Low immunogenicity of quadrivalent meningococcal vaccines in solid organ transplant recipients.

B. Wyplosz, O. Derradji, E. Hong, H. François, A. Durrbach, J.-C. Duclos-Vallée, D. Samuel, L. Escaut, O. Launay, D. Vittecoq, et al.

► To cite this version:

B. Wyplosz, O. Derradji, E. Hong, H. François, A. Durrbach, et al.. Low immunogenicity of quadrivalent meningococcal vaccines in solid organ transplant recipients.. *Transplant Infectious Disease*, 2015, 17 (2), pp.322-327. 10.1111/tid.12359 . pasteur-02013270

HAL Id: pasteur-02013270

<https://hal-pasteur.archives-ouvertes.fr/pasteur-02013270>

Submitted on 30 Mar 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives| 4.0 International License

Title: Low immunogenicity of quadrivalent meningococcal vaccines in solid-organ transplant recipients

Authors: Wyplosz B¹, Derradji O¹, Hong E², François H^{3,4}, Durrbach A^{3,4}, Duclos-Vallée JC^{4,5}, Samuel D^{4,5}, Escaut L¹, Launay O⁶, Vittecoq D^{1,3}, Taha M-K²

- 1. Assistance publique-hôpitaux de Paris, CHU Bicêtre, service de maladies infectieuses et tropicales, centre de vaccinations internationales, Le Kremlin-Bicêtre, France
- 2. Institut Pasteur, Invasive bacterial infections Unit, Paris, France
- 3. Assistance publique-hôpitaux de Paris, CHU Bicêtre, néphrologie, Le Kremlin-Bicêtre, France
- 4. Université Paris Sud, faculté de médecine, Paris, France
- 5. Assistance publique-hôpitaux de Paris, hôpital universitaire Paul Brousse, centre hépatobiliaire, Villejuif, France
- 5. Assistance publique-hôpitaux de Paris, hôpital Necker, néphrologie, Paris, France
- 6. Paris Descartes University, INSERM, CIC BT505, and AP-HP, Cochin Hospital, CICBT505, Paris, France

Corresponding author:

Dr Benjamin Wyplosz
Centre de vaccinations internationales
Service de maladies infectieuses et tropicales,
Hôpital de Bicêtre, 94275 Le Kremlin-Bicêtre, France
Tel: 00 33 (1) 45 21 74 25
Fax: 00 33 (2) 45 21 74 23
Email: benjamin.wyplosz@bct.aphp.fr

Running title: Meningococcal immunization after transplantation

Keywords: antibody response, immunization, solid-organ transplantation, meningococcal vaccine

Abbreviations: SOT: solid-organ transplantation; hSBA: human serum bactericidal assay; MenA: *Neisseria meningitidis* serogroup A; MenC *Neisseria meningitidis* serogroup C; MenY: *Neisseria meningitidis* serogroup Y; MenW: *Neisseria meningitidis* serogroup W

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Abstract (153 words)

Immunization against meningococcal disease is recommended for solid-organ transplant (SOT) recipients at high risk for meningococcal disease or travelling to an endemic country. However, the immunogenicity of meningococcal vaccines has not been studied in this population. We analyzed the immune response of quadrivalent (A, C, Y, W) polysaccharidic non-conjugate and conjugate meningococcal vaccines in kidney- and liver-transplant patients using bactericidal assays against the targeted serogroups. Upon vaccination with a non-conjugate (n=5) or a conjugate vaccine (n=10), respectively, 40% and 50% of patients were able to mount an immune response achieving at least the threshold correlated with protection defined as human serum bactericidal antibody titers of ≥ 4 . Responders showed only partial and low responses (titers ≤ 64), thus predicting a rapid decline in bactericidal response. Only one patient developed a booster response to preexisting immunity. Our data argue for the need of additional measures for SOT recipients when they are at risk of meningococcal disease.

Introduction

Vaccines currently available against *Neisseria meningitidis* are composed of capsular polysaccharides or recombinant proteins. Capsular-based vaccines are of two types: non-conjugate polysaccharidic and conjugate vaccines. Conjugate vaccines are preferred over non-conjugate vaccines due to their increased immunogenicity in both children and adults, and their ability to generate a T-cell response that can induce an immunological memory (1).

Two kinds of quadrivalent meningococcal vaccines (against serogroups A, C, Y and W) are available in Europe and the US: non-conjugate polysaccharidic vaccines (Menomune®, Mencevax®) and conjugate vaccines (Menactra®, Menveo®, Nimenrix®). They are recommended for subjects at high risk for meningococcal disease as well as for travelers to an endemic area of meningococcal disease, such as countries within the African meningitis-belt during the dry season (December to June) or to Saudi Arabia during the Hajj or Umrah pilgrimage (2). In the US, the conjugate quadrivalent ACYW vaccine is also used routinely in adolescents due to the higher prevalence of serogroup Y (3).

Solid-organ transplant (SOT) recipients should be vaccinated against meningococcal disease when they are at risk (such as functional or anatomical asplenia) or before travelling to endemic areas. As there is no published data on the immune response to quadrivalent meningococcal vaccines in adult transplant and concerns have been raised about their efficacy after transplantation (4, 5), we took advantage of our travel clinic to assess the immunogenicity of quadrivalent vaccines in SOT recipients traveling to sub-Saharan African countries.

Methods

The study population is a subset from an already published prospective study that established a cohort of SOT travelling patients since 2007. Indeed, we have established a cohort of liver and kidney transplant recipients planning to travel abroad (Centre de vaccinations internationales,

Hôpital de Bicêtre, Le Kremlin-Bicêtre, France) (4). Between November 2009 and June 2013, we systematically investigated all of them who planned to travel to a country within the African meningitis-belt during the epidemic season (December to June). Patients were immunized from November 2009 to March 2010 with a quadrivalent ACYW meningococcal non-conjugate polysaccharidic vaccine (Mencevax®, GlaxoSmithKline laboratories or Menomune®, Sanofi Pasteur MSD), and from April 2010 to June 2013 with a conjugate polysaccharidic vaccine (Menveo®, Novartis vaccines and diagnostics). Self-reported adverse events were recorded in medical charts. Sera were sampled before and at least 14 days after immunization and frozen at – 20°C. All patients gave their oral consent for the humoral response to vaccination to be tested. Serological analyses were performed at the *Centre national de référence des méningocoques* (Institut Pasteur, Paris, France) using hSBA, which is the reference method for assessing the humoral response to meningococcal vaccination: hSBA titers of ≥ 4 are correlated with protection in seronegative patients or the presence of a fourfold rise in hSBA titers in patients with pre-vaccination hSBA titers of ≥ 4 (5, 6).

Results

From November 2009 to June 2013, 15 SOT recipients were referred to our travel clinic for a meningococcal vaccination prior to visiting a country within the African meningitis-belt during the epidemic season (Table 1). Their median age was 56 years (IQR: 44–64); four patients (27%) were female. Fourteen (93%) patients were born in a sub-Saharan African country and planned to travel home. No patient had a history of meningococcal disease or previous meningococcal immunization. Eight (53%) patients had undergone kidney transplantation, six (40%) patients a liver transplantation, and one patient a double-organ transplantation. At the time of immunization, 92% patients received either a triple or a double immunosuppressive-therapy regimen (Table 1).

Corticosteroids (87%), tacrolimus (73%), and mycophenolate mofetil (66%) were the most commonly prescribed drugs.

All patients received a dose of quadrivalent meningococcal vaccine at a median of 3 years (IQR: 2–5) after transplantation (Table 1). From November 2009 to March 2010, five patients were immunized with a non-conjugate vaccine; from April 2010 to March 2013, 10 patients were immunized with a conjugate quadrivalent vaccine. Sera were collected at a median of 49 days (IQR: 23–77) after immunization.

In the non-conjugate vaccine group, all five patients were seronegative for the four vaccine meningococcal serogroups (hSBA ≤ 2) prior to vaccination but one patient showed a titre of 4 for group Y (MenY). After vaccination, two (40%) patients had a protective response to *N. meningitidis* group C (MenC) (hSBA ≥ 4). The patient that already had a titer of 4 for MenY did not show any increase in this titer after vaccination. None of the patients had detectable hSBA titers to the *N. meningitidis* groups W (MenW) or A (MenA).

In the conjugate vaccine group, six of the ten patients had at least one protective meningococcal titer (hSBA ≥ 4) prior to vaccination: MenA: $n = 2$, MenC: $n = 6$, MenW: $n = 3$, and MenY: $n = 2$ (Figure 1, Table 2). Among these 6 patients, a characteristic booster response (a fourfold increase of hSBA titer) was only obtained in one patient with a previous MenC protective titer.

Five of the 10 patients in the conjugate vaccine group with seronegative hSBA titers developed protective immunity (hSBA ≥ 4) against at least one serogroup: MenA: $n = 1$, MenC: $n = 1$, MenY: $n = 2$, and both MenC and MenW: $n = 1$. Only one subject achieved hSBA titers as high as 64 against serogroup MenY (Figure 1D). Finally, we did not observe any different immune responses between kidney- and liver-transplant recipients.

Discussion

Our data show that immune responses to both quadrivalent polysaccharide non-conjugate and conjugate vaccines are impaired in adult SOT patients. Indeed, low bactericidal response (hSBA titers: 4–64) against one or two serogroups were observed but none responded to all meningococcal serogroups. In healthy subjects of the same age range (56–65 years), both types of quadrivalent vaccines induce high levels of hSBA titers (>64). The proportion of vaccinees reaching protective antibody titers varies between 63% (serogroup A) and 98% (serogroup W) (7). In our responders, the low bactericidal titers against meningococci predicted that the bactericidal response would rapidly decline (8). The presence of protective SBA titers prior to vaccination is most likely due to carriage of meningococci that is encountered in about 10% of the general population (9).

To the best of our knowledge, this is the first study to evaluate immune responses to quadrivalent meningococcal vaccines in immunocompromised adults. In other groups of adults at high-risk for meningococcal disease, the immune response to meningococcal vaccination has only been studied in asplenic individuals. An impaired antibody response to meningococcal C conjugate vaccine has been observed using a human SBA (hSBA): 67–80% of patients reached protective antibody titers compared to 98% in the control group, and responders had significantly lower geometric mean titers than controls (10, 11). In contrast, immune responses to meningococcal conjugate vaccines have been assessed in various groups of pediatric immunocompromised patients. After a single dose of monovalent meningococcal C conjugate vaccine, only 6 (25%) out of 24 children on maintenance chemotherapy for acute leukemia and one (20%) out of five bone-marrow-transplant recipients developed protective anti-MenC antibody titers as measured by hSBA (12). In HIV-infected adolescents, response rates to serogroups A, C, W, and Y were 68%, 52%, 73%, and 63%, respectively, and were significantly decreased in subjects with CD4 <25%, a HIV viral load >400 copies/mL, or having CDC Class B or C at entry into the study (13).

Conversely, the proportion of children achieving protective anti-MenC antibody titers ranged between 96% and 100% in SOT-transplant recipients ($n = 10$) (14), juvenile idiopathic arthritis patients ($n = 157$) (15), and in children that were revaccinated after a hematopoietic stem-cell transplantation ($n = 18$) (16) or completion of chemotherapy for acute leukemia ($n = 28$) (17). The higher bactericidal responses in those latter studies may be explained by the fact that vaccination was performed prior to transplantation (16, 17) and/or that antibody levels were measured by SBA using rabbit serum that give higher titers than using human serum (13-15). It is noteworthy that the high SBA titers in these SOT children waned rapidly, which further suggests an impaired sustained immune response (14).

The size of our study population does not allow making general inferences from our data. Our recruitment was restricted by the inclusion criteria (travelers to Sub-Saharan Africa during the epidemic season and close contact with local populations) and the non-recommendation of quadrivalent meningococcal vaccines in general population. Another limitation is that a high proportion of our patients were born in an African country. However, so far, no data indicate differential immunogenicity of conjugate meningococcal vaccines in African or other ethnic populations (18, 19).

Our data and the report of meningococcal sepsis despite prior vaccination in a SOT patient receiving eculizumab treatment (20-22) indicate that the prevention of meningococcal disease in SOT patients should not only rely on a single dose of quadrivalent vaccine as it may only provide partial and short lasting protection. Consequently, an appropriate antibiotic preventive treatment should be given to all SOT patients at high risk of meningococcal disease and vaccination of household contacts of patient (a cocooning strategy) may also allow indirect protection. Transplant candidates are not considered at risk for meningococcal disease but, if

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

travelling prospect to endemic area is identified, they should optimally be immunized before transplantation and early in the course of their disease.

Acknowledgments: All cases of vaccination failure were transmitted to the French pharmacovigilance network (*Centre régional de pharmacovigilance*, Henri Mondor) and registered under the numbers PC20130491 to PC20130505.

The authors want to thank M. Gaël Berthelot from the Centre hépato-biliaire (Hôpital Paul Brousse) for his help in collecting data and referring the patients, and to Laurent Tzara (CHU Bicêtre) who kindly assisted us by collecting blood samples from participants.

Disclosure section: The authors of this manuscript have no conflicts of interest to disclose.

Funding source: none.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table 1. Characteristics of patients and results of serological tests from 15 SOT recipients vaccinated with a non-conjugate ($n = 5$) or a conjugate ($n = 10$) ACYW meningococcal vaccine.

Table 2. Numbers of subjects with a protective bactericidal level before and after quadrivalent meningococcal vaccination.

Figure 1. Antibody response after immunization with a quadrivalent meningococcal conjugate vaccine: hSBA titers are shown prior to vaccination and after one dose of conjugate vaccine. **A.** After one dose of conjugate vaccine, patient #2 developed a protective titer (hSBA =4) against *Neisseria meningitidis* MenA whereas patient #10 lost his protective titer. **B.** Patients #3 and #9 developed protective titers (hSBA ≥ 4) against *N. meningitidis* MenC whereas patients #5 and #10 lost their protective titers. **C.** Patient #3 developed a protective titer (hSBA =8) against *N. meningitidis* MenW whereas patient #10 lost his protective titer. **D.** Patients #8 and #10 developed protective titer against *N. meningitidis* MenY.

References

1. Poolman J and Borrow R. Hyporesponsiveness and its clinical implications after vaccination with polysaccharide or glycoconjugate vaccines. *Expert Rev Vaccines* 2011; 10(3): 307-322.
2. Kotton CN and Hibberd PL. Travel medicine and transplant tourism in solid organ transplantation. *Am J Transplant* 2013; 13 Suppl 4: 337-347.
3. Meningococcal conjugate vaccines policy update: booster dose recommendations. *Pediatrics* 2011; 128(6): 1213-1218.
4. Wyplosz B, Burdet C, Francois H et al. Persistence of yellow fever vaccine-induced antibodies after solid organ transplantation. *Am J Transplant* 2013; 13(9): 2458-2461.
5. Borrow R, Balmer P, and Miller E. Meningococcal surrogates of protection--serum bactericidal antibody activity. *Vaccine* 2005; 23(17-18): 2222-2227.
6. Caron F, du Chatelet IP, Leroy JP et al. From tailor-made to ready-to-wear meningococcal B vaccines: longitudinal study of a clonal meningococcal B outbreak. *Lancet Infect Dis* 2011; 11(6): 455-463.
7. Stambouliau D, Lopardo G, Lopez P et al. Safety and immunogenicity of an investigational quadrivalent meningococcal CRM(197) conjugate vaccine, MenACWY-CRM, compared with licensed vaccines in adults in Latin America. *Int J Infect Dis* 2010; 14(10): e868-875.
8. Snape MD, Kelly DF, Lewis S et al. Seroprotection against serogroup C meningococcal disease in adolescents in the United Kingdom: observational study. *Bmj* 2008; 336(7659): 1487-1491.
9. Yazdankhah SP and Caugant DA. *Neisseria meningitidis*: an overview of the carriage state. *J Med Microbiol* 2004; 53(Pt 9): 821-832.
10. Balmer P, Falconer M, McDonald P et al. Immune response to meningococcal serogroup C conjugate vaccine in asplenic individuals. *Infect Immun* 2004; 72(1): 332-337.
11. Meerveld-Eggink A, de Weerd O, de Voer RM et al. Impaired antibody response to conjugated meningococcal serogroup C vaccine in asplenic patients. *Eur J Clin Microbiol Infect Dis* 2011; 30(5): 611-618.
12. Yu JW, Borkowski A, Danzig L, Reiter S, Kavan P, and Mazer BD. Immune response to conjugated meningococcal C vaccine in pediatric oncology patients. *Pediatr Blood Cancer* 2007; 49(7): 918-923.
13. Siberry GK, Williams PL, Lujan-Zilbermann J et al. Phase I/II, open-label trial of safety and immunogenicity of meningococcal (groups A, C, Y, and W-135) polysaccharide diphtheria toxoid conjugate vaccine in human immunodeficiency virus-infected adolescents. *Pediatr Infect Dis J* 2010; 29(5): 391-396.
14. Zlomy M, Elias J, Vogel U et al. Immunogenicity of conjugate meningococcus C vaccine in pediatric solid organ transplant recipients. *Vaccine* 2011; 29(37): 6163-6166.
15. Zonneveld-Huijssoon E, Ronaghy A, Van Rossum MA et al. Safety and efficacy of meningococcal c vaccination in juvenile idiopathic arthritis. *Arthritis Rheum* 2007; 56(2): 639-646.
16. Patel SR, Ortin M, Cohen BJ et al. Revaccination with measles, tetanus, poliovirus, *Haemophilus influenzae* type B, meningococcus C, and pneumococcus vaccines in children after hematopoietic stem cell transplantation. *Clin Infect Dis* 2007; 44(5): 625-634.

17. Patel SR, Ortin M, Cohen BJ et al. Revaccination of children after completion of standard chemotherapy for acute leukemia. Clin Infect Dis 2007; 44(5): 635-642.

18. Meningococcal vaccines: WHO position paper, November 2011. Weekly epidemiological record 2011; 47(86): 521–540.

19. Sow SO, Okoko BJ, Diallo A et al. Immunogenicity and safety of a meningococcal A conjugate vaccine in Africans. N Engl J Med 2011; 364(24): 2293-2304.

20. Almac Pharma Services. Soliris (ecalizumab) - EU summary of product characteristics. Craigavon, United Kingdom. , 2013.

21. Alexion Pharmaceuticals Inc. Ecalizumab (Soliris): Highligths of prescribing information. 2011.

22. Struijk GH, Bouts AH, Rijkers GT, Kuin EA, ten Berge IJ, and Bemelman FJ. Meningococcal sepsis complicating eculizumab treatment despite prior vaccination. Am J Transplant 2013; 13(3): 819-820.

Table 1. Characteristics of patients and results of serological tests from 15 SOT recipients vaccinated with a non-conjugate ($n = 5$) or a conjugate ($n = 10$) ACYW meningococcal vaccine.

At immunization	Non conjugate vaccine ($n = 5$)	Conjugate vaccine ($n = 10$)
Age (years), median (IQR)	61 (44-65)	56 (46-61)
Women, n (%)	2 (40)	2 (20)
Country of birth		
Sub-Saharan country, n (%)	5 (100)	9 (90)
Type of solid-organ transplant		
Kidney, n (%)	4 (80)	4 (40)
Liver, n (%)	1 (20)	5 (50)
Kidney and liver, n (%)	0 (0)	1 (10)
Pre-transplant disease		
Hypertension	3 (60)	3 (30)
Post-hepatitis cirrhosis/hepatocarcinoma	1 (20)	5 (50)
Other diseases	1 (20)	2 (20)
Number of immunosuppressive drugs (n)		
2	4	3
3	1	7
Type of immunosuppressive drug		
Calcineurin inhibitors	5 (100)	8 (80)
<i>Cyclosporine</i> , n (%)	0	2
<i>Tacrolimus</i> , n (%)	5	6
Purine-synthesis inhibitors	5 (100)	7 (70)
<i>Mycophenolate mofetil</i> , n (%)	4	6

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

<i>Azathioprine, n (%)</i>	1	1
Inhibitor of the target-of-rapamycin	0 (0)	3 (30)
<i>Sirolimus, n (%)</i>	0	1
<i>Everolimus, n (%)</i>	0	2
Prednisone	4 (80)	9 (90)
Intravenous immunoglobulins	1	4
<hr/>		
Median interval between:		
SOT and immunization, years (IQR)	5 (4-5)	2 (1-3)
Immunization and serology, days (IQR)	49 (21-77)	46 (24-76)
<hr/>		

* Menomune® (n=2), Mencevax® (n=3)

† Menveo® (n=10)

§ Senegal (n=4), Mali (n=3), Central African Republic (n=3), Togo (n=2), Cameroon (n=1), Angola (n=1)

° Other diseases were polycystic kidney disease (n=2), diabetic nephropathy (n=1)

‡ hSBA: human serum bactericidal assay

¶ Two sera were positive out of 10 tested for MenY antibodies

Table 2. Numbers of subjects with a protective bactericidal level before and after quadrivalent meningococcal vaccination.

	Vaccinees				Responders to vaccination*	
	Non conjugate vaccine (<i>n</i> = 5)		Conjugate vaccine (<i>n</i> = 10)		All patients (N=15)	
	Baseline <i>n</i> (%)	Post- vaccination <i>n</i> (%)	Baseline <i>n</i> (%)	Post- vaccination <i>n</i> (%)	hSBA ≥ 4 in naïve patients <i>n</i> (%)	4-fold increase of hSBA titer <i>n</i> (%)
MenA	0	0	2 (20)	2 (20)†	1 (7)	0
MenC	0	2 (40)	6 (60)	6 (60)‡	4 (27)	1 (17)
MenW	0	0	3 (30)	3 (30) §	1 (7)	0
MenY	1 (20)	1 (20)	2 (20)	4 (40)	2 (13)	0

*Responders are those who archived a hSBA titer of at least 4 if pre-vaccination titers was <4 or those showed 4-fold increase of hSBA if pre-vaccination titre was ≥ 4 .

†After one dose of conjugate vaccine, one patient developed a protective titer (hSBA ≥ 4) against *N. meningitidis* MenA whereas another patient lost his protective titer.

‡Two patients developed protective titers (hSBA ≥ 4) against *N. meningitidis* MenC whereas two other patients lost their protective titers. One out of six patients (17%) had a 4-fold increase in antibody level.

§One patient developed a protective titer (hSBA ≥ 4) against *N. meningitidis* MenW whereas another patient lost his protective titer.

hSBA: human serum bactericidal assay

Figure 1. Antibody response after immunization with a quadrivalent meningococcal conjugate vaccine: hSBA titers are shown prior to vaccination and after one dose of conjugate vaccine. **A.** After one dose of conjugate vaccine, patient #2 developed a protective titer (hSBA =4) against *Neisseria meningitidis* MenA whereas patient #10 lost his protective titer. **B.** Patients #3 and #9 developed protective titers (hSBA ≥4) against *N. meningitidis* MenC whereas patients #5 and #10 lost their protective titers. **C.** Patient #3 developed a protective titer (hSBA =8) against *N. meningitidis* MenW whereas patient #10 lost his protective titer. **D.** Patients #8 and #10 developed protective titer against *N. meningitidis* MenY.