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Preservation of adaptive immunity after nonmyeloablative hematopoietic cell transplantation in adults with sickle cell disease (PROTECT study)

Elisabeth Dovern[1,2*], Maud Zwolsman[1,2,3*], Abraham Goorhuis[2,4], Bart J. Biemond[1,2,5], Katja C. Wolthers[6], Erfan Nur[1,2,3,5]

* ED and MZ contributed equally as co-first authors

[1] Department of Hematology, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

[2] Amsterdam Institute for Infection and Immunity, Amsterdam UMC

[3] Department of Blood Cell Research, Sanquin Research and Landsteiner Laboratory, Amsterdam, The Netherlands

[4] Department of Infectious Diseases, Amsterdam UMC, Amsterdam, the Netherlands

[5] Cancer Center Amsterdam, Amsterdam UMC

[6] Department of Medical Microbiology and Infection prevention, Amsterdam UMC, Amsterdam, the Netherlands

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Corresponding author: E. Nur, De Boelelaan 1117, 1081HV Amsterdam, The Netherlands; Email: e.nur@amsterdamumc.nl

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The data that support the findings of this study are available on reasonable request from the

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Conflict of interest statement

ED: no conflict of interest

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EN: Novartis (research funding, consultancy, speakers bureau), Vertex (speakers bureau).

Author contributions

EN, AG, and ED conceptualized the study. ED and EN designed the research protocol. ED and EN recruited all study participants. ED vaccinated patients. ED and MZ gathered data. KW delivered the virus IgG titers. MZ performed the statistical analyses and created the figures and tables. ED, MZ, and EN interpreted data and drafted the manuscript. All authors critically reviewed the manuscript.

Clinical trial registration

The trial was registered with clinicaltrials.gov (NCT05200338).

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In patients with sickle cell disease (SCD), nonmyeloablative matched sibling donor (MSD) hematopoietic cell transplantation (HCT) with alemtuzumab (1mg/kg) and low dose (3 Gy) total body irradiation (TBI) typically results in stable mixed chimerism with donor T-cell chimerism of > 50%. In contrast, haploidentical HCT with reduced intensity conditioning (RIC), including antithymocyte globulin (ATG), thiotepa, and post-transplantation cyclophosphamide (PTCy) typically results in full donor chimerism. Previous studies, primarily focusing on malignant hematological conditions, have demonstrated that patients undergoing allogeneic HCT lose their vaccination-derived immunity after transplantation.[1-3] Consequently, comprehensive post-transplantation revaccination is standard practice for all recipients of allogeneic HCT.[4, 5]

We hypothesized that mixed chimerism after nonmyeloablative MSD transplantation for SCD results in better long-term preservation of recipient-derived adaptive immunity than haploidentical transplantation with full donor chimerism, potentially eliminating the need for revaccination. We evaluated preservation of vaccination-derived immunity in adults with SCD after either nonmyeloablative MSD or RIC haploidentical transplantation.

To confirm that the antibody response measured after transplantation is recipient-derived and not donor-derived, we also investigated immune responses to hepatitis B virus (HBV) vaccinations in a subgroup of patients receiving hematopoietic stem cells from donors who had not been exposed to HBV (vaccination). Finally, we characterized the dynamics of immune reconstitution within the first 24 months post-transplantation by measuring lymphocyte subsets.

Adult patients (>18 years) with SCD who underwent allogeneic HCT at Amsterdam UMC were eligible for inclusion. Patients received either nonmyeloablative MSD transplantation or RIC haploidentical transplantation, as previously described.[6, 7] All MSD recipients received hydroxyurea/azathioprine preconditioning for 3 months prior to HCT. Other pre-transplant treatment as well as indications for transplantation were comparable between MSD and haploidentical recipients (**Table S1**). This study was approved by the institutional review board (2021 091/NL77161.018.21) and carried out in accordance with the Declaration of Helsinki 2013, clinicaltrials.gov (NCT05200338). The primary objective was to evaluate the durability of immune responses against pre-transplant vaccinations (measles, rubella, and pneumococcus), comparing nonmyeloablative MSD transplantation (mixed chimerism) to RIC haploidentical transplantation (full chimerism) in SCD patients. Secondary objectives included response to HBV vaccination in a subgroup of patients to determine whether the post-transplant immunity was recipient-derived, and assessment of immune reconstitution. Antibody titers against measles, rubella and *Streptococcus pneumoniae* were collected at baseline (pre-transplant) and +6, +12, and +24 months post-transplantation. Patients receiving revaccination were censored for that specific pathogen beyond this timepoint. The standard revaccination protocol is described in **Table S2**. Immune reconstitution was assessed by measuring lymphocyte subsets (CD3+, CD4+, CD8+, CD19+,

and natural killer (NK) cells) and serum IgG levels. Patients receiving immunomodulatory therapies, such as rituximab, were censored from immune reconstitution assessment after the first dose.

We compared preservation of immunity and immune reconstitution between groups using Fisher's exact test and Mann-Whitney U test, respectively (R, version 2024.12.1). A p-value <0.05 was considered statistically significant.

Twenty-four MSD transplantation recipients and 14 haploidentical transplantation recipients were included (**Figure 1)**. For the HBV subgroup analysis, six patients scheduled for MSD transplantation, six patients scheduled for haploidentical transplantation, and six non-transplant control SCD patients were included (**Figure 1**). Seven of the 18 patients included in the HBV subgroup analysis had already been vaccinated against HBV and did not require additional doses, while 11 subjects received Engerix-B® HBV vaccination (**Table S3**). Given that vaccine-derived pneumococcal immunity typically wanes after five years, the timing of pre-transplant vaccination is relevant for post-transplant durability. In the MSD group, patients had received their pneumococcal vaccination a median of 3 years (range 1-6) prior to transplantation, compared to 2 years (range 0-5) in the haploidentical group. The median follow-up period was 43 months (IQR 31-71). In the MSD group, median chimerism at 1 year post-transplant was 68% (IQR 59-79) in the T cell fraction and 100% (IQR 92-100) in the myeloid fraction. In the haploidentical group, median T cell and myeloid chimerism were both 100% (IQR 100-100) 1 year post-transplant. Sirolimus was tapered from 12 months post-transplantation and discontinued in all patients at median 15 (IQR 14-16) months post-transplantation. The duration of sirolimus use was comparable between the MSD (median 15 months, IQR 14-18) and haploidentical group (14 months, IQR 13-16). Four patients in the haploidentical group developed chronic GvHD, one with skin GvHD resolved readily with topical therapy, the other three were still using systemic immunosuppression at the time of these analyses (18-34 months post-transplantation).

For measles, 21 patients in the MSD group were seropositive at baseline (**Figure 2A**). During post-transplant follow-up, 18/21 patients (85.7%) preserved immunity, while three fell below the protective threshold, one of whom had received rituximab post-transplantation. In the haploidentical group, 10 patients were seropositive at baseline, with 7/10 (70%) preserving their immunity during post-transplant follow-up, while three lost their immunity. This difference was not statistically significant (p=0.36).

For rubella, 20 patients in the MSD group were seropositive at baseline, and 19 (95%) of them remained seropositive during post-transplant follow-up (**Figure 2B**). The only subject who lost immunity, had received rituximab shortly after transplantation. In the haploidentical group, 12 patients were seropositive at baseline, with 8 of them (66.7%) remaining seropositive and the other four (33.3%) gradually losing their immunity after the transplantation. Preservation of immunity against rubella was better in the MSD group than in the haploidentical group (p=0.053).

For pneumococcal strains, 19/20 (95%) patients in the MSD group preserved immunity during follow-up. Nine patients who did not receive a revaccination demonstrated immunity at 24 months post-transplantation. In the haploidentical group, only 1/6 (16.7%) of the evaluable patients preserved immunity after transplantation (p=0.005, **Figure 2C**). The number of evaluable patients varied for each pathogen due to differences in baseline serostatus and revaccination timing.

All 12 subjects in the HBV subgroup analysis were anti-HBs seropositive at baseline (**Figure 2D**). In the months following HCT, antibody titers of 3/6 MSD patients (50%) decreased below the protective threshold. Two of these patients (subjects 1 and 3) had received rituximab due to Epstein-Barr virus reactivation. In the haploidentical HBV subgroup 2/6 subjects (33.3%) lost protective immunity. In non-transplant control patients, 5/6 subjects were seropositive, with one non-responder at baseline. At twelve months post-vaccination, one subject lost immunity (**Figure 2D**). There were no significant differences in immunity preservation between the three groups (p>0.05).

At baseline, median CD19+ cell counts and total IgG levels were higher than reference values in both transplant groups. In the months following HCT, decreases in lymphocyte counts and IgG levels were observed in both groups (**Figure 3**). Between +12 and +24 months, all subsets recovered to levels within or above reference values. The MSD group maintained significantly higher levels of total IgG. Absolute CD3+ and CD4+ cell counts at +3 months were significantly higher in patients receiving haploidentical transplantations (following ATG and PTCy) than in patients receiving MSD transplantation (following alemtuzumab): CD3+ 0.35 $x10^9$/L vs 0.11 $x10^9$/L, respectively, p = 0.008; CD4+ 0.30 $x10^9$/L vs 0.05 x 10^9/L, respectively, p=0.001.

In line with our hypothesis, analysis of MSD transplantations (mixed chimerism) showed stable antibody titers against measles (85.7%), rubella (95%), and *Streptococcus pneumoniae* (95%) for up to 24 months after transplantation. The MSD transplantation recipients who did lose immunity had low baseline titers or were treated with rituximab post-transplantation. The proportion of patients preserving their pre-transplant immunity was smaller in the haploidentical group compared to the MSD group. Although the majority of haploidentical transplant recipients (full donor chimerism) preserved immunity against measles (70%) and rubella (66.7%) until 2 years post-transplantation, a significant proportion (1/3) of these patients has a period of susceptibility to these infections as the live attenuated vaccine against measles, mumps and rubella (MMR) is generally given after 2 years post-transplantation.

Our findings demonstrate better preservation of immunity compared to earlier studies in patients undergoing allogeneic HCT for malignant hematological conditions.[1, 8] Previous studies showed an association between the intensity of the conditioning regimen and antibody titers, with more profound loss of immunity in subjects who had received myeloablative conditioning. This probably contributes to the difference found in our cohort, in which patients receiving MSD transplantation were treated

with nonmyeloablative conditioning and those receiving haploidentical transplantation with a more intensive RIC.[6, 7] Furthermore, in contrast to patients with malignancies, SCD patients undergoing HCT are not heavily pretreated with chemotherapy, which might have significant impact on lymphocytes involved in preservation of immunity.

In the HBV subgroup analysis, preservation of anti-HBV response between the transplant groups and the non-transplant SCD patients was comparable, indicating that the preservation of pre-transplant immunity is recipient-derived, as all the donors had not been exposed to HBV (vaccination). Similarly, the persistence of anti-pneumococcal immunity also indicates post-transplant preservation of recipient-derived immunity as donors had not been vaccinated against *Streptococcus pneumoniae.* While we cannot rule out transfer of some donor immunity for measles and rubella, the better immunity preservation in patients with mixed chimerism (MSD recipients) compared to full chimerism (haploidentical recipients) argues against donor-derived immunity.

Our findings suggest that revaccination might not be needed or can be postponed until at least 24 months post-transplantation in SCD patients undergoing nonmyeloablative MSD transplantation resulting in mixed chimerism. Delayed revaccination might be beneficial since a more mature immune system probably results in improved vaccination response post-transplantation. For the haploidentical transplant recipients, the variability in immunity preservation between subjects and pathogens limits recommendations.

Immune reconstitution dynamics in adult SCD patients undergoing HCT have not been well characterized previously. ATG and PTCy both affect immune reconstitution, with PTCy being associated with a more profound decline in NK, T and B cells in the first month after transplantation.[9] Alemtuzumab has shown to have a stronger depleting effect on CD8+ cells than ATG, possibly explaining the differences found in CD8+ cells at +3 months between the MSD and haploidentical groups.[10] Despite these different approaches, immune reconstitution was generally swift in both transplant groups.

Limitations of the study include the small sample size and revaccination schedules precluding long-term assessment. Importantly, vaccine-derived immunity can be lost up to 10 years post-transplantation.[11-13]

In conclusion, we demonstrate that in SCD patients, nonmyeloablative MSD transplantation leads to more durable preservation of pre-transplant immunity compared to haploidentical transplantation with RIC. Immune reconstitution was comparable between both groups. While revaccination programs might be delayed to at least 2 years post-transplantation, a prospective study using titer-guided revaccinations might establish whether revaccination after nonmyeloablative MSD transplantation in SCD patients can be entirely abandoned.

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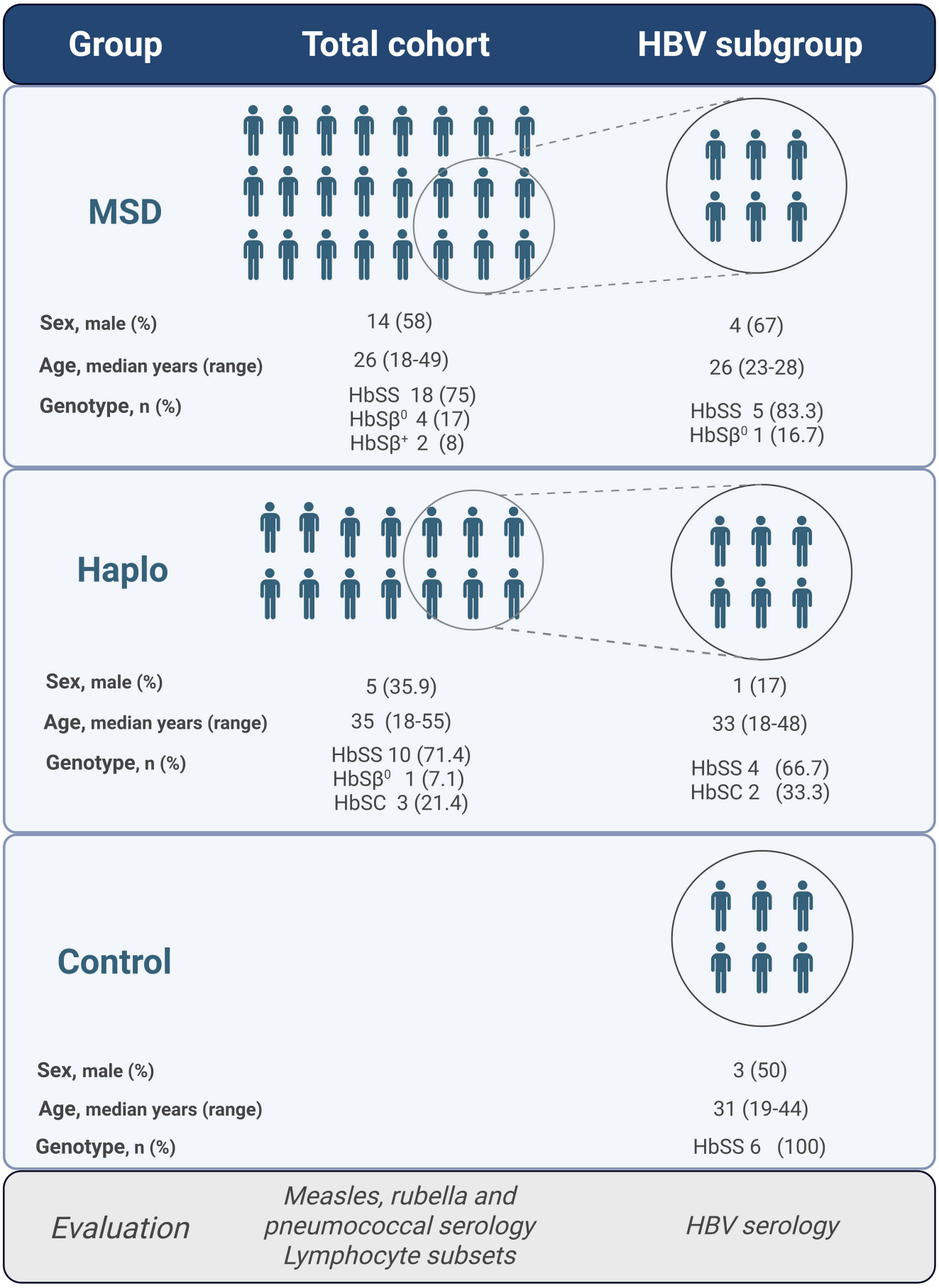
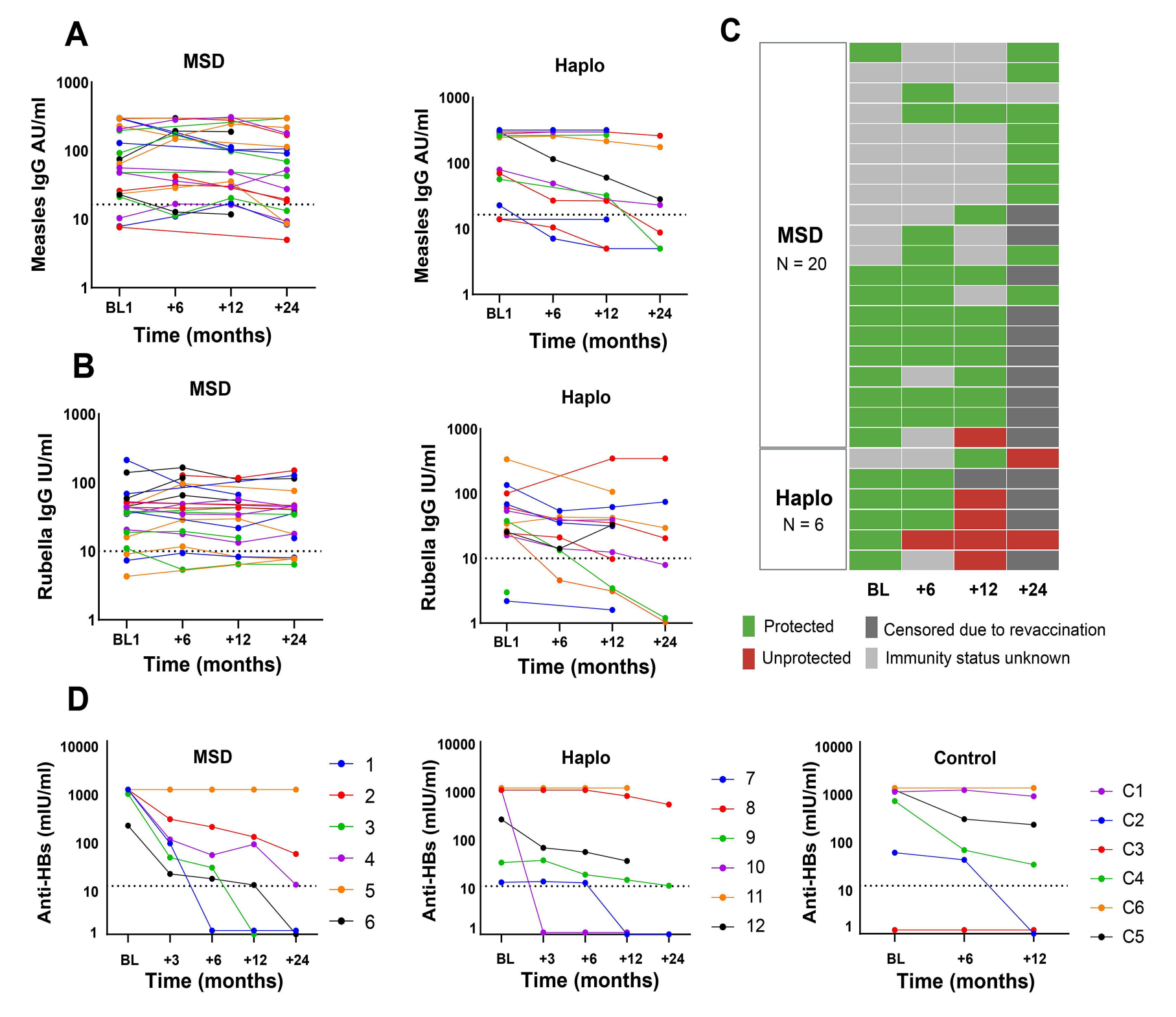
FIGURE LEGENDS

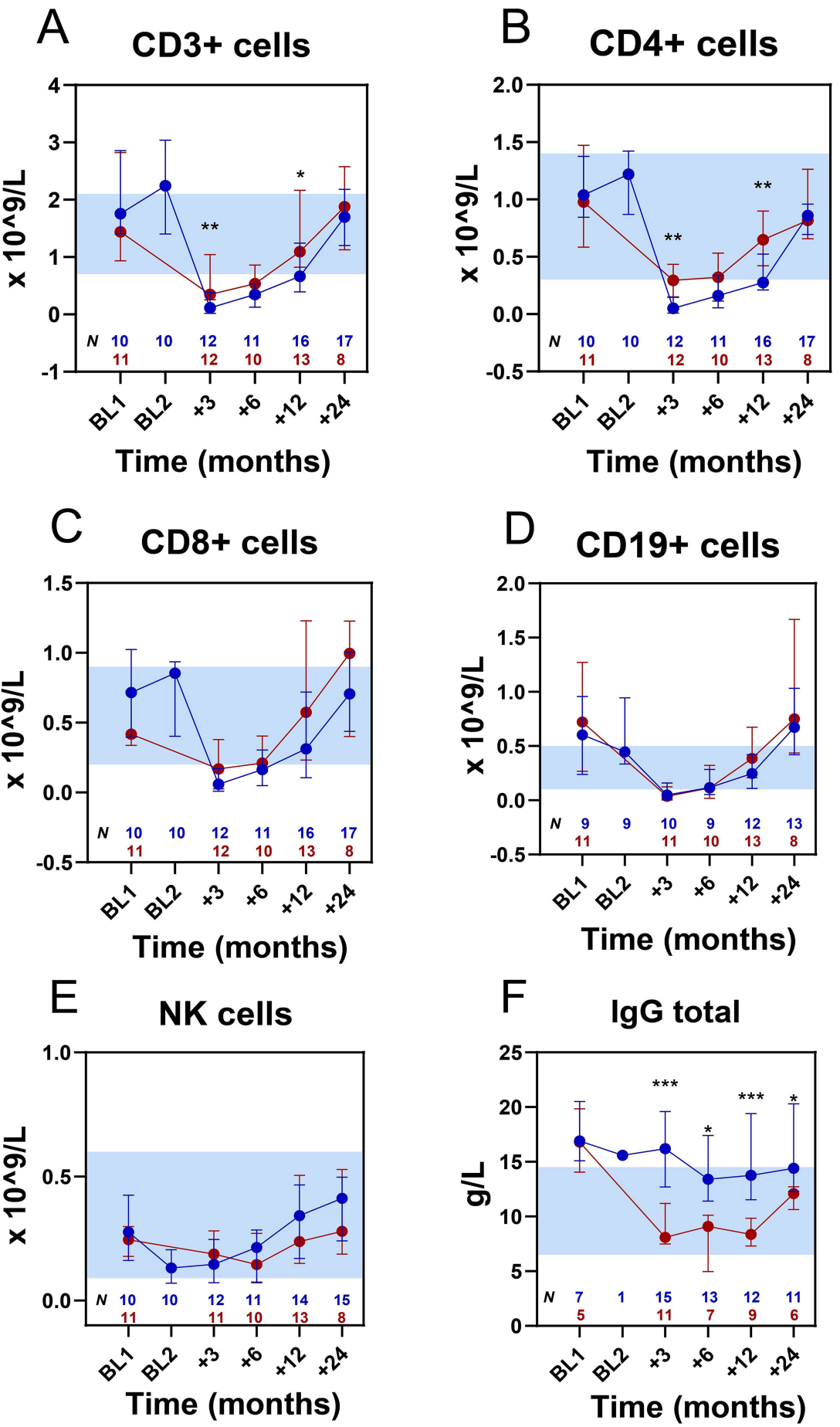
Figure 1. Baseline characteristics and cohort composition.
The study includes two cohorts: The total cohort includes all MSD (n=24) and haploidentical (n=14) transplant recipients from Amsterdam UMC. This total cohort involves serology for measles, rubella, and *Streptococcus pneumoniae*, as well as lymphocyte subset evaluation. Within the total cohort, an HBV subgroup (circled) also underwent HBV serology assessment, including MSD recipients (n=6), haploidentical recipients (n=6), and non-transplant SCD controls (n=6). MSD = matched sibling donor; HBV = hepatitis B virus. *Created with Biorender.com*

Figure 2. Preservation of immunity against measles, rubella and Streptococcus pneumoniae.
Course of measles (**A**) and rubella (**B**) specific IgG titers in the months following hematopoietic cell transplantation (HCT) for MSD (left) and haploidentical (right) groups. Protective threshold is indicated by the dotted line. Measles seropositivity cutoff value >16.5 AU/mL. Rubella cutoff value >10 IU/mL. Each line represents an individual subject. (**C**) Course of immunity against *Streptococcus pneumoniae* infection at baseline (BL), +6, +12 and +24 months after HCT for MSD and haploidentical transplant recipients. Each row represents an individual subject. Subjects without any data regarding pneumococcal immunity and subjects with only baseline available are not shown. For the single value ELISA, subjects with a titer above 37 mg/L are considered immune. For the multiple subvariant test, subjects with antibody titers above 1.0 µg/mL for 6 or more pneumococcal serotypes are considered immune. **(D)** Course of anti-HBs titers in the matched sibling donor (left), haploidentical (middle) and non-transplant control patient (right) subgroups. Protective threshold is indicated by dotted line (> 10 mIU/mL). Each line represents an individual subject. Anti-HBs = antibodies against HBs; BL = baseline; MSD = matched sibling donor.

Figure 3. Immune reconstitution after transplantation.
Time courses of absolute CD3+ **(A),** CD4+ **(B)**, CD8+ **(C)**, CD19+ **(D)**, NK **(E)** subsets, and total IgG **(F)**. Data points show medians for MSD (blue) and haploidentical (red) groups; error bars represent inter quartile range (IQR). Blue box indicates normal reference values. Numbers show sample size (N) per group at each timepoint. P-values are calculated using the Mann-Whitney U test; significance levels: * ($p<0.05$), ** ($p<0.01$), *** ($p<0.001$). BL1 = baseline; BL2 = after preconditioning, but before conditioning (MSD only, haploidentical patients received no preconditioning); MSD = matched sibling donor; NK = natural killer.


Group
Total cohort
HBV subgroup
MSD
Sex, male (%)
14 (58)
4 (67)
Age, median years (range)
26 (18-49)
26 (23-28)
Genotype, n (%)
HbSS 18 (75)
HbSβ0 4 (17)
HbSβ+ 2 (8)
HbSS 5 (83.3)
HbSβ0 1 (16.7)
Haplo
Sex, male (%)
5 (35.9)
1 (17)
Age, median years (range)
35 (18-55)
33 (18-48)
Genotype, n (%)
HbSS 10 (71.4)
HbSβ0 1 (7.1)
HbSC 3 (21.4)
HbSS 4 (66.7)
HbSC 2 (33.3)
Control
Sex, male (%)
3 (50)
Age, median years (range)
31 (19-44)
Genotype, n (%)
HbSS 6 (100)
Evaluation
Measles, rubella and pneumococcal serology
Lymphocyte subsets
HBV serology


A
MSD
Measles IgG AU/ml
1000
100
10
1
BL1
+6
+12
+24
Time (months)
Haplo
Measles IgG AU/ml
1000
100
10
1
BL1
+6
+12
+24
Time (months)
B
MSD
Rubella IgG IU/ml
1000
100
10
1
BL1
+6
+12
+24
Time (months)
Haplo
Rubella IgG IU/ml
1000
100
10
1
BL1
+6
+12
+24
Time (months)
C
MSD
N = 20
Haplo
N = 6
BL
+6
+12
+24
Protected
Censored due to revaccination
Unprotected
Immunity status unknown
D
MSD
Anti-HBs (mIU/ml)
10000
1000
100
10
1
BL
+3
+6
+12
+24
Time (months)
1
2
3
4
5
6
Haplo
Anti-HBs (mIU/ml)
10000
1000
100
10
1
BL
+3
+6
+12
+24
Time (months)
7
8
9
10
11
12
Control
Anti-HBs (mIU/ml)
10000
1000
100
10
1
BL
+6
+12
Time (months)
C1
C2
C3
C4
C6
C5


A
CD3+ cells
x 10^9/L
4
3
2
1
0
-1
**
*
N 10 10 12 11 16 17
11 12 10 13 8
BL1 BL2 +3 +6 +12 +24
Time (months)
B
CD4+ cells
x 10^9/L
2.0
1.5
1.0
0.5
0.0
-0.5
**
**
N 10 10 12 11 16 17
11 12 10 13 8
BL1 BL2 +3 +6 +12 +24
Time (months)
C
CD8+ cells
x 10^9/L
1.5
1.0
0.5
0.0
-0.5
N 10 10 12 11 16 17
11 12 10 13 8
BL1 BL2 +3 +6 +12 +24
Time (months)
D
CD19+ cells
x 10^9/L
2.0
1.5
1.0
0.5
0.0
-0.5
N 9 9 10 9 12 13
11 11 10 13 8
BL1 BL2 +3 +6 +12 +24
Time (months)
E
NK cells
x 10^9/L
1.0
0.5
0.0
N 10 10 12 11 14 15
11 11 10 13 8
BL1 BL2 +3 +6 +12 +24
Time (months)
F
IgG total
g/L
25
20
15
10
5
0
***
***
*
*
N 7 1 15 13 12 11
5 11 7 9 6
BL1 BL2 +3 +6 +12 +24
Time (months)

Supplementary material

Table S1. Pre-transplant treatment and transplantation indications

	MSD (n=24)	**Haploidentical (n=14)**
Treatment before transplantation		
Hydroxyurea, n(%)*	24 (100%)	5 (35.7%)
Azathioprine, n(%)*	24 (100%)	NA
Chronic red blood cell transfusion, n(%)	5 (20.8%)	6 (42.9%)
*Indication for transplantation***		
Acute chest syndrome, n(%)	14 (58.3%)	9, (64.3%)
Vaso-occlusive episodes, n(%)	17 (70.8%)	12 (85.7%)
Stroke, n(%)	3 (12.5%)	2 (14.3%)
Pulmonary hypertension, n(%)	5 (20.8%)	4 (28.6%)
Avascular osteonecrosis, n(%)	9 (37.5%)	5 (35.7%)
Chronic kidney injury, n(%)	2 (8.3%)	2 (14.3%)
Iron overload, n(%)	3 (12.5%)	3 (21.4%)
Delayed hemolytic transfusion reaction, n(%)	1 (4.2%)	0 (0%)

*all patients planned for matched sibling donor (MSD) transplantation received hydroxyurea/azathioprine preconditioning therapy during 3 months prior to transplantation.
**the majority of patients had >1 indication for transplantation

Table S2. Revaccination schedule for all allogeneic hematopoietic cell transplantation recipients at Amsterdam University Medical Centers

Timepoint	**Earliest administration after hematopoietic cell transplantation (HCT)**	**Vaccinations**
Day 0	From 4-6 months after HCT	• PCV20 (1) (20-valent conjugated pneumococcal vaccine) • COVID-19 mRNA (1)
Month 1	From 5-7 months after HCT	• PCV20 (2) • COVID-19 mRNA (2) • Influenza (current season)
Month 2	From 6-8 months after HCT	• PCV20 (3) • COVID-19 mRNA (3)
Month 5	From 9-10 months after HCT	• COVID-19 mRNA (Booster)
Month 8	From 12-14 months after HCT	• PCV20 (4) • Vaxelis® (1) (Diphtheria, Pertussis, Tetanus, Poliomyelitis, *Haemophilus influenzae* type b, Hepatitis B) • Shingrix® (1) (recombinant *Varicella zoster* vaccine)
Month 9	From 13-15 months after HCT	• Vaxelis® (2) • Nimenrix® (1) (quadrivalent meningococcal A/C/W/Y vaccine) • Bexsero® (1) (meningococcal B vaccine)
Month 10	From 14-16 months after HCT	• Vaxelis® (3) • Shingrix® (2)
Year 1	From 16-18 months after HCT	• Bexsero® (2) • Nimenrix® (2)
Year 2	From 24 months after HCT (Only in case of negative titers at year 1)	• MMR (measles, mumps, rubella) (conditions for vaccination: no immunosuppression, no GvHD, and CD4 count > 200 x 10^6/L) • PCV20 (5)

Table S3. Timing of hepatitis B virus vaccinations

Patient	1st dose (days)	2nd dose (days)	3d dose (days)
1*	-167	- 160	-138
2*	-170	-162	-140
3	-274	-247	-219
4*	-178	-171	-156
5	Previously vaccinated		
6	Previously vaccinated		
7	Previously vaccinated		
8*	-44	-37	-24
9	Previously vaccinated		
10	-58	-45	-24
11	Previously vaccinated		
12	Previously vaccinated		
C1	Previously vaccinated		
C2	0	+56	+84
C3	0	+29	+56
C4	0	+43	+70
C5	0	+28	+64
C6	0	+49	+77

For patients 1 to 12, date of transplantation is day 0. For control (C) patients 1 to 6, date of first vaccination is day 0.

*patients who received vaccinations in a super accelerated schedule.