A re-assessment of 4CMenB vaccine effectiveness against serogroup B meningococcal disease in England based on an incidence model

Supplementary information

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S1 Relationship between impact, uptake and effectiveness

The vaccine impact VI during a country-level immunization program depends on both direct and indirect effectiveness, and on the proportion of the considered population that has been vaccinated.[1] When indirect effects (i.e., disease risk reduction in the whole population, including non-vaccinated, due to a vaccine-induced decrease in pathogen's transmissibility) are absent or negligible, especially at the beginning of the campaign, VI simply equals VE multiplied by the proportion of vaccinated persons (i.e., the vaccine uptake). This simple mathematical relationship has been already used to evaluate the possible effectiveness of a vaccine for which impact and uptake are known.[2] We provide here its formal derivation.

The direct vaccine effectiveness VE_i after $i = 0, 1, \dots, n$ doses is defined[1] as one minus the incidence rate (IR) ratio of vaccinated with exactly i doses and non-vaccinated, indicated with $i = 0$:

$$VE_i = 1 - \frac{IR_i}{IR_0}. \tag{S1}$$

The vaccine impact[3] VI, also known as overall vaccine effect[1], is defined as one minus the incidence rate ratio between two populations, A and B:

$$VI = 1 - \frac{IR_A}{IR_B}. \tag{S2}$$

Population A is the population in which the immunization program is implemented. In general, depending on the uptake, such population consists of non-vaccinated, partially vaccinated and fully vaccinated. It follows that

$$IR_A = \sum_{i=0}^{n} x_i IR_i\,, \tag{S3}$$

where x_i is the proportion of population that received i doses. Population B is a control: subjects should be the most possible similar to population A, except that they are all non-vaccinated (in ecological studies, B is often the same population A before introducing the vaccine).[3] Therefore,

$$IR_B = IR_0 \tag{S4}$$

Substituting formulas S3 and S4 in S2, using formula S2, we derive

$$VI = 1 - \sum_{i=0}^{n} x_i + \sum_{i=0}^{n} x_i VE_i\,. \tag{S5}$$

Since by definition $\sum_{i=0}^{n} x_i = 1$, the first two terms cancel out, so that

$$VI = \sum_{i=1}^{n} x_i VE_i\,, \tag{S6}$$

where the sum can start from $i = 1$ since the effectiveness of zero doses is trivially null, $VE_0 = 0$.

Therefore, the impact of a vaccination program with multiple doses is the sum of the VEs of each dose weighted by the proportions of population vaccinated with such number of doses. This simple formula holds in ideal situations where both incidence rates and uptake proportions do not vary with age, time and other possible confounding factors. Also, it is valid only when

indirect effects are small or absent, otherwise additional factors could be needed in formulas S3 and S4, depending on the frequency of between-subjects contacts that determine transmission.

The vaccination schedule in the 4CMenB national immunization program here considered was composed of three doses. Hence formula S6 becomes:

$$VI = x_1 VE_1 + x_2 VE_2 + x_3 VE_3 \,. \qquad \text{(S7)}$$

S2 Cases data

Our data on cases were counts of serogroup B invasive meningococcal disease (IMD) in England, before and during 4CMenB national immunization program, stratified by age group, year and doses received (Table S1). These data were provided by Public Health England.[4]

Table S1. Serogroup B IMD case counts shared by PHE and used for our re-assessment

Age group	Doses received	Year of surveillance (September-August)						
		2011-12	2012-13	2013-14	2014-15	2015-16	2016-17	2017-18
0-1 m	**0**	14	12	19	10	7	8	10
2-3 m	**0**	26	20	18	18	3	8	11
	1	-	-	-	-	8	13	9
	2	-	-	-	-	-	-	-
	3	-	-	-	-	-	-	-
4-11 m	**0**	113	103	86	74	36	1	5
	1	-	-	-	-	13	8	10
	2	-	-	-	-	9	12	13
	3	-	-	-	-	-	-	-
1 y	**0**	88	77	40	80	57	13	3
	1	-	-	-	-	0	0	0
	2	-	-	-	-	1	7	4
	3	-	-	-	-	0	9	7
2 y	**0**	49	56	28	34	42	47	7
	1	-	-	-	-	-	0	0
	2	-	-	-	-	-	1	2
	3	-	-	-	-	-	0	10
3 y	**0**	32	27	19	21	21	24	27
	1	-	-	-	-	-	-	0
	2	-	-	-	-	-	-	0
	3	-	-	-	-	-	-	0
4 y	**0**	29	26	18	9	22	19	21
5-14 y	**0**	45	60	39	48	61	46	55
15-24 y	**0**	79	74	63	52	75	92	94
25-44 y	**0**	31	33	26	19	19	27	25
45+ y	**0**	81	73	55	56	78	72	72

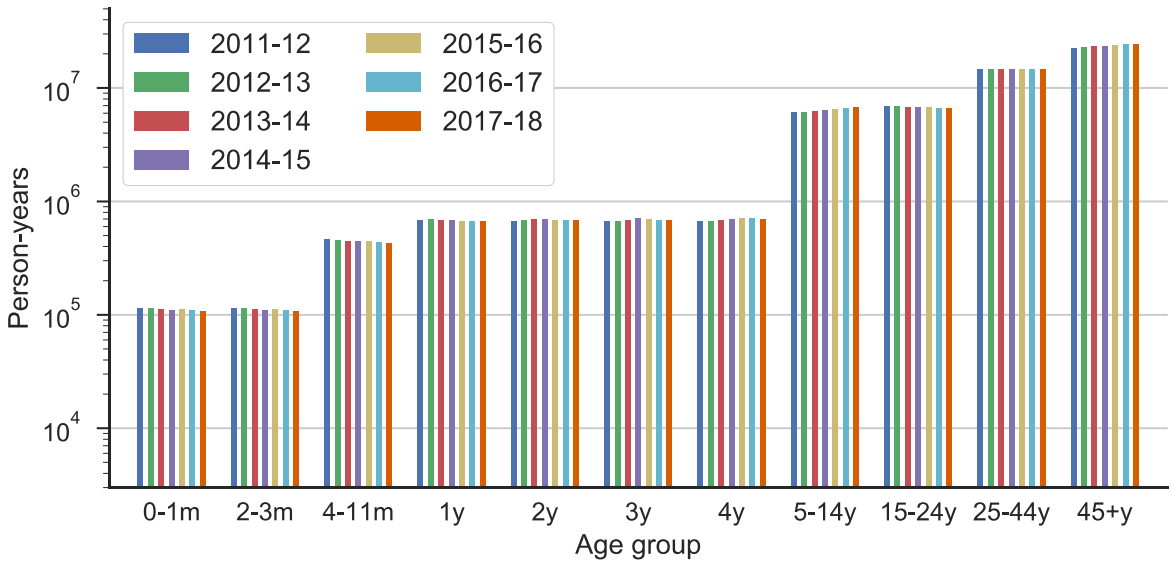
m: months; y: years.

S3 Vaccine uptake and person-years data

We received data on 4CMenB's uptake from Public Health England. We calculated the monthly proportions of the vaccinated population by month of age and number of doses from uptake statistics, following the same approach of the original study analysis.[4] First, we combined two datasets: i) monthly uptake data for each cohort reaching 6, 12 and 18 months of age, and ii) daily uptake data from nearly 60,000 individuals (30,000 for the booster dose) from different geographical areas across England. Then, uptake curves were shifted by 14 days to take into account the time needed to develop an immune response. We considered non-vaccinated 100% of the population born before May 2015.

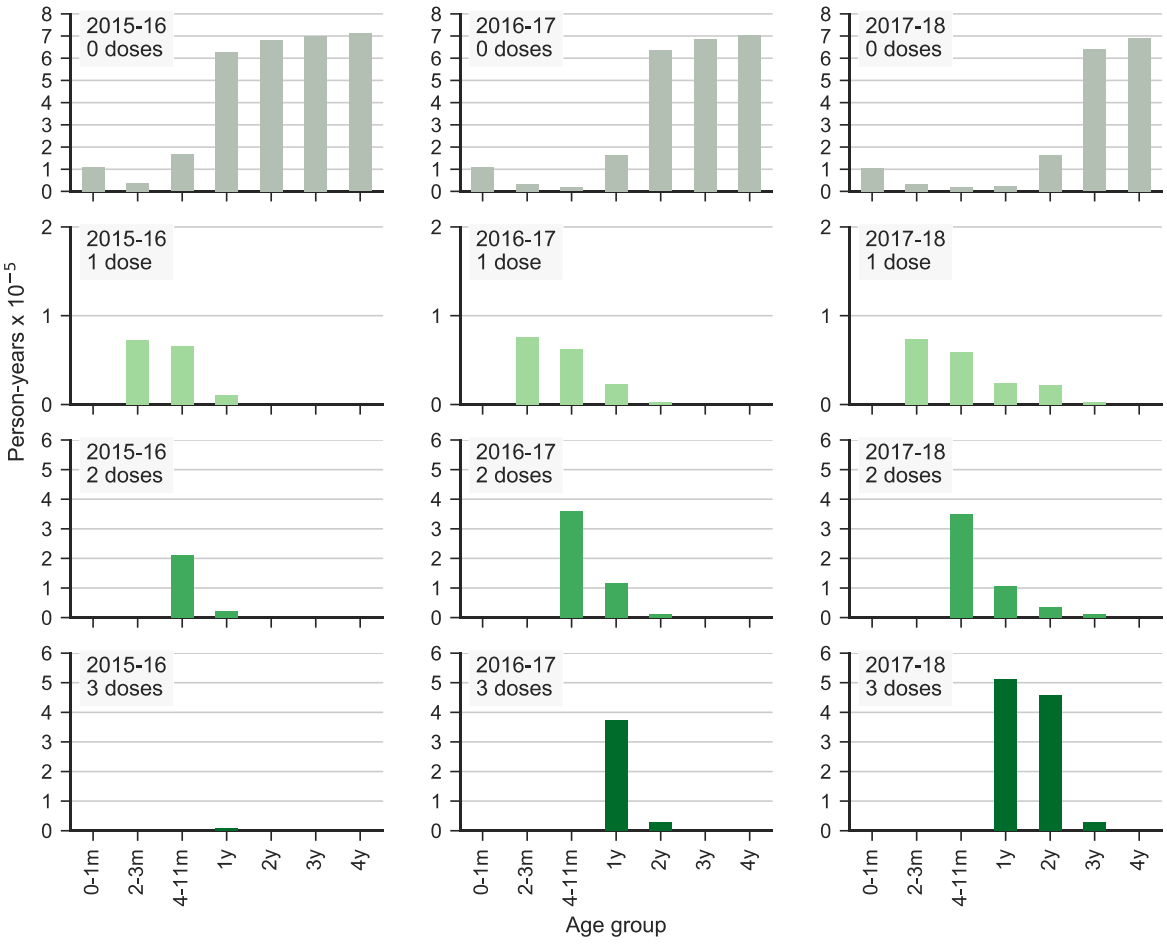
The annual number of person-years by age, stratified by number of vaccine doses injected, was derived combining England's population estimates with vaccine uptake. First, we downloaded England's mid-year population estimates by year of age from the United Kingdom's Office for National Statistics (https://www.ons.gov.uk). Then, we interpolated the data to mid-months (from September 2011 to August 2018) and month of age. After that, we used the above described proportions of vaccinated individuals to further stratify England's population by the number of vaccine doses received, from zero to three doses. Subsequently, we aggregated the population in the same age groups used for disease cases. Finally, we summed over months of time and divided by twelve, in order to calculate the annual number of person-years for each age group and number of doses received. The resulting person-years are plotted in Figure S1 and Figure S2.

Figure S1. Person-years by age and year



Total number of person-years by age group (horizontal axis) and year (September-August, different colors). We report here person-years independently on the number of doses that they received (reported in figure S2).
m: months; y: years.

Figure S2. Person-years / 100,000 by age, year and doses received



Person-years by age (from 0-1 m to 4 y, horizontal axes), year (2015-2018, columns) and number of doses received (0-3, rows). We report here only age groups and years where the national immunization program was implemented. All the other age groups and years that are exclusively composed by non-vaccinated are reported in figure S1.
m: months; y: years.

S4 Model's inference

We used Bayesian inference to fit the IMD incidence model (equation 2 in the main manuscript), with non-informative prior distributions[5] on ρ, θ and σ_β. We numerically derived posterior distributions using Markov chain Monte Carlo sampling with 40,000 iterations (4 independent chains of size 10,000 after additional 5,000 burned tuning steps for each chain). Sampling was performed through the No-U-Turn sampler of Python's PyMC3 package, a self-tuning variant of Hamiltonian Monte Carlo.[6–8]
Table S2 reports all the parameters.

Table S2. Best estimates of the parameters

Parameter	Posterior mean [95%BCI]
$\rho_{0–1m}$	-9.20 [-9.42; -8.98]
$\rho_{2–3m}$	-8.58 [-8.76; -8.40]
$\rho_{4–11m}$	-8.48 [-8.58; -8.38]
ρ_{1y}	-9.20 [-9.30; -9.09]
ρ_{2y}	-9.67 [-9.79; -9.55]
ρ_{3y}	-10.24 [-10.40; -10.09]
ρ_{4y}	-10.43 [-10.59; -10.26]
$\rho_{5\text{-}14y}$	-11.75 [-11.86; -11.65]
$\rho_{15\text{-}24y}$	-11.41 [-11.50; -11.33]
$\rho_{25\text{-}44y}$	-13.26 [-13.41; -13.11]
$\rho_{\geq 45y}$	-12.74 [-12.83; -12.65]
θ_1	-0.409 [-0.687; -0.132]
θ_2	-1.549 [-1.861; -1.257]
θ_3	-1.616 [-2.020; -1.214]
σ_β	0.151 [0.063; 0.266]

The model and its parameters ρ, θ and σ_β are defined in the main manuscript (methods section). BCI: Bayesian credible intervals; m: months; y: years.

S5 Model's predictions

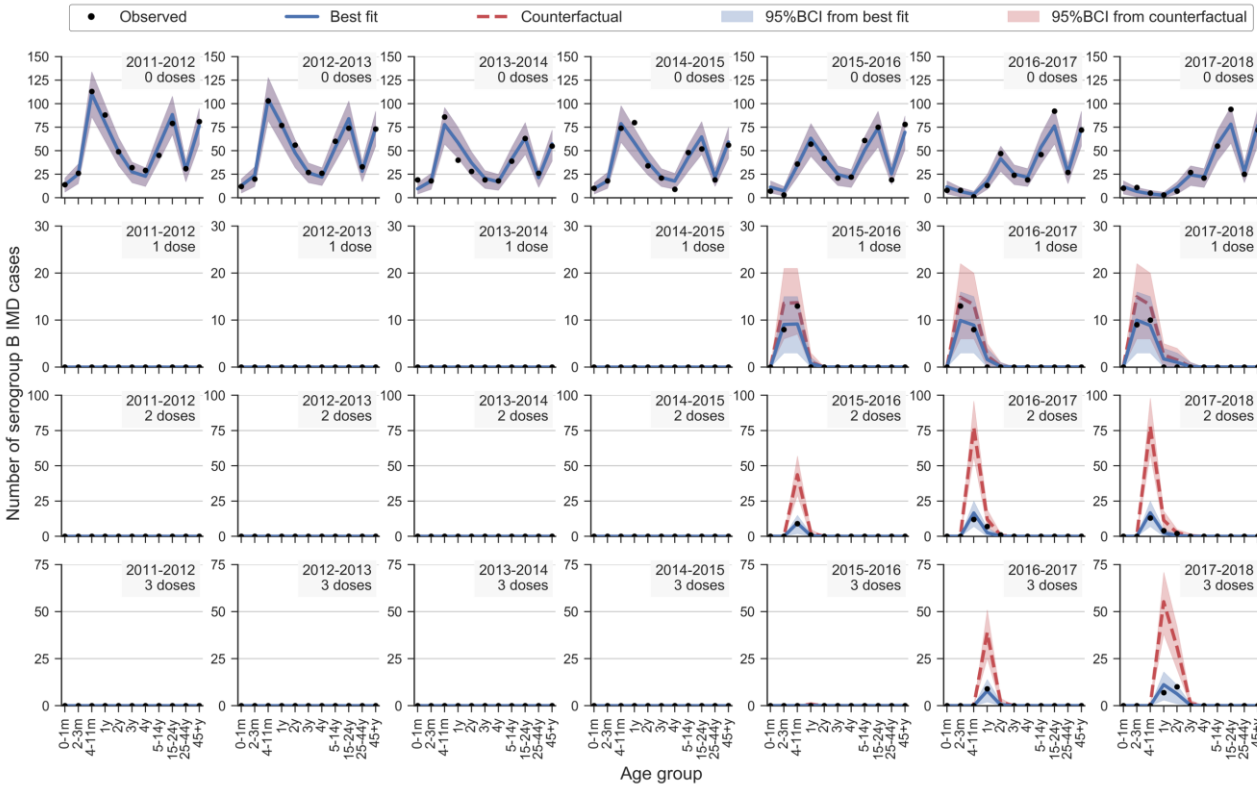
We sampled from posterior distributions (100,000 iterations) to generate posterior predictive distributions for model's best-fitting parameters and expected cases.

Parameters' posterior predictive distributions were used to calculate P values. For example, the probability that the VE after one dose is not higher than zero was calculated as the fraction of samples for which $\theta_1 \geq 0$ (i.e., for which $VE_1 \leq 0$, according to equation 3 of the main text).

Predictions of the number of expected cases for the no-vaccination scenario (the counterfactual, namely Z) were sampled in the same manner of the expected cases Y, except that all the effectiveness parameters were fixed to zero. Disease burden reduction imputable to the vaccine was calculated subtracting the two predictive distributions as $Z - Y$.

In Figure S3 we compare observed data with expected cases. The data (i.e., disease case counts, also reported in table S1, here shown as black points) are stratified by age, time and number of doses received, and were reported in England between September 2011 and August 2018. Blue lines represent expected case counts from the best fit. Red lines represent expected counterfactual case counts, that could have emerged if no vaccination program was implemented.

Figure S3. Case data and model predictions by age, time and doses received



Each plot reports as black points the yearly number of observed serogroup B IMD case counts by age for a different year and number of doses received (from zero to three). Expected case counts from incidence model's best-fit are shown as blue lines. In red, counterfactual case counts, generated through the same model when setting to zero all the VE parameters. The blue and red semi-transparent regions are the 95%BCI of the corresponding curves.
BCI: Bayesian credible intervals; m: months; y: years.

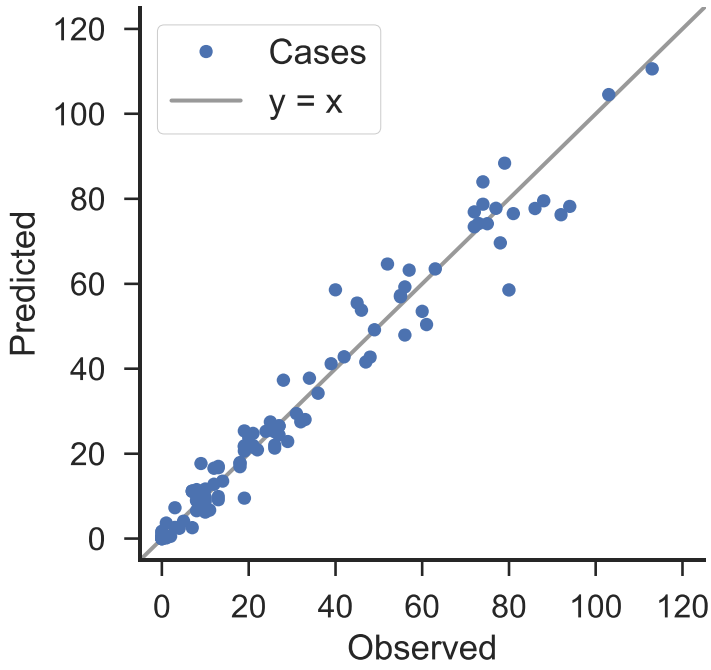
S6 Predictive accuracy of the incidence model

We quantified the predictive accuracy of the incidence model (equation 2 in the main text) for expected *vs.* observed cases using the Bayesian R-squared[9] (variance of the predicted values divided by the variance of predicted values plus the expected variance of the errors):

$$R^2 = 0.963.$$

Figure S4 shows predicted (expected) cases vs. observed cases.

Figure S4. Predicted vs. observed cases



S7 Comparison between models

We compared the incidence model that we used (equation 2 in the main manuscript) with a second model that does not take in account time trends, i.e., the same model when β_t is fixed to zero. To do so, we calculated deviances of the two models using through two different criteria for each model: the widely applicable information criteria and leave-one-out cross validation. Both are available in Python's PyMC3 package.[6] Table S3 shows results: both the metrics indicate that the inclusion of time parameters improved predictions (lower deviance), despite the higher complexity of the model.

Table S3. Models' comparison

Model	Deviance	
	WAIC	LOO
MenB incidence model (Eq. 2, main text)	619.9	622.6
MenB incidence model without adjusting for time (β_t fixed to zero in Eq. 2, main text)	670.6	671.1

Deviance of the tested models calculated using the widely applicable information criterion (WAIC) and leave-one-out (LOO) cross validation. Lower values indicate that the model provides a better fit.

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