

SENSITIVITY ANALYSIS OF A MODEL USED TO PREDICT THE COST EFFECTIVENESS OF BEXSERO FOR IMMUNISATION AGAINST MENINGOCOCCAL DISEASE IN THE UNITED KINGDOM

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INTRODUCTION

- Neisseria meningitidis* remains a major cause of bacterial meningitis and sepsis in the UK with >80% of the confirmed invasive meningococcal disease (IMD) cases in 2010-2012 being serogroup B.
- Bexsero is the first meningococcal vaccine that can potentially provide protection against the majority of meningococcal disease caused by serogroup B.
- Bexsero has demonstrated immunogenicity against serogroup B *Neisseria meningitidis* in age groups from infants through adolescents, and is approved by EMA for individuals >2 months.
- In July 2013, the Joint Committee on Vaccination and Immunisation (JCVI) concluded that routine infant or toddler immunisation using Bexsero is highly unlikely to be cost effective at any vaccine price, and that adolescent immunisation is highly unlikely to be cost effective if the vaccine has little or no impact on meningococcal carriage. These conclusions contradict recently published, peer-reviewed findings.
- To demonstrate the impact of changing key inputs on cost effectiveness, we repeated the cost effectiveness sensitivity analysis and examined the effect of changing input parameters, in particular when multiple parameters were adjusted simultaneously.

SUMMARY

- The model used in this analysis is similar to Christensen's, and reproduces published findings demonstrating that infant and adolescent Bexsero vaccination strategies could be cost effective in the UK, even if the model is populated with conservative input assumptions.
- To reach the conclusion that Bexsero vaccination could not be cost effective at any price, key input assumptions must be decreased substantially below the values used in published models, or multiple input values must simultaneously be decreased.
- If the model is populated with evidence-based data which reflect the devastating impact and cyclical epidemiology of MenB disease, the cost-effectiveness of infant and adolescent vaccination strategies improves, and the economically justifiable price per vaccine dose increases.
- The impact on cost effectiveness is relatively modest if key parameters are adjusted one at a time, but the effects are considerable if two or three key inputs are considered in combination.
- Infants under two years of age are at greatest risk of meningococcal disease. Vaccination strategies that provide direct protection of infants are more attractive because disease burden is reduced more quickly in this group. Even if Bexsero has good carriage impact, adolescent-only vaccination strategies may take 20 years for infants to be well protected, leading to substantial suffering and loss of life.

METHODS

- A published transmission model has been adapted to assess the potential long-term effectiveness of Bexsero compared with the standard of care.
- The model was populated with UK-specific demographic data and calibrated to adequately simulate the transmission dynamics of meningococcal disease in the UK.
- Two vaccination strategies were assessed: An infant strategy involving a "3+1" schedule of Bexsero administration at 2, 3, 4 and 12 months of age and an adolescent strategy based on the administration of two Bexsero doses at 14 years of age.
- Published input parameters from Christensen et al were used for the reference case cost-effectiveness analysis wherever possible. Necessary amendments to the Christensen model were: the inclusion of separate values for MATS efficacy and vaccine efficacy (instead of a combined value); the assumption that adolescents require two vaccine doses (instead of 3); the use of a real-life contact matrix (instead of an "academic" diagonal matrix)⁸.
- After populating the cost-effectiveness model with input values reproducing as far as possible the published parameters, the impact of modulating key input assumptions was assessed:
 - Key input assumptions were individually decreased from reference case values, and the impact on cost-effectiveness (in an equivalent presentation as an economically justifiable price) of infant and adolescent vaccination strategies determined.
 - Key input assumptions were increased from reference case values, individually and in combination, on the basis of updated evidence-based estimates.
- Declining discounting rates for both costs and benefits (3.5% up to 30 years, 3% for years 31 to 75 and 2.5% for years ≥76), and a willingness-to-pay level of £30,000 per QALY gained were assumed throughout.
- Key input assumptions are displayed in Table 1
- Additional analyses were undertaken to estimate the number of infant and adolescent vaccination strategies, assuming a carriage impact of 60% (as used in Christensen) or 30%. Assumed duration of vaccine protection was 18 months (infants <1 year old), 36 months (children 1-3 years old) and 120 months (children >3 years old).

Parameter	Reference case assumptions ¹	Latest available evidence-based estimate
IMD cases (HES data all serogroups, England)	1799	1799
Proportion of IMD survivors with sequelae	9%	20.1% ^{2,3}
Impact on IMD survivors QoL (i.e. disability score)	0.2	0.2
Case fatality rate	4%	5.6% ^{4,5}
Strain coverage	73%	88% ⁶
Impact on carriage	60%	85% ⁷
Population pyramid	Academic (calculated from all-cause mortality table)	Real-life ⁸
Impact on carers	No	Yes ^{10, 11, 12}

RESULTS

- Using reference case assumptions for key input parameters, both infant and adolescent Bexsero vaccination programmes could be cost effective at positive prices in the UK (Table 2). The economically justifiable prices per vaccine dose would be £41.45 for an adolescent vaccination strategy and £7.20 per vaccine dose for an infant vaccination strategy (Table 2) – the latter being comparable to the economically justifiable price of £9 calculated by Christensen et al.¹
- Modulating input estimates for disease incidence, vaccine strain coverage, and frequency and quality of life impact of long-term sequelae among IMD survivors had the greatest impact on cost effectiveness.
- Infant and adolescent vaccination programmes remain cost-effective at positive prices if input assumptions relating to the frequency and impact of long-term sequelae, case fatality or carriage impact are individually decreased to their minimum possible values, whilst maintaining reference case assumptions for other parameters.
- Infant and adolescent vaccination programmes are not cost-effective at any price if input assumptions relating to disease incidence or strain coverage are decreased substantially from reference case values used by Christensen et al to unrealistic low values.
- Adjusting individual input assumptions from reference case values to latest evidence-based estimates increased the economically justifiable prices per vaccine dose for both infant and adolescent vaccination strategies (Table 3).
- Adjusting the estimated proportion of IMD survivors with long-term sequelae had the greatest effect on cost effectiveness and justifiable price. For the infant vaccination strategy, the economically justifiable price was more than doubled when using the higher input assumption (Table 3).
- Adjusting the estimate of strain coverage also had a considerable impact on the economically justifiable price for infant and adolescent vaccination strategies (Table 3).
- Adjusting estimates of other input values (CFR, carriage impact, population pyramid and impact on carers) had modest effects on the economically justifiable price when undertaken in isolation.
- Simultaneously adjusting two assumptions from reference case values to latest evidence-based estimates had a considerable impact on the justifiable price (and therefore the cost effectiveness) of infant and adolescent vaccination strategies (Table 4).
- For the infant vaccination strategy, economically justifiable prices per vaccine dose ranged from £10 to £20, compared with £7.20 in the reference case (Table 4).
- For the adolescent vaccination strategy, economically justifiable prices per vaccine dose ranged from £52 to £82, compared with £41.45 in the reference case.
- Simultaneously adjusting the estimated proportion of IMD survivors with long-term sequelae and the estimated vaccine strain coverage rate had the greatest impact on the economically justifiable price.
- If three input assumptions were increased from reference case values to the latest available estimates, the impact on the justifiable price (and therefore cost effectiveness) of infant and adolescent vaccination strategies was profound (Figure 1).
- Using the latest evidence-based estimates of carriage impact, the economically justifiable prices per vaccine dose for an adolescent vaccination strategy ranged from £40-£150, depending on the input estimates used for the frequency and quality-of-life impact of long-term sequelae in IMD survivors.
- For an infant-only vaccination strategy, prices of over £35 per vaccine dose could be economically justified if the Christensen model is populated with plausible evidence based input assumptions for three key input parameters
- Children below 2 years of age represent the most vulnerable population segment. Assuming an impact on carriage of 60%, it takes about 17 years until an adolescent vaccination program provides the same protection as routine infant vaccination (Figure 2a).
- Assuming 30% carriage impact, it takes approximately two generations (48 years) until an adolescent vaccination program provides the same protection as routine infant vaccination for children below 2 years of age (Figure 2b).

Figure 2a. Estimated IMD cases averted in children below 2 years of age for infant (2, 3, 4, 12m) and adolescent (14yrs)vaccination strategies within 100 years after start of vaccination program, assuming 60% carriage impact

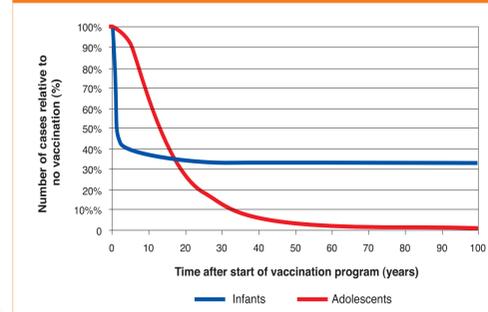
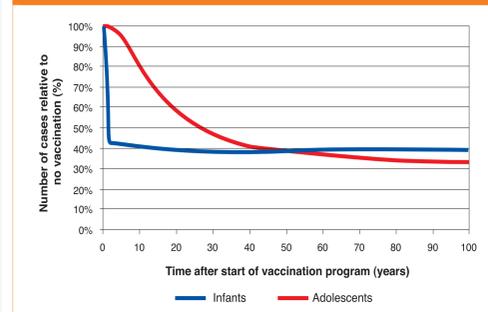


Figure 2b. Estimated IMD cases averted in children below 2 years of age for infant (2, 3, 4, 12m) and adolescent (14yrs)vaccination strategies within 100 years after start of vaccination program, assuming 30% carriage impact



CONCLUSIONS

- The model used in this analysis is similar to Christensen's, and reproduces published findings demonstrating that infant and adolescent Bexsero vaccination strategies could be cost effective in the UK, even if the model is populated with conservative input assumptions.
- To reach the conclusion that Bexsero vaccination could not be cost effective at any price, key input assumptions must be decreased substantially below the values used in published models, or multiple input values must simultaneously be decreased.
- If the model is populated with evidence-based data which reflect the devastating impact and cyclical epidemiology of MenB disease, the cost-effectiveness of infant and adolescent vaccination strategies improves, and the economically justifiable price per vaccine dose increases.
- The impact on cost effectiveness is relatively modest if key parameters are adjusted one at a time, but the effects are considerable if two or three key inputs are considered in combination.
- Infants under two years of age are at greatest risk of meningococcal disease. Vaccination strategies that provide direct protection of infants are more attractive because disease burden is reduced more quickly in this group. Even if Bexsero has good carriage impact, adolescent-only vaccination strategies may take 20 years for infants to be well protected, leading to substantial suffering and loss of life.

Table 2. The impact of lowering individual input parameter values on the economic justifiable price of infant and adolescent vaccination strategies. Shown for each parameter is either the value at which the economically justifiable price falls below £0.00, or the economically justifiable price when that input is reduced to the minimum possible value.

Parameter	Reference case value	Infant vaccination		Adolescent vaccination	
		Value with zero justifiable price	Justifiable price at minimum possible value	Value with zero justifiable price	Justifiable price at minimum possible value
IMD cases (HES data all serogroups England)	1799	789	-	213	-
Proportion of IMD survivors with sequelae	9%	-	£0.29 (if no survivors with sequelae)	-	£18.86 (if no survivors with sequelae)
Impact on IMD survivors QoL (i.e. disability score)	0.2	-	£4.38 (if no disability for survivors)	-	£32.30 (if no disability for survivors)
Case fatality rate	4%	-	£2.47 (if CFR is zero)	-	£21.27 (if CFR is zero)
Strain coverage (serogroup B, MATS)	73%	23%	-	4%	-
Impact on carriage	60%	-	£3.56 (if no impact on carriage)	-	£0.52 (if no impact on carriage)
Economically justifiable price (model populated with reference case assumptions)		£7.20		£41.45	

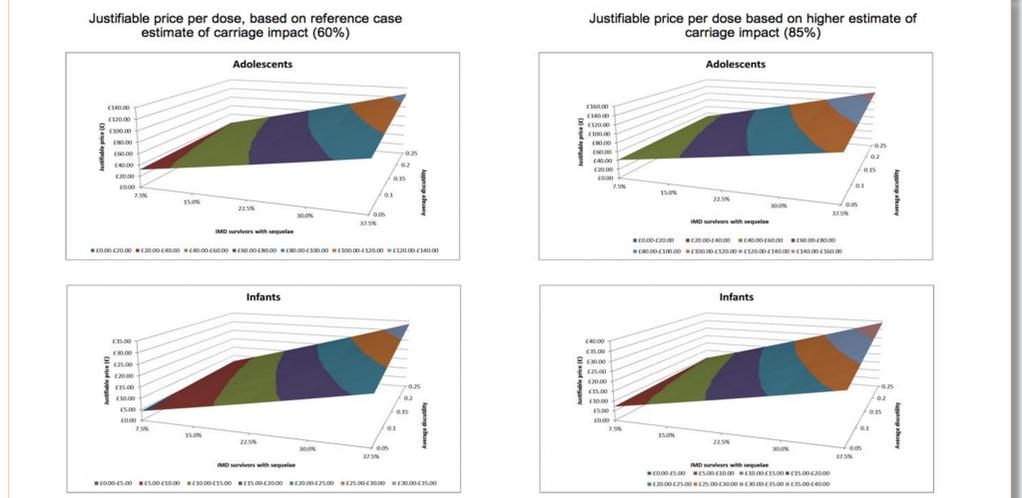
Table 3. Impact on economically justifiable price of increasing key input assumptions in isolation, whilst maintaining reference-case estimates for all other values

Input parameter	Adjustment made to individual input assumption:		Economically justifiable price per vaccine dose if individual input parameter is changed from reference case estimate to latest evidence-based estimate (percentage increase from reference case price)	
	From (reference case)	To (latest evidence based estimate)	Infants	Adolescents
Proportion of IMD survivors with sequelae	9%	20.1%	£ 16.01 (+122.4%)	£ 70.29 (+69.6%)
Case fatality rate	4%	5.6%	£ 9.09 (+26.3%)	£ 49.53 (+19.5%)
Strain coverage	73%	88%	£11.05 (+53.5%)	£54.68 (+31.9%)
Carriage impact	60%	85%	£ 8.61 (+19.6%)	£ 46.26 (+11.6%)
Population pyramid	Academic	Real-life	£ 8.94 (+24.2%)	£ 48.85 (+17.9%)
Impact on carers	No	Yes	£ 8.80 (+22.2%)	£ 46.82 (+13.0%)

Table 4. Economically justifiable price per dose for infant and adolescent vaccination strategies: the impact of modulating two key inputs simultaneously (replacing reference case estimates with latest evidence-based estimates in each case), whilst maintaining lowest estimates for all other input values

2nd input parameter changed	1st input parameter changed					Economically justifiable prices per dose for infant vaccination strategy (percentage increase from reference case price)
	Sequelae (freq)	Impact on carers	CFR	Strain coverage	Carriage impact	
Sequelae (freq)	£ 75.67 (+82.6%)	£ 77.91 (+88.0%)	£ 81.70 (+97.1%)	£ 78.09 (+88.4%)	£ 78.09 (+88.4%)	Economically justifiable prices per dose for adolescent vaccination strategy (percentage increase from reference case price)
Impact on carers	£ 17.62 (+144.7%)	£ 54.90 (+32.4%)	£ 54.68 (+31.9%)	£ 52.19 (+25.9%)	£ 52.19 (+25.9%)	
CFR	£ 17.79 (+147.1%)	£ 10.69 (+48.5%)	£ 57.76 (+39.3%)	£ 55.14 (+33.0%)	£ 55.14 (+33.0%)	
Strain coverage	£ 19.43 (+169.9%)	£ 11.05 (+53.5%)	£ 11.34 (+57.5%)	£ 55.40 (+33.7%)	£ 55.40 (+33.7%)	
Carriage impact	£ 18.26 (+153.6%)	£ 10.38 (+44.2%)	£ 10.76 (+49.4%)	£ 10.69 (+48.5%)	£ 10.69 (+48.5%)	

Figure 1. Economically justifiable prices per vaccine dose for infant and adolescent vaccination strategies: the impact of simultaneously modulating three key inputs. Plausible ranges of values were used for the frequency and quality-of-life impact of long-term sequelae in IMD survivors, assuming carriage impact of either 60% or 85%



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