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Relationship between T-cell-dependent and T-cell-independent vaccines after neurotrauma; is the B-cell response preserved?

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ABSTRACT

Background: After trauma and central nervous system (CNS) injury, trauma-induced immune deficiency syndrome (TIDS) and CNS injury-induced immune deficiency syndrome (CIDS) may negatively affect responses to T-cell-dependent vaccines, such as pneumococcal conjugate vaccine (PCV) recommended after basilar fracture. This study (NCT02806284) aimed to investigate whether there after neurotrauma is a correlation between T-cell-dependent and independent vaccine responses and, thus, if B-cell activity is similarly depressed and whether the T-cell-dependent response is possible to predict.

Methods: Adult patients with basilar fracture (n = 33) and those undergoing pituitary gland surgery (n = 23) were within 10 days vaccinated with a T-cell-dependent vaccine against *Haemophilus influenzae* type b (Hib) and a T-cell-independent pneumococcal polysaccharide vaccine (PPSV). Samples reflecting the systemic inflammatory response and pre- and post-vaccination antibody levels after 3–6 weeks against Hib and PPSV were collected and determined by enzyme immunoassays.

Results: High and significant correlations were detected in the responses to different pneumococcal serotypes, but none between the Hib and PPSV responses. No differences in trauma scores, C-reactive protein, IL-6, IL-10, pentraxin 3, fractalkine or calprotectin plasma concentrations or in ex vivo TNF- α , IL-6 or IL-10 responses to endotoxin were found between Hib vaccination responders and non-responders.

Conclusions: There was no correlation between the pneumococcal responses and that to Hib, indicating that B-cell function is not similarly depressed as T-cell function. Grading of the trauma or parameters reflecting the innate immune response could not predict the T-cell-dependent vaccine response. There is a need of further studies evaluating the vaccine response after neurotrauma.

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Introduction

Neurotrauma is one of the leading causes of death and major disability.¹ In addition to the risk of neurological harm, skull trauma puts the patient at risk for infectious complications such as meningitis, most notably after basilar skull fracture.² Because *Streptococcus pneumoniae* is the most common pathogen in post-traumatic meningitis, pneumococcal vaccination is recommended in national guidelines.³ Because the risk of meningitis is at its peak during the first posttraumatic weeks but also persists for many years, both short- and long-term protection against pneumococci seem to be of importance.^{4–7} Protection against as many serotypes as possible might be an advantage given that no specific serotype seems to predominate in causing meningitis.^{8–10} In the USA, the Advisory Committee on Immunization Practices (ACIP) recommends that adults aged ≥ 19 years with cerebrospinal fluid (CSF) leak should receive one dose of pneumococcal conjugate vaccine (PCV15 or PCV20) and in the case of PCV15 a subsequent pneumococcal polysaccharide vaccine (PPSV23) 2 months later.¹¹ The Swedish recommendations have recently been updated to correspond to the ACIP guidelines.¹² None of these guidelines mention optimal timing of the first vaccination and the question when to vaccinate in relation to the trauma remains open.

Not only microbes but also trauma activate innate immunity causing both pro- and anti-inflammatory responses¹³ and similar activation has been shown after elective surgery.¹⁴ Over time the anti-inflammatory response might become more dominating resulting in a pronounced decrease in T-cell function,^{15–17} which can be referred to as posttraumatic immunosuppression or trauma-induced immune deficiency syndrome (TIDS). In patients with neurotrauma, innate and adaptive immunity may be globally downregulated to prevent post-injury autoimmune reactions.¹⁸ Patients with injuries of the central nervous system (CNS) may consequently show signs of a specific CNS injury-induced immune deficiency syndrome (CIDS), that may add to TIDS.

In CIDS there is a reduced number of T-helper cells and decreased T-cell activity in the form of response to phytohemagglutinin, delayed hypersensitivity to common antigens and cytokine production ex vivo.^{19,20} Recent studies from our group indicate that neurotrauma patients may have an impaired response after vaccination with a T-cell-dependent vaccine against *Haemophilus influenzae* type b (Hib) during the first 10 posttraumatic days,²¹ in contrast to the response after a T-cell-independent polysaccharide vaccine against pneumococci.²² These results

suggest that B-cell function might be preserved in the early phase after neurotrauma. However, they do not exclude an additional B-cell dysfunction in patients demonstrating severe signs of CIDS, a knowledge that might be of importance for the future optimal management of these patients. The results in these two studies were obtained from the same individuals making it possible to analyze B-cell function after antigen stimulation *in vivo* and its relation to varying T-cell depression at the individual level and answer the question whether severely depressed T-cell responses also were associated with low or suboptimal B-cell responses.

If patients with depressed T-cell function are to be vaccinated with an alternative schedule, it will be of interest to easily identify these patients. Since it has been proposed and there are experimental data indicating that the T-cell insufficiency is caused by factors present in plasma,¹⁹ an additional aim was to analyze plasma biomarkers reflecting different segments of the trauma-induced inflammatory response as well as the severity of the trauma in relation to the T-cell response.

Material and methods

Patients

Patients aged ≥ 18 years admitted to the Department of Neurosurgery, Uppsala University Hospital, were prospectively included and assigned to one of two groups: either the neurotrauma (NT) or the neurosurgery (NS) group. These patient cohorts have been described elsewhere.^{21,22} Briefly, the NT group consisted of patients with basilar skull fracture with or without visible CSF leak and the NS group of patients scheduled for elective, transsphenoidal pituitary gland surgery. The NS patients were expected to have a more limited neurotraumatic inflammatory insult and, therefore, included in order to expand the range in the neuroinflammatory response.

Consecutive patients were screened and included when vaccination and follow-up were possible to perform and informed consent had been obtained. Patients or next of kin were asked about previous vaccinations against pneumococci. The study was registered at ClinicalTrials.gov, NCT02806284.

Vaccination

As the T-cell-independent activation all patients received a single injection of 0.5 ml Pneumovax® (Sanofi Pasteur MSD AB, Lyon, France) (PPSV23) containing 25 μg of purified capsular polysaccharide from each of the 23 serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9 V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F) in the upper left arm. At the same time, all patients also received a single injection of 0.5 ml the T-cell-dependent Act-HIB® (Sanofi Pasteur MSD, Lyon, France), a conjugate vaccine against Hib, in the upper right arm. A 0.5 ml dose of this vaccine contains 10 μg of Hib polysaccharide conjugated to 24 μg of tetanus protein. Due to the risk of bleeding in some of the patients, all vaccinations were administered as subcutaneous injections. The vaccinations were performed on the same occasion within 10 days after trauma or surgery.

Whole blood and sera collection

Pre-vaccination sera and whole blood samples for lipopolysaccharide (LPS) stimulation were collected just before vaccination. Post-vaccination sera were obtained 3 and 6 weeks after vaccination.

Analysis

In pre- and post-vaccination sera, serotype-specific anti-polysaccharide binding IgG antibody levels to PCV7 serotypes 4, 6B, 9 V, 14, 18C, 19F and 23F as well as IgG antibody concentrations to Hib polysaccharide were determined by enzyme immunoassays which are established and accredited methodology.^{23,24} An anti-Hib polysaccharide concentration of 0.15–1.0 $\mu\text{g}/\text{ml}$ has been associated with long-term protection against invasive Hib infection after vaccination of children.²⁵ Following the post-vaccination concentration peak there is a gradual fall and based on previous experience in children,²⁴ a post-vaccination titer of 10 times the above proposed protective concentration, 10 $\mu\text{g}/\text{ml}$, was chosen as the target level for responders to the Hib vaccination in the present study.²¹

Concentrations of CRP and calprotectin were measured with particle enhanced turbidimetric assay (PETIA) technology using a Mindray BS380 chemistry analyzer (Mindray) and CRP reagents (6K2602, Abbott Laboratories) and calprotectin reagents (GCAL, Gentian AS). Concentrations of C \times 3CL1/ Fractalkine (DY365), IL-6 (DY206), IL-10 (DY217B) and pentraxin 3 (PTX3) (DY1826) were analyzed with commercial sandwich ELISA (R&D Systems). The ELISAs had a total coefficient of variation of approximately 6–7%.

The reasons for using these analyses were that TNF- α and IL-6 are major pro-inflammatory cytokines that act locally to increase vascular permeability as well as recruit and activate cells at sites of trauma or infection by upregulating chemokines such as fractalkine.^{26,27} TNF- α and IL-6 also stimulate the liver production of various proteins (e.g. CRP and PTX3) of the acute phase response.²⁸ Calprotectin was analyzed as a marker of metal binding antimicrobial proteins and IL-10 for its anti-inflammatory properties, which include inhibition of the production and effects of inflammatory cytokines.^{27,29}

In a subset of 30 patients (20 NT, 10 NS) heparinized whole blood from patients was incubated for 4 hours at 37°C with a standardized stimulation solution containing cell culture medium with LPS in a concentration of 500 pg/ml (Milenia *ex vivo* stimulation kit). Concentrations of IL-6, IL-10 and TNF- α in the supernatant were determined by commercial sandwich ELISA.

Trauma scoring

The Glasgow Coma Scale (GCS), Injury Severity Score (ISS) and New Injury Severity Score (NISS) were used to define injury severity in the NT group. A GCS ≤ 8 was defined as severe head injury, ISS ≥ 16 as severe injury and NISS ≥ 16 as major trauma.³⁰

Statistics

The vaccination response was calculated as the difference between the logarithmically transformed concentrations in the post-immunization and the pre-immunization sera which signifies fold antibody increases. Post-immunization concentrations were obtained from the 6-week samples when available; if not, the 3-week post-vaccination concentrations were used. The Spearman rank correlation test was performed to analyze the relationship between the mean pneumococcal polysaccharide responses and the different serotype-specific responses. The same test was employed when analyzing the association between the pneumococcal response and that caused by the Hib vaccine. To avoid multiple statistical testing in the primary analysis a mean pneumococcal response from all seven serotypes was calculated for each individual and used in the analysis provided the correlation between this mean response and each of the serotype-specific responses exceeded 0.5. The number of patients was based on the power calculation in the previous study of the Hib response.²¹ In the prediction of the T-cell-dependent response, the response to the Hib vaccine was analyzed and in the NT group a comparison of ISS, NISS and GCS levels as well as pre-vaccination concentrations of the inflammatory parameters in responders and non-responders was made by the Mann Whitney-U test. Because the response/non-response is a dichotomous variable, Spearman rank correlations were also calculated between Hib antibody response and the potential predictive parameters. Statistical calculations were performed using Prism (v6.0, GraphPad Software, San Diego, CA, USA). A significance level of 0.05 was selected.

Ethical considerations

The study protocol was approved by the Regional Ethical Review Board at Uppsala University, Sweden (reference number 00–254).

Results

Fifty-six patients (NT = 33, NS = 23) were enrolled in the study. In the NT group 11 patients demonstrated a GCS of ≤ 8 , 24 patients an ISS of ≥ 16 and 31 a NISS of ≥ 16 . Patient characteristics are shown in Table 1. None of the patients reported previous vaccination against pneumococci or Hib. Six-week post-vaccination sera were not available in 11 patients (10 NT and 1 NS patients) and in these patients the 3-week post-vaccination sera were used. Three- and 6-week post-vaccination sera were obtained on day 21 (median, range 13 to 27 days) and day 42 (median, range 34 to 52 days), respectively.

Analysis of the uniformity of the responses to different pneumococcal serotypes

The correlation coefficients between the calculated mean pneumococcal response and the seven serotype responses demonstrated a mean correlation coefficient of 0.64 ± 0.05 , Table 2. Serotypes 4 and 23 F demonstrated somewhat weaker associations than the other serotypes but exceeded 0.5, indicating a good relationship between the mean pneumococcal response parameter and all of the serotypes included. Accordingly, this

Table 1. Patient characteristics, type of trauma/surgery and trauma scoring.

	Neurotrauma	Neurosurgery
Number of patients	33	23
Age median (yrs) (range)	40 (22–85)	59 (29–82)
Gender M/F	30/3	14/9
Median time from trauma/surgery to vaccination, (days) (range)	6 (1–10)	3 (1–6)
<i>Cause of neurotrauma</i>		
Assault	0	-
Traffic accident	19	-
Explosion	2	-
Falling accident	10	-
Other or uncertain	2	-
<i>Type of neurotrauma</i>		
Skull fracture	33	0
Intracranial hemorrhage	22	0
Transsphenoidal pituitary gland surgery	0	23
<i>Trauma scoring</i>		
Glasgow Coma Scale < 8	11	-
Injury Severity Score > 16	24	-
New Injury Severity Score > 16	31	-

Table 2. Correlation coefficients between the responses to the different pneumococcal serotypes and the calculated mean pneumococcal response in the NT and NS groups (n = 56).

Pneumococcal serotype	Mean pneumococcal response ^a	4	6B	9V	14	18C	19F	23F
4	0.56***	-						
6B	0.64***	0.39**	-					
9V	0.68***	0.29*	0.43**	-				
14	0.71***	0.31*	0.31*	0.34*	-			
18C	0.66***	0.17	0.30*	0.44**	0.45*	-		
19F	0.66***	0.23	0.34*	0.41**	0.41*	0.41**	-	
23F	0.59***	0.25	0.30*	0.45**	0.30*	0.19	0.32*	-
Mean \pm SD	0.64 \pm 0.05	0.27 \pm 0.08	0.35 \pm 0.05	0.39 \pm 0.06	0.35 \pm 0.06	0.33 \pm 0.13	0.35 \pm 0.07	0.30 \pm 0.09

^aRepresents the mean of all serotype-specific responses in each patient.

* $p < 0.05$; ** $p < .01$; *** $p < .001$.

mean pneumococcal concentration could be used as the principal parameter for the T-cell independent polysaccharide response in the primary analysis of the relationship to the T cell dependent Hib response. Table 2 also shows the correlation analyses between the different serotypes and in 17/21 analyses there were significant parallel responses. In the analyses of serotypes 4 and 23F some of the responses did not reach statistical significance.

Relationship between the pneumococcal response and the response to Hib

In the NT+NS groups the mean pneumococcal response was 0.87 ± 0.42 and the Hib response 1.61 ± 0.87 , consistent with 7- and 40-fold increases of the antibody levels. Corresponding responses in the NT group alone were 0.92 ± 0.41 and 1.65 ± 0.95 . In the primary analysis there was no correlation between the T-cell-independent mean pneumococcal response, expressed as fold antibody increase, and that to the T-cell-dependent Hib vaccine with a correlation coefficient of only 0.13. This is shown in Table 3, which also shows the correlations between different pneumococcal serotype responses and that to Hib in the NT+NS group and in the NT and NS groups alone. The absence of covariation is most marked in the NT group with a correlation coefficient between the mean pneumococcal response and that to Hib of 0.01, whereas this coefficient was 0.32 in the NS group, a difference that proved to be statistically significant in a post-hoc analysis ($p < .05$). When analyzing the correlation between Hib and pneumococcal post-vaccination antibody concentrations, a similar result was obtained (Appendix A).

Details in the pneumococcal response in responders and non-responders to the Hib vaccine are shown in Appendix B. Of the 15 patients that did not reach the criteria for response to the Hib vaccination, 9 (60%) demonstrated a more than four-fold increase in the mean response to the pneumococcal antigens.

Prediction of non-response to the Hib vaccine

In the NT group there were no differences in median scores (with interquartile range) of 11 (8–15), 17 (13–26) and 27 (22–43) in responders and 12.5 (6–14.25), 18 (16.75–21) and 27 (23.5–32) in non-responders, for GCS, ISS and NISS, respectively. Pre-vaccination concentrations of CRP, IL-6, IL-10, PTX3, fractalkine and calprotectin in NS+NT groups are

shown in Figure 1. There were no differences between responders and non-responders. Nor were there any differences between responders and non-responders in the concentrations of TNF- α , IL-6, IL-10 and after ex vivo LPS stimulation. Spearman rank correlation using continuous fold increase data revealed no significant correlations in the NS+NT groups between pre-vaccination concentrations of inflammatory cytokines or LPS ex vivo responses and the response to the Hib vaccine. There were also no significant correlations between GCS, ISS and NISS and the responses to the Hib vaccine in the NT group ($r = 0.11$ – 0.06).

Discussion

In this clinical prospective study, no correlation was found between the T-cell-dependent and the T-cell-independent responses indicating that there is no general T- and B-cell depression in CIDS. T-cell depression could not be predicted by severity of the trauma or markers of the innate immune response.

In the absence of actual data and a relatively low correlation to two of the serotypes the significant correlation between the investigated serotype-specific anti-pneumococcal polysaccharide antibody responses makes it reasonable to hypothesize that there were similar responses to most of the other serotypes included in PPSV23, a finding in accordance with earlier studies, although not investigated in the post-traumatic setting.^{31,32}

In TIDS the immunosuppression has been characterized by decreases in the capacity of monocytes to produce inflammatory cytokines after Toll-like receptor (TLR) stimulation and of antigen-presenting cells to prime antigen on type II major histocompatibility complex molecules as well as a reduced number of CD4 and CD8 positive lymphocytes.^{15,17} After severe head injury ex vivo analyses have shown that dendritic cells displays less TLR activity and T-helper cells express less IL-2 receptor, transferrin receptor and HLA-DR molecules, whereas the proliferative response to the B-cell mitogen pokeweed stays unaffected³³ indicating that CIDS affects antigen presenting cells and T-cells more than B-cells.^{18–3334–35} In the present investigation the T- and B-cell responses were analyzed after antigen presentation in vivo. Vaccine response to PPSV is dependent on an adequate B-cell function, whereas vaccination with the conjugate vaccine against Hib is reliant on both B- and T-cell activity.³⁶ Of special interest was whether a severe defect T-cell response in CIDS also was associated with a more

Table 3. Correlation coefficients between mean pneumococcal and different serotype responses and that to Hib in the combined and separate NT and NS groups.

Pneumococcal serotype	NT + NS groups n = 56	NT group n = 33	NS group n = 23
Mean pneumococcal response	0.13	−0.01	0.32
4	0.27	0.09	0.54
6B	0.05	−0.10	0.29
9V	0.18	−0.03	0.51
14	−0.10	−0.18	0.06
18C	0.10	0.12	0.03
19F	0.11	0.04	0.21
23F	0.01	−0.05	0.18

NT=neurotrauma; NS=neurosurgery.

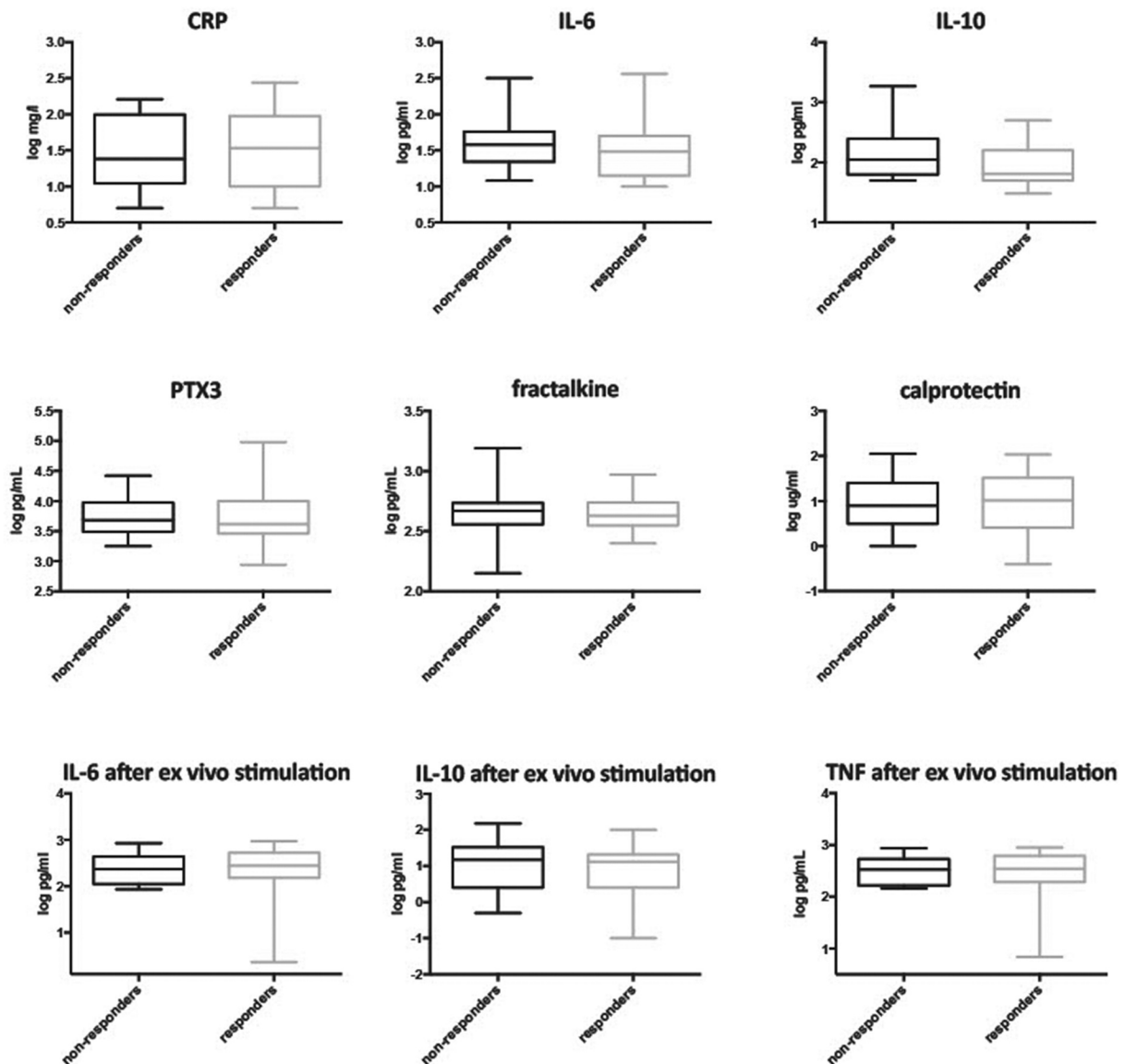


Figure 1. Pre-Vaccination concentrations of selected parameters in non-responders and responders to the Hib vaccine in the neurosurgery and neurotrauma groups. The line represents the median, the box extends from the 25th to the 75th percentile and whiskers range from min to max values.

general depressive effect also including the B-cells. Our previously published data agree with the ex vivo findings, lending some support to a preserved B-cell function in neurotrauma.^{21,22} The results of the present study with a total lack of correlation between the responses to the two vaccines among the NT patients further demonstrate that there is no general decline in T- and B-cell responses and that T-cell depression in patients with CIDS seems not to be linked even to a minor reduction in B-cell activity. The low-grade correlation in the NS group with only moderate trauma suggests that other factors than CIDS might affect the T- and B-cell responses in this group. Together with our previous findings of similar responses to PPSV in the early posttraumatic period of neurotrauma as in controls, the result of the present investigation indicates a preserved B-cell response in CIDS.

If patients with pronounced CIDS should rely on another vaccination program, it was of interest to investigate whether patients with a reduce response to a T-cell dependent vaccine

could be identified before start of vaccination. This might be done by an ex vivo conjugate vaccine stimulation of the patient's lymphocytes but such analyses are laborious, need several days for lymphocytes proliferation³⁷ and are not available in clinical practice. However, we speculated that the downregulation of lymphocyte function might be associated with the magnitude of the trauma or, because TLR signaling is affected in CIDS,³⁵ with more easily measured parameters of the innate immune system. Regrettably, none of the clinical scores representing trauma and neurotrauma or the parameters of the innate inflammatory reaction used in the present study could separate non-responders from responders.

The major strength of our study is the design, involving simultaneous administration of two vaccines that allows investigations of the T-cell-dependent and T-cell-independent responses in the same patient under the same conditions. Expressing the antibody response as fold increases eliminates differences in pre-vaccination levels. However, because some

individuals with high pre-vaccination antibody concentrations may have difficulties to increase their levels several fold, the analyses were also performed using post-vaccination concentrations with similar results as for fold increases.

There are several limitations. First, post-vaccination sera at 6 weeks were replaced by 3-week sera in 11 patients in whom 6-week sera could not be obtained. Even if there were about 10% higher antibody levels in the 3-week sera, they were of equal magnitude for the two vaccines and the correlation between 3- and 6-week sera in patients sampled at both time points were very high ($r = 0.8-0.95$) suggesting that this change in sampling time point did not appreciably affect the results. Second, the construction of a mean pneumococcal response for the correlation analysis with the Hib response in the statistical plan might be perceived as a limitation but, on the contrary, given the high correlation to the individual strain responses, it is a strength avoiding multiple testing problems that might have occurred in this primary analysis if seven correlation analyses with all pneumococcal strains had been performed. In addition, Table 3 indicates that the results in the NT group were not different when the individual serotypes were analyzed. However, it must be emphasized that the level of protection is not related to the mean pneumococcal titer but to specific serotype antibody level and that the threshold for protection might differ between serotypes. Furthermore, it may be argued that healthy controls should have been included in the study. However, the underlying condition and independent variable of the patients analyzed in the present study was a reduced T-cell response of varying degree making analysis in healthy individuals of limited value.

It would also have been worthy to measure monocyte expression of HLA-DR as a marker of monocyte deactivation and a low T-cell response. However, at the time of planning the study this analysis could only be performed on fresh samples and the method was not available in-house. Nevertheless, TNF- α production from LPS-stimulated monocytes, which has been shown to correlate well with the HLA-DR expression, might serve as a substitute.³⁸⁻⁴⁰ Antibody concentrations in our study were determined by enzyme immunoassays and the effect of neurotrauma and neurosurgery on opsonophagocytic activity (OPA) is not known. Antibodies analyzed by enzyme immunoassay, however, generally correlate with OPA and therefore the effect on the present results should be limited.^{41,42} Antibiotic treatment can confound OPA results and for this reason it might be of limited value in the ICU setting.⁴³ All vaccinations were administered subcutaneously and not intramuscularly to avoid concerns about the increased bleeding risk in trauma patients and this uncommon route of administration might be considered a limitation. However, PPSV23 and conjugated Hib vaccine have been shown to display similar immunogenicity if administered either intramuscularly or subcutaneously why this most probably have not affected the results.^{44,45} Finally, as described in our previous publication, underlying diseases might affect the response to vaccination and, thus, possibly also the relationship between T- and B-cell responses.²¹ In this study, 4 patients (2 in the NT group and 2 in the NS group) suffered from diabetes mellitus or malignancy. However, performing the analyses with or without these individuals does not affect the results.

To our knowledge, no studies ensuring the response after neurotrauma were performed before changing the recommendations from PPSV23 to the conjugate vaccines. Our previously published data^{21,22} together with the results of the present study emphasize the need for a prospective randomized trial to settle an optimal vaccination schedule after neurotrauma. In such a trial it would be of interest to compare the vaccination response after PCV20, alternatively PCV15 followed by PPSV23 after 8 weeks, according to the ACIP recommendations, either early during the first days after the trauma or later in the course with that after early PPSV23 followed by a PCV vaccination 1 year later. Of particular interest is whether a booster response will be obtained after PPSV at 8 weeks in the PCV non-responders.

Conclusion

No correlation was found between the T-cell-dependent and T-cell-independent responses, indicating that B-cell function is not similarly depressed as T-cell function, thus supporting previous ex vivo findings of a preserved B-cell function in patients with CIDS. It was not possible to predict the T-cell-dependent vaccine response by grading the trauma or by parameters reflecting the innate immune response. The effect of different vaccination schedules should be determined in prospective trials.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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Appendix A

Table A1. Correlation coefficients between mean pneumococcal and different serotype responses and that to Hib, expressed as post-vaccination antibody concentration, in the combined and separate neurotrauma (NT) and neurosurgery (NS) groups.

pneumococcal serotype	NT + NS groups n = 56	NT group n = 33	NS group n = 23
Mean pneumococcal response	0.05	-0.08	0.28
4	0.14	0.18	-0.01
6B	0.05	-0.05	0.31
9V	0.17	0.07	0.38
14	-0.02	-0.07	0.09
18C	0.17	0.14	0.28
19F	0.10	0.01	0.34
23F	0.25	0.33	0.14

Appendix B

Table B1. Pneumococcal response expressed as fold antibody increase in responders and non-responders to Hib vaccine.

Pneumococcal serotype	Responders to Hib NS +NT	Non-responders to Hib NS+NT	Responders to Hib NS	Non-responders to Hib NS	Responders to Hib NT	Non-responders to Hib NT
Mean pneumococcal response	0.91 ± 0.38	0.79 ± 0.51	0.82 ± 0.37	0.70 ± 0.61	0.97 ± 0.38	0.80 ± 0.47
4	1.18 ± 0.62	0.89 ± 0.58	1.07 ± 0.62	0.80 ± 0.66	1.26 ± 0.62	0.94 ± 0.56
6B	0.70 ± 0.62	0.53 ± 0.63	0.73 ± 0.51	0.27 ± 0.81	0.68 ± 0.71	0.68 ± 0.48
9V	0.88 ± 0.56	0.68 ± 0.68	0.97 ± 0.57	0.77 ± 0.99	0.81 ± 0.55	0.63 ± 0.47
14	1.03 ± 0.78	1.12 ± 0.88	0.76 ± 0.61	0.98 ± 0.42	1.25 ± 0.84	1.21 ± 1.08
18C	0.96 ± 0.61	0.81 ± 0.76	0.95 ± 0.67	0.86 ± 0.58	0.97 ± 0.59	0.78 ± 0.88
19F	0.65 ± 0.50	0.48 ± 0.71	0.57 ± 0.46	0.33 ± 0.78	0.71 ± 0.53	0.56 ± 0.69
23F	0.81 ± 0.62	0.86 ± 0.57	0.75 ± 0.62	0.90 ± 0.79	0.86 ± 0.64	0.82 ± 0.44

Table B2. Pneumococcal response expressed as post-vaccination antibody concentrations in responders and non-responders to Hib vaccine.

Pneumococcal serotype	Responders to Hib NS +NT	Non-responders to Hib NS+NT	Responders to Hib NS	Non-responders to Hib NS	Responders to Hib NT	Non-responders to Hib NT
Mean pneumococcal response	18.4 ± 19.9	18.7 ± 19.3	15.1 ± 17.1	10.0 ± 10.1	20.8 ± 20.6	23.5 ± 23.0
4	3.6 ± 6.8	6.3 ± 13.3	1.5 ± 1.6	3.7 ± 3.5	5.2 ± 8.6	7.9 ± 16.8
6B	7.1 ± 10.6	3.6 ± 4.7	5.7 ± 6.8	1.0 ± 1.3	8.2 ± 12.8	5.2 ± 5.4
9V	11.0 ± 16.0	5.4 ± 5.3	12.1 ± 19.0	4.6 ± 5.6	10.2 ± 13.6	6.0 ± 5.4
14	66.4 ± 114.9	81.7 ± 116.1	48.2 ± 104.5	42.1 ± 77.3	79.9 ± 122.6	105.5 ± 132.2
18C	11.9 ± 17.8	17.2 ± 21.5	23.5 ± 27.5	9.7 ± 9.4	12.6 ± 14.8	13.2 ± 21.8
19F	14.0 ± 20.2	13.8 ± 25.4	9.4 ± 9.4	5.2 ± 9.2	17.3 ± 25.1	19.0 ± 30.8
23F	8.8 ± 9.6	6.4 ± 7.5	5.0 ± 4.1	3.9 ± 5.1	11.6 ± 11.5	7.9 ± 8.5