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REVIEW

A review of complement sources used in serum bactericidal assays for evaluating immune responses to meningococcal ACWY conjugate vaccines

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ABSTRACT

Invasive meningococcal disease is rare and potentially devastating but often vaccine-preventable. Evaluation of meningococcal vaccine effectiveness is impractical owing to relatively low disease incidence; protection is therefore estimated using serum bactericidal antibody (SBA) assays. Original experiments on natural immunity established a titer of ≥4 as the correlate of protection for SBA assays using human complement (hSBA), but human complement is relatively difficult to obtain and standardize. Use of baby rabbit complement (rSBA assays), per standard guidelines for serogroups A and C, generally results in comparatively higher titers. Postlicensure effectiveness data for serogroup C conjugate vaccines support acceptance of rSBA titers ≥8 as the correlate of protection for this serogroup, but no thresholds have been formally established for serogroups A, W, and Y. Studies evaluating MenACWY-TT (Nimenrix®; Pfizer Inc, Sandwich, UK) immunogenicity have used both hSBA and rSBA assays, and ultimately suggest that rSBA may be more appropriate for these measurements.

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Introduction

Meningococcal disease is caused by the Gram-negative bacterium *Neisseria meningitidis*, an obligate human pathogen.[1] The bacterium may colonize the nasopharynx in an asymptomatic state known as carriage.[1] Occasionally meningococci will invade the bloodstream to cause invasive meningococcal disease (IMD); IMD can manifest as septicemia and/or meningitis, which occur when the bacteria primarily proliferate in the blood or cerebrospinal fluid, respectively.[1] Incidence of IMD is generally low but varies by region; for instance, in 2016, incidence in the European Union was 0.64 per 100,000 population[2] whereas in the United States it was 0.12 per 100,000.[3] Despite low incidence, IMD can progress in a matter of hours and can be fatal in approximately 7% to 23% of cases;[4–7] a substantial percentage of survivors suffer permanent sequelae such as limb loss, neurologic deficits, or hearing impairment.[8] IMD disproportionately affects certain age groups: infants and young children, adolescents and young adults, and older adults (≥65 years of age).[4,5]

Although 12 meningococcal serogroups have been identified, the majority of disease is caused by serogroups A, B, C, W, and Y.[9] Vaccines are available to prevent disease caused by each of these serogroups. There are 3 currently licensed conjugate vaccines targeting meningococcal serogroups A, C, W, and Y (MenACWY vaccines); each vaccine includes capsular polysaccharides from each of the 4 serogroups individually conjugated to a carrier protein. These quadrivalent conjugate vaccines include MenACWY-D (Menactra®; Sanofi Pasteur, Swiftwater, PA, USA), which uses diphtheria toxoid (D) as the carrier protein;[10] MenACWY-CRM_{197} (Menveo®; GlaxoSmithKline, Rixensart, Belgium), which uses a non-toxic mutant of diphtheria protein, CRM_{197};[11] and MenACWY-TT (Nimenrix®; Pfizer Inc, Sandwich, UK), which uses tetanus toxoid (TT).[12] Several monovalent meningococcal conjugate vaccines targeting a single serogroup are also available, including MenC-TT (Neis-Vac-C™; Pfizer Ltd, Kent, UK)[13] and MenC-CRM_{197} (Menjugate®; GlaxoSmithKline Vaccines Srl, Siena, Italy),[14] which both contain serogroup C polysaccharides and use TT and CRM_{197}, respectively, as carrier proteins. MenA-TT (MenAfriVac; Serum Institute of India, Pune, India) is a monovalent serogroup A meningococcal vaccine that uses TT as a carrier protein.[15] In addition, Hib-MenC-TT (Menitorix®; GlaxoSmithKline) is a combination conjugate vaccine containing both MenC, conjugated to TT, and *Haemophilus influenzae* type b.[16] Although serogroup B meningococcal vaccines based on capsular polysaccharides are poorly immunogenic,[17,18] MenB vaccines targeting conserved subcapsular antigens have become available in recent years; these include MenB-FHbp (Trumenba®, bivalent rLP2086; Pfizer Inc, Philadelphia, PA)[19] and 4CMenB (Bexsero®, MenB-4C; GlaxoSmithKline Vaccines Srl).[20]

As discussed in more detail below, the serum bactericidal antibody (SBA) assay has become a surrogate method for evaluating meningococcal vaccine efficacy. This article reviews the use of SBA assays in development of different meningococcal vaccines, with particular focus on differences between assays using human (hSBA) or baby rabbit (rSBA) complement. Studies evaluating immune responses to MenACWY-TT are presented in detail to highlight such differences and provide an update to an earlier review of

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MenACWY-TT studies.[21] Postlicensure effectiveness findings are also presented in the context of immunogenicity studies.

The SBA assay

Because meningococcal disease is currently relatively rare, studies evaluating efficacy of meningococcal vaccines would require impractically large sample sizes.[22] For this reason, it became necessary to develop a surrogate measure with which efficacy could be more easily determined.

In 1969, Goldschneider and colleagues published a seminal paper describing the use of SBA assays and the correlation of results with susceptibility to meningococcal disease.[23] To perform the SBA assay, sera from subjects were serially diluted and incubated with a suspension containing a given meningococcal strain; in most experiments, exogenous human complement lacking bactericidal activity to the tested strains was then added (Figure 1[24]). Bactericidal activity was determined based on the efficiency of bacterial killing compared with controls, with SBA titers defined as the highest dilution of sera at which ≥50% killing occurred. The authors tested sera from newly enlisted military recruits for SBA activity against circulating serogroup C meningococcal strains that later infected 54 recruits; 5.6% of cases and 82.2% of controls (10 randomly selected men in the same training platoon for each given case) had baseline sera with SBA titers ≥4. These findings suggested that SBA titers ≥4 might be indicative of protection from serogroup C IMD. Much higher percentages of controls compared with serogroup C cases also had SBA titers ≥4 against serogroup A and B strains,[23] indicating that SBA activity was mediated by subcapsular antigens in addition to capsular polysaccharides.[25] Goldschneider and colleagues also demonstrated that the presence of SBA titers ≥4 against representative strains from serogroups A, B, and C was inversely proportional to IMD incidence across age groups (through age 26 years), providing additional indirect evidence for the correlation of SBA titers ≥4 and protection from IMD.[23]

Because evaluating meningococcal vaccine efficacy in clinical trials is impractical owing to the low incidence rate of IMD, the SBA assay became especially useful as a surrogate measure of vaccine efficacy. Several years after the publication of the experiments by Goldschneider and colleagues, the World Health Organization (WHO) stipulated the use of SBA assays using baby rabbit complement to demonstrate efficacy for potential licensure of meningococcal polysaccharide vaccines targeting serogroups A and C.[24] Guidelines specified that vaccines should induce a ≥4-fold rise in SBA titers in ≥90% of tested subjects.

Sources of complement used for the SBA assay

The original experiments establishing the correlation between SBA and protection from IMD used human complement (ie, sera containing complement proteins) for performing the SBA assay.[23] However, finding suitable human donors can be challenging. Ideally, serum from agammaglobulinemic individuals should be used because it lacks antibodies capable of contributing to bactericidal activity in the assay, but this is a relatively rare condition and most of these individuals receive treatment containing replacement immunoglobulins.[26,27] Human complement must therefore be sourced from the relatively few individuals who lack intrinsic bactericidal activity against meningococcus but still exhibit normal complement hemolytic

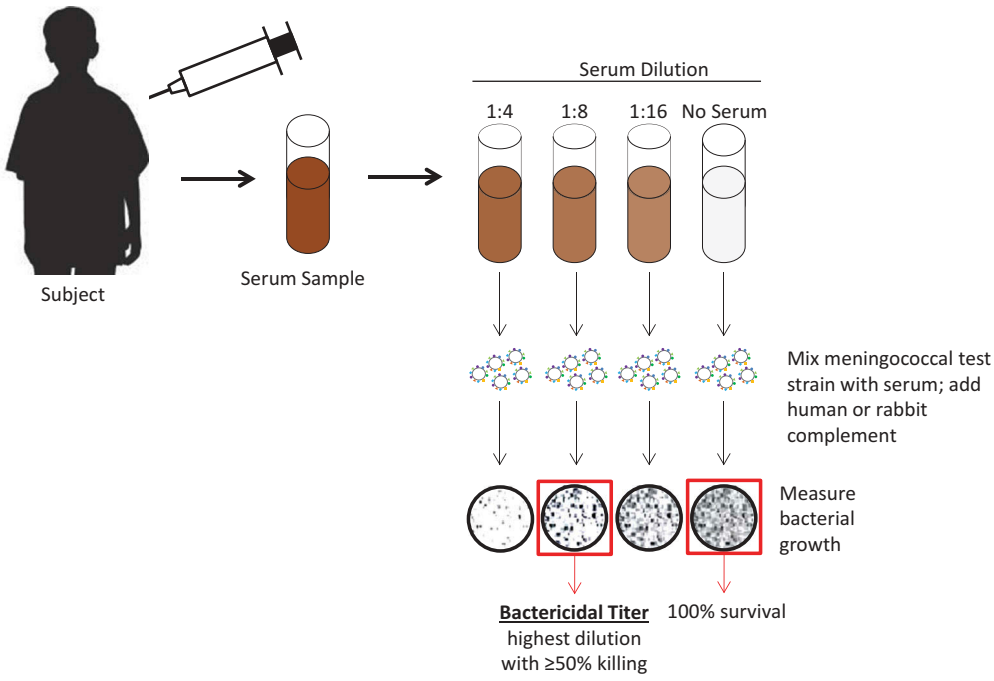

Figure 1. Schematic illustrating serum bactericidal antibody assay using either human or baby rabbit complement. For serogroups A and C, the World Health Organization guidelines stipulate that complement sourced from baby rabbits should be used.[24] For the subject shown, the SBA titer would be 8. SBA = serum bactericidal antibody. Figure has been adapted with permission from Gandhi A, Balmer P, York LJ. Characteristics of a new meningococcal serogroup B vaccine, bivalent rLP2086 (MenB-FHbp; Trumenba®). Postgrad Med. 2016;128(6):548–556.

activity (CH_{50}).[26,28] Furthermore, each human donor must be screened for each meningococcal strain to be tested before each donation to ensure that natural immunity has not been acquired.[28] The difficult task of standardization of human complement across laboratories presents an additional challenge to the use of hSBA assays.[29]

For serogroup A and C vaccines, complement sourced from baby rabbits was used as an alternative to human complement because it was more easily available in large batches and subject to standardization; results with human and baby rabbit complement also seemed to correlate with one another in initial studies.[24,29] rSBA assays thus became the standard surrogate for evaluating meningococcal vaccine efficacy and subsequent licensure. A 1997 study by the US Centers for Disease Control and Prevention (CDC) demonstrated the reproducibility of a standardized rSBA assay method, in which the critical parameters of target strains, incubation times, and complement sources were specified, for serogroups A and C in multiple laboratories across different countries.[30] Of note, interlaboratory variability still exceeded intralaboratory variability, indicating that additional parameters contributed to assay results.[30]

Over time, it became apparent that results from rSBA and hSBA assay analyses did not necessarily correlate with one another. For serogroup C, one study using sera from toddlers and young children vaccinated with MenC-CRM_{197} identified rSBA titers ≥128 as reliable predictors of hSBA titers ≥4 (using complement from adult donors; ≥80% sensitivity), but most subjects with hSBA titers ≥4 had rSBA titers ≤128.[27] Another study for serogroup C demonstrated that rSBA cutoffs of <8 and ≥128 reliably predicted proportions of subjects with hSBA titers <4 and ≥4, respectively, but rSBA titers between 8 and 64 were poorly predictive.[31] A more recent study similarly found higher titers measured by rSBA compared with hSBA assays; results additionally demonstrated that although rSBA and hSBA titers were reasonably correlated for serogroup C, they were not correlated for serogroups A and Y.[32] It is not clear whether the general discrepancy between rSBA and hSBA results reflect overestimation of rSBA assays, underestimation of hSBA assays, or both;[32,33] however, the correlation of rSBA titers ≥8 with vaccine effectiveness for serogroup C in postlicensure studies[34] (discussed in the "Correlation of Observed Protection With Serology" section below) suggests that the ≥4 cutoff for hSBA may be overly conservative.[25] The differences between rSBA and hSBA titers are thought to be due, at least partially, to meningococcal factor H binding protein, which binds specifically to human factor H to ultimately enable evasion of complement-mediated killing.[35,36] Relatedly, it has been shown that human antibody subclasses may differentially interact with human and rabbit complement.[37]

It is important to note that specific rSBA and hSBA assays usually differ from one another beyond the source of complement. For example, meningococcal test strains may differ across laboratories.[21,33] These factors are also important to consider when comparing different assays and are discussed in greater detail in the "Assays and Strains Used in Different Laboratories" section below.

Of note, a modified version of the hSBA assay was developed in recent years; this high-throughput, automatable method involves using a colored indicator of cell metabolic activity in a liquid medium that can be correlated with hSBA titers.[38] Assay results have been demonstrated to correlate with those from conventional hSBA assays,[38] and some recent analyses have used this modified assay.[39,40]

Serogroup B vaccines

A 1983 publication demonstrated that subjects with high rSBA titers against serogroup B meningococcal strains had much lower or even nonexistent bactericidal activity to the same strains in hSBA assays.[41] This discrepancy is likely related to anti-MenB polysaccharide antibodies being primarily of the immunoglobulin M subclass, which features relatively low avidity that can further be affected by complement source among other variables.[41]

An international meeting in 2006 emphasized that human complement was the only acceptable source for SBA assays evaluating MenB vaccines.[42] Serogroup B vaccine licensure has generally relied on the percentages of subjects with hSBA titers of ≥4 or ≥4-fold rises in hSBA titers from pre- to postvaccination;[43] the more recent licensure of subcapsular-based MenB vaccines has therefore been based on hSBA data.[19,20,44,45]

Effectiveness data from outer membrane vesicle vaccines have been shown to correlate with hSBA serology.[46,47] For a more recently licensed subcapsular-based vaccine, 4CMenB, effectiveness was estimated at 82.9% (95% CI: 24.1, 95.2) among UK infants;[48,49] this high percentage validated the use of hSBA assays for predicting vaccine-induced protection.

Complement sources used in studies of serogroup A, C, W, and Y vaccines

In the United Kingdom, MenC conjugate vaccines were licensed on the basis of robust immune responses demonstrated in the rSBA assay; efficacy studies were not required because of demonstrated correlations between efficacy and serologic correlates of protection for meningococcal polysaccharide vaccines in toddlers.[31,50] A MenC conjugate vaccine program was subsequently broadly implemented in 1999 on the basis of these immunogenicity data; titers ≥8 were proposed to indicate protection[31,50] and were demonstrated to inversely correlate with disease.[51] Coupled with postlicensure data (discussed in greater detail later), these findings led rSBA titers ≥8 to become the generally accepted correlate of protection for MenC conjugate vaccines.[43]

The clinical development program of MenA-TT followed the UK MenC program and used the rSBA assay.[52] Licensure was obtained in India in late 2009 and for countries in the African meningitis belt in 2010 after prequalification by WHO.[52] Similarly, recently published results from a phase 1 study of an investigational MenACWXY vaccine intended to target increased rates of serogroup X disease in Africa used rSBA assays for immunogenicity evaluations.[53]

MenACWY conjugate vaccines have often been licensed on the basis of either hSBA or rSBA assay data, or both. MenACWY-D, the first MenACWY conjugate vaccine licensed by the US Food and Drug Administration, was licensed in 2005 primarily on the basis of rSBA assay data.[54]

On the other hand, in 2010, MenACWY-CRM$_{197}$ was approved in the United States at least partially on the basis of hSBA assay data.[55] In Europe, MenACWY-CRM$_{197}$ was licensed in 2009 on the basis of hSBA assay data, although some rSBA assay data were also included in the assessment report.[56] Conversely, European licensure of MenACWY-TT in 2012 relied primarily on rSBA assay results, with some hSBA assay data included in the assessment report.[57]

Complement sources used in MenACWY-TT studies

Studies evaluating immune responses to MenACWY-TT have used rSBA or hSBA assays or both (Tables S1–S5).[58–79] In a number of studies spanning multiple age groups, hSBA titers for serogroup A rapidly or steeply declined after vaccination,[60,65,67–69,76,78] whereas those studies that evaluated both hSBA and rSBA did not generally observe similar decreases in rSBA titers (Figures 2 and 3).[65,68,69,76,78] For unknown reasons, several of these studies also observed somewhat more rapid declines in hSBA for other serogroups compared with rSBA titers.[68,76,78] These findings, coupled with previously described data identifying rSBA titers between 8 and 64 as poorly predictive of hSBA titers ≥4 for serogroup C[31] (despite subsequent correlation of MenC rSBA titers ≥8 with effectiveness[34]), suggest that hSBA assay results may underestimate immune responses for MenACWY-TT.[25]

Additionally, several MenACWY-TT studies indicated lower initial immune responses in hSBA assays to serogroups W and Y compared with rSBA assays;[62,68,76,78] this was especially evident in toddlers given a single initial dose (Figures 2 and 3).[62,76,78] However, when evaluated at later time points, hSBA titers increased over time despite a lack of additional dosing.[68,76,78] In contrast, rSBA titers were generally high after initial vaccination and gradually declined when later time points were evaluated.[58,61–66,68–79] Such observations from earlier studies have been noted in a previous review by Findlow and Borrow,[21] and similar findings from the newer studies provide further evidence of these persistent trends.

These observations collectively suggest that rSBA assays are a more appropriate method than hSBA assays for measuring

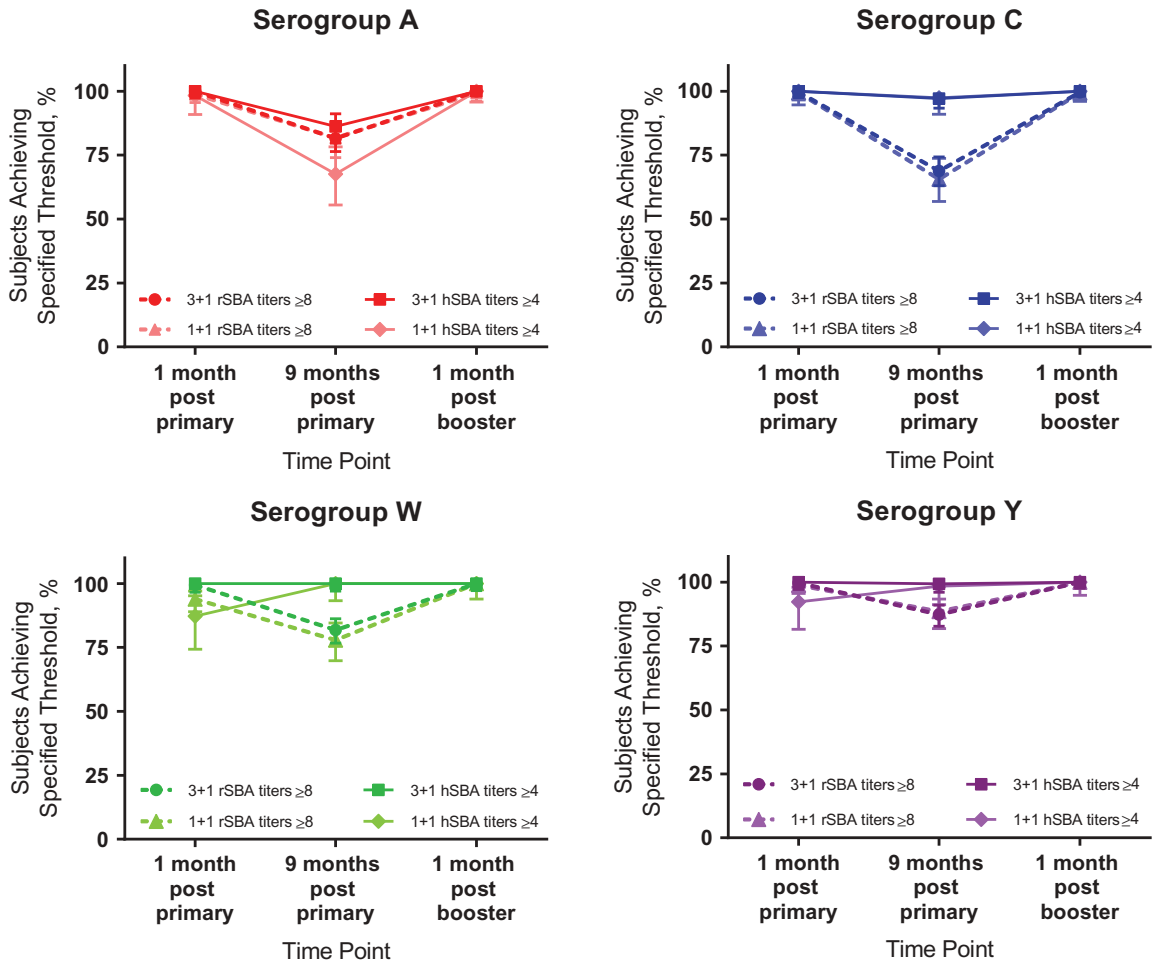

Figure 2. Percentages of infants/toddlers with rSBA titers ≥8 or hSBA titers ≥4 for serogroups A, C, W, and Y at various time points after vaccination with either 3 primary doses of MenACWY-TT (at 2, 4, and 6 months of age) followed by a booster dose at 15–18 months of age (3 + 1 schedule) or 1 primary dose of MenACWY-TT at 6 months of age followed by a booster dose at 15–18 months of age (1 + 1 schedule). Data are plotted as percentages along with 95% CIs. hSBA = serum bactericidal antibody assay using human complement; MenACWY-TT = meningococcal serogroups A, C, W, and Y conjugate vaccine using tetanus toxoid as a carrier protein; rSBA = serum bactericidal antibody assay using rabbit complement. Data are from Dbaibo G, Tinoco Favila JC, Traskine M, Jastorff A, Van der Wielen M. Immunogenicity and safety of MenACWY-TT, a meningococcal conjugate vaccine, co-administered with routine childhood vaccine in healthy infants: a phase III, randomized study. Vaccine. 2018;36(28):4102–4111.

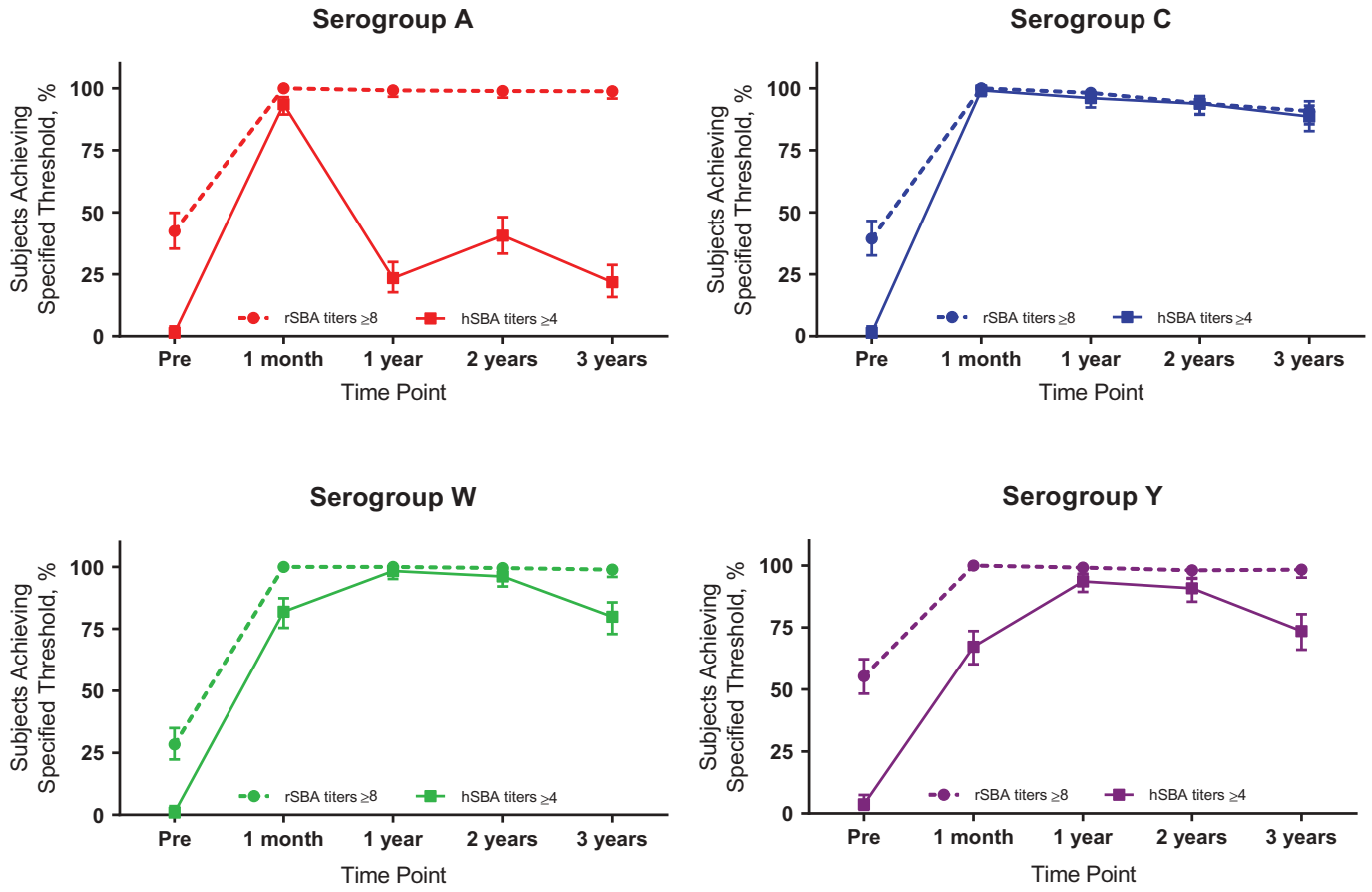

Figure 3. Percentages of toddlers with rSBA titers ≥8 or hSBA titers ≥4 for serogroups A, C, W, and Y at various time points before or after vaccination with 1 dose of MenACWY-TT at 12 to 23 months of age. Data are plotted as percentages along with 95% CIs. hSBA = serum bactericidal antibody assay using human complement; MenACWY-TT = meningococcal serogroups A, C, W, and Y conjugate vaccine using tetanus toxoid as a carrier protein; pre = prevaccination; rSBA = serum bactericidal antibody assay using rabbit complement. Data are from Vesikari T, Forsten A, Boutriau D, Bianco V, Van der Wielen M, Miller JM. Randomized trial to assess the immunogenicity, safety and antibody persistence up to three years after a single dose of a tetravalent meningococcal serogroups A, C, W-135 and Y tetanus toxoid conjugate vaccine in toddlers. Hum Vaccin Immunother. 2012;8(12):1892–1903.

immune responses and antibody persistence to MenACWY-TT, particularly for serogroup A. In general, hSBA assay results presented in MenACWY-TT studies do not show a clear trend across serogroups.[60,62,65,67–69,74,76,78]

Correlation of observed protection with serology

Postlicensure studies of vaccine effectiveness have served as critical sources for validation and refinement of the use of SBA assays. For MenC vaccines implemented in the United Kingdom beginning in 1999, a study performed before vaccine introduction indicated that the proportions of individuals with rSBA titers ≥8 were inversely correlated with disease incidence across age groups.[51] Subsequently, effectiveness data in multiple age groups (ranging from 90.1–100%) suggested that the percentage of subjects with rSBA titers of ≥128 dramatically underestimated effectiveness; titers of ≥4 or ≥8 were more reflective of observed effectiveness.[34] A later study found that overall vaccine effectiveness estimates were comparatively slightly lower for routine vaccination (83%) but similar for catch-up programs; effectiveness was generally higher within 1 year of vaccination compared with later time points.[80]

In 2011, WHO noted that although use of hSBA titers ≥4 or rSBA titers ≥8 have been used for vaccine licensure for serogroups A, W, and Y, these thresholds have not been formally correlated with protection for these serogroups.[81] In 2010, the CDC described a vaccine effectiveness study for MenACWY-D that found a decrease in effectiveness from 91% at 1 year postvaccination to 58% at 2 to 5 years postvaccination.[82] These findings corresponded with serologic results available at the time from 5 different studies, which relied on both hSBA and rSBA assays and used a variety of cutoffs (4 or 8 for hSBA and 128 for rSBA assays). These analyses led the CDC to recommend a booster MenACWY vaccine dose at age 16 years in order to maximize protection during the peak risk period of 16–21 years. A more recent study similarly found that effectiveness of MenACWY-D for serogroups C and Y declined over time since vaccination (from 79% within 1 year of vaccination to 61% between 3–8 years of vaccination);[83] these data parallel serologic results indicating decreasing proportions of subjects with hSBA titers ≥8 over time.[84] Additionally, for MenA-TT, serologic data collected 1 month postvaccination from 2 studies,

1 in toddlers 12 to 23 months of age and 1 in subjects 2 to 29 years of age, in various regions in Africa in 2006 indicated that 96% of toddlers and 78% of older subjects had ≥4-fold increases in rSBA titers.[85] Impact data indicated that MenA incidence decreased by 94% in vaccinated areas compared with unvaccinated areas in 2012,[86] and a study analyzing data from 2011 to 2015 found a >99% reduction in confirmed MenA cases in African countries following MenA-TT vaccination campaigns.[87] These findings support the use of rSBA data for MenA-TT vaccine licensure.

For MenACWY-TT in particular, recent effectiveness data against serogroup W following the 2014 introduction of the vaccine into the Chilean national immunization program for toddlers indicated that effectiveness was 100% and 92.3% in 2015 and 2016, respectively.[88] MenACWY-TT is also being used in a nationwide program in England that began in 2015 and mainly targets adolescents.[89,90] In the first year of the program, there was a 69% reduction in MenW cases among 2015 school leavers, the first cohort to be vaccinated at general medical practices, despite only 36.6% vaccine coverage.[89] The epidemiologic year 2017/2018 was the first year since 2011/2012 that MenW cases declined overall; decreases observed in age groups other than those targeted for vaccination suggest that herd protection has played a role in this reduction.[91]

Assays and strains used in different laboratories

Approaches to SBA assays, including strain selection, have varied among different laboratories. The standardized method for MenA and MenC rSBA assays published in 1997 specified use of specific strains for these assays.[30] Of note, a single representative strain for each serogroup can be used in the case of a vaccine targeting a serogroup-specific capsular polysaccharide;[92] the strain recommended for serogroup C evaluations is the same one originally used in the Goldschneider experiments.[23,30] For vaccines targeting subcapsular antigens which are not serogroup-specific (ie, currently available MenB vaccines), the choice of strains required for SBA assays to access broad protection is more complicated.[92]

In 2011, GlaxoSmithKline laboratories reported that use of a MenA strain (strain 3125) different from that specified in the standardized method[30] (strain F8238) might be more appropriate for evaluation of MenA immune responses.[93] This suggestion was based on strain 3125 belonging to an immunotype more commonly associated with invasive MenA strains, whereas the strain F8238 immunotype was more commonly associated with carrier strains. Studies across multiple age groups indicated higher levels of natural immunity to strain F8238 as compared with strain 3125 when evaluated in rSBA. By contrast, postvaccination immune responses were similar for the 2 strains, indicating that strain 3125 more accurately captured vaccine-induced protection and that rSBA results using strain F8238 might be artificially high. A recent MenACWY-TT study indicates continued use of strain 3125.[69] As might be expected, differences in strain selection and other aspects of protocol dictate the inherent complexity in comparing results across different laboratories.[21,33] Relatedly, rSBA assays for MenACWY-TT immunogenicity assessments began being performed by Public Health England rather than GlaxoSmithKline laboratories beginning around 2011,[94,95] with one study directly noting the resulting difficulties in correlating immunogenicity results from the 2 laboratories.[74]

Discussion

Serum bactericidal antibody assays are the accepted surrogate measure of efficacy for meningococcal vaccines.[43] Parameters used in SBA assays can vary, with the choice of rabbit or human complement often having a profound effect on study results.[27,31,32,41] Current guidelines specify use of rSBA assays for serogroups A and C vaccines and hSBA assays for serogroup B subcapsular vaccines.[24,42]

Postlicensure effectiveness studies for vaccines targeting serogroups C, A, and W support the use of rSBA for licensure of these vaccines. The correlation between effectiveness and rSBA titers ≥1:8 was formally established for MenC vaccines both before and after their introduction in the United Kingdom.[34,51] Subsequently, the widespread use of MenA-TT in Africa enabled postlicensure evaluations of impact which paralleled estimates of protection based on rSBA data.[85–87] More recently, for serogroup W, recent data demonstrating high impact and effectiveness following MenACWY-TT vaccination programs in England and Chile[88,89,91] support the primary use of rSBA data for licensure of this vaccine.[57] Based on these observations for serogroups C, A, and W, it is likely that rSBA data is similarly accurate for meningococcal conjugate vaccines targeting serogroup Y.

In contrast to rSBA data, hSBA data from recent MenACWY-TT studies corroborate previously published data questioning the validity of these results for evaluating immunogenicity of this vaccine.[21] Specific concerns relate to lower responses to primary vaccination as measured in hSBA compared with rSBA assays,[62,65,68,76,78] particularly for toddlers after 1 dose.[62,76,78] Even more strikingly, some studies feature a more rapid decline of hSBA compared with rSBA titers, which is particularly notable for serogroup A, as well as an increase over time in initially lower responses for serogroups W and Y despite lack of additional dosing.[60,65,67–69,76,78] There is no readily available explanation for these perplexing hSBA assay results, which are also in conflict with observed effectiveness data.[88,89,91] These findings collectively suggest that rSBA assays are the appropriate method for measuring immune responses in MenACWY-TT studies, whereas hSBA assays may be less relevant for these evaluations. Data from MenACWY-CRM$_{197}$[96] and MenA-TT[97] studies also demonstrate serogroup A titers that rapidly wane in hSBA compared with rSBA. Rapidly waning serogroup A hSBA titers have also been observed for MenACWY-D.[84] These data suggest that observations regarding MenACWY-TT may be extrapolated to meningococcal conjugate vaccines using diverse carrier proteins, in that rSBA assays may be preferable to hSBA assays for immunogenicity evaluations.[96]

Meningococcal vaccine immunogenicity evaluations remain limited by several considerations. As mentioned, standardization of the hSBA assay continues to be challenging,[28,29] and despite more formal standardization of the rSBA assay with regard to certain parameters,[30] laboratories likely differ with regard to others. Additionally, although rSBA titers ≥8

are generally considered to correlate with protection for MenACWY vaccines, these have only been formally correlated with effectiveness for serogroup C.[81]

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