4, 31, 32] Same frequency assumed for serogroup B and all serogroups. High: Bettinger estimates.[31] Low: Healy in <5 years and base case -30% for other ages. See 3.1.7 and 6.2.4.[4]
- **≤4 years**	0.215	High and low scenarios	0.102	0.267	
- **5-19 years**	0.086	High and low scenarios	0.066	0.106	
- **20+ years**	0.116	High and low scenarios	0.089	0.144	
QALY utilities					
QALY utility for susceptibles and survivors of IMD without sequelae	0.86 (Variable by age)	-	-	-	UK population norms from EQ-5D;[101] applied to the static model only.
QALY loss for survivors with sequelae	0.074	Gamma (5.94, 0.01) High scenario	-	0.30	Base case from MOSAIC MenB study (courtesy of Helen Johnson, LSHTM).[32] High: QoL loss in survivors of MenC.[39, 45] See 6.4.

Parameter	Base case	Uncertainty	Low scenario	High scenario	References, sources and notes
Vaccination parameters					
Vaccination uptake – Routine vaccination, free of charge (%)					Vaccine coverage surveys in the three Belgian entities in recent years (weighted pooled estimates) for vaccines with similar situation and expert opinion. When no information was available for the 3rd or booster dose, the drop-out rate observed with similar vaccines was applied to the previous dose uptake. See 6.1.2.
- **Infant immunisation priming course**	55	High and low scenarios	49	93	
- **Infant immunisation booster**	50	High and low scenarios	43	91	
- **Adolescent immunisation**	60	High and low scenarios	42	82	
Vaccination uptake – Partly reimbursed vaccination (%)					
- **Infant immunisation priming course**	50	High and low scenarios	34	65	
- **Infant immunisation booster**	40	High and low scenarios	25	52	
- **Adolescent immunisation**	30	High and low scenarios	21	39	
Vaccination uptake – Private market vaccination (%)					
- **Infant immunisation priming course**	20	High and low scenarios	10	30	
- **Infant immunisation booster**	10	High and low scenarios	10	30	
- **Adolescent immunisation**	10	High and low scenarios	10	30	
Vaccine strain coverage (%)	78[l]	High and low scenarios	50	85	Vogel et al. and internal Novartis data.[19] Base case: EU average. High: France data. Low: EU average proportion of strains covered by ≥2 antigens. See 6.2.2.
Vaccine efficacy against disease, infant schedule 3+1 doses (%)	95	Low scenario	77	-	% vaccinees above SBA threshold among infants,[56-58] and adolescent.[59] Additional data from Novartis.[130] Low scenario only applied to dynamic model, based on 20% reduction of base case. See 6.3.1.
Vaccine efficacy against disease, adolescent (%)	100	Low scenario	73	-	
Vaccine efficacy against carriage (%)	0	High scenario	-	30	No efficacy demonstrated (base case).[78] High scenario based on (non-significant) efficacy on acquisition of serogroup B, in the dynamic model only. See 6.3.3.
Average duration of vaccine protection (months)					Exponential modelling of % vaccinees above SBA threshold over time after vaccination, based on SBA data from literature and Novartis.[56, 59, 62, 130] See 4.1.2.
- **Infant immunisation primary doses**	22	High and low scenarios	16	26	
- **Infant immunisation booster**	27	High and low scenarios	17	36	
- **Adolescent immunisation**	73	High and low scenarios	69	105	
Rate of adverse reactions (number of vaccine doses resulting in 1 reaction)					
- **Mild reaction, infants**	100	High and low scenarios	225	38	Frequency of adverse events in trials and frequency of consultation for vaccine adverse event from Belgium.[56, 57, 59, 95, 96, 98] See 4.3 and 6.3.4.
- **Mild reaction, adolescents**	868	High and low scenarios	1429	370	
- **Serious reaction, infants**	282	High and low scenarios	643	118	
- **Serious reaction, adolescents**	719 790	High and low scenarios	0	1208	

[l] Age-specific proportions were used for the static model, but are not provided here (unpublished).

Parameter	Base case	Uncertainty	Low scenario	High scenario	References, sources and notes
Cost of treatment					
Acute care hospitalization costs (cost per stay in hospital, €) – Serogroup B					The national database from the Belgian Technical Cell (coupled "Hospital Clinical Records" and "Hospital Billing Data" – MZG-RHM/AZV-SHA) coupled to the NRC database (for confirmation of *Neisseria meningitidis* and serotyping). Data from the years 2004-2010. High and low scenarios are 25 and 75 percentiles and are applied in the deterministic dynamic model only. See 6.5.1 and 6.7.1.
- **<1 year**	7320.26	Gamma (2.25, 3247.07) High and low scenarios	4254.49	8066.55	
- **1-4 years**	6228.36	Gamma (3.38, 1842.24) High and low scenarios	4163.19	6814.24	
- **5-9 years**	5510.99	Gamma (9.39, 586.88) High and low scenarios	4162.36	6498.02	
- **10-19 years**	7934.41	Gamma (2.50, 3169.29) High and low scenarios	4562.10	8607.59	
- **20+ years**	9989.20	Gamma (2.26, 4422.53) High and low scenarios	5660.07	11 642.21	
Acute care hospitalization costs (cost per stay in hospital, €) – All serogroups					The national database from the Belgian Technical Cell (coupled "Hospital Clinical Records" and "Hospital Billing Data" – MZG-RHM/AZV-SHA) coupled to the NRC database (for confirmation of *Neisseria meningitidis* and serotyping). Data from the years 2004-2010. See 6.5.1 and 6.7.1. Used in "all serogroups" scenario only.
- **<1 year**	7195.07	Gamma(2.28, 3161.41)	-	-	
- **1-4 years**	6242.73	Gamma(3.36, 1856.83)	-	-	
- **5-9 years**	5959.91	Gamma(4.77, 1250.40)	-	-	
- **10-19 years**	7917.83	Gamma(2.50, 3163.16)	-	-	
- **20+ years**	10 516.10	Gamma(1.76, 5962.90)	-	-	
Cost of follow-up, all ages, for those without sequelae (€)	97.14	Gamma (100, 0.97) High and low scenarios	79.03	117.08	Belgian reimbursement scheme. High and low scenarios are 95%CI and are used in the dynamic model only. See 6.5.2.
Cost of support/care for those with sequelae (€)					Former reports from the Belgian Health Care Knowledge Centre, the Belgian reimbursement scheme (i.e. "nomenclature", which contains the unit costs of all health care services reimbursed in Belgium), the database from the Belgian Technical Cell (coupled "Hospital Clinical Records" and "Hospital Billing Data") for specific APR-DRG/ICD-9-CM codes, BCFI-CBIP drug prices. High and low scenarios are 95%CI and are only applied to the dynamic model. See 6.5.3.
- **One off, serogroup B**	Variable by age	Gamma (variable by age) High and low scenarios	Variable by age	Variable by age	
- **One off, all serogroups**	Variable by age	Gamma (variable by age) High and low scenarios	Variable by age	Variable by age	
- **Annual, serogroup B**	Variable by age	Gamma (variable by age) High and low scenarios	Variable by age	Variable by age	
- **Annual, all serogroups**	Variable by age	Gamma (variable by age) High and low scenarios	Variable by age	Variable by age	
Cost of public health response					
Cost of public health response to a case (€)	86.89 (Variable by age)	Gamma (variable by age) High and low scenarios	Variable by age	Variable by age	Data or expert opinion from regional public health officers, BCFI-CBIP drug prices and FedWeb. High and low scenarios are 95%CI and are only applied to the dynamic model. See 6.5.4.

Parameter	Base case	Uncertainty	Low scenario	High scenario	References, sources and notes
Cost of post vaccine surveillance (€)	25 000	Gamma (44.44, 562.50)	-	-	Report from the WIV-ISP on the financing the Belgian reference laboratories.[131] See 6.5.5.4.
Cost of vaccination					
Cost per vaccine dose (€)					Prices set at the Federal Public Service Economy, which are not published yet, and a report on the negotiated price reductions obtained in Belgium for other vaccines.[114] See 6.5.5.1.
- **Routine vaccination, free of charge**	Not public	High and low scenarios	Not public	Not public	
- **Partly reimbursed vaccination**	Not public	Low scenario	Not public	-	
- **Private market vaccination**	Not public	-	-	-	
Vaccine administration costs – Routine vaccination free of charge (€)					Vaccine coverage surveys reporting about the type of vaccine administrator in the three Belgian entities (weighted pooled estimates) for vaccines with similar situation, Belgian reimbursement scheme (i.e. "nomenclature", which contains the unit costs of all health care services reimbursed in Belgium). High and low scenarios are 95%CI and are only applied to the deterministic dynamic model. Adolescent vaccination strategies simulated in the dynamic model only. Vaccine administration costs for adolescents in the private market assumed not to vary. See 6.5.5.2 and 6.7.1.
- **Infant priming course**	34.22	Gamma (44.44, 0.77) High and low scenarios	24.91	44.99	
- **Infant booster**	16.26	Gamma (44.44, 0.37) High and low scenarios	11.84	21.38	
- **Adolescent**	9.58	High and low scenarios	6.97	12.59	
Vaccine administration costs – Partly reimbursed vaccination (€)					
- **Infant priming course**	32.16	Gamma (44.44, 0.72) High and low scenarios	23.40	42.27	
- **Infant booster**	16.26	Gamma (44.44, 0.37) High and low scenarios	11.84	21.38	
- **Adolescent**	9.58	High and low scenarios	6.97	12.59	
Vaccine administration costs – Private market vaccination (€)					
- **Infant priming course**	48.20	Gamma (100.00, 0.48) High and low scenarios	39.21	58.09	
- **Infant booster**	23.53	Gamma (100.00, 0.24) High and low scenarios	19.14	28.35	
- **Adolescent**	23.05	-	-	-	
Cost of vaccine adverse event reaction (per event, €)					Mild: surveys about consultation rate to GP/paediatrician in the three communities, Belgian reimbursement scheme. Severe: data from the Belgian Technical Cell: coupled "Hospital Clinical Records" and "Hospital Billing Data" for hospital stays due to febrile convulsions post vaccination. High and low scenarios are 95%CI, only applied to the dynamic model. See 6.5.5.3 and 6.7.1.
- **Mild reaction, infants**	29.96	Gamma (5.43, 5.52) High and low scenarios	10.30	59.92	
- **Mild reaction, adolescents**	23.05	High and low scenarios	7.93	46.10	
- **Severe reaction, all**	2135.63	Gamma (4.11, 519.92) High and low scenarios	595.14	4642.23	

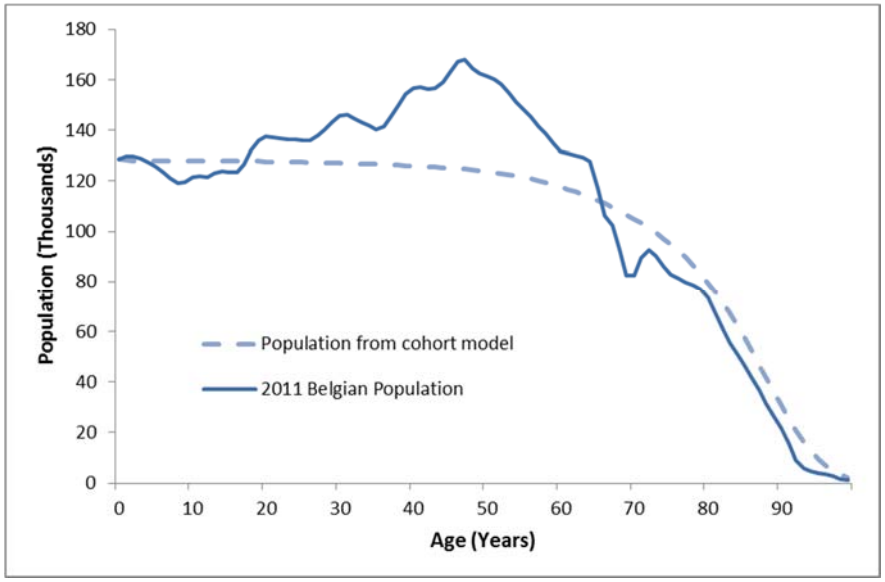
NRC: National Reference Center; MZG-RHM: Minimale Ziekenhuisgegevens – Résumé Hospitalier Minimum; AZV-SHA: Anoniem Ziekenhuis Verblijf – Séjour Hospitalier Anonyme; BCFI-CBIP: Belgisch Centrum voor Farmacotherapeutische Informatie – Centre Belge d'Information Pharmacothérapeutique; WIV-ISP: Wetenschappelijk Instituut Volksgezondheid – Institut Scientifique de Santé Publique.

7 MODEL VALIDATION

7.1 Population

Figure 11 compares the population, by age, of a single birth cohort followed over the time horizon of the model (100 years) to that of the real population for Belgium in 2011. The single birth cohort population declines smoothly over time according to age-specific natural mortality rates. The differences to the Belgian population are due to variations in births, deaths and migrations over time. In order to allow for improved comparisons between the static and the dynamic models, the dynamic population structure is assumed to be the same as the smooth curve seen in the static model from a single birth cohort. Thus while the static and the dynamic models can be used to simulate the number of predicted cases arising, the actual number of cases arising, or averted, may be higher or lower, depending on the changing population structures over time.

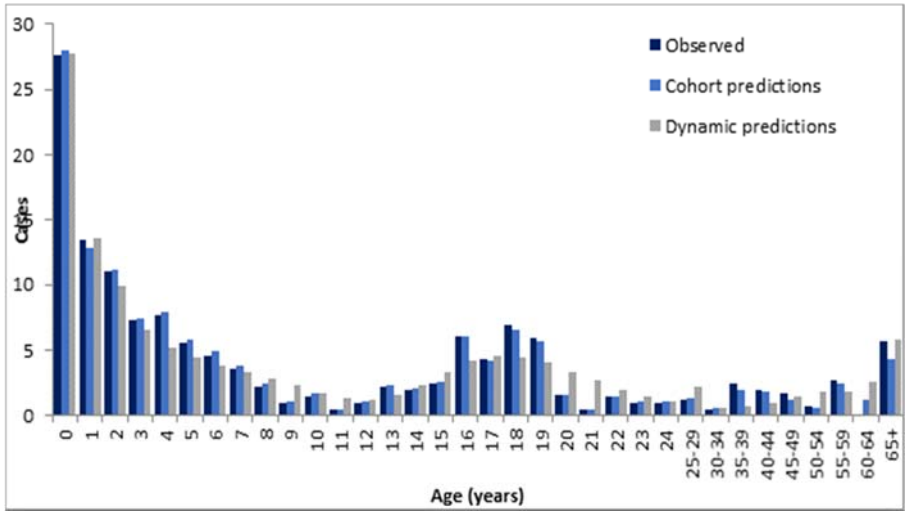
Figure 11 – Comparison of population figures from the baseline static model (single birth cohort) and the Belgian population in 2011



7.2 Cases predicted

Overall, both the static and dynamic models provide a good representation of the annual number of cases observed by age (Figure 12). The dynamic model predicts a lower number of cases in adolescents (aged 16-19 years) and a higher number of cases in young adults (aged 20-29 years). However, these differences involved very small number of cases and would have limited effect on the results of vaccination, due to waning after adolescent doses.

Figure 12 – Comparison of the average annual number of serogroup B meningococcal disease cases in Belgium without vaccination against MenB and those predicted in the base case static and dynamic models, by age group



8 RESULTS FROM THE STATIC MODEL

Epidemiological and cost-effectiveness results of the static model for the three base case infants vaccination policies (routine, partly reimbursed and private vaccination) are presented in sections 8.1 and 8.2. Scenario analyses (see 6.7.2) were undertaken for the routine and partly reimbursed vaccination policies, these results are presented in sections 8.3 and 8.5.

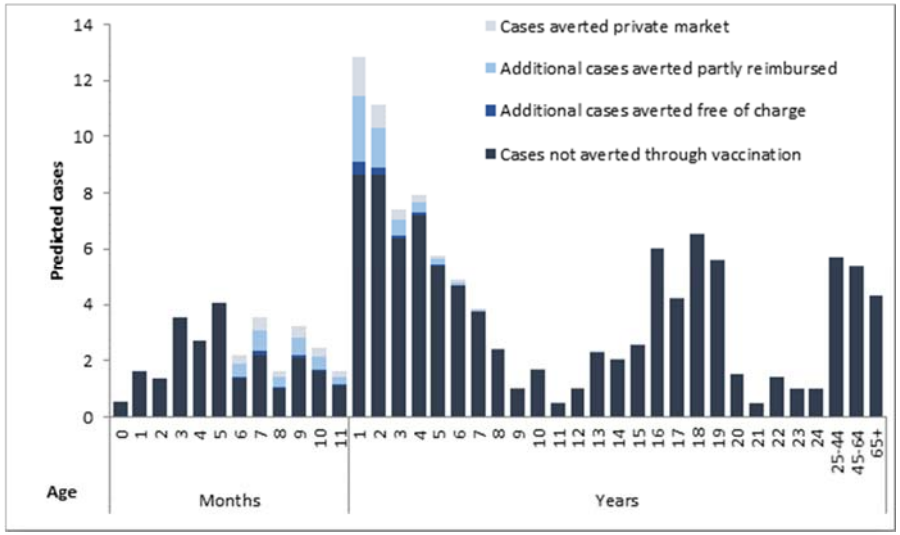
The results from the static model are the mean result from 1000 probabilistic runs of the model. Note that not all parameters are probabilistic (see Table 38 and Table 42).

8.1 Clinical impact of different vaccination policies

In the current situation, the model predicts that 139 cases of serogroup B meningococcal disease, resulting in 20 cases with sequelae and 7 deaths (490 quality adjusted life years lost), would occur over the lifetime of a single birth cohort (128 605 individuals) with the costs of treatment and long-term care totalling €5.8 million.

The base case model involves routine vaccination (i.e. free of charge) at 3, 5, 6 and 12 months with a 55% uptake for the third primary dose and 50% for the booster, assuming a 95% vaccine efficacy and 27 months protection after the booster. Under the base case, 14 of these cases (10.3%) and 1 death could be prevented through infant vaccination with 4CMenB (Table 43, Figure 13). Figure 13 shows the number of cases of meningococcal disease by age predicted by the model and the number of cases averted under the three infant immunisation policies. Protection from vaccination is assumed to occur one month following the second dose of vaccine, thus the first cases are averted in six month old infants. The booster dose at 12 months of age provides an average of 27 months protection, but due to waning protection from vaccination, the proportion of cases averted declines with increasing age. If the vaccine was offered on the private market only (i.e. fully charged) the model predicts that only 5 cases would be averted, due to the low assumed vaccine uptake under this policy, i.e. 20% and 10% uptake for primary doses and booster, respectively; an extra 8 cases are predicted to be averted if the vaccine was partly reimbursed (uptake 50% for primary doses and 40% for booster) and a further 1 case averted if the vaccine were to be offered free of charge (i.e. in the routine immunisation schedule).

Figure 13 – Serogroup B meningococcal cases averted by age with infant vaccination at 3, 5, 6 and 12 months for different immunisation policies, routine vaccine free of charge (base case), partly reimbursed or private market

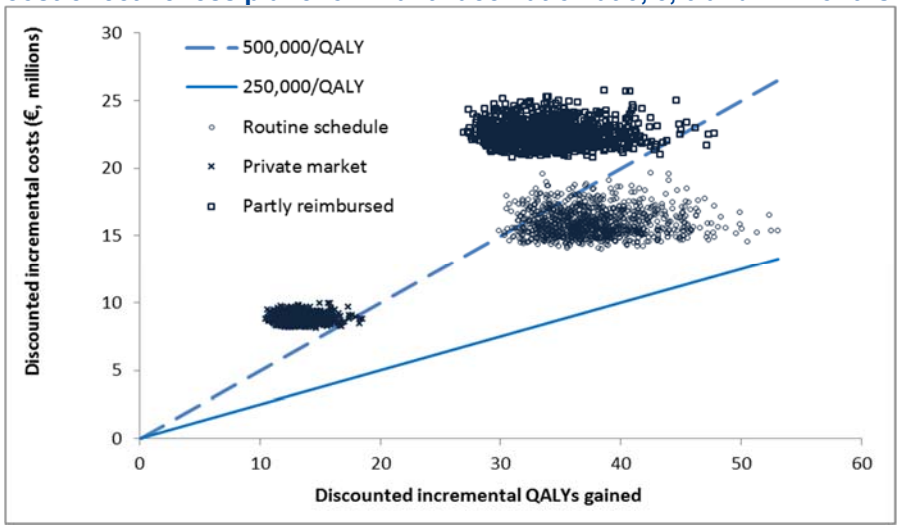


8.2 Cost-effectiveness of different vaccination policies

The cost-effectiveness of the three vaccination policies considered is presented in Table 43. All policies (free of charge, partly reimbursed, private market) resulted in very high cost per quality adjusted life year gained values over €400 000 under base case conditions. The policy with vaccine offered free of charge is the most economically favourable policy of the three considered, albeit with a high cost per quality adjusted life year gained; vaccine uptake is assumed to be higher in this policy, averting more cases of disease and the cost of the vaccine is assumed to be lower compared to the other policies. Reducing the cost per dose of the vaccine improves the cost-effectiveness of vaccination, however at a willingness to pay of €20 000, €30 000, or €40 000 per quality adjusted life year gained none of the three policies would be considered cost-effective at any vaccine price (i.e. strategies were not cost-effective even when the vaccine price was reduced to €0). Vaccine price is considered separately from other costs of

the vaccine programme, thus even with a vaccine price of €0 per dose there are considerable costs of vaccine administration and adverse vaccine reactions.

Figure 14 – Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for infant vaccination at 3, 5, 6 and 12 months



Lines indicate selected incremental cost-effectiveness ratios

The cost-effectiveness plane illustrating the joint distribution of incremental costs and quality adjusted life years gained from the 1000 probabilistic simulations of the baseline is shown in Figure 14; lines indicating selected incremental cost-effectiveness ratios are also presented. At a given willingness to pay, simulations falling below these lines would be deemed cost-effective, and those above, not cost-effective. These results for varying amounts of willingness to pay are most easily presented in a cost-effectiveness acceptability curve (CEAC, Figure 15). For the base case model with vaccination at 3, 5, 6 and 12 months of age, the CEAC cuts the vertical axis at 0 because none of the simulation results are cost saving. As the willingness to pay increases, a greater proportion of simulations are deemed cost-effective; at a willingness to pay of €500 000 per quality adjusted life year gained, 91.5% of the simulations for routine vaccination are classified as cost-effective.

Figure 15 – Cost-effectiveness acceptability curves for the base case static model (3, 5, 6 + 12 months vaccination) for the three vaccination policies

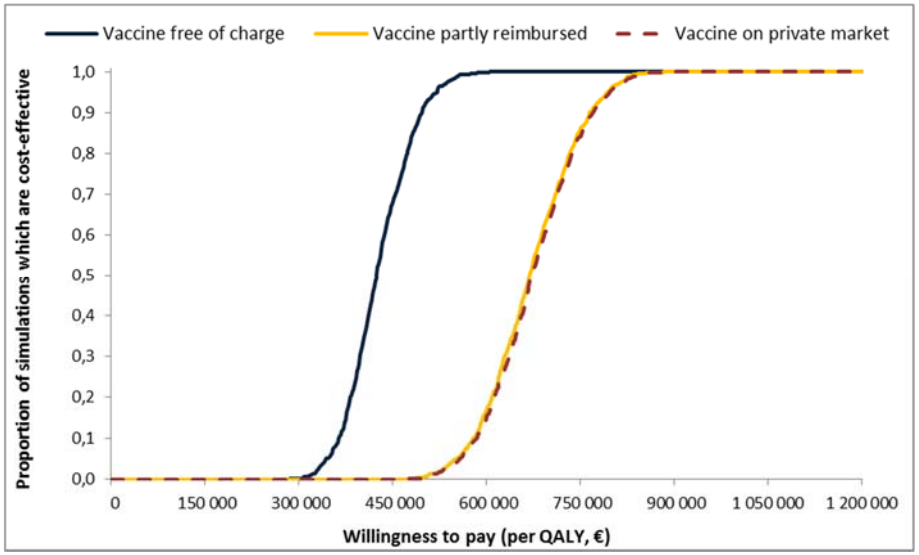


Table 43 – Results from the static model, comparison of vaccination strategies and scenarios (vaccination vs. no vaccination)

Scenario description	Undiscounted						Discounted[a]			
	Cases averted (%)	Cases with sequelae averted	Deaths averted	Life Years Saved	QALY gained	Net cost of vaccination (millions)[b]	Cost per case averted	Cost per death averted	Cost per Life Year Saved	Cost per QALY gained
Base-case analyses										
3, 5, 6 +12 months vaccine free of charge (C1)	14 (10)	3	1	56	65	€15.6M	€1 133 400	€23 134 800	€492 500	€422 700
3, 5, 6 +12 months vaccine partly reimbursed (C2)	13 (9)	3	1	50	58	€22.3M	€1 780 800	€36 315 900	€773 100	€663 600
3, 5, 6 +12 months vaccine private market (C3)	5 (4)	1	0	19	23	€8.7M	€1 796 000	€36 523 100	€777 400	€667 800
Scenario analyses with the 3, 5, 6 +12 months, vaccine free of charge strategy (C1)										
All serogroup	16 (9)	3	1	68	77	€15.5M	€1 038 400	€18 882 200	€401 900	€355 000
Increased incidence and case fatality rates	34 (10)	7	2	139	158	€14.5M	€464 700	€9 000 700	€191 700	€167 000
78% strain coverage in all ages	15 (11)	3	1	59	68	€15.6M	€1 081 000	€21 943 800	€467 000	€401 200
Lower vaccine strain coverage	9 (6)	2	0	34	39	€15.9M	€1 850 800	€38 279 200	€815 600	€698 300
Higher vaccine strain coverage	15 (11)	3	1	60	70	€15.5M	€1 058 800	€21 340 100	€454 100	€391 100
Lower rates of vaccine uptake	13 (9)	3	1	49	57	€13.8M	€1 127 200	€23 002 000	€489 700	€420 300
Higher rates of vaccine uptake	24 (18)	5	1	95	110	€26.9M	€1 145 300	€23 393 800	€498 000	€427 400
Shorter duration of vaccine protection	12 (8)	2	1	47	55	€15.7M	€1 381 000	€27 251 500	€579 200	€498 900
Longer duration of vaccine protection	16 (12)	3	1	61	71	€15.5M	€1 004 800	€21 057 900	€448 900	€384 500
Higher rates of vaccine adverse reactions	14 (10)	3	1	56	65	€18.6M	€1 347 100	€27 497 300	€585 400	€502 400
High proportion of people with sequelae	14 (10)	4	1	56	69	€15.4M	€1 128 600	€23 038 000	€490 400	€396 700
Alternative assumption for quality of life loss for survivors with sequelae (0.3 utility loss)	14 (10)	3	1	56	115	€15.6M	€1 133 400	€23 134 800	€492 500	€239 100
Lower vaccine cost	14 (10)	3	1	56	65	€13.1M	€954 400	€19 482 300	€414 700	€356 000
Higher vaccine cost	14 (10)	3	1	56	65	€18.6M	€1 343 400	€27 422 600	€583 800	€501 000
20 year time horizon	14 (12)	3	1	13	16	€16.2M	€1 143 500	€23 340 800	€1 401 400	€1 172 900
3% discounting for costs and benefits	14 (10)	3	1	56	65	€15.6M	€1 155 100	€23 500 900	€755 500	€643 800
Best case	71 (20)	17	4	284	343	€17.0M	€285 400	€5 576 100	€119 000	€98 300
Worst case	4 (4)	0	0	11	12	€19.7M	€4 435 700	€138 292 600	€2 939 500	€2 688 900

Scenario description	Undiscounted						Discounted[a]			
	Cases averted (%)	Cases with sequelae averted	Deaths averted	Life Years Saved	QALY gained	Net cost of vaccination (millions)[b]	Cost per case averted	Cost per death averted	Cost per Life Year Saved	Cost per QALY gained
Scenario analyses with the 3, 5, 6 +12 months, vaccine partly reimbursed (C2)										
All serogroup	14 (8)	3	1	61	69	€22.1M	€1 633 100	€29 651 500	€631 100	€557 700
Lower vaccine strain coverage	8 (6)	2	0	31	35	€22.5M	€2 901 400	€59 953 500	€1 277 400	€1 093 800
Higher vaccine strain coverage	14 (10)	3	1	54	63	€22.2M	€1 662 500	€33 473 100	€712 300	€613 500
Shorter duration of vaccine protection	11 (8)	2	1	43	49	€22.4M	€2 171 800	€42 806 800	€909 800	€783 900
Longer duration of vaccine protection	15 (10)	3	1	55	64	€22.2M	€1 578 400	€33 051 200	€704 500	€603 600
Alternative assumption for quality of life loss for survivors with sequelae (0.3 utility loss)	13 (9)	3	1	50	104	€22.3M	€1 780 800	€36 315 900	€773 100	€375 500
Best case	37 (11)	9	2	151	181	€10.3M	€321 100	€6 257 500	€133 500	€110 400
Worst case	3 (3)	0	0	8	8	€17.1M	€5 662 700	€175 855 600	€3 737 700	€3 421 900

a: figures rounded to nearest 100. b: additional cost of vaccination less costs averted through reduction in cases. M: million.

8.3 Financial impact of different vaccination policies

The total costs of treatment and/or vaccination for the three base case infant vaccination policies (routine, partly reimbursed and private market vaccination) are presented in Table 44.

Under the current situation of no vaccination, the total costs of treating serogroup B meningococcal cases occurring over the lifetime of a birth cohort amount €5.8 million. Of this cost, only €0.3 (private market vaccination) to €0.8 million (routine and partly reimbursed vaccination) would be averted through reductions in cases if 4CMenB vaccination is introduced and reaches the uptakes simulated in the base case, while the additional costs of vaccination would range from €9 (private market vaccination) to €23 million (partly reimbursed vaccination).

Introducing routine infant vaccination with 4CMenB is expected to cost €16.4 million annually (including the patient share) which would cover the costs of the vaccine itself (€10.8 millions), its administration and the treatment of the adverse vaccine reactions. With increased rates of vaccine uptake (93% for the priming course and 91% for the booster, instead of 55% and 50% in the base case), up to €1.4 million can be avoided in treatment costs but vaccination is expected to cost €28.3 million annually, with €18.7 million for the vaccine products.

Table 44 – Financial impact (undiscounted costs) of different vaccination strategies over the lifetime of a single birth cohort, health care payer costs including the patients share

Vaccination scenarios	NO VACCINATION - Treatment costs	VACCINATION - Treatment and vaccination costs	Incremental costs of vaccination versus no vaccination[a]	Details for VACCINATION		
				Vaccination costs[b]	Cost of vaccine doses	Treatment costs averted
3, 5, 6+12 months vaccination – Base case parameters						
Vaccine free of charge (C1)	€5.8M	€21.4M	€15.6M	€16.4M	€10.8M	€0.8M
Vaccine partly reimbursed (C2)	€5.8M	€28.1M	€22.3M	€23.0M	€18.2M	€0.8M
Vaccine private market (C3)	€5.8M	€14.5M	€8.7M	€9.0M	€6.7M	€0.3M
3, 5, 6+12 months vaccination – Higher rates of vaccine uptake						
Vaccine free of charge (C1)	€5.8M	€32.7M	€26.9M	€28.3M	€18.7M	€1 .4M

M: million. a: incremental cost of vaccination vs. no vaccination = vaccination costs minus treatment costs averted through reduction in cases, or "vaccination" total costs minus total costs under 'no vaccination' policy. b: costs as a result of vaccination including vaccine doses, administration and adverse reactions due to vaccination.

8.4 Scenario analysis

Univariate and multivariate (all serogroups and best and worst case) scenario analyses were undertaken for the routine and partly reimbursed infant vaccination policies, these results are presented in Table 43. A selection of the results shown on the cost-effectiveness plane are also presented in appendix.

Incidence and case fatality, serogroup B versus all serogroup

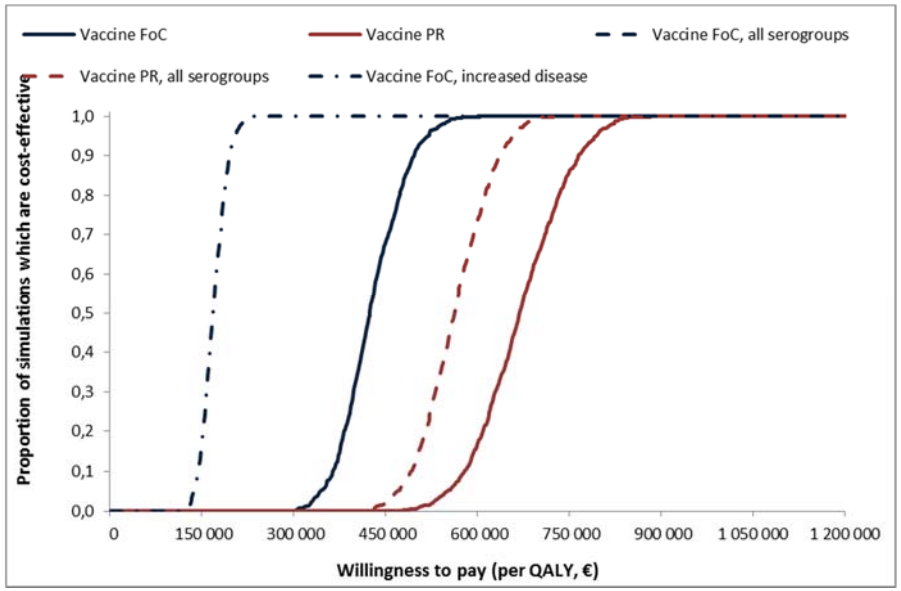
Increasing the incidence and case fatality from the base case (139 cases and 7 deaths annually) to the high incidence and case fatality scenario (351 cases and 25 deaths annually) results in a greater number of cases being averted through vaccination and a corresponding decrease in the cost per quality adjusted life year gained (from €422 700 to €167 000 per quality adjusted life year gained, Figure 16).[m]

Scenarios including all serogroups, rather than just serogroup B as in the base case are also more economically favourable, though the incremental cost-effectiveness ratios remain high (€355 000 for the vaccine free of charge policy, €557 700 for the partly reimbursed policy).

Duration of vaccine protection

Increasing the assumed duration of vaccine protection results in vaccination averting more cases of disease with a corresponding decrease in the cost per quality adjusted life year gained. The model predicts that for routine infant vaccination (3, 5, 6 + 12 months) increasing the assumed average protection from 22 months prior to boosting and 27 months thereafter, to 26 months prior to boosting and 36 months thereafter, would avert an additional 2 cases, reducing the cost per quality adjusted life year gained to €384 500 under the vaccine free of charge policy, and to €603 600 under the vaccine partly reimbursed policy.

Figure 16 – Cost-effectiveness acceptability curves for infant vaccination (3, 5, 6 + 12 months) with different assumptions about incidence and case fatality and comparing all serogroup to a serogroup B only model, vaccination free of charge (FoC) or partly reimbursed (PR)

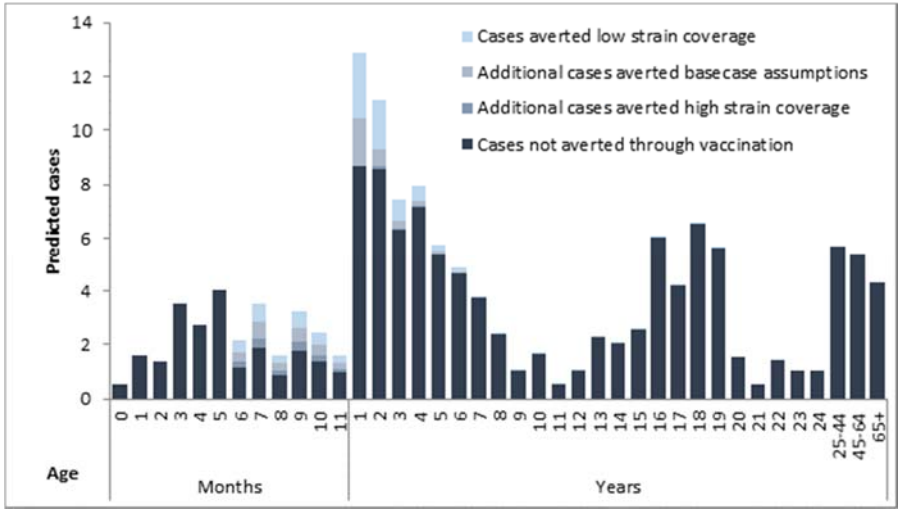


[m] Note that the proportion of cases averted through vaccination slightly decreases with increasing incidence (9.7% cases averted under high incidence compared to 10.3% in the base case) due to different age distribution of the high incidence scenario based on 1999-2001 real data (lower proportion of <1 year of age).

Vaccine strain coverage

Figure 17 shows the predicted number of cases under different assumptions of vaccine strain coverage. With low vaccine strain coverage (38% in <1 year olds, 43% in 1 year olds, 59% in 2-5 year olds and 54% >5 years) 9 cases of disease are predicted to be averted through routine infant immunisation implemented under a free of charge policy, with a resulting increase in the cost per QALY gained to €698 300, compared to the base case. An additional 6 cases would be averted over the lifetime of the cohort if the vaccine strain coverage was high (90% in <1 year olds, 63% in 1 year olds, 82% in 2-5 year olds and 86% >5 years), reducing the cost per QALY gained to €391 100.

Figure 17 – Serogroup B meningococcal cases averted by age, infant vaccination at 3, 5, 6 + 12 months for different assumptions of vaccine strain coverage, vaccine free of charge policy



Quality of life and rate of sequelae

Increasing the quality of life loss for survivors with sequelae from 0.074 to 0.30 or increasing the assumed proportion with sequelae increases the QALY gain resulting in vaccination appearing more economically favourable; however the cost per QALY gained remains over €230 000 (Figure 18).

Vaccine adverse reactions

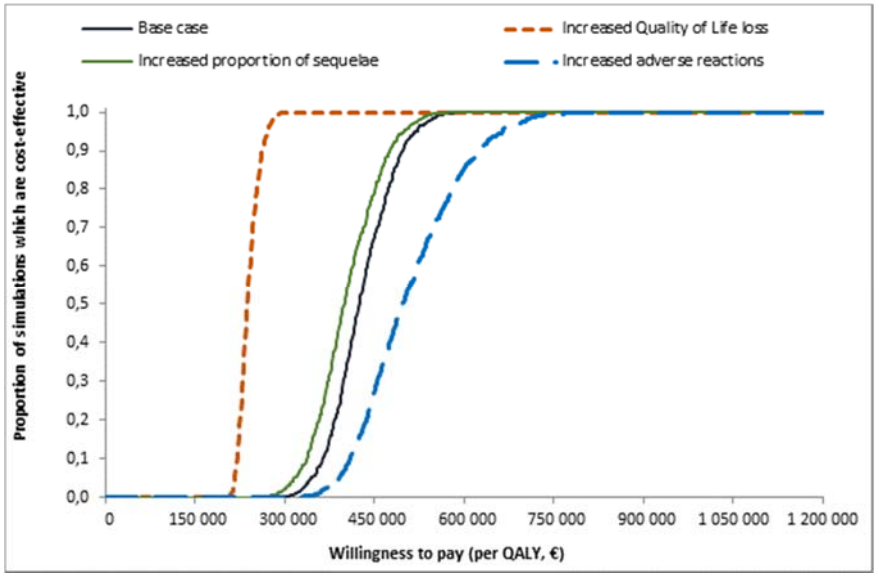
In the base case model with the vaccine provided free of charge an estimated 2757 mild reactions and 976 severe reactions are predicted with vaccination at 3, 5, 6 + 12 months. With higher rates of adverse reactions (1 in 38 doses resulting in a mild reaction, 1 in 118 doses resulting in a severe reaction), this is predicted to increase to 2336 severe reactions and 7255 mild reactions for a single birth cohort. This increase in adverse reactions leads to an increase in the cost of treating reactions and an increase in the cost per quality adjusted life year gained to €502 400 (Figure 18).

Vaccine uptake

With increased rates of vaccine uptake greater numbers of cases are averted (from 14 to 24 cases under the vaccine free of charge policy), but the vaccination programme is more costly (including more adverse events, i.e. from 2757 to 4744 vaccine reactions requiring outpatient visits and from 976 to 1680 vaccine reactions requiring hospitalisation). This results in a slightly increased cost per QALY gained (€422 700 to €427 400) for two reasons. First, the high uptake values do not result from a linear increase of the base case values: they are based on real-life data of similar situations and the high uptake of the booster dose (91% i.e. a 82% relative increase from the 50% of the base case) results in a higher relative increase compared to the high uptake of the 3rd primary dose (93% i.e. a 69% relative increase from the 55% of the base case). This translates into a higher cost per QALY because the booster dose is less efficient in the sense that it prevents less cases per dose due to a lower burden in the second year of life. If we set a linear increase for both uptakes in the high uptake scenario, the cost per QALY gained becomes lower than in the base case because the total fixed costs of post vaccination surveillance remain constant at €25 000 and are thus reduced when distributed per dose. Second, discounting is playing a role as this model simulates vaccination of a single

birth cohort. As vaccination occurs in the first year only, vaccination costs are not discounted while benefits are discounted over the person's lifetime.

Figure 18 – Cost-effectiveness acceptability curves for infant vaccination (3, 5, 6 + 12 months vaccination) with different assumptions about the proportion of people with sequelae, quality of life loss in those with sequelae and adverse reaction from vaccination, vaccination free of charge policy



Discount rate and time horizon

The choice of discount rate used has a large impact on the perceived cost-effectiveness of vaccination. Analyses were principally undertaken using 3.0% discounting for costs and 1.5% discounting for benefits, changing this to 3.0% for both costs and benefits increases the cost per quality adjusted life year gained from €422 700 to €643 800. Altering the time horizon of the model from 100 years to 20 years also has a large impact on the results.

The benefits from vaccination accrue over the lifetime of the person vaccinated, but only a fraction of this is captured in the 20 year time horizon scenario which leads to an increase in the cost-effectiveness ratio of vaccination from €422 700 to €1 172 900 under the vaccine free of charge scenario.

Best and worst case scenarios

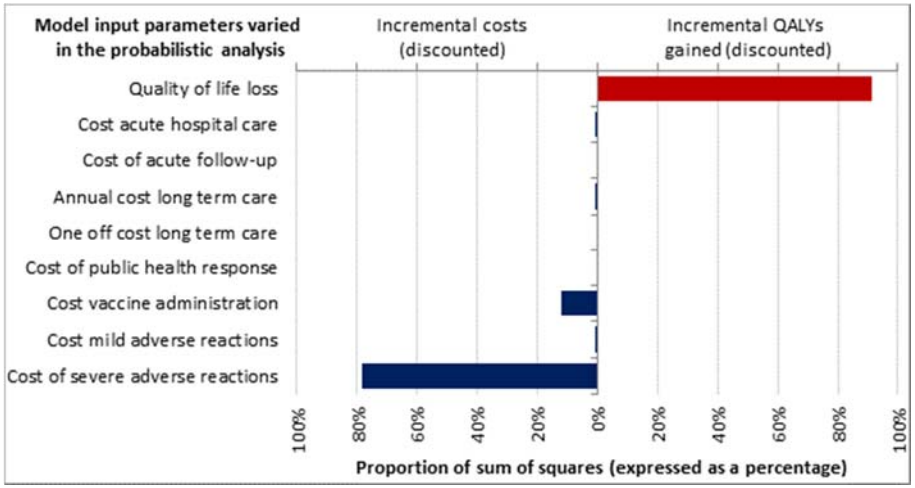
'Best case' and 'worst case' scenarios are extreme scenarios because all the vaccine favourable or unfavourable assumptions are unlikely to coincide, however the results help to frame the range of possible outcomes. Parameters altered to be particularly vaccine favourable or unfavourable included (Table 41): incidence and case fatality rates, vaccine strain coverage, vaccine uptake, duration of vaccine protection, the proportion of people with sequelae following disease, proportion of adverse reactions and vaccine cost per dose. Under the most favourable assumptions the cost per quality adjusted life year gained decreased from €422 700 to €98 300 under the routine free of charge vaccination policy. At a willingness to pay of €40 000 vaccination could be cost-effective with a vaccine price of €5 per dose or €1 per dose at a willingness to pay of €30 000; with a willingness to pay of €20 000 vaccination would not be cost-effective at any vaccine price.

8.5 Analysis of covariance

In order to assess the importance of individual stochastic parameters to the model, an ANCOVA (analysis of covariance) analysis was undertaken (Figure 19). Note that, in the current model, the ANCOVA analysis is limited by the fact that only some parameters were defined with probabilistic distributions (e.g. only the Qol and costs parameters, with the exception of the vaccine cost per dose), the remaining parameters being deterministic (see 6.7). Further, the ANCOVA analysis only provides an approximate result for the proportion of the variation of the incremental costs and QALYs gained explained by each stochastic input parameter, as ANCOVA assumes a linear relationship between the input and output parameters, which does not hold for the static model. It is still useful, however, in providing an understanding of the relative effect of the different parameters included in the probabilistic analysis.

As would be expected uncertainty around the quality of life loss experienced by those with sequelae drives the variation in the incremental quality adjusted life years gained in the model. For costs, strikingly the model is most sensitive to costs of severe adverse reactions. This result may be caused by the relatively wide distribution of the cost around this parameter (95%CI €595.14 to €4642.23 per event). Further, vaccination and thus adverse events are common in the model, but cases are not, so whilst the costs of acute treatment for disease are high with a wide distribution they are 'used' considerably less often in the model thus have less influence.

Figure 19 – ANCOVA analysis of proportion of sum of squares for discounted incremental costs (left) and discounted incremental benefits (right) explained by uncertainty in the stochastic parameters for the base case static model (3, 5, 6 + 12 months schedule)



Note: R^2 = 1.00 for incremental costs and 1.00 for incremental QALYs.

9 RESULTS FROM THE DYNAMIC MODEL

In the dynamic model, two hypotheses are simulated. The vaccine is first assumed to have no efficacy against carriage to provide the base case analyses for the adolescent strategies (infant strategies are also modelled here to be compared to the static model). In an alternative scenario, we assumed 30% vaccine efficacy against MenB carriage acquisition (see 6.3.3). Due to limited data on the vaccine efficacy against carriage and available data suggesting no statistically significant impact on MenB, results from this alternative scenario should be considered as a with caution.

A summary of the epidemiological and cost-effectiveness results for different vaccination policies (routine, partly reimbursed and private vaccination), target groups (infants, adolescents and infants combined to adolescents) and vaccine efficacies against transmission (0% and 30%) are presented in sections 9.1 and 9.2.

A number of scenario analyses (see 6.7.2) were undertaken for the combined infant and adolescent routine and partly reimbursed vaccination policies, assuming a 30% effect of the vaccine against carriage acquisition, the latter two strategies being the reference strategies of the dynamic model. The results of the scenario analyses are presented in section 9.3.

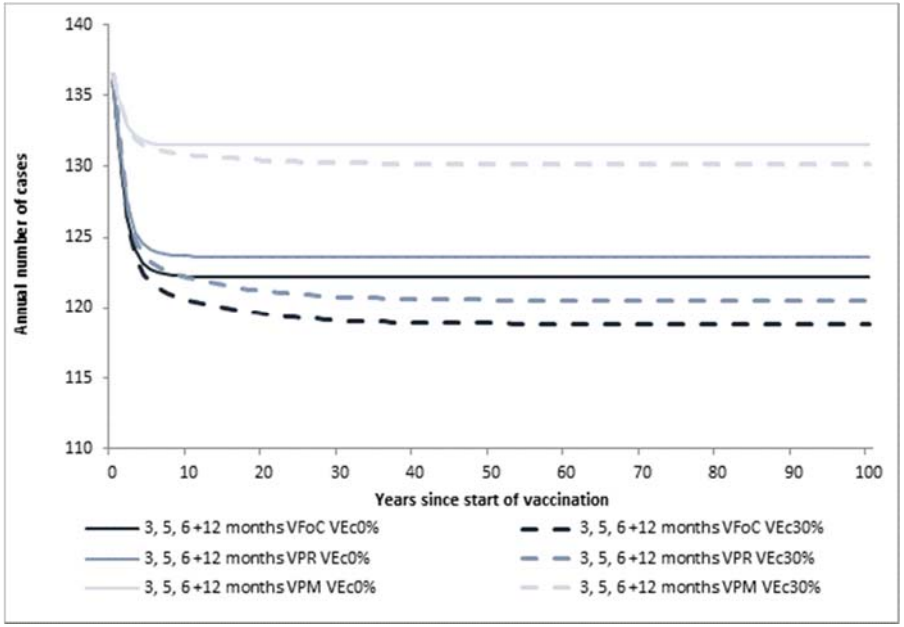
9.1 Clinical impact of different vaccination strategies

The dynamic model considers annual vaccination of birth cohorts over the time horizon of the model and is able to capture herd effects from vaccination. In the current situation of no vaccination, the model predicts that 13 641 cases of serogroup B meningococcal disease, resulting in 1957 cases with sequelae and 730 deaths, would occur over a 100 year period, with the costs of treatment and long-term care totalling €387.2 million.

The base case analysis of adolescent strategies (0% efficacy on carriage) shows that only 6% of cases are averted over a 100 year period under routine vaccination, and this proportion decreases to 3% and 1% under the partial reimbursement and private market policies (Table 45). The base case analysis of infant strategies in the dynamic model (0% efficacy on carriage) is difficult to compare to those simulated by the static model due to its different structure, but the proportion of cases averted is similar in both models, ranging 4-10% (Table 43 and Table 45).

As expected, assuming the 4CMenB vaccine is effective against carriage acquisition (scenario analysis) increases the number of cases averted for each vaccination strategy compared to no efficacy against carriage (Table 45). However, the herd effects seen under infant vaccination alone are limited (Figure 20, Figure 23) because meningococcal carriage prevalence is low in young children.

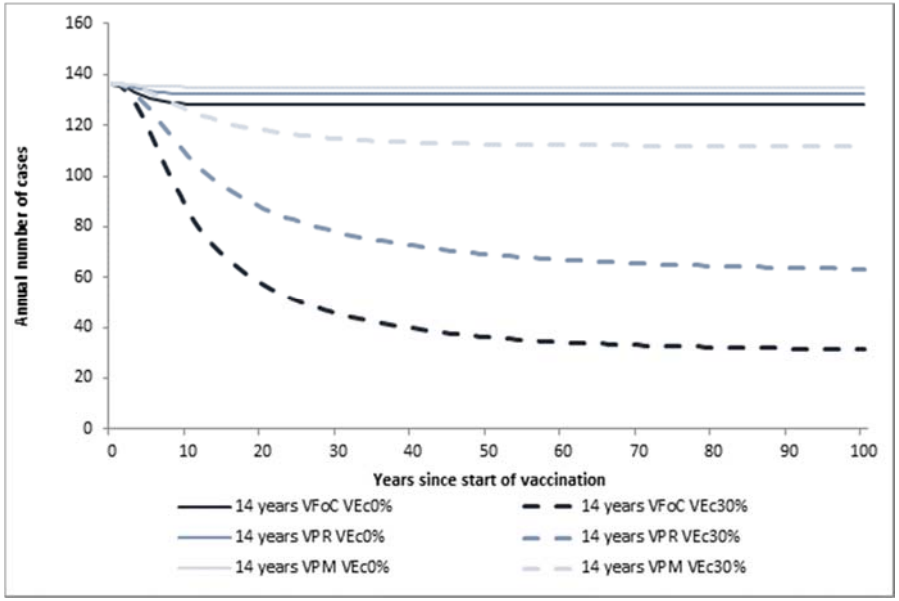
Figure 20 – Effect on annual disease cases of 3, 5, 6 + 12 month vaccination with varying assumptions about the vaccine effect against carriage acquisition for different immunisation policies



Note the vertical axis does not start at 0. VEc: vaccine effect against carriage acquisition; VFoC: routine vaccination free of charge; VPR: partly reimbursed vaccination; VPM: private market vaccination.

If the vaccine protects against carriage, sustained reductions in case numbers could be achieved through routine vaccination of adolescents (Figure 21 and Figure 24); such a strategy results in a long term reduction in cases as it constantly targets the age group where carriage is thought to be high. It does, however, take time for the herd effects to filter through the population, thus large reductions in case numbers are only seen some 10 years after the start of immunisation. The vaccine free of charge policy results in the greatest number of cases averted, of the three policies considered, due to the higher vaccine uptake assumed under this strategy.

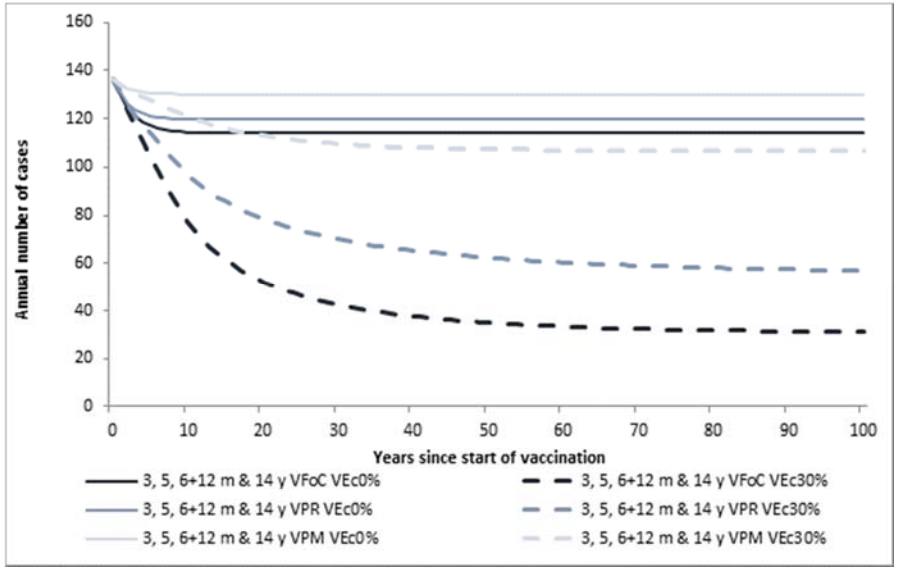
Figure 21 – Effect on annual disease cases of 14 year old vaccination with varying assumptions about the vaccine effect against carriage acquisition for different immunisation policies



VEc: vaccine effect against carriage acquisition; VFoC: routine vaccination free of charge; VPR: partly reimbursed vaccination; VPM: private market vaccination.

Routine adolescent vaccination could be combined with routine infant vaccination to have a greater impact on averted case numbers in the short term (Figure 22, Figure 25).

Figure 22 – Effect on annual disease cases of 3, 5, 6 + 12 months and 14 year olds vaccination with varying assumptions about the vaccine effect against carriage acquisition for different immunisation policies



VEc: vaccine effect against carriage acquisition; VFoC: routine vaccination free of charge; VPR: partly reimbursed vaccination; VPM: private market vaccination; m: month; y: year.

Figure 23 – Cases averted by age at selected time points since the start of vaccination from the dynamic model, infant vaccination at 3, 5, 6 and 12 months assuming the vaccine is in the routine schedule

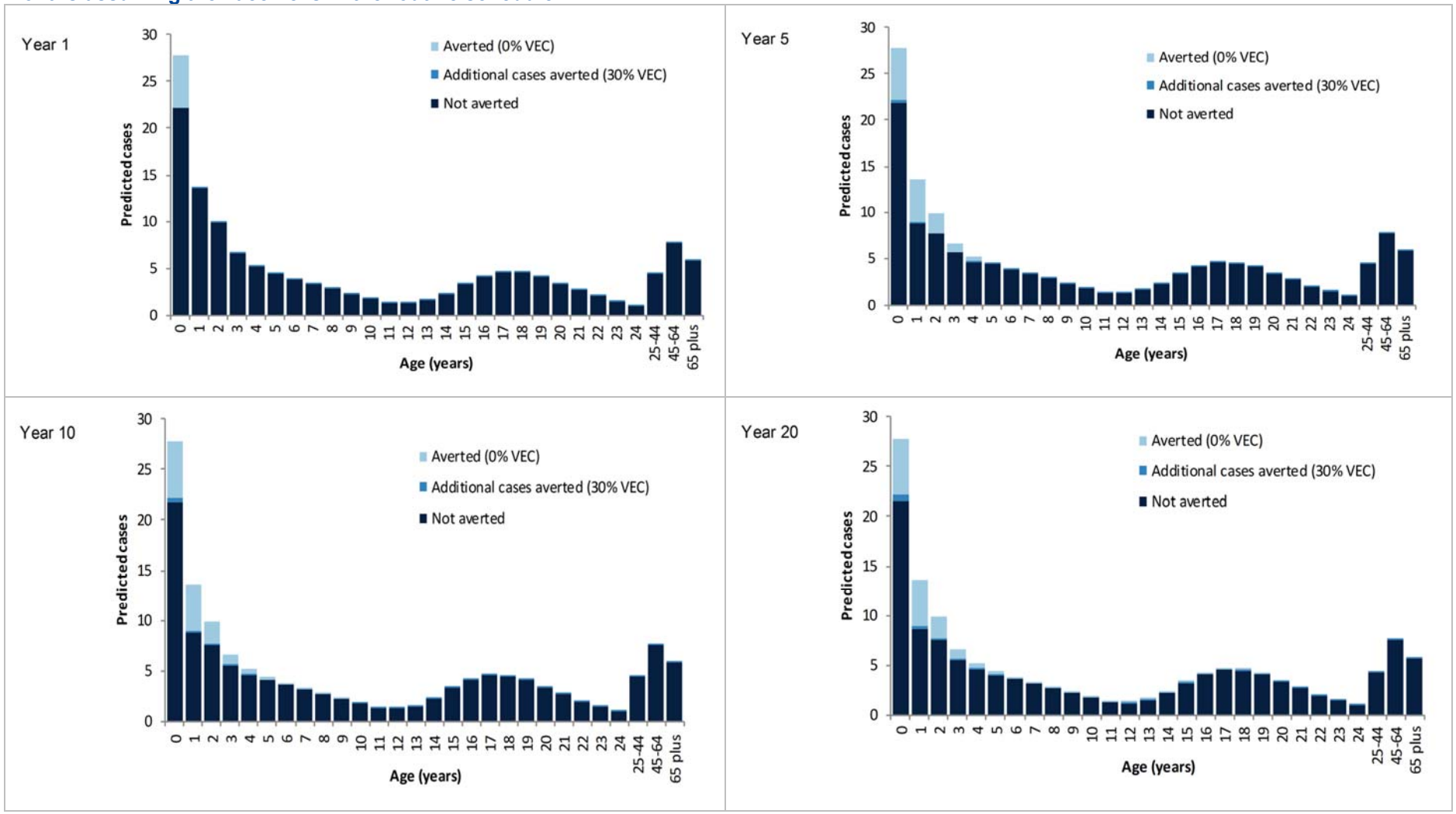


Figure 24 – Cases averted by age at selected time points since the start of vaccination from the dynamic model, adolescent vaccination at 14 years assuming the vaccine is in the routine schedule

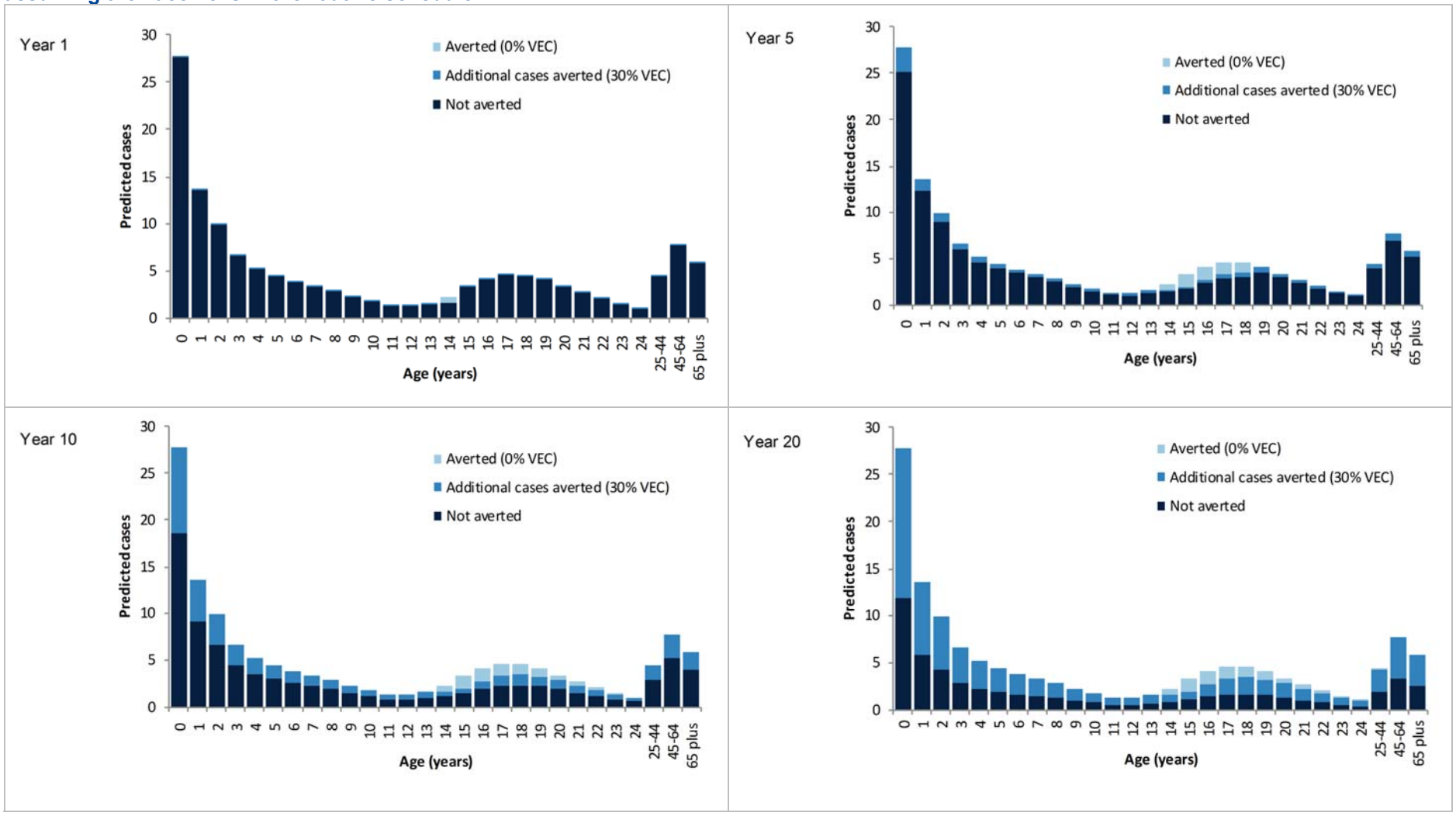


Figure 25 – Cases averted by age at selected time points since the start of vaccination from the dynamic model, vaccination at 3, 5, 6 + 12 months and 14 years assuming the vaccine is in the routine schedule

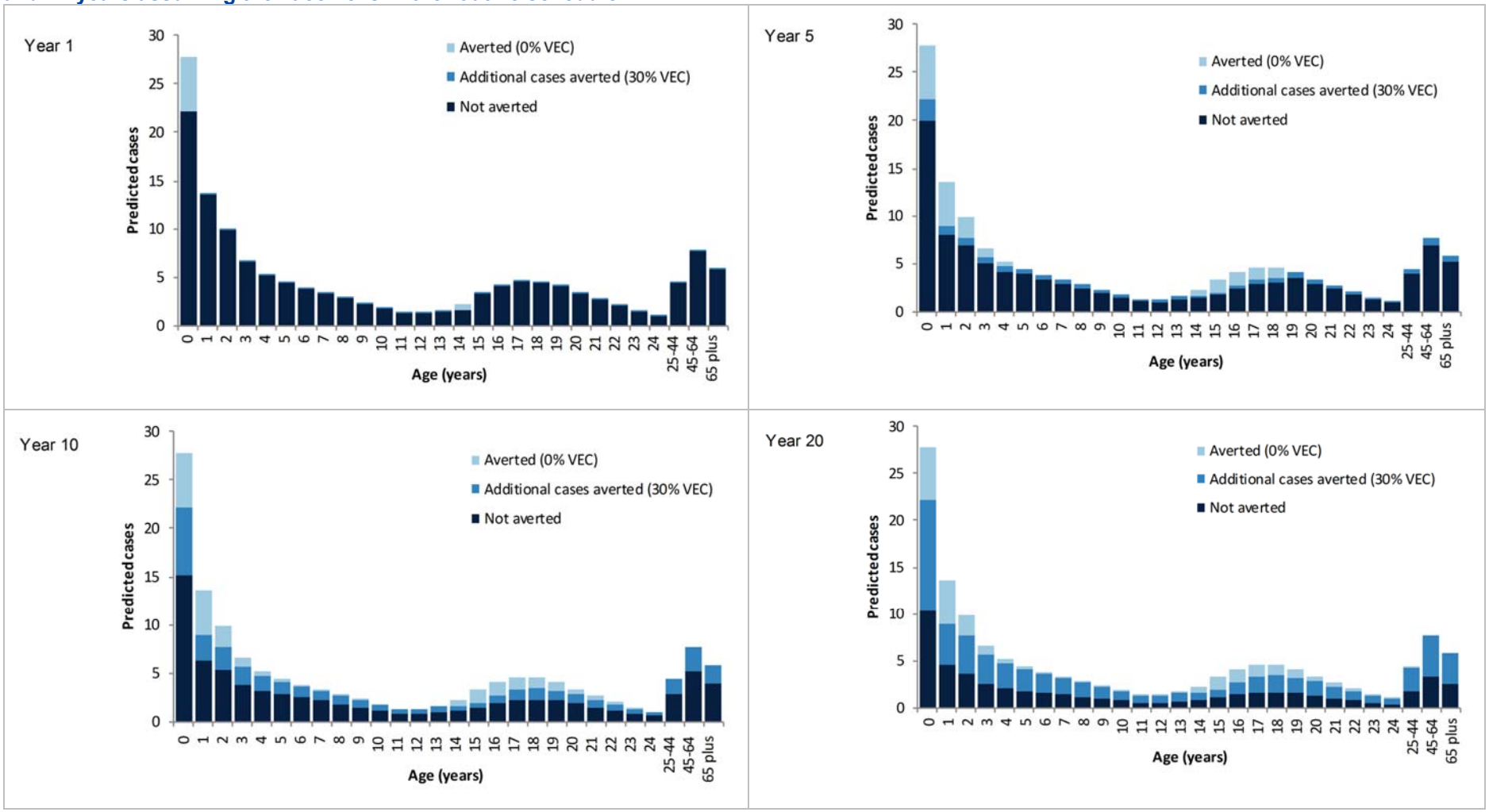


Table 45 – Results from the dynamic model, comparison of vaccination strategies (vaccination vs. no vaccination)[a]

	Undiscounted						Discounted[b]			
Scenario description	Cases averted (%)	Cases with sequelae averted	Deaths averted	Life Years Saved	QALY gained	Net cost of vaccination[c]	Cost per case averted	Cost per death averted	Cost per Life Year Saved	Cost per QALY gained
Routine vaccination policy, free of charge										
3, 5, 6 + 12 months vaccination										
- **0% VE against carriage**	1403 (10)	280	69	3332	4299	€1597.7M	€723 400	€14 590 000	€391 200	€303 300
- **30% VE against carriage**	1699 (12)	325	85	3914	5015	€1589.5M	€603 800	€12 091 500	€333 900	€260 700
14 years vaccination										
- **0% VE against carriage**	791 (6)	69	39	1676	1886	€735.9M	€600 600	€12 105 300	€354 100	€314 600
- **30% VE against carriage**	8904 (65)	1273	476	17642	21353	€518.0M	€47 700	€893 900	€29 400	€24 400
3, 5, 6 + 12 months and 14 years vaccination										
- **0% VE against carriage**	2193 (16)	349	109	5007	6184	€2331.1M	€679 100	€13 693 800	€378 400	€306 500
- **30% VE against carriage**	9180 (67)	1326	490	18611	22596	€2151.7M	€166 300	€3 123 100	€100 600	€83 000
Partly reimbursed vaccination policy										
3, 5, 6 + 12 months vaccination										
- **0% VE against carriage**	1261 (9)	252	62	2999	3869	€2260.3M	€1 133 300	€22 837 700	€612 300	€474 800
- **30% VE against carriage**	1532 (11)	293	77	3532	4525	€2252.8M	€944 600	€18 901 600	€522 000	€407 500
14 years vaccination										
- **0% VE against carriage**	395 (3)	34	20	838	943	€640.9M	€1 043 500	€21 031 500	€615 100	€546 500
- **30% VE against carriage**	5925 (43)	842	317	11510	13910	€496.2M	€66 800	€1 251 500	€41 700	€34 600
3, 5, 6 + 12 months and 14 years vaccination										
- **0% VE against carriage**	1656 (12)	286	82	3836	4811	€2898.7M	€1 111 400	€22 396 600	€612 500	€488 500
- **30% VE against carriage**	6676 (49)	982	354	13426	16360	€2772.3M	€293 100	€5 534 400	€178 000	€146 300
Private market vaccination policy										
3, 5, 6 + 12 months vaccination										
- **0% VE against carriage**	489 (4)	98	24	1166	1504	€880.6M	€1 138 000	€22 874 300	€613 200	€475 700
- **30% VE against carriage**	604 (4)	116	30	1396	1788	€877.3M	€933 300	€18 640 200	€514 800	€402 000
14 years vaccination										
- **0% VE against carriage**	132 (1)	11	7	279	314	€249.8M	€1 219 500	€24 576 900	€718 800	€638 700
- **30% VE against carriage**	2090 (15)	295	112	4135	4992	€198.1M	€73 500	€1 378 900	€45 400	€37 700
3, 5, 6 + 12 months and 14 years vaccination										
- **0% VE against carriage**	621 (5)	109	31	1446	1818	€1127.9M	€1 152 500	€23 178 300	€632 300	€502 900
- **30% VE against carriage**	2592 (19)	390	137	5313	6499	€1076.4M	€290 600	€5 518 100	€174 400	€142 800

a: unlike the static model, the dynamic model considers multiple cohorts over the time horizon of the model (100 years), thus under the 'no vaccination' model much large number of cases are seen, and can be averted, compared to the static model which principally considers a single cohort only. Please see the methods section 5.1 for further details. b: figures rounded to nearest 100. c: additional cost of vaccination less costs averted through reduction in cases. M: millions.

9.2 Cost-effectiveness of different vaccination strategies

The cost-effectiveness of different vaccination strategies with varying assumptions about the vaccine efficacy against carriage acquisition and under different vaccination policies and target groups are shown in Table 45. Compared to the static model (Table 43), infant vaccination assuming no herd effects in the dynamic model appears more economically favourable, principally because multiple vaccination cohorts are considered and differential discounting is applied;[132] however, the cost per quality adjusted life year gained remains high at over €300 000.

For all strategies, vaccination appears more cost-effective if the vaccine is assumed to prevent a proportion (30%) of MenB carriage acquisition. However in infants the reduction in the cost per QALY gained is small (from €303 300 to €260 700), and assuming the vaccine can disrupt carriage infant strategies are the least attractive economically, compared to strategies targeting adolescents. Formal incremental analysis (see 5.2) of different strategies confirm routine infant vaccination alone is dominated when herd effects are assumed (Table 46, results for 0% vaccine efficacy against carriage to be found in appendix). Strategies including routine vaccination of adolescents alone appear much more economically attractive assuming herd effects. Despite the limited impact on case numbers in the short-term with routine adolescent vaccination, due to the lower number of doses required for such strategies (compared with routine infant immunisation) and the sustained reduction in cases achieved in the longer-term with herd effects the cost per quality adjusted life year gained for routine vaccination for 14 year olds reduces from €314 600 to €24 400.

Reducing the cost per dose of the vaccine improves the cost-effectives of immunisation. For vaccination at 3, 5, 6 + 12 months and 14 years assuming a 30% vaccine efficacy against carriage acquisition, vaccination would be cost-effective at €12 per vaccine dose at a willingness to pay of €40 000, or €5 per vaccine dose at a willingness to pay of €30 000 under the routine vaccination policy. Corresponding vaccine prices for the partly reimbursed vaccination policy are €10 and €4. Neither policy could be cost-effective at a willingness to pay of €20 000 at any vaccine price.

Table 46 – Incremental costs and benefits of alternative vaccination strategies, ranked by discounted total cost of the strategies, 30% vaccine efficacy against carriage acquisition

	Total cost of treatment / vaccination	QALYs gained	Incremental cost	Incremental QALYs gained	Cost per QALY gained (rounded)
Routine vaccination policy					
Current situation	€89.7M	0	-	-	
14 year	€289.6M	8207	€199.9M	8207	€24 400
3, 5, 6 + 12 month	€614.1M	2012	€324.5M	-6196	Dominated
3, 5, 6 + 12 month and 14 year	€821.4M	8812	€531.8M	605	€879 500
Partly reimbursed vaccination policy					
Current situation	€89.7M	0	-	-	
14 year	€272.4M	5285	€182.7M	5285	€34 600
3, 5, 6 + 12 month	€829.2M	1815	€556.8M	-3470	Dominated
3, 5, 6 + 12 month and 14 year	€1015.6M	6329	€743.2M	1044	€711 800
Private market vaccination policy					
Current situation	€89.7M	0	-	-	
14 year	€161.6M	1908	€71.9M	1908	€37 700
3, 5, 6 + 12 month	€377.8M	717	€216.2M	-1191	Dominated
3, 5, 6 + 12 month and 14 year	€449.4M	2519	€287.9M	612	€470 700

Each strategy is compared to the strategy above unless dominated. A strategy is dominated if its effectiveness is lower and its costs higher than the strategy above.

9.3 Scenario analysis

Univariate and multivariate (all serogroup and best and worst-case) scenario analyses, as defined in section 6.7.2 above, were undertaken for two reference strategies: combined infant and adolescent routine and partly reimbursed vaccination policies, assuming a 30% effect of the vaccine against carriage acquisition. Results are presented in Table 47 and Table 48.

Incidence, case-fatality and strain coverage

Similarly to the static model, vaccination appears more economically favourable when either the incidence of disease and case-fatality rates or the strain coverage is higher. With increased incidence (351 cases assumed per year) and case fatality rates (25 deaths per year) the cost per quality adjusted life year gained reduces considerably from €83 000 in the reference strategy (routine vaccination at 3, 5, 6 + 12 months and 14 years) to €22 500. With increased strain coverage (85% compared to 78% in the base case) 73% of cases are averted under a 3, 5, 6+12 months and 14 years vaccination policy with vaccination offered free of charge, a 5 percentage point increase compared to the reference strategy, which leads to a reduction in cost per QALY gained to €76 500.

Vaccine uptake

As expected, increasing the uptake of vaccination increases the number of cases averted, from 59% in the low vaccine uptake scenario to 71% in the high vaccine uptake scenario for the infant and adolescent vaccine free of charge strategy. However, increasing the uptake of vaccination results in increasing costs per quality adjusted life year gained to €123 100 due to continuous vaccination of an increasing number of people and the use of differential discounting.

Quality of life and rate of sequelae

Increasing the quality of life loss experienced by survivors with sequelae or increasing the assumed proportion of people with sequelae improves the cost-effectiveness of vaccination, although in both cases this remains above €50 000 per quality adjusted life year gained.

Discount rate

The choice of discount rate again has a large effect on the results, with scenarios using 3% discounting for costs and benefits (compared to 3% for costs and 1.5% for benefits) appearing considerably less cost-effective; €186 500 with 3% discounting compared to €83 000 in the reference strategy for the 3, 5, 6 + 12 months and 14 years vaccination strategy with vaccination offered free of charge.

Duration of vaccine protection and vaccine efficacy against disease

As with the static model increasing the average duration of protection from vaccination increases the number of cases averted, resulting in vaccination appearing more economically favourable (Table 47 and Table 48). If the average of duration of protection afforded by a 3, 5, 6 + 12 months and 14 years vaccination strategy with vaccination offered free of charge were increased (to 26 months prior to boosting and 36 months thereafter in infants and 105 months in adolescents), the proportion of cases averted over 100 years is predicted to increase from 67% to 69%, with a reduction in the cost per quality adjusted life year gained from €83 000 to €79 000. Reducing the assumed vaccine efficacy against disease (from 95% to 73% in infants and 100% to 77% in adolescents), but maintaining a 30% assumed vaccine efficacy against carriage results in a small increase in the cost per QALY gained from €83 000 to €84 100.

Cost per vaccine dose, vaccine administration costs

Reducing the cost of the vaccine or the cost of administration improves the cost-effectiveness of vaccination, as expected; for 3, 5, 6 + 12 months and 14 years immunisation with vaccination offered free of charge the cost per quality adjusted life year gained increases from €68 400 to €100 200 with an increase in vaccine price from the low to the high vaccine cost scenario.

Vaccine adverse reactions

Assuming higher rates of adverse reaction (to approximately 2.5 times that observed in the reference strategy) increases the cost per quality adjusted life year gained from €83 000 to €95 300.

MenB carriage prevalence and serogroup B versus all serogroup scenario, assuming herd effects

If the carriage prevalence of MenB is higher than assumed in the reference strategy, or if all serogroups are considered rather than MenB only, a lower proportion of cases are averted. This may seem counterintuitive because, in the absence of indirect effects, vaccination with a vaccine effective against all serogroups would avert more cases and have a lower cost per QALY gained. In these two scenarios, case-carrier ratios are lower because there are more carriers for the estimated number of cases (which is fixed in this scenario), so when we assume an efficacy against carriage acquisition, the 30% vaccine efficacy against carriage has a more limited effect than in the base case because many more carriers are assumed under these scenarios (e.g. peak at 23.7% for all serogroups compared to 7.6% serogroup B in the base case) and thus much more transmission. In that scenario, the lower case-carrier ratio becomes important because disrupting carriage has a lower impact on reducing the cases of disease. As a result the herd effects seen in the long term in the all serogroup or high carriage model are lower than in the base case model. This results in an increase in the cost per quality adjusted life year gained of vaccination from €83 000 to €98 800 for all serogroups and to €88 700 for a higher carriage prevalence of MenB.

Table 47 – Results from the dynamic model, scenario analyses of vaccination at 3, 5, 6 + 12 months and 14 years assuming 30% vaccine efficacy against carriage acquisition and vaccine free of charge policy (vaccination vs. no vaccination)

	Undiscounted						Discounted[a]			
Scenario description	Cases averted (%)	Cases with sequelae averted	Deaths averted	Life Years Saved	QALY gained	Net cost of vaccination (millions)[b]	Cost per case averted	Cost per death averted	Cost per Life Year Saved	Cost per QALY gained
Reference scenario	*9180 (67)*	*1326*	*490*	*18 611*	*22 596*	*€2151.7M*	*€166 300*	*€3 123 100*	*€100 600*	*€83 000*
All serogroup	6416 (36)	926	425	15 838	18 691	€2213.6M	€232 500	€3 523 700	€116 400	€98 800
Higher serogroup B carriage prevalence	8522 (62)	1266	452	17 442	21 268	€2164.4M	€180 100	€3 400 100	€108 000	€88 700
Increased incidence and case fatality rates	23 606 (67)	3375	1677	64 384	74 661	€1764.7M	€58 000	€817 500	€26 100	€22 500
Low vaccine strain coverage (50%)	5988 (44)	866	320	12 226	14 848	€2236.9M	€259 200	€4 862 800	€156 200	€128 900
High vaccine strain coverage (85%)	9929 (73)	1433	530	20 097	24 400	€2131.8M	€153 200	€2 876 900	€92 700	€76 500
Lower rates of vaccine uptake	8104 (59)	1176	432	16 167	19 646	€1765.4M	€157 700	€2 967 400	€96 300	€79 400
Higher rates of vaccine uptake	9724 (71)	1406	519	20 251	24 613	€3596.7M	€251 300	€4 719 700	€149 300	€123 100
Shorter duration of vaccine protection	9065 (66)	1308	484	18 301	22 210	€2155.9M	€169 400	€3 178 200	€102 700	€84 800
Longer duration of vaccine protection	9463 (69)	1365	505	19 385	23 535	€2142.2M	€159 200	€2 988 800	€95 700	€79 000
Higher rates of vaccine adverse reactions	9180 (67)	1326	490	18 611	22 596	€2484.2M	€190 900	€3 585 100	€115 500	€95 300
High proportion of people with sequelae	9180 (67)	1646	490	18 611	23 560	€2108.7M	€164 700	€3 091 700	€99 600	€78 900
QoL loss for survivors with sequelae (0.3 loss)	9180 (67)	1326	490	18 611	34 712	€2151.7M	€166 300	€3 123 100	€100 600	€54 200
Lower vaccine administration costs	9180 (67)	1326	490	18 611	22 596	€2017.3M	€156 400	€2 936 500	€94 600	€78 100
Lower vaccine cost	9180 (67)	1326	490	18 611	22 596	€1756.0M	€137 100	€2 573 500	€82 900	€68 400
Higher vaccine cost	9180 (67)	1326	490	18 611	22 596	€2616.1M	€200 700	€3 768 300	€121 400	€100 200
20 year time horizon	1097 (40)	162	58	457	549	€467.3M	€389 800	€7 431 100	€964 900	€803 600
3% discounting for costs and benefits	9180 (67)	1326	490	18 611	22 596	€2151.7M	€296 900	€5 589 700	€225 600	€186 500
Best case	27 644 (79)	4911	1962	77 730	93 262	€1546.2M	€47 200	€666 600	€20 800	€17 400

Worst case[c]	734 (7)	66	17	796	1017	€3328.0M	€2 866 100	€125 982 000	€3 370 900	€2 638 700
Lower vaccine efficacy against disease (73% infants, 77% adolescents)	9133 (67)	1318	488	18 449	22 396	€2153.7M	€167 900	€3 151 100	€101 900	€84 100

a: figures rounded to nearest 100. b: additional cost of vaccination less costs averted through reduction in cases. c: worst case assuming 0% vaccine efficacy against carriage acquisition. M: million.

Table 48 – Results from the dynamic model, scenario analyses of vaccination at 3, 5, 6 + 12 months and 14 years assuming 30% vaccine efficacy against carriage acquisition and vaccine partly reimbursed policy (vaccination vs. no vaccination)

	Undiscounted						Discounted[a]			
Scenario description	**Cases averted (%)**	**Cases with sequelae averted**	**Deaths averted**	**Life Years Saved**	**QALY gained**	**Net cost of vaccination (millions)[b]**	**Cost per case averted**	**Cost per death averted**	**Cost per Life Year Saved**	**Cost per QALY gained**
Reference scenario	*6676 (49)*	*982*	*354*	*13 426*	*16 360*	*€2772.3M*	*€293 100*	*€5 534 400*	*€178 000*	*€146 300*
All serogroup	3974 (22)	608	255	9943	11 869	€2832.4M	€468 900	€7 344 300	€233 400	€195 900
Low vaccine strain coverage (50%)	5005 (37)	731	267	9849	11 981	€2820.7M	€401 900	€7 560 400	€247 600	€203 800
High vaccine strain coverage (85%)	6960 (51)	1027	369	14 100	17 189	€2763.3M	€279 000	€5 272 900	€168 700	€138 500
Lower rates of vaccine uptake	4962 (36)	734	263	10 026	12 226	€1858.7M	€264 800	€5 009 100	€160 500	€131 800
Higher rates of vaccine uptake	7962 (58)	1165	424	16 019	19 502	€3623.3M	€319 600	€6 023 600	€193 900	€159 500
Shorter duration of vaccine protection	6363 (47)	935	339	12 810	15 595	€2781.2M	€308 500	€5 808 100	€187 100	€153 900
Longer duration of vaccine protection	7583 (56)	1108	403	15 143	18 429	€2749.6M	€257 900	€4 864 200	€157 400	€129 500
QoL loss for survivors with sequelae (0.3 loss)	6676 (49)	982	354	13 426	25 277	€2772.3M	€293 100	€5 534 400	€178 000	€94 900
3% discounting for costs and benefits	6676 (49)	982	354	13 426	16 360	€2772.3M	€529 300	€10 022 000	€402 600	€331 300
Best case	23 915 (68)	4284	1687	64 374	77 381	€972.1M	€39 300	€559 000	€17 900	€14 900
Worst case[c]	458 (4)	42	11	545	687	€2630.8M	€3 622 100	€145 363 000	€3 889 200	€3 088 000

a: figures rounded to nearest 100. b: additional cost of vaccination less costs averted through reduction in cases. c: worst case assuming 0% vaccine efficacy against carriage acquisition. M: million.

Mixing patterns

For routine infant vaccination, more cases were predicted to be averted when population mixing patterns were based on a simple preferential mixing structure (2384 cases averted), compared to survey data from POLYMOD used in the base case (1699 cases averted) assuming a 30% vaccine efficacy against carriage acquisition (Figure 26, Table 49). Contrastingly, when infants and adolescents are vaccinated, fewer cases are averted under preferential mixing (8008) than POLYMOD (9180). Consequently the cost per QALY gained decreases for routine infant vaccination (from €260 700 to €192 400) and increases for infants and adolescents vaccination (from €83 000 to €99 800) when using preferential mixing instead of POLYMOD. Smoothed data on leisure contacts from POLYMOD were used in the base-case analyses and these data fit less well to the assumed carriage prevalence curve, compared to using a simple preferential mixing structure, thus the carriage prevalence profile by age differs between these two scenarios.

Figure 26 – Effect on annual disease cases of vaccination assuming 30% vaccine efficacy against carriage under different assumptions for population mixing, routine vaccination policy

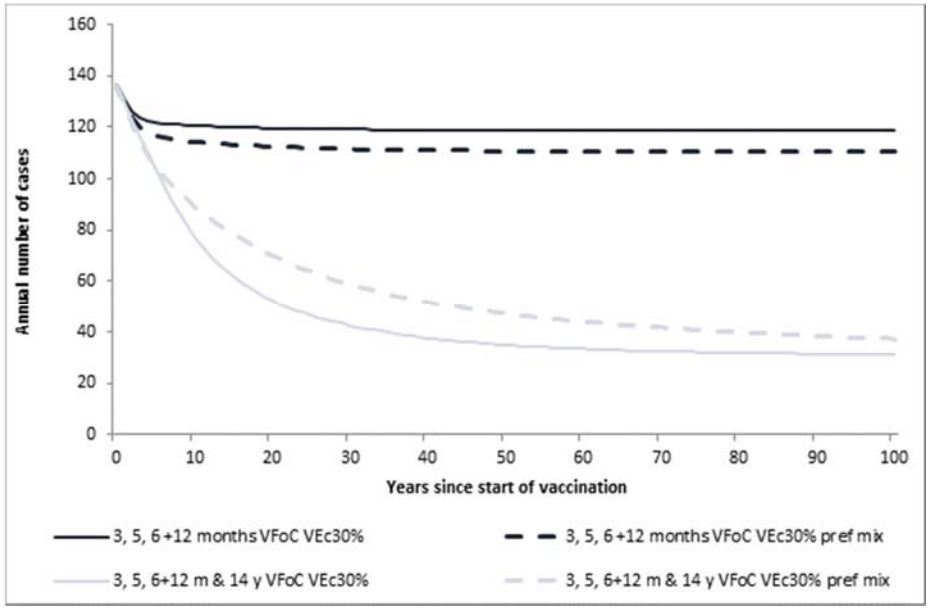


Table 49 – Results from the dynamic model, scenario analysis on mixing patterns (vaccination vs. no vaccination)

	Undiscounted						Discounted[a]			
Scenario description	Cases averted (%)	Cases with sequelae averted	Deaths averted	Life Years Saved	QALY gained	Net cost of vaccination (millions)[b]	Cost per case averted	Cost per death averted	Cost per Life Year Saved	Cost per QALY gained
Reference strategies, POLYMOD mixing structure, routine vaccination policy, 30% VE against carriage										
3, 5, 6 + 12 months	1699 (12)	325	85	3914	5015	€1589.5M	€603 800	€12 091 500	€333 900	€260 700
3, 5, 6 + 12 months and 14 years	9180 (67)	1326	490	18 611	22 596	€2151.7M	€166 300	€3 123 100	€100 600	€83 000
Preferential population mixing within 1 year of age, routine vaccination policy, 30% VE against carriage										
3, 5, 6 + 12 months	2384 (18)	441	117	5295	6777	€1567.8M	€431 300	€8 807 500	€246 200	€192 400
3, 5, 6 + 12 months and 14 years	8008 (59)	1166	421	15 779	19 225	€2185.1M	€196 500	€3 753 300	€121 400	€99 800

a: figures rounded to nearest 100. b: additional cost of vaccination less costs averted through reduction in cases. M: million.

10 USE OF 4CMENB IN OUTBREAKS OR CLUSTERS

Although it was initially planned to include a research question on the use of 4CMenB as response to MenB outbreaks or clusters of cases,[n] this strategy was not studied for the following reasons.

Prevention activities and responses to outbreaks and clusters are the responsibility of the communities in Belgium.[o] The policies are thus defined at community level. So far, French and Flemish Communities have not recommended vaccination (e.g. using MenC vaccine for MenC clusters) in response to outbreaks or clusters.[133, 134] Experts of the communities who contributed at our expert meetings also felt that the new 4CMenB vaccine would not represent a potential strategy for cluster and outbreak response, due to the time needed to mount an immune response, the number of doses required to protect previously unvaccinated subjects (at least two doses, according to age group), and the high effectiveness and efficiency of antibiotic prophylaxis, as described below.

First, immune responses after 4CMenB doses are only measured one month after vaccination, and data on possible protection in a shorter period after vaccination are not yet available. Protection one month after vaccination has limited value in immediate public health response, as studies have shown that secondary (or at least subsequent) cases are mostly found within the first month after an index case (89% of secondary cases occurred in the first 21 days in a Belgian study).[5] Detailed data on past IMD clusters are not available from Belgium, but a recent analysis of clusters in France indicated that 83% of secondary cases (65/93) occurred within 4 weeks after the primary case.[135]

Second, immunogenicity data shows that at least two doses are required to generate a sufficient immune response in vaccinees. The need for a third dose has been demonstrated in those of 1-2 years of age and is still being assessed by longer follow-up studies for other age groups. Among young infants (in which incidence is highest), protection is known to be maximised only after a 3-dose primary schedule. Multiple dose administration to large population groups would present high logistical challenges from a public health response perspective.

Third, antibiotic prophylaxis of contacts of a case is considered as an effective strategy in Belgium to limit the occurrence of secondary cases and thus prevent clusters or outbreaks. In the rare case of clusters, policies differ across communities but wider antibiotic prophylaxis is recommended (e.g. extend from close contacts to the entire classroom)[133] in each community. Although vaccination presents the advantage of protecting contacts in the longer term (as the effect of chemoprophylaxis declines after 30 days),[136] there are other questions on the persistence of protection after vaccination with 4CMenB. There are also important differences in efficiency between the two strategies when applied to contacts of sporadic cases. The number of household contacts needed to treat to prevent a case was estimated at 218 (121 to 1135) in a recent meta-analysis.[137] A European study on meningococcal C vaccination from the same group estimated that between 640 and 1680 household contacts need to be vaccinated to prevent a case.[136] The recent MenB study in France has estimated this number at 8800 for 4CMenB vaccination based on data on secondary cases.[135]

For these reasons, other countries such as France and England do not recommend use of meningococcal B vaccination of contacts of a sporadic cases as public health response.[135, 138]

However, both countries have issued guidance on 4CMenB vaccination in occurrence of clusters and outbreaks.[135, 138] For instance, French recommendations advise vaccination of persons belonging to the same group in situation of clusters due to vaccine preventable strains in this group, according to defined criteria, on the basis of a detailed description of past clusters.[135] It should be noted that the analysis based on recent clusters (≥2 cases) estimated that 4CMenB vaccination in these situations would have

[n] There are no standard definition for clusters or outbreaks. The following definition for cluster is used in Flanders: at least three related IMD cases caused by the same strain and responsible for increased incidence during at least 3 months (i.e. minimum twenty times higher than what is considered as normal for the population).[133] No definition is provided in Wallonia.[134] In France, a cluster is defined as ≥2 linked cases in the same community or social group.[135]

[o] Belgian Communities are federated entities in charge of preventive medicine and disease control (among other competencies).

prevented only 0.1 cases per year on average.[135] English recommendations advise vaccination of household contacts when two cases have occurred in the same family, to the group in which a cluster of vaccine preventable strains has been confirmed and in a community in which the age-specific attack rate of vaccine preventable strains exceed 40 per 100 000 in a defined geographical boundary over a three-month period.[138] Belgian data indicate no recent clusters or outbreaks of meningococcal B cases, as opposed to e.g. monoclonal outbreaks in Northern France, clusters in schools and colleges in England and Wales or to serogroup C IMD which caused outbreaks in Antwerp in 2001-02.[123, 139] Although reasons for this difference are unknown, they are unlikely to be due to difference in surveillance systems as the hospital discharge database (MZG-RHM), including all hospitalized cases in Belgium, does not indicate a high or substantially increased incidence per region in the last nine years. The highest incidence for overall IMD was observed in Wallonia in 2005 and is below 4 per 100 000 persons (3.8 per 100 000). Although no specific threshold is defined in Belgium for mass vaccination, these incidences lay well below the Center for Disease Control and Prevention (CDC) threshold for mass vaccination in outbreaks (10 per 100 000) or the threshold above defined in England (40 per 100 000). However, more detailed analysis e.g. per province or municipality and over shorter time frames would be needed to exclude past clusters. Another obstacle in Belgium is the current lack of laboratory tests to investigate if a serogroup B strain is vaccine-preventable or not.

However, a prolonged “cluster” of B:NT:P1.14 was described in Belgium over 2006-09, spreading over a wide area of Flanders and a 4 year-duration.[140] An unpublished occurrence of several cases due to the same strain was also reported in Belgium over a few months in 2013 (C. Schirvel, personal communication). In those cases of protracted high incidence or in situations of large outbreaks due to vaccine-preventable strains, meningococcal vaccination could be a useful control measure, provided that clinical protection is ensured over a sufficient period (high SBA titres in adults are not documented beyond six months after vaccination).[18]

These proposals could be re-evaluated when better data on the true 4CMenB effectiveness, the level of protection according to time after vaccination, precise dose schedule and the duration of protection are available, and certainly if localised increases of meningococcal disease emerge and are considered as public health threats at community level.

11 DISCUSSION

11.1 4CMenB vaccination

This study explores the potential clinical impact and cost-effectiveness of a range of vaccination strategies using the new meningococcal vaccine 4CMenB (Bexsero) in Belgium. Three main vaccination policies were considered in the Belgian setting: 4CMenB recommended free of charge in the routine vaccination calendar (e.g. as PCV7); 4CMenB recommended and partly reimbursed (e.g. as rotavirus vaccines); and private market only, i.e. 4CMenB available in pharmacies at full charge (e.g. as for varicella vaccine). Each of these policies were applied to two target groups (infants and adolescents), alone or combined.

It should be noted that there is considerable uncertainty in the analyses, especially around vaccine properties (i.e. proportion of vaccine-preventable strains, efficacy and duration of protection), but also around future evolution of meningococcal disease and expected vaccine uptake. For instance, the vaccine parameters combine sparse data on correlates and surrogates of protection (MATS and SBA). These results should thus be taken with caution in the absence of robust data on efficacy/effectiveness and vaccine waning. For that reason, uncertainty was extensively explored through probabilistic sensitivity analyses - when possible - and through scenario analyses, considering higher and/or lower assumptions for a range of uncertain parameters. It is possible however, that we did not cover the entire uncertainty around some parameters.

11.1.1 If 4CMenB has no effect on transmission (base case)

In the base case analysis, we assumed no vaccine effect on transmission (no indirect effect), vaccine effects limited to serogroup B IMD disease (following the EMA indication), and relatively low vaccine uptakes (i.e. 50% for infant booster doses if free of charge) as the vaccine is administered separately from other vaccines, and has a high reactogenicity. In this conservative base case, vaccinating infants would only prevent 5-14 cases (4-10% of the total 139 cases predicted over the lifetime of a cohort), 1-3 cases with sequelae and 0-1 deaths per year; and would only gain 23-65 QALYs, depending on the vaccination policy. This low proportion of averted cases is due to the assumed late protection of infants (at around 6 months of age, after the peak of infant incidence) and of short duration. Due to the

high costs of vaccination (i.e. vaccine doses, administration and side effects) and to the few IMD treatment costs avoided, the three infant vaccine policies would present unfavourable cost-effectiveness ratios, all above €400 000 per QALY gained. Vaccination of adolescents (14 year age cohort) in the absence of indirect effect, explored through a transmission dynamic model, would prevent only 1-6% of all cases and is even less cost-effective than the infant strategy (higher cost per QALY gained).[p] Reducing the vaccine cost per dose, even at €0, would not result in cost-effective strategies at any of the willingness to pay thresholds explored (€20 000, €30 000 or €40 000 per QALY gained), due to the other vaccination costs (high vaccine administration costs related to separate visits and costs of adverse events).

Routine infant vaccination at 50% uptake would generate an estimated 2757 and 976 adverse events attributable to the vaccine, requiring outpatient and inpatient care respectively, with subsequent high costs due to the high numbers of vaccinated. However, most adverse events described with 4CMenB were of short duration and resolved spontaneously.

When no effect on transmission is assumed, univariate scenario analysis shows that routine infant vaccination prevents the highest number of cases if incidence rises to the highest values observed in the last 35 years (34 cases prevented or 10%), followed by a scenario of high vaccine uptakes - similar to other routine vaccines (24 cases or 18% if uptake ranges 91-93%). The maximum number of prevented deaths would occur under high incidence and case fatality rate but does not exceed 4 deaths a year. A higher and lower proportion of strain coverage (MATS) would result in 11% and 6% prevented cases, respectively. Under a hypothetical best case scenario under which parameters are simultaneously set at the most vaccine favourable values, 71 IMD cases (20%) and four deaths could be prevented by routine vaccination of infants. None of these scenario yielded a favourable cost-effectiveness ratio: the best case is the most cost-effective scenario but would still cost €98 000 per QALY gained compared to no vaccination.

Other European cost-effectiveness studies found similar health impact and unfavourable cost-effectiveness results when no effect on transmission is assumed.[81, 99, 141] A recent French evaluation predicted that routine vaccination of infants would prevent 10% and 17% of cases (at 100 years through a dynamic model) with uptake at 50% and 80% respectively, while vaccination of 50% adolescents would prevent 5% of cases, similarly to our analysis.[q,99] Although parameters for costs and vaccine adverse events differed substantially, these strategies also presented cost-effectiveness ratios above €400 000 per QALY gained for a vaccine price at €40 (as in our base case for infant routine policy). In the Netherlands, routine vaccination of 95% infants would prevent 14% of cases at a cost per QALY gained at €244 000 under a societal perspective with a vaccine price at €40.[141] Adding adolescent vaccination would increase the cost per QALY gained. In a UK study published in 2013, routine vaccination of 91% infants would prevent 28% of cases and cost £164 000 per QALY gained with a similar vaccine price but lower costs for vaccine administration and adverse events.[81] However, this study estimated that routine infant strategies could be considered cost-effective in England (i.e. <£30 000 per QALY) if the vaccine would cost around £9 per dose.[r]

11.1.2 If 4CMenB may prevent transmission

In a scenario assuming an indirect effect with a 30% reduction in carriage acquisition (dynamic model), routine infant vaccination would not prevent many more cases (12%) compared to the base case (10%) because carriage is low in young children, and would still not be cost-effective (€260 700/QALY gained). But substantially greater decreases in cases could be achieved through adolescent vaccination in routine and partly reimbursed policies (65% and 43% respectively) with favourable cost-effectiveness

p As the dynamic model computes cases and deaths prevented for multiple cohorts over a 100 year horizon, we cannot compare the health impacts explored by the dynamic model to those explored by the cohort model that only considers a single cohort (i.e. infant vaccination). Only the proportion of cases prevented is thus reported for the dynamic model.

q The base case results of the Belgian study were estimated by the cohort static model, but our dynamic model predicted the same proportion of cases prevented for multiple cohorts over a period of 100 years, which are thus totally comparable to those of France.

r An update of this study was conducted in 2013-14 but was unpublished at the time of writing this report.

ratios, because carriage is high in this age group and vaccinating them is assumed to reduce transmission substantially. Costs per QALY gained of these adolescent strategies would be in the range of those estimated for recently introduced vaccines in Belgium: €24 400 and €34 600 per QALY gained for routine and partly reimbursed 4CMenB vaccination policies, respectively, compared to €10 000 and €33 000 per QALY gained for routine infant PCV7 vaccination (2+1 doses assuming no replacement) and Human Papillomavirus vaccination of 12 year-old girls (3+1 doses), respectively (see also section 5.7).[s, 89, 90] Adolescent vaccination would also result in a long term reduction in cases due to sustained reduction of transmission. However, these results would be achieved after 100 years only and large reductions in cases are only observed 10-20 years after the start of vaccination. In the short-term, routine infant vaccination prevents more cases.

The combination of both routine strategies (infant and adolescent) would reduce cases in both the short term and the long term (67% overall after 100 years), but would cost €83 000 per QALY gained compared to no vaccination and over €800 000 per QALY gained compared to adolescent vaccination alone. In the scenario analysis, this combination strategy would cost ≤€30 000 per QALY gained (compared to no vaccination) only if the incidence and case fatality rate were substantially increased, if the vaccine price is reduced to ≤€5 per dose or in the best case scenario (€22 500, €30 000 and €17 400 per QALY gained respectively). With increased strain coverage only 5% point more cases are averted compared to the base case coverage, at a cost of €76 500 per QALY gained. Other varying assumptions do not result in favourable cost-effective ratio for routine combined policy. The other combined policies (partly reimbursed or private market) would cost more than €140 000 per QALY gained; the partial reimbursement policy would be below €30 000 per QALY gained if the vaccine price were €4 per dose or less.

Other EU studies used other assumptions but they show similar patterns under the assumption of indirect effects. In the French analysis, vaccinating adolescents is the most cost-effective strategy as well, but the proportion of averted cases and the cost-effectiveness ratio are less favourable than in our analysis (23% and €144 750 per QALY gained with update at 80% respectively) and all combined strategies cost above €250 000 per QALY gained.[99] The UK study also indicates that adolescent vaccination is the most cost-effective strategy but slightly less cost-effective than in our study at a similar vaccine price and an assumed 60% effect on carriage (£40 200 per QALY gained).[81] Routine infant vaccination and other combined strategies are all above £80 000 per QALY gained.

Our analyses thus suggest that 4CMenB would prevent a substantial number of cases and be reasonably cost-effective only if efficacy on carriage can be assumed and large proportions of adolescents are vaccinated. However, this would only be achieved in the very long term while meningococcal disease would keep affecting young children. The combined vaccination of adolescents and infants would result in an attractive cost-effectiveness ratio only if the vaccine price could be dramatically reduced. These predictions are however assuming a 30% efficacy on carriage which has not been yet demonstrated. This parameter is thus a key factor to determine if 4CMenB vaccination could be cost-effective in a Belgian setting. Only future studies can produce the evidence required to provide confidence in our results.

11.1.3 Use of 4CMenB in control of clusters and outbreaks

No 4CMenB vaccination in case of clusters of cases or outbreaks is proposed, as this strategy has the following disadvantages: immune response is only documented 30 days after vaccination – a period after which only few subsequent cases occur, immunity is unknown for one or two doses in infants and waning occurs rapidly. Antibiotic prophylaxis is considered as an effective and efficient strategy in these situations, and the

[s] Caution should be exercised however when comparing the results of a study with other (non-)introduced interventions in the past. Decisions are rarely made on the basis of cost-effectiveness considerations alone and it is thus not clear whether economic or other arguments (e.g. therapeutic value, ethical and organisational issues, etc.) have been considered or played a decisive role in the decision-making process. Moreover comparisons with ICERs calculated in the past is only warranted if the ICERs are obtained in the same way, i.e. using the same methodology and under the same conditions (costs, existing technologies, experience, etc.).

advantage of 4CMenB vaccination in addition to chemoprophylaxis seems thus limited based on current knowledge. Likewise, no MenC vaccination has been included in the responses to clusters and outbreaks in Belgium, although the vaccine is known to be very effective.

11.2 Strengths and limitations

The strengths of this analysis include the following aspects:

- Two different types of model were used to assess the potential impact of the new vaccine. The static model conservatively assumes the vaccine will only afford direct protection; the dynamic model also allows the effect of disrupting carriage acquisition and resulting herd effects to be considered.
- These models use Belgian data to the largest extent possible, including the latest available data, based on several complementary sources. It is the first time in Belgium that the Reference Laboratory data and hospital discharge databases have been linked to derive serogroup-specific parameters. The models also incorporate data from studies not yet published (MOSAIC data courtesy of Helen Johnson, LSHTM).
- Extensive sensitivity analyses were performed to assess the importance of uncertainty around the model parameters. Due to the current lack or conflicting evidence around the values of some parameters this was best done using univariate and multivariate (including best and worst case) scenario analyses in both models.

The limitations of this work include:

- The full vaccine characteristics are not yet known. The vaccine licensure was based on surrogates of protection, the true vaccine efficacy is largely unknown, and it is difficult to predict the likely duration of protection afforded. This is even more difficult as 4CMenB is a multi-component protein-based vaccine and responses to each component appear to wane at different rates. Furthermore, results from long-term follow-up are not yet available. These uncertain parameters are explored through scenario analyses in both models. We varied vaccine parameters mostly based on more or less favourable studies (based on SBA results) but it is possible that we did not cover the entire range of possibilities in the scenario analysis. For instance, we could expect that a much longer duration of protection conferred by infant vaccination (i.e. longer than the 36 months simulated in the high scenario) would present more favourable results. We also assumed that immunity would be acquired one month following vaccination (starting at the second dose), as no data are available after a shorter period, implying that the protection can only start at six month of age in infants (i.e. 1 month after the second dose). It is however probable that the immune response would be protective after a shorter delay, as simulated in some other studies.[101, 142] We did not run specific scenario for that because the potential difference in the number of avoided cases would be minimal (i.e. only 4 cases per year are predicted at 5 months of age and only a proportion would be effectively protected).
- The proportion of serogroup B strains that will be prevented by this multi-component vaccine is also unknown in Belgium as no MATS testing could be performed in Belgium. Furthermore, MATS strain coverage data is not a direct measure of true efficacy. However, the scenario analyses using relatively extreme range of values (50-85%) did not yield very different results, as the difference was 6 cases per year in routine infant vaccination strategy when no effect on transmission is assumed. If we assume a 30% effect on carriage, a higher coverage would still not be cost-effective for a combined strategy involving infant and adolescents (€76 500). However, adolescent strategy with lower MATS coverage has not been calculated.
- By lack of data, quality of life losses to patients during the acute phase of the illness has not been included in the models. Although the impact on QoL loss is likely to be considerable during the acute phase of the disease, its overall impact on the total QoL is likely to be small because of its short duration compared to the time horizon of the model. Quality of life losses to caregivers were not included either. Although MenB sequelae in children will have a substantial impact on their caregivers for many years, inclusion of carer QALYs is thought to have limited impact on the cost-effectiveness results due to the small number of cases in this study. A substantially higher quality of life loss for persons with IMD sequelae (from 0.074 to 0.30) was simulated in sensitivity analyses. Although this favoured the cost-effectiveness results, the vaccination strategies simulated would still not be cost-effective (e.g. €239 100 per QALY gained for routine infant vaccination instead of over €400 000 in the base case). Quality of life loss for adverse events

resulting from vaccination has not been included either (as in any of the MenB vaccine economic evaluations so far). Including it would make vaccination less attractive, also because vaccine adverse events, though relatively mild and transient, are expected to affect a large number of subjects.

- The opportunity cost of vaccine administration in the under-5 clinics (K&G-ONE) was assumed to be €10 on average, whether the vaccine is administered within a new or an existing K&G-ONE consultation. Discussion with experts in the field revealed that this cost may be underestimated. If this cost was increased this would make the cost-effectiveness of the different vaccination strategies even worse.
- In this study, estimates to derive the treatment costs per severe vaccine adverse event appeared to be higher than in other studies. Hospital stay due to any severe vaccine adverse event were attributed a unit cost of €2135 (95%CI €595 to €4642). This cost was derived by considering all Belgian hospital stays with a principal diagnosis of febrile convulsion in patients aged 0-18 years (MZG-RHM/AZV-SHA data from the Belgian Technical Cell for the years 2007-2010). Hospitalization costs were £421 for anaphylactic reaction in the UK,[81] and €1329, €2097 and €2716 for febrile convulsion, juvenile arthritis and Kawasaki disease in France.[99] Although our cost appears slightly higher than in other studies, this may simply reflect true differences in clinical practice and organization of the health care sector.
- The other factor influencing the total cost of treating vaccine adverse event, i.e. the proportion of doses leading to hospitalisation for adverse reaction in Belgian practice, was estimated at 1 per 282 doses for infants and 1 per 720 000 in adolescents in our study. This was higher than the estimates for the French model[99] – which was however based on the same studies – due to the inclusion of cases of “fever observed in the hospital” among hospitalised adverse reactions in Belgium and among hospital outpatient visits in France. We believe that our choice corresponds to the Belgian health care system. The English model used much lower rates from the MenC vaccine which presents lower reactogenicity, and OMV MenB vaccines. At that time 4CMenB safety data were not yet available. Further, the same frequency was applied to both infants and adolescents.[81]
- The dynamic model structure used does not allow for the potential negative effects of meningococcal carriage reduction, such as the loss of natural boosting or replacement by other serogroups or other pathogens, as observed for the 7-valent pneumococcal conjugate vaccine.
- The probabilistic sensitivity analysis in the static model was partial in that only cost and QoL parameters were allowed to vary according to a defined distribution instead of all uncertain parameters. However performing a probabilistic sensitivity analysis on all parameters is not likely to generate considerable simulations that would be considered favourable, as most of the simulations would remain high in the North-East quadrant of the cost-effectiveness plane.
- The dynamic model is not probabilistic, so parameter uncertainty in this model is not fully assessed. However, scenario analyses investigated the effect of a number of parameters and most other parameters were comprehensively investigated in the cohort model.
- The two mixing patterns used in the dynamic model might not fully cover the risk of carriage acquisition in young infants for whom transmission are likely to occur more in households or child care settings. However, we do not expect that more informed transmission patterns would produce different results because of the low carriage (and thus low transmission) in this group.
- No catch-up vaccination was considered in this study as this strategy was not deemed relevant by Belgian decision-makers in vaccination, due to a relatively low disease burden and high number of doses (two to three), at ages at which no vaccination or medical visit is planned. Although catch-up strategies showed high and rapid reduction of cases in other studies, number of cases increased in the long term to return to the same incidence as reached without catch-up vaccination.[81, 99]

11.3 Implications for practice

Whatever decision on 4CMenB is taken, i.e. to include it in the routine calendar, to reimburse it or to leave it simply available to those who agree to pay for it, it will have a number of implications that must be taken into account, at individual and population level.

Regardless of any cost-effectiveness criteria, if it is decided to include 4CMenB in the routine vaccine schedule, there are two main options for infant vaccination. The first one is to administer 4CMenB at different visits than the ones planned for routine vaccines to avoid the high rates of adverse events in concomitant administration, as proposed in this study for most doses. In that case, the infant vaccine schedule will become crowded, from three to five vaccination visits before 12 months of age, involving higher costs. In addition, under 5 clinics (ONE and K&G) and school services (CLB-PMS) will face operational challenges to organize these additional visits (or add vaccination to existing visits). Even in this option, the rate of high fever seems higher than for other vaccines, i.e. 3% with fever >39°C for routine vaccines vs. 6% for 4CMenB administered alone.[57] The other option is to administer 4CMenB together with routine vaccines. But the high rates of high fever will necessitate educating parents on how to manage fever (or administer prophylactic paracetamol) and this may undermine the confidence in the vaccination programme overall.

If it is decided to reimburse 4CMenB partially, accessibility will be lower compared to the routine schedule option as parents would have to pay between around €50 and €150 per infant for 3+1 doses.[t] If vaccination remains at the choice of parents on clinician advice (private market), the cost would be much higher obviously.[t] In both options, inequity will occur, as seen for PCV7 before it was introduced (2004-2006). In both cases, it is also important to warn parents that high fever may occur.

If no universal (routine) vaccination is decided, a question remains as to whether groups at high risk should be targeted for vaccination. Although there are no SBA data in this group so far, it is known that some groups may be at higher medical risk of developing IMD, such as those with complement deficiency and asplenia. Vaccination should be considered on an ad hoc basis, in discussion between clinicians and parents. In the UK, the Joint Committee on Vaccination and Immunisation (JCVI) interim decision not to introduce 4CMenB generated many reactions from clinicians, academics and meningitis charities. It is unclear whether such reactions would occur in Belgium. The pressure to use the vaccine in case of clusters or outbreaks would certainly be high, although evidence of its effectiveness in such situations is lacking or questionable.

So far (up to July 2014), there are no possibilities to monitor vaccine failures nor vaccine effectiveness as the MATS test – which should allow vaccine-preventable strains to be distinguished from others - strains – has not been made available by the vaccine manufacturer to Belgium. Other options (e.g. to get suspected vaccine failures tested in another country) have not been considered thus far. Besides this problem of availability, it is not clear to what extent the MATS test is reliable in identifying vaccine-preventable strains and it is still owned and managed by Novartis only.

Whatever decisions will be taken, it should be reminded that meningococcal disease is a devastating disease with high fatality, and has important long-term impacts on the life of those affected and their parents/caregivers. This cost-effectiveness analysis took into account some of the consequences of this disease on the health care costs and the quality of life of cases, but does not integrate the full extent of human suffering following disease. It should also be clear that decisions on vaccine policies in Belgium are based on several factors, including the impact on individuals and the society, and that cost-effectiveness is only one of these factors.

---

[t] Depending on the reimbursement category (B, C, Cs or Cx). The computation cannot be provided as the prices are not published at the time of writing this report.

11.4 Future perspective

This study is based on a high number of assumptions due to current lack of data on the vaccine effect, on clinical disease and on carriage, on the persistence of protection and on the proportion of strains covered by the vaccine. As of June 2014, no country has yet introduced universal vaccination with 4CMenB at national level. However, vaccination is being implemented locally in a few countries, whether as universal infant vaccination in some regions or as response to an increase in incidence or to outbreaks. England and Wales are also planning to introduce it providing that vaccine prices are lowered to reach cost-effectiveness. It is thus expected that some national programmes will include it in the future and that wider trials will provide better information on the effect on carriage. We can thus expect that new evidence will be generated in the future, and the predictions of this study may need to be revisited based on new data. However, the scenario analyses indicate that the key parameter that may change the results of this study would be a positive effect on MenB carriage; changes in other parameters would not make 4CMenB vaccination a cost-effective intervention in the absence of effect on carriage, as seen in the best-case analyses.

This study did not include vaccination strategies using a 2+1 dose schedule as immunogenicity data are not yet publicly available (study data due in 2015 at the earliest). At the time of writing this report, available data show a rapid waning after the three doses primary schedule and thus suggest that a 2-dose primary schedule would provide even less protection in an age of high incidence (before booster). However, this schedule has been selected for future implementation in England & Wales and immunogenicity data are should be available in the near future. It is thus likely that the first available and robust effectiveness data will be based on a 2+1 vaccination status in that country. Although this schedule was not simulated in our study, an indication of the potential difference in cost-effectiveness results between the 3+1 schedule of this study and a 2+1 schedule can be provided by England & Wales prediction: moving from a 2, 3, 4 and 12 month to a 2, 4 and 12 month strategy in the England base case dynamic model (30% vaccine efficacy against carriage acquisition) reduced the cost per QALY gained by 26%.

Other vaccines to prevent MenB disease are being developed. The next expected vaccine is the bivalent recombinant lipoprotein 2086 vaccine from Pfizer, which entered in Phase III in 2012, and showed favourable SBA results although not indicated for infants.[100] Our study is only based on characteristics of the 4CMenB vaccine and cannot be extended to other MenB vaccines.

12 CONCLUSIONS

Meningococcal disease is a devastating disease, which can be rapidly fatal and has important long-term impact on the life of those affected and their parents/caregivers. This cost-effectiveness study did not integrate the full extent of human suffering due to IMD. Decisions on vaccine policies are obviously based on several factors, including impact on individuals and the society, and cost-effectiveness is only one of these factors. Nevertheless, cost-effectiveness models throw a useful light on the opportunity (if any) of the different vaccination options.

These models have shown that the introduction of a routine immunisation programme with 4CMenB can reduce meningococcal disease in Belgium, but involves a high frequency of adverse events, though principally mild and transient, following vaccination.

If the vaccine does not disrupt group B carriage the greatest number of cases are averted through routine combined infant and adolescent routine vaccination policy. However the cost per quality adjusted life year gained of such a strategy is above €300 000.

If the vaccine is able to disrupt carriage acquisition, greater decreases in cases can be achieved through vaccination. In the short-term, this is best achieved through routine infant vaccination, and in the long term strategies including routine adolescent vaccination result in higher and sustained reductions in cases over the long term. Infant strategies alone, with or without indirect effects, have limited impact and cannot be considered cost-effective.

Most strategies considered (including scenario analyses) resulted in very high costs per QALY gained, over €100 000. Only a few analyses assuming 30% vaccine efficacy against carriage acquisition in the dynamic model presented more favourable cost-effective ratios. First, routine adolescent vaccination alone presented cost-effectiveness ratios that are similar to those estimated for other vaccines recently introduced. Second, infant and adolescent vaccination combined presented cost per QALY gained below €40 000 only under high incidence and case fatality or ‘best case’ assumptions. It is important to note, however, that in the dynamic model, the use of continuous vaccination (100 birth cohorts) and differential discounting results in vaccination appearing more economically favourable than in the static model. Besides the effect on carriage, the epidemiological and economic models were sensitive to a number of the parameters considered, particularly: disease incidence, case-fatality rate, vaccine profile, vaccine uptake, the cost of the vaccination programme, population mixing, carriage prevalence and the discounting rate used.

The results of this study may need to be revisited when new evidence becomes available, in particular the effect of 4CMenB on carriage.

APPENDICES

APPENDIX 1. REVIEW OF THE LITERATURE ON QUALITY OF LIFE

Appendix 1.1. Search strategies

Table 50 – QoL search strategies for CRD HTA and CRD NHS EED

Date	**24/09/2013**		
Database	**CRD HTA & CRD NHS EED**		
Date covered	**No restriction**		
Search strategy	#	Searches	**Results**
	1	MeSH DESCRIPTOR Neisseria meningitidis EXPLODE ALL TREES	4
	2	MeSH DESCRIPTOR Meningococcal Infections EXPLODE ALL TREES	23
	3	MeSH DESCRIPTOR Meningitis, Meningococcal EXPLODE ALL TREES	7
	4	#1 OR #2 OR #3	23
	5	#4 FROM 2009 TO 2013	6
Note			

Table 51 – QoL search strategy for Medline (OVID)

Date	**24/09/2013**		
Database	**Ovid MEDLINE(R)**		
Date covered	**1946 to September Week 2 2013**		
Search strategy	**#**	**Searches**	**Results**
	1	exp Neisseria meningitidis/	8359
	2	exp Meningococcal Infections/	9752
	3	exp Meningitis, Meningococcal/	4971
	4	1 or 2 or 3	13808
	5	"Quality of Life"/	118786
	6	“Quality-Adjusted Life Years”/	7191
	7	"Value of Life"/	5490
	8	(health utilit* index or HUI).mp.	1070
	9	(short form health survey or SF-36 or SF-6D).mp.	13812

	10	(euroqol or EQ-5D).mp.	3583
	11	(qaly or quality-adjusted life year* or quality adjusted life year).mp.	9811
	12	standard gamble.mp.	656
	13	(time-trade off or time trade-off or TTO).mp.	978
	14	exp Cost-Benefit Analysis/	61052
	15	exp "Costs and Cost Analysis"/	181993
	16	(cost-effectiveness or cost-utility).mp.	34322
	17	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	313583
	18	4 and 17	114
	19	limit 18 to yr="2009 -Current"	27
Note	mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier		

Table 52 – QoL search strategy for "Pre" Medline (OVID)

Date	**24/09/2013**		
Database	**Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations**		
Date covered	**September 23, 2013**		
Search strategy	**#**	**Searches**	**Results**
	1	["Quality of Life"/]	0
	2	[Quality-Adjusted Life Years/]	0
	3	["Value of Life"/]	0
	4	(health utilit* index or HUI).mp.	86
	5	(short form health survey or SF-36 or SF-6D).mp.	999
	6	(euroqol or EQ-5D).mp.	408
	7	(qaly or quality-adjusted life year* or quality adjusted life year).mp.	588
	8	standard gamble.mp.	32
	9	(time-trade off or time trade-off or TTO).mp.	79
	10	[exp Cost-Benefit Analysis/]	0
	11	[exp "Costs and Cost Analysis"/]	0
	12	(cost-effectiveness or cost-utility).mp.	2709
	13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	4199
	14	neisseria meningitidis.mp.	227
	15	meningococcal infection*.mp.	42
	16	meningococcal disease*.mp.	114
	17	meningo*.mp.	1085
	18	14 or 15 or 16 or 17	1170
	19	13 and 18	5
	20	limit 19 to yr="2009 -Current"	3
Note	mp=heading words, abstract, title, country as subject		

Table 53 – QoL search strategy for PsycINFO (OVID)

Date	**24/09/2013**		
Database	**PsycINFO**		
Date covered	**2002 to September Week 3 2013**		
Search strategy	**#**	**Searches**	**Results**
	1	"Quality of Life"/	18986
	2	"Quality-Adjusted Life Years"/	0
	3	"Value of Life"/	0
	4	(health utilit* index or HUI).mp.	530
	5	(short form health survey or SF-36 or SF-6D).mp.	7039
	6	(euroqol or EQ-5D).mp.	1219
	7	(qaly or quality-adjusted life year* or quality adjusted life year).mp.	669
	8	standard gamble.mp.	126
	9	(time-trade off or time trade-off or TTO).mp.	155
	10	exp Cost-Benefit Analysis/	0
	11	exp "Costs and Cost Analysis"/	11876
	12	(cost-effectiveness or cost-utility).mp.	3684
	13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	36757
	14	neisseria meningitidis.mp.	23
	15	meningococcal infection*.mp.	2
	16	meningococcal disease*.mp.	26
	17	meningo*.mp.	394
	18	14 or 15 or 16 or 17	404
	19	13 and 18	9
	20	limit 19 to yr="2009 -Current"	3
Note	mp=heading words, abstract, title, country as subject		

Table 54 – QoL search strategy for Econlit (OVID)

Date	**24/09/2013**		
Database	**Econlit**		
Date covered	**1961 to August 2013**		
Search strategy	**#**	**Searches**	**Results**
	1	["Quality of Life"/]	0
	2	[Quality-Adjusted Life Years/]	0
	3	["Value of Life"/]	0
	4	(health utilit* index or HUI).mp.	74
	5	(short form health survey or SF-36 or SF-6D).mp.	51
	6	(euroqol or EQ-5D).mp.	88
	7	(qaly or quality-adjusted life year* or quality adjusted life year).mp.	308
	8	standard gamble.mp.	67
	9	(time-trade off or time trade-off or TTO).mp.	116
	10	[exp Cost-Benefit Analysis/]	0
	11	[exp "Costs and Cost Analysis"/]	0
	12	(cost-effectiveness or cost-utility).mp.	1867
	13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	2277
	14	neisseria meningitidis.mp.	1
	15	meningococcal infection*.mp.	0
	16	meningococcal disease*.mp.	3
	17	meningo*.mp.	5
	18	14 or 15 or 16 or 17	6
	19	13 and 18	0
Note	mp=heading words, abstract, title, country as subject		

Table 55 – QoL search strategy for Embase

Date	**24/09/2013**		
Database	**Embase**		
Date covered	-		
Search strategy	**#**	**Searches**	**Results**
	1	'neisseria meningitidis'/exp	12305
	2	'meningococcosis'/exp	10825
	3	'meningococcemia'/exp	1308
	4	'epidemic meningitis'/exp	3894
	5	#1 OR #2 OR #3 OR #4	18999
	6	'quality adjusted life year'/exp	10938
	7	'quality of life'/exp	243245
	8	'economic evaluation'/exp	201692
	10	'sf-36':ab,ti	17039
	14	'sf-6d':ab,ti	535
	15	'eq-5d':ab,ti	4250
	16	'tto':ab,ti	812
	17	'euroqol':ab,ti	2747
	18	'hui':ab,ti	1776
	19	'qaly':ab,ti	6334
	20	#6 OR #7 OR #8 OR #10 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	428127
	21	#5 AND #20	311
	22	#21 AND (2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py)	129
	23	#21 AND (2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py) AND ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it)	35
	24	#21 AND (2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py) AND 'nonhuman'/de	26
	25	#23 OR #24	56
	26	#22 NOT #25	73

Appendix 1.2. Selection of the studies

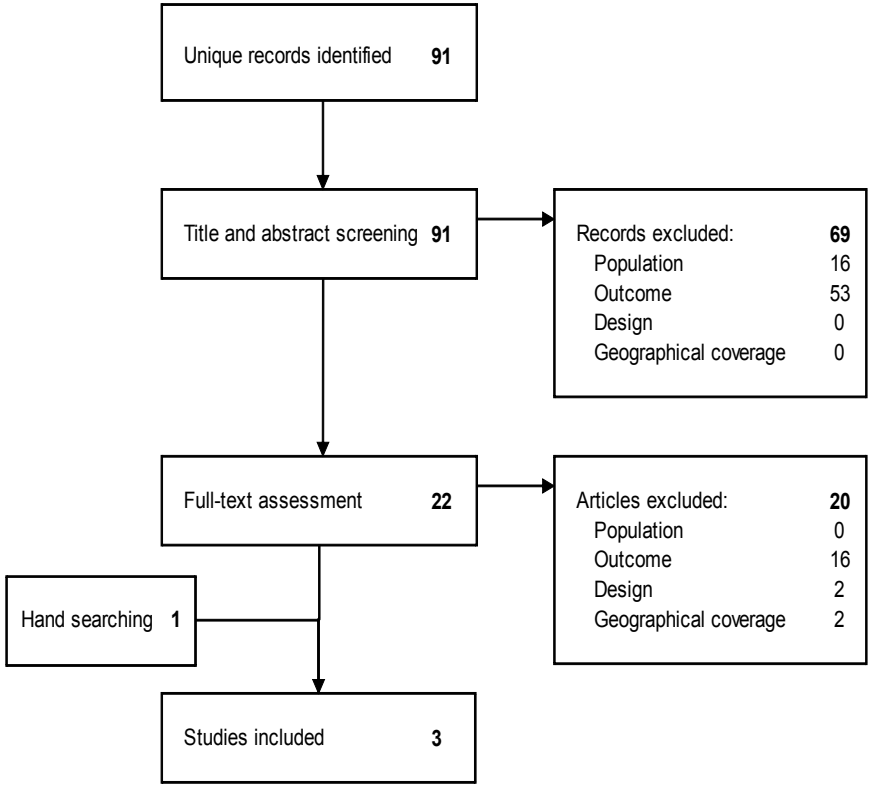
The searches on the electronic databases returned 112 citations. After exclusion of 21 duplicates, 91 unique citations were left.

Table 56 – QoL references identified by the electronic searches

Electronic database	References identified (2009 to September 2013)
CDR HTA & NHS EED	6
Medline (OVID)	27
Pre-Medline (OVID)	3
PsycINFO	3
Econlit	0
EMBASE	73
Total references identified	112
Duplicates	21
Total	**91**

Of the 91 unique records identified, 69 were discarded based on title and abstract, leaving 22 references for full-text evaluation. Another 20 references were excluded at this stage, mostly because of they did not report QoL scores (outcome criteria). Many of those excluded references were cost-utility analyses in which QoL values were not directly estimated but selected from the literature (secondary studies). We identified two primary studies reporting original QoL weights on the burden of meningococcal diseases. An additional QoL study was further added, identified through personal communication with one of the co-authors of this report (Christensen H.) who agreed to share the data in confidentiality. Although the QoL results of this study are still unpublished at the time of writing, its methodology is already published and judged highly relevant to our purpose.[32]

Figure 27 – Flowchart of the QoL literature selection process



APPENDIX 2. ICD-9-CM CODES

Table 57 – ICD-9-CM codes used to select the Hospital Clinical Records

ICD-9-CM	Description
036	Meningococcal infection
036.0	Meningococcal meningitis Cerebrospinal fever (meningococcal) Meningitis: cerebrospinal epidemic
036.1	Meningococcal encephalitis
036.2	Meningococcemia Meningococcal septicemia
036.3	Waterhouse-Friderichsen syndrome, meningococcal Meningococcal hemorrhagic adrenalitis Meningococcic adrenal syndrome Waterhouse-Friderichsen syndrome NOS (not otherwise specified)
036.4	Meningococcal carditis
036.40	Meningococcal carditis, unspecified
036.41	Meningococcal pericarditis
036.42	Meningococcal endocarditis
036.43	Meningococcal myocarditis
036.8	Other specified meningococcal infections
036.81	Meningococcal optic neuritis
036.82	Meningococcal arthropathy
036.89	Other
036.9	Meningococcal infection, unspecified

APPENDIX 3. COSTS OF IMD PATIENTS WITH SEQUELAE

Appendix 3.1. Serogroup B

Table 58 – Average age-specific cost of care per IMD patient with sequelae, serogroup B, base case (Health care payer costs, €2012 values)

Age of cohort (years)	Acute one-off costs						Lifelong annual costs					
	Base case	Distribution	Alpha	Beta	Lower 95%CI	Upper 95%CI	Base case	Distribution	Alpha	Beta	Lower 95%CI	Upper 95%CI
0	1434	Gamma	44.44	32.26	1044	1885	3355	Gamma	44.44	75.49	2442	4411
1	1434	Gamma	44.44	32.26	1044	1885	3355	Gamma	44.44	75.49	2442	4411
2	1434	Gamma	44.44	32.26	1044	1885	3355	Gamma	44.44	75.49	2442	4411
3	1434	Gamma	44.44	32.26	1044	1885	3355	Gamma	44.44	75.49	2442	4411
4	1434	Gamma	44.44	32.26	1044	1885	3355	Gamma	44.44	75.49	2442	4411
5	91	Gamma	44.44	2.04	66	119	3336	Gamma	44.44	75.06	2428	4386
6	91	Gamma	44.44	2.04	66	119	3318	Gamma	44.44	74.65	2415	4362
7	91	Gamma	44.44	2.04	66	119	3306	Gamma	44.44	74.39	2407	4347
8	91	Gamma	44.44	2.04	66	119	3297	Gamma	44.44	74.19	2400	4335
9	91	Gamma	44.44	2.04	66	119	3294	Gamma	44.44	74.12	2398	4331
10	91	Gamma	44.44	2.04	66	119	3290	Gamma	44.44	74.02	2395	4325
11	91	Gamma	44.44	2.04	66	119	3288	Gamma	44.44	73.99	2393	4323
12	91	Gamma	44.44	2.04	66	119	3286	Gamma	44.44	73.93	2391	4320
13	91	Gamma	44.44	2.04	66	119	3279	Gamma	44.44	73.78	2387	4311
14	91	Gamma	44.44	2.04	66	119	3274	Gamma	44.44	73.66	2383	4304
15	91	Gamma	44.44	2.04	66	119	3267	Gamma	44.44	73.51	2378	4295
16	91	Gamma	44.44	2.04	66	119	3255	Gamma	44.44	73.23	2369	4279
17	91	Gamma	44.44	2.04	66	119	3244	Gamma	44.44	73.00	2361	4265
18	45	Gamma	44.44	1.02	33	60	3228	Gamma	44.44	72.63	2349	4244
19	45	Gamma	44.44	1.02	33	60	3215	Gamma	44.44	72.33	2340	4226
20	3445	Gamma	44.44	77.52	2508	4529	3225	Gamma	44.44	72.56	2347	4240
21	3445	Gamma	44.44	77.52	2508	4529	3228	Gamma	44.44	72.64	2350	4244
22	3445	Gamma	44.44	77.52	2508	4529	3238	Gamma	44.44	72.86	2357	4257
23	3445	Gamma	44.44	77.52	2508	4529	3243	Gamma	44.44	72.96	2360	4263
24	3445	Gamma	44.44	77.52	2508	4529	3247	Gamma	44.44	73.07	2364	4269
25	3445	Gamma	44.44	77.52	2508	4529	3247	Gamma	44.44	73.07	2364	4269
26	3445	Gamma	44.44	77.52	2508	4529	3247	Gamma	44.44	73.07	2364	4269
27	3445	Gamma	44.44	77.52	2508	4529	3250	Gamma	44.44	73.12	2365	4272
28	3445	Gamma	44.44	77.52	2508	4529	3253	Gamma	44.44	73.18	2367	4276
29	3445	Gamma	44.44	77.52	2508	4529	3253	Gamma	44.44	73.18	2367	4276

Age of cohort (years)	Acute one-off costs						Lifelong annual costs					
	Base case	Distribution	Alpha	Beta	Lower 95%CI	Upper 95%CI	Base case	Distribution	Alpha	Beta	Lower 95%CI	Upper 95%CI
30	3445	Gamma	44.44	77.52	2508	4529	3253	Gamma	44.44	73.18	2367	4276
31	3445	Gamma	44.44	77.52	2508	4529	3255	Gamma	44.44	73.23	2369	4279
32	3445	Gamma	44.44	77.52	2508	4529	3255	Gamma	44.44	73.23	2369	4279
33	3445	Gamma	44.44	77.52	2508	4529	3255	Gamma	44.44	73.23	2369	4279
34	3445	Gamma	44.44	77.52	2508	4529	3255	Gamma	44.44	73.23	2369	4279
35	3445	Gamma	44.44	77.52	2508	4529	3255	Gamma	44.44	73.23	2369	4279
36	3445	Gamma	44.44	77.52	2508	4529	3255	Gamma	44.44	73.23	2369	4279
37	3445	Gamma	44.44	77.52	2508	4529	3255	Gamma	44.44	73.23	2369	4279
38	3445	Gamma	44.44	77.52	2508	4529	3256	Gamma	44.44	73.25	2370	4280
39	3445	Gamma	44.44	77.52	2508	4529	3265	Gamma	44.44	73.47	2377	4293
40	3445	Gamma	44.44	77.52	2508	4529	3265	Gamma	44.44	73.47	2377	4293
41	3445	Gamma	44.44	77.52	2508	4529	3265	Gamma	44.44	73.47	2377	4293
42	3445	Gamma	44.44	77.52	2508	4529	3265	Gamma	44.44	73.47	2377	4293
43	3445	Gamma	44.44	77.52	2508	4529	3271	Gamma	44.44	73.59	2381	4300
44	3445	Gamma	44.44	77.52	2508	4529	3272	Gamma	44.44	73.63	2382	4302
45	3445	Gamma	44.44	77.52	2508	4529	3272	Gamma	44.44	73.63	2382	4302
46	3445	Gamma	44.44	77.52	2508	4529	3275	Gamma	44.44	73.69	2384	4306
47	3445	Gamma	44.44	77.52	2508	4529	3275	Gamma	44.44	73.69	2384	4306
48	3445	Gamma	44.44	77.52	2508	4529	3277	Gamma	44.44	73.73	2385	4308
49	3445	Gamma	44.44	77.52	2508	4529	3279	Gamma	44.44	73.78	2387	4311
50	3445	Gamma	44.44	77.52	2508	4529	3279	Gamma	44.44	73.78	2387	4311
51	3445	Gamma	44.44	77.52	2508	4529	3279	Gamma	44.44	73.78	2387	4311
52	3445	Gamma	44.44	77.52	2508	4529	3279	Gamma	44.44	73.78	2387	4311
53	3445	Gamma	44.44	77.52	2508	4529	3282	Gamma	44.44	73.84	2389	4314
54	3445	Gamma	44.44	77.52	2508	4529	3282	Gamma	44.44	73.84	2389	4314
55	3445	Gamma	44.44	77.52	2508	4529	3284	Gamma	44.44	73.88	2390	4317
56	3445	Gamma	44.44	77.52	2508	4529	3286	Gamma	44.44	73.93	2391	4320
57	3445	Gamma	44.44	77.52	2508	4529	3286	Gamma	44.44	73.93	2391	4320
58	3445	Gamma	44.44	77.52	2508	4529	3288	Gamma	44.44	73.99	2394	4323
59	3445	Gamma	44.44	77.52	2508	4529	3293	Gamma	44.44	74.08	2397	4329
60	3445	Gamma	44.44	77.52	2508	4529	3293	Gamma	44.44	74.08	2397	4329
61	3445	Gamma	44.44	77.52	2508	4529	3293	Gamma	44.44	74.08	2397	4329
62	3445	Gamma	44.44	77.52	2508	4529	3293	Gamma	44.44	74.08	2397	4329
63	3445	Gamma	44.44	77.52	2508	4529	3293	Gamma	44.44	74.08	2397	4329
64	3445	Gamma	44.44	77.52	2508	4529	3293	Gamma	44.44	74.08	2397	4329
65	3445	Gamma	44.44	77.52	2508	4529	3293	Gamma	44.44	74.08	2397	4329

Age of cohort (years)	Acute one-off costs						Lifelong annual costs					
	Base case	Distribution	Alpha	Beta	Lower 95%CI	Upper 95%CI	Base case	Distribution	Alpha	Beta	Lower 95%CI	Upper 95%CI
66	3445	Gamma	44.44	77.52	2508	4529	3298	Gamma	44.44	74.21	2401	4336
67	3445	Gamma	44.44	77.52	2508	4529	3298	Gamma	44.44	74.21	2401	4336
68	3445	Gamma	44.44	77.52	2508	4529	3298	Gamma	44.44	74.21	2401	4336
69	3445	Gamma	44.44	77.52	2508	4529	3301	Gamma	44.44	74.27	2403	4340
70	3445	Gamma	44.44	77.52	2508	4529	3304	Gamma	44.44	74.34	2405	4344
71	3445	Gamma	44.44	77.52	2508	4529	3304	Gamma	44.44	74.34	2405	4344
72	3445	Gamma	44.44	77.52	2508	4529	3304	Gamma	44.44	74.34	2405	4344
73	3445	Gamma	44.44	77.52	2508	4529	3308	Gamma	44.44	74.43	2408	4349
74	3445	Gamma	44.44	77.52	2508	4529	3309	Gamma	44.44	74.45	2409	4350
75	3445	Gamma	44.44	77.52	2508	4529	3309	Gamma	44.44	74.45	2409	4350
76	3445	Gamma	44.44	77.52	2508	4529	3309	Gamma	44.44	74.45	2409	4350
77	3445	Gamma	44.44	77.52	2508	4529	3309	Gamma	44.44	74.45	2409	4350
78	3445	Gamma	44.44	77.52	2508	4529	3312	Gamma	44.44	74.51	2410	4354
79	3445	Gamma	44.44	77.52	2508	4529	3314	Gamma	44.44	74.57	2412	4357
80	3445	Gamma	44.44	77.52	2508	4529	3314	Gamma	44.44	74.57	2412	4357
81	3445	Gamma	44.44	77.52	2508	4529	3322	Gamma	44.44	74.75	2418	4368
82	3445	Gamma	44.44	77.52	2508	4529	3328	Gamma	44.44	74.88	2422	4375
83	3445	Gamma	44.44	77.52	2508	4529	3330	Gamma	44.44	74.93	2424	4378
84	3445	Gamma	44.44	77.52	2508	4529	3330	Gamma	44.44	74.93	2424	4378
85	3445	Gamma	44.44	77.52	2508	4529	3330	Gamma	44.44	74.93	2424	4378
86	3445	Gamma	44.44	77.52	2508	4529	3330	Gamma	44.44	74.93	2424	4378
87	3445	Gamma	44.44	77.52	2508	4529	3330	Gamma	44.44	74.93	2424	4378
88	3445	Gamma	44.44	77.52	2508	4529	3330	Gamma	44.44	74.93	2424	4378
89	3445	Gamma	44.44	77.52	2508	4529	3330	Gamma	44.44	74.93	2424	4378
90	3445	Gamma	44.44	77.52	2508	4529	3346	Gamma	44.44	75.28	2435	4399
91	3445	Gamma	44.44	77.52	2508	4529	3346	Gamma	44.44	75.28	2435	4399
92	3445	Gamma	44.44	77.52	2508	4529	3346	Gamma	44.44	75.28	2435	4399
93	3445	Gamma	44.44	77.52	2508	4529	3346	Gamma	44.44	75.28	2435	4399
94	3445	Gamma	44.44	77.52	2508	4529	3346	Gamma	44.44	75.28	2435	4399
95	3445	Gamma	44.44	77.52	2508	4529	3346	Gamma	44.44	75.28	2435	4399
96	3445	Gamma	44.44	77.52	2508	4529	3346	Gamma	44.44	75.28	2435	4399
97	3445	Gamma	44.44	77.52	2508	4529	3346	Gamma	44.44	75.28	2435	4399
98	3445	Gamma	44.44	77.52	2508	4529	3346	Gamma	44.44	75.28	2435	4399
99	3445	Gamma	44.44	77.52	2508	4529	3346	Gamma	44.44	75.28	2435	4399
100	3445	Gamma	44.44	77.52	2508	4529	3346	Gamma	44.44	75.28	2435	4399

Appendix 3.2. All serogroups

Table 59 – Average age-specific cost of care per IMD patient with sequelae, all serogroups, scenario analysis (Health care payer costs, €2012 values)

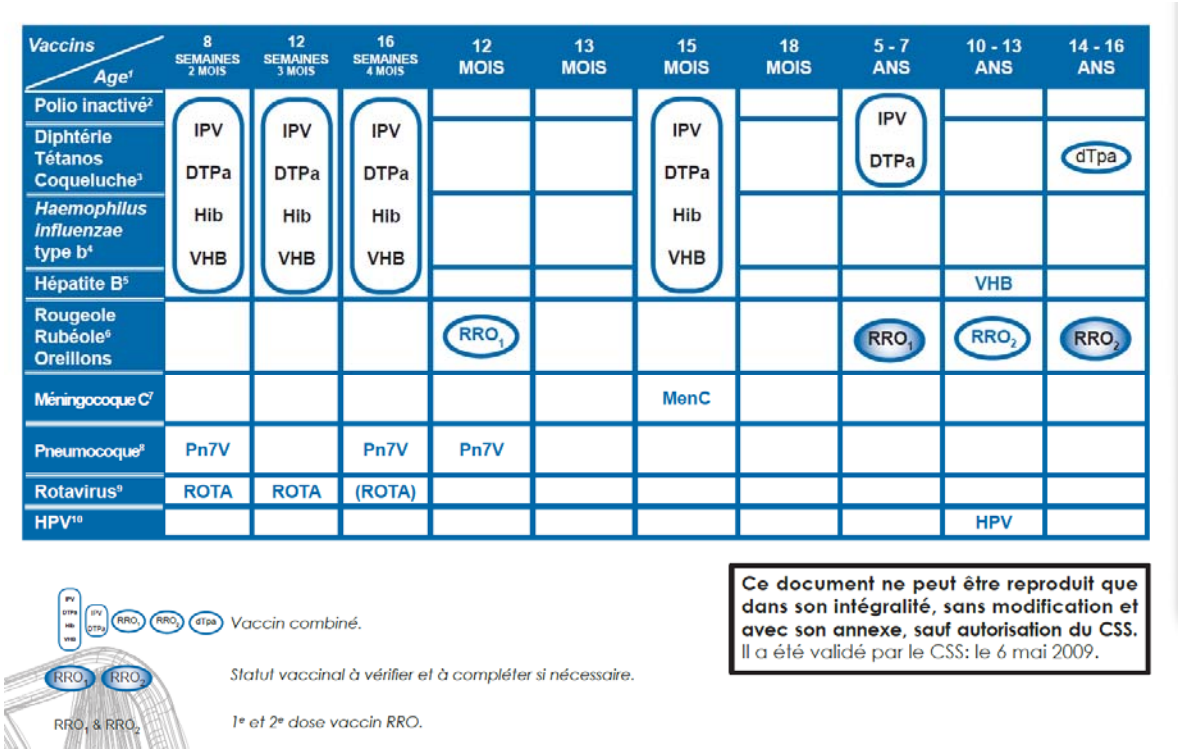
Age of cohort (years)	Acute one-off costs						Lifelong annual costs					
	Mean	Distribution	Alpha	Beta	Lower 95%CI	Upper 95%CI	Mean	Distribution	Alpha	Beta	Lower 95%CI	Upper 95%CI
0	676	Gamma	44.44	15.21	492	889	2686	Gamma	44.44	60.42	1955	3531
1	676	Gamma	44.44	15.21	492	889	2686	Gamma	44.44	60.42	1955	3531
2	676	Gamma	44.44	15.21	492	889	2686	Gamma	44.44	60.42	1955	3531
3	676	Gamma	44.44	15.21	492	889	2686	Gamma	44.44	60.42	1955	3531
4	676	Gamma	44.44	15.21	492	889	2686	Gamma	44.44	60.42	1955	3531
5	1699	Gamma	44.44	38.23	1237	2234	2794	Gamma	44.44	62.86	2034	3673
6	1699	Gamma	44.44	38.23	1237	2234	2899	Gamma	44.44	65.22	2110	3811
7	1699	Gamma	44.44	38.23	1237	2234	2963	Gamma	44.44	66.67	2157	3896
8	1699	Gamma	44.44	38.23	1237	2234	3033	Gamma	44.44	68.24	2207	3987
9	1699	Gamma	44.44	38.23	1237	2234	3058	Gamma	44.44	68.80	2226	4020
10	1699	Gamma	44.44	38.23	1237	2234	3083	Gamma	44.44	69.36	2244	4053
11	1699	Gamma	44.44	38.23	1237	2234	3091	Gamma	44.44	69.54	2250	4063
12	1699	Gamma	44.44	38.23	1237	2234	3107	Gamma	44.44	69.90	2261	4084
13	1699	Gamma	44.44	38.23	1237	2234	3154	Gamma	44.44	70.96	2296	4146
14	1699	Gamma	44.44	38.23	1237	2234	3183	Gamma	44.44	71.62	2317	4185
15	1699	Gamma	44.44	38.23	1237	2234	3219	Gamma	44.44	72.42	2343	4231
16	1699	Gamma	44.44	38.23	1237	2234	3285	Gamma	44.44	73.91	2391	4319
17	1699	Gamma	44.44	38.23	1237	2234	3370	Gamma	44.44	75.82	2453	4430
18	1651	Gamma	44.44	37.15	1202	2171	3463	Gamma	44.44	77.92	2521	4553
19	1651	Gamma	44.44	37.15	1202	2171	3541	Gamma	44.44	79.66	2577	4655
20	3689	Gamma	44.44	83.00	2685	4850	3555	Gamma	44.44	79.99	2588	4674
21	3689	Gamma	44.44	83.00	2685	4850	3563	Gamma	44.44	80.17	2593	4684
22	3689	Gamma	44.44	83.00	2685	4850	3574	Gamma	44.44	80.41	2601	4699
23	3689	Gamma	44.44	83.00	2685	4850	3579	Gamma	44.44	80.53	2605	4706
24	3689	Gamma	44.44	83.00	2685	4850	3585	Gamma	44.44	80.65	2609	4713
25	3689	Gamma	44.44	83.00	2685	4850	3585	Gamma	44.44	80.65	2609	4713
26	3689	Gamma	44.44	83.00	2685	4850	3595	Gamma	44.44	80.88	2616	4726
27	3689	Gamma	44.44	83.00	2685	4850	3597	Gamma	44.44	80.94	2618	4729
28	3689	Gamma	44.44	83.00	2685	4850	3602	Gamma	44.44	81.04	2622	4735
29	3689	Gamma	44.44	83.00	2685	4850	3607	Gamma	44.44	81.15	2625	4742
30	3689	Gamma	44.44	83.00	2685	4850	3607	Gamma	44.44	81.15	2625	4742
31	3689	Gamma	44.44	83.00	2685	4850	3609	Gamma	44.44	81.20	2627	4745
32	3689	Gamma	44.44	83.00	2685	4850	3616	Gamma	44.44	81.36	2632	4754

Age of cohort (years)	Acute one-off costs						Lifelong annual costs					
	Mean	Distribution	Alpha	Beta	Lower 95%CI	Upper 95%CI	Mean	Distribution	Alpha	Beta	Lower 95%CI	Upper 95%CI
33	3689	Gamma	44.44	83.00	2685	4850	3616	Gamma	44.44	81.36	2632	4754
34	3689	Gamma	44.44	83.00	2685	4850	3621	Gamma	44.44	81.47	2635	4760
35	3689	Gamma	44.44	83.00	2685	4850	3621	Gamma	44.44	81.47	2635	4760
36	3689	Gamma	44.44	83.00	2685	4850	3621	Gamma	44.44	81.47	2635	4760
37	3689	Gamma	44.44	83.00	2685	4850	3623	Gamma	44.44	81.52	2637	4763
38	3689	Gamma	44.44	83.00	2685	4850	3625	Gamma	44.44	81.56	2638	4766
39	3689	Gamma	44.44	83.00	2685	4850	3635	Gamma	44.44	81.79	2646	4779
40	3689	Gamma	44.44	83.00	2685	4850	3635	Gamma	44.44	81.79	2646	4779
41	3689	Gamma	44.44	83.00	2685	4850	3639	Gamma	44.44	81.88	2649	4784
42	3689	Gamma	44.44	83.00	2685	4850	3639	Gamma	44.44	81.88	2649	4784
43	3689	Gamma	44.44	83.00	2685	4850	3645	Gamma	44.44	82.01	2653	4792
44	3689	Gamma	44.44	83.00	2685	4850	3647	Gamma	44.44	82.05	2654	4795
45	3689	Gamma	44.44	83.00	2685	4850	3647	Gamma	44.44	82.05	2654	4795
46	3689	Gamma	44.44	83.00	2685	4850	3652	Gamma	44.44	82.18	2658	4802
47	3689	Gamma	44.44	83.00	2685	4850	3654	Gamma	44.44	82.22	2660	4804
48	3689	Gamma	44.44	83.00	2685	4850	3656	Gamma	44.44	82.26	2661	4807
49	3689	Gamma	44.44	83.00	2685	4850	3660	Gamma	44.44	82.35	2664	4812
50	3689	Gamma	44.44	83.00	2685	4850	3662	Gamma	44.44	82.39	2665	4814
51	3689	Gamma	44.44	83.00	2685	4850	3669	Gamma	44.44	82.56	2671	4824
52	3689	Gamma	44.44	83.00	2685	4850	3679	Gamma	44.44	82.77	2678	4837
53	3689	Gamma	44.44	83.00	2685	4850	3683	Gamma	44.44	82.86	2680	4842
54	3689	Gamma	44.44	83.00	2685	4850	3687	Gamma	44.44	82.95	2683	4847
55	3689	Gamma	44.44	83.00	2685	4850	3688	Gamma	44.44	82.99	2685	4849
56	3689	Gamma	44.44	83.00	2685	4850	3690	Gamma	44.44	83.04	2686	4852
57	3689	Gamma	44.44	83.00	2685	4850	3692	Gamma	44.44	83.08	2688	4855
58	3689	Gamma	44.44	83.00	2685	4850	3697	Gamma	44.44	83.18	2691	4860
59	3689	Gamma	44.44	83.00	2685	4850	3701	Gamma	44.44	83.27	2694	4865
60	3689	Gamma	44.44	83.00	2685	4850	3701	Gamma	44.44	83.27	2694	4865
61	3689	Gamma	44.44	83.00	2685	4850	3701	Gamma	44.44	83.27	2694	4865
62	3689	Gamma	44.44	83.00	2685	4850	3705	Gamma	44.44	83.36	2697	4871
63	3689	Gamma	44.44	83.00	2685	4850	3709	Gamma	44.44	83.46	2700	4877
64	3689	Gamma	44.44	83.00	2685	4850	3709	Gamma	44.44	83.46	2700	4877
65	3689	Gamma	44.44	83.00	2685	4850	3709	Gamma	44.44	83.46	2700	4877
66	3689	Gamma	44.44	83.00	2685	4850	3715	Gamma	44.44	83.58	2704	4884
67	3689	Gamma	44.44	83.00	2685	4850	3715	Gamma	44.44	83.58	2704	4884
68	3689	Gamma	44.44	83.00	2685	4850	3715	Gamma	44.44	83.58	2704	4884

Age of cohort (years)	Acute one-off costs						Lifelong annual costs					
	Mean	Distribution	Alpha	Beta	Lower 95%CI	Upper 95%CI	Mean	Distribution	Alpha	Beta	Lower 95%CI	Upper 95%CI
69	3689	Gamma	44.44	83.00	2685	4850	3718	Gamma	44.44	83.65	2706	4888
70	3689	Gamma	44.44	83.00	2685	4850	3723	Gamma	44.44	83.77	2710	4895
71	3689	Gamma	44.44	83.00	2685	4850	3726	Gamma	44.44	83.83	2712	4898
72	3689	Gamma	44.44	83.00	2685	4850	3729	Gamma	44.44	83.90	2714	4902
73	3689	Gamma	44.44	83.00	2685	4850	3735	Gamma	44.44	84.03	2718	4910
74	3689	Gamma	44.44	83.00	2685	4850	3738	Gamma	44.44	84.10	2721	4914
75	3689	Gamma	44.44	83.00	2685	4850	3747	Gamma	44.44	84.30	2727	4926
76	3689	Gamma	44.44	83.00	2685	4850	3753	Gamma	44.44	84.44	2731	4934
77	3689	Gamma	44.44	83.00	2685	4850	3759	Gamma	44.44	84.57	2736	4941
78	3689	Gamma	44.44	83.00	2685	4850	3768	Gamma	44.44	84.77	2742	4953
79	3689	Gamma	44.44	83.00	2685	4850	3774	Gamma	44.44	84.91	2747	4961
80	3689	Gamma	44.44	83.00	2685	4850	3777	Gamma	44.44	84.99	2749	4966
81	3689	Gamma	44.44	83.00	2685	4850	3784	Gamma	44.44	85.15	2755	4975
82	3689	Gamma	44.44	83.00	2685	4850	3792	Gamma	44.44	85.32	2760	4985
83	3689	Gamma	44.44	83.00	2685	4850	3796	Gamma	44.44	85.42	2763	4991
84	3689	Gamma	44.44	83.00	2685	4850	3796	Gamma	44.44	85.42	2763	4991
85	3689	Gamma	44.44	83.00	2685	4850	3801	Gamma	44.44	85.53	2767	4997
86	3689	Gamma	44.44	83.00	2685	4850	3801	Gamma	44.44	85.53	2767	4997
87	3689	Gamma	44.44	83.00	2685	4850	3807	Gamma	44.44	85.67	2771	5006
88	3689	Gamma	44.44	83.00	2685	4850	3807	Gamma	44.44	85.67	2771	5006
89	3689	Gamma	44.44	83.00	2685	4850	3816	Gamma	44.44	85.86	2778	5017
90	3689	Gamma	44.44	83.00	2685	4850	3829	Gamma	44.44	86.16	2787	5034
91	3689	Gamma	44.44	83.00	2685	4850	3829	Gamma	44.44	86.16	2787	5034
92	3689	Gamma	44.44	83.00	2685	4850	3829	Gamma	44.44	86.16	2787	5034
93	3689	Gamma	44.44	83.00	2685	4850	3829	Gamma	44.44	86.16	2787	5034
94	3689	Gamma	44.44	83.00	2685	4850	3829	Gamma	44.44	86.16	2787	5034
95	3689	Gamma	44.44	83.00	2685	4850	3869	Gamma	44.44	87.04	2816	5086
96	3689	Gamma	44.44	83.00	2685	4850	3869	Gamma	44.44	87.04	2816	5086
97	3689	Gamma	44.44	83.00	2685	4850	3869	Gamma	44.44	87.04	2816	5086
98	3689	Gamma	44.44	83.00	2685	4850	3869	Gamma	44.44	87.04	2816	5086
99	3689	Gamma	44.44	83.00	2685	4850	3869	Gamma	44.44	87.04	2816	5086
100	3689	Gamma	44.44	83.00	2685	4850	3869	Gamma	44.44	87.04	2816	5086

APPENDIX 4. INFANT VACCINE CALENDAR IN BELGIUM

Figure 28 – Infant routine vaccine calendar, Superior Health Council, 2009



Vaccins / Age[1]	8 SEMAINES 2 MOIS	12 SEMAINES 3 MOIS	16 SEMAINES 4 MOIS	12 MOIS	13 MOIS	15 MOIS	18 MOIS	5 - 7 ANS	10 - 13 ANS	14 - 16 ANS
Polio inactivé[2]	IPV	IPV	IPV			IPV		IPV		
Diphtérie Tétanos Coqueluche[3]	DTPa	DTPa	DTPa			DTPa		DTPa		dTpa
Haemophilus influenzae type b[4]	Hib	Hib	Hib			Hib				
Hépatite B[5]	VHB	VHB	VHB			VHB			VHB	
Rougeole Rubéole[6] Oreillons				RRO_1				RRO_1	RRO_2	RRO_2
Méningocoque C[7]						MenC				
Pneumocoque[8]	Pn7V		Pn7V	Pn7V						
Rotavirus[9]	ROTA	ROTA	(ROTA)							
HPV[10]									HPV	

Source and further details: Superior Health Council, http://www.health.fgov.be/internet2Prd/groups/public/@public/@shc/documents/ie2divers/4938405_fr.pdf

APPENDIX 5. DYNAMIC MODEL EQUATIONS, POPULATION MIXING AND RISK OF DISEASE GIVEN INFECTION

The following text is adapted from Christensen *et al.*[37]

Appendix 5.1. Transmission dynamic model equations

The model can be expressed by the following set of differential equations (please refer to the main text including Figure 8 for an explanation of the symbols used). For time points other than year end and points of vaccination:

$$\frac{dS_i(t)}{dt} = -S_i(t)(\lambda_{mi}(t) + \lambda_{ni}) + (M_i(t) + N_i(t))r$$

$$\frac{dSVI_i(t)}{dt} = -SVI_i(t)\big((1-\kappa)\lambda_{mi}(t)\big) - SVI_i(t)\lambda_{ni} - SVI_i(t)w + (MVI_i(t) + NVI_i(t))r$$

$$\frac{dSV_i(t)}{dt} = -SV_i(t)(\lambda_{mi}(t) + \lambda_{ni}) + \big(MV_i(t) + NV_i(t)\big)r + SVI_i(t)w$$

$$\frac{dM_i(t)}{dt} = -M_i(t)r + S_i(t)\lambda_{mi}(t)$$

$$\frac{dMVI_i(t)}{dt} = SVI_i(t)\big((1-\kappa)\lambda_{mi}(t)\big) - MVI_i(t)r - MVI_i(t)w$$

$$\frac{dMV_i(t)}{dt} = SV_i(t)\lambda_{mi}(t) - MV_i(t)r + MVI_i(t)w$$

$$\frac{dN_i(t)}{dt} = -N_i(t)r + S_i(t)\lambda_{ni}$$

$$\frac{dNVI_i(t)}{dt} = SVI_i(t)\lambda_{ni} - NVI_i(t)r - NVI_i(t)w$$

$$\frac{dNV_i(t)}{dt} = SV_i(t)\lambda_{ni} - NV_i(t)r + NVI_i(t)w$$

The model is structured into 100 single year of age (*i*) compartments (0 to 99 years). At the end of each year individuals in compartment *i* move into compartment *i+1*; all those aged 99 are assumed to die and births are introduced into the susceptible compartment S_0. Individuals are moved from the unvaccinated into the vaccinated compartments (*VI*) according to the age-specific uptake, *u*, the first time they receive a vaccine dose. Protection from vaccination can wane (at a rate equal to the inverse of the average duration of protection), in which case individuals move into the vaccinated, not-immune compartments (V). At the point of booster vaccination, a proportion of those in ages eligible for a booster dose in the vaccinated, not-immune compartments (*V*), are moved back into the vaccinated and immune compartments.

Appendix 5.2. Mixing patterns – simple preferential mixing

We adapted the formula developed by Trotter *et al.* for the model under consideration here (for preferential mixing within 1 year of age), such that:

$$\lambda_{i(t)} = \beta_i \left(\varepsilon \left(\sum_{i-1}^{i+1} I_{i(t)} \right) + (1-\varepsilon) \left(\sum_{i=0}^{i=99} I_{i(t)} \right) \right)$$

Mixing was assumed to be preferential within 1 year of a given age group with degree *ε*, with individuals mixing with all age groups randomly with degree 1-*ε*. For ages 0 and 99, the equation is modified in that ages 0 and 1, and 98 and 99, contribute to the preferential mixing band respectively. The *βi* values here are unknown, but if a system is at equilibrium, epidemiological data can be used to derive estimates for the force of infection, *λi*, and through rearrangement of the equation above *βi* values can then be derived. Optimal *ε* values were calculated for a given duration of carriage by minimising the sum of squares between the prevalence of carriers in the model (averaged over 1 year) and that obtained from the carriage systematic review, once the model had been allowed to stabilise (100 years).

Appendix 5.3. Transmission dynamic model parameter fitting

Appendix 5.3.1. Estimating the age-specific force of infection

Estimates of the force of infection, λ_i, were calculated from the carriage prevalence curve from a recent systematic review.[7] In models considering MenB only, this carriage curve for all serogroups was multiplied by a proportion estimated from the literature for MenB strains. In the base case fixed effect estimates from the all countries model was used. A SIS static model was developed in Berkeley Madonna[79] with 100 single year of age classes, with age as a proxy for time and the model run in years. The force of infection for this model, written as a difference equation, is presented in below:

$$\lambda_i = \frac{(I_{i+1} - I_i + rI_i)}{S_i}$$

Where S_i is the number of susceptible individuals in age group i, and I_i, is the number of carriers (M_i and N_i). The population of each year of age was set to 1 and estimates of the number of susceptible and carrier individuals for each year of age were obtained from the carriage prevalence (proportion) curve, as follows:

$$S_i = 1 - carriage\ prevalence_i$$
$$I_i = carriage\ prevalence_i$$

Appendix 5.3.2. Estimating the risk of disease given infection (case-carrier ratio)

Cases of invasive disease are not explicitly included in the model, but are a function of the number of new infections (carriers) arising over time. Cases were generated using a case-carrier ratio, similar to that used by Trotter *et al*. in their models of MenC vaccination,[6, 117] by fitting a model to age-specific carriage and disease data. We used one function to generate a case: carrier ratio (Φ_i, where i = age) for children aged under 2 years, where most cases of invasive disease arise. Preliminary analysis indicated a suitable function would be one which increased in very young children, peaking in 4-6 month olds, and declining thereafter.

$$\Phi_i = \frac{(\rho + \varepsilon i + \sigma i^2)}{(1 + \tau i + \upsilon i^2)} + \delta$$

We used a second function for individuals aged 2 years and over, where our analyses suggested a steeply declining case: carrier ratio until the age of 12-13 years old, with a slight increase in teenagers, a decrease towards 40 years of age and increasing slightly thereafter.

$$\Theta_i = \frac{(\rho + \varepsilon i + \sigma i^2 + \omega i^3 + \varsigma^4)}{(1 + \tau i + \upsilon i^2 + \kappa i^3)}$$

A Poisson model was used to fit the parameters to the disease data, as described by Trotter *et al*.;[6] the fitted values for the functions using POLYMOD leisure contacts are presented in Table 60 and are shown visually in Figure 29 and Figure 30.

Table 60 – Parameters for the risk of disease given infection (Φ_i and Θ_i) for the baseline dynamic model (using mixing based on POLYMOD leisure contacts), estimated using disease incidence data from 2009-2010, and a carriage duration of 6 months

Parameter	Children aged under 2 years	Individuals aged 2 years and over
ρ	2.2961E-03	5.3368E-02
ε	1.5731E-02	-1.1448E-02
σ	9.0557E-03	8.6480E-04
τ	-3.2846E+00	-2.6481E-05
υ	6.3868E+00	2.9256E-07
δ	5.0962E-04	-
ω	-	5.2001E+00
ς	-	-6.9028E-01
κ	-	2.5323E-02

Figure 29 – Case-carrier ratio 'observed' and fitted values for those aged under 2 years (base case dynamic model)

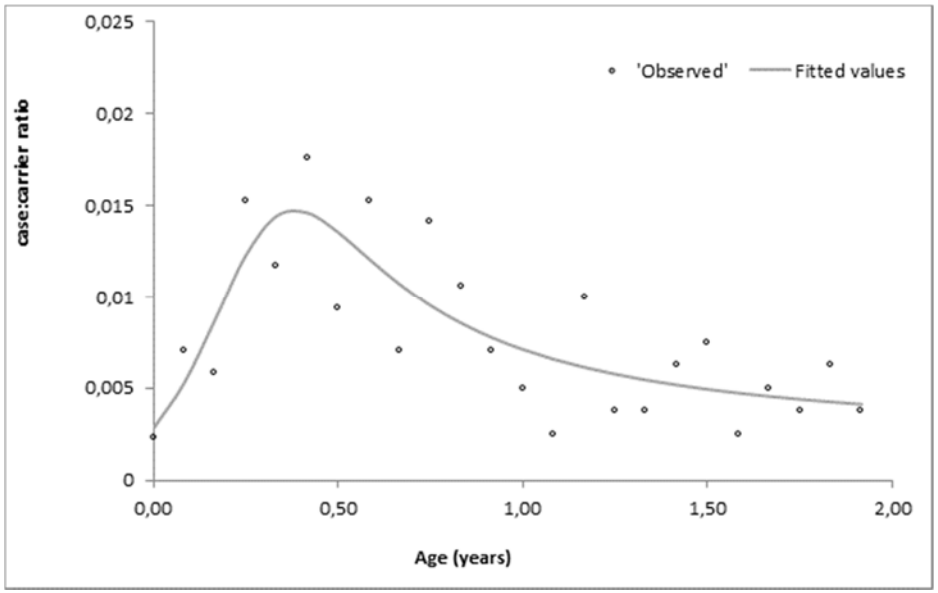
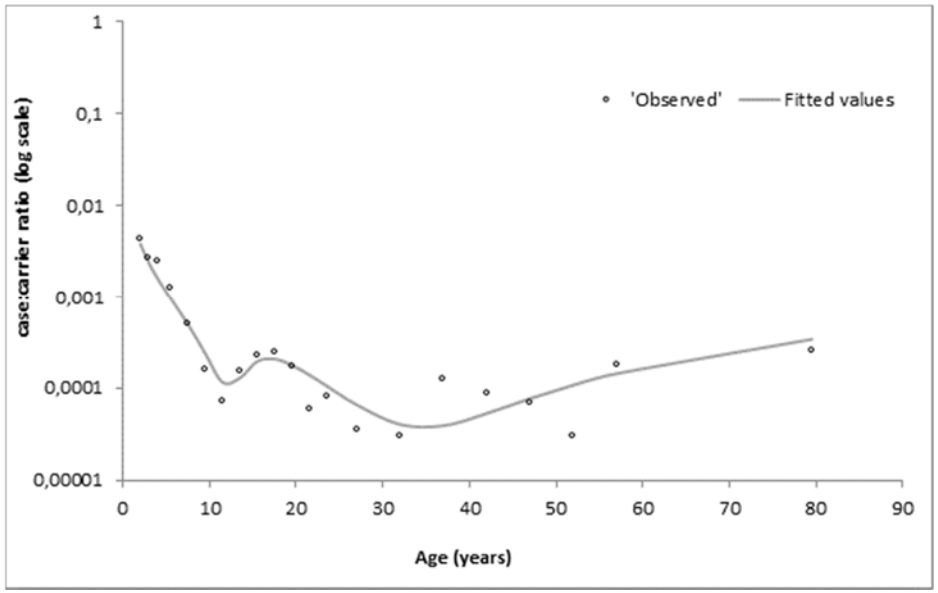


Figure 30 – Case-carrier ratio 'observed' and fitted values for those aged 2 years and over (base case dynamic model)



APPENDIX 6. COST OF PUBLIC HEALTH INTERVENTIONS FOR CONTACTS OF AN IMD CASE

Flanders recommends azithromycin (500 mg for adults and 10mg/kg for children) as chemoprophylaxis to close contacts of an IMD case (e.g. parents, siblings, friends, staff…). The cost of this prophylaxis per contact is valued at €4.16 (i.e. (€9.65 + €6.99) / 4), assuming a family composed of 2 adults and 2 children will typically be treated with one box of 6*250 mg pills (€9.65) and one bottle of 15 ml syrup (€6.99). Drugs are valued at their generic cost.[15] As they were no complete data on numbers of contacts treated by chemoprophylaxis in Flanders, we assumed that the estimated 7.2 contacts treated per IMD case in an English study could be used as a proxy for Flanders, as guidelines are similar between these two regions; this number was considered as reasonable by Flanders stakeholder (personal communication Geert Top). The total cost of chemoprophylaxis in Flanders is thus estimated at €29.95 per IMD case.

The chemoprophylaxis recommended by Wallonia to IMD contacts is ciprofloxacin as first choice (500 mg per adult and 15mg/kg for children). The cost of this prophylaxis per contact is valued at €2.19, assuming a family composed of 2 adults and 2 children will typically be treated with one box of 10*250 mg pills (€8.78). In Wallonia, the guidelines consider that all children in the same day-care and all kindergarten classmates of a IMD case are close contacts and should be treated, which results in a much higher average number of treated contacts than in Flanders. In the period January-September 2013, notification data from Wallonia reported an average of 23 contacts treated per IMD case (after excluding one case for which guidelines were not respected). We assumed that the first 10 contacts to a case are a mix of adults (e.g. teachers…) and children to whom we apply the above €2.19 cost per contact (10 * €2.19 = €21.95). All other treated contacts are assumed to be classmates or children at day-care and their chemoprophylaxis costs are age and weight-dependent.

The remaining 33.5 (43.5 – 10, Table 30) contacts among 1 to 4 year-old require a 125 mg ciprofloxacin dose each, which is covered by two boxes of 10*250 mg breakable pills (2 * €8.78 = €17.56). The 30 (40 – 10) 5 to 9 year-old contacts require a 250 mg ciprofloxacin dose each, which is covered by 4 boxes of 10*250 mg pills, including some wastage (4 * €8.78 = €35.12). The 3.2 (13.2 – 10) 10 to 19 year-old contacts require a 500 mg ciprofloxacin dose each, which is covered by 1 box of 10*250 mg pills (€8.78). The resulting total age-specific costs of chemoprophylaxis in Wallonia are presented in section 6.5.4.

Two hours of public health professional time (1 hour for a nurse and 1 hour for a doctor) were further included per IMD case for managing the case, i.e. for contacts tracing and arranging prophylaxis. Based on the annual salary grids published on the website of the federal personnel and on an estimated 225 working days per year, the hourly costs of a nurse and a doctor appointed by the Belgian public sector were calculated at €20.46 and €36.71, respectively.[112]

APPENDIX 7. INCREMENTAL COST-EFFECTIVENESS ANALYSIS, DYNAMIC MODEL WITH 0% VACCINE EFFICACY AGAINST CARRIAGE

Table 61 – Incremental costs and benefits of alternative vaccination strategies, ranked by discounted total cost of the strategies, 0% vaccine efficacy against carriage acquisition

	Total cost treatment / vaccination	QALYs gained	Incremental cost	Incremental QALYs gained	Cost per QALY gained (rounded)	Cost per QALY gained (rounded)
Routine vaccination policy						
Current situation	€89.7M	0	-	-		
14 years	€330.6M	766	€240.9M	766	*€314 600*	Dominated
3, 5, 6 +12 months	€615.7M	1734	€285.0M	968	€294 300	€303 300
3, 5, 6 +12 months and 14 years	€855.8M	2500	€240.1M	766	€313 600	€313 600
Partly reimbursed vaccination policy						
Current situation	€89.7M	0	-	-		
14 years	€299.0M	383	€209.3M	383	*€546 500*	Dominated
3, 5, 6 +12 months	€830.7M	1561	€531.7M	1178	€451 400	€474 800
3, 5, 6 +12 months and 14 years	€1039.2M	1944	€208.5M	383	€544 600	€544 600
Private market vaccination policy						
Current situation	€89.7M	0	-	-		
14 years	€171.2M	128	€81.5M	128	*€638 700*	Dominated
3, 5, 6 +12 months	€378.4M	607	€207.2M	479	€432 300	€475 700
3, 5, 6 +12 months and 14 years	€459.1M	734	€80.7M	128	€632 400	€632 400

Each strategy is compared to the strategy above unless dominated. Italic font shows extended dominance of the strategy as its cost per QALY gained is higher than that of the next, more effective strategy. The extended dominated strategy is therefore excluded from consideration and new cost per QALY gained using the appropriate comparator are computed (see last column). M: million.

APPENDIX 8. MONTE CARLO SIMULATION RESULTS ON THE COST-EFFECTIVENESS PLANE FOR THE SCENARIO ANALYSES OF THE STATIC MODEL

Figure 31 – Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the static model all meningococcal serogroups, vaccine free of charge scenario

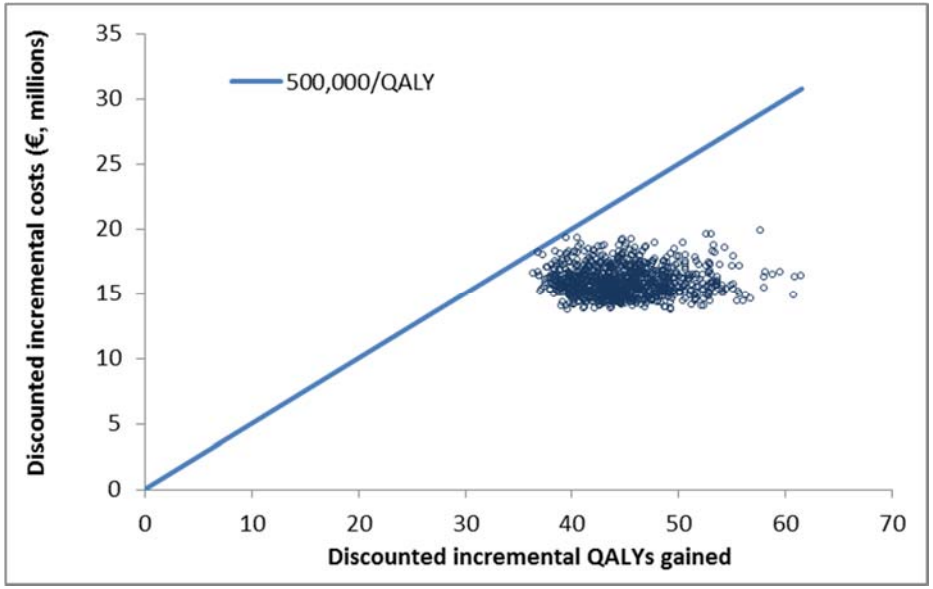


Figure 32 – Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the static model high incidence, vaccine free of charge scenario

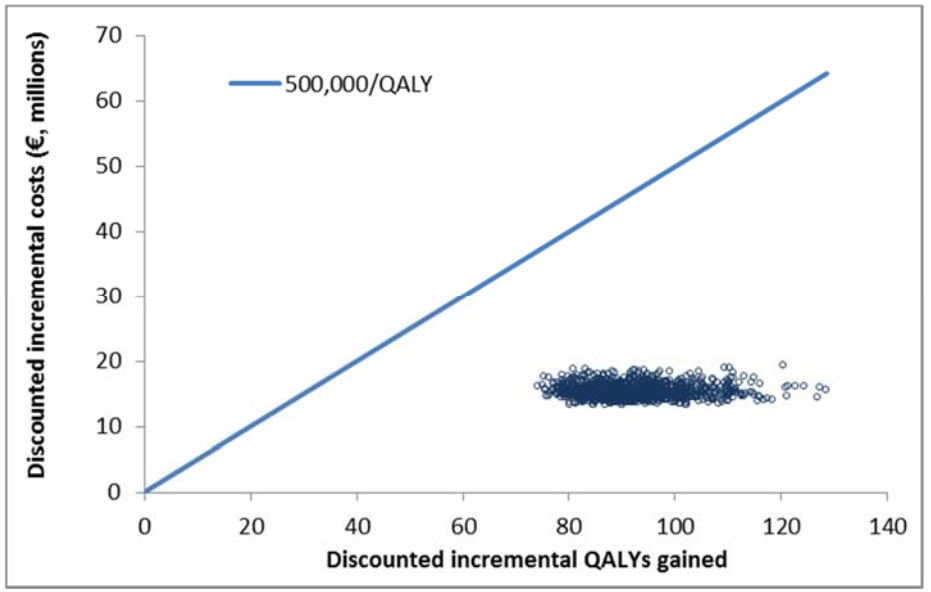


Figure 33 – Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the static model low vaccine strain coverage, vaccine free of charge scenario

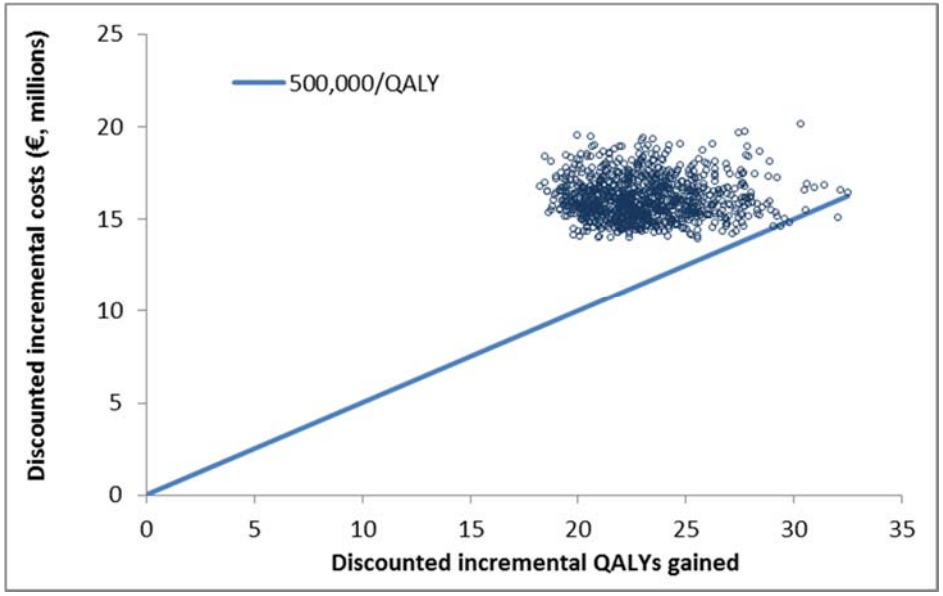


Figure 34 – Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the static model high vaccine strain coverage, vaccine free of charge scenario

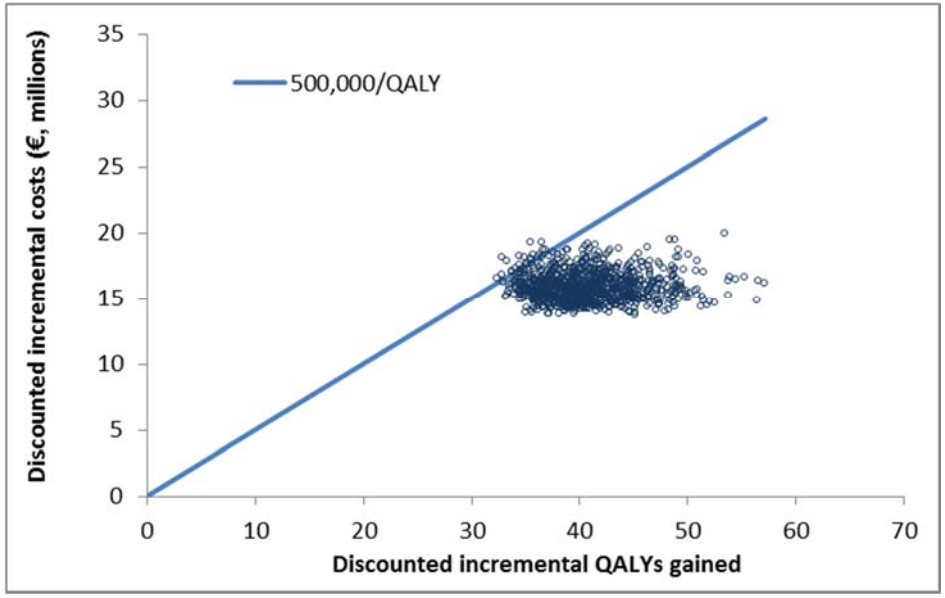


Figure 35 – Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the static model low uptake of vaccine, vaccine free of charge scenario

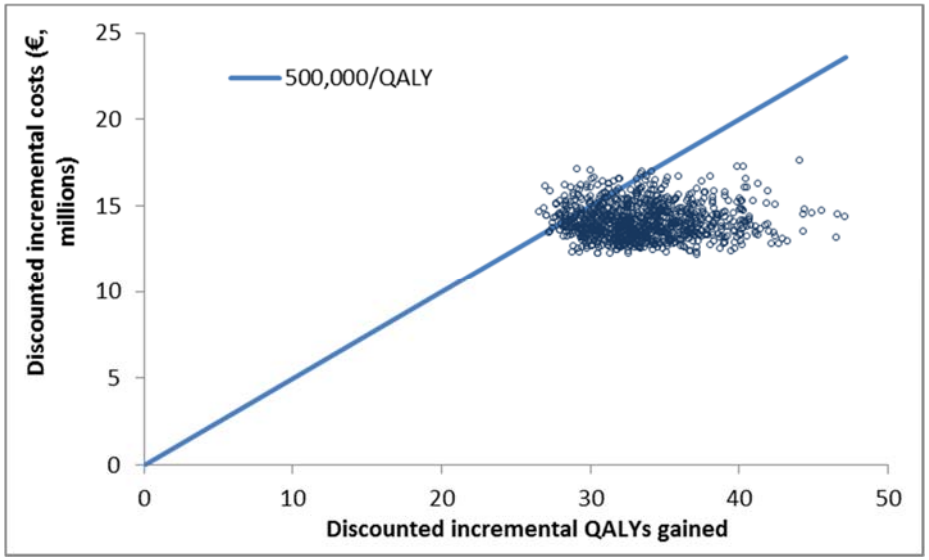


Figure 36 – Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the static model high vaccine uptake, vaccine free of charge scenario

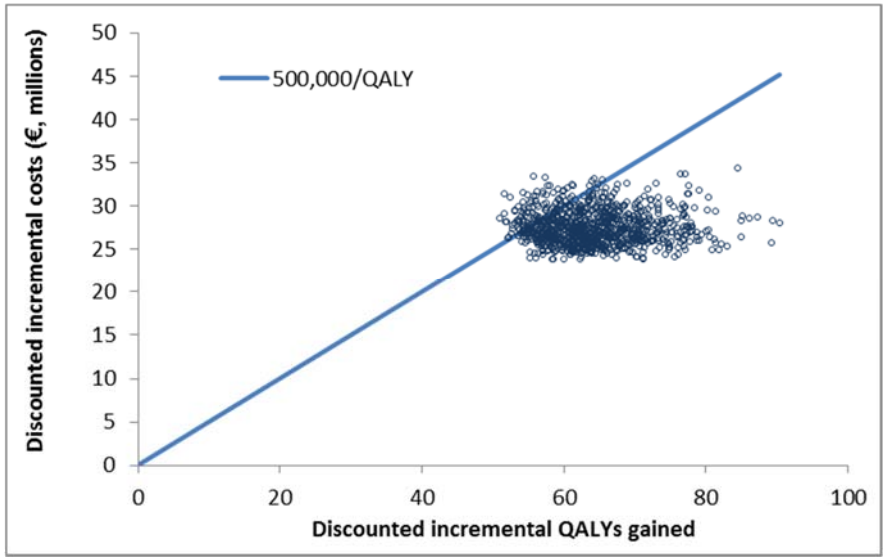


Figure 37 – Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the static model low duration of protection, vaccine free of charge scenario

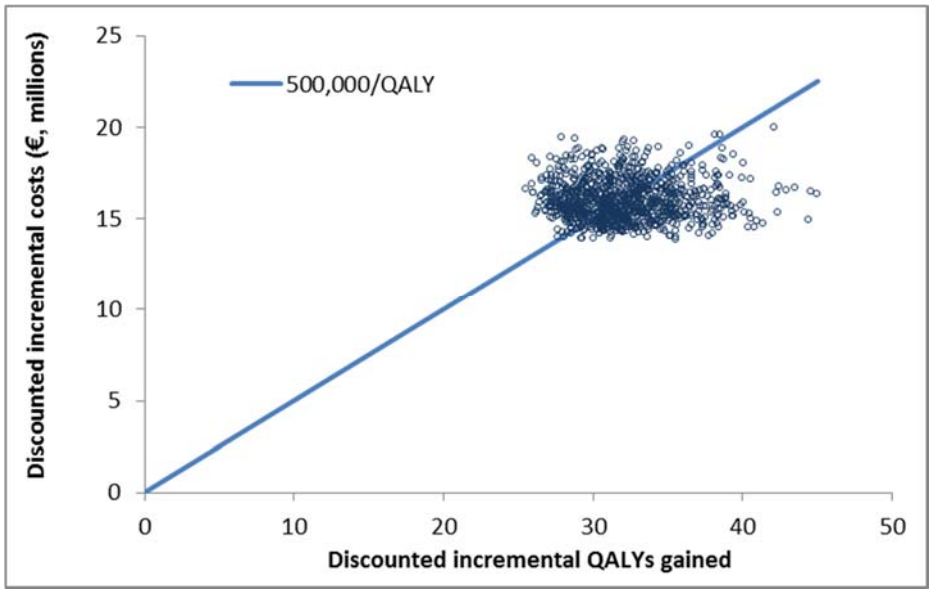


Figure 38 – Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the static model high duration of protection, vaccine free of charge scenario

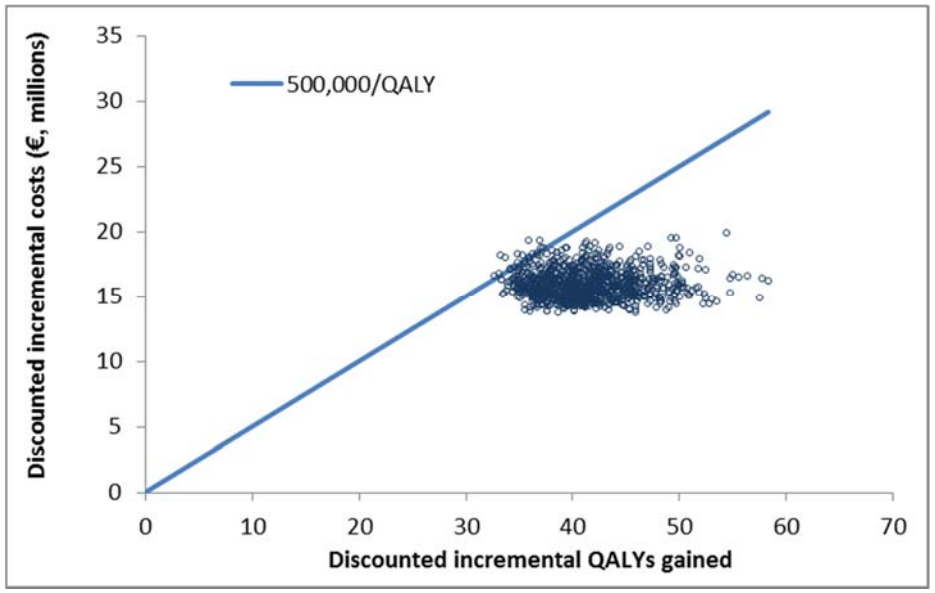
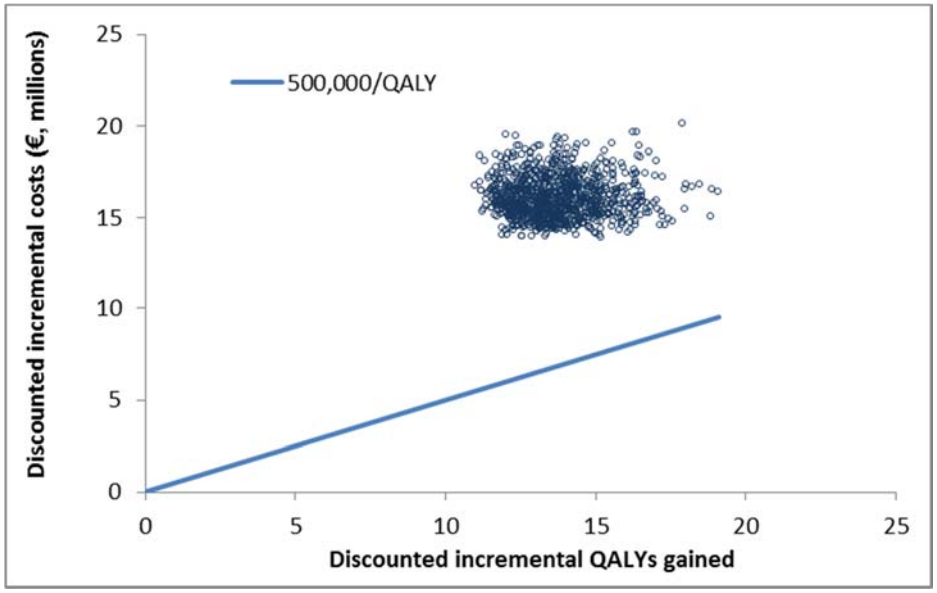


Figure 39 – Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the static model 20 year time horizon, vaccine free of charge scenario



REFERENCES

1. European Centre for Disease Prevention and Control. Surveillance of invasive bacterial diseases in Europe, 2011. Stockholm: ECDC; 2013.
2. Erickson L, De Wals P. Complications and Sequelae of Meningococcal Disease in Quebec, Canada, 1990–1994. Clinical Infectious Diseases. 1998;26(5):1159-64.
3. Gottfredsson M, Reynisson IK, Ingvarsson RF, Kristjansdottir H, Nardini MV, Sigurdsson JF, et al. Comparative Long-term Adverse Effects Elicited by Invasive Group B and C Meningococcal Infections. Clinical Infectious Diseases. 2011;53(9):e117-e24.
4. Healy CM, Butler KM, Smith EOB, Hensey OP, Terence B, Moloney AC, et al. Influence of Serogroup on the Presentation, Course, and Outcome of Invasive Meningococcal Disease in Children in the Republic of Ireland, 1995–2000. Clinical Infectious Diseases. 2002;34(10):1323-30.
5. De Wals P, Hertoghe L, Borlée-Grimée I, De Maeyer-Cleempoel S, Reginster-Haneuse G, Dachy A, et al. Meningococcal disease in Belgium. Secondary attack rate among household, day-care nursery and pre-elementary school contacts. J Infect. 1981;3, Supplement 1(0):53-61.
6. Trotter CL, Gay NJ, Edmunds WJ. The natural history of meningococcal carriage and disease. Epidemiology & Infection. 2006;134(03):556-66.
7. Christensen H, May M, Bowen L, Hickman M, Trotter CL. Meningococcal carriage by age: a systematic review and meta-analysis. Lancet Infect Dis. 2010;10(12):853-61.
8. Carion F, Hanquet G, Vrints M, Bertrand S, Collard J-M. Epidemiology and surveillance of meningococcal disease in Belgium. In: Proceedings of European Monitoring Group on Meningococci (EMGM); 2006; Rome, Italy.
9. De Wals P, Deceuninck G, Lefebvre B, Boulianne N, De Serres G. Effectiveness of serogroup C meningococcal conjugate vaccine: a 7-year follow-up in Quebec, Canada. Pediatr Infect Dis J. 2011;30(7):566-9.

10. Trotter CL, Andrews NJ, Kaczmarski EB, Miller E, Ramsay ME. Effectiveness of meningococcal serogroup C conjugate vaccine 4 years after introduction. Lancet. 2004;364(9431):365-7.
11. Trotter CL, Maiden MC. Meningococcal vaccines and herd immunity: lessons learned from serogroup C conjugate vaccination programs. Expert Rev Vaccines. 2009;8(7):851-61.
12. Maiden MC, Stuart JM, Group UKMC. Carriage of serogroup C meningococci 1 year after meningococcal C conjugate polysaccharide vaccination. Lancet. 2002;359(9320):1829-31.
13. Maiden MC, Ibarz-Pavon AB, Urwin R, Gray SJ, Andrews NJ, Clarke SC, et al. Impact of meningococcal serogroup C conjugate vaccines on carriage and herd immunity. J Infect Dis. 2008;197(5):737-43.
14. Trotter CL, Edmunds WJ. Reassessing the cost-effectiveness of meningococcal serogroup C conjugate (MCC) vaccines using a transmission dynamic model. Med Decis Making. 2006;26(1):38-47.
15. Centre Belge d'Information Pharmacothérapeutique. Répertoire Commenté des Médicaments CBIP/BCFI, editor. Gent; 2014.
16. Snape MD, Dawson T, Oster P, Evans A, John TM, Ohene-Kena B, et al. Immunogenicity of two investigational serogroup B meningococcal vaccines in the first year of life: a randomized comparative trial. Pediatr Infect Dis J. 2010;29(11):e71-9.
17. Holst J, Oster P, Arnold R, Tatley MV, Naess LM, Aaberge IS, et al. Vaccines against meningococcal serogroup B disease containing outer membrane vesicles (OMV): lessons from past programs and implications for the future. Hum Vaccin Immunother. 2013;9(6):1241-53.
18. CHMP. Assessment report Bexsero. London: European Medicines Agency; 2013. Procedure No. EMEA/H/C/002333
19. Vogel U, Taha M-K, Vazquez JA, Findlow J, Claus H, Stefanelli P, et al. Predicted strain coverage of a meningococcal multicomponent vaccine (4CMenB) in Europe: a qualitative and quantitative assessment. The Lancet Infectious Diseases. 2013;13:416-25.
20. Theeten H, Hens N, Aerts M, Vandermeulen C, Roelants M, Hoppenbrouwers K, et al. Common attitudes about concomitant vaccine injections for infants and adolescents in Flanders, Belgium. Vaccine. 2009;27(13):1964-9.
21. De Wals P, Hertoghe L, De Maeyer S, Gilquin C, Minne A, Thiers G, et al. Validity of the recording of meningococcal disease according to various sources of information. J Infect. 1984;9(2):185-9.
22. European Centre for Disease Prevention and Control. Surveillance of invasive bacterial diseases in Europe 2008/2009. Stockholm: ECDC; 2011. Available from: http://www.ecdc.europa.eu/en/publications/Publications/1107_SUR_IBD_2008-09.pdf
23. De Maeyer S, Seba JM, Reginster G. Epidemiology of meningococcal meningitis in Belgium. J Infect. 1981;3, Supplement 1(0):63-70.
24. Carion F, Van Looveren M, Goossens H. New epidemiological features of meningococcal disease in Belgium. Euro Surveill. 1997;2(10):80.
25. Howitz M, Lambertsen L, Simonsen JB, Christensen JJ, Molbak K. Morbidity, mortality and spatial distribution of meningococcal disease, 1974–2007. Epidemiology & Infection. 2009;137(11):1631-40.
26. Jensen ES, Schønheyder HC, Lind I, Berthelsen L, Nørgård B, Sørensen HT. Neisseria meningitidis phenotypic markers and septicaemia, disease progress and case-fatality rate of meningococcal disease: a 20-year population-based historical follow-up study in a Danish county. Journal of Medical Microbiology. 2003;52(2):173-9.
27. de Greeff SC, de Melker HE, Schouls LM, Spanjaard L, van Deuren M. Pre-admission clinical course of meningococcal disease and opportunities for the earlier start of appropriate intervention: a prospective epidemiological study on 752 patients in the Netherlands, 2003-2005. European Journal of Clinical Microbiology and Infectious Diseases. 2008;27(10):985-92.
28. Parent I. Les infections invasives à méningocoques en France en 2011 : principales caractéristiques épidémiologiques. Bulletin épidémiologique hebdomadaire. 2012;49-50:569-73.

29. Ladhani SN, Flood JS, Ramsay ME, Campbell H, Gray SJ, Kaczmarski EB, et al. Invasive meningococcal disease in England and Wales: implications for the introduction of new vaccines. Vaccine. 2012;30(24):3710-6.
30. Borg J, Christie D, Coen PG, Booy R, Viner RM. Outcomes of meningococcal disease in adolescence: Prospective, matched-cohort study. Pediatrics. 2009;123(3):e502-e9.
31. Bettinger JA, Scheifele DW, Le Saux N, Halperin SA, Vaudry W, Tsang R, et al. The disease burden of invasive meningococcal serogroup B disease in Canada. Pediatr Infect Dis J. 2013;32(1):e20-5.
32. Viner RM, Booy R, Johnson H, Edmunds WJ, Hudson L, Bedford H, et al. Outcomes of invasive meningococcal serogroup B disease in children and adolescents (MOSAIC): a case-control study. Lancet Neurol. 2012;11(9):774-83.
33. Edmond K, Clark A, Korczak VS, Sanderson C, Griffiths UK, Rudan I. Global and regional risk of disabling sequelae from bacterial meningitis: a systematic review and meta-analysis. The Lancet Infectious Diseases. 2010;10(5):317-28.
34. National Collaborating Centre for Women's and Children's Health. Bacterial meningitis and meningococcal septicaemia in children. London: 2010. NICE Clinical Guidelines
35. Kaplan SL, Schutze GE, Leake JAD, Barson WJ, Halasa NB, Byington CL, et al. Multicenter Surveillance of Invasive Meningococcal Infections in Children. Pediatrics. 2006;118(4):e979-e84.
36. Trotter CL, Fox AJ, Ramsay ME, Sadler F, Gray SJ, Mallard R, et al. Fatal outcome from meningococcal disease – an association with meningococcal phenotype but not with reduced susceptibility to benzylpenicillin. Journal of Medical Microbiology. 2002;51(10):855-60.
37. Christensen H. Modelling the impact of vaccination targeted against serogroup B meningococcal disease. PhD dissertation. University of Bristol, School of Social and Community Medicine.; 2011.
38. Ruedin HJ, Ess S, Zimmermann HP, Szucs T. Invasive meningococcal and pneumococcal disease in Switzerland: cost-utility analysis of different vaccine strategies. Vaccine. 2003;21(27-30):4145-52.
39. De Wals P, Erickson L. Economic analysis of the 1992-1993 mass immunization campaign against serogroup C meningococcal disease in Quebec. Vaccine. 2002;20(21-22):2840-4.
40. Buysse CM, Raat H, Hazelzet JA, Hulst JM, Cransberg K, Hop WC, et al. Long-term health status in childhood survivors of meningococcal septic shock. Arch Pediatr Adolesc Med. 2008;162(11):1036-41.
41. Kramer MS, Etezadi-Amoli J, Ciampi A, Tange SM, Drummond KN, Mills EL, et al. Parents' versus physicians' values for clinical outcomes in young febrile children. Pediatrics. 1994;93(5):697-702.
42. Oostenbrink R, HA AM, Essink-Bot ML. The EQ-5D and the Health Utilities Index for permanent sequelae after meningitis: a head-to-head comparison. J Clin Epidemiol. 2002;55(8):791-9.
43. Bennett JE, Sumner W, 2nd, Downs SM, Jaffe DM. Parents' utilities for outcomes of occult bacteremia. Arch Pediatr Adolesc Med. 2000;154(1):43-8.
44. Stouthard M, Essink-Bot M-L, Bonsel G, Barendregt J, Kramers P, van de Water H, et al. Disability weights for diseases in the Netherlands. Department of Public Health, Erasmus University Rotterdam, the Netherlands; 1997.
45. Erickson LJ, De Wals P, McMahon J, Heim S. Complications of meningococcal disease in college students. Clin Infect Dis. 2001;33(5):737-9.
46. van de Beek D, Schmand B, de Gans J, Weisfelt M, Vaessen H, Dankert J, et al. Cognitive impairment in adults with good recovery after bacterial meningitis. J Infect Dis. 2002;186(7):1047-52.
47. Koomen I, Raat H, Jennekens-Schinkel A, Grobbee DE, Roord JJ, van Furth M. Academic and behavioral limitations and health-related quality of life in school-age survivors of bacterial meningitis. Qual Life Res. 2005;14(6):1563-72.

48. Buysse CM, Raat H, Hazelzet JA, Vermunt LC, Utens EM, Hop WC, et al. Long-term health-related quality of life in survivors of meningococcal septic shock in childhood and their parents. Qual Life Res. 2007;16(10):1567-76.
49. Allport T, Read L, Nadel S, Levin M. Critical illness and amputation in meningococcal septicemia: is life worth saving? Pediatrics. 2008;122(3):629-32.
50. Buysse CM, Raat H, Hazelzet JA, Hop WC, Maliepaard M, Joosten KF. Surviving meningococcal septic shock: health consequences and quality of life in children and their parents up to 2 years after pediatric intensive care unit discharge. Crit Care Med. 2008;36(2):596-602.
51. Schmand B, de Bruin E, de Gans J, van de Beek D. Cognitive functioning and quality of life nine years after bacterial meningitis. J Infect. 2010;61(4):330-4.
52. Borrow R, Balmer P, Miller E. Meningococcal surrogates of protection--serum bactericidal antibody activity. Vaccine. 2005;23(17-18):2222-7.
53. Vipond C, Care R, Feavers IM. History of meningococcal vaccines and their serological correlates of protection. Vaccine. 2012;30 Suppl 2:B10-7.
54. CHMP. Bexsero. Annex I - Summary of product characteristics. London: European Medicines Agency; Updated 2014. 24/10/2013 Bexsero -EMEA/H/C/002333 -II/05
55. Gill CJ. Novel assessment of a novel meningitis B vaccine. The Lancet Infectious Diseases. 2013.
56. Vesikari T, Esposito S, Prymula R, Ypma E, Kohl I, Toneatto D, et al. Immunogenicity and safety of an investigational multicomponent, recombinant, meningococcal serogroup B vaccine (4CMenB) administered concomitantly with routine infant and child vaccinations: results of two randomised trials. Lancet. 2013;381(9869):825-35.
57. Gossger N, Snape MD, Yu LM, Finn A, Bona G, Esposito S, et al. Immunogenicity and tolerability of recombinant serogroup B meningococcal vaccine administered with or without routine infant vaccinations according to different immunization schedules: a randomized controlled trial. JAMA. 2012;307(6):573-82.
58. Findlow J, Borrow R, Snape MD, Dawson T, Holland A, John TM, et al. Multicenter, Open-Label, Randomized Phase II Controlled Trial of an Investigational Recombinant Meningococcal Serogroup B Vaccine With and Without Outer Membrane Vesicles, Administered in Infancy. Clinical Infectious Diseases. 2010;51(10):1127-37.
59. Santolaya ME, O'Ryan ML, Valenzuela MT, Prado V, Vergara R, Munoz A, et al. Immunogenicity and tolerability of a multicomponent meningococcal serogroup B (4CMenB) vaccine in healthy adolescents in Chile: a phase 2b/3 randomised, observer-blind, placebo-controlled study. Lancet. 2012;379(9816):617-24.
60. McQuaid F, Snape MD, John TM, Kelly S, Robinson H, Houlden J, et al. Persistence of Bactericidal Antibodies to 5 Years of Age Following Immunization with Serogroup B Meningococcal Vaccines at 6, 8, 12 and 40 Months of Age. The Pediatric Infectious Disease Journal. 2014;Publish Ahead of Print:10.1097/INF.0000000000000327.
61. Snape MD, Saroey P, John TM, Robinson H, Kelly S, Gossger N, et al. Persistence of bactericidal antibodies following early infant vaccination with a serogroup B meningococcal vaccine and immunogenicity of a preschool booster dose. Canadian Medical Association Journal. 2013;185(15):E715-E24.
62. Santolaya ME, O'Ryan M, Valenzuela MT, Prado V, Vergara RF, Muñoz A, et al. Persistence of antibodies in adolescents 18−24 months after immunization with one, two, or three doses of 4CMenB meningococcal serogroup B vaccine. Human Vaccines & Immunotherapeutics. 2013;9(11):2304-10.
63. Snape MD, Philip J, John TM, Robinson H, Kelly S, Gossger N, et al. Bactericidal antibody persistence 2 years after immunization with 2 investigational serogroup B meningococcal vaccines at 6, 8 and 12 months and immunogenicity of preschool booster doses: a follow-on study to a randomized clinical trial. Pediatr Infect Dis J. 2013;32(10):1116-21.
64. Cohn AC, Messonnier NE. Inching toward a serogroup B meningococcal vaccine for infants. JAMA. 2012;307(6):614-5.

65. Galloway Y, Stehr-Green P, McNicholas A, O'Hallahan J. Use of an observational cohort study to estimate the effectiveness of the New Zealand group B meningococcal vaccine in children aged under 5 years. International Journal of Epidemiology. 2009;38(2):413-8.
66. Holst J, Feiring B, Fuglesang JE, Hoiby EA, Nokleby H, Aaberge IS, et al. Serum bactericidal activity correlates with the vaccine efficacy of outer membrane vesicle vaccines against Neisseria meningitidis serogroup B disease. Vaccine. 2003;21(7-8):734-7.
67. Goldschneider I, Gotschlich EC, Artenstein MS. Human immunity to the meningococcus. I. The role of humoral antibodies. J Exp Med. 1969;129(6):1307-26.
68. Pollard AJ, Galassini R, van der Voort EM, Booy R, Langford P, Nadel S, et al. Humoral immune responses to Neisseria meningitidis in children. Infect Immun. 1999;67(5):2441-51.
69. World Health Organization. Requirements for meningococcal polysaccharide vaccine. Geneva: World Health Organization; 1976. Technical report series 594
70. Borrow R, Carlone GM, Rosenstein N, Blake M, Feavers I, Martin D, et al. Neisseria meningitidis group B correlates of protection and assay standardization--international meeting report Emory University, Atlanta, Georgia, United States, 16-17 March 2005. Vaccine. 2006;24(24):5093-107.
71. Frasch CE, Borrow R, Donnelly J. Bactericidal antibody is the immunologic surrogate of protection against meningococcal disease. Vaccine. 2009;27, Supplement 2(0):B112-B6.
72. Andrews N, Borrow R, Miller E. Validation of serological correlate of protection for meningococcal C conjugate vaccine by using efficacy estimates from postlicensure surveillance in England. Clin Diagn Lab Immunol. 2003;10(5):780-6.
73. Borrow R, Andrews N, Goldblatt D, Miller E. Serological basis for use of meningococcal serogroup C conjugate vaccines in the United Kingdom: reevaluation of correlates of protection. Infect Immun. 2001;69(3):1568-73.
74. Vogel U, Stefanelli P, Vazquez J, Taha M-K, Claus H, Donnelly J. The use of vaccine antigen characterization, for example by MATS, to guide the introduction of meningococcus B vaccines. Vaccine. 2012;30, Supplement 2(0):B73-B7.
75. Donnelly J, Medini D, Boccadifuoco G, Biolchi A, Ward J, Frasch C, et al. Qualitative and quantitative assessment of meningococcal antigens to evaluate the potential strain coverage of protein-based vaccines. Proc Natl Acad Sci U S A. 2010;107(45):19490-5.
76. Plikaytis BD, Stella M, Boccadifuoco G, DeTora LM, Agnusdei M, Santini L, et al. Interlaboratory standardization of the sandwich enzyme-linked immunosorbent assay designed for MATS, a rapid, reproducible method for estimating the strain coverage of investigational vaccines. Clin Vaccine Immunol. 2012;19(10):1609-17.
77. Frosi G, Biolchi A, Lo Sapio M, Rigat F, Gilchrist S, Lucidarme J, et al. Bactericidal antibody against a representative epidemiological meningococcal serogroup B panel confirms that MATS underestimates 4CMenB vaccine strain coverage. Vaccine. 2013;31(43):4968-74.
78. Read R. Impact of Quadrivalent Conjugate (MenACWY-CRM) and Serogroup B (4CMenB) Meningococcal Vaccines on Meningococcal Carriage in English University Students. In: Proceedings of Meningitis Research Foundation's 2013 conference; 2013; London: Meningitis Research Foundation. Available from: http://www.slideshare.net/meningitis/1340-robert-c-read-28276214
79. Macey R, Oster G. Berkeley Madonna. 8.3.14 ed. 2006.
80. Edmunds WJ, Medley GF, Nokes DJ. Evaluating the cost-effectiveness of vaccination programmes: a dynamic perspective. Stat Med. 1999;18(23):3263-82.
81. Christensen H, Hickman M, Edmunds WJ, Trotter CL. Introducing vaccination against serogroup B meningococcal disease: an economic and mathematical modelling study of potential impact. Vaccine. 2013;31(23):2638-46.
82. Caugant DA, Tzanakaki G, Kriz P. Lessons from meningococcal carriage studies. FEMS Microbiol Rev. 2007;31(1):52-63.
83. Cleemput I, Neyt M, Van de Sande S, Thiry N. Belgian guidelines for economic evaluations and budget impact analyses : second edition.

Health Technology Assessment (HTA). Brussels: Belgian Health Care Knowledge Centre (KCE); 2012. KCE Reports 183C (D/2012/10.273/54) Available from: https://kce.fgov.be/sites/default/files/page_documents/KCE_183C_economic_evaluations_second_edition_0.pdf

84. SPF Economie PME, Classes moyennes et Energie. Prix à la consommation à partir de 1920 et indice santé à partir de 1994 [Web page].Brussels;2013 [cited 12/2013]. Available from: http://economie.fgov.be/fr/statistiques/chiffres/economie/prix_consommation/indice_sante/
85. Statistics Belgium. Tables de mortalité annuelles en âges exacts (1994-2011), Belgique [Web page].Brussels: SPF Economie, P.M.E., Classes moyennes et Energie;2013 [cited 4/12/2013]. Available from: http://statbel.fgov.be/fr/modules/publications/statistiques/population/downloads/tables_de_mortalite.jsp
86. Briggs AH, Claxton K, Sculpher MJ. Decision Modelling for Health Economic Evaluation. Oxford: Oxford University Press 2006.
87. Scientific Institute of Public Health (WIV-ISP). Standardized Procedures for Mortality Analysis - Beglium [Web page].Brussels;2013 [cited 12/2013]. Available from: https://www.wiv-isp.be/epidemio/spma
88. Cleemput I, Neyt M, Thiry N, De Laet C, Leys M. Threshold values for cost-effectiveness in health care Health Technology Assessment (HTA). Brussels: Belgian Health Care Knowledge Centre (KCE); 2008 14/01/2009. KCE Reports 100C (D/2008/10.273/96) Available from: https://kce.fgov.be/sites/default/files/page_documents/d20081027396.pdf
89. Beutels P, Van Damme P, Oosterhuis-Kafeja F. Effects and costs of pneumococcal conjugate vaccination of Belgian children. Health Technology Assessment (HTA). Brussels: Belgian Health Care Knowledge Centre (KCE); 2006 22/06/2006. KCE Reports 33C (D/2006/10.273/54) Available from: https://kce.fgov.be/sites/default/files/page_documents/d20061027354.pdf
90. Thiry N, Lambert M-L, Cleemput I, Huybrechts M, Neyt M, Hulstaert F, et al. HPV Vaccination for the Prevention of Cervical Cancer in Belgium: Health Technology Assessment. Health Technology Assessment (HTA). Brussels: Belgian Health Care Knowledge Centre (KCE); 2007 17/10/2007. KCE Reports 64C (D/2007/10.273/43) Available from: https://kce.fgov.be/sites/default/files/page_documents/d20071027343.pdf
91. Bilcke J, Marais C, Benson O, van Hoek AJ, Lejeune O, Callens M, et al. Cost-utility of Vaccination against Chickenpox in Children and against Herpes Zoster in Elderly in Belgium. Health Technology Assessment (HTA). Brussels: Belgian Health Care Knowledge Centre (KCE); 2010 19/01/2011. KCE Reports 151 Available from: https://kce.fgov.be/publication/report/cost-utility-of-vaccination-against-chickenpox-in-children-and-against-herpes-zos
92. Beutels P, Luyten J, Lejeune O, Hens N, Bilcke J, De Schrijver K, et al. Evaluation of universal and targeted hepatitis A vaccination programs in Belgium. Health Technology Assessment (HTA). Brussels: Belgian Health Care Knowledge Centre (KCE); 2009 09/01/2009. KCE Reports 98 Available from: https://kce.fgov.be/publication/report/evaluation-of-universal-and-targeted-hepatitis-a-vaccination-programs-in-belgium
93. Godin I, De Smet P, Favresse D, Moreau N, Parent F. Tableau de bord de la santé en Communauté française de Belgique, Service Communautaire en Promotion Santé SIPES (ESP-ULB). Bruxelles: 2007. Available from: http://sipes.ulb.ac.be/index.php?option=com_mtree&task=att_download&link_id=29&cf_id=24
94. Robert E, Swennen B. Enquête de couverture vaccinale des enfants de 18 à 24 mois en Communauté française (Bruxelles excepté). Brussels: Direction générale de la Santé de la Communauté française; 2009. Available from: http://www.sante.cfwb.be/index.php?id=4259
95. Robert E, Swennen B. Enquête de couverture vaccinale des enfants de 18 à 24 mois en région de Bruxelles-Capitale. Brussels: Observatoire de la Santé et du Social de Bruxelles-Capitale; 2012.

Available from: http://www.observatbru.be/documents/news-items/news-enquete-couverture-vaccinale-2012.xml?lang=fr

96. Theeten H, Roelants M, Lernout T, Braeckman T, Hens N, Hoppenbrouwers K, et al. Studie van de vaccinatiegraad bij jonge kinderen en adolescenten in Vlaanderen in 2012. Brussels: Vlaams Agentschap Zorg en Gezondheid; 2013. Available from: https://www.zorg-en-gezondheid.be/vaccinatiegraad/
97. Vellinga A, Depoorter A, Van Damme P. Vaccinatiegraad in Vlaanderen 1999. Vlaamse Gemeenschap; 1999.
98. Robert E, Swennen B. Enquete de couverture vaccinale des enfants de 18 à 24 mois en region de Bruxelles-Capitale. ULB, Ecole de Santé Publique; 2006.
99. Lecocq H, Parent du Châtelet I, Taha M-K, Lévy-Bruhl D, Dervaux B. Analyse coût/efficacité de la vaccination par le vaccin Bexsero® contre les infections invasives à méningocoque de sérogroupe B (IIM B). Paris: HAUT CONSEIL DE LA SANTE PUBLIQUE, COMMISSION SPECIFIQUE « MALADIES TRANSMISSIBLES », COMITE TECHNIQUE DES VACCINATIONSHCSP; 2013. ANNEXE 1 du rapport du HCSP
100. Richmond PC, Marshall HS, Nissen MD, Jiang Q, Jansen KU, Garces-Sanchez M, et al. Safety, immunogenicity, and tolerability of meningococcal serogroup B bivalent recombinant lipoprotein 2086 vaccine in healthy adolescents: a randomised, single-blind, placebo-controlled, phase 2 trial. Lancet Infect Dis. 2012;12(8):597-607.
101. Kind P, Hardman G, Macran S. UK population norms for EQ-5D. Discussion paper 172. Centre for Health Economics, The University of York; 1999. Available from: https://www.york.ac.uk/media/che/documents/papers/discussionpapers/CHE%20Discussion%20Paper%20172.pdf
102. National Institute for Health and Disability Insurance (RIZIV-INAMI). Belgian reimbursement Scheme ("Nomenclature/Nomenclatuur") [Web page].Brussels;2014 [cited 02/2014]. Available from: http://www.inami.fgov.be/care/fr/nomenclature/
103. Van Impe M-F. L'accréditation. 2011. National Institute for Health and Disability Insurance (INAMI - RIZIV). Bulletin d'information 2011/4. Available from: https://www.inami.fgov.be/presentation/fr/publications/news-bulletin/2011-4/index.htm
104. Beguin C, Deggouj N, Debaty M, Gerkens S, Van den Steen D, Roberfroid D, et al. Hearing aids in Belgium: health technology assessment. Health Technology Assessment (HTA). Brussels: Belgian Health Care Knowledge Centre (KCE); 2008 03/11/2008. KCE Reports 91C (D/2008/10.273/69) Available from: https://kce.fgov.be/sites/default/files/page_documents/d20081027369.pdf
105. Cleemput I, Beguin C, de la Kethulle Y, Gerkens S, Jadoul M, Verpooten G, et al. Organisation and financing of chronic dialysis in Belgium. Health Technology Assessment (HTA). Brussels: Belgian Health Care Knowledge Centre (KCE); 2010 10/02/2010. KCE Reports 124C (D/2010/10.273/13) Available from: https://kce.fgov.be/sites/default/files/page_documents/d20101027313.pdf
106. Kiekens C, Van Rie K, Leys M, Cleemput I, Smet M, Kesteloot K, et al. Organisation and financing of musculoskeletal and neurological rehabilitation in Belgium. Health Services Research (HSR). Brussels: Belgian Health Care Knowledge Centre (KCE); 2007 09/07/2007. KCE Reports 57 Available from: https://kce.fgov.be/publication/report/organisation-and-financing-of-musculoskeletal-and-neurological-rehabilitation-in-
107. Lannoo E, Larmuseau D, Van Hoorde W, Ackaert K, Lona M, Leys M, et al. Chronic care of persons with acquired brain injury between the age of 18 and 65 years. Health Services Research (HSR). Brussels: Belgian Health Care Knowledge Centre (KCE); 2007 29/03/2007. KCE Reports 51 Available from: https://kce.fgov.be/publication/report/chronic-care-of-persons-with-acquired-brain-injury-between-the-age-of-18-and-65-y
108. Cellule Technique pour la gestion des données RHM-RFM - Technische Cel voor het beheer van de MZG-MFG data. Feedback financier par pathologie [Web page].Brussels;2014 [cited 02/2014]. Available from: https://tct.fgov.be/webetct/etct-web/
109. Diamond G. La réadaptation après un implant cochléaire. In: Proceedings of Colloque CDRP InterVal; 2009; Québec, Canada.

110. Van Acker K, Oleen-Burkey M, De Decker L, Vanmaele R, Van Schil P, Matricali G, et al. Cost and resource utilization for prevention and treatment of foot lesions in a diabetic foot clinic in Belgium. Diabetes Res Clin Pract. 2000;50(2):87-95.
111. Statistics Belgium. Population par sexe, groupe et classe d'âges 1990-2008. La Belgique et par région [Web page].Brussels: SPF Economie, P.M.E., Classes moyennes et Energie;2014 [cited 01/2014]. Available from: http://statbel.fgov.be/fr/modules/publications/statistiques/population/downloads/population_par_sexe_groupe_et_classe_d_ges_la_belgique_et_par_region.jsp
112. FedWeb - Portail du personnel fédéral. Echelles de traitement [Web page].Brussels;2014 [cited 01/2014]. Available from: http://www.fedweb.belgium.be/fr/remuneration_et_avantages/traitement/echelles_de_traitement/
113. Drieskens S, Van der Heyden J, Hesse E, Gisle L, Demarest S, Tafforeau J. Enquête de santé, 2008. Rapport III – Consommation de soins. Brussels: Scientific Institute of Public Health - Directorate Public Health and Surveillance; 2010. Available from: https://his.wiv-isp.be/SitePages/Reports.aspx
114. National Institute for Health and Disability Insurance (RIZIV-INAMI). Article 56 - UGPP - Campagne de prévention vaccination 2004-2007. Brussels: 2007. Available from: http://www.inami.fgov.be/drug/fr/statistics-scientific-information/vaccination/index.htm
115. De Wals P, Gilquin C, De Maeyer S, Bouckaert A, Noel A, Lechat MF, et al. Longitudinal study of asymptomatic meningococcal carriage in two Belgian populations of schoolchildren. J Infect. 1983;6(2):147-56.
116. Claus H, Maiden MC, Wilson DJ, McCarthy ND, Jolley KA, Urwin R, et al. Genetic analysis of meningococci carried by children and young adults. J Infect Dis. 2005;191(8):1263-71.
117. Trotter CL, Gay NJ, Edmunds WJ. Dynamic models of meningococcal carriage, disease, and the impact of serogroup C conjugate vaccination. Am J Epidemiol. 2005;162(1):89-100.
118. Mossong J, Hens N, Jit M, Beutels P, Auranen K, Mikolajczyk R, et al. Social contacts and mixing patterns relevant to the spread of infectious diseases. PLoS Med. 2008;5(3):e74.
119. Wallinga J, Teunis P, Kretzschmar M. Using data on social contacts to estimate age-specific transmission parameters for respiratory-spread infectious agents. Am J Epidemiol. 2006;164(10):936-44.
120. Hens N, Ayele GM, Goeyvaerts N, Aerts M, Mossong J, Edmunds JW, et al. Estimating the impact of school closure on social mixing behaviour and the transmission of close contact infections in eight European countries. BMC Infect Dis. 2009;9:187.
121. Hens N, Goeyvaerts N, Aerts M, Shkedy Z, Van Damme P, Beutels P. Mining social mixing patterns for infectious disease models based on a two-day population survey in Belgium. BMC Infect Dis. 2009;9:5.
122. Bogaert D, Hermans PW, Boelens H, Sluijter M, Luijendijk A, Rumke HC, et al. Epidemiology of nasopharyngeal carriage of Neisseria meningitidis in healthy Dutch children. Clin Infect Dis. 2005;40(6):899-902.
123. Delbos V, Lemee L, Benichou J, Berthelot G, Taha MK, Caron F, et al. Meningococcal carriage during a clonal meningococcal B outbreak in France. Eur J Clin Microbiol Infect Dis. 2013;32(11):1451-9.
124. Fitzpatrick PE, Salmon RL, Hunter PR, Roberts RJ, Palmer SR. Risk factors for carriage of Neisseria meningitidis during an outbreak in Wales. Emerg Infect Dis. 2000;6(1):65-9.
125. MacLennan J, Kafatos G, Neal K, Andrews N, Cameron JC, Roberts R, et al. Social behavior and meningococcal carriage in British teenagers. Emerg Infect Dis. 2006;12(6):950-7.
126. Cookson ST, Corrales JL, Lotero JO, Regueira M, Binsztein N, Reeves MW, et al. Disco fever: epidemic meningococcal disease in northeastern Argentina associated with disco patronage. J Infect Dis. 1998;178(1):266-9.
127. Imrey PB, Jackson LA, Ludwinski PH, England AC, 3rd, Fella GA, Fox BC, et al. Outbreak of serogroup C meningococcal disease

associated with campus bar patronage. Am J Epidemiol. 1996;143(6):624-30.

128. Mandal S, Wu HM, MacNeil JR, Machesky K, Garcia J, Plikaytis BD, et al. Prolonged University Outbreak of Meningococcal Disease Associated With a Serogroup B Strain Rarely Seen in the United States. Clinical Infectious Diseases. 2013;57(3):344-8.
129. Honish L, Soskolne CL, Senthilselvan A, Houston S. Modifiable risk factors for invasive meningococcal disease during an Edmonton, Alberta outbreak, 1999-2002. Can J Public Health. 2008;99(1):46-51.
130. Novartis. The data on bactericidal antibody persistence per age groups (internal data). 2013.
131. Hanquet G. Financement des laboratoires de référence (LR): estimation d'un budget. In. Brussels: Scientific Institute of Public Health (ISP-WIV); 2005.
132. O'Mahony JF, de Kok IM, van Rosmalen J, Habbema JD, Brouwer W, van Ballegooijen M. Practical implications of differential discounting in cost-effectiveness analyses with varying numbers of cohorts. Value Health. 2011;14(4):438-42.
133. Vlaams Agentschap Zorg en Gezondheid. Meningokokkose − meningokokkenziekte. Richtlijnen Infectieziektebestrijding Vlaanderen. In; 2013.
134. Fédération Wallonie Bruxelles, WIV-ISP. Information sur les maladies infectieuses. In: MATRA, editor. Infections invasives à méningocoque. Brussels; 2014.
135. Haut Conseil de la santé publique. Vaccination contre les infections invasives à méningocoque B. Place du vaccin Bexsero. Paris: 2013. Avis et Rapports
136. Hoek MR, Christensen H, Hellenbrand W, Stefanoff P, Howitz M, Stuart JM. Effectiveness of vaccinating household contacts in addition to chemoprophylaxis after a case of meningococcal disease: a systematic review. Epidemiol Infect. 2008;136(11):1441-7.
137. Purcell B, Samuelsson S, Hahne SJ, Ehrhard I, Heuberger S, Camaroni I, et al. Effectiveness of antibiotics in preventing meningococcal disease after a case: systematic review. BMJ. 2004;328(7452):1339.
138. Ladhani N, Cordery R, Mandal S, Christensen H, Campbell H, Borrow R, et al. Preventing secondary cases of invasive meningococcal capsular group B (MenB) disease: benefits of offering vaccination in addition to antibiotic chemoprophylaxis to close contacts of cases in the household, educational setting, clusters and the wider community. In. 1.1 (April 2014) ed. London: Public Health England; 2014.
139. De Schrijver K, Maes I. An outbreak of serogroup C meningococcal disease in the province of Antwerp (Belgium) in 2001-2002. Eur J Epidemiol. 2003;18(11):1073-7.
140. Bertrand S, Van Meervenne E, De Baere T, Vanhoof R, Collard J-M, Ruckly C, et al. Detection of a geographical and endemic cluster of hyper-invasive meningococcal strains. Microbes and Infection. 2011;13(7):684-90.
141. Pouwels KB, Hak E, van der Ende A, Christensen H, van den Dobbelsteen GPJM, Postma MJ. Cost-effectiveness of vaccination against meningococcal B among Dutch infants: Crucial impact of changes in incidence. Human Vaccines & Immunotherapeutics. 2013;9(5):1129-38.
142. Huels J, Clements KM, McGarry LJ, Hill GJ, Wassil J, Kessabi S. Modelled evaluation of multi-component meningococcal vaccine (Bexsero(R)) for the prevention of invasive meningococcal disease in infants and adolescents in the UK. Epidemiol Infect. 2013:1-13.