Vaccine 34 (2016) 3412–3419

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Epidemiological impact and cost-effectiveness of universal vaccination with Bexsero® to reduce meningococcal group B disease in Germany

Hannah Christensen[a,*], Tom Irving[c], Judith Koch[b], Caroline L. Trotter[d], Bernhard Ultsch[b], Felix Weidemann[b], Ole Wichmann[b], Wiebke Hellenbrand[b]

[a] School of Social and Community Medicine, University of Bristol, Oakfield House, Oakfield Grove, Bristol BS8 2BN, England, United Kingdom
[b] Robert Koch Institute, Seestr. 10, 13353 Berlin, Germany
[c] School of Social and Community Medicine, University of Bristol, Canynge Hall, 39 Whatley Road, Bristol BS8 2PS, United Kingdom
[d] Disease Dynamics Unit, Department of Veterinary Medicine, University of Cambridge, Madingley Road, Cambridge CB3 0ES, United Kingdom

ARTICLE INFO

Article history:
Received 6 January 2016
Received in revised form 31 March 2016
Accepted 1 April 2016
Available online 22 April 2016

Keywords:
Meningococcal disease
Serogroup B
Model
Cost-effectiveness

ABSTRACT

Bexsero, a new vaccine against serogroup B meningococcal disease (MenB), was licensed in Europe in January 2013. In Germany, Bexsero is recommended for persons at increased risk of invasive meningococcal disease, but not for universal childhood vaccination. To support decision making we adapted the independently developed model for England to the German setting to predict the potential health impact and cost-effectiveness of universal vaccination with Bexsero® against MenB disease. We used both cohort and transmission dynamic mathematical models, the latter allowing for herd effects, to consider the impact of vaccination on individuals aged 0–99 years. Vaccination strategies included infant and adolescent vaccination, alone or in combination, and with one-off catch-up programmes. German specific data were used where possible from routine surveillance data and the literature. We assessed the impact of vaccination through cases averted and quality adjusted life years (QALY) gained and calculated costs per QALY gained. Assuming 65% vaccine uptake and 82% strain coverage, infant vaccination was estimated to prevent 15% (34) of MenB cases over the lifetime of one birth cohort. Including herd effects from vaccination increased the cases averted by infant vaccination to 22%, with an estimated 8461 infants requiring vaccination to prevent one case. In the short term the greatest health benefit is achieved through routine infant vaccination with large-scale catch-up, which could reduce cases by 24.9% after 5 years and 27.9% after 10 years. In the long term (20+ years) policies including routine adolescent vaccination are most favourable if herd effects are assumed. Under base case assumptions with a vaccine list price of €96.96 the incremental cost-effectiveness ratio (ICER) was >€500,000 per QALY for all considered strategies. Given the current very low incidence of MenB disease in Germany, universal vaccination with Bexsero® would prevent only a small absolute number of cases, at a high overall cost.

1. Introduction

In Germany, an average of 243 cases and 20 deaths of invasive meningococcal disease (IMD) due to serogroup B (MenB) were reported to the Robert Koch Institute (RKI) each year between 2009 and 2012 (statutory surveillance data, RKI, personal communication). Over this period MenB accounted for 68.5% of IMD cases; 22% were due to MenC, 5.2% due to MenY, 3.4% due to MenW and the remainder due to groups A, Z and 29E. While most people recover, the disease can leave survivors with a range of disabling sequelae, from deafness to amputation [1]. As in other European countries, annual IMD incidence has decreased markedly in Germany, with MenB IMD decreasing from a mean of 0.49 to 0.30 cases/100,000 inhabitants from 2002–2005 to 2009–2012, and MenC IMD from 0.18 to 0.11 cases/100,000 inhabitants [2]. The decrease in MenC disease was disproportionately greater than for MenB disease due to the introduction of MenC vaccine for one-year old children in 2006 [3,4]. Quadrivalent MenACWY vaccination is not recommended as part of the routine vaccination programme

* Corresponding author. Tel.: +44 117 33 14056.
E-mail addresses: Hannah.christensen@bristol.ac.uk (H. Christensen), tom.j.irving@gmail.com (T. Irving), KochJ@rki.de (J. Koch), clt56@cam.ac.uk (C.L. Trotter), UltschB@rki.de (B. Ultsch), WeidemannF@rki.de (F. Weidemann), WichmannO@rki.de (O. Wichmann), HellenbrandW@rki.de (W. Hellenbrand).

http://dx.doi.org/10.1016/j.vaccine.2016.04.004

Table 1
Vaccination strategies against group B meningococcal disease modelled with base case vaccination parameters.[a]

Routine vaccination	Months protection[b]	One-off catch-up[c]	Months protection
Routine infant/toddler strategies			
2, 3, 4, +12 months	[18, 36]	–	
2, 3, 4, +12 months	[18, 36]	1–4 years (0, 2 schedule)	[60]
2, 3, 4, +12 months	[18, 36]	1–4 years (0, 2 schedule) 5–17 years (0, 2 schedule)	[60]
2, 4, 6 +12 months	[18, 36]	–	
2, 4, 6 +12 months	[18, 36]	1–4 years (0, 2 schedule) 5–17 years (0, 2 schedule)	[60]
6, 8, 12 months	[36]	–	
6, 8, 12 months	[36]	1–4 years (0, 2 schedule) 5–17 years (0, 2 schedule)	[60]
Routine infant/toddler plus adolescent strategies			
2, 3, 4, +12 months and	[18, 36]		
12 year olds (0, 2 schedule)	[60]		
6, 8, 12 months and	[36]		
12 year olds (0, 2 schedule)	[60]		
Routine adolescent strategies alone			
12 year olds (0, 2 schedule)	[60]		
12 year olds (0, 2 schedule)	[60]	13–17 years (0, 2 schedule)	[60]

[a] Strategies involving routine 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 2, 3, 4 months at a monthly rate of 1/18 and following the booster at 12 months there is waning protection at a monthly rate of 1/36.
[c] For one-off catch-up campaigns the months of administration are provided to indicate the dosing schedule e.g. 1–4 years: 0, 2 indicates 2 vaccine doses given 2 months apart in children aged 1–4 years.

in Germany, but is recommended for those at increased risk after individual risk assessment, such as household contacts of cases, laboratory workers and immunocompromised persons [5].

In January 2013 Bexsero® became the first vaccine to be licensed in the EU to provide broad protection against MenB disease. This vaccine is based upon a number of surface proteins and an outer membrane vesicle component, and is thus potentially immunogenic against strains with sufficient expression of the vaccine antigens regardless of the capsular group [6]. In Germany the Standing Committee on Vaccination (Ständige Impfkommission, STIKO) is the independent advisory group whose recommendations are required for inclusion of a vaccine in the national vaccination schedule and for reimbursement by statutory health insurance. Currently STIKO recommends Bexsero® for persons at increased risk of acquiring IMD, but not for universal childhood vaccination [7]. Modelling the potential impact of a new vaccine on disease burden provides valuable evidence to STIKO and while assessment of the cost-effectiveness of a new vaccine is not obligatory for development of a STIKO recommendation, results are valuable for deciding on an overall immunisation strategy.

To support decision making in Germany we adapted the independently developed model for England [8] to the German setting to predict the potential health impact and cost-effectiveness of universal vaccination with Bexsero® against MenB disease.

2. Methods

2.1. Models

We used two models to estimate the potential impact of universal Bexsero® vaccination in Germany due to the uncertainty about the effect of the vaccine on carriage [9]: a cohort model allowing for direct vaccine protection against disease only, and a dynamic transmission model that includes additional vaccine protection against carriage. These models are described fully elsewhere [8]. Due to existent universal MenC vaccination in Germany and an extremely low incidence of meningococcal disease due to non-B serogroups (0.15 cases per 100,000 from 2009 to 2012), we considered MenB disease exclusively in the models.

Both models are age-structured with yearly age classes; individuals are born susceptible. Upon disease, quality of life losses for the acute episode were included. Following disease, individuals have three possible outcomes: survival without sequelae, survival with sequelae (with a reduced quality of life) or death. Those dying from the disease are assumed to lose the average life expectancy for the age at which they die. Individuals may die from other causes; published mortality rates were adjusted to remove deaths due to meningococcal disease as these are explicitly modelled. Vaccine induced protection was assumed to start one month after the second vaccine dose and we allowed for waning protection (modelled as a constant rate set to the reciprocal of the average duration of vaccine protection). We considered several vaccination strategies (Table 1), comparing these to no universal vaccination against MenB and treating cases as they arise, over a 100 year time horizon.

2.1.1. Cohort model specific details

A Markov model with monthly cycles was used (Appendix). Disease cases were generated through applying the age-specific probability of disease to the susceptible population; survivors of disease were removed from the susceptible pool. Years of life were weighted by the age-specific quality of life. Cohort sizes were based upon 2011 population statistics. Single birth cohorts were considered for routine infant or toddler vaccination; multiple cohorts were considered for strategies with catch-up vaccination.

2.1.2. Dynamic model specific details

Transmission of meningococcal carriage was represented using a Susceptible-Infected-Susceptible (SIS) model [10] without considering co-infection [11] and using a daily time step (Appendix). Disease cases were generated by applying an age-specific case:carrier ratio to the number of new carriage acquisitions. Vaccinated individuals with immunity could have protection against carriage acquisition (initially assumed to be 30% reduction in carriage acquisition) as well as disease.

Table 2
Epidemiological impact and cost-effectiveness of Bexsero vaccination against MenB disease in Germany assuming direct vaccine protection only, estimated using a cohort model.

Scenario description	Undiscounted							Costs/benefits discounted at 3.0%
	Cohorts included	Cases averted (%)	Cases with sequelae averted	Deaths averted	Life Years Saved	QALYs gained	Net cost of vaccination (€M)	Cost(€)/QALY gained (€96.96/dose)
2, 3, 4 and 12 months	1	34(15)	4	3	239	235	191.1[a]	2,015,300
2, 3, 4 and 12 months with 2 dose catch-up in 1–4 years	5	63(7)	7	5	425	420	364.1	2,154,800
2, 3, 4 and 12 months with 2 dose catch-up in 1–17 years	18	145(6)	16	10	715	726	971.2	3,228,000
2, 4, 6 and 12 months	1	32(14)	4	3	231	227	191.0	2,089,700
2, 4, 6 and 12 months with 2 dose catch-up in 1–17 years	18	143(6)	16	10	707	718	971.2	3,264,500
6, 8, 12 months	1	25(11)	3	2	186	182	143.1	1,963,100
6, 8, 12 months with 2 dose catch-up in 1–17 years	18	137(5)	15	9	662	673	923.3	3,309,900

[a] For a single birth cohort, without vaccination against MenB the cost of treating and caring for the estimated 224 cases that would occur over the lifetime of the cohort is €5.1 M; vaccinating the birth cohort would cost an estimated €191.9 M and would result in an estimated €873,500 in healthcare savings.

2.2. Model parameters

Details of the data sources used to estimate parameters are summarised below with full details provided in Appendix.

National surveillance data from RKI were used to estimate age-specific disease incidence (data from 2009 to 2012) and case fatality (2002 to 2012) for MenB disease; the longer time period was used for case fatality due to the small annual number of meningococcal deaths. For the dynamic model MenB carriage prevalence estimates were based on a systematic review of all serogroup carriage combined with serogroup specific information from a carriage study in Germany [12].

Each case was assumed to be hospitalised, with 48% requiring ambulance transfer. The proportion of survivors with mild and severe sequelae was estimated from the literature [13–17,1]. Quality of life losses for survivors with sequelae were based on currently unpublished data from the MOSAIC study, a case–control study of MenB survivors in the UK [1]; losses for carers of a person with sequelae were also considered [18].

Acute health care costs included the cost of: ambulance transfer; hospitalisation; hearing assessment; and public health management. Costs due to loss of work were also included. The costs of aftercare included one follow-up appointment for those aged under 5 years, cochlear implants (0.4% of survivors), scarring treatment (4%), physical therapy (1.9%) and logopaedics treatment (3.7% of survivors under 19 years) for the year following illness. Annual support costs were included for mild sequelae (unilateral hearing loss) and severe sequelae (which included amputations, major [bilateral] hearing loss, and epilepsy). We assumed that all cases with an amputation would result in a 50% work loss over their lifetime, either for a parent or for themselves at a later time.

We considered several vaccination strategies including routine infant immunisation at varying ages with or without a catch-up campaign (Table 1). In the dynamic model we investigated routine adolescent vaccination (12 year olds) alone, or in combination with an infant programme. Vaccination uptake was estimated based on the uptake of other vaccines with similar age-specific schedules in current use. Vaccine strain coverage was estimated using results of the Meningococcal antigen typing system (MATS) assay on German strains [6,19]. The 2015 pharmacy retail price of €96.96 was used as the cost per vaccine dose. Costs of vaccine administration were estimated from administration costs for other vaccines in Germany. We included the costs of hospitalisation for severe fever and anaphylaxis as possible adverse events following vaccination, but did not include possible quality of life losses associated with adverse events, which were assumed to resolve quickly.

2.3. Effectiveness analyses

We calculated the number needed to vaccinate (NNV) to prevent one case by dividing the number of persons vaccinated by the number of cases averted under various model assumptions.

2.4. Cost-effectiveness analyses

Health outcomes were defined as cases averted, deaths averted and quality adjusted life years (QALYs) gained under vaccination. All costs were measured in Euros at 2013 prices, with previous costs adjusted based on the German consumer price index [20]. In the base case, future costs and benefits were discounted back to their present value at a rate of 3.0% as recommended in Germany [21] and the analysis was undertaken from the payer perspective.

2.5. Scenario analyses

Parameter uncertainty was handled through scenario analyses and by probabilistic sensitivity analyses (PSA). Factors considered in scenario analyses included: disease incidence, population mixing, vaccination uptake, strain coverage, vaccine price, societal perspective (with and without the addition of quality of life losses for carers and costs for work loss) and discount rates. The PSA was used to characterise the uncertainty around other model parameters (Appendix).

3. Results

3.1. Health impact

3.1.1. Cohort model: direct effects (no vaccine effects on carriage)

Table 2 shows the predicted impact of vaccination in birth cohorts (663,026 individuals in a single birth cohort) over their lifetime. In the absence of MenB vaccination the model estimates 224 cases of MenB disease and 19 deaths would occur over a cohort's lifetime. Assuming 65% vaccine uptake and 82% strain coverage, vaccinating infants with a 2, 3, 4 + 12 months schedule is estimated to avert 34 (15%) of these cases and 3 deaths, with a similar number prevented under a 2, 4, 6 + 12 months programme (Fig. 1). Vaccination at 6, 8, 12 months of age averted 25 cases as the assumed

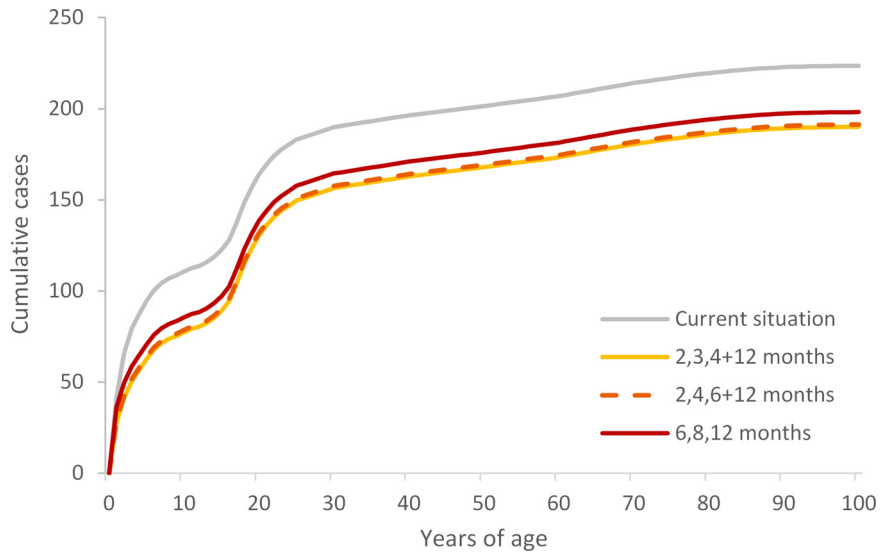

Fig. 1. Predicted cumulative cases by year over the lifetime of a single birth cohort under different vaccination scenarios.

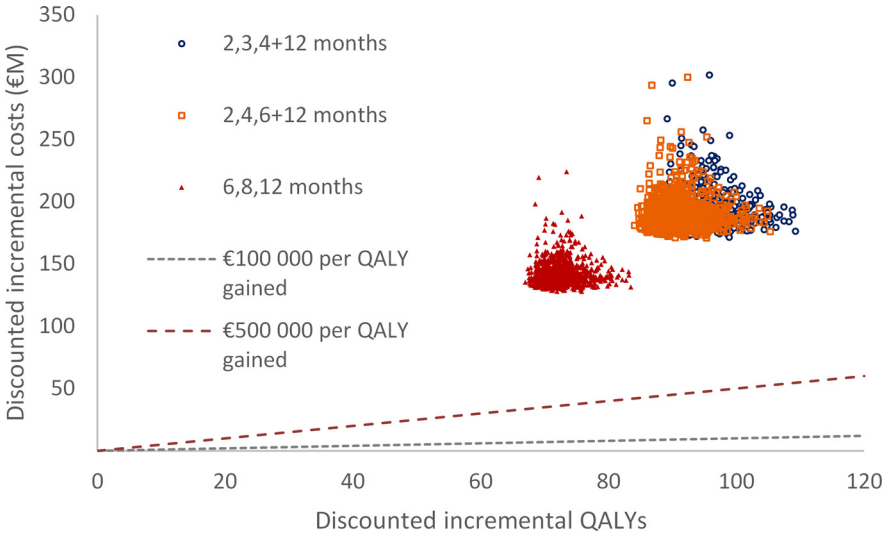

Fig. 2. Results of 1000 Monte Carlo simulation predictions of difference vaccination strategies presented on the cost-effectiveness plane.

increased duration of protection does not compensate for missing the cases that occur before vaccination. To consider catch-up strategies additional birth cohorts are included. Adding a large one-off catch-up strategy for 1–17 year olds to the routine infant schedule averted more cases. However, the percentage averted is reduced (from 15% to 6%) because incidence and assumed vaccine uptake are lower in 1–17 year olds compared to under one-year olds.

3.1.2. Dynamic transmission model: incorporating herd effects following vaccination

We assumed a 30% vaccine efficacy against acquisition. When considering routine infant vaccination alone, strategies starting earlier in life remained most favourable in reducing cases. The greatest health benefit in the short term, however, is achieved through routine infant vaccination with large-scale catch-up, which could reduce cases by 24.9% after 5 years and 27.9% after 10 years (Fig. 3). In the long term (20 years or more) policies including routine vaccination of 12 year olds are most favourable; after 50 years routine adolescent vaccination leads to an annual case reduction of 37.9% compared to no vaccination (Fig. 3).

3.1.3. Number needed to vaccinate

Considering direct effects only (no herd protection) 12,668 children would need to receive the vaccine to prevent a single case over a cohort's lifetime with a 2, 3, 4 + 12 months schedule. Assuming 30% vaccine effectiveness against carriage, this reduces to 8461 children and becomes even more favourable if older children are also vaccinated, reducing to 6373 children for the vaccination strategy 6, 8, 12 months +12 years.

4. Economic impact and cost-effectiveness

At a vaccine price per dose of €96.96 vaccination of infants at 2, 3, 4 + 12 months within the cohort model is expected to cost €191.9 M annually (Table 2). The predicted reduction in healthcare costs over a cohort's lifetime as a result of direct vaccine effects is €873,500 with a resulting incremental cost-effectiveness ratio (ICER) of €2.0 M per QALY gained. Assuming direct vaccine effects only, all vaccination strategies considered resulted in very high ICERs, with strategies that included catch-up being least favourable (Table 2, Fig. 2). Allowing for herd effects improves the cost-effectiveness of vaccination, however, the ICER remains

Table 3
Epidemiological impact and cost-effectiveness of Bexsero vaccination against MenB disease in Germany allowing for herd effects, estimated using a dynamic transmission model.

Scenario description	Undiscounted						Costs/benefits discounted at 3.0%			
	Cases averted (%)	Cases with sequelae averted	Deaths averted	Life Years Saved	QALYs gained	Net cost of vaccination (€M)	Cost (€)/QALY gained (€96.96/dose)	Cost (€)/QALY gained (€60/dose)	Cost (€)/QALY gained (€30/dose)	Cost (€)/QALY gained (€0/dose)
Assuming 30% vaccine efficacy against carriage										
2, 3, 4 and 12 months	5094 (22)	557	450	20,363	23,176	18,713.8	1,391,300	918,300	534,400	150,500
2, 3, 4 and 12 months with 2 dose catch-up in 1–4 years	5192 (23)	568	458	20,856	23,739	18,877.7	1,369,600	903,500	525,100	146,800
2, 3, 4 and 12 months with 2 dose catch-up in 1–17 years	5720 (25)	627	499	23,059	26,302	19,398.6	1,257,200	827,400	478,500	129,500
2, 4, 6 and 12 months	4967 (22)	543	439	19,851	22,590	18,716.2	1,429,400	943,500	549,100	154,700
2, 4, 6 and 12 months with 2 dose catch-up in 1–17 years	5598 (25)	613	489	22,577	25,750	19,400.9	1,283,000	844,300	488,300	132,300
6, 8, 12 months	4214 (19)	460	377	16,810	19,112	14,029.0	1,280,900	845,400	491,800	138,300
6, 8, 12 months and 12 years	10,308 (45)	1134	859	32,918	38,200	20,756.6	998,900	652,600	371,600	90,500
12 years	7455 (33)	822	602	20,959	24,636	6704.9	540,800	345,500	187,000	28,500
12 years with 2 dose catch-up in 13–17 years	7790 (34)	859	630	22,526	26,431	6902.3	520,100	332,300	179,800	27,300
Assuming 60% vaccine efficacy against carriage										
2, 3, 4 and 12 months	6318 (28)	692	554	24,512	27,963	18,692.9	1,160,100	765,400	445,100	124,700
2, 3, 4 and 12 months with 2 dose catch-up in 1–17 years	7386 (33)	810	639	28,987	33,158	19,368.4	982,600	646,200	373,200	100,200
2, 4, 6 and 12 months	6197 (27)	678	544	24,020	27,401	18,695.2	1,185,900	782,500	455,000	127,600
6, 8, 12 months	5494 (24)	601	485	21,132	24,102	14,007.2	1,022,200	674,300	391,800	109,400
6, 8, 12 months and 12 years	14,267 (63)	1568	1197	44,277	51,483	20,692.9	744,300	485,800	275,900	66,100
12 years	11,964 (53)	1317	990	33,825	39,649	6633.7	337,600	214,900	115,400	15,800
12 years with 2 dose catch-up in 13–17 years	12,554 (55)	1382	1041	36,536	42,750	6825.9	322,800	205,400	110,200	15,000

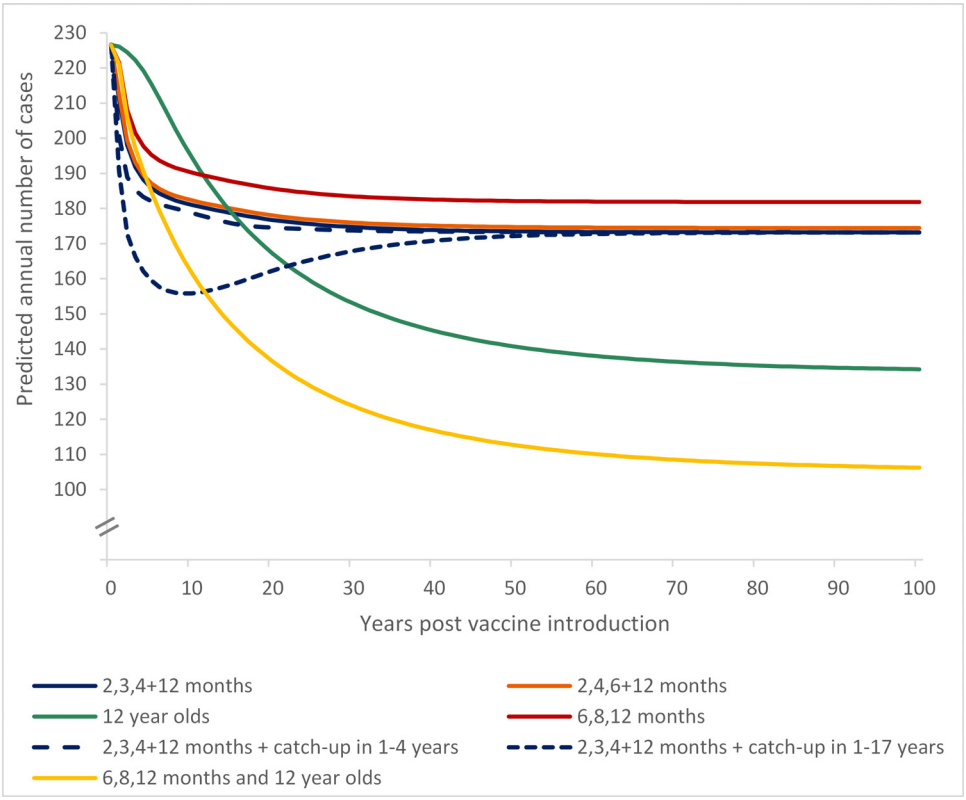

Fig. 3. Predicted annual cases of MenB disease under different vaccination scenarios, assuming herd effects (30% vaccine efficacy against carriage, note the scaling of the *Y*-axis).

over €500,000 for all considered strategies (Table 3). The inclusion of herd effects makes catch-up in addition to routine infant immunisation more economically favourable than routine infant immunisation alone. The lowest ICERs in this context are produced by strategies with routine adolescent immunisation (Table 3), due to the reduced dosing schedule and therefore lower costs for vaccination, and consistent targeting of those with high meningococcal carriage prevalence.

5. Sensitivity analyses

Increasing vaccine uptake in infants from 65% to 70% resulted in an estimated 1% point increase in cases averted assuming direct protection only or 2% point increase when including herd effects. Increasing the strain coverage to 92% resulted in a 2% point increase in averted cases assuming direct protection only or 3% point increase allowing for herd effects. Allowing for lower vaccine strain coverage in infants compared to older age groups (<1 year 68%; 1–9 years 88%; 10–19 years 86%; 20–49 years 79%; 50+ years 76%, see Appendix) reduced the estimated cases directly averted from 34 to 32 over the cohort's lifetime. Altering the assumption about population mixing to one based on self-reported contacts in Germany rather than a simple structure also reduced the proportion of predicted cases averted through vaccination from 22% to 19% in the dynamic model (Appendix). Both models were also sensitive to disease incidence (Appendix). ICERs remained very high even when using vaccine favourable assumptions or allowing for herd effects. From the societal perspective ICERs were lower, but remained over one million Euros per QALY gained even when allowing for herd effects (Appendix). Reducing the cost of the vaccine considerably reduced the ICER, however the cost per QALY gained remained over €100,000 even with a vaccine price of €0 and including herd effects (up to 60% efficacy against carriage acquisition) for the infant strategies. Routine adolescent vaccination strategies assuming indirect protection were more economically favourable, but the vaccine would have to be priced at less than €1 a dose for the ICER to fall below €30,000 per QALY gained. Of the parameters considered probabilistically in the cohort model, the incremental costs of vaccination were most sensitive to the vaccine administration costs and the rates of adverse vaccine reactions; incremental QALYs gained were most sensitive to the quality of life loss utilities and to a lesser extent the proportion of people with sequelae associated with disease and long-term sequelae (Appendix).

6. Discussion

6.1. Principal findings

Model predictions suggest that only a small proportion and low absolute number of MenB cases could be prevented each year in Germany if Bexsero® vaccination was introduced at 2, 3, 4+12 months and if the vaccine had no impact on carriage. This low absolute impact is due to the very low MenB incidence and only moderate anticipated vaccination uptake in Germany. Delaying the age at which the vaccine course is started reduces the potential health impact because young infants are at greatest risk of disease. The limited impact of MenB vaccination in the German setting is also reflected in very high NNVs. High NNVs (over 30,000) were also estimated for MenB infant vaccination in Canada [22]. For comparison, much lower NNVs have been estimated to prevent one influenza-related hospitalisation when vaccinating children aged 6–23 months with an influenza vaccine at 50% efficacy (NNV 1031–3050) [23] and an estimated 80 children would need to receive rotavirus vaccination to prevent one hospitalisation [24].

In terms of economic impact, all modelled strategies for the use of Bexsero® vaccination in Germany were associated with ICERs over €500,000 per QALY gained under base case conditions. This was driven by the low absolute number of preventable cases predicted, particularly by the models that assumed no herd effects, however, evidence for an impact on carriage is uncertain [25,26].

6.2. Strengths and limitations

Our models use the latest available German specific data where possible and the use of a transmission dynamic model allows for indirect vaccine benefits (herd effects). Both payer and societal perspectives were explored. There is considerable uncertainty in some of the parameters used in the models and this was addressed using a partial probabilistic approach in the cohort model and scenario analyses in both models.

The models here consider MenB disease only, as we considered the impact on other serogroups would be very limited given their low incidence (there were only 42, 6 and 7 cases annually of MenC, W and Y, respectively in under 20 year olds from 2009 to 2012) and MenC vaccination coverage in targeted cohorts is already very high [27]. There were limited available data on the incidence and costs associated with long term sequelae in Germany. Consequently, we did not include long-term costs for mild learning disability or institutional care for patients with severe disability, making our cost estimate for severe sequelae rather conservative [8,28–32]. We did include costs for rehabilitation, physical therapy, and speech therapy in the year after illness for a proportion of the patients. Not including the full range and costs of possible sequelae from meningococcal disease will have increased the estimated cost per QALY gained of the vaccination strategies, however in sensitivity analyses ICERs remained high even when the proportion of patients with sequelae and their associated costs were increased. In other aspects the model parameters were potentially vaccine favourable. For instance, we did not include quality of life losses from adverse vaccine reactions, allowances for strain replacement or potential deleterious effects of reducing meningococcal transmission. In addition, duration of protection in scenarios that included catch-up vaccination of toddlers may be overoptimistic based on a recently published small study of hSBA persistence [33].

6.3. Comparison with other studies

Modelling and cost-effectiveness studies on the use of Bexsero® have been published for England [8,34], the Netherlands [30], France [35], Belgium [32] and Canada [29]. In Spain the direct health impact alone was considered [36]. As for the German models presented here, the England and Belgian analyses included the use of dynamic transmission models to appropriately allow for any herd effects. In France herd effects were estimated through incorporation into a Markov model and direct protection was principally considered in the Dutch and the Canadian studies primarily due to limited evidence of the effect of Bexsero® on meningococcal carriage and transmission. The predictions here for vaccination in Germany are in line with those estimated elsewhere, namely that in the absence of herd effects routine immunisation early in life offers the greatest health impact, but with the inclusion of herd effects routine immunisation of teenagers becomes the best long-term strategy. Although the ICERs under base case conditions have been found to be high in all countries considered thus far, those presented for Germany are amongst the highest to date. This is in part explained by a higher vaccine price, the lower sequelae costs assigned to MenB patients as well as the very low MenB incidence (lower only in the Canadian model that also estimated high ICERs > $CDN 3 Million for infant vaccination).

6.4. Implications for policy makers

Our models suggest that maximal health impact in the short term could be achieved in Germany by vaccinating infants early in life. However, a recent study of paediatricians in Germany suggested only 13.4% of physicians preferred this strategy, in contrast to the 66.7% who preferred vaccination at 6, 8, 12 months (14% chose neither schedule) [37]. Paediatricians were concerned about acceptance and safety of concomitant vaccination and possible parental refusal of other recommended vaccines since vaccinating MenB early in life would usually involve three vaccine shots per appointment. Thus, any immunisation decision will need to balance the potential benefits of any given vaccination strategy, the likelihood of the strategy being adopted in practice, as well as potentially unfavourable effects on the uptake of other vaccines.

7. Conclusions

Given the current very low incidence of MenB disease in Germany, implementation of universal infant vaccination with Bexsero® would prevent only a small absolute number of cases. If the vaccine has an effect on carriage, the prevented number of cases and deaths increase significantly when vaccinating adolescents alone or – even more – when adding adolescent vaccination to a routine infant vaccination strategy. Whilst cost-effectiveness is not a central requirement for immunisation decision-making in Germany, the majority of scenarios considerably exceeded commonly used economic willingness to pay thresholds.

Funding: This work was supported by the Robert Koch Institute. HC's work was supported by the National Institute for Health Research [RDA/03/07/014 and PDF-2012-05-245]. This work is produced by the authors under the terms of these research training fellowships issued by the NIHR. HC is a member of the NIHR Health Protection Research Unit in Evaluation of Interventions at University of Bristol. The views expressed in this publication are those of the authors and not necessarily those of the NHS, The National Institute for Health Research or the Department of Health. The NIHR had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflicts of interest: CLT reports receiving a consulting payment from GSK in 2013. HC reports receiving an honoraria, paid to her employer, from Sanofi Pasteur in 2015. Remaining authors: no reported conflicts.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2016.04.004.

References

[1] Viner RM, Booy R, Johnson H, Edmunds WJ, Hudson L, Bedford H, et al. Outcomes of invasive meningococcal serogroup B disease in children and adolescents (MOSAIC): a case-control study. Lancet Neurol 2012;11(9):774–83.
[2] Ciaravino G. Surveillance of invasive bacterial diseases in Europe, 2012. European Centre for Disease Prevention and Control; 2015.
[3] Wiese-Posselt M, Hellenbrand W, Siedler A, Mayer C. Universal childhood immunisation with pneumococcal vaccine and meningococcal serogroup C vaccine introduced in Germany. Euro Surveill 2006;11(9):E060907.4.
[4] Hellenbrand W, Elias J, Wichmann O, Dehnert M, Frosch M, Vogel U. Epidemiology of invasive meningococcal disease in Germany: 2002–2010, and impact of vaccination with meningococcal C conjugate vaccine. J Infect 2013;66(1):48–56.
[5] Empfehlungen der Ständigen Impfkommission (STIKO) am Robert Koch-Institut/Stand: August 2015. Epidemiologisches Bulletin 2015;34:327–62.

[6] Vogel U, Taha M-K, Vazquez JA, Findlow J, Claus H, Stefanelli P, et al. Predicted strain coverage of a meningococcal multicomponent vaccine (4CMenB) in Europe: a qualitative and quantitative assessment. Lancet Infect Dis 2013;13(5):416–25.
[7] Robert Koch Institute. Wissenschaftliche begründung. Aktualisierung der meningokokken-impfempfehlung: anwendung des meningokokken-B-impfstoffs bei personen mit erhöhtem risiko für meningokokken-erkrankungen. Epidemiol Bull 2015;37:394–410.
[8] Christensen H, Hickman M, Edmunds WJ, Trotter CL. Introducing vaccination against serogroup B meningococcal disease: an economic and mathematical modelling study of potential impact. Vaccine 2013;31(23):2638–46.
[9] Martin NG, Snape MD. A multicomponent serogroup B meningococcal vaccine is licensed for use in Europe: what do we know, and what are we yet to learn? Expert Rev Vaccines 2013;12(8):837–58.
[10] Trotter CL, Gay NJ, Edmunds WJ. The natural history of meningococcal carriage and disease. Epidemiol Infect 2006;134(3):556–66.
[11] Caugant DA, Tzanakaki G, Kriz P. Lessons from meningococcal carriage studies. FEMS Microbiol Rev 2007;31(1):52–63.
[12] Claus H, Maiden MCJ, Wilson DJ, McCarthy ND, Jolley KA, Urwin R, et al. Genetic analysis of meningococci carried by children and young adults. J Infect Dis 2005;191(8):1263–71.
[13] Bettinger JA, Scheifele DW, Le Saux N, Halperin SA, Vaudry W, Tsang R, et al. The disease burden of invasive Meningococcal Serogroup B disease in Canada. Pediatr Infect Dis J 2013;32(1):e20–5.
[14] Erickson L, De Wals P. Complications and sequelae of meningococcal disease in Quebec: Canada, 1990–1994. Clin Infect Dis 1998;26(5):1159–64.
[15] Gottfredsson M, Reynisson IK, Ingvarsson RF, Kristjansdottir H, Nardini MV, Sigurdsson JF, et al. Comparative long-term adverse effects elicited by invasive Group B and C meningococcal infections. Clin Infect Dis 2011;53(9):e117–24.
[16] Healy CM, Butler KM, Smith EOB, Hensey OP, Terence B, Moloney AC, et al. Influence of serogroup on the presentation: course, and outcome of invasive Meningococcal Disease in children in the Republic of Ireland, 1995–2000. Clin Infect Dis 2002;34(10):1323–30.
[17] Howitz M, Lambertsen L, Simonsen B, Christensen JJ, Molbak K. Morbidity: mortality and spatial distribution of meningococcal disease, 1974–2007. Epidemiol Infect 2009;137(11):1631–40.
[18] Al-Janabi H, Van Exel J, Brouwer W, Trotter C, Glennie L, Hannigan L, et al. Measuring health spillovers for economic evaluation: a case study in meningitis. Health Econ 2015.
[19] Claus H, Vogel U, de Paola R, Stella M, Wichmann O, Hellenbrand W. Meningococcal antigen typing system (MATS) based coverage for Bexsero on invasive MenB strains isolated from infants aged less than one year in Germany 2007–2013. In: International Pathogenic Neisseria Conference. 2014.
[20] Destatis Statistisches Bundesamt. Preisindex für Verbrauchs- und Gebrauchsgüter; 2015. Available from: www.destatis.de/DE/ZahlenFakten/GesamtwirtschaftUmwelt/Preise/Verbraucherpreisindizes/Tabellen_/VerbrauchsGebrauchsgueter.html?cms_gtp=146580_list%253D2%2526146578_slot%253D2&https=1.
[21] Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden. Version 4.2 vom 22.04.2015; 2015.
[22] Dang V, Jamieson FB, Wilson S, Rawte P, Crowcroft NS, Johnson K, et al. Epidemiology of serogroup B invasive meningococcal disease in Ontario, Canada, 2000 to 2010. BMC Infect Dis 2012;12:202.
[23] Lewis E, Griffin M, Szilagyi P, Zhu Y, Edwards K, Poehling K. Childhood influenza: number needed to vaccinate to prevent 1 hospitalization or outpatient visit. Pediatrics 2007;120(3):467–72.
[24] Robert Koch Institute. Empfehlung und wissenschaftliche Begründung der Empfehlung zur Rotavirus-Standardimpfung von Säuglingen. Epidemiol Bull; 2013. p. 35.
[25] Read RC, Baxter D, Chadwick DR, Faust SN, Finn A, Gordon SB, et al. Effect of a quadrivalent meningococcal ACWY glycoconjugate or a serogroup B meningococcal vaccine on meningococcal carriage: an observer-blind, phase 3 randomised clinical trial. Lancet 2014;384(9960):2123–31.
[26] McNamara LA, Shumate AM, Johnsen P, MacNeil JR, Patel M, Bhavsar T, et al. First use of a serogroup B meningococcal vaccine in the US in response to a university outbreak. Pediatrics 2015;135(5):798–804.
[27] Rieck T, Feig M, Eckmanns T, Benzler J, Siedler A, Wichmann O. Vaccination coverage among children in Germany estimated by analysis of health insurance claims data. Hum Vaccines Immunother 2014;10(2):476–84.
[28] Christensen H, Trotter CL, Hickman M, Edmunds WJ. Re-evaluating cost effectiveness of universal meningitis vaccination (Bexsero) in England: modelling study. Br Med J 2014;349.
[29] Tu HAT, Deeks SL, Morris SK, Strifler L, Crowcroft N, Jamieson FB, et al. Economic evaluation of meningococcal serogroup B childhood vaccination in Ontario: Canada. Vaccine 2014;32(42):5436–46.
[30] Pouwels KB, Hak E, van der Ende A, Christensen H, van den Dobbelsteen GPJM, Postma MJ. Cost-effectiveness of vaccination against meningococcal B among Dutch infants: crucial impact of changes in incidence. Hum Vaccines Immunother 2013;9(5):1129–38.
[31] Lecocq H, Parent du Châtelet I, Kheir Taha M, Lévy-Bruhl D, Dervaux B. Analyse coût/efficacité de la vaccination par le vaccin Bexsero® contre les infections invasives à méningocoque de sérogroupe B (IIM B). Paris: ANNEXE 1 du rapport du HCSP Vaccination par le vaccin méningococcique Bexsero®; 2014.
[32] Hanquet G, Christensen H, Agnew E, Trotter C, Robays J, Dubois C, et al. Modelling the potential impact of Bexsero introduction in Belgium; 2014. Brussels.
[33] McQuaid F, Snape MD, John TM, Kelly S, Robinson H, Houlden J, et al. Persistence of bactericidal antibodies to 5 years of age after immunization with serogroup b meningococcal vaccines at 6, 8, 12 and 40 months of age. Pediatr Infect Dis J 2014;33(7):760–6.
[34] Huels J, Clements KM, McGarry LJ, Hill GJ, Wassil J, Kessabi S. Modelled evaluation of multi-component meningococcal vaccine (Bexsero®) for the prevention of invasive meningococcal disease in infants and adolescents in the UK. Epidemiol Infect 2013, http://dx.doi.org/10.1017/S095026881300294X (online first).
[35] Le Haut Conseil de la santé publique. Vaccination contre les infections invasives à méningocoque B Place du vaccin Bexsero®; 2013.
[36] Presentation of programs and immunization record. Public Health Commission Interterritorial Council of the National Health System. Ministry of Health SSaEMWG. Vaccination against invasive meningococcal disease caused by serogroup B and its possible use in public health; 2013.
[37] Takla A, Wichmann O, Koch J, Terhardt M, Hellenbrand W. Survey of pediatricians in Germany reveals important challenges for possible implementation of meningococcal B vaccination. Vaccine 2014;32(48):6349–55.