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1 **LONG-TERM IMMUNITY TO MEASLES AFTER ALLOGENEIC HAEMATOPOIETIC CELL**

2 **TRANSPLANTATION: FACTORS ASSOCIATED WITH SEROPROTECTION BEFORE REVACCINATION**

3

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33

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37

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Abstract

Measles can be a life-threatening infection in immunocompromised patients, especially after allogeneic haematopoietic cell transplantation (HCT) because of the corresponding loss of immunity. However, measles vaccines are live-attenuated, which is why measles vaccinations are recommended only in seronegative HCT recipients and in specific conditions. Few data exist, however, on the rates of seroprotection to measles with the current conditioning regimens and in long-term follow-up. The objectives of the study were to assess measles immunity before considering vaccination in a cohort of allogeneic HCT long-term survivors and to identify the factors associated with seropositivity/seroprotection. One hundred and twenty-six patients transplanted 1–39 years ago (median: 9 years) were assessed for measles immunity. Measles immunoglobulin (Ig)G titers were determined with an automated chemiluminescent immunoassay. Seropositivity/seroprotection was defined by IgG titers > 16.5 UA/mL. Most patients were transplanted for acute leukaemia (61%) and after a reduced-intensity (RIC) or nonmyeloablative (NMA) regimen in 46% of them. Here, 78/126 (62%) of the patients were seropositive/seroprotected for measles. Among the seropositive patients, the patients who had been vaccinated before transplant had lower median IgG titers (48 UA/mL) than those who had not (116 UA/mL). Myeloproliferative disorder, RIC or NMA conditioning and absence of acute grade ≥ 2 graft-versus-host disease were associated with seropositivity/seroprotection. With a 62% rate of seropositivity/seroprotection for measles at a median of nine years after transplant, our findings strongly support a systematic assessment of antimeasles antibody titers to avoid unnecessary vaccination in seroprotected patients.

63 **INTRODUCTION**

64

65 Measles is a life-threatening viral infection that may occur after allogeneic haematopoietic cell
66 transplantation (HCT), and until now, there has been no active antiviral treatment (1, 2). After the
67 introduction of the measles vaccine in the early 1980s, a decreased vaccinal coverage of the
68 population was observed in many countries, leading to measles re-emergence, an increased risk of
69 outbreaks worldwide and of the life-threatening disease appearing in immunocompromised patients.
70 The worldwide number of measles deaths remains around 100,000 yearly (3, 4). In Europe, the
71 number of measles cases reported in 2018 was three times that in 2017 and 15 times that in 2016
72 (4). In France, where the percentage of measles vaccinations is not optimal (78% in two-year-old
73 children in 2010 according to the French Health and Solidarity Ministry (5)), an outbreak of more
74 than 20,000 cases was observed between 2008 and 2011 (6), with a later persistence of an endemic
75 situation (7). Because measles is highly transmissible, outbreaks are more likely to occur in crowded
76 locations, like with the outbreak reported in a jail in Arizona in 2016 (8). Because of their loss of
77 measles immunity as soon as the first year after transplant (9), HCT recipients are especially
78 threatened by these outbreaks. Indeed, several outbreaks have been reported in haematological
79 wards. In the context of a measles outbreak in Sao Paulo in 1997, Machado et al. observed eight
80 cases of measles in HCT recipients, which pushed them to implement a wide vaccination programme
81 of the HCT population (2). Ge et al. reported an outbreak of 23 cases of measles in a paediatric onco-
82 haematology department in Shanghai in 2015, with direct transmission of measles between at least
83 20 of the patients (1).

84 Studies performed 15–30 years ago showed that three years after transplant, a significant proportion
85 of allogeneic HCT recipients was seropositive for measles before any post-transplant measles
86 vaccination; this occurs in roughly 40–60% of the cases, with a progressive decline of specific
87 immunoglobulin G (IgG) concentrations seen over time. However, these data were mostly obtained
88 in young HCT recipients mainly transplanted with HLA-identical donors and conditioned with

89 myeloablative (MA) regimens(10-14) . More recently, measles seropositivity averaged 20–45% in
90 small cohorts of adults, including patients transplanted after reduced-intensity (RIC) or
91 nonmyeloablative (NMA) conditioning regimens (15, 16), and the seropositivity rate reached 60% in
92 children (17).

93 The recently published European Conference on Infections in Leukaemia (ECIL) guidelines for
94 vaccination in HCT recipients (18) recommend assessing measles antibody titers starting from two
95 years after HCT and to vaccinate only seronegative patients, here providing strict criteria to minimise
96 both the risk of vaccine-induced measles – no graft-versus-host disease (GvHD), no
97 immunosuppressive drugs, no relapse of the underlying disease – and the risk of inefficacy of a live-
98 attenuated vaccine – no immunoglobulin administration since several months. In the case of an
99 outbreak, patients can be vaccinated one year after HCT in the absence of high immunosuppression
100 criteria. Previous Infectious Diseases Society of America (IDSA) guidelines have already
101 recommended a similar strategy (19).

102 Although immunocompromised patients do not respond to vaccination as well as healthy individuals,
103 allogeneic HCT recipients can respond to the measles-mumps-rubella (MMR) vaccine in 65–100% of
104 the cases (2, 11, 15, 20, 21).

105 The objectives of the current study were to assess measles immunity before considering vaccination
106 in a cohort of HCT survivors, including patients conditioned with RIC or NMA regimens, and to
107 identify the factors associated with seropositivity/seroprotection.

108

109 **METHODS AND PATIENTS**

110

111 ***Patients***

112 From September 2017 to February 2019, allogeneic HCT adult recipients who had not been
113 vaccinated for measles since HCT were routinely screened for measles immunity at a transplant
114 consultation. Clinical data were collected from the medical charts. The acute GvHD was graded

115 according to Glucksberg classification (22) and chronic GvHD according to NIH classification (23).
116 Conditioning regimens were classified according to the EBMT-CIBMTR definitions (24), and RIC and
117 NMA were pooled. According to French Health Public Law (CSP Art L1121-1.1), this type of
118 investigation does not require specific informed consent or ethics committee approval.

119

120 ***Seropositivity/seroprotection assessment and definition***

121 Measles IgG titers were determined using an automated chemiluminescent immunoassay (CLIA)
122 (Liaison Measles IgG Kit, Liaison XL analyser, Diasorin, Italy) and are expressed in quantified arbitrary
123 units (UA/mL). The cut-off value of 15 UA/ml is equivalent to 175 mIU/mL, which is the WHO
124 standard. According to the manufacturer's guidelines, titers between 13.5 and 16.5 UA/mL were
125 considered indeterminate, while titers below 13.5 UA/mL define seronegativity and titers above 16.5
126 UA/mL define seropositivity/seroprotection. Titers over the limit of quantification of 300 were
127 considered as expressing as > 300 UA/mL (25, 26) .

128

129 ***Statistical methods***

130 The qualitative variables were described as numbers (%) and compared using the chi-squared test or
131 Fisher exact test, as appropriate. Quantitative variables were described as the median or mean
132 (range) and compared using the Kruskal-Wallis test. The risk factors for seropositivity/seroprotection
133 were analysed. ORs were estimated separately for factors yielding a P value < 0.20 in the univariate
134 analysis by using logistic regression models. Variables yielding P values < 0.20 in the univariate
135 analyses were considered for the multivariate analyses. P values \leq 0.05 were considered significant.
136 All tests were two-tailed. All statistical analyses were performed using STATA Statistical Software V
137 12.0 (Stata Corporation, College Station, TX, USA).

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139

140

141 **RESULTS**

142

143 ***Characteristics of the patients***

144 One hundred and twenty-six adult patients who were transplanted in our department a median of
145 nine years ago (1–39 years) were included (Table 1). Briefly, the patients were transplanted from
146 1979–2017 at a median age of 43 years, mostly for acute leukaemia in complete remission. The
147 median age at assessment was 54 years. Nine patients received two to four doses of rituximab
148 between transplant and assessment at a median of 4.4 years (1.3–7.0) before assessment. No patient
149 had been diagnosed with measles or had received a measles vaccination since transplant. None of
150 them had received immunoglobulins during the prior six months.

151

152 ***Seropositivity/seroprotection rates***

153 Overall, 78 of the 126 (62%) patients had IgG titers > 16.5 UA/mL and were considered seropositive.
154 Two patients had antibody titers in the grey zone between 13.5 and 16.5 UA/mL and were pooled
155 with seronegative patients. The median IgG concentration in seropositive patients was 109.5 UA/mL
156 (range: 16.5–300). The distribution of the IgG titers in the 78 seropositive patients is shown in Figure
157 1. Twenty-three of the 78 seropositive patients (29%) had IgG titers above 300 UA/mL. Comparing
158 the seropositivity rates and the median measles Ab titers according to the time elapsed between HCT
159 and assessment (≤ 5 years, 5-10 years, 10-20 years or ≥ 20 years), we did not find any difference
160 between groups (data not shown), However, the median measles IgG titers in patients who
161 underwent allogeneic HCT more than 5 years ago was numerically lower (median 37.5 UA/mL) than
162 those of patients who underwent allogeneic HCT less than 5 years ago (103 UA/mL) but the
163 difference was not significant ($p=0.06$)(Figure 2).
164 Eighteen patients declared a past history of measles before transplant, 27 patients did not, and 81
165 patients did not remember. The median IgG concentration was higher in patients with a
166 pretransplant history of measles (86.8 UA/mL) than in patients without (21.2 UA/mL) ($p = 0.003$).

167 Among the seropositive patients, the median IgG concentration was higher in the patients with a
168 pretransplant history of measles (195 UA/mL) than in the patients without (49 UA/mL) ($p < 0.001$).
169 Twelve patients had been vaccinated with an MMR vaccine before transplant, 48 patients had not,
170 and 66 patients did not remember. Patients who had been vaccinated ($n = 12$) tended to have lower
171 measles IgG concentrations (median 20.8 UA/mL) than patients who had not ($n = 48$) (median 51.4
172 UA/mL) ($p = 0.08$). Among the seropositive patients, patients who had been vaccinated ($n=7$) had
173 lower measles IgG concentrations (48 UA/mL) than the patients who had not ($n= 34$) (116 UA/mL) (p
174 $= 0.02$).

175 Considering that the measles vaccine was introduced in the French vaccine agenda in 1982, we
176 compared the seropositivity rates and IgG titers of the 21 patients born starting from 1982 to those
177 of the 105 patients born before 1982. The rate of seropositivity was not different in patients born
178 before or after 1982 (57% versus 63% respectively, $p = 0.62$), but the median measles IgG
179 concentration in seropositive patients was higher in patients born before 1982 (136.5 UA/mL) than in
180 patients born in 1982 or after (55.1 UA/mL) ($p = 0.008$).

181

182 ***Factors associated with seropositivity/seroprotection***

183 The univariate analysis of the factors associated with measles seropositivity/seroprotection is shown
184 in Table 2. Seropositive patients were older than seronegative patients, both at transplant and at the
185 time of assessment. As for age, we first looked at the seropositivity rates and Ab titers according to
186 the recipient age by decade. The number of patients per decade group was between 4 and 28
187 patients. We failed to find any difference between these groups. Therefore, age was split at the
188 median for the OR calculation. Myeloproliferative disorders and the absence of GvHD at any time
189 since HCT were significantly associated with seropositivity/seroprotection. HLA-identical donor,
190 RIC/NMA regimen and relapse of the underlying disease between HCT and assessment tended to be
191 associated with measles seropositivity.

192 In the multivariate analysis (Table 3), myeloproliferative disorders, RIC/ NMA and the absence of
193 previous acute GvHD grade ≥ 2 were associated with seropositivity/seroprotection.

194

195 **DISCUSSION**

196

197 In a cohort of 126 allogeneic HCT recipients, 62% were seropositive/seroprotected to measles a
198 median of nine years after transplant before any post-transplant MMR vaccination. This first finding
199 encourages an assessment of measles serology according to the IDSA (27) and ECIL guidelines (18)
200 because our results indicate that only 38% of the patients would be potential candidates for MMR
201 vaccination after allogeneic HCT, regardless of other criteria

202 Previous studies have shown that in allogeneic HCT recipients, measles seropositivity/seroprotection
203 rates can range from 20–67% (10-13, 15-17, 21), with decreasing titers of IgG antibodies over time
204 (10, 12, 15) especially during the first year after transplant (9). However, none of these prior studies
205 have assessed patients for such a long time – up to 40 years – after transplant, as in our study.

206 Seropositivity before revaccination was shown to be associated with a lack of acute grade ≥ 2 GvHD
207 (10, 16). Conflicting results have been published about the relationship between chronic GvHD and
208 seropositivity (10, 15). It has been also shown that the probability of remaining seropositive for
209 measles was higher in patients who got measles before transplant than in patients vaccinated before
210 transplant, a finding that is consistent with higher antibody titers after natural infection than after
211 vaccination types (2, 9, 11, 12, 14).

212 Our cohort mainly differs from previous series in terms of age, type of donors, conditioning regimens
213 and time elapsed after transplant, hence providing key information on measles immunity in the
214 current conditions of allogeneic HCT and with a long follow-up. As in previous studies, we found that
215 GvHD, especially acute grade ≥ 2 GvHD, had a negative impact on measles immunity. Additionally, we
216 found that patients who had been transplanted with RIC or NMA conditioning had higher rates of
217 seropositivity/seroprotection than patients transplanted with an MA regimen. In previous studies,

218 conditioning was totally or mainly myeloablative (10-13, 16), precluding the finding of any
219 association between measles immunity and the type of conditioning. It should be noted that RIC and
220 NMA conditioning are mainly proposed to older patients who have not been vaccinated during
221 childhood but who mostly went through natural measles. Therefore, these patients were found to
222 have pretransplant titers higher than the younger vaccinated patients (9). In our study,
223 myeloproliferative disorders were also associated with seropositivity/seroprotection, perhaps
224 because these patients did not usually receive chemotherapy before transplant. However, due to the
225 small number of patients in this group (n= 16), this finding deserves to be confirmed on larger
226 cohorts. Contrary to Ljungman et al. (10, 12), we did not find any association between age and
227 seropositivity in the multivariate analysis, probably because of the association between age and
228 conditioning. Finally, our study suggests considering two groups of measles seropositive HCT
229 recipients with different antibody titer ranges: the first one with measles IgG concentrations in the
230 low range of seropositivity between 16.5 and 100 UA/mL, who were mainly the younger patients and
231 vaccinated before transplant, and the second one with antibody concentrations above 300 UA/mL,
232 who were mainly older patients with natural pretransplant measles. The surprising issue in our whole
233 cohort is a pretty high rate of protection before revaccination, suggesting an antibody production
234 that persists despite transplant and that could be either from the recipient or from the donor,
235 especially in the older patients who got measles during childhood and were transplanted with
236 RIC/NMA regimens. The recently published position of the American Society for Transplantation and
237 Cell Therapy (ASTCT) about measles prevention (28) is to recommend measles vaccination of HCT
238 recipients from 24 months after transplant - and sometimes earlier in specific situations -
239 irrespectively of measles antibody titers. This is in disagreement with the IDSA (19) and the ECIL 7
240 (18) guidelines which propose to vaccinate only seronegative patients in order to avoid the risk of a
241 live-attenuated vaccine in patients whose immunity may not be fully repaired. The position of the
242 ASTCT is based on several studies showing that the measles-specific antibody titers wane over time
243 after transplant, and should be expected to be very low, and even zero, in long-term recipients, so

244 that finally the vaccination will be necessary one day. These studies, however, included no, or very
245 few patients more than 10 years after transplant, and did not include or did not mention RIC or NMA
246 conditioning (10, 12, 15). Our study shows that more than 20 years after transplant, 67% of the
247 patients are seroprotected against measles. Although the risk of vaccine-induced measles is likely
248 extremely low in patients transplanted years before and off any immunosuppressant, at least
249 checking the serology should be necessary for patients who still receive low-dose
250 immunosuppression or have persistent symptoms of chronic GvHD. Further studies are needed to
251 support one or the other strategy: universal vaccination irrespectively of measles serology, or
252 vaccination only for seronegative patients.

253 We recognise the limits of our study: First, it is a monocentric study. However, because every patient
254 was followed in our department, this led to robust, exhaustive and long-term data. Second, we did
255 not use the functional plaque reduction neutralisation test (PRNT), which measures neutralising
256 antibodies and is the gold standard for evaluating measles humoral immunity. However, this test
257 lacks standardisation and automation and is not available in routine laboratories. Moreover, several
258 studies have shown the excellent sensitivity and specificity of the ELISA and CLIA assays and their
259 good correlation with the PRNT tests (25). Detection of measles IgG in serum is therefore widely used
260 as evidence of immunity (25, 29) . Third, the antibody assessment was performed only once and at
261 different times after transplant for different patients, which precludes any individual assessment of
262 the kinetics of IgG. However, assessing the measles serologic status on an individual basis is a real-life
263 concern when deciding whether to administer MMR vaccination. Fourth, we did not get the measles
264 history, serological status and vaccine status of the donor, which may have had an impact on the
265 long-term seroprotection/seropositivity of the recipient. Finally, we were unable to obtain exhaustive
266 data about previous MMR vaccinations and pretransplant measles of our cohort. This is easily
267 explained by the median age of our patients (54 years), with patients sometimes being as old as 79
268 years and who may have forgotten such benign events of childhood after a malignant disease. We
269 tried to overcome this issue by looking at the seroprotection rates and IgG titers according to the

270 date of birth of the patient regarding the French recommendations for vaccinating healthy children.
271 Vaccine coverage of children in France was 32% only in 1985 and 80% in 1994, with a great variation
272 according to the areas. Since that time, the vaccine coverage has followed a plateau, never going
273 over 85% (5, 30). However, Créteil, which is in the Paris area, is among the better covered areas, and
274 this suggests that most of the patients we transplanted and were born from 1982 and after were
275 vaccinated. This is, however, a rough estimation.

276

277 **CONCLUSION**

278 Sixty-two percent of allogeneic HCT patients were seropositive/seroprotected for measles at a
279 median of nine years after HCT and before receiving a new vaccination. The only factors strongly
280 associated with seropositivity/seroprotection were myeloproliferative disorders, RIC or NMA
281 conditioning and the absence of previous acute GvHD grade ≥ 2 . In patients without chronic GvHD,
282 who are candidates for MMR vaccination starting from two years after transplant, the immune status
283 to measles is mostly unpredictable. Therefore, a systematic assessment of antimeasles Ab titers is
284 warranted even decades after transplant when the patient has not been revaccinated, as
285 recommended in the IDSA and ECIL guidelines for avoiding unnecessary vaccinations in immunised
286 patients and to protect at-risk patients.

287

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289

290 **Contribution:** CR, FR and CC designed the study, collected the data, analysed the results and drafted

291 the manuscript; AAM and FR ran the laboratory analyses and interpreted the data; LC collected the

292 transplant data; CR, RR, ML, FB and SM managed the patients and critically revised the paper. All

293 authors approved the final version of the manuscript.

294

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Table 1: Characteristic of the 126 patients assessed for measles seropositivity after allogeneic HCT

Age at transplant, median (extrems), years		43 (13-68)
Age at time of assessment, median (extrems), years		54 (21-79)
Median time elapsed between HCT and assessment (extrems), years		9 (1, 39)
Sex Female		61 (48%)
Male		65 (52%)
Haematological disease	Acute myeloid leukaemia	55 (43.5%)
	Acute lymphoblastic leukaemia	23 (18%)
	Myelodysplastic syndrome	5 (4%)
	Lymphoproliferative disorder	20 (16%)
	Myeloproliferative disorder	16 (13%)
	Non-malignant disease	7 (5.5%)
Disease status at transplant*	Complete remission or chronic phase	115 (91%)
	Other	11 (9%)
Donor	Matched related	75 (59.5%)
	Matched unrelated	36 (28.5%)
	Mismatched	9 (7%)
	Cord Blood Unit	6 (5%)
Age of the donor at transplant, years		37 (7-71)
Stem cell source	Bone marrow	57 (45%)
	Peripheral blood stem cells	63 (50%)

	Cord blood unit	6 (5%)
Conditioning	Myeloablative	68 (54%)
	Reduced-intensity or nonmyeloablative	58 (46%)
GvHD at any time between HCT and assessment		79 (63%)
GvHD treated at time of assessment		16 (13%)
Relapse of the underlying disease between HCT and assessment		17 (14%)
Rituximab administered between HCT and assessment		9 (7%)

*The seven patients with non-malignant diseases were pooled with patients in complete remission

Table 2: Univariate analysis of the factors associated with measles seropositivity after allogeneic HCT

	Seropositive patients (n=78)	Seronegative patients (n=48)	p	OR [CI95%] ^a	p
Sex, female	37 (61%)	24 (39%)	0.78		
Age at transplant (median, range)	47.5 (15-68)	39 (13-65)	0.03	2.40 [1.15-5.01] ^b	0.02
Age at the time of assessment (median, range)	59 (21-79)	51 (23-78)	0.02	2.12 [1.02-4.41] ^c	0.04
Age of the donor at transplant (median, range)	38 (7-66)	34 (10-71)	0.22		
Haematological disease			0.12		
Acute leukaemia or myelodysplastic syndrome	47 (57%)	36 (43%)		1	
Lymphoproliferative disorder	13 (65%)	7 (35%)		1.42 [0.51-3.93]	0.50
Myeloproliferative disorder	14 (87.5%)	2 (12.5%)		5.36 [1.14-25.11]	0.03
Non-malignant disease	4 (57%)	3 (43%)		1.02 [0.21-4.85]	0.98
Complete remission or chronic phase at transplant ^d	70 (61%)	8 (73%)	0.53		
Match related donor	50 (67%)	25 (33%)	0.18	1.64 [0.79-3.41]	0.18
Stem cell source			0.3		
Bone marrow	32 (56%)	25 (44%)			
Peripheral stem cell	43 (68%)	20 (32%)			
Cord blood unit	3 (50%)	3 (50%)			
Reduced intensity or nonmyeloablative conditioning	41 (71%)	17 (29%)	0.06	2.02 [0.96-4.23]	0.06
Absence of GvHD at any time between HCT and assessment	35 (74%)	12 (26%)	0.03	2.44 [1.11-5.39]	0.03
Absence of previous acute GvHD grade ≥ 2	54 (71%)	22 (29%)	0.009	2.66 [1.26-5.60]	0.01

Absence of previous extensive chronic GvHD	64 (67%)	32 (33%)	0.05	2.29 [0.99-5.26]	0.05
Relapse of the underlying disease between HCT and assessment	13 (76%)	4 (24%)	0.18	2.2 [0.67-7.19]	0.19
Rituximab administered between HCT and assessment	4 (44%)	5 (56%)	0.3		
Absolute lymphocyte count at time of assessment, ($\times 10^9/L$), median (range)	2450 (870-7100)	2450 (1500-5300)	0.64		
Serum gammaglobulin levels at time of assessment (g/L), median(range)	9.4 (4.2-17)	9.5 (4.8-20)	0.62		

^a Odd Ratio [Confidence Interval 95%]

^b cut-off of 43 years (median)

^c cut-off of 56 years (median)

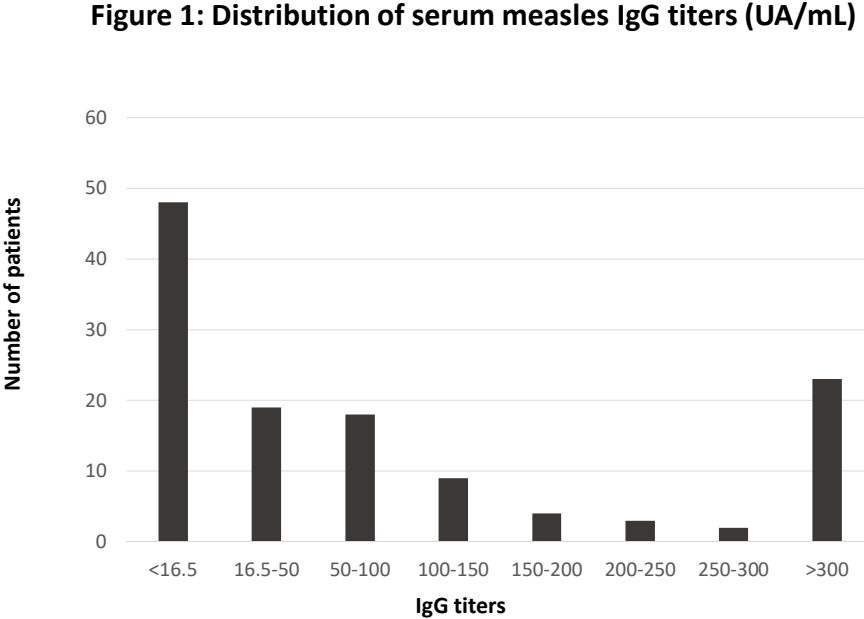
^d The 7 patients with non-malignant disease were pooled with complete remission patients

Table 3 : Multivariate analysis of the factors associated with measles seropositivity after allogeneic HCT

	OR	p
Haematological disease		
Acute leukaemia or myelodysplastic syndrome	1	
Lymphoproliferative disorder	1.28 [0.43-3.83]	0.66
Myeloproliferative disorder	5.56 [1.13-27.27]	0.04
Non-malignant disease	1.00 [0.18-5.67]	1.00
Reduced-intensity or nonmyeloablative conditioning	2.92 [1.28-6.66]	0.01
Absence of previous acute GvHD grade ≥ 2	2.79 [1.25-6.27]	0.01
Absence of previous extensive chronic GvHD	2.03 [0.81-5.11]	0.13

Legend of figure 1

Distribution of serum measles immunoglobulin G titers (UA/mL)



Legend of figure 2 : Measles antibody titers according to the time elapsed between HCT and assessment (Box plot showing IQ25 and IQ75, median (line), mean (cross), different values (points) and standard deviation (error bar)).

