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Pooled-sera hSBA titres predict individual seroprotection in infants and toddlers vaccinated with 4CMenB

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SUMMARY

The Serum Bactericidal Antibody assay with human complement (hSBA) using individual immune sera is a surrogate of protection for meningococcal vaccines. Strain coverage of 4CMenB, a licensed vaccine against serogroup B meningococcal (MenB) disease, has been extensively assessed in hSBA using pooled sera, directly or through the Meningococcal Antigen Typing System (MATS). The extent to which pooled-sera hSBA titres reflect individual protection is not yet fully understood.

We analysed more than 17000 individual hSBA titres from infants and toddlers vaccinated with 4CMenB, pooled-serum hSBA titres from subsets therein and MATS data from a 40 strain panel representative of invasive MenB disease in England and Wales.

Individual hSBA titres segregated in two normal distributions, respectively from responding and non-responding subjects (fit_model-data: $r = 0.996$, p-values <0.05). No individual subject showed abnormally high titres compared to the distributions. Also, when sera from the same subjects were tested individually and in pool, pooled-sera titre and average of individual titres from the same group were substantially indistinguishable ($r = 0.97$, p-value «0.001).

We identified a robust mathematical relationship between the mean of individual hSBA titres and the proportion of subjects achieving a protective titre (seroprotection rate, $r = 0.95$, p-value «0.001). Using this relation, the seroprotection rate in 15 groups of vaccinees tested against 11 diverse meningococcal isolates was accurately predicted by the hSBA titre of the respective pooled sera (average prediction error 9%).

Finally, strains defined covered by MATS had on average 77% predicted seroprotection rate (interquartile range, IQR: 66–100%) and 39% for non-covered strains (IQR: 19–46%).

We conclude that seroprotection rates in infants and toddlers vaccinated with 4CMenB can be accurately predicted by pooled-serum hSBA, and that strain coverage defined by MATS is associated with high seroprotection rates.

Summary: The Serum Bactericidal Antibody assay (SBA) from individual sera is a surrogate of protection for meningococcal vaccines. We show that SBA performed on pooled sera predicts individual protection.

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1. Introduction

Neisseria meningitidis, a gram-negative bacterium classified into 12 serogroups on the basis of their polysaccharide capsule causes more than 120,0000 cases of invasive meningococcal disease (IMD) per year [1]. Serogroup B *N. meningitidis* (MenB) is the leading cause of IMD in developed countries [2,3]. A genome-based approach, reverse vaccinology [4], was applied to develop the recently approved, protein-based four-component 4CMenB vaccine [5] against MenB disease [6–8].

The impact of a protein-based vaccine on IMD will largely depend on both the proportion of subjects mounting a protective immune response (the "seroprotection rate") and the proportion of MenB strains susceptible to the response elicited ("strain coverage").

The Serum Bactericidal Antibody assay with human complement (hSBA, [9]) is accepted as a surrogate of protection in the clinical evaluation of meningococcal vaccines [10,11]. The relationship between seroprotection and protection from IMD should be further clarified for 4CMenB by UK's national immunisation campaign started in September 2015. The result of the assay is a titre,

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i.e. the number of times a serum can be diluted and still remains capable of killing the cells of the bacterium.

The plasticity of the meningococcal genome facilitates the adaptation of surface structures to changing environments through a variety of genetic mechanisms [12]. These result in a high variability of sequence and level of surface expression for 4CMenB antigens, affecting strain susceptibility to vaccine-induced antibodies.

Using hSBA to evaluate the potential effectiveness of protein-based vaccines would require testing the serum of many subjects against many different isolates – an arduous undertaking because of the time required and of serum limitations, especially for infants.

Multiple individual sera can be pooled to reduce the experimental workload, by testing strains in pooled-sera hSBA to determine vaccine strain coverage. A further simplification was provided by a novel assay that does not require the use of human serum, the Meningococcal Antigen Typing System (MATS) [13,14]. MATS, developed to facilitate studies of large strain panels, was shown to accurately predict pooled-sera hSBA results [15].

Both the pooled-sera hSBA and the MATS used to determine 4CMenB strain coverage [16–18] are based on the assumption that pooled sera, obtained by mixing equal amounts of sera from individual subjects in randomized controlled clinical trials, adequately reflect the average response to vaccination of the individual subjects in the group. This assumption was never confirmed experimentally, and could be violated by highly heterogeneous individual immune responses in the pool and/or synergistic effects among sub-bactericidal antibody levels in different subjects.

To verify the significance of pooled sera as indicators of individual responses to vaccination with 4CMenB, here we analysed two distinct hSBA datasets: i) 16858 titres from 5250 infants and toddlers vaccinated with 4CMenB in late-stage clinical trials against seven MenB strains [19,20] and ii) matched individual and pooled-sera hSBAs from 431 infant and toddler vaccinees, generated in the present study against 11 MenB strains expressing different combinations of high, medium and low amounts of 4CMenB antigens.

To substantiate the validity of the 4CMenB strain coverage predictions, on which basis the vaccine was approved for use in humans, results were applied to a third dataset of pooled-sera hSBA and MATS data from a panel of 40 isolates representative of serogroup B IMD in England and Wales [15].

2. Materials and methods

2.1. hSBA assays

The Serum Bactericidal Antibody assay with human complement (hSBA) was performed as previously described (see [9] and supplemental Materials and methods).

The assay generating interpolated titres was validated for the majority of strains, and the interpolated titre value of 5 was shown to provide 95% confidence of exceeding the value of 4, the established correlate of protection for IMD [10]. Five was considered the protective hSBA threshold in all analyses.

2.2. Datasets

Three datasets were used in the present study: 1) and 3) from previous studies, 2) newly generated here.

1) Classification of individual hSBA titres into 86 groups. 16858 hSBA titres against 7 MenB strains from sera of infants and toddlers immunized with 4CMenB in late-stage clinical studies [19,20] were classified in groups for subsequent analysis as follows: titres from i) subjects immunized with the same immunization schedule, ii) in the same study, iii) tested at the same schedule-timepoint, iv) against the same strain, were grouped. Eighty-six groups were defined, with group sizes varying from 16 to 558 (see Table S1).
2) Paired individual and pooled-sera hSBA titres. Newly generated hSBA results from 431 infant and toddler sera, banked from a Phase 3 clinical trial [20], were tested both individually and in pools against 11 MenB strains. Each pool was composed of sera from 30 randomly selected subjects and hSBA tests were performed on blood draws taken 1 and 6 months post-3rd dose. As summarized in Table S2, MenB strains were purposely selected to represent low, medium and high MATS relative potencies for the 4CMenB antigens, both in isolation and in combination, and diverse antigenic genotypes.
3) Matched pooled-sera hSBA titres and MATS data from 40 MenB isolates representative of IMD in England and Wales in 2007–2008 [15] (Table S3).

2.3. Mathematical model for hSBA titre density

For each group i in Table S1, the density distribution of $\log_2$ individual hSBA titres have been described by a mixture f_i of two gaussian distributions:

$$f_i(x) = (1 - w_i) \cdot \overline{N_o}(0, \sigma_0) + w_i \cdot \overline{N_1}(\mu_i, \sigma_i) \quad (1)$$

where x is the discretized $\log_2$ hSBA titre, $\overline{N_o}$ is the positive half of a Gaussian distribution centred at zero with the standard deviation $\sigma_0 = \log_2(5)/3$, $\overline{N_1}$ is a positively defined Gaussian distribution with mean μ_i and standard deviation σ_i, and w_i is the relative weight of $\overline{N_1}$ to $\overline{N_o}$ in the mixture f_i (further details in supplemental Materials and methods).

2.4. Functional relationship between arithmetic mean of individual titres and rate of protection

Given the arithmetic mean titre x of a group, the correspondent seroprotection rate (SR) was predicted with the logistic function:

$$\mathrm{SR} = \left(1 + \exp\left(b\left(\log\left(\frac{x}{e}\right)\right)\right)\right)^{-f} \quad (2)$$

with minimum 0%, maximum 100%, b, e, and f as free parameters.

2.5. Statistical analyses

Non-linear regressions of Eqs. (1) and (2) to data were obtained by the least-squares method as implemented in the *nls* and *drc* packages of R version 3.0.2 (http://www.r-project.org/).

Goodness of fit for each model was quantified by the Pearson correlation coefficient r between raw and fitted data, as implemented in the function *cor.test()* of R version 3.0.2.

The precision of prediction for each mathematical model was measured by the Mean Absolute prediction Error (MAE [21]).

3. Results

3.1. Individual titres from responding and non-responding subjects are described by two distinct normal distributions, respectively

Nine of the 86 groups of subjects in dataset 1 (Table S1) had seroprotection rates (i.e. the proportion of subjects with an hSBA titre ≥ 5, see Materials and methods) $\leq$20%, 17 groups between 20 and 80%, and 60 groups responded >80%.

Fig. 1 shows the distribution of $\log_2$ hSBA titres for three typical groups of vaccinees with different seroprotection rates, with titres from non-responding subjects coloured in red and from responders in blue.

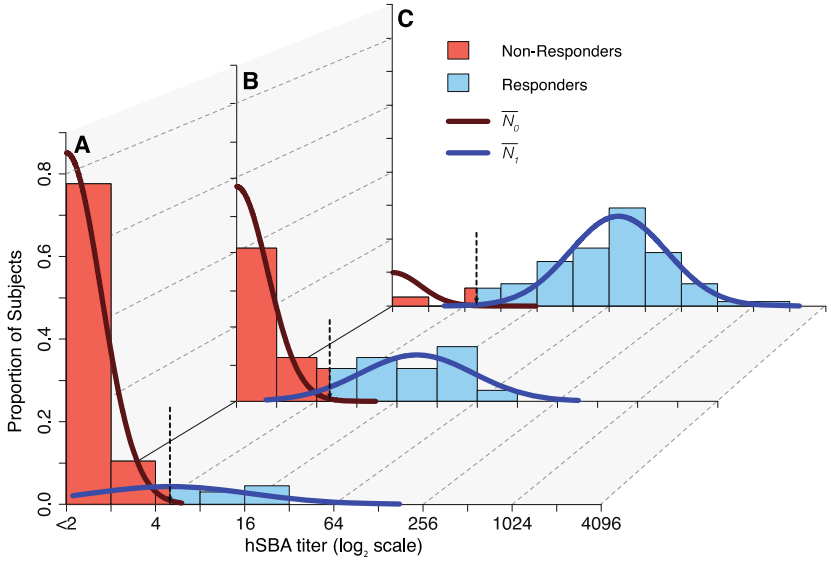

Fig. 1. Distributions of individual hSBA titres. Shown, as histograms for three typical groups of subjects with different seroprotection rates (SR: 12% (A), 47% (B) and 99% (C) - in Table S1 respectively group 25, 48, and 79), is the proportion of subjects having an hSBA titre comprised between the lower (included) and the upper (excluded) limit of each histogram's bar. The dashed line marks the protective titre threshold of 5. Non-responders and responders are red and blue-shaded, respectively. The solid curves indicate the best fit to data of $\overline{N_0}$ (red) and $\overline{N_1}$ (blu) components in Eq. (1).

In each of the 86 groups (Fig. S1), titres from responding subjects were always clustered around a single value, and bell-shape distributed. The density of titres from non-responding subjects peaked at zero and rapidly decreased towards the titre of value 5.

This behaviour of the hSBA titre density in each group i can be described mathematically by a mixture f_i of two truncated Gaussian distributions $\overline{N_0}$ and $\overline{N_1}$ (red and blue respectively in Fig. 1) as described in Eq. (1).

$\overline{N_1}$ describes hSBA titres from responding subjects, and in each group it can have a different mean, standard deviation and weight. $\overline{N_0}$ describes hSBA titres from non-responders, is always centred at zero and has a fixed standard deviation such that >99% of the density corresponds to titres <5.

In each group, we determined the best fit of Eq. (1) to data. In 82 of the 86 groups, we estimated all parameters for $\overline{N_0}$ and $\overline{N_1}$. The remaining four subject groups were fitted only with the $\overline{N_0}$ component of Eq. (1) due to the absence of responders.

Eq. (1) accurately described the experimental distributions of hSBA titres in all groups (median correlation raw – fitted data 0.996, range @95%: 0.75–1.00, all p-values <0.05, see Figs. S1 and S2). The average across groups for the standard deviation σ was 1.14 (range @95%: 0.75–1.74, Fig. S3C), i.e. approximately one step-2 dilution, indicating a compact distribution of the hSBA titres around the mean value.

Comparison between mathematical parameters in Eq. (1) and their serological meaning (see Fig. S3) confirmed that, in all groups of subjects analysed: i) titres from responding and non-responding subjects can be modelled separately, ii) titres from responding subjects are clustered around a well-defined mean-value, iii) no highly heterogeneous individual immune responses were observed.

3.2. The arithmetic mean of individual hSBA titres predicts the proportion of responders

Fig. 2 shows, for each group of subjects listed in Table S1, the percentage of individuals with an hSBA titre ≥ 5 (seroprotection rate), versus the arithmetic mean of the same titres. When the mean titre lies approximately between 2 and 64, the seroprotection rate grows proportionally. When the mean is greater than 64 or lower than 2, the seroprotection rate approaches 100 and 0%, respectively.

Overall, the logistic function of the arithmetic mean of the hSBA titres described in Eq. (2) predicted accurately the seroprotection rate (correlation raw-fitted data $r = 0.95$, p-value «0.001). Fig. S4 shows the comparison between predicted and measured seroprotection rate. A MAE of 5% (range @95%: 0.0–21%) and an absolute bias of 0.9% indicated consistent precision and accuracy for the prediction. In summary, results indicated that Eq. (2) is a mathematical relationship that can be used to accurately predict the seroprotection rate of a group of vaccinees from the average of their individual hSBA titres.

3.3. Pooled-sera hSBA titres correspond to the arithmetic mean of the titres from individual sera composing the pool

Fig. 3 shows hSBA titres from both pools and the individual subjects composing each pool generated in this study from dataset 2 (see Materials and methods and Table S2).

Each of the 13 measurable pooled-sera titres (≥2) matched closely the mean of the corresponding individual hSBA titres

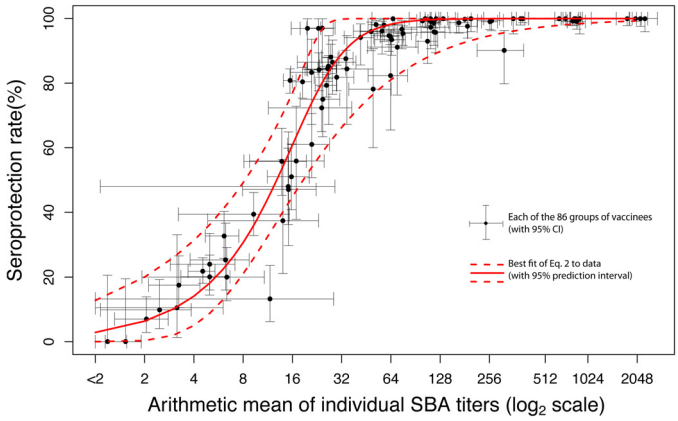

Fig. 2. Relationship between seroprotection rate and average of individual hSBA titres. The seroprotection rate (% of subjects with hSBA titres ≥5) vs. the arithmetic mean of all hSBA titres is shown for each of the 86 groups of vaccinees. The continuous red curve is the best least-square fit of Eq. (2) to data, obtained for $b = -2.8841$, $e = 21.9464$ and $f = 0.3986$. Dashed red curves represent the 95% prediction interval.

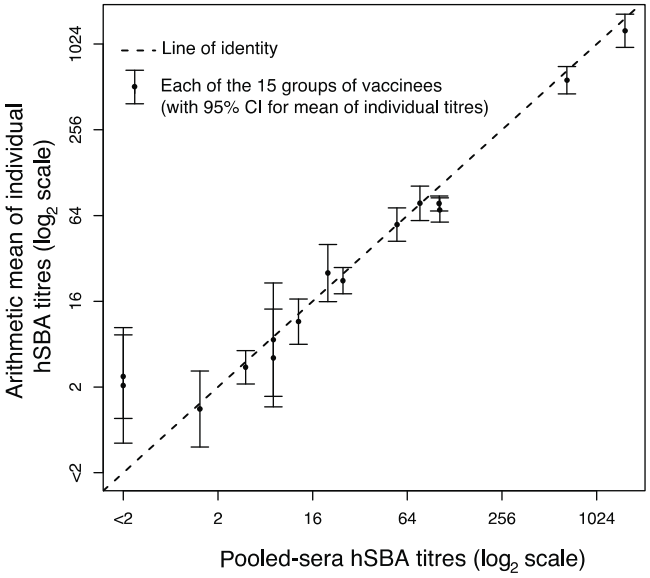

Fig. 3. Relationship between pooled-sera titres and arithmetic mean of individual titres. Pooled-sera hSBA titres vs. arithmetic mean of individual titres from subjects composing the pool, for the 15 groups of subjects described in Table S2.

(Fig. 3). In two groups, the non-measurable pooled-sera titre (<2) slightly underestimated the average individual responses which, however, remained below the seroprotection threshold (< 5). Overall, the measurable pooled-sera titres corresponded to the mean of the titres composing the pool with a correlation of $r = 0.97$ (p-value «0.001) and a MAE of 1.4%, indicating lack of measurable synergistic effects among sub-bactericidal antibody levels in different subjects.

3.4. Pooled-sera hSBA titres predict the proportion of individuals protected from disease

Having observed i) a robust mathematical relationship between seroprotection rate and mean individual titres (Eq. (2)) and ii) a substantial identity between mean individual and pooled-sera titres (Fig. 3), we used Eq. (2) to correlate pooled-sera hSBA titres and seroprotection rate.

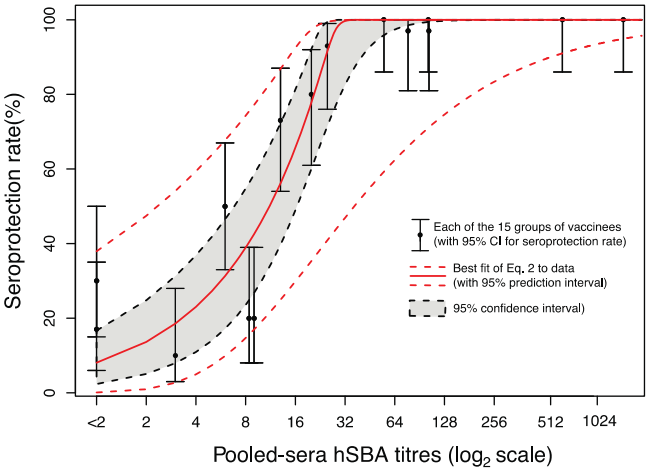

Fig. 4. Relationship between pooled-sera hSBA titres and seroprotection rate. Pooled-sera hSBA titres vs. seroprotection (percentage of sera composing the pool with hSBA titre ≥5) for the 15 groups of subjects described in Table S2. The solid red line is the best fit of Eq. (2) to data. Dashed lines are the 95% confidence interval (black) and the 95% prediction interval (red).

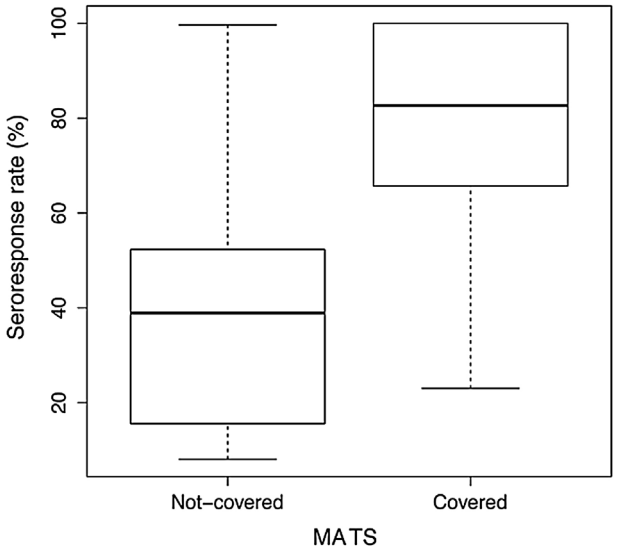

Fig. 5. Predicted seroprotection by MATS coverage in England and Wales. Boxplot of seroprotection rates for 40 strains representative of IMD in England and Wales, predicted from pooled-sera hSBA titres through Eq. (3). Left: 12 strains predicted not-covered by MATS. Right: 28 strains predicted covered by MATS. The Box plots indicate The central box represents half of the covered/not-covered strains with whiskers representing the upper (75%) and lower quartiles (25%) of strains. The median predicted seroprotection rates is indicated by the thick line. The whiskers above and below the box show the locations of the minimum and maximum.

Fig. 4 shows, for the all the subjects analysed in dataset 2 (see Materials and methods and Table S2), the seroprotection rate vs. the pooled-sera hSBA titre. The solid red curve shows the best fit of Eq. (2) to experimental data:

$$SR = \left(1 + \exp\left(-17.977\left(\log\left(\frac{x}{27.897}\right)\right)\right)\right)^{-0.042} \quad (3)$$

were SR is the seroprotection rate for a group of subjects vs. a given strain at a given timepoint, and x is the corresponding pooled-sera titre.

Despite the limited number of individual sera composing each pool, results indicate that Eq. (3) describes adequately the direct relationship between individual and pooled-sera hSBA titres (raw-fitted data correlation $r = 0.94$, p-value «0.001). The shaded area in the graph indicates the 95% regression confidence interval, corresponding to a MAE of 9% (min–max: 0.0–23%) and absolute bias of -0.7%. Albeit slightly larger than the precision of arithmetic mean titre vs. seroprotection rate – due to the smaller size of dataset 2 vs. dataset 1 – these values confirm that the proportion of infants and toddlers reaching seroprotection in a group receiving the 4CMenB vaccine can be reliably predicted by the hSBA titer of the group pooled-serum.

3.5. MATS coverage is associated with high predicted seroprotection

We applied Eq. (3) to predict seroprotection rates for each strain in dataset 3 (see Table S3), a panel of 40 strains representative of serogroup B IMD in England and Wales. Pooled-sera hSBA titres from infant vaccinees (hSBA strain coverage 88%, CI@95%: 72–95%) and MATS values (MATS strain coverage 70%, CI@95%: 55–85%) were previously determined [15].

Fig. 5 shows the distribution of predicted seroprotection rates against strains deemed covered and those not covered by MATS. The predicted average seroprotection rate was 77% [IQR: 66–100%] and 39% [IQR: 19–46%] for strains covered and not-covered in MATS, respectively, corresponding to an overall predicted seroprotection

of 65% [IRQ: 39–100%], a value similar to the strain coverage predicted by MATS.

4. Discussion

The Serum Bactericidal Antibody assay with human complement (hSBA) from pooled sera has been used, directly or through the MATS assay, to support the development and strain coverage estimation of the 4CMenB vaccine [13,15,16,22]. The use of pooled-sera titres was motivated by the observation that antibodies contained in individual sera, once pooled, are mutually diluted in the overall solution. As in any proportional dilution process, the titre of the pooled serum is expected to be the average of the individual titres from subjects composing the pool and to reflect the "typical" response to vaccination of the individual subjects in the group.

However, two effects could violate this assumption. First, if a minority of subjects in a group of vaccinees mounted a very high response, while all others mounted no response at all, the pool may still have some measurable killing activity, leading to an overestimation of the proportion of subjects protected from disease. Second, sub-bactericidal levels of antibodies in different subjects, binding the same or different antigens, could synergistically contribute to killing in the pool not reflecting actual individual protection [23–25].

Here, we have re-analysed a broad database of individual hSBA results collected in late stage 4CMenB clinical studies, observing that the individual hSBA responses to 4CMenB were always distributed according to a regular pattern. Irrespective of the magnitude of titres measured, strain tested, number of doses and size of the group investigated, titres were always clustered in two distinct components, above and below the protective threshold of 5, where titre frequency was always at its minimum, i.e. subjects rarely mounted a response "at threshold".

Titres from responding subjects were always compactly distributed around their $\log_2$ hSBA mean with spread comparable to assay variability, and this mean was proportional to the seroprotection rate. In other words, when a few subjects mounted a protective response, their hSBA titres were low and close to the immunogenicity threshold; when many subjects responded to vaccination, their individual titres were all high.

A consequence of this regular behaviour is that the arithmetic mean of all hSBA titres in a group of vaccinees (responding or not responding to vaccination) was mathematically linked to the proportion of subjects mounting a protective titre, explaining why pooled sera can be used to predict seroprotection.

Results indicate that, when sera from infants and toddlers vaccinated with 4CMenB are pooled, synergistic effects previously proposed [25] across adult subjects do not reach a level to significantly alter the pool-average relationship. Eleven MenB strains expressing variable amounts and combinations of vaccine antigens were used for this analysis, one of which had a similar antigenic assortment to the strain reported in Vu et al. [25] (fHbp variant 2.19 and NHBA medium expression). In our data, the lack of synergistic effects was clear, with only one deviation observed below the limit of detection, but in the opposite direction to that proposed: the pool titre (<2) was slightly lower than the mean of the corresponding individual titres (4.1–4.7). The different age groups could easily explain the apparent discrepancy between the two studies, as pre-existing immunity due to carriage of meningococci in older age groups can expand the antibody repertoire compared to younger subjects [26].

Taken together, the homogeneity of individual responses and the lack of significant synergy in pooled sera justify the high quality of the mathematical relationship between pooled-sera hSBA titres and seroprotection derived in Eq. (3) ($r = 0.94$, p-value «0.001), although the relatively small sample size investigated (30 subjects per strain per visit) led to sizable prediction intervals. Direct application of this relationship to a panel of isolates representative of MenB IMD in England and Wales, previously tested in MATS and pooled-sera hSBA, predicted high rates of seroprotection for MATS-covered isolates (IQR 66–100%), and non-negligible seroprotection also for isolates not covered by MATS (IQR 19–46%), further supporting the use of MATS as a conservative tool to predict and monitor the impact of 4CMenB on IMD [27].

Even if an individual strain considered as "covered" may still cause disease in some vaccinated subjects – MATS coverage thresholds were defined to predict pooled-sera hSBA titres ≥ 8 [13], associated with ~40% of protection based on Eq. (3) – when strain collections representative of the real circulating disease are analysed, the overall results are robust and consistent.

Limitations of the present study include the number of subjects that could be tested in matched individual-pools. A much larger study would be necessary to extend the sample size, given the significant volume of infant serum required and the logistic requirements of the assay. Also, a single surrogate of protection was analysed here (hSBA), and only in infants and toddlers.

Interestingly, the predictive function identified here was valid both for pre- and post-booster timepoints in toddlers, but it is not obvious how these results would translate to older age groups, such as adolescents and adults, where baseline immunity induced by natural exposure and broader antibody repertoire could act as confounding factors.

As the 4CMenB vaccine was licensed based on the hSBA as a surrogate for protection, there is no direct evidence yet of its protective efficacy. The vaccine is being rolled out as part of the UK's national infant immunisation programme, which should in due course provide evidence of its effectiveness. We believe that the results presented in this study provide a useful hypothesis to be verified prospectively in the context of the 4CMenB implementation programs, when the validity of pooled hSBA and MATS as assays predicting protection and vaccine antigen coverage respectively could be unambiguously assessed.

Conflicts of Interest

Potential conflicts of interest: S.B., A.K. and D.M. are employees of GlaxoSmithKline Vaccines and P.B. is a PRA Health Sciences consultant assigned to GlaxoSmithKline Vaccines.

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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.2016.04.009.

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