KCE REPORT 231S

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

SUPPLEMENT

Belgian Health Care Knowledge Centre

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KCE REPORT 231S
HEALTH TECHNOLOGY ASSESSMENT

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APPENDIX

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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.
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MODELLING THE POTENTIAL IMPACT OF BEXSERO INTRODUCTION IN BELGIUM

A report prepared by Hannah Christensen, Emily Agnew, and Caroline Trotter on behalf of the Bristol-KCE collaboration*

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Note:
This document provides a report of the work undertaken by collaborators at the University of Bristol, UK and the Belgian Health Care Knowledge Centre (KCE), pre-publication, ***in confidence****. Further details, excluded here for the sake of brevity, are available on request.*

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Contents:

A. SUMMARY

Background

- A new meningococcal vaccine with the capacity to protect against capsular group B disease (Bexsero) was licensed in the EU in January 2013.
- Policy makers need to make decisions about whether and how best to use this vaccine. Mathematical and economic models which estimate the potential impact and cost-effectiveness of different vaccine strategies are useful tools for informing these decisions.
- The aim of this project is to use such models to evaluate the potential impact and cost-effectiveness of Bexsero vaccine programmes in Belgium.

Methods

- The extent of the impact that Bexsero may have on disrupting carriage acquisition remains uncertain. For this reason, two types of model - a cohort model assuming direct protection only, and a transmission dynamic model incorporating herd effects - were developed to evaluate the potential impact and cost-effectiveness of Bexsero.
- These models were originally developed to examine the potential impact and cost-effectiveness of 'MenB' vaccines in England. The models have been updated here to address similar questions on the use of Bexsero in Belgium.
- Models are parameterised using a range of contemporary data sources including: disease incidence, mortality data and sequelae estimates from KCE; quality of life losses from recent case-control studies; cost data from the payer perspective; and for the dynamic model, age-specific carriage prevalence estimates from a systematic review.
- Uncertainty in these parameters is considered through scenario analysis in both models, and additional probabilistic analysis in the cohort model.

Results – cohort model

- The cohort model considering MenB disease only, predicts routine infant vaccination (3, 5, 6+12 months, 55% uptake of primary doses, 50% uptake of booster) could prevent 10.3% (n=14) of meningococcal group B cases.
- All strategies considered resulted in high costs per QALYs gained; none were cost-effective at a €40,000 per QALY gain willingness to pay threshold.
- If the vaccine price per dose could be reduced scenarios combining the most vaccine favourable assumptions would be cost effective if the vaccine cost less than €6 a dose, assuming a willingness to pay of €40,000 per QALY gained.

Results – dynamic model

- Greater health benefits are seen when the vaccine is assumed to generate herd effects as well as affording direct protection. In this case strategies targeting teenagers (14 year olds), where carriage prevalence is thought to be high, maximises case reduction. The greatest short-term reduction in cases is seen with routine infant and adolescent vaccination.
- If the vaccine has a 30% vaccine efficacy against MenB carriage acquisition the annual number of cases could be reduced by 12% after 10 years through implementing routine infant vaccination, or 34% through implementing routine adolescent vaccination.
- Vaccination appears more economically favourable if the vaccine efficacy against carriage is increased, however the cost per QALY gained remains high (>€40,000 per quality adjusted life year gained) for most (88%) of the scenarios considered.
- Scenarios with routine adolescent vaccination or infant and adolescent vaccination with high incidence and case fatality or 'best case' assumptions would be cost-effective at a willingness to pay of €40,000 per quality adjusted life year gained assuming 30% vaccine efficacy against MenB carriage acquisition.

Conclusions

- These models have shown that the introduction of a routine immunisation programme with Bexsero has the capacity to reduce meningococcal disease in Belgium, albeit at high cost, and that a greater number of cases would be averted if the vaccine is able to induce herd effects.

B. INTRODUCTION

A new meningococcal vaccine developed and manufactured by Novartis, Bexsero, was granted an EU license in January 2013. This is the first licensed vaccine to offer broad protection against serogroup B (MenB) disease. The development of such a vaccine has been hampered by the fact that the MenB capsule shares structural similarity with human neural proteins, resulting in poor immune responses to vaccines based on the capsule and the possibility of generating autoimmunity[1]. Bexsero, however, is based upon a number of surface proteins and outer membrane vesicles, and is able to protect against strains with sufficient expression of the vaccine antigens regardless of the capsular group[2].

Mathematical and economic models can be used to predict the potential impact of interventions, such as vaccination. They can be used to explore the impact of several different strategies, not all of which could be evaluated experimentally, and thus can be used as an additional tool by policy makers to inform decision making. Mathematical and economic models of meningococcal carriage, disease and vaccination were developed and parameterised for England[3] to predict the potential impact of Bexsero in terms of cases and deaths averted and the cost-effectiveness of a range of introductory strategies. The models are relevant to other countries with a similar meningococcal epidemiology to the UK that are looking to make decisions regarding the introduction of Bexsero.

Through a collaboration between the researchers who developed the models for England at the University of Bristol, and those at the Belgian Health Care Knowledge Centre (KCE), the England models have been adapted and re-parameterised for the Belgian situation. Two types of model have been considered, because of ongoing uncertainty about the ability of the vaccine to prevent carriage acquisition in addition to disease. The cohort model assumes that the vaccine protects against disease, but has no effect on transmission and carriage of meningococci. The transmission dynamic model additionally allows the effects of the vaccine on carriage to be modelled and is thus able to capture herd effects[4]. This report presents results from both of these models for a number of different vaccination strategies and scenario analyses relevant to the Belgian situation. Key outputs of the models include: cases and deaths averted, life years saved, quality adjusted life years gained and cost-effectiveness.

C. MODELS, PARAMETERS AND DATA SOURCES

MODELS

Two types of model were developed using Berkley Madonna software[5] to predict the impact of vaccination: a cohort model, which assumes direct protection only and a transmission dynamic model, which also allows the effect of the vaccine on carriage, and thus wider herd protection effects, to be estimated[4]. The models used to assess the potential impact of Bexsero in England have previously been described[3]. 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.

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 or for survivors without sequelae. Those dying from the disease were assumed to lose the average life expectancy for the age at which they died. The principal 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; Bexsero is a protein based vaccine and is not targeted at the meningococcal capsule therefore may provide protection against non-MenB serogroups[6]. In the base case the incidence was based on data from 2009 to 2010. 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. 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. Several vaccination scenarios were modelled, in each case the model results were 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). Quality of life losses for vaccine-related adverse reactions were not included. The base case for the time horizon for both models was 100 years; but in scenario analyses a 20 year time horizon was 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.

MODEL STRUCTURE – COHORT SPECIFIC DETAILS

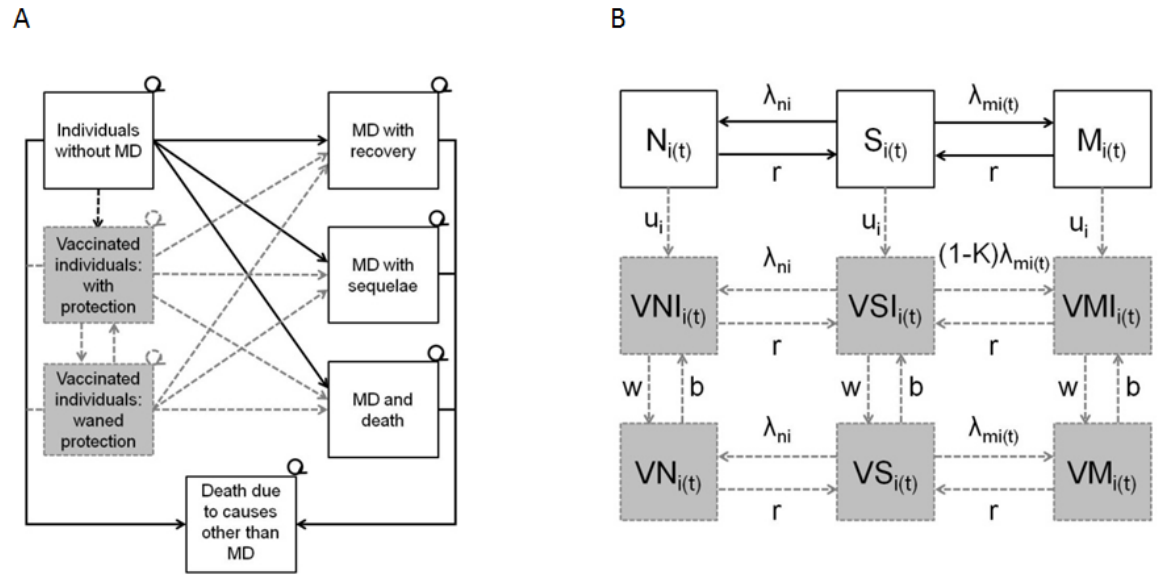
The cohort model is constructed using a Markov model, with monthly time steps (Figure 1, A). Individuals are born susceptible and cases arise by multiplying the age-specific probability of disease by the susceptible population. We assumed individuals only have disease once and are removed from the susceptible pool. Years of life are weighted by the age-specific quality of life. The cohort sizes were based upon population figures for 2011. For infant vaccination a single birth cohort was considered.

MODEL STRUCTURE – DYNAMIC SPECIFIC DETAILS

A Susceptible-Infected-Susceptible (SIS) model was used to represent the transmission of meningococcal carriage (Figure 1, B), with a daily time step. Model equations are presented in Appendix 1. This structure was chosen because individuals are expected to have multiple episodes of asymptomatic carriage of meningococci in their lifetimes[7]. Current evidence suggests carriage of multiple meningococcal strains is rare[8], 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) clear carriage to return to the susceptible state. Population mixing is based on mixing patterns from self-reported leisure contacts in Belgium (POLYMOD). In an alternative scenario, individuals are assumed to mix preferentially i.e. are considerably more likely to mix with individuals within 1 year of their own age (Appendix). Cases are generated by applying an age-specific case:carrier ratio to the number of new carriage acquisitions (Appendix). 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 cohort model[a], to aid comparisons between the cohort and dynamic results.

[a] A single birth cohort was followed through the cohort model allowing for deaths due to meningococcal disease and mortality due to other causes; the single year of age population which resulted, was used as the population within the dynamic model.

Figure 1. Simplified structures of the cohort (A) and dynamic (B) models (taken from Christensen et al.[3])



The 'no vaccination' model consists of white boxes and solid arrows; the 'with vaccination' model includes shaded boxes and dashes arrows in addition. (A) Cohort 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; κ, vaccine efficacy against carriage acquisition; u, vaccine uptake; w, waning vaccine protection; b, vaccination booster; i, age; t, time.

PARAMETERS AND DATA SOURCES

Data for model parameters were principally provided by KCE; parameters used are summarised in Table 1. The different vaccine strategies simulated are summarised in Table 2.

Table 1. Summary of parameter values

Parameter	BE Base case	BE distribution	Low scenario	High scenario	References/Sources and Notes
Epidemiological parameters					
Carriage prevalence	Variable by age	-	-	-	MenB carriage prevalence estimated by applying a proportion (0.32) of MenB from [9] to the carriage prevalence estimated from a systematic review (all countries model)[10]. In an alternative scenario higher serogroup B carriage prevalence (0.47 proportion applied) was assumed, based on a study in Germany[11].
Disease incidence (per 100,000) - all serogroups	1.7 (Variable by age)	-	-	-	NRC (% serogroup B) and hospital databases (minimal clinical data or MCD) for number of disease cases. Include principal and any diagnosis for code 036, new hospital stays 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)	High scenario: from high serogroup B incidence period (1999-2001). Based on serogroup B data from NRC, corrected for under-reporting estimated by age groups based on MCD data in 2007-10, assuming constant underreporting rates. Low scenario: projecting the current decrease of serogroup B in recent years (2003-2012), using a Poisson linear regression including year and population, applying the same age distribution as 2007-12 and same under-reporting.
Case fatality rate (%) - all serogroups	7.0 (Variable by age)	-	-	-	NRL data, linked to hospital stays (MCD) with meningoccocal code (036). Deaths from both sources are included (2004-10).
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: 2010 CFR much higher in all sources, 2008-10 data are used for high scenario to avoid small numbers, but CFR of base case are kept for 1-9 years because low in all high CFR periods. Low: 2001 and 2006 years (2001 corrected for incomplete reporting of deaths in WIV dataset - because never linked to MCD).
Years of life lost	Variable by age	-	-	-	Statistics Belgium, natural deaths, 2011
Natural mortality rates	Variable by age	-	-	-	Statistics Belgium, natural deaths, 2011
Population birth cohort	128,605	-	-	-	'Statistics Belgium'. Data for 2011
Long-term effects of meningococcal disease					
Proportion of survivors with sequelae ≤4 years	0.215	High and low scenarios	0.102	0.267	Studies from EU, US and Canadian settings[12-17]. As only one study (per age group) was available for the all serogroup proportion of sequelae (incomplete for all ages), the same
Proportion of survivors with sequelae 5-	0.086	High and low scenarios	0.066	0.106	

Parameter	BE Base case	BE distribution	Low scenario	High scenario	References/Sources and Notes
19 years					percentage of serogroup B has been assumed (the majority of current strains are serogroup B). High scenario from [12], low scenario from [16] or base case -30% when no specific study.
Proportion of survivors with sequelae 20+ years	0.116	High and low scenarios	0.089	0.144	
QALY utilities					
QALY utility for susceptibles and survivors of MD without sequelae	0.86 (Variable by age)	-	-	-	UK population norms from EQ-5D[18]; applied to the cohort model only.
QALY loss for survivors with sequelae	0.074	Gamma (5.94, 0.01) High scenario	-	0.3	High scenario assumes that QoL loss in survivors of MenB with sequelae is high and is equal to the QoL loss in survivors of MenC[13, 19].
Vaccination parameters					
Vaccination uptake - infant immunisation priming course: routine vaccination, free of charge (%)	55	High and low scenarios	49	93	Vaccine coverage surveys in the three Belgian entities in recent years and expert opinion. The BE uptake of vaccines with similar situation have been selected and an average coverage estimated. When no information was available for the 3rd or booster dose, the drop-out rate observed with similar vaccines has been applied to the previous dose coverage.
Vaccination uptake - infant immunisation booster: routine vaccination, free of charge (%)	50	High and low scenarios	43	91	
Vaccination uptake - adolescent immunisation: routine vaccination, free of charge (%)	60	High and low scenarios	42	82	
Vaccination uptake - infant immunisation priming course: partly reimbursed (%)	50	High and low scenarios	34	65	
Vaccination uptake - infant immunisation booster: partly reimbursed (%)	40	High and low scenarios	25	52	
Vaccination uptake - adolescent immunisation: partly reimbursed (%)	30	High and low scenarios	21	39	
Vaccination uptake - infant immunisation priming course: private market (%)	20	High and low scenarios	10	30	
Vaccination uptake - infant immunisation booster: private market (%)	10	High and low scenarios	10	30	

Parameter	BE Base case	BE distribution	Low scenario	High scenario	References/Sources and Notes
Vaccination uptake - adolescent immunisation: private market (%)	10	High and low scenarios	10	30	
Vaccine strain coverage in dynamic model, all ages (%)	78	High and low scenarios	50	85	Base case = EU average. High scenario= France data. Low scenario = EU average proportion of strains covered by ≥2 antigens. Age-specific proportions were used for the static model, but are not provided here (unpublished internal Novartis data).
Vaccine efficacy against disease, infant immunisation (%)	95	Low scenario	77	-	Proportion of vaccinated subjects that show a SBA response. For infants, studies from Findlow, Gossger and Vesikari; for adolescent doses, studies from Santaloya + data provided by Novartis. Low scenario only applied to dynamic model.
Vaccine efficacy against disease, adolescent vaccination (%)	100	Low scenario	73	-	
Vaccine efficacy against carriage acquisition (%)	30	-	-	-	Assumed based on [20]. Used in the dynamic model only.
Average duration of vaccine protection - infant immunisation after primary doses (months)	22	High and low scenarios	16	26	Studies and persistence data provided by published studies and by Novartis for later follow-up data ([21, 22] for infants, [22, 23] for infant booster, [24] for adolescents).
Average duration of vaccine protection - infant immunisation after booster (months)	27	High and low scenarios	17	36	
Average duration of vaccine protection - adolescent immunisation (months)	73	High and low scenarios	69	105	
Rate of mild adverse reactions, infants (number of vaccine doses resulting in 1 reaction)	100	High and low scenarios	225	38	[21, 22, 24] and frequency of consultation for vaccine adverse event from Belgium.
Rate of mild adverse reactions, adolescents (number of vaccine doses resulting in 1 reaction)	868	High and low scenarios	1429	370	
Rate of serious adverse reactions, infants (number of vaccine doses resulting in 1 reaction)	282	High and low scenarios	643	118	
Rate of serious adverse reactions, adolescents (number of vaccine doses resulting in 1 reaction)	719790	High and low scenarios	0	1208	
Cost of treatment					
Cost per spell in hospital, (€) <1 year - serogroup B	7320.26	Gamma (2.25, 3247.07) High and low scenarios	4254.49	8066.55	The national database from the Belgian Technical Cell (coupled "Hospital Clinical Records" and "Hospital Billing

Parameter	BE Base case	BE distribution	Low scenario	High scenario	References/Sources and Notes
Cost per spell in hospital, (€) 1-4 years - serogroup B	6228.36	Gamma (3.38, 1842.24) High and low scenarios	4163.19	6814.24	Data") coupled to the national database from the Scientific Institute of Public Health ("confirmation of *Neisseria Meningitidis* and serotyping). High and low scenarios are 25 and 75% confidence intervals and are applied in the dynamic model only.
Cost per spell in hospital, (€) 5-9 years - serogroup B	5510.99	Gamma (9.39, 586.88) High and low scenarios	4162.36	6498.02	
Cost per spell in hospital, (€) 10-19 years - serogroup B	7934.41	Gamma (2.50, 3169.29) High and low scenarios	4562.10	8607.59	
Cost per spell in hospital, (€) 20+ years - serogroup B	9989.20	Gamma (2.26, 4422.53) High and low scenarios	5660.07	11642.21	
Cost per spell in hospital, (€) <1 year - all serogroups	7195.07	Gamma(2.28, 3161.41)	-	-	The national database from the Belgian Technical Cell (coupled "Hospital Clinical Records" and "Hospital Billing Data") coupled to the national database from the Scientific Institute of Public Health (confirmation of Neisseria Meningitidis and serotyping)
Cost per spell in hospital, (€) 1-4 years - all serogroups	6242.73	Gamma(3.36, 1856.83)	-	-	
Cost per spell in hospital, (€) 5-9 years - all serogroups	5959.91	Gamma(4.77, 1250.40)	-	-	
Cost per spell in hospital, (€) 10-19 years - all serogroups	7917.83	Gamma(2.50, 3163.16)	-	-	
Cost per spell in hospital, (€) 20+ years - all serogroups	10516.10	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. Applies to those without sequelae only. High and low scenarios only applied to dynamic model.
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	a. Databases from the Walloon and Flemsish communities (number of contacts per IMD case). b. Centre Belge d'Information Pharmacothérapeutique / Belgisch Centrum voor Farmacotherapeutische Informatie (which contains the unit cost of all pharmaceuticals licensed in Belgium). c. FedWeb - Portail du personnel fédéral (wages of doctors and nurses appointed in the public sector). High and low scenarios only applied to dynamic model.
Cost of post vaccine surveillance (€)	25000.00	Gamma (44.44, 562.50)	-	-	An unpublished report from the Belgian Scientific Institute of Public Health (2005) estimating a budget for the financing of the Belgian reference laboratories.
Long-term effects of meningococcal disease					
Cost of support/care for those with	Variable by age	Gamma (variable by age)	Variable by age	Variable by age	a. Former KCE (Belgian Health Care Knowledge Centre)

Parameter	BE Base case	BE distribution	Low scenario	High scenario	References/Sources and Notes
sequelae, one off, serogroup B (€)		High and low scenarios			reports. b. Belgian reimbursement scheme (i.e. "nomenclature", which contains the unit costs of all health care services reimbursed in Belgium). c. The National database from the Belgian Technical Cell (coupled "Hospital Clinical Records" and "Hospital Billing Data") for specific APR-DRG or ICD-9-CM codes. d. Centre Belge d'Information Pharmacothérapeutique / Belgisch Centrum voor Farmacotherapeutische Informatie (which contains the unit cost of all pharmaceuticals licensed in Belgium). High and low scenarios only applied to dynamic model.
Cost of support/care for those with sequelae, one off, all serogroups (€)	Variable by age	Gamma (variable by age) High and low scenarios	Variable by age	Variable by age	
Cost of support/ care for those with severe sequelae, annual, serogroup B (€)	Variable by age	Gamma (variable by age) High and low scenarios	Variable by age	Variable by age	
Cost of support/ care for those with severe sequelae, annual, all serogroups (€)	Variable by age	Gamma (variable by age) High and low scenarios	Variable by age	Variable by age	
Vaccination					
Cost per vaccine dose, routine vaccination free of charge(€)	Not public	High and low scenarios	Not public	Not public	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.
Cost per vaccine dose, partly reimbursed (€)	Not public	High and low scenarios	Not public	-	The price cannot be higher than the base-case in the partly reimbursed strategy.
Cost per vaccine dose, private market (€)	Not public	-	-	-	
Cost of routine administration, free of charge, primary (three dose total, €)	34.22	Gamma (44.44, 0.77) and high and low scenarios	24.91	44.99	Belgian reimbursement scheme (i.e. "nomenclature", which contains the unit costs of all health care services reimbursed in Belgium). High and low scenarios only applied to dynamic model.
Cost of routine administration, free of charge, booster (per dose, €)	16.26	Gamma (44.44, 0.37) and high and low scenarios	11.84	21.38	
Cost of routine administration, free of charge, adolescent (per dose, €)	9.58	High and low scenarios	6.97	12.59	
Cost of routine administration, partly reimbursed, primary (three dose total, €)	32.16	Gamma (44.44, 0.72) and high and low scenarios	23.40	42.27	
Cost of routine administration, partly reimbursed, booster (per dose, €)	16.26	Gamma (44.44, 0.37) and high and low scenarios	11.84	21.38	
Cost of routine administration, partly reimbursed, adolescent (per dose, €)	9.58	High and low scenarios	6.97	12.59	
Cost of routine administration, private market, primary (three dose total, €)	48.20	Gamma (100.00, 0.48) and high and low scenarios	39.21	58.09	
Cost of routine administration, private market, booster (per dose, €)	23.53	Gamma (100.00, 0.24) and high and low scenarios	19.14	28.35	

Parameter	BE Base case	BE distribution	Low scenario	High scenario	References/Sources and Notes
Cost of routine administration, private market, adolescent (per dose, €)	23.05	-	-	-	No scenario as fixed parameter.
Adverse reaction (minor) GP/paediatrician consult cost for infants(€)	29.96	Gamma (5.43, 5.52) High and low scenarios	10.30	59.92	Belgian reimbursement scheme (i.e. "nomenclature", which contains the unit costs of all health care services reimbursed in Belgium). Belgian Health Interview Survey. High and low scenarios only applied to dynamic model.
Adverse reaction (minor) GP consult cost for adolescents(€)	23.05	Gamma (5.43, 4.24) High and low scenarios	7.93	46.10	
Adverse reaction (severe) cost (€)	2135.63	Gamma (4.11, 519.92) High and low scenarios	595.14	4642.23	National database from the Belgian Technical Cell: coupled "Hospital Clinical Records" and "Hospital Billing Data". Cost (in €) per hospital stay due to convulsions post vaccination. High and low scenarios only applied to dynamic model.

Best and worst case parameter combinations

Cohort model, combination of parameters for best case: increased incidence and case fatality rates; higher vaccine strain coverage; higher rates of vaccine uptake; longer duration of protection from vaccination (lower rate of vaccine waning protection); lower rates of vaccine adverse reactions (mild and serious); high proportion of people with sequelae; lower vaccine cost per dose.
Cohort model, combination of parameters for worst case: lower incidence and case-fatality rate; lower vaccine strain coverage; lower rates of vaccine uptake; shorter duration of protection from vaccination (higher rate of vaccine waning protection); higher rates of vaccine adverse reactions (mild and serious); low proportion of people with sequelae; higher vaccine cost per dose (routine vaccination only).
Dynamic model, combination of parameters for best case: increased incidence and case fatality rates; higher vaccine strain coverage; higher rates of vaccine uptake; longer duration of protection from vaccination (lower rate of vaccine waning protection); lower rates of vaccine adverse reactions (mild and serious); high proportion of people with sequelae, lower cost per vaccine dose; lower vaccine administration costs (lower 95% CI of distribution); lower cost of mild vaccine adverse event (lower 95% CI of distribution); lower cost of severe vaccine adverse event (lower 95% CI of distribution); higher cost of meningococcal disease treatment(75th percentile of distribution); higher cost of meningococcal disease follow-up care (upper 95% CI of distribution); higher cost of meningococcal sequelae (upper 95% CI of distribution); higher cost of public health response to a case (upper 95% CI of distribution).
Dynamic model, combination of parameters for worst case: lower incidence and case-fatality rate; lower vaccine strain coverage; lower rates of vaccine uptake; shorter duration of protection from vaccination (higher rate of vaccine waning protection); higher rates of vaccine adverse reactions (mild and serious); low proportion of people with sequelae; higher vaccine cost per dose (routine vaccination, no herd effects only); higher vaccine administration costs (upper 95% CI of distribution); higher cost of mild vaccine adverse (upper 95% CI of distribution); higher cost of severe vaccine adverse event (upper 95% CI of distribution); lower cost of meningococcal disease treatment (25th percentile of distribution); lower cost of meningococcal disease follow-up care (lower 95% CI of distribution); lower cost of meningococcal sequelae (lower 95% CI of distribution); lower cost of public health response to a case (lower 95% CI of distribution).

NRL, National Reference Laboratory

Table 2. Vaccination strategies modelled with base case vaccination parameters[a]

Vaccination	Months protection[b]
Infant strategies	
3, 5, 6, +12 months	[22,27]
Infant and adolescent strategies	
3, 5, 6, +12 months and	[22,27]
14 year olds (0, 2 schedule)	[73]
Adolescent strategies	
14 year olds (0, 2 schedule)	[73]

The duration of vaccine protection (Table 2) was assumed based on evidence from published studies and clinical trial data of Bexsero. Clinical trial data of Bexsero has shown rapid waning of antibodies against some antigens in those vaccinated in infancy, though responses can be boosted with an additional vaccine dose; increased GMTs have been observed after the booster compared to the priming course[22]. The effectiveness of the MenC vaccine was found to be superior in older children compared to infants more than one year following vaccination and trials of Bexsero in adolescents have shown over 64% of individuals maintain putatively protective antibody titres 18-24 months post vaccination[25].

Three different vaccine policies were considered: vaccine provided free of charge (i.e. included in the routine vaccine schedule), vaccine partly reimbursed or private market only. These payment scenarios affect the modelled cost of the vaccine, vaccine uptake and costs of administration (Table 3). The reference year for the model is 2012. Costs were measured in Euros at 2012 prices; costs from previous years were updated to 2012 values using the Health Consumer price indices. 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 3.0% was applied to costs and 1.5% was applied to benefits. The cost-effectiveness (utility) analysis was undertaken from the payer perspective.

Table 3. Vaccination scenarios and associated parameters

Vaccination scenario	Uptake of vaccine doses			Vaccine administration cost per dose		
	Primary (%)	Booster (%)	Adolescent (%)	Primary (€)	Booster (€)	Adolescent (€)
Routine, free of charge	55	50	60	11.41	16.26	9.58
Partly reimbursed	50	40	30	10.72	16.26	9.58
Private market	20	10	10	16.07	23.53	23.05

Uncertainty around the model parameters was handled in two ways: (1) by running both models under a number of different scenarios and (2) by making the cohort model partially probabilistic. The model was run under different scenarios including: disease incidence, case fatality rate, vaccination uptake, vaccine strain coverage, duration of protection, proportions with sequelae, quality of life loss for survivors with sequelae, carriage prevalence, vaccine efficacy against disease, rate of adverse reactions, and discount rates. Probabilistic sensitivity analysis was used to characterise the uncertainty around quality of life loss and all costs, with the exception of the vaccine cost per dose. In this probabilistic analysis distributions were used to represent input parameters instead of point

[a] Strategies involving adolescent vaccination were implemented in the dynamic model only.

[b] Waning protection from vaccination was implemented as a rate equal to 1/months protection. Where two values are specified this is the duration of protection following the priming course and then the booster, for example there is waning protection following the 3 dose course at 3, 5, 6 months at a monthly rate of 1/22 and following the booster at 12 months there is waning protection at a monthly rate of 1/27.

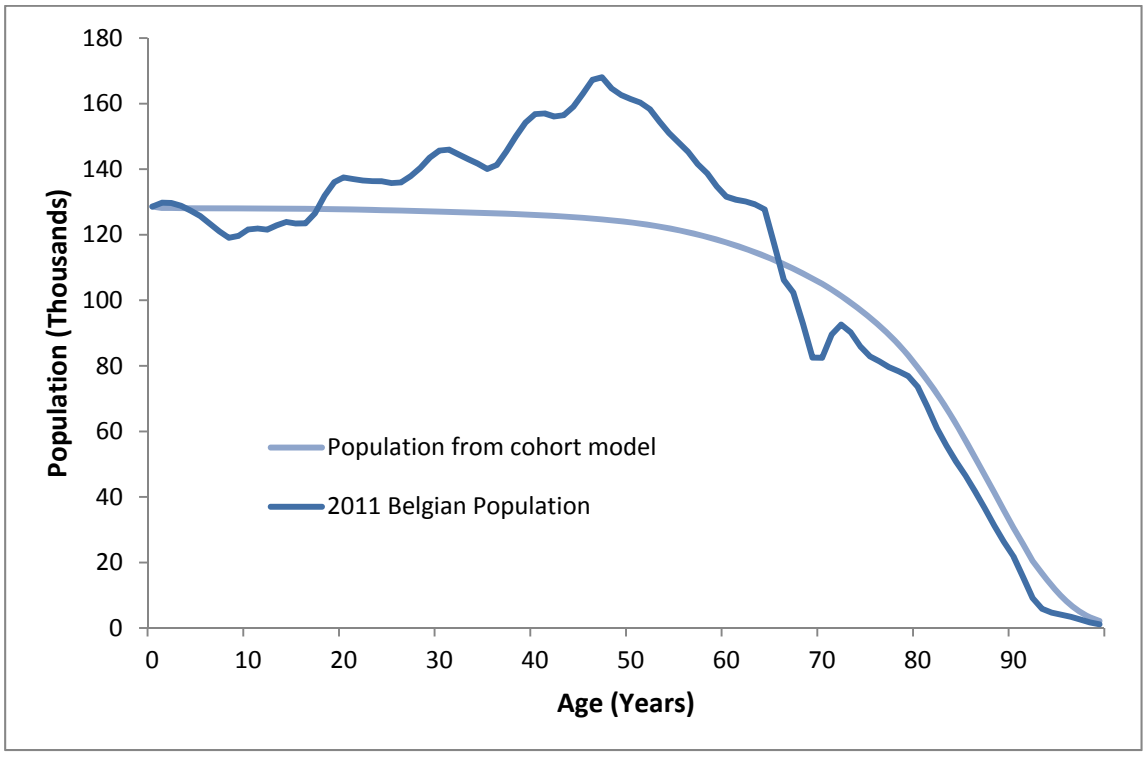
estimates; 1000 simple random samples of these distributions were then propagated through the model to provide a distribution in the output parameters.

D. Model validation

Population

Figure 2 compares the population, by age, of a single birth cohort followed over the time horizon of the model (100 years) to that of the 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 cohort and the dynamic model, the dynamic population structure is assumed to be the same as the smooth curve seen in the cohort model from a single birth cohort. Thus while the two models can be used to predict the number of cases arising, the actual number of cases arising, or averted, may be higher or lower, depending on the changing population structures over time.

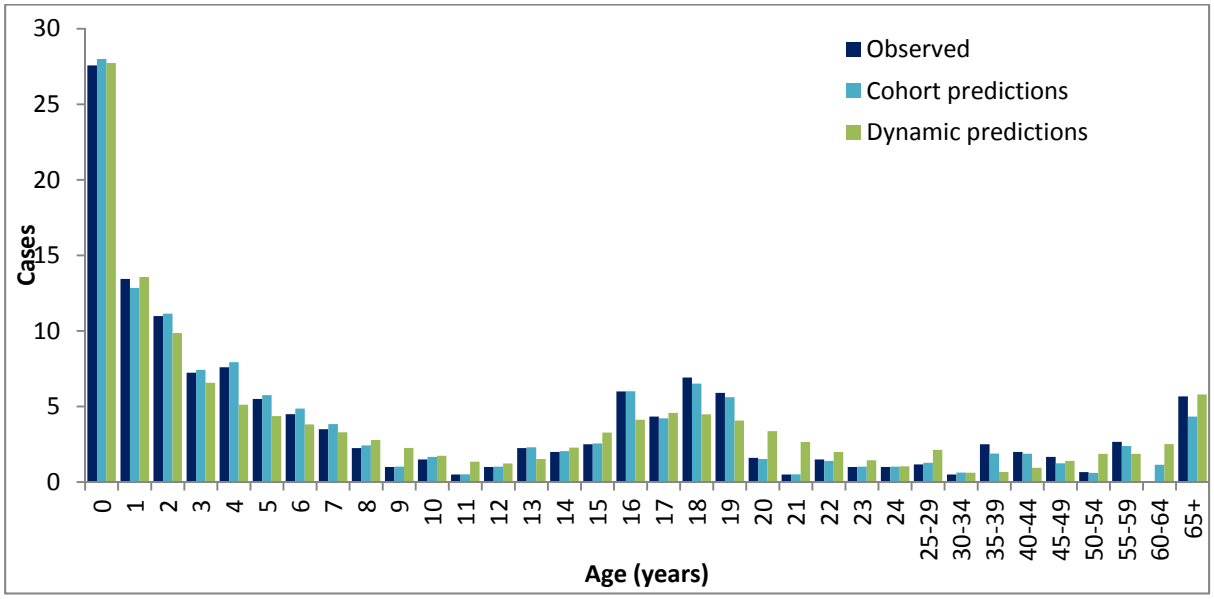
Figure 2. Comparison of population figures from the baseline cohort model (single birth cohort) and the Belgian population in 2011



Cases predicted

Both the cohort and dynamic models provide a good representation of the annual number of cases observed by age (Figure 3).

Figure 3. Comparison of the average annual number of serogroup B meningococcal disease cases in without vaccination against MenB and those predicted in the base case cohort and dynamic models, by age group



E. RESULTS

RESULTS FROM THE COHORT MODEL[c]

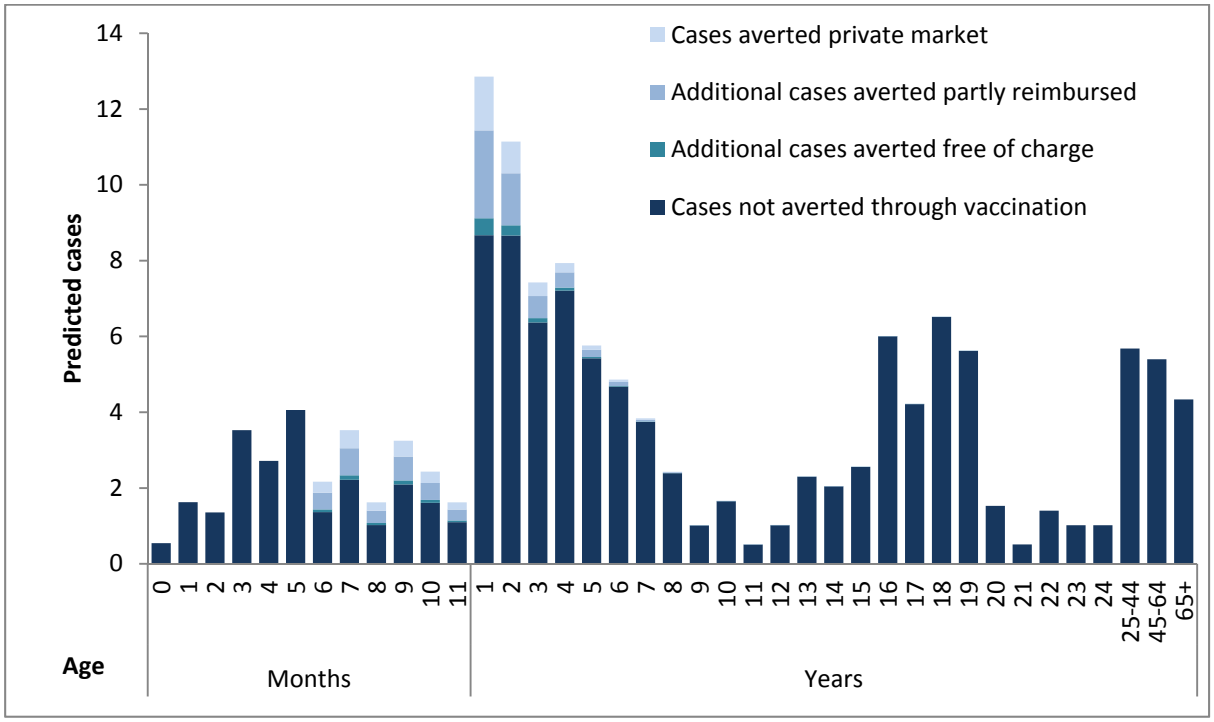
Base case parameters – epidemiological impact of different vaccination strategies

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 €5.8M. The base case model (routine vaccination at 3, 5, 6+12 months, 55% uptake for the primary dose and 50% for the booster, 95% vaccine efficacy, 27 months protection after the booster) predicts 14 of these cases (10.3%) and 1 death could be prevented through infant vaccination with a new meningococcal vaccine (Table 4, Figure 4).

Figure 4 shows the number of cases of meningococcal disease by age predicted by the model and the number of cases averted under routine 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 the model predicts 5 cases would be averted, due to the low assumed vaccine uptake under this policy; an extra 8 cases are predicted to be averted if the vaccine was partly reimbursed and a further 1 case averted if the vaccine were to be offered free of charge (i.e. in the routine immunisation schedule).

[c] The results from the cohort model are the mean result from 1000 probabilistic runs of the model; please note not all parameters are probabilistic, see Table 1 for details.

Figure 4. Cases averted by age, infant vaccination at 3, 5, 6 +12 months for different immunisation policies, vaccine free of charge (base case), partly reimbursed or private market



Base case parameters – cost-effectiveness of different vaccination policies

The cost-effectiveness of the vaccine strategies considered is presented in Table 4. 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 scenario, averting more cases of disease and the cost of the vaccine is assumed to be lower compared to the other strategies. 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.

The cost-effectiveness plane illustrating the joint distribution of incremental costs and quality adjusted life years gained from the 1,000 probabilistic simulations of the baseline is shown in Figure 5; 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 6). For the base case model with vaccination at 3, 5, 6+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 are classified as cost-effective.

Figure 5. Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for infant (3, 5, 6 + 12 months) vaccination, with lines indicating selected incremental cost-effectiveness ratios

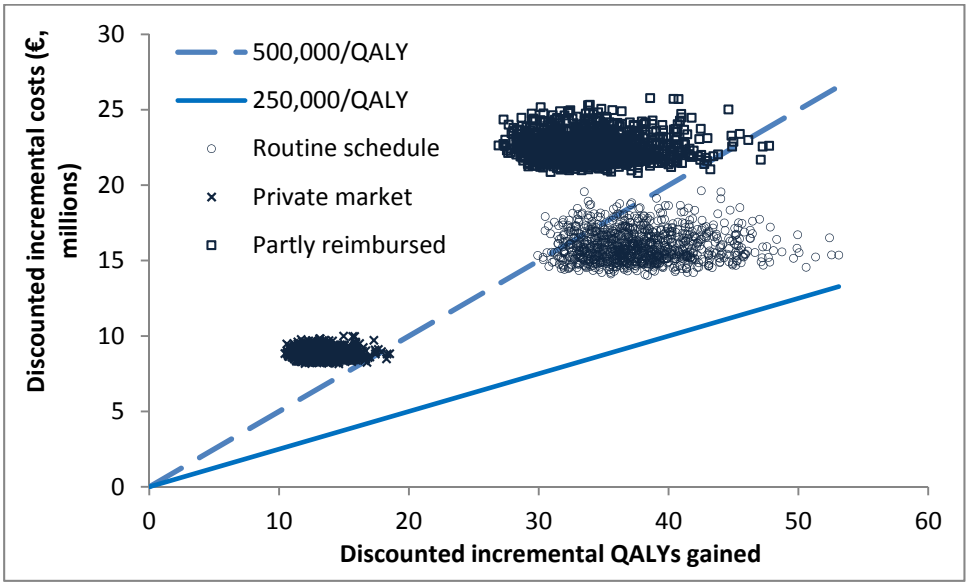
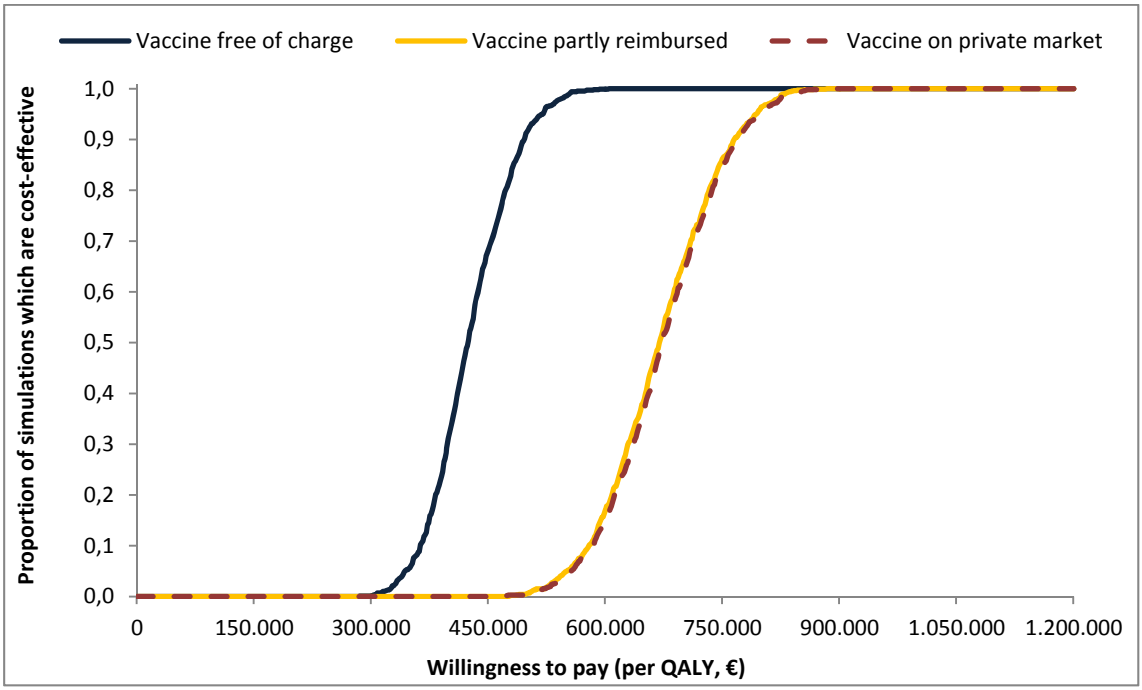


Figure 6. Cost-effectiveness acceptability curves for base case cohort model (3, 5, 6 + 12 months vaccination) for the three vaccine policies



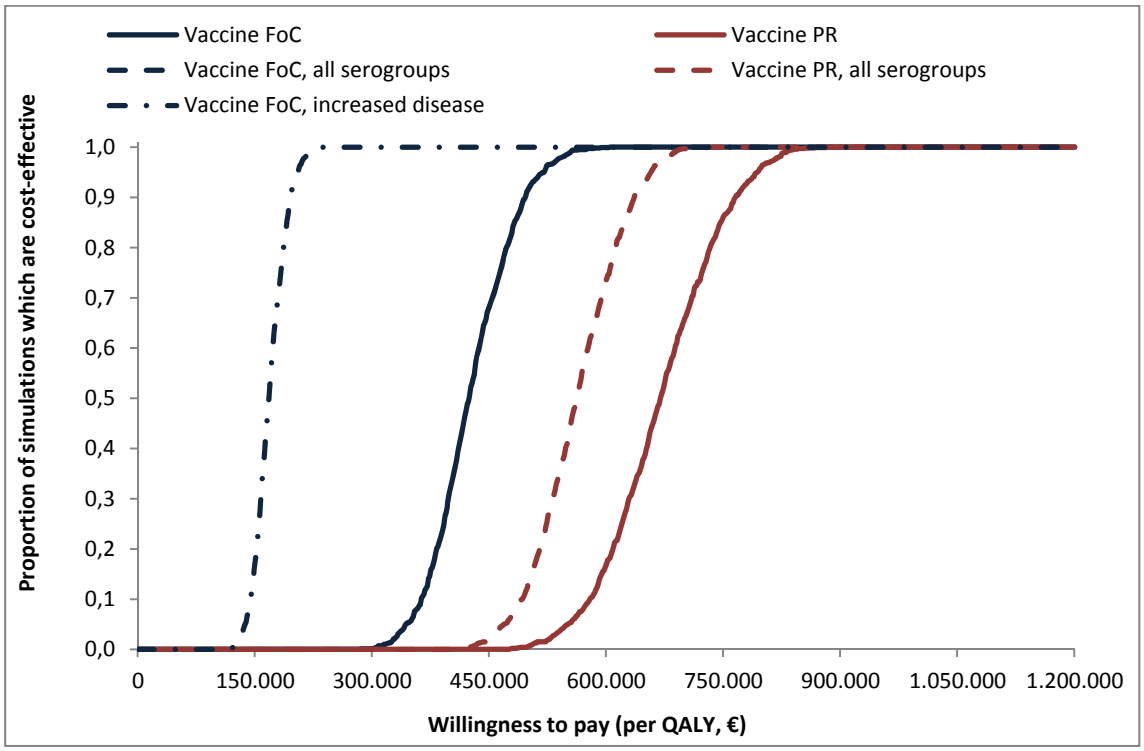
Scenario analysis

A number of scenario analyses were undertaken for the routine infant vaccination schedule, these results are presented in Table 4; results shown on the cost-effectiveness plane are presented in the Appendix.

Increasing the incidence and case fatality from the base case (139 cases and 7 deaths annually) to the high incidence 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 (to €167,000 per quality adjusted life year gained, Figure 7), despite the proportion of cases averted through vaccination decreasing with increasing incidence (9.7% cases averted under increased incidence and case fatality scenario, compared to 10.3% in the base case). 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).

Figure 7. 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)



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 8. Cases averted by age, infant vaccination at 3, 5, 6 +12 months for different assumptions of vaccine strain coverage, vaccine free of charge policy

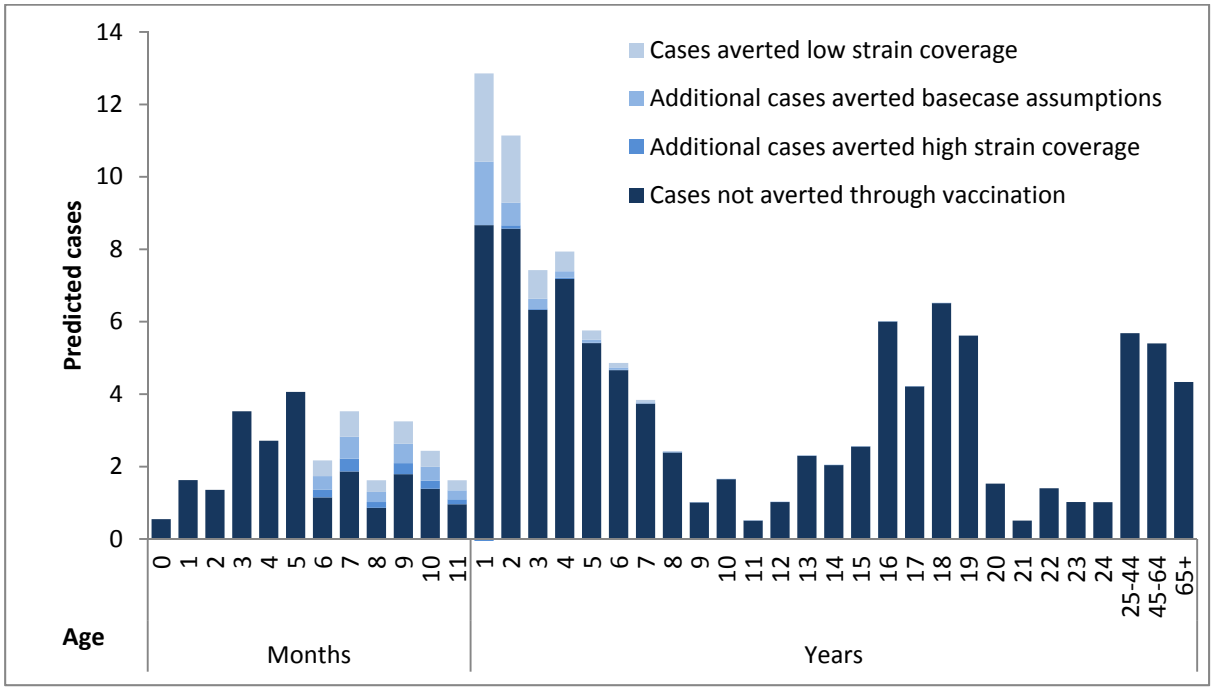
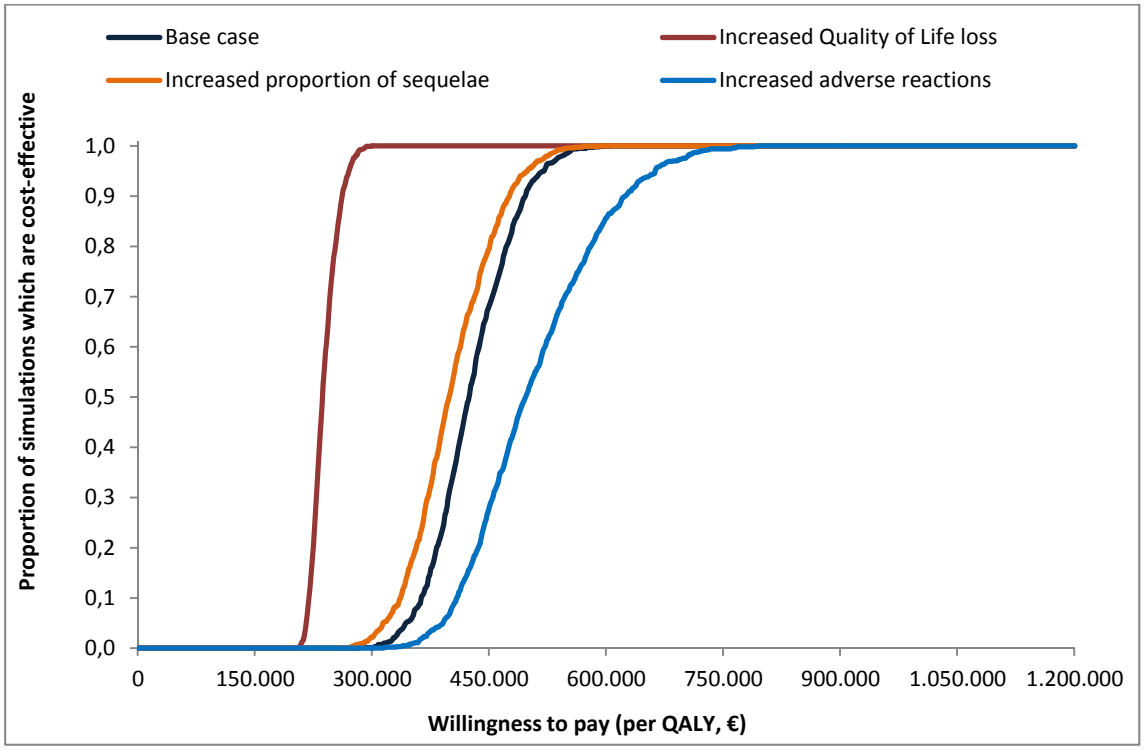


Figure 8 shows the predicted number of cases under different assumptions of vaccine strain coverage. With low vaccine strain coverage (38% in <1 year olds, 43% in 1 year olds, 59% in 2-5 year olds and 54% >5 years) 9 cases of disease are predicted to be averted through routine infant immunisation implemented 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.

Increasing the quality of life loss for survivors with sequelae or increasing the assumed proportion with sequelae increases the QALY gain resulting in vaccination appearing more economically favourable, however the cost per QALY gain remains over €200,000 (Figure 9).

In the base case model with the vaccine provided free of charge an estimated 2,757 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 2,336 severe reactions and 7,255 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 9).

Figure 9. 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



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 and combined with differential discounting this results in an increased cost per quality adjusted life year gained (€422,700 to €427,400).

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 of vaccination from €422,700 to €1,172,900 under the vaccine free of charge scenario.

For two vaccine policies 'best case' and 'worst case' scenarios were considered. These 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: incidence and case fatality rates, strain coverage, vaccine uptake, duration of protection, the proportion of people with sequelae following disease, proportion of adverse reactions and vaccine cost. Under the most favourable assumptions the cost per quality adjusted life year gained decreased from €422,700 to €98,300 under the vaccine free of charge 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.

In order to assess the importance of individual parameters to the model, an ANCOVA (analysis of covariance) analysis was undertaken (Figure 10). This analysis only provides an approximate result for the proportion of the variation of the costs and QALYs gained explained by each parameter, as ANCOVA assumes a linear relationship between the input and output parameters, which does not hold for the cohort model. It is still useful, however, in providing an understanding of the relative effect of different parameters. 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 is caused by a high assumed rate of adverse reactions with high cost and a wide distribution (95% confidence interval for this parameter €595.14 to €4642.23 per event). 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 10: ANCOVA analysis of proportion of sum of squares for discounted incremental costs (left) and discounted incremental benefits (right) explained by uncertainty in the parameters for the base case cohort model (3, 5, 6+12 months schedule)

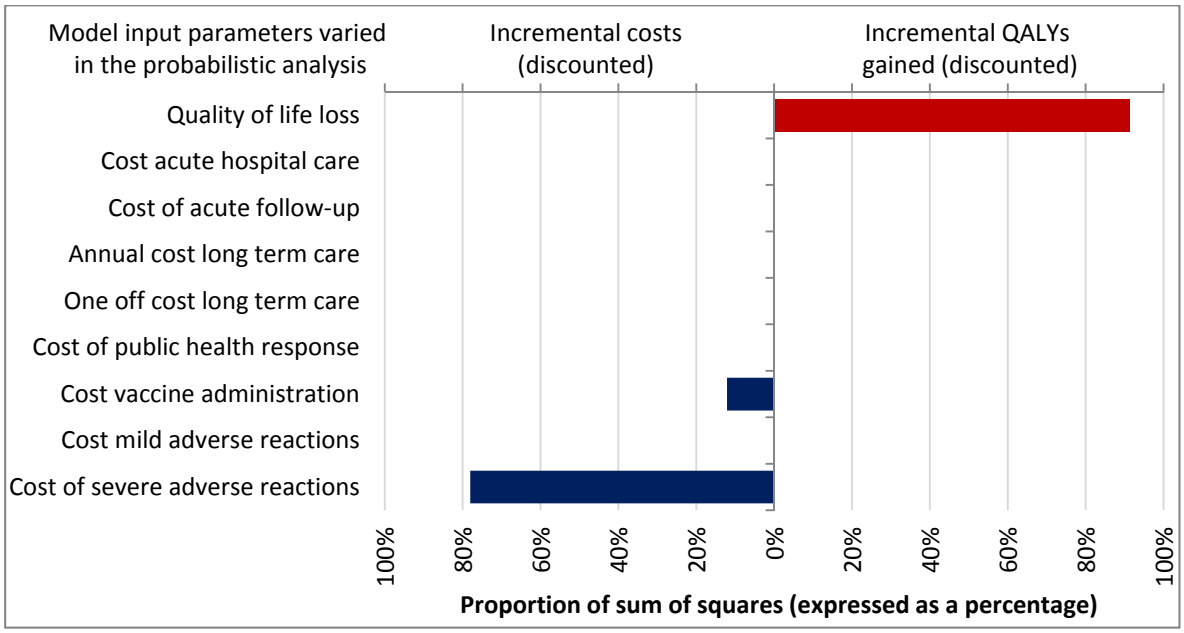


Table 4. Results from the cohort model, comparison of vaccination strategies and scenarios (vaccination vs. no vaccination)

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
Principal results										
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										
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	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

Table continued overleaf

[a] Figures rounded to nearest 100.

[b] Additional cost of vaccination less costs averted through reduction in cases.

Table continued from previous page

Scenario description	Undiscounted						Discounted[c]			
	Cases averted (%)	Cases with sequelae averted	Deaths averted	Life Years Saved	QALY gained	Net cost of vaccination (millions)[d]	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										
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

[c] Figures rounded to nearest 100.

[d] Additional cost of vaccination less costs averted through reduction in cases.

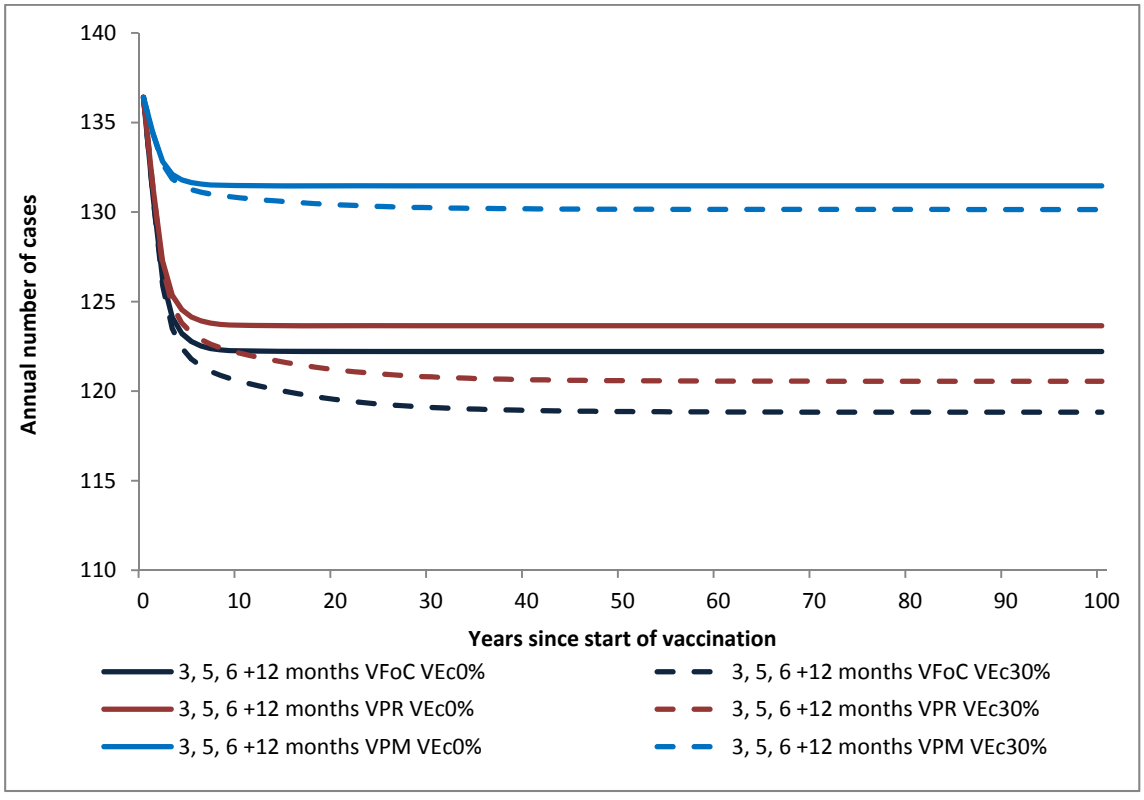
RESULTS FROM THE DYNAMIC MODEL

Base case parameters – epidemiological impact of different vaccination policies

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, the model predicts that 13,641 cases of serogroup B meningococcal disease, resulting in 1,957 cases with sequelae and 730 deaths, would occur over a 100 year period with the costs of treatment and long-term care totalling €387.2M over the time horizon of the model. In the base case model the vaccine was assumed to have 30% vaccine efficacy against MenB carriage acquisition; for comparison with the cohort model no herd effects were also considered. A summary of the results for different vaccination policies are presented in Table 5 and for the scenario analyses in Table 12, Table 13 and Table 14.

As expected, increasing the assumed vaccine efficacy against carriage acquisition for each strategy increases the number of cases averted. However, the herd effects seen under infant vaccination alone are limited (Figure 11, Figure 14) because meningococcal carriage prevalence is low in young children.

Figure 11. Effect on annual disease cases of 3, 5, 6+12 month vaccination with varying assumptions about the vaccine effect against carriage acquisition (VEc) for different immunisation policies, vaccine free of charge (base case, VFoC), partly reimbursed (PR) or private market (PM)(please note the vertical axis does not start at 0)



If the vaccine protects against acquisition of carriage, sustained reductions in case numbers could be achieved through routine vaccination of adolescents (Figure 12 and Figure 15); such a strategy results in a long term reduction in cases as it constantly targets the age group where carriage is through 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 increased vaccine uptake assumed under this strategy. Routine adolescent vaccination could be combined with routine infant vaccination to have a greater impact on case numbers in the short term (Figure 13, Figure 16).

Figure 12. Effect on annual disease cases of 14 year old vaccination with varying assumptions about the vaccine effect against carriage acquisition (VEc) for different immunisation policies, vaccine free of charge (base case, VFoC), partly reimbursed (PR) or private market (PM)

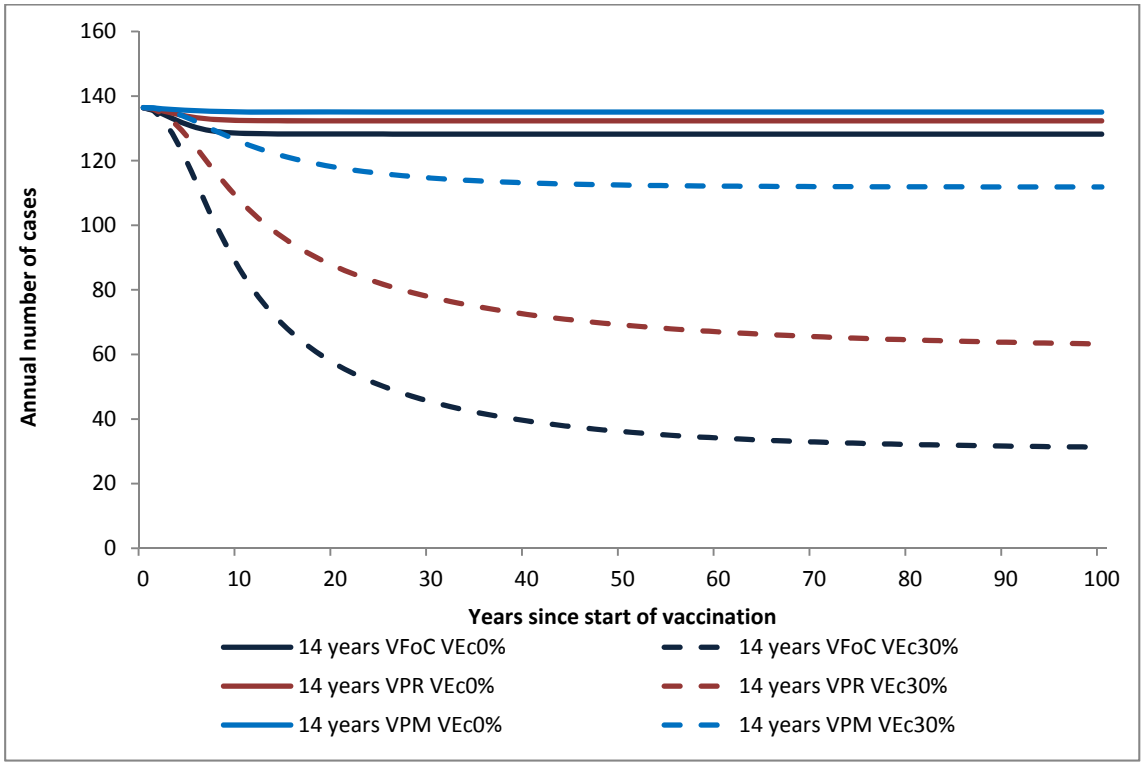


Figure 13. Effect on annual disease cases of 3, 5, 6+12months and14 year olds vaccination with varying assumptions about the vaccine effect against carriage acquisition (VEc) for different immunisation policies, vaccine free of charge (base case, VFoC), partly reimbursed(PR), or private market (PM)

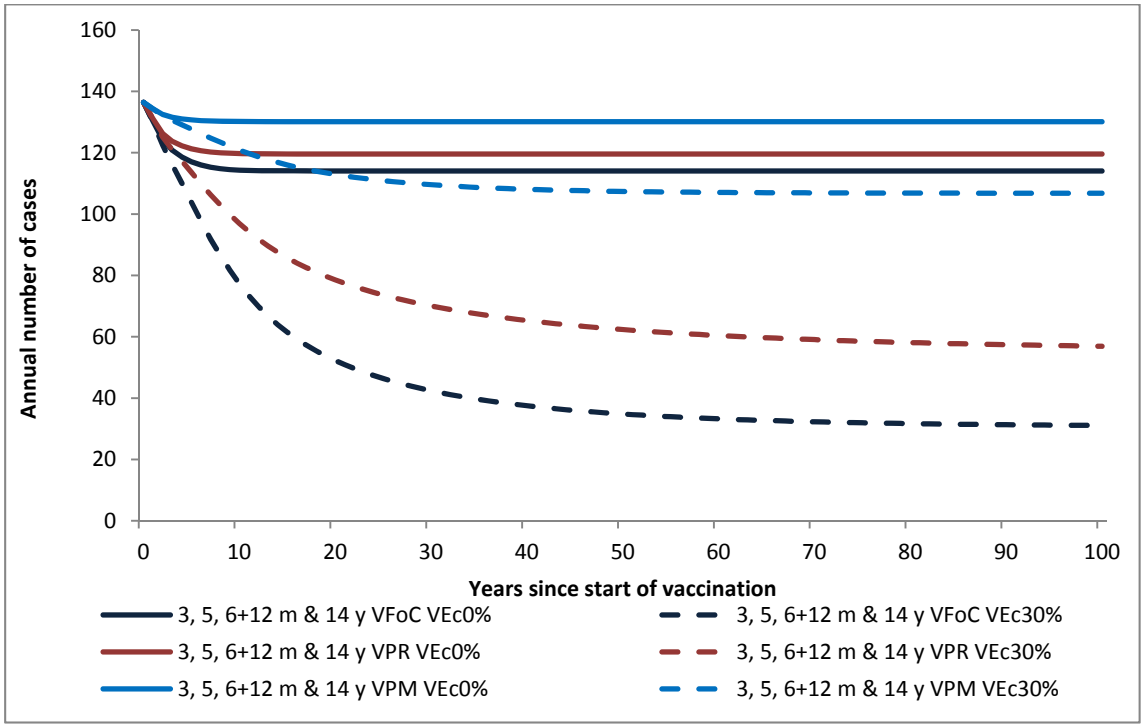


Figure 14. Cases averted by age at selected time points since the start of vaccination from the dynamic model, infant vaccination at 3, 5, 6+12 months assuming the vaccine is in the routine schedule

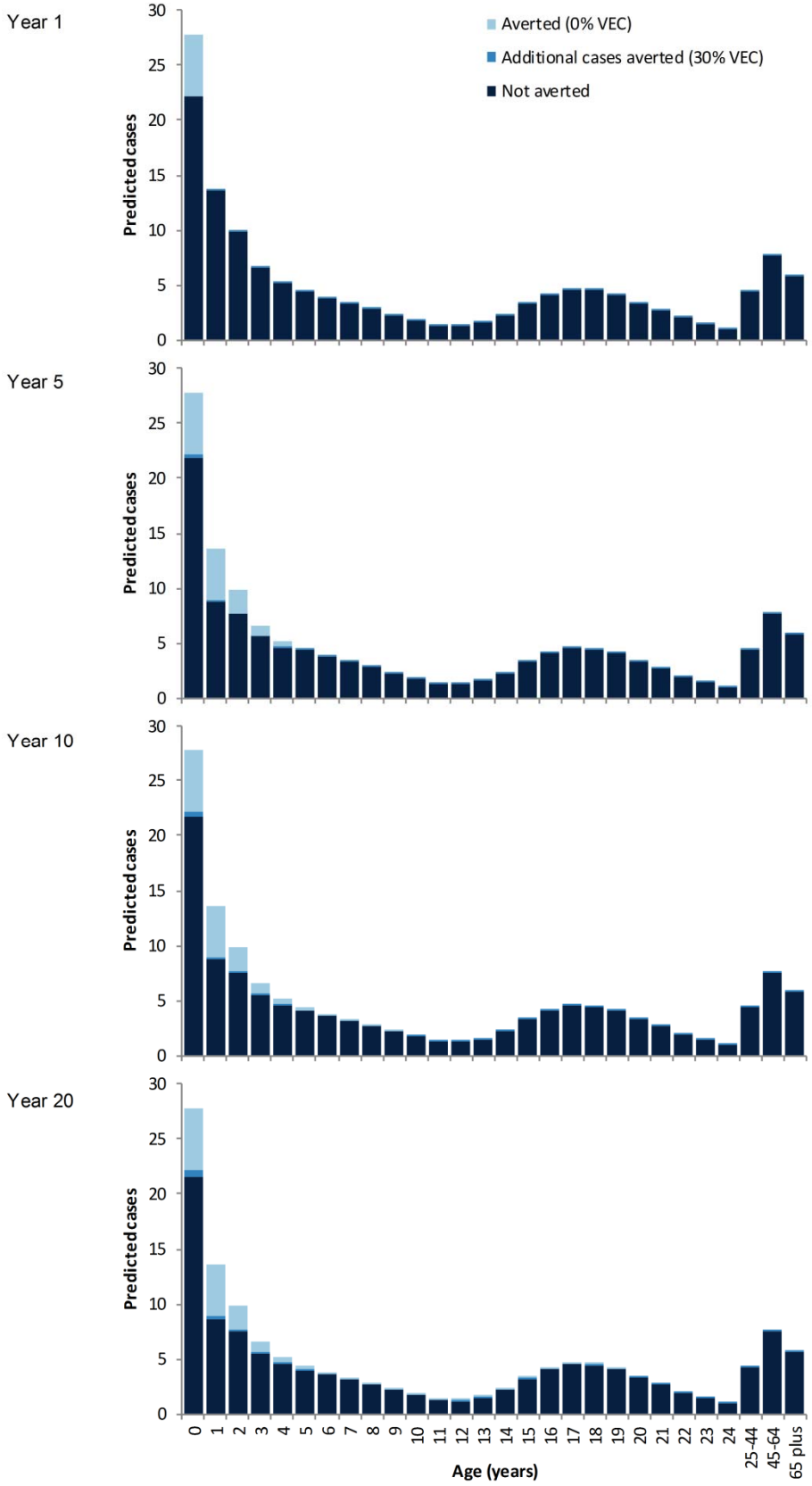


Figure 15. Cases averted by age at selected time points since the start of vaccination from the dynamic model, adolescent vaccination at 14 years assuming the vaccine is in the routine schedule

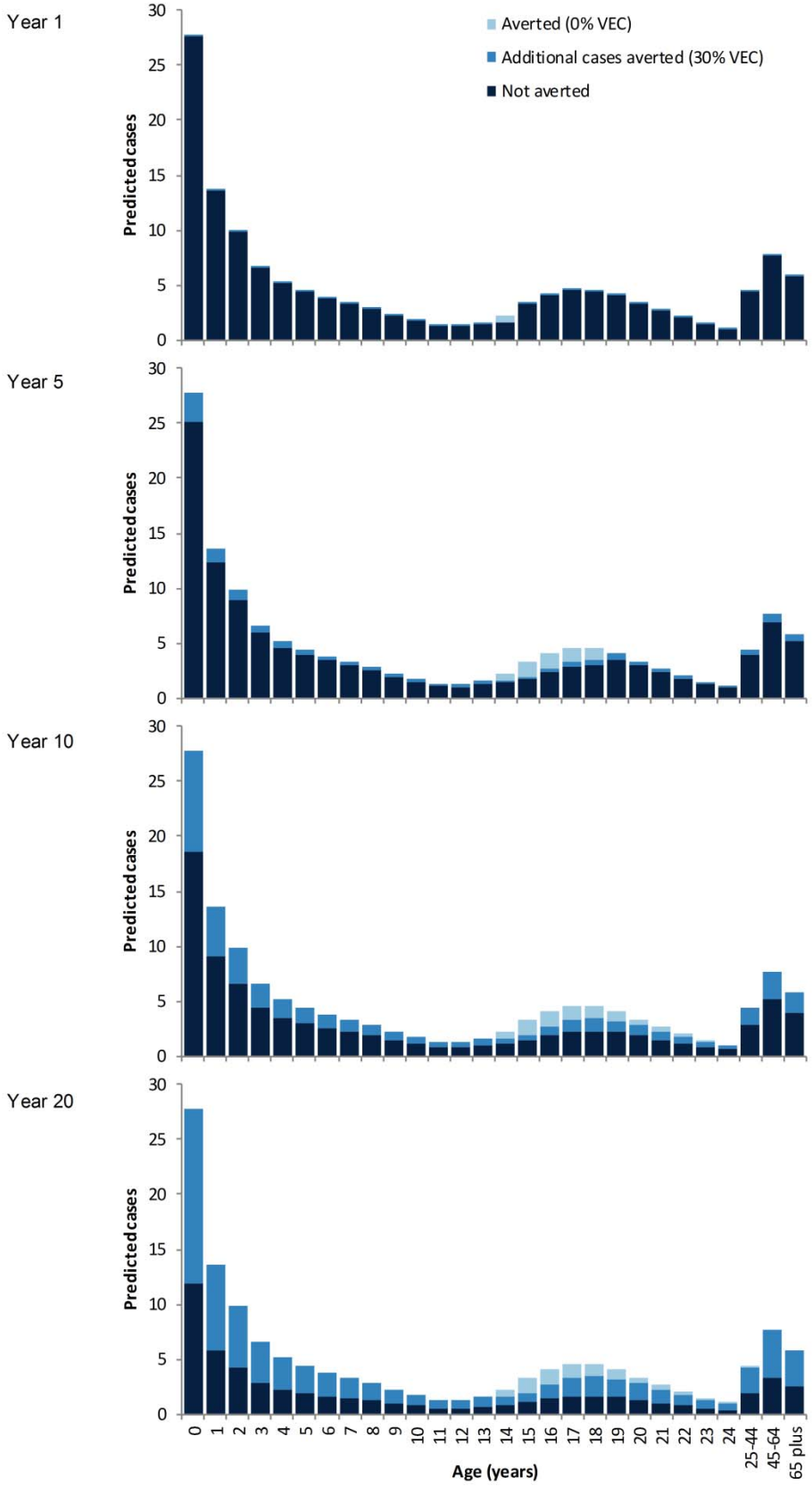


Figure 16. Cases averted by age at selected time points since the start of vaccination from the dynamic model, adolescent vaccination at 3, 5, 6+12 months and 14 years assuming the vaccine is in the routine schedule

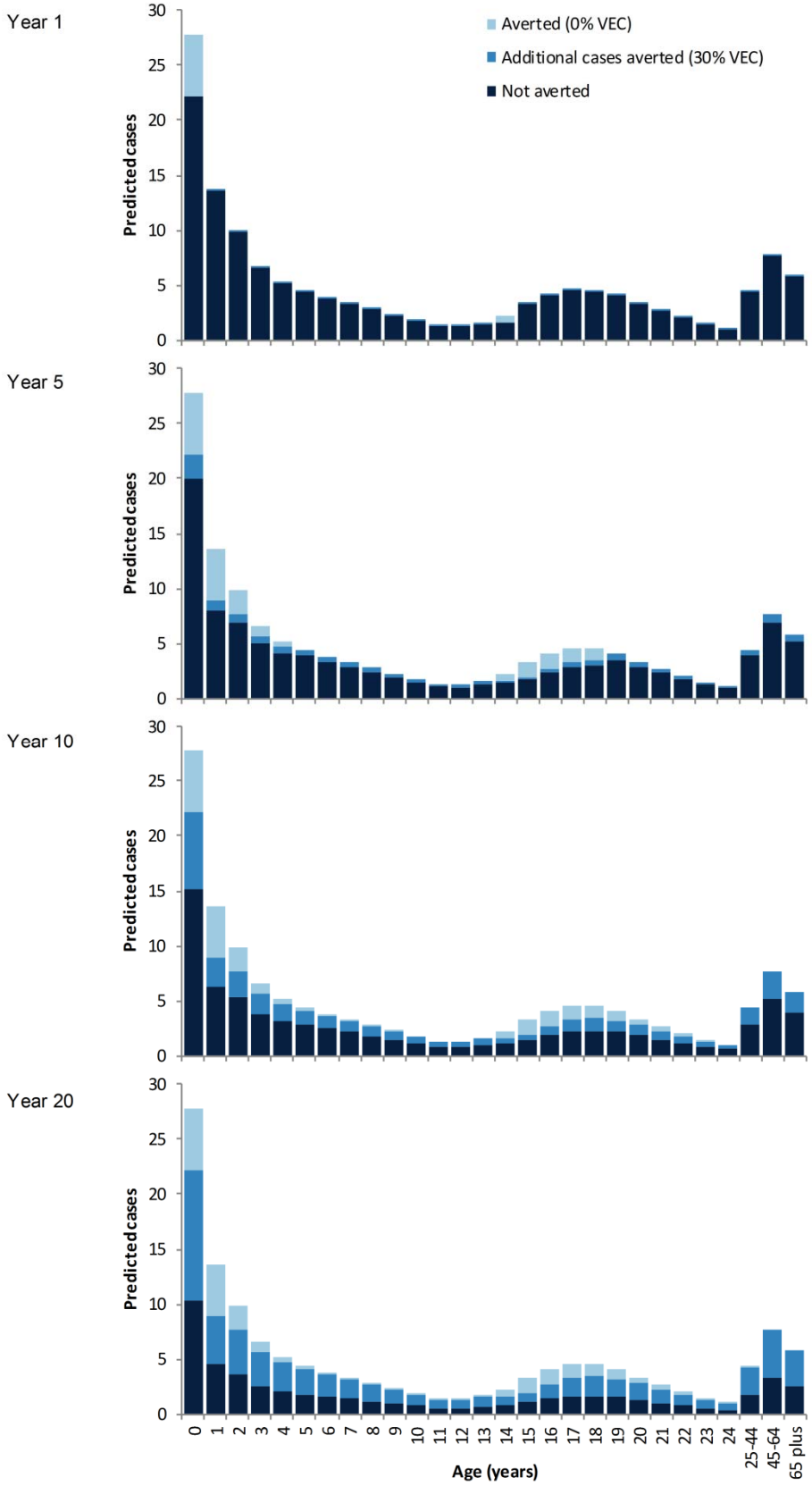


Table 5. Results from the dynamic model, comparison of vaccination strategies (vaccination vs. no vaccination) [a]

Scenario description	Undiscounted						Discounted[b]			
	Cases averted (%)	Cases with sequelae averted	Deaths averted	Life Years Saved	QALY gained	Net cost of vaccination (millions)[c]	Cost per case averted	Cost per death averted	Cost per Life Year Saved	Cost per QALY gained
3, 5, 6 +12 months Vaccine free of charge policy										
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
3, 5, 6 +12 months Vaccine partly reimbursed policy										
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
3, 5, 6 +12 months Vaccine on private market only policy										
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 Vaccine free of charge policy										
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
14 years Vaccine partly reimbursed policy										
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
14 years Vaccine on private market only policy										
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

Table continued overleaf

[a] Unlike the cohort 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 cohort model which principally considers a single cohort only. Please see the methods section for further details.

[b] Figures rounded to nearest 100.

[c] Additional cost of vaccination less costs averted through reduction in cases.

Table continued from previous page

Scenario description	Undiscounted						Discounted[d]			
	Cases averted (%)	Cases with sequelae averted	Deaths averted	Life Years Saved	QALY gained	Net cost of vaccination (millions)[e]	Cost per case averted	Cost per death averted	Cost per Life Year Saved	Cost per QALY gained
3, 5, 6 +12 months and 14 years Vaccine free of charge policy										
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
3, 5, 6 +12 months and 14 years Vaccine partly reimbursed policy										
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
3, 5, 6 +12 months and 14 years Vaccine on private market only policy										
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

[d] Figures rounded to nearest 100.
[e] Additional cost of vaccination less costs averted through reduction in cases.

Table 6. Incremental costs and benefits of alternative vaccination strategies, ranked by discounted net cost of vaccination[f], vaccine free of charge policy, 0% vaccine efficacy against carriage acquisition

	Cost treatment/ vacc.	QALYs gained	Inc. cost	Inc. QALYs gained	Cost per QALY gained (rounded)
Current situation	€89.7M	0	-	-	
14 years	€330.6M	766	€240.9M	766	€314,600
3, 5, 6 +12 months	€615.7M	1734	€285.0M	968	€294,300
3, 5, 6 +12 months and 14 years	€855.8M	2500	€240.1M	766	€313,600

Table 7. Incremental costs and benefits of alternative vaccination strategies, ranked by discounted net cost of vaccination[a], vaccine partly reimbursed policy, 0% vaccine efficacy against carriage acquisition

	Cost treatment/ vacc.	QALYs gained	Inc. cost	Inc. QALYs gained	Cost per QALY gained (rounded)
Current situation	€89.7M	0	-	-	
14 years	€299.0M	383	€209.3M	383	€546,500
3, 5, 6 +12 months	€830.7M	1561	€531.7M	1178	€451,400
3, 5, 6 +12 months and 14 years	€1039.2M	1944	€208.5M	383	€544,600

Table 8. Incremental costs and benefits of alternative vaccination strategies, ranked by discounted net cost of vaccination[a], vaccine on private market only policy, 0% vaccine efficacy against carriage acquisition

	Cost treatment/ vacc.	QALYs gained	Inc. cost	Inc. QALYs gained	Cost per QALY gained (rounded)
Current situation	€89.7M	0	-	-	
14 years	€171.2M	128	€81.5M	128	€638,700
3, 5, 6 +12 months	€378.4M	607	€207.2M	479	€432,300
3, 5, 6 +12 months and 14 years	€459.1M	734	€80.7M	128	€632,400

[f] Each strategy is compared to the strategy above unless dominated.

Table 9. Incremental costs and benefits of alternative vaccination strategies, ranked by discounted net cost of vaccination[g], vaccine free of charge policy, 30% vaccine efficacy against carriage acquisition

	Cost treatment/ vacc.	QALYs gained	Inc. cost	Inc. QALYs gained	Cost per QALY gained (rounded)	
Current situation	€89.7M	0	-	-		
14 years	€289.6M	8207	€199.9M	8207	€24,400	
3, 5, 6 +12 months	€614.1M	2012	€324.5M	-6196	(€52,400)	Dominated
3, 5, 6 +12 months and 14 years	€821.4M	8812	€531.8M	605	€879,500	

Table 10. Incremental costs and benefits of alternative vaccination strategies, ranked by discounted net cost of vaccination[g], vaccine partly reimbursed policy, 30% vaccine efficacy against carriage acquisition

	Cost treatment/ vacc.	QALYs gained	Inc. cost	Inc. QALYs gained	Cost per QALY gained (rounded)	
Current situation	€89.7M	0	-	-		
14 years	€272.4M	5285	€182.7M	5285	€34,600	
3, 5, 6 +12 months	€829.2M	1815	€556.8M	-3470	(€160,500)	Dominated
3, 5, 6 +12 months and 14 years	€1015.6M	6329	€743.2M	1044	€711,800	

Table 11. Incremental costs and benefits of alternative vaccination strategies, ranked by discounted net cost of vaccination[g], vaccine on private market only policy, 30% vaccine efficacy against carriage acquisition

	Cost treatment/ vacc.	QALYs gained	Inc. cost	Inc. QALYs gained	Cost per QALY gained (rounded)	
Current situation	€89.7M	0	-	-		
14 years	€161.6M	1908	€71.9M	1908	€37,700	
3, 5, 6 +12 months	€377.8M	717	€216.2M	-1191	(€181,500)	Dominated
3, 5, 6 +12 months and 14 years	€449.4M	2519	€287.9M	612	€470,700	

[g] Each strategy is compared to the strategy above unless dominated.

Table 12. 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)

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	*9180 (67)*	*1326*	*490*	*18611*	*22596*	*€2151.7M*	*€166,300*	*€3,123,100*	*€100,600*	*€83,000*
All serogroup	6416 (36)	926	425	15838	18691	€2213.6M	€232,500	€3,523,700	€116,400	€98,800
Higher serogroup B carriage prevalence	8522 (62)	1266	452	17442	21268	€2164.4M	€180,100	€3,400,100	€108,000	€88,700
Increased incidence and case fatality rates	23606 (67)	3375	1677	64384	74661	€1764.7M	€58,000	€817,500	€26,100	€22,500
Low vaccine strain coverage (50%)	5988 (44)	866	320	12226	14848	€2236.9M	€259,200	€4,862,800	€156,200	€128,900
High vaccine strain coverage (85%)	9929 (73)	1433	530	20097	24400	€2131.8M	€153,200	€2,876,900	€92,700	€76,500
Lower rates of vaccine uptake	8104 (59)	1176	432	16167	19646	€1765.4M	€157,700	€2,967,400	€96,300	€79,400
Higher rates of vaccine uptake	9724 (71)	1406	519	20251	24613	€3596.7M	€251,300	€4,719,700	€149,300	€123,100
Shorter duration of vaccine protection	9065 (66)	1308	484	18301	22210	€2155.9M	€169,400	€3,178,200	€102,700	€84,800
Longer duration of vaccine protection	9463 (69)	1365	505	19385	23535	€2142.2M	€159,200	€2,988,800	€95,700	€79,000
Higher rates of vaccine adverse reactions (mild and serious)	9180 (67)	1326	490	18611	22596	€2484.2M	€190,900	€3,585,100	€115,500	€95,300
High proportion of people with sequelae	9180 (67)	1646	490	18611	23560	€2108.7M	€164,700	€3,091,700	€99,600	€78,900
Alternative assumption for quality of life loss for survivors with sequelae (0.3 utility loss)	9180 (67)	1326	490	18611	34712	€2151.7M	€166,300	€3,123,100	€100,600	€54,200
Lower vaccine administration costs	9180 (67)	1326	490	18611	22596	€2017.3M	€156,400	€2,936,500	€94,600	€78,100
Lower vaccine cost	9180 (67)	1326	490	18611	22596	€1756.0M	€137,100	€2,573,500	€82,900	€68,400
Higher vaccine cost	9180 (67)	1326	490	18611	22596	€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	18611	22596	€2151.7M	€296,900	€5,589,700	€225,600	€186,500
Best case	27644 (79)	4911	1962	77730	93262	€1546.2M	€47,200	€666,600	€20,800	€17,400
Lower vaccine efficacy against disease (73% infants, 77% adolescents)	9133 (67)	1318	488	18449	22396	€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.

Table 13. 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)

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	*6676 (49)*	*982*	*354*	*13426*	*16360*	*€2772.3M*	*€293,100*	*€5,534,400*	*€178,000*	*€146,300*
All serogroup	3974 (22)	608	255	9943	11869	€2832.4M	€468,900	€7,344,300	€233,400	€195,900
Low vaccine strain coverage (50%)	5005 (37)	731	267	9849	11981	€2820.7M	€401,900	€7,560,400	€247,600	€203,800
High vaccine strain coverage (85%)	6960 (51)	1027	369	14100	17189	€2763.3M	€279,000	€5,272,900	€168,700	€138,500
Lower rates of vaccine uptake	4962 (36)	734	263	10026	12226	€1858.7M	€264,800	€5,009,100	€160,500	€131,800
Higher rates of vaccine uptake	7962 (58)	1165	424	16019	19502	€3623.3M	€319,600	€6,023,600	€193,900	€159,500
Shorter duration of vaccine protection	6363 (47)	935	339	12810	15595	€2781.2M	€308,500	€5,808,100	€187,100	€153,900
Longer duration of vaccine protection	7583 (56)	1108	403	15143	18429	€2749.6M	€257,900	€4,864,200	€157,400	€129,500
Alternative assumption for quality of life loss for survivors with sequelae (0.3 utility loss)	6676 (49)	982	354	13426	25277	€2772.3M	€293,100	€5,534,400	€178,000	€94,900
3% discounting for costs and benefits	6676 (49)	982	354	13426	16360	€2772.3M	€529,300	€10,022,000	€402,600	€331,300
Best case	23915 (68)	4284	1687	64374	77381	€972.1M	€39,300	€559,000	€17,900	€14,900

[a] Figures rounded to nearest 100.
[b] Additional cost of vaccination less costs averted through reduction in cases.

Table 14. Results from the dynamic model, scenario analyses of vaccination (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
3, 5, 6 +12 months and 14 years vaccine free of charge policy, 0% VE against carriage										
Base case	*2193 (16)*	*349*	*109*	*5007*	*6184*	*€2331.1M*	*€679,100*	*€13,693,800*	*€378,400*	*€306,500*
Worst case	734 (7)	66	17	796	1017	€3328.0M	€2,866,100	€125,982,000	€3,370,900	€2,638,700
3, 5, 6 +12 months and 14 years vaccine partly reimbursed policy, 0% VE against carriage										
Base case	*1656 (12)*	*286*	*82*	*3836*	*4811*	*€2898.7M*	*€1,111,400*	*€22,396,600*	*€612,500*	*€488,500*
Worst case	458 (4)	42	11	545	687	€2630.8M	€3,622,100	€145,363,000	€3,889,200	€3,088,000
Preferential population mixing within 1 year of age, vaccine free of charge 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	15779	19225	€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.

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 are shown in Table 5. Compared to the cohort model, 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[26]; however, the cost per quality adjusted life year gained remains high at over €300,000. 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 quality adjusted life year gained is small, and assuming the vaccine can disrupt carriage such strategies are the least attractive economically, formal incremental analysis of different strategies confirm routine infant vaccination alone is dominated when herd effects are assumed (Table 9, Table 10 and Table 11). Strategies including routine vaccination of adolescents 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 vaccine free of charge policy. Corresponding vaccine prices for the partly reimbursed policy are €10 and €4. Neither policy could be cost-effective at a willingness to pay of €20,000 at any vaccine price.

Scenario analysis

A number of scenario analyses were undertaken for the dynamic model, these are presented in Table 12, Table 13, Table 14, and Figure 17. Similarly to the cohort model, vaccination appears more economically favourable when either the incidence of disease or the strain coverage is higher. With increased incidence (351 cases assumed per year) and case fatality rates the cost per quality adjusted life year gained reduces considerably from €83,000 in the base case 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 base case.

As expected, increasing the uptake of vaccination increases the number of cases averted, from 60% in the low vaccine uptake scenario to 72% in the high vaccine uptake scenario for the vaccine free of charge policy. However, increasing the uptake of vaccination results in increasing costs per quality adjusted life year gained due to continuous vaccination of an increasing number of people and the use of differential discounting. 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.

The choice of discount rate again has a large effect of results, with scenarios using 3% discounting for costs and benefits (compared to 3% for costs and 1.5% for benefits in the base case) appearing considerably less cost-effective; €185,500 with 3% discounting compared to €83,000 in the base case for the 3, 5, 6+12 months and 14 years vaccination policy with vaccination offered free of charge.

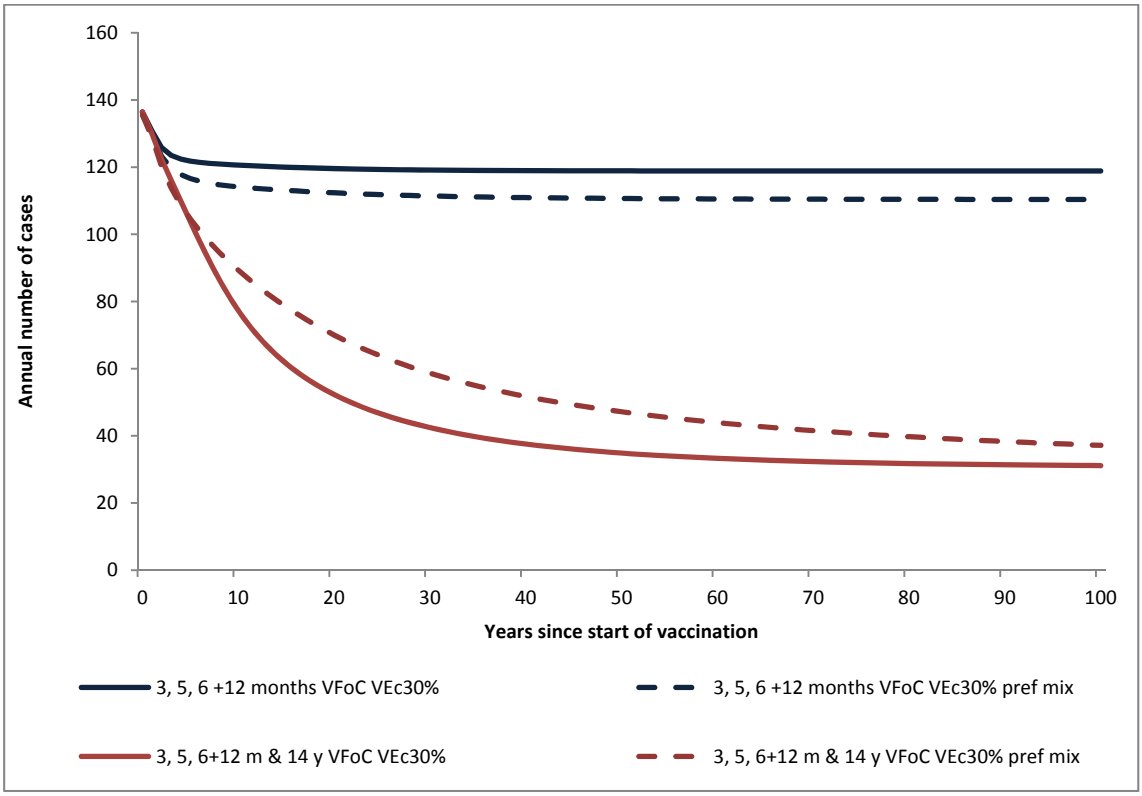
As with the cohort model increasing the average duration of protection from vaccination increases the number of cases averted, resulting in vaccination appearing more economically favourable (Table 12 and Table 13). If the average of duration of protection afforded by a 3, 5, 6+12 months and 14 years vaccination policy 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.

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

If the carriage prevalence of MenB is higher than assumed in the base case, or if all serogroups are considered rather than MenB only, a lower proportion of cases are averted because in such scenarios disrupting carriage has a lower impact on reducing the cases of disease. This results in an increase in the cost per quality adjusted life year gained of vaccination.

For routine infant vaccination, fewer cases were predicted to be averted when population mixing patterns were based on a simple preferential mixing structure compared to survey data from POLYMOD (used in the base case) assuming a 30% vaccine efficacy against carriage acquisition (Figure 17, Table 14). Contrastingly, when infants and adolescents are vaccinated, more cases are averted under POLYMOD than preferential mixing. Smoothed data on leisure contacts from POLYMOD were used in the principal 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 17. Effect on annual disease cases of vaccination assuming 30% vaccine efficacy against carriage under different assumptions for population mixing, vaccine free of charge policy



E. STRENGTHS AND LIMITATIONS

This work has illustrated the potential epidemiological impact and cost-effectiveness of a range of introductory strategies for the new meningococcal vaccine Bexsero.

Strengths include:

- Two different types of model were used to assess the potential impact of the new vaccine. The cohort 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 the latest available data for Belgium and data from studies not yet published have also been incorporated (MOSAIC data courtesy of Helen Johnson, LSHTM).
- Sensitivity analyses were performed to assess the importance of uncertainty around the model parameters; this was done using a partial probabilistic approach in the cohort model and scenario analyses in both models.

Some limitations of this work are:

- The full vaccine characteristics are not yet known. The vaccine is a multi-component protein-based vaccine, which makes it difficult to predict the likely duration of protection afforded (particularly as responses to each component appear to wane at different rates) and results from long-term follow-up are not yet available. Furthermore, strain coverage data are based on a MATS assay which is not a direct measure of true efficacy.
- Quality of life loss for the person with disease during the acute phase of the illness has not been included in the models.
- 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.
- The dynamic model is not probabilistic, so parameter uncertainty in this model is not fully assessed. However, scenario analysis investigated the effect of a number of parameters and most other parameters were comprehensively investigated in the cohort model.

F. CONCLUSIONS

These models have shown that the introduction of a routine immunisation programme with Bexsero has the capacity to reduce meningococcal disease in Belgium. If the vaccine does not disrupt group B carriage the greatest number of cases are averted through routine and adolescent infant vaccination under a vaccine free of charge 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 substantially 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 sustained reductions in cases.

Most strategies considered resulted in very high costs per quality adjusted life year gained, over €100,000. In the dynamic model assuming 30% vaccine efficacy against carriage acquisition routine adolescent vaccination or infant and adolescent vaccination with high incidence and case fatality or 'best case' assumptions would be cost-effective at a willingness to pay of €40,000 per quality adjusted life year gained. 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 cohort model. 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.

In summary, the models predict that meningococcal disease in Belgium could be reduced through the introduction of Bexsero vaccination and that considerably more cases would be averted if the vaccine is able to induce herd immunity effects.

APPENDIX 1. DYNAMIC MODEL EQUATIONS, POPULATION MIXING AND ESTIMATING THE RISK OF DISEASE GIVEN INFECTION

The following text is adapted from Christensen *et al.*[3]

TRANSMISSION DYNAMIC MODEL EQUATIONS

The model can be expressed by the following set of differential equations (please refer to the main text including Figure 1 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.

MIXING PATTERNS

A simple assumption of random mixing is inappropriate for meningococcal disease because the force of infection is age-dependent[27]. We explored the effects of two preferential mixing structures: a pattern based upon survey data from self-reported contacts[28] and a simple mixing pattern based upon Trotter *et al.*[27].

Mixing based upon survey data

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[29]. The method presented by Wallinga *et al.*[29] was used to derive the social contract matrix using unpublished smoothed data

from POLYMOD[28] for Belgian respondents reporting leisure contacts (Niel Hens, personal communication). We chose leisure contacts because these data provided the best fit to the carriage data of the contact types reported in POLYMOD (data not shown).

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).

TRANSMISSION DYNAMIC MODEL PARAMETER FITTING

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[10]. 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 cohort model was developed in Berkeley Madonna[5] 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:

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

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 MCC vaccination[7, 27], 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.*[7]; the fitted values for the functions using POLYMOD leisure contacts are presented in Table A 1 and are shown visually in Figure A 1 and Figure A 2.

Table A 1. 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 A 1. Case:carrier ratio 'observed' and fitted values for those aged under 2 years (base case dynamic model)

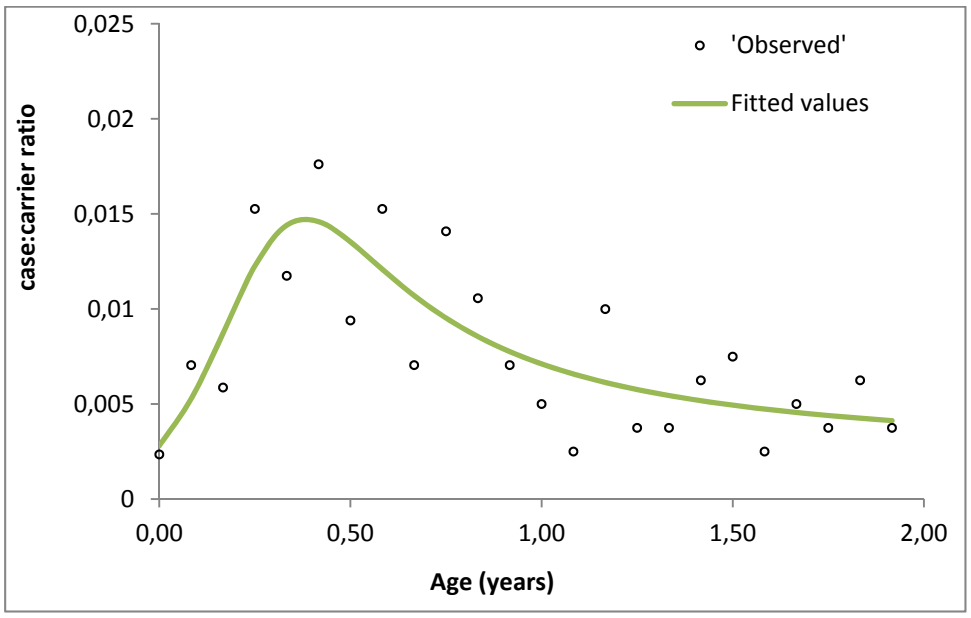
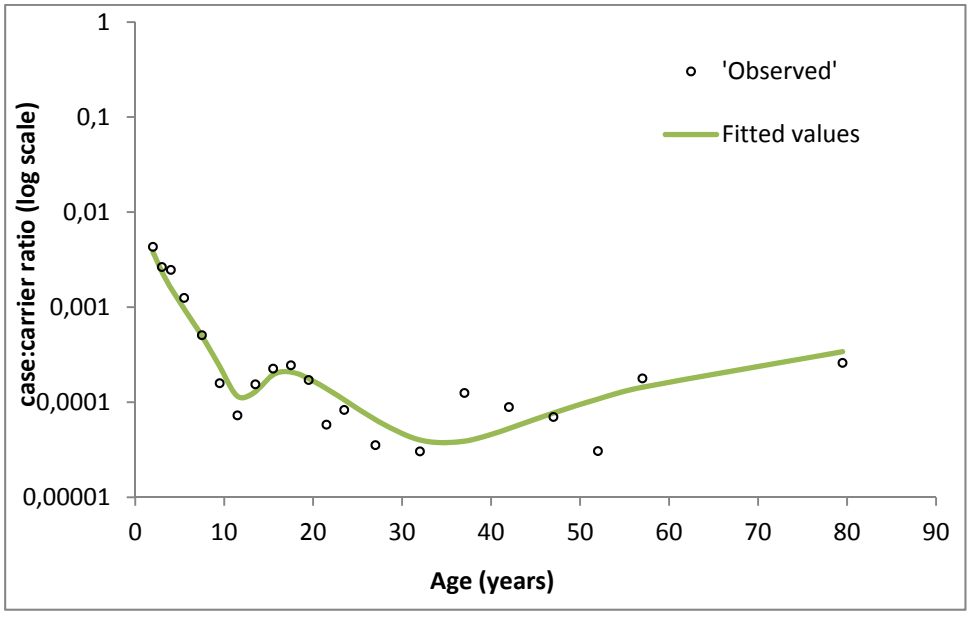


Figure A 2. Case:carrier ratio 'observed' and fitted values for those aged 2 years and over (base case dynamic model)



APPENDIX 2. COST-EFFECTIVENESS PLANES FOR COHORT MODEL SCENARIOS

Figure A 3. Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the cohort model vaccine partly reimbursed scenario

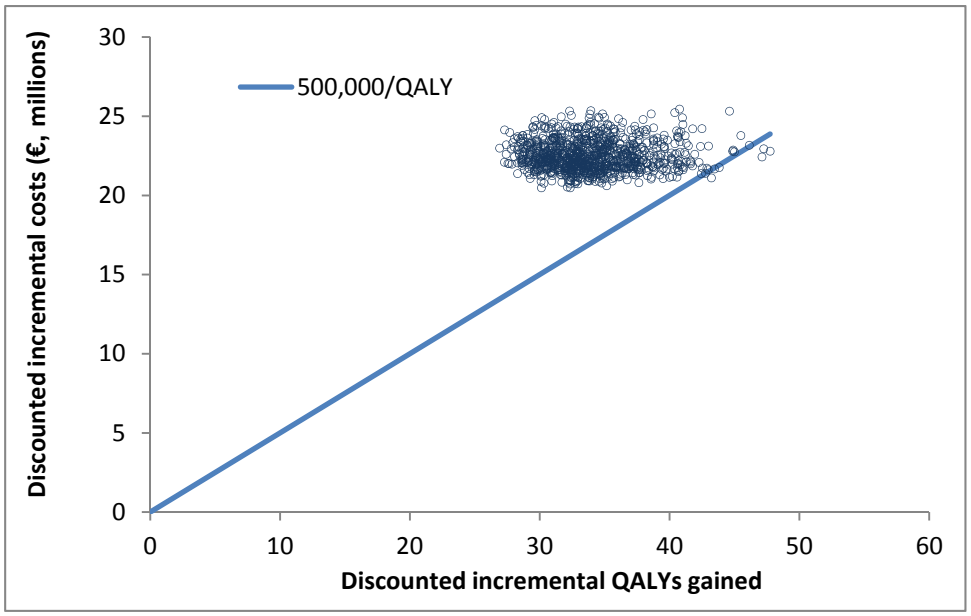


Figure A 4. Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the cohort model vaccine in private market scenario

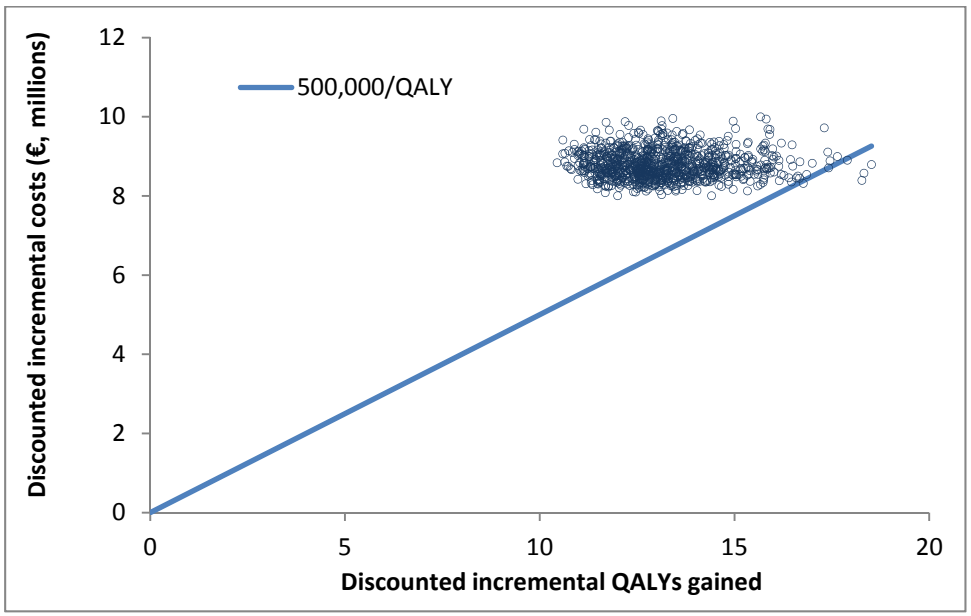


Figure A 5. Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the cohort model all meningococcal serogroups, vaccine free of charge scenario

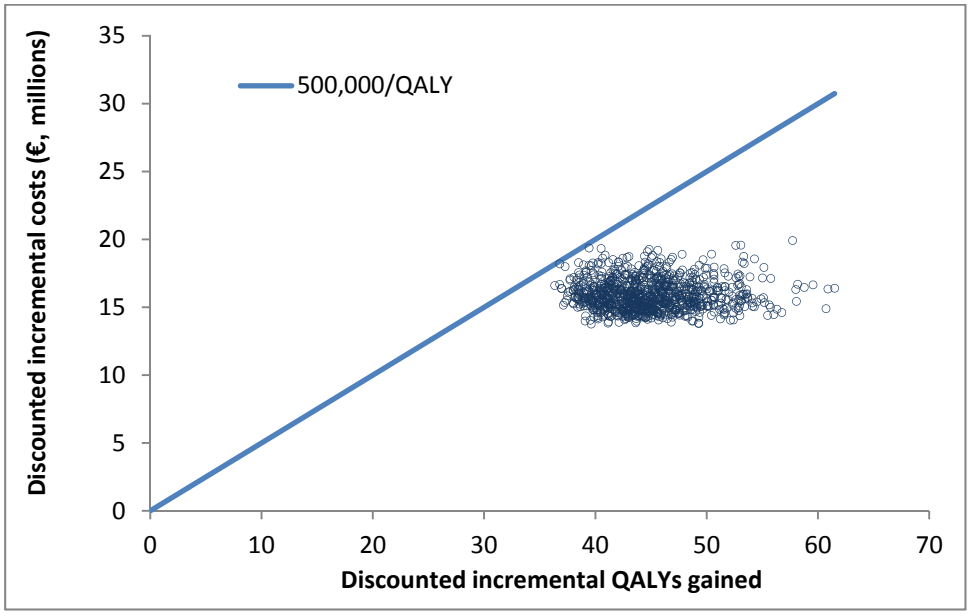


Figure A 6. Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the cohort model high incidence, vaccine free of charge scenario

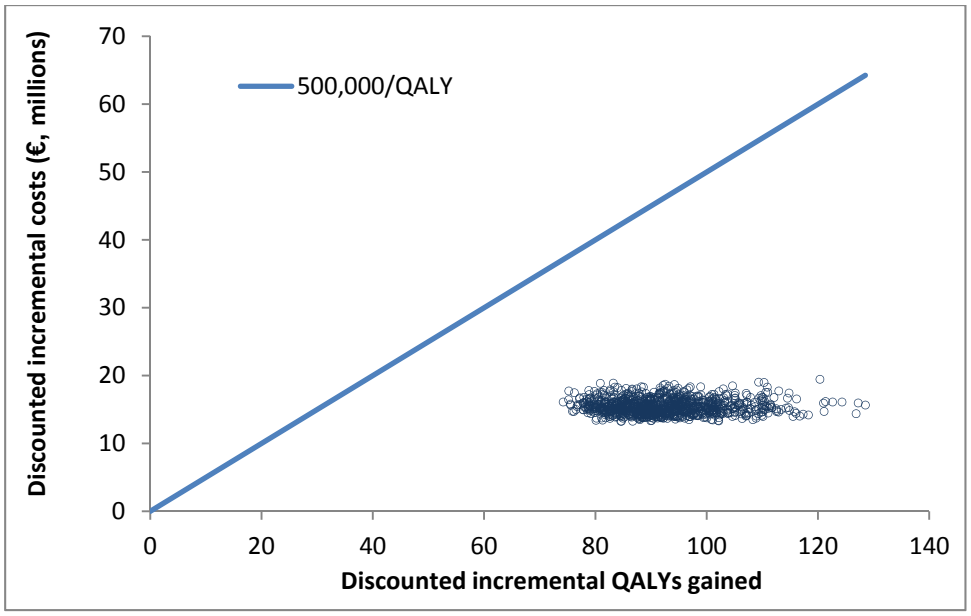


Figure A 7. Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the cohort model low vaccine strain coverage, vaccine free of charge scenario

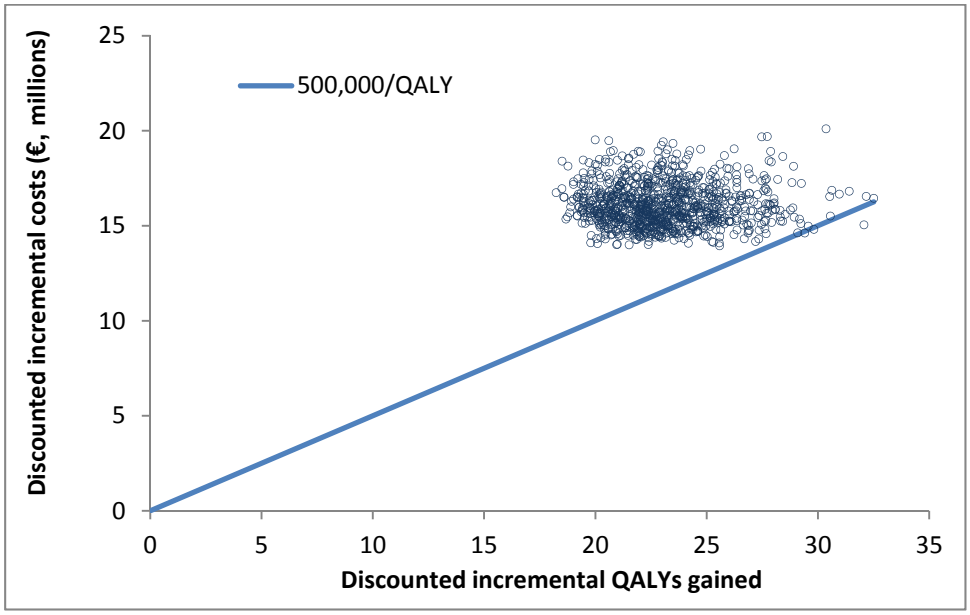


Figure A 8. Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the cohort model high vaccine strain coverage, vaccine free of charge scenario

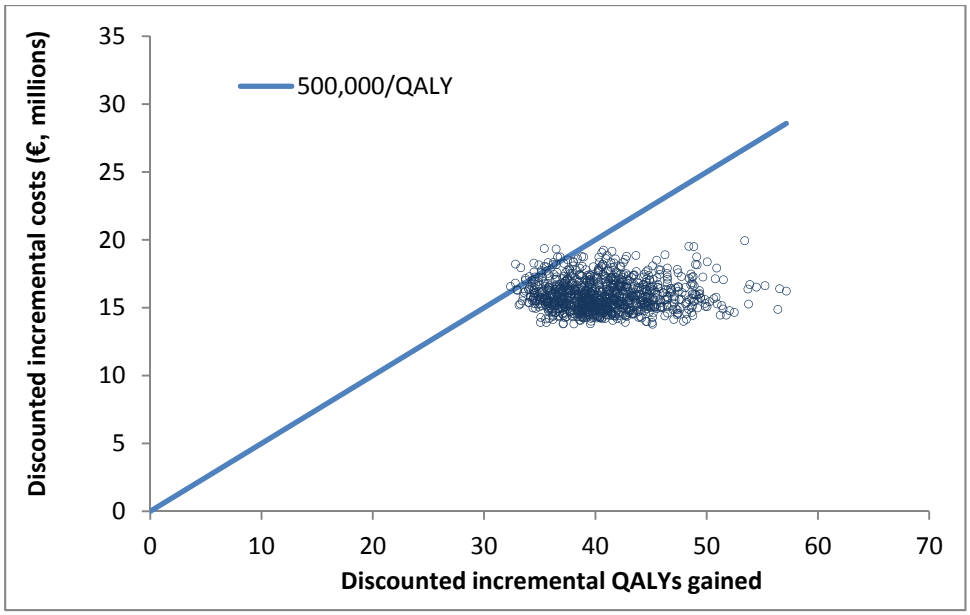


Figure A 9. Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the cohort model low uptake of vaccine, vaccine free of charge scenario

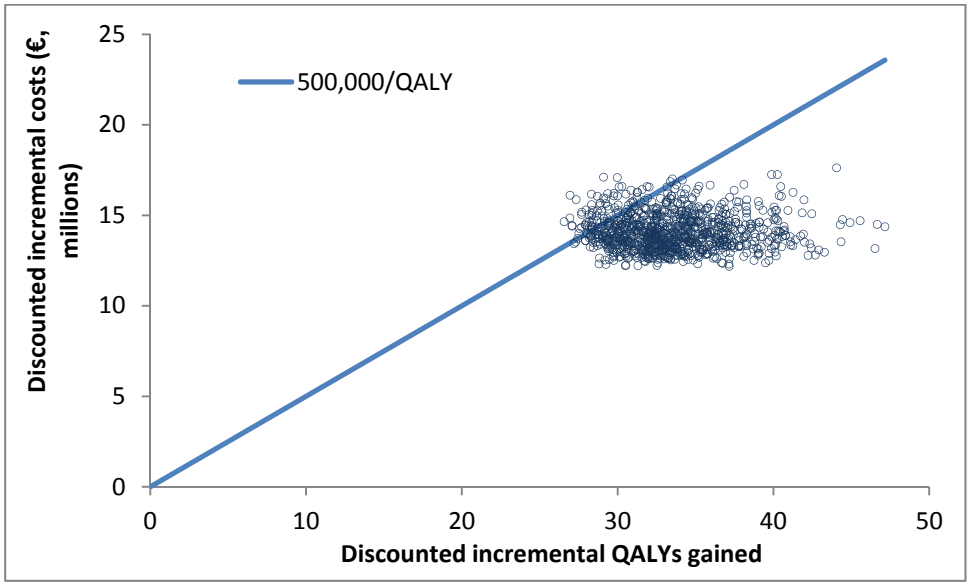


Figure A 10. Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the cohort model high vaccine uptake, vaccine free of charge scenario

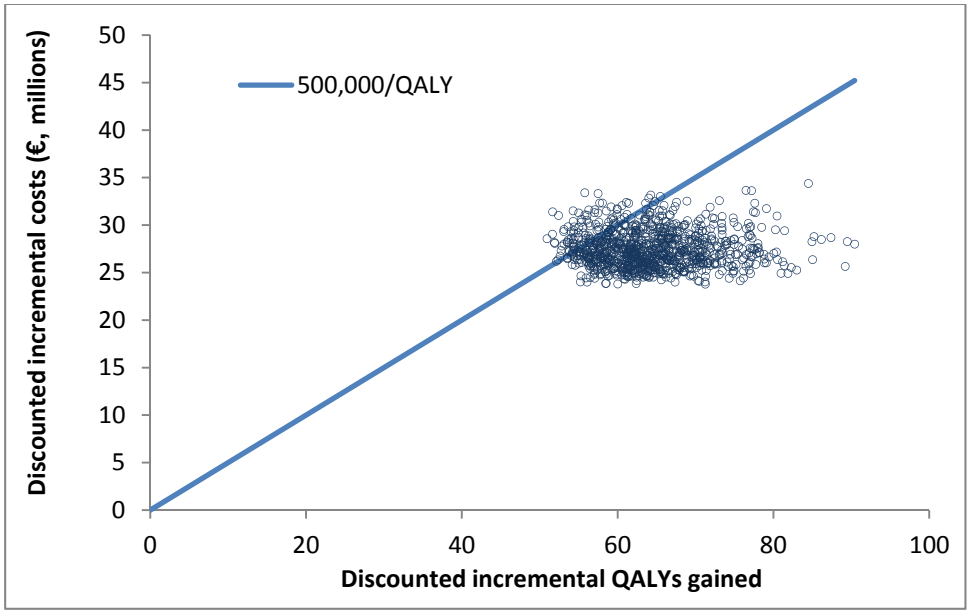


Figure A 11. Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the cohort model low duration of protection, vaccine free of charge scenario

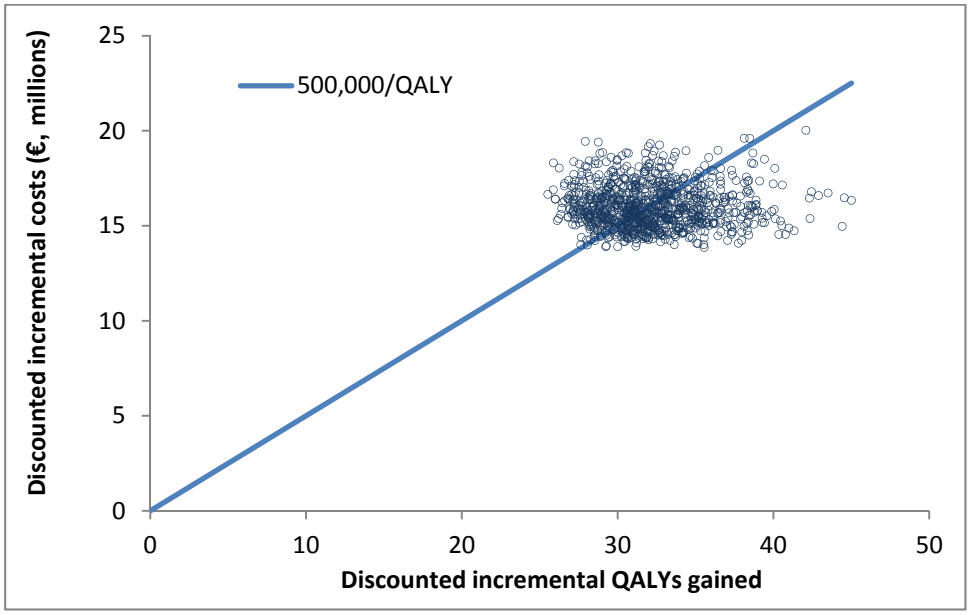


Figure A 12. Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the cohort model high duration of protection, vaccine free of charge scenario

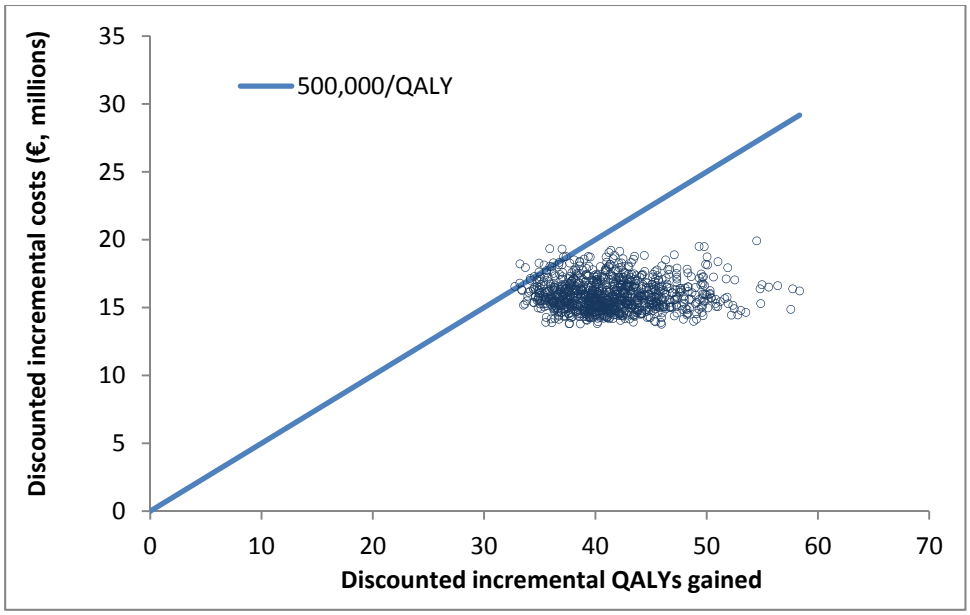


Figure A 13. Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the cohort model high rates of vaccine adverse reactions, vaccine free of charge scenario

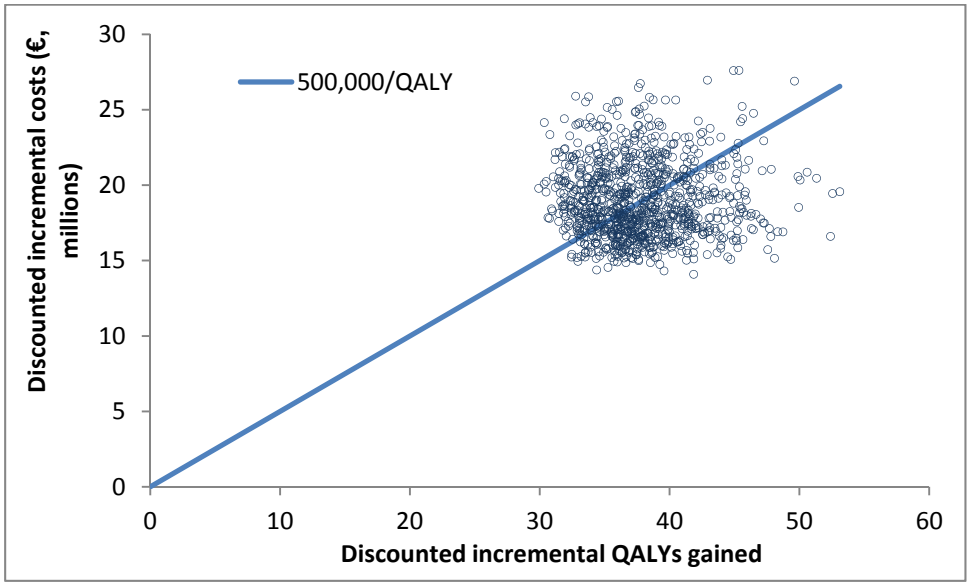


Figure A 14. Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the cohort model high proportion of sequelae, vaccine free of charge scenario

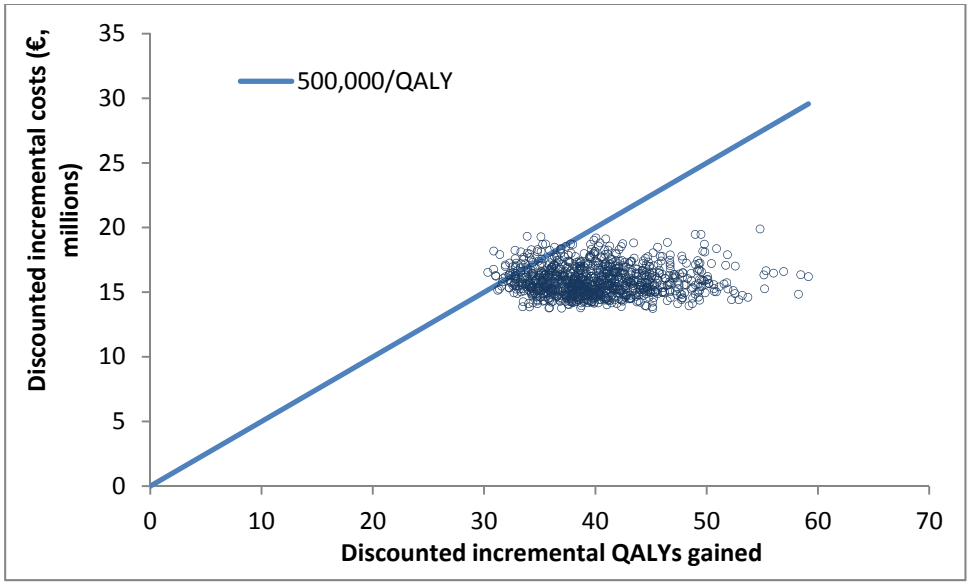


Figure A 15. Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the cohort model low vaccine costs, vaccine free of charge scenario

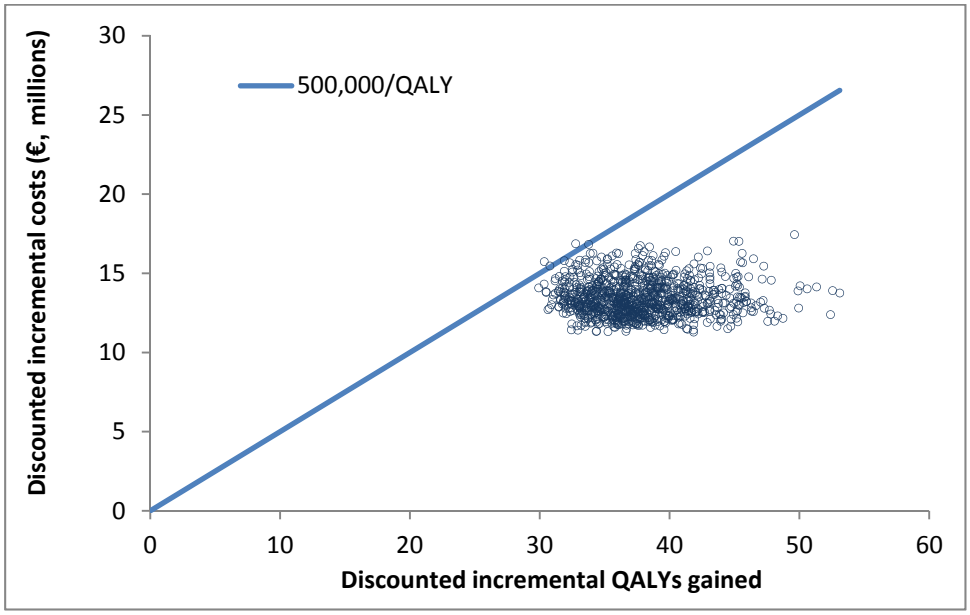


Figure A 16. Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the cohort model high vaccine costs, vaccine free of charge scenario

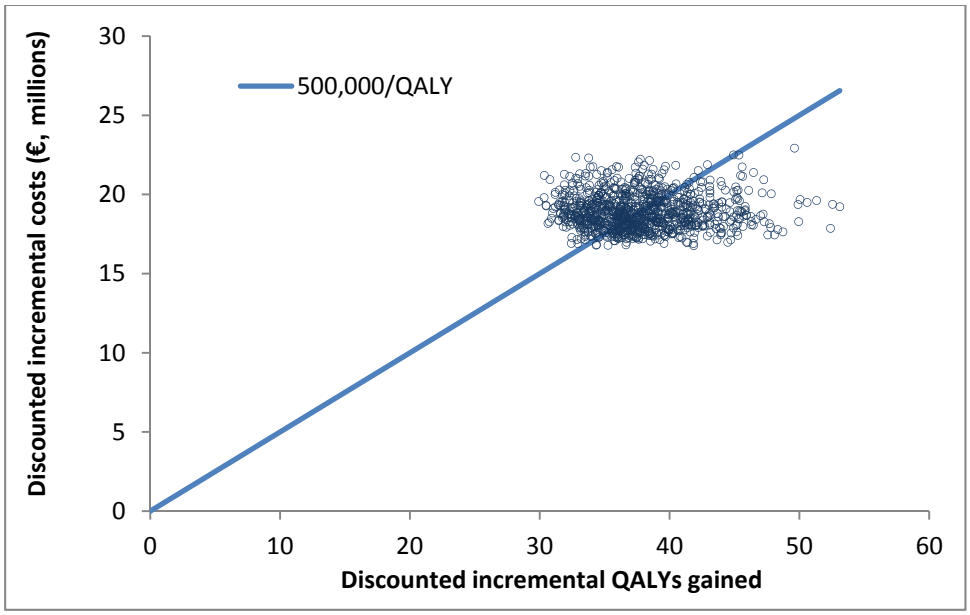


Figure A 17. Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the cohort model 20 year time horizon, vaccine free of charge scenario

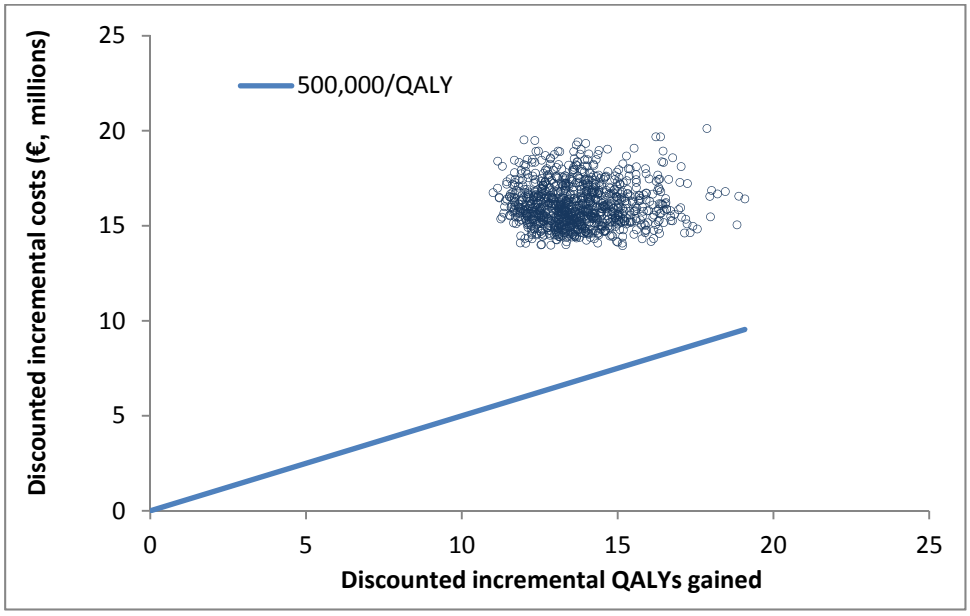


Figure A 18. Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the cohort model 3% discounting for costs and benefits, vaccine free of charge scenario

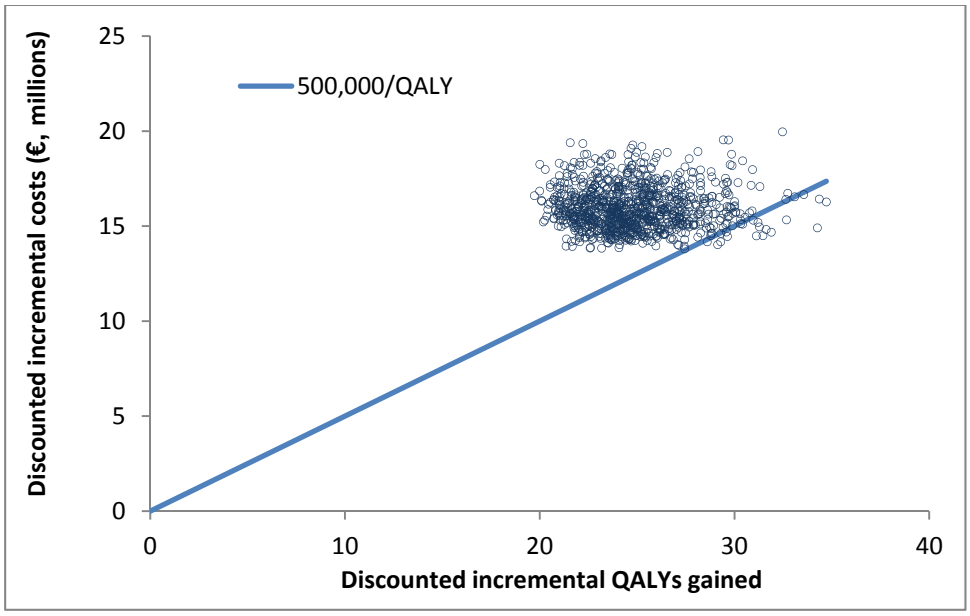


Figure A 19. Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the partly reimbursed scenario with all serogroups cohort model

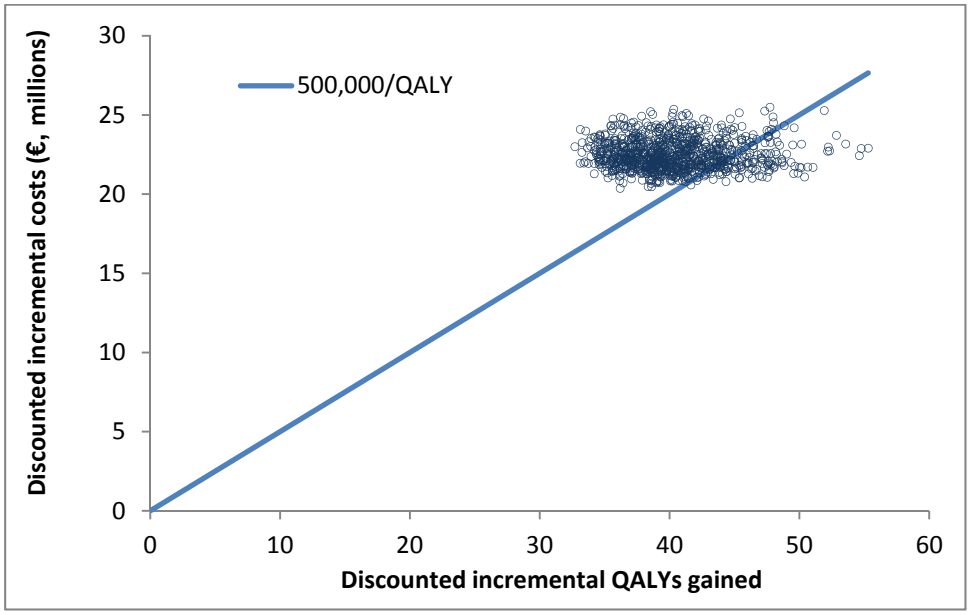


Figure A 20. Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the partly reimbursed scenario with low strain coverage cohort model

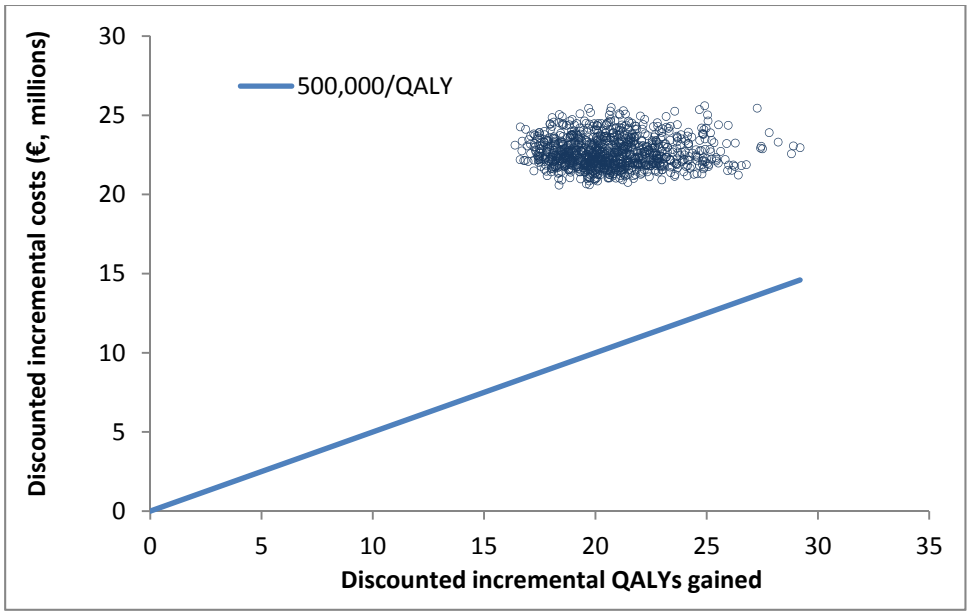


Figure A 21. Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the partly reimbursed scenario with high strain coverage cohort model

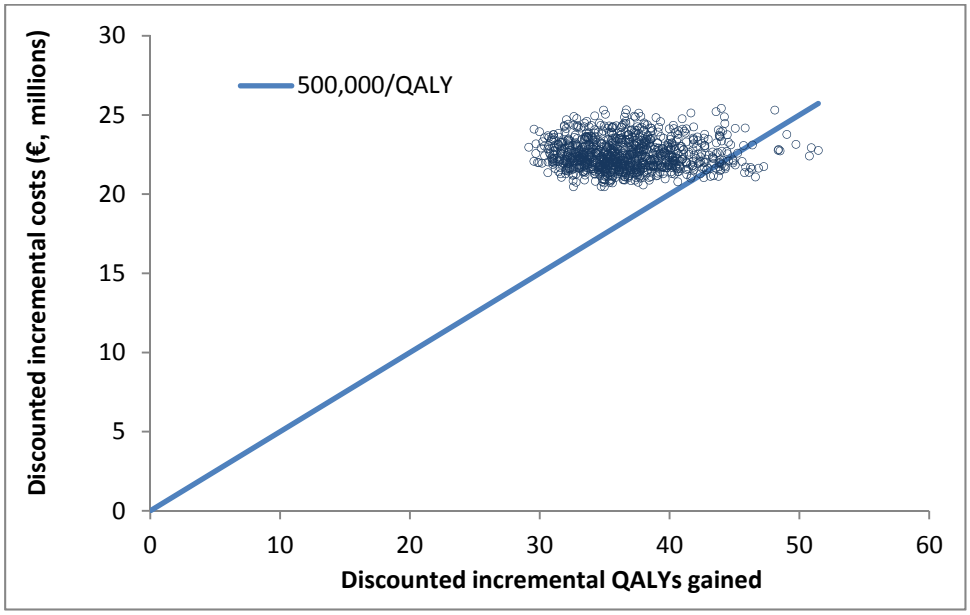


Figure A 22. Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the partly reimbursed scenario with short duration of protection cohort model

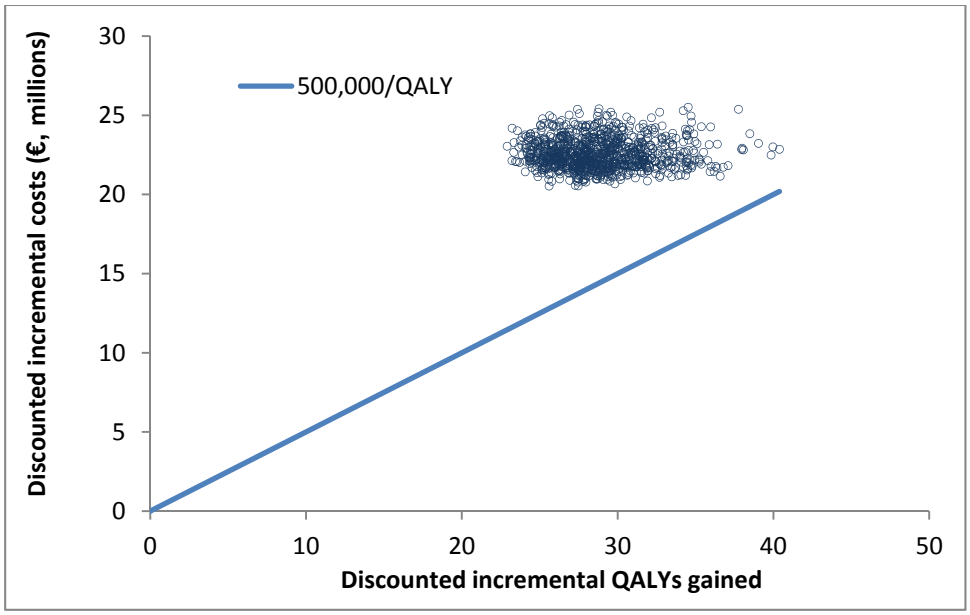


Figure A 23. Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the partly reimbursed scenario with long duration of protection cohort model

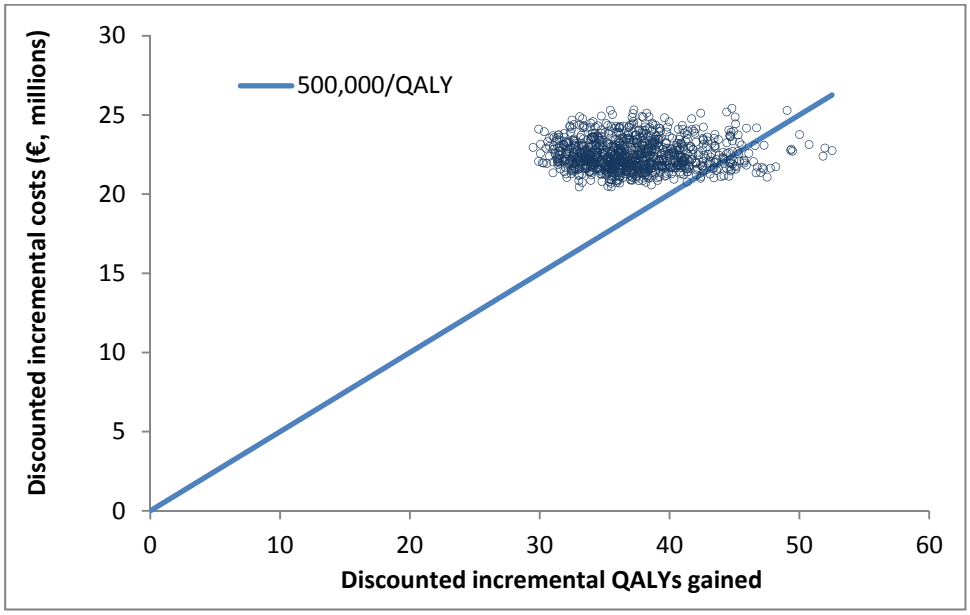


Figure A 24. Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the free of charge scenario with best case parameters cohort model

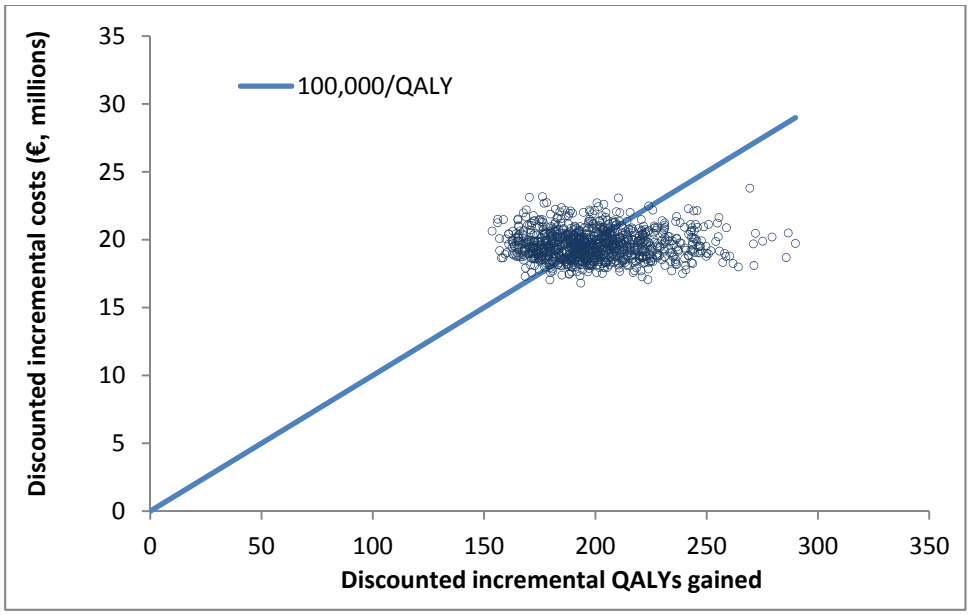


Figure A 25. Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the partly reimbursed scenario with best case parameters cohort model

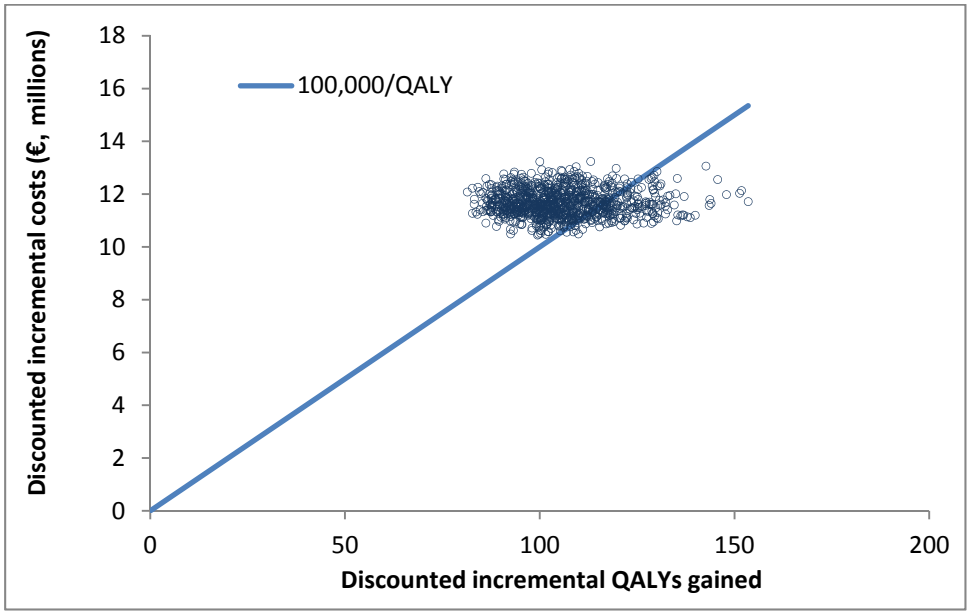


Figure A 26. Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the free of charge scenario with worst case parameters cohort model

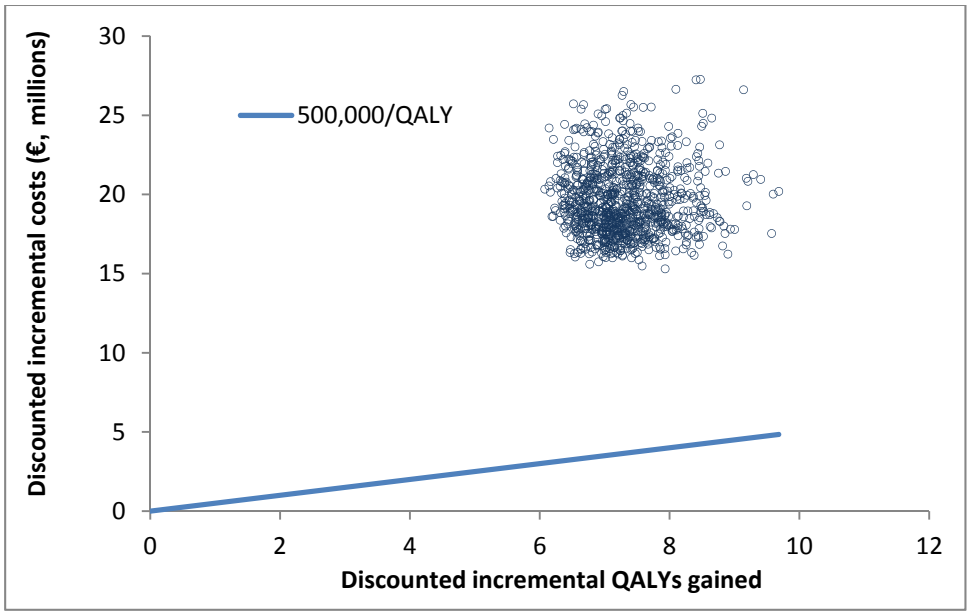


Figure A 27. Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the partly reimbursed scenario with worst case parameters cohort model

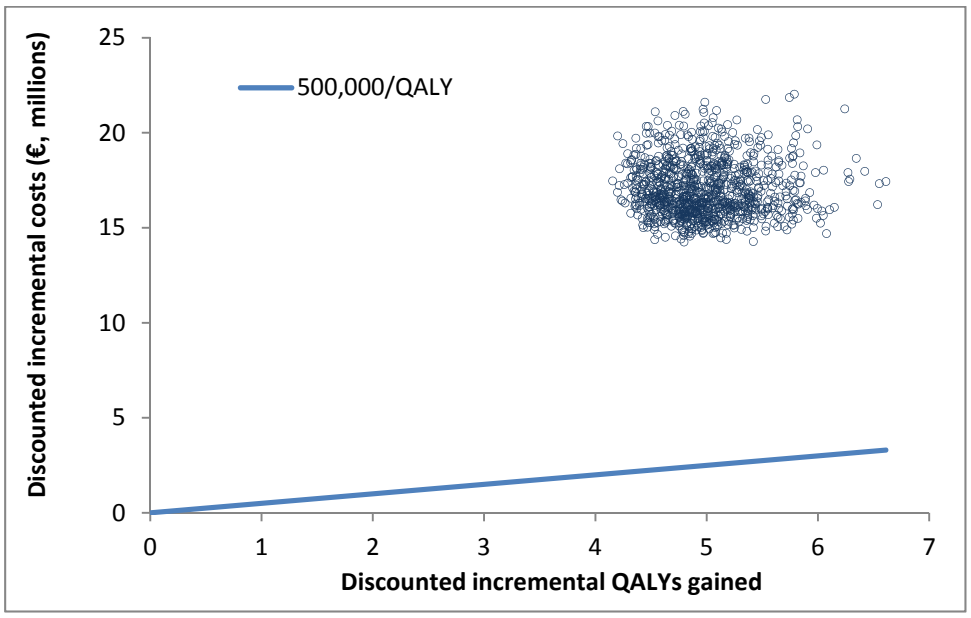
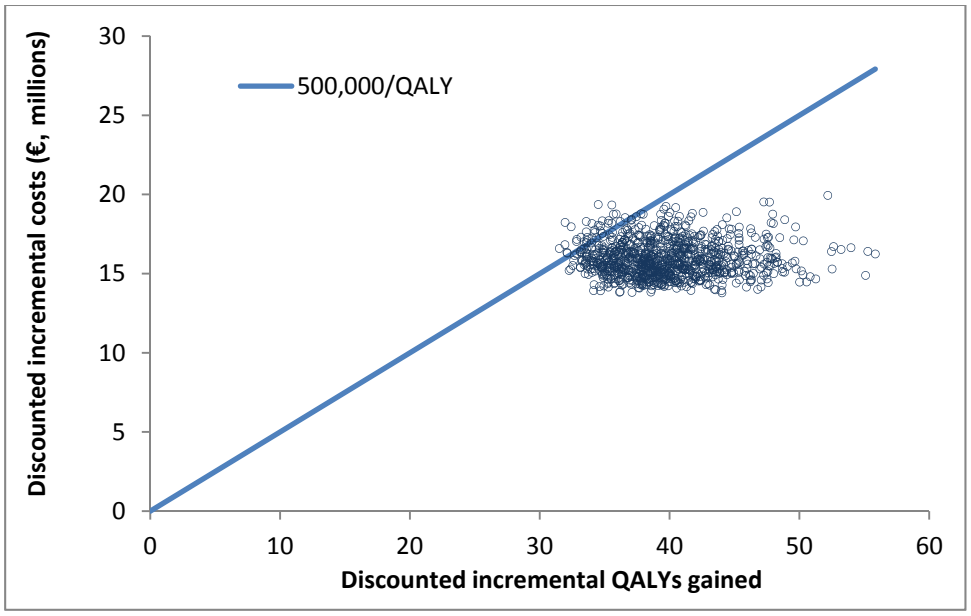


Figure A 28. Monte Carlo simulation results (1000 simulations) on the cost-effectiveness plane for the cohort model 78% vaccine strain coverage, vaccine free of charge scenario



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