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Anticapsular polysaccharide meningococcal antibodies in Israeli military recruits: immune status and the effect of simultaneous administration of immune globulin on the response to polysaccharide vaccine☆

Orit Shapira-Nahor[a], Itamar Grotto[b], Amos Adler[a], Yosef Mandel[b], Isaac Ashkenazi[b], Colin Block[a,*]

[a] *Department of Clinical Microbiology and Infectious Diseases, Hadassah-University Hospital, P.O. Box 12000, Jerusalem 91120, Israel*
[b] *Epidemiology Section, Medical Corps, Israel Defense Force, Mil. Post 02149, Jerusalem, Israel*

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Abstract

The effect of the administration of immune globulin (Ig), given during summer months to prevent hepatitis A, on the immune response to a simultaneously administered quadrivalent meningococcal polysaccharide vaccine (QMPV) was studied in Israeli military recruits. Data were obtained for the first time regarding the immune status of an Israeli population. Anticapsular polysaccharide antibodies were determined using a standardized ELISA assay before, 2 weeks and 3 months after QMPV immunization with or without Ig in two groups of recruits chosen to span the date determining seasonal administration or non-administration of Ig. Pre-vaccination antibody concentrations were $\geq$2 μg/ml in 98.4 and 38.9% of subjects against serogroups A and C meningococci, respectively. These levels are consistent with the extremely low incidence of disease due to serogroup A in Israel, and with the previously documented occurrence of serogroup C disease in servicemen and women. Co-administration of Ig was associated with some reduction in antibody concentrations 3 months after vaccination, especially against serogroup A meningococci ($P < 0.05$), but not to an extent likely to be of clinical significance.

Keywords: *N. meningitidis*; Immune globulin; Polysaccharide vaccine

1. Introduction

The introduction of routine immunization of Israel Defense Force (IDF) recruits with quadrivalent meningococcal polysaccharide vaccine (QMPV) afforded a unique opportunity to study the effect of simultaneous administration of immune globulin (Ig) on the antibody response to the vaccine. In addition, measurement of pre-vaccination antibody levels would provide hitherto unavailable information on the immune status of young Israelis entering compulsory military service against meningococcal disease. Of particular interest would be immunity against disease due to serogroup A *Neisseria meningitidis*, which is exceptionally rare in Israel [1].

Until the recent introduction of active immunization against hepatitis A, recruits assigned to field units during the summer were given Ig intramuscularly as a preventive measure [2,3], at the same time as they received the meningococcal vaccine. The simultaneous administration of vaccines and Ig has been of interest in a number of settings, including prevention of hepatitis A [4–6] , poliomyelitis [7], tetanus [8,9] and measles and rubella [10]. Different interpretations exist as to the effect of passively administered antibodies on the response to vaccines. With the exception of co-administration with live vaccines, this practice has not been thought to interfere sufficiently with the development of protective antibody concentrations as to warrant more than minor adjustments to immunization schedules.

Most cases of meningococcal disease in Israel have been caused by serogroup B *N. meningitidis* in recent years [1], whereas the majority of cases among military personnel have been due to the potentially vaccine-preventable serogroups C and Y [11]. Using a standardized ELISA assay for antibodies to serogroups A and C, this study was intended to provide data on pre-recruitment antibody levels and on the effect of simultaneous passive immunization on antibody responses to purified A and C meningococcal polysaccharides (MPSs).

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* Corresponding author. Tel.: +972-2-6776543; fax: +972-2-6419545.
E-mail address: block@md.huji.ac.il (C. Block).

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2. Materials and methods

2.1. Study population

This study was based on the routine immunization procedures carried out in the IDF. Whereas QMPV is administered year-round, Ig was only given during summer months (July–December). Groups of inductees to be included in the study were chosen to span the date of change regarding administration or non-administration of Ig. The study was approved by the Human Studies Review Committee of the IDF Medical Corps.

One hundred and eighty-five healthy recruits, including 93 women and 92 men aged 18 years agreed to participate, representing 70% of eligible subjects. These were divided into two groups on the basis of administration of Ig: 88 received QMPV with Ig (group 1) and 97 QMPV alone (group 2). The vaccine was administered 2–3 min before the Ig, which was given as a 2 ml intramuscular injection.

Serum samples were obtained immediately before vaccination and 2 weeks and 3 months later, for measurement of antibody responses to the meningococcal A and C components of the vaccine. We chose a 2-week interval for several reasons. Adult antibody responses to MPS vaccine have been shown to peak at 2 weeks [12]; other studies have also used short intervals of 10–14 days [13,14]; and finally, a greater interval would have resulted in a smaller number of sera being obtained. Difficulties in reaching soldiers after their dispersal to units scattered all over the country and after subsequent re-assignments indeed resulted in a reduction of individuals available for follow-up blood samples at the intervals required by the study protocol.

2.1.1. Vaccination

All recruits were immunized with quadrivalent meningococcal A, C, Y, W135 polysaccharide vaccine (Mencevax, SmithKline Beecham). It was not possible to include a control group who received Ig alone. None of the subjects had been previously vaccinated with a meningococcal vaccine, nor had a known history of invasive meningococcal disease.

2.2. Antibody assays

Sera were stored at −70 °C until antibody assays were performed. All assays were performed by one individual (AA) under blinded conditions on coded serum samples. Serum total antibody concentrations (IgA + IgM + IgG) to the serogroups A and C meningococcal polysaccharide (MPS) antigens were measured by a standardized ELISA technique [15,16] . The A and C antigens, standard reference serum and the methylated human serum albumin were kindly provided by Dr. G. Carlone and Dr. L.B. Pais, CDC, Atlanta. In both the anti-MPS-A and anti-MPS-C assays, bound antibodies were detected by alkaline phosphatase conjugated goat anti-human affinity isolated antibodies (Sigma, Israel).

Antibody concentrations were calculated from standard curves derived in each experiment. Each serum dilution was assayed in duplicate, and the total meningococcal A and C antibody concentrations (in μg/ml) were determined by averaging all values from each dilution that fell within the working range of the standard curve (absorbance values between approximately 0.05 and 2). The curves were based on the CDC1992 standard reference serum which has anti-MPS-A and anti-MPS-C antibody concentrations of 135.8 and 32.0 μg/ml, respectively [17]. In order to ensure reproducibility between the experiments, quality control solutions provided by the CDC were used.

2.3. Definition of immunity

There is no clear definition of anticapsular antibody concentrations that confer protection. Estimates have varied from 0.5 to 2 μg/ml [18–21]. A total anticapsular antibody concentration of 2 μg/ml was mooted as a possible reference datum for protection in clinical trials of group A polysaccharide vaccine in which antibody levels were measured by radioimmunoassay [22]. This was based partly on observations in the Finnish military in which 60% of unvaccinated adults had antibody concentrations ≥2μg/ml, and partly on apparent vaccine efficacy in children of all age groups. Even children aged 3–5 months reached a mean concentration of 1.5 μg/ml. A serum antibody concentration, determined by ELISA, of ≥2μg/ml has also been used to indicate seroconversion in a study of group C polysaccharide vaccine [23]. This value was therefore taken as the arbitrary estimate for immunity in this study.

2.4. Data analysis

Geometric mean antibody concentrations (GMCs) and 95% confidence intervals were determined from $\log_n$-transformed concentrations. The association of gender with antibody levels was evaluated using the *t*-test. One-way analysis of variance (ANOVA) and the general linear model (GLM) with repeated measures were used to assess time and group effects taking into account subjects for whom pairs or triplets of sera were available at 2 weeks and 3 months, respectively. Differences between extent of the antibody response in the two groups 2 weeks after immunization were evaluated using the Chi-square test (with continuity correction where cell frequencies of <5 were encountered). The possibility that higher pre-vaccination antibody concentrations might influence the extent of the antibody response was explored by correlating (Pearson) baseline concentrations with fold-increases after 2 weeks. Analyses were performed using the SPSS statistical package (SPSS Inc., Chicago, IL).

Table 1
Pre-immunization total anticapsular polysaccharide antibody concentrations in Israeli military recruits

	n	GMC[a] (95% confidence interval)	Immune[b] (%)
Anti-MPS[a]-A			
Females	93	10.4 (9.35–11.54)[c]	100
Males	92	5.8 (5.16–6.47)[c]	96.7
Total	185	7.8 (7.11–8.47)	98.4
Anti-MPS-C			
Females	93	1.6 (0.87–2.33)[d]	31.2
Males	92	2.0 (1.20–2.83)[d]	46.7
Total	185	1.8 (1.59–2.03)	38.9

[a] GMC: geometric mean concentration; MPS: meningococcal polysaccharide.
[b] Percent individuals with antibody concentrations: ≥2 μg/ml.
[c] $P < 0.001$.
[d] $P = 0.167$.

3. Results

3.1. Pre-immunization antibody concentrations

Antibody levels against A and C polysaccharides were measured prior to immunization in all 185 soldiers. GMCs (μg/ml) of anti-MPS-A and anti-MPS-C antibodies, 95% confidence intervals and the percentage of subjects with antibody level above 2 μg/ml are shown in Table 1. Interestingly, it was found that women had significantly higher anti-MPS-A antibodies (10.39 μg/ml) compared to men (5.78 μg/ml, $t = 6.28$, $P < 0.001$). Anti-C levels were lower and statistically similar in both sexes (2.01 and 1.60 μg/ml for men and women, respectively).

3.2. Post-immunization antibody concentrations and the effect of immune globulin

Paired sera were available at 2 weeks from 131 recruits, and all three sera at 3 months from 41 recruits. GMCs (μg/ml) of anti-MPS-A and anti-MPS-C antibodies with 95% confidence intervals by groups of Ig, vaccination and time are presented in Table 2. There was no significant difference in antibody levels before immunization between groups 1 and 2, which was important in evaluating their comparability since they were assessed sequentially in time.

Two weeks after vaccination, the mean concentrations of anti-MPS antibodies were highly increased in both group 1 ($P < 0.001$), which received QMPV + Ig, and group 2 ($P < 0.001$) which received only QMPV (8.5- and 10.9-fold, respectively for anti-MPS-A, and 21.5- and 23.5-fold for anti-MPS-C). The differences between the groups for both anti-MPS-A and anti-MPS-C at 2 weeks were not statistically significant.

Three months post-immunization, the elevation in antibody concentrations was maintained in group 2. Group 1 showed some depression of the concentrations compared with the values at 2 weeks. Despite the reduction in the number of subjects examined at 3 months, the decrease was statistically significant for anti-MPS-A antibodies, both for all subjects ($P = 0.046$, Table 2) and for subjects from whom a full set of three sera had been collected. The 3-month GMCs for the latter were 81.5 (95% CI 62.8–105.9) μg/ml for group 2 versus 33.6 (21.1–53.4) μg/ml for group 1 ($P = 0.003$). The differences for anti-MPS-C antibodies were not significant ($P = 0.122$ for all subjects, Table 2). For those with all three sera, GMCs at 3 months were 52.2 (36.8–73.9) μg/ml for group 2 versus 25.3 (17.2–37.2) μg/ml for group 1 ($P = 0.132$).

All vaccinated individuals tested had antibody levels above 2 μg/ml against both MPS-A and MPS-C at 2 weeks and 3 months following vaccination. There was a significant negative correlation between the extent of the rise in antibody concentration and the pre-vaccination concentration. The Pearson correlation between baseline anti-MPS-A concentration and the fold-difference at 2 weeks was −0.313 (2-tailed $P < 0.001$). The corresponding value for anti-MPS-C was −0.256 (2-tailed $P = 0.003$). This association was enhanced when the vaccine-only group 2 was considered (Pearson correlation −0.422 for anti-MPS-A, and −0.472 for anti-MPS-C, $P = 0.001$ and $P < 0.001$,

Table 2
Geometric mean antibody concentrations (μg/ml) with 95% confidence interval of all subjects by timing of blood samples

Group[a]	Timing of sample		
	Pre-immunization	2 weeks	3 months
Anti-MPS[b]-A			
1 (*n*)	8.4 (7.48–9.53) (*88*)	70.3 (57.31–86.20) (*72*)	39.2 (23.22–66.13)[c] (*14*)
2 (*n*)	7.2 (6.34–8.15) (*97*)	78.5 (66.34–92.97) (*59*)	86.9 (66.10–114.12)[c] (*27*)
Anti-MPS-C			
1 (*n*)	1.5 (1.28–1.78) (*88*)	32.5 (26.05–40.54) (*72*)	27.2 (19.31–38.21)[d] (*14*)
2 (*n*)	2.1 (1.76–2.50) (*97*)	49.2 (41.67–58.17) (*59*)	49.1 (35.54–67.78)[d] (*27*)

[a] Group 1 received vaccine + Ig; group 2 received vaccine alone.
[b] MPS: meningococcal polysaccharide.
[c] $P = 0.046$.
[d] $P = 0.122$.

respectively). Conversely, it was weakened for group 1 (Pearson correlation −0.228 for anti-MPS-A, $P = 0.054$; and −0.189 for anti-MPS-C, $P = 0.113$).

4. Discussion

This study has for the first time provided data regarding the immune status of an Israeli population, in this case military recruits, against meningococcal disease. The relatively high anti-MPS-A concentrations in >98% of subjects is consistent with the rarity of disease due to this serogroup, while the apparent lack of protective anti-MPS-C in >60% of the recruits concords with the previously observed occurrence of serogroup C disease in this population [11]. We showed further that the contemporaneous administration of Ig with QMPV has a relatively minor and probably clinically insignificant effect on the immune response to *N. meningitidis*.

Antibody concentrations against serogroups A and C only were evaluated in this study, since the reference serum CDC1992, has had standard concentrations assigned for these serogroups [17]. Furthermore, the use of standardized methods [15,16] allowed comparisons with previously published data. In the event, few studies involving polysaccharide vaccines and using these methods and the same reference serum have appeared in the literature, so that some comparative data have also been taken from studies in which a previously-used well characterized reference serum (PB-2) was used, and some from studies which used radioimmunoassay methods. The availability of other investigations for comparison is further limited by the fact that few of them have involved adults.

Another problematic issue is our use of the ≥2 μg/ml cut-off value for protection from invasive meningococcal disease. This concentration was proposed on the basis of Finnish clinical trials [22], and although it is not considered well established, it has frequently provided a reference point for discussion of immune status.

4.1. Pre-vaccination antibody concentrations

Relatively high pre-vaccination concentrations of anti-MPS-A antibodies were found in our recruit population in comparison with Air Force recruits in the USA [24] and adult vaccinees in Finland [22,25]. In the US study, which employed the same ELISA method used by us, 41 inductees with a mean age of 20.6 years had a geometric mean anti-MPS-A concentration of 1.17 μg/ml prior to immunization compared with 7.8 μg/ml in Israeli recruits. Ten of these (24.4%) had values ≥2 μg/ml, compared with 98.4% of 185 Israelis tested. This finding is of interest particularly considering the rarity of serogroup A disease in Israel. In the Finnish studies, antibody concentrations were determined by radioimmunoassay. The pre-vaccination geometric mean concentration in 34 adults was 2.9 μg/ml in one study [25]. In the earlier study [22], from which the ≥2 μg/ml protection cut-off emerged, the pre-immunization concentration in an unspecified number of adults in the armed forces was given as 2.05 μg/ml.

Anti-MPS-C antibody concentrations were much lower before immunization: 1.8 μg/ml in Israeli and 0.66 μg/ml in the USA inductees. Here again, fewer USA personnel (14.6%) were considered protected compared with their Israeli counterparts (38.9%). In a study of the response in children to group C polysaccharide antigen, pre-immunization data were available for 40 adult controls between the ages of 20 and 30 years: 1.01 μg/ml geometric mean anti-MPS-C antibodies, with 9 (22.5%) having ≥2 μg/ml [23].

There is no explanation for the gender difference found in our study, and few data are available for comparison. Whereas we found that females had significantly higher concentrations of anti-MPS-A than males before immunization, the study in the USA Air Force recruits showed that females had significantly higher pre-vaccination levels of both anti-MPS-A and anti-MPS-C [24]. Further studies will be required to determine whether these differences are rooted in biological or statistical factors such as selection bias or other confounding factors.

4.2. Response to vaccination and the influence of immune globulin

We observed the expected good response to immunization at 2 weeks, whether Ig had been given with the vaccine or not. The magnitude of the rise in antibody concentrations was comparable with some other studies, and higher than others, although such comparisons may not always be appropriate. In one Finnish study [25], which was carried out using a different polysaccharide vaccine and very different methodology, the geometric mean concentration of total anti-MPS-A at 2 weeks increased 3-fold, whereas in our study it increased 8.5- to 10.9-fold, in the earlier Finnish study 9.7-fold [22], and in the US Air Force study 11.4-fold (at 1 month) [24].

Considering anti-MPS-C, the increases we observed in both groups were higher than for anti-MPS-A (22.5-fold for group 1 and 23.5-fold for group 2). This is more or less consistent with the more marked increase in anti-MPS-C found in the US Air Force inductees (39-fold at 1 month) and in the adult controls in the serogroup C pediatric study (32.9-fold at 6 weeks) [23].

Differences between groups 1 and 2 were evident at 3 months after immunization. The unfortunate inability to locate and draw blood from all the vaccinees at 2 weeks and especially at 3 months weakened the power of this study to test the statistical significance of the reduction in antibody concentrations of the group which received Ig with the vaccine. Despite this, we found that the reduction in the anti-MPS-A response was indeed significant, both when considering all cases, and recruits for whom all three sera were available. This phenomenon likely has little, if any, clinical significance, at least in the short term. This interpretation is

based on the following observations. The antibody concentrations in the group which received the Ig remained well elevated at 3 months; the lowest concentrations observed for both anti-MPS-A and anti-MPS-C being >5 times higher than the putative protective concentration of 2 μg/ml. The 75% of this group had >7 times, and 50% had >19 times the protective concentration. Furthermore, the vaccine proved to be effective in eliminating meningococcal disease due to serogroups C and Y in immunized Israeli soldiers during their compulsory service. This was initially documented in a short-term study [26], and has held until early 2002 (data of the Epidemiology Section of the IDF Medical Corps).

The mechanism by which Ig might interfere with the antibody response to the polysaccharide vaccine is unknown. A small hint may perhaps be found in our observation that the negative association between pre-immunization antibody concentrations and the extent of the response to immunization, was much weaker in recruits who received Ig together with the vaccine. It might be reasoned that some kind of self-regulating system may influence the strength of the response in the absence of Ig, but that exogenous Ig might have obscured the modulating effect of pre-existing antibodies in such a system. In addition, the exogenous Ig might indeed simply reduce the amount of antigen available, resulting in a lesser stimulation of the immune response.

The possibility that the exogenous Ig administered to the recruits had an effect on the measurement of antibody concentrations could not be addressed in this study, primarily since design constraints precluded an appropriate control group. We also did not assay the antibody concentrations in the Ig which was used. In an earlier investigation of the effect of simultaneous administration of Ig on the response to hepatitis A vaccine [4], it was shown that anti-hepatitis A antibodies derived from the Ig injection were measurable at 2 weeks, but virtually undetectable at 12 weeks.

The issue of simultaneous administration of vaccines and Ig has been of concern in several areas. Studies of contemporaneous administration of hepatitis A vaccine and Ig have been interpreted in different ways. A group in The Netherlands [6], showed a twofold reduction in geometric mean titers in recipients of Ig, and raised the question of the need for an earlier booster dose. A study in the IDF [4] demonstrated a significant reduction in antibody concentrations, and despite the observation that even the reduced responses were adequate for protection, the investigators proposed that an additional booster dose should be considered in vaccines receiving Ig at the same time. In another study [5], reduced antibody concentrations were found at all time points after immunization, but these were simply judged not to be of clinical significance. Studies of the effect of Ig or even human tetanus Ig on the humoral response to tetanus toxoid led to the conclusion that passive immunization did not interfere with vaccine immunogenicity [8,9] .

An opportunity to assess the effect of Ig on live, oral poliomyelitis vaccine (OPV) was exploited during a small outbreak of polio in Israel in the late 1980s, when military recruits were given OPV and Ig or OPV alone. Ig was found not to affect the antibody response to OPV [7]. On the other hand, the antibody response to measles and rubella vaccines was shown to be significantly delayed by high doses of Ig, prompting the investigators to suggest that the intervals between administration of Ig and measles and rubella vaccines be adjusted on the basis of the Ig dose [10].

In conclusion, we have shown that simultaneous administration of Ig with the QMPV has a dampening effect on the geometric mean concentrations of anticapsular antibodies of group A and probably of group C meningococci at 3 months after immunization; but that the concentrations achieved were nevertheless well above what is considered a protective level. A further indication of the lack of clinical impact of the reduction in immunity is that the introduction of vaccination has up till now eliminated the occurrence of groups C and Y meningococcal disease in the IDF. In addition, the relatively high pre-vaccination anti-MPS-A concentrations, and the finding that >98% of the recruits had concentrations in excess of 2 μg/ml, offer a tempting explanation for the rarity of serogroup A disease in Israel. The source of these antibodies is unknown. Serogroup A *N. meningitidis* has been encountered extremely infrequently in carrier studies in Israeli civilians and military personnel [27–30], so it is likely that other cross-reacting antigens have been the stimulus.

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