Revaccination with pneumococcal conjugate vaccine five years after primary immunization improves immunity in patients with chronic lymphocytic leukemia

Magdalena Kättström,[1] Bertil Uggla,[1] Camilla Virta,[2] Merit Melin,[2] Nina Ekström,[2] Anders Magnuson,[3] Per-Ola Andersson,[4] Ylva Hammarlund,[5] Sandra Lockmer,[6] Ingmar Nilsson,[7] Daniel Roth,[8] Magnus Svensson,[9] Tobias Tolf,[10] Eva Kimby,[6] Torbjörn Norén[11] and Simon Athlin[12]

[1]Section of Hematology, Department of Medicine, Faculty of Medicine and Health, Örebro University, Örebro, Sweden; [2]Department of Public Health, Finnish Institute for Health and Welfare, Helsinki, Finland; [3]Clinical Epidemiology and Biostatistics, School of Medical Sciences, Faculty of Medicine and Health, Örebro University, Örebro, Sweden; [4]Section of Hematology and Coagulation, Department of Specialist Medicine, Sahlgrenska University Hospital, Göteborg, Sweden; [5]Department of Medicine, Falun Hospital, Falun, Sweden; [6]Division of Hematology, Department of Medicine Huddinge, Karolinska Institute, Stockholm, Sweden; [7]Department of Medicine, Karlstad Hospital, Karlstad, Sweden; [8]Institution of Clinical Sciences, Faculty of Medicine, Lund University Hospital, Lund, Sweden; [9]Department of Medicine, Eskilstuna Hospital, Eskilstuna, Sweden; [10]Department of Medical Sciences, Section of Hematology, Uppsala University, Uppsala, Sweden; [11]Department of Laboratory Medicine, Clinical Microbiology, Faculty of Medicine and Health, Örebro University, Örebro, Sweden and [12]School of Medical Sciences, Faculty of Medicine and Health, Örebro University, Örebro, Sweden

Correspondence: M. Kättström
Magdalena.Kattstrom@regionorebrolan.se

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Supplemental Data

Supplemental Methods

1. Inclusion Criteria for Revaccination: CLL patients and Controls

CLL Patients:

CLL patients who were previously enrolled in the Pneumococcal Vaccination Study 0887x1-20003 (EudraCT No: 2009-012642-22) and had received either PCV13 or PPSV23 were eligible for evaluation of long-term immune response. Eligibility for revaccination was determined based on the absence of exclusion criteria. Notably, ongoing or recent CLL-specific treatments were not considered exclusion criteria.

If a patient had received an additional pneumococcal vaccine outside the study protocol after the initial vaccination, the vaccine type and administration date were recorded in the Case Report Form (CRF). If this additional vaccination had been given within the last 12 months, the patient could only participate in the long-term immune response evaluation (Visit 1). However, if more than 12 months had passed since the additional vaccine was administered, the patient became eligible for revaccination.

Control Group:

A control group of immunocompetent individuals that received either PCV13 or PPSV23 approximately 3–5 years earlier was recruited in Region Örebro County through vaccine registries, public notices, and social media. Participants in the control group were eligible for long-term immune response evaluation and revaccination, provided they did not meet any exclusion criteria outlined in the study protocol.

2. Exclusion criteria for revaccination in CLL patients and controls

CLL patients

1. Patients receiving high dose corticosteroids (≥20 mg Prednisolone) or other immunosuppressive drugs that is not part of active CLL treatment (criteria for inclusion after discontinuing high dose corticosteroid treatment, see section 7.3).
2. Patients who have had an allergic reaction to any vaccination in the past.
3. Patients with a positive DAT (Direct Antiglobulin Test) or known present or previous haemolysis, ITP and Guillain-Barre.
4. Patients failing to give informed consent.
5. Patients with ongoing immunoglobulin therapy.
6. Patients with known HIV infection.
7. Patients who have received a pneumococcal vaccine outside the study protocol within the last 12 months.
8. Active febrile infection.
9. Increased bleeding risk due to severe thrombocytopenia or other coagulopathies that would, in the opinion of the investigator, contraindicate intramuscular injection (for treatment with oral anticoagulation therapy, see section 7.3).

Controls

1. Serious chronic disorder including chronic obstructive pulmonary disease (COPD) requiring supplemental oxygen treatment, end-stage renal disease, clinically unstable cardiac disease, or any other disorder that, in the investigator's opinion, excludes the subject from participating in the study.
2. Known or suspected immunodeficiency or other conditions associated with immunosuppression including immunoglobulin class/subclass deficiencies with or without substitution treatment, splenectomy in the medical history, generalized malignancy, human immunodeficiency virus (HIV) infection, haematological malignancies, bone marrow or organ transplant in the medical history.
3. Subjects receiving treatment with high dose corticosteroids (≥20 mg Prednisolone) or other immunosuppressive drugs or planned to receive through study participation.
4. Subjects who have had an allergic reaction to any component of PCV13 in the past.
5. Subjects with known present or previous haemolysis, ITP and Guillain-Barre.
6. Subjects failing to give informed consent.
7. Subjects who have received a pneumococcal vaccine after the primary vaccination approximately 3-5 years ago.
8. Active febrile infection.
9. Increased bleeding risk due to severe thrombocytopenia or other coagulopathies that would, in the opinion of the investigator, contraindicate intramuscular injection (for treatment with oral anticoagulation therapy, see section 7.3).

3 Criteria for temporary delay of vaccine administration

A subject may be included in the study once the condition(s) has/have resolved and no other exclusion criteria are met:

1. Febrile illness (oral temperature ≥100.4°F [38°C]) or other acute illness. Fever and symptoms must have resolved > 48 hours before vaccination.

2. Antibiotic therapy should not have been administered within 72 hours before vaccination

3. Receipt of any inactivated vaccine within 14 days and any live vaccine within 28 days before test vaccination.

4. For patients/controls that are treated with NOAK (Non-vitamin K Oral Anticoagulant) the injection should be given as close as possible to the next dose. After the vaccination, at least two hours should pass before the intake of the next dose. For patients/controls treated with VKA (vitamin K antagonists) with or without one antiplatelet drug, PK should be < 3,0 (measured within 7 days prior to vaccination). For patients/controls treated with VKA in combination with two antiplatelet drugs, PK should be measured the same day and should be ≤1,8. It is recommended to put pressure on the injection site for 10 minutes after vaccination in this patient/control group and to examine the injection site after the patient/control is leaving the clinic.

5. If systemic high dose corticosteroids (≥20 mg Prednisolone) have been administered short term (<14 days) for treatment of an acute illness, subjects should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before investigational product administration. If systemic high dose corticosteroids have been administered for more than two weeks, a wash-out period of at least 8 weeks is needed before vaccination.

Additional details about the study's design and implementation:

- All tests were performed and analyzed at the local hospital and the results were evaluated according to local reference levels.

- The study was monitored by the Clinical Trials Unit in Region Örebro County.
- The serological assay was performed and validated by the Finnish Institute for Health and Welfare (THL), Helsinki, Finland and accredited by the Finnish Accreditation Service according to accreditation requirement SFS-EN ISO/IEC 17025.
- Pneumococcal vaccines used in the study: PCV13 (Pfizer, Prevenar13®), pneumococcal polysaccharides conjugated to CRM197 carrier protein, and the vaccine includes serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. PPSV23 (MSD, Pneumovax®) is not conjugated but includes the same serotypes as PCV13, except 6A, and additionally 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F and 33F. The vaccines were administered by intramuscular injection according to standard recommendations.
- At each study visit, a case report form (CRF) was used, and study participants were monitored with blood samples and nasopharyngeal swabs. Adverse events (AE) and serious adverse events (SAE) were reported until 8 weeks after last revaccination.
- Patients who had received additional pneumococcal vaccinations outside the study protocols were excluded from the analysis.

Supplemental Table 1. Comparison of serotype specific IgG geometric mean concentrations (GMC; µg/ml) and geometric mean ratios (GMR) with 95% confidence intervals (95% CI) between and within group A and B of CLL patients before revaccination, 8 weeks after revaccination 1, 8 weeks after revaccination 2 and 12 months after revaccination 1 with mixed model analysis. GMC Geometric mean concentration; GMR Geometric mean ratio; CI Confidence interval; Group A: CLL patients PCV13+PCV13+PPSV13; Group B: CLL patients PPSV23+PCV13+PCV13.

Between groups

	Before revaccination				8 weeks after revaccination 1				8 weeks after revaccination 2				12 months after revaccination 1			
	Group A (n=36)	Group B (n=38)	Group A vs. B		Group A (n=29)	Group B (n=34)	Group A vs. B		Group A (n=27)	Group B (n=33)	Group A vs. B		Group A (n=25)	Group B (n=32)	Group A vs. B	
Serotype	GMC	GMC	GMR (95% CI)	P	GMC	GMC	GMR (95% CI)	P	GMC	GMC	GMR (95% CI)	P	GMC	GMC	GMR (95% CI)	P
1	0.14	0.07	1.9 (0.7-5.0)	0.17	0.60	0.22	3.2 (1.2-8.3)	**0.021**	0.79	0.37	2.3 (0.9-6.1)	0.094	0.41	0.24	2.0 (0.7-5.3)	0.17
3	0.08	0.07	1.1 (0.5-2.2)	0.79	0.20	0.14	1.4 (0.7-2.8)	0.37	0.22	0.25	0.8 (0.4-1.7)	0.66	0.14	0.14	1.0 (0.5-2.0)	0.97
4	0.09	0.03	2.9 (0.9-8.3)	0.050	0.56	0.13	5.3 (1.8-15.7)	**0.003**	0.69	0.22	3.0 (1.0-9.1)	**0.047**	0.41	0.14	2.6 (0.9-7.9)	0.090
5	0.10	0.07	1.4 (0.5-3.5)	0.51	0.40	0.21	2.2 (0.8-5.6)	0.11	0.42	0.22	1.9 (0.7-4.9)	0.20	0.21	0.16	1.5 (0.6-4.0)	0.38
6B	0.11	0.11	1.0 (0.4-2.5)	0.95	0.42	0.21	2.1 (0.8-5.5)	0.13	0.41	0.34	1.1 (0.4-2.9)	0.83	0.22	0.24	1.0 (0.4-2.7)	0.99
7F	0.53	0.27	2.0 (0.8-4.9)	0.14	1.01	0.62	1.9 (0.8-4.9)	0.16	1.35	0.74	1.8 (0.7-4.5)	0.22	1.02	0.54	1.7 (0.7-4.3)	0.27
9V	0.19	0.13	1.4 (0.5-3.7)	0.47	0.64	0.38	1.6 (0.6-4.3)	0.32	0.88	0.51	1.5 (0.6-4.1)	0.39	0.45	0.33	1.4 (0.5-3.6)	0.54
14	0.92	0.62	1.5 (0.5-4.0)	0.43	1.57	0.77	1.8 (0.7-5.0)	0.23	1.78	0.89	1.6 (0.6-4.5)	0.33	1.18	0.76	1.5 (0.6-4.1)	0.41
18C	0.69	0.55	1.2 (0.5-2.9)	0.62	2.38	1.14	2.1 (0.9-5.0)	0.094	2.51	1.47	1.7 (0.7-4.2)	0.22	1.64	1.00	1.6 (0.7-3.9)	0.28
19A	0.60	0.54	1.1 (0.4-2.9)	0.84	1.52	0.85	1.3 (0.5-3.4)	0.59	1.38	1.24	0.8 (0.3-2.0)	0.59	1.02	0.77	0.8 (0.3-2.3)	0.75
19F	0.36	0.20	1.8 (0.7-4.7)	0.23	1.50	0.52	3.1 (1.2-8.4)	**0.023**	1.74	0.86	1.7 (0.6-4.7)	0.27	1.32	0.63	1.6 (0.6-4.3)	0.37
23F	0.36	0.17	2.1 (0.7-6.0)	0.17	1.53	0.40	3.8 (1.3-11.3)	**0.015**	1.43	0.67	2.2 (0.7-6.5)	0.16	0.82	0.40	2.0 (0.7-6.0)	0.20

Within groups

	Change 8 weeks after revaccination 1 vs. before revaccination						Change 8 weeks after revaccination 2 vs. before revaccination					
	Group A		Group B		Group A vs. B		Group A		Group B		Group A vs. B	
Serotype	GMR (95% CI)	P	GMR (95% CI)	P	GMR (95% CI)	P	GMR (95% CI)	P	GMR (95% CI)	P	GMR (95% CI)	P
1	4.6 (3.0-7.1)	**<0.001**	2.8 (1.9-4.2)	**<0.001**	1.6 (0.9-2.9)	0.10	5.8 (3.7-9.0)	**<0.001**	4.9 (3.2-7.3)	**<0.001**	1.2 (0.6-2.2)	0.57
3	2.7 (2.0-3.7)	**<0.001**	2.2 (1.6-2.9)	**<0.001**	1.2 (0.8-1.9)	0.31	2.9 (2.1-4.0)	**<0.001**	3.7 (2.7-5.0)	**<0.001**	0.8 (0.5-1.2)	0.30
4	7.2 (4.4-11.8)	**<0.001**	3.9 (2.5-6.2)	**<0.001**	1.8 (0.9-3.6)	0.079	7.7 (4.6-12.9)	**<0.001**	7.3 (4.6-11.7)	**<0.001**	1.0 (0.5-2.1)	0.87
5	4.3 (3.0-6.2)	**<0.001**	2.7 (2.0-3.8)	**<0.001**	1.6 (0.9-2.6)	0.063	4.3 (3.0-6.2)	**<0.001**	3.1 (2.2-4.4)	**<0.001**	1.4 (0.8-2.3)	0.21
6B	4.0 (2.7-5.9)	**<0.001**	1.8 (1.3-2.7)	**<0.001**	2.2 (1.3-3.6)	**0.004**	3.8 (2.6-5.7)	**<0.001**	3.4 (2.3-4.8)	**<0.001**	1.1 (0.7-2.0)	0.62
7F	2.2 (1.6-3.0)	**<0.001**	2.2 (1.7-3.0)	**<0.001**	1.0 (0.6-1.5)	0.95	2.5 (1.8-3.5)	**<0.001**	2.8 (2.1-3.8)	**<0.001**	0.9 (0.6-1.4)	0.95
9V	3.6 (2.5-5.3)	**<0.001**	3.2 (2.3-4.4)	**<0.001**	1.1 (0.7-1.9)	0.57	4.4 (3.0-6.3)	**<0.001**	4.0 (2.9-5.7)	**<0.001**	1.1 (0.6-1.8)	0.77
14	1.7 (1.4-2.2)	**<0.001**	1.4 (1.1-1.7)	**0.002**	1.2 (0.9-1.7)	0.20	1.9 (1.5-2.5)	**<0.001**	1.8 (1.4-2.2)	**<0.001**	1.1 (0.8-1.5)	0.53
18C	3.6 (2.6-5.0)	**<0.001**	2.1 (1.6-2.9)	**<0.001**	1.7 (1.1-2.7)	**0.020**	3.9 (2.8-5.4)	**<0.001**	2.8 (2.0-3.8)	**<0.001**	1.4 (0.9-2.2)	0.15
19A	2.3 (1.7-3.2)	**<0.001**	2.0 (1.5-2.6)	**<0.001**	1.2 (0.8-1.8)	0.43	2.1 (1.6-2.9)	**<0.001**	3.1 (2.3-4.1)	**<0.001**	0.7 (0.4-1.1)	0.089
19F	4.1 (2.7-6.1)	**<0.001**	2.3 (1.6-3.4)	**<0.001**	1.7 (1.0-3.0)	**0.043**	4.1 (2.7-6.2)	**<0.001**	4.2 (2.9-6.1)	**<0.001**	1.0 (0.6-1.7)	0.92
23F	4.3 (2.8-6.6)	**<0.001**	2.4 (1.6-3.5)	**<0.001**	1.8 (1.0-3.2)	**0.037**	4.0 (2.6-6.1)	**<0.001**	3.8 (2.6-5.6)	**<0.001**	1.0 (0.6-1.9)	0.87

	Change 8 weeks after revaccination 2 vs. 8 weeks after revaccination 1						Change 12 months after revaccination 1 vs. before revaccination					
	Group A		Group B		Group A vs. B		Group A		Group B		Group A vs. B	
Serotype	GMR (95% CI)	P	GMR (95% CI)	P	GMR (95% CI)	P	GMR (95% CI)	P	GMR (95% CI)	P	GMR (95% CI)	P
1	1.2 (0.8-2.0)	0.32	1.7 (1.1-2.6)	**0.009**	0.7 (0.4-1.3)	0.30	3.3 (2.1-5.3)	**<0.001**	3.2 (2.1-4.9)	**<0.001**	1.0 (0.5-1.9)	0.93
3	1.1 (0.8-1.5)	0.73	1.7 (1.3-2.3)	**<0.001**	0.6 (0.4-0.9)	**0.037**	1.8 (1.3-2.5)	**<0.001**	2.0 (1.5-2.7)	**<0.001**	0.9 (0.6-1.4)	0.64
4	1.1 (0.6-1.8)	0.78	1.9 (1.2-3.0)	**<0.001**	0.6 (0.3-1.2)	0.12	4.3 (2.6-7.3)	**<0.001**	4.8 (3.0-7.7)	**<0.001**	0.9 (0.4-1.8)	0.78
5	1.0 (0.7-1.4)	0.99	1.2 (0.8-1.6)	0.41	0.9 (0.5-1.4)	0.57	2.5 (1.7-3.7)	**<0.001**	2.2 (1.6-3.1)	**<0.001**	1.1 (0.7-1.9)	0.64
6B	1.0 (0.6-1.4)	0.85	1.8 (1.2-2.6)	**0.001**	0.5 (0.3-0.9)	**0.022**	2.4 (1.6-3.6)	**<0.001**	2.3 (1.6-3.4)	**<0.001**	1.0 (0.6-1.8)	0.90
7F	1.1 (0.8-1.6)	0.39	1.3 (0.9-1.7)	0.11	0.9 (0.6-1.4)	0.67	1.8 (1.3-2.5)	**<0.001**	2.1 (1.6-2.8)	**<0.001**	0.8 (0.5-1.3)	0.49
9V	1.2 (0.8-1.7)	0.36	1.3 (0.9-1.8)	0.16	0.9 (0.6-1.6)	0.79	2.5 (1.7-3.7)	**<0.001**	2.6 (1.9-3.7)	**<0.001**	0.9 (0.6-1.6)	0.85
14	1.1 (0.9-1.4)	0.33	1.3 (1.0-1.6)	**0.043**	0.9 (0.6-1.2)	0.52	1.5 (1.2-1.9)	**0.001**	1.5 (1.2-1.8)	**<0.001**	1.0 (0.7-1.4)	0.90
18C	1.1 (0.8-1.5)	0.71	1.3 (0.9-1.8)	0.094	0.8 (0.5-1.3)	0.40	2.6 (1.8-3.6)	**<0.001**	1.9 (1.4-2.7)	**<0.001**	1.3 (0.8-2.1)	0.24
19A	0.9 (0.7-1.2)	0.58	1.6 (1.2-2.1)	**0.002**	0.6 (0.4-0.9)	**0.014**	1.6 (1.2-2.2)	**0.004**	2.1 (1.5-2.8)	**<0.001**	0.8 (0.5-1.2)	0.24
19F	1.0 (0.7-1.5)	0.98	1.8 (1.2-2.6)	**0.002**	0.6 (0.3-0.9)	**0.038**	2.7 (1.8-4.1)	**<0.001**	3.0 (2.1-4.4)	**<0.001**	0.9 (0.5-1.5)	0.65
23F	0.9 (0.6-1.4)	0.73	1.6 (1.1-2.4)	**0.016**	0.6 (0.3-1.0)	0.061	2.5 (1.6-3.8)	**<0.001**	2.6 (1.7-3.8)	**<0.001**	1.0 (0.5-1.7)	0.91

	Change 12 months after revaccination 1 vs. 8 weeks after revaccination 2					
	Group A		Group B		Group A vs. B	
Serotype	GMR (95% CI)	P	GMR (95% CI)	P	GMR (95% CI)	P
1	0.6 (0.4-0.9)	**0.021**	0.7 (0.4-1.0)	0.054	0.9 (0.5-1.6)	0.65
3	0.6 (0.4-0.9)	**0.008**	0.5 (0.4-0.7)	**<0.001**	1.1 (0.7-1.8)	0.54
4	0.6 (0.3-0.9)	**0.035**	0.7 (0.4-1.1)	0.081	0.9 (0.4-1.8)	0.67
5	0.6 (0.4-0.9)	**0.006**	0.7 (0.5-1.0)	0.052	0.8 (0.5-1.4)	0.45
6B	0.6 (0.4-0.9)	**0.028**	0.7 (0.5-1.0)	0.052	0.9 (0.5-1.6)	0.72
7F	0.7 (0.5-0.9)	**0.042**	0.7 (0.6-0.9)	**0.046**	1.0 (0.6-1.5)	0.84
9V	0.6 (0.4-0.9)	**0.006**	0.7 (0.5-0.9)	**0.016**	0.9 (0.5-1.5)	0.64
14	0.8 (0.6-0.9)	**0.042**	0.8 (0.7-1.0)	0.12	0.9 (0.6-1.3)	0.63
18C	0.7 (0.5-0.9)	**0.022**	0.7 (0.5-0.9)	**0.026**	0.9 (0.6-1.5)	0.82
19A	0.7 (0.5-1.0)	0.081	0.7 (0.5-0.9)	**0.007**	1.1 (0.7-1.7)	0.62
19F	0.6 (0.4-0.9)	**0.048**	0.7 (0.5-1.1)	0.089	0.9 (0.5-1.6)	0.73
23F	0.6 (0.4-0.9)	**0.034**	0.7 (0.5-0.9)	**0.046**	0.9 (0.5-1.7)	0.79

Supplemental Table 2. Comparison of IgG antibody concentrations (GMC;µg/ml) between and within CLL patients (group A and B) and controls (group C and D) before revaccination, 8 weeks after revaccination and 12 months after revaccination with mixed model analysis. GMC Geometric mean concentration; GMR Geometric mean ratio; CI Confidence interval. [a] Adjusted for pre-treatment (PCV13 or PPSV23). In CLL patient group had 36 of 74 (48.6%) and in control group 9 of 31 (29.0%) PCV13 as pre-treatment.

Between groups

	Before revaccination				8 weeks after revaccination				12 months after revaccination			
	CLL patients (n=74)	Controls (n=31)	Patients vs. Controls		CLL patients (n=63)	Controls (n=31)	Patients vs. Controls		CLL patients (n=57)	Controls (n=31)	Patients vs. Controls	
Serotype	GMC	GMC	Adjusted GMR [a] (95% CI)	P	GMC	GMC	Adjusted GMR [a] (95% CI)	P	GMC	GMC	Adjusted GMR [a] (95% CI)	P
1	0.10	0.51	0.2 (0.1-0.4)	**<0.001**	0.35	2.81	0.1 (0.04-0.2)	**<0.001**	0.30	1.24	0.2 (0.1-0.5)	**<0.001**
3	0.07	0.14	0.5 (0.3-0.9)	**0.021**	0.17	0.46	0.4 (0.2-0.7)	**0.001**	0.14	0.21	0.6 (0.3-1.2)	0.19
4	0.05	0.23	0.2 (0.1-0.5)	**0.001**	0.26	2.26	0.1 (0.04-0.2)	**<0.001**	0.22	1.00	0.2 (0.1-0.5)	**0.001**
5	0.08	0.27	0.3 (0.1-0.7)	**0.005**	0.28	1.57	0.2 (0.1-0.4)	**<0.001**	0.18	0.67	0.3 (0.1-0.6)	**0.003**
6B	0.11	0.55	0.2 (0.1-0.5)	**<0.001**	0.29	2.95	0.1 (0.03-0.2)	**<0.001**	0.23	1.57	0.2 (0.1-0.4)	**<0.001**
7F	0.37	0.52	0.6 (0.3-1.3)	0.21	0.78	2.66	0.3 (0.1-0.6)	**<0.001**	0.72	1.46	0.4 (0.2-0.9)	**0.038**
9V	0.16	0.27	0.5 (0.2-1.2)	0.12	0.48	1.64	0.3 (0.1-0.6)	**0.002**	0.38	0.78	0.4 (0.2-1.0)	0.062
14	0.75	1.45	0.5 (0.2-1.1)	0.10	1.07	4.80	0.2 (0.1-0.5)	**<0.001**	0.92	3.16	0.3 (0.1-0.8)	**0.011**
18C	0.61	2.75	0.2 (0.1-0.5)	**<0.001**	1.60	9.52	0.2 (0.1-0.3)	**<0.001**	1.24	5.05	0.2 (0.1-0.5)	**<0.001**
19A	0.57	1.58	0.3 (0.1-0.8)	**0.010**	1.11	6.41	0.2 (0.1-0.4)	**<0.001**	0.87	3.21	0.3 (0.1-0.7)	**0.007**
19F	0.27	1.19	0.2 (0.1-0.5)	**<0.001**	0.84	4.59	0.1 (0.06-0.3)	**<0.001**	0.87	2.34	0.3 (0.1-0.7)	**0.004**
23F	0.24	0.52	0.4 (0.2-1.0)	0.063	0.74	2.97	0.2 (0.1-0.5)	**<0.001**	0.55	1.47	0.4 (0.1-0.9)	**0.030**

Within groups

	Change 8 weeks after revaccination vs. baseline						Change 12 months after revaccination vs. baseline					
	CLL patients		Controls		CLL patients vs. Controls		CLL patients		Controls		CLL patients vs. Controls	
Serotype	Adjusted GMR [a] (95% CI)	P	Adjusted GMR [a] (95% CI)	P	Adjusted GMR [a] (95% CI)	P	Adjusted GMR [a] (95% CI)	P	Adjusted GMR [a] (95% CI)	P	Adjusted GMR [a] (95% CI)	P
1	2.8 (1.9-4.0)	**<0.001**	4.7 (3.0-7.3)	**<0.001**	0.6 (0.3-0.9)	**0.047**	3.2 (2.2-4.6)	**<0.001**	2.3 (1.5-3.7)	**<0.001**	1.4 (0.8-2.3)	0.71
3	2.3 (1.7-2.9)	**<0.001**	3.1 (2.2-4.2)	**<0.001**	0.7 (0.5-1.1)	0.10	2.0 (1.5-2.6)	**<0.001**	1.5 (1.1-2.0)	**0.014**	1.4 (0.9-2.0)	0.10
4	3.3 (2.2-5.1)	**<0.001**	7.3 (4.4-12.1)	**<0.001**	0.4 (0.2-0.8)	**0.009**	3.9 (2.5-6.0)	**<0.001**	3.8 (2.3-6.4)	**<0.001**	1.0 (0.6-1.8)	0.97
5	2.7 (1.9-3.9)	**<0.001**	5.1 (3.3-7.7)	**<0.001**	0.5 (0.3-0.9)	**0.012**	2.3 (1.6-3.2)	**<0.001**	2.4 (1.6-3.7)	**<0.001**	0.9 (0.6-1.5)	0.79
6B	1.8 (1.3-2.5)	**<0.001**	4.2 (2.8-6.3)	**<0.001**	0.4 (0.3-0.7)	**<0.001**	2.1 (1.5-3.0)	**<0.001**	2.6 (1.8-4.0)	**<0.001**	0.8 (0.5-1.3)	0.36
7F	2.1 (1.5-2.8)	**<0.001**	4.9 (3.4-7.0)	**<0.001**	0.4 (0.3-0.7)	**<0.001**	2.1 (1.5-2.9)	**<0.001**	2.9 (2.0-4.2)	**<0.001**	0.7 (0.5-1.1)	0.14
9V	2.9 (2.1-4.0)	**<0.001**	5.5 (3.7-8.1)	**<0.001**	0.5 (0.3-0.8)	**0.005**	2.4 (1.7-3.4)	**<0.001**	2.8 (1.9-4.2)	**<0.001**	0.9 (0.5-1.4)	0.54
14	1.3 (0.9-1.6)	0.076	2.9 (2.1-4.0)	**<0.001**	0.4 (0.3-0.6)	**<0.001**	1.4 (1.1-1.9)	**0.008**	2.1 (1.6-2.9)	**<0.001**	0.7 (0.5-0.9)	**0.031**
18C	2.2 (1.6-3.0)	**<0.001**	3.0 (2.1-4.4)	**<0.001**	0.7 (0.5-1.1)	0.16	2.0 (1.5-2.8)	**<0.001**	1.7 (1.2-2.5)	**0.004**	1.2 (0.7-1.8)	0.48
19A	2.0 (1.5-2.6)	**<0.001**	3.9 (2.8-5.4)	**<0.001**	0.5 (0.3-0.8)	**<0.001**	2.0 (1.5-2.6)	**<0.001**	2.1 (1.5-2.9)	**<0.001**	0.9 (0.6-1.4)	0.73
19F	2.4 (1.8-3.4)	**<0.001**	3.4 (2.3-4.9)	**<0.001**	0.7 (0.5-1.1)	0.16	2.9 (2.1-4.1)	**<0.001**	2.0 (1.3-2.9)	**<0.001**	1.5 (0.9-2.3)	0.10
23F	2.1 (1.5-3.0)	**<0.001**	4.5 (2.9-6.8)	**<0.001**	0.5 (0.3-0.8)	**0.003**	2.2 (1.6-3.2)	**<0.001**	2.6 (1.7-4.0)	**<0.001**	0.8 (0.5-1.4)	0.55

	Change 12 months vs. 8 weeks after revaccination					
	CLL patients		Controls		CLL patients vs. Controls	
Serotype	Adjusted GMR [a] (95% CI)	P	Adjusted GMR [a] (95% CI)	P	Adjusted GMR [a] (95% CI)	P
1	1.1 (0.8-1.7)	0.51	0.5 (0.3-0.8)	**0.002**	2.3 (1.3-3.9)	**0.002**
3	0.9 (0.7-1.2)	0.36	0.5 (0.3-0.7)	**<0.001**	1.8 (1.3-2.7)	**0.001**
4	1.2 (0.7-1.8)	0.49	0.5 (0.3-0.9)	**0.013**	2.2 (1.2-4.0)	**0.009**
5	0.8 (0.6-1.2)	0.31	0.5 (0.3-0.7)	**<0.001**	1.7 (1.1-2.8)	**0.027**
6B	1.2 (0.8-1.7)	0.36	0.6 (0.4-0.9)	**0.030**	1.9 (1.1-3.0)	**0.012**
7F	1.0 (0.7-1.4)	0.98	0.6 (0.4-0.9)	**0.006**	1.7 (1.1-2.6)	**0.019**
9V	0.8 (0.6-1.2)	0.33	0.5 (0.3-0.8)	**<0.001**	1.6 (1.0-2.6)	**0.032**
14	1.1 (0.9-1.5)	0.36	0.7 (0.5-0.9)	**0.042**	1.6 (1.1-2.2)	**0.017**
18C	0.9 (0.7-1.3)	0.62	0.6 (0.4-0.8)	**0.004**	1.6 (1.0-2.5)	**0.035**
19A	1.0 (0.7-1.3)	0.94	0.5 (0.4-0.8)	**<0.001**	1.8 (1.2-2.6)	**0.002**
19F	1.2 (0.9-1.7)	0.26	0.6 (0.4-0.9)	**0.009**	2.0 (1.3-3.2)	**0.002**
23F	1.1 (0.7-1.5)	0.75	0.6 (0.4-0.9)	**0.015**	1.8 (1.1-3.0)	**0.022**

Supplemental Table 3. Comparison of serological protection (SP) and serological response (SR) between and within group C and D of controls before revaccination, 8 weeks after revaccination and 12 months after revaccination with mixed model analysis. RR Relative risk ratio; CI Confidence interval; NA Not applicable; Group C: Controls PCV13 / PCV13; Group D: Controls PPSV23 / PCV13. [a] SP Serological protection defined as ≥0.35 ug/ml in at least nine (70 %) of the 12 serotypes. [b] SP Serological protection defined as ≥1.3 ug/ml in at least nine (70 %) of the 12 serotypes. [c] SR Serological response defined as 2-fold increase above IgG levels ≥ 0.35 ug/ml in at least nine (70%) of the 12 serotypes compared to baseline. [d] Fisher exact test when mixed model analysis did not converge due to sparse data [efg] Exact McNemar test when mixed model analysis did not converge due to sparse data e0 of 22 vs. 10 of 22, f 2 of 9 vs. 3 of 9, g 0 of 22 vs. 2 of 22

Between groups

	Before revaccination				8 weeks after revaccination				12 months after revaccination			
	Group C (n=9)	Group D (n=22)	Group C vs. D		Group C (n=9)	Group D (n=22)	Group C vs. D		Group C (n=9)	Group D (n=22)	Group C vs. D	
	n (%)	n (%)	RR (95% CI)	P	n (%)	n (%)	RR (95% CI)	P	n (%)	n (%)	RR (95% CI)	P
SP ≥ 0.35 ug/ml [a]	4 (44.4)	6 (27.3)	1.6 (0.6-4.5)	0.35	9 (100.0)	16 (72.7)	1.4 (1.1-1.8)	**0.016**	8 (88.9)	14 (63.6)	1.4 (0.9-2.1)	0.10
SP ≥ 1.3 ug/ml [b]	2 (22.2)	0 (0.0)	NA	0.077 [d]	8 (88.9)	10 (45.4)	2.0 (1.2-3.3)	**0.012**	3 (33.3)	2 (9.1)	3.7 (0.7-18.9)	0.12
SR 2 fold increase [c]	NA	NA	NA	NA	5 (55.6)	8 (36.4)	1.5 (0.7-3.5)	0.31	4 (44.4)	2 (9.1)	4.9 (1.0-22.7)	**0.043**

Within groups

	Change 8 weeks after revaccination vs. before revaccination						Change 12 months after revaccination vs. before revaccination					
	Group C		Group D		Group C vs. D		Group C		Group D		Group C vs. D	
	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P
SP ≥ 0.35 ug/ml [a]	2.2 (1.1-4.7)	**0.032**	2.7 (1.4-5.1)	**0.003**	0.8 (0.3-2.3)	0.73	2.0 (0.9-4.0)	0.054	2.3 (1.2-4.6)	**0.016**	0.9 (0.3-2.3)	0.76
SP ≥ 1.3 ug/ml [b]	4.0 (1.2-13.5)	**0.026**	NA	**0.002**[e]	NA	NA	NA	0.99[f]	NA	0.50[g]	NA	NA
SR 2 fold increase [c]	NA		NA		NA	NA	NA	NA	NA	NA	NA	NA

	Change 12 months vs. 8 weeks after revaccination					
	Group C		Group D		Group C vs. D	
	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P
SP ≥ 0.35 ug/ml [a]	0.9 (0.7-1.1)	0.33	0.9 (0.7-1.1)	0.16	1.0 (0.7-1.4)	0.92
SP ≥ 1.3 ug/ml [b]	0.4 (0.1-0.9)	**0.034**	0.2 (0.1-0.7)	**0.012**	1.9 (0.4-8.9)	0.43
SR 2 fold increase [c]	0.8 (0.5-1.2)	0.33	0.2 (0.1-0.8)	**0.026**	3.2 (0.9-11.7)	0.079

Supplemental Table 4. Comparison of serotype specific IgG antibody concentrations (GMC; µg/ml) between and within group C and D of controls before revaccination, 8 weeks after revaccination and 12 months after revaccination with mixed model analysis. GMC Geometric mean concentration; Geometric mean ratio; CI Confidence interval; Group C: Controls PCV13 / PCV13; Group D: Controls PPSV23 / PCV13

Between groups

	Before revaccination				8 weeks after revaccination				12 months after revaccination			
	Group C (n=9)	Group D (n=22)	Group C vs. D		Group C (n=9)	Group D (n=22)	Group C vs. D		Group C (n=9)	Group D (n=22)	Group C vs. D	
Serotype	GMC	GMC	GMR (95% CI)	P	GMC	GMC	GMR (95% CI)	P	GMC	GMC	GMR (95% CI)	P
1	0.47	0.53	0.9 (0.2-3.0)	0.84	4.01	2.43	1.6 (0.5-5.7)	0.43	1.35	1.20	1.1 (0.3-3.9)	0.85
3	0.31	0.10	3.0 (1.1-8.3)	**0.034**	0.92	0.34	2.7 (0.9-7.3)	0.058	0.40	0.16	2.6 (0.9-7.1)	0.068
4	0.12	0.30	0.4 (0.1-2.0)	0.27	4.28	1.74	2.5 (0.5-12.3)	0.27	1.40	0.87	1.6 (0.3-8.0)	0.56
5	0.36	0.24	1.5 (0.3-7.6)	0.60	3.02	1.20	2.5 (0.5-12.5)	0.26	0.92	0.59	1.6 (0.3-7.7)	0.59
6B	1.52	0.36	4.1 (0.9-18.7)	0.065	16.14	1.47	11.0 (2.4-49.6)	**0.002**	6.59	0.87	7.5 (1.7-34.1)	**0.009**
7F	1.04	0.40	2.6 (0.9-7.1)	0.060	7.53	1.73	4.3 (1.6-11.8)	**0.004**	2.65	1.14	2.3 (0.8-6.3)	0.10
9V	0.98	0.16	6.2 (1.7-23.3)	**0.006**	11.15	0.75	14.9 (4.0-55.7)	**<0.001**	4.08	0.40	10.2 (2.7-38.2)	**<0.001**
14	1.99	1.28	1.6 (0.4-6.0)	0.52	12.89	3.21	4.0 (1.0-15.6)	**0.045**	5.11	2.60	2.0 (0.5-7.6)	0.33
18C	2.78	2.74	1.0 (0.3-3.1)	0.98	11.41	8.83	1.3 (0.4-3.9)	0.65	4.89	5.12	0.9 (0.3-2.9)	0.93
19A	2.11	1.40	1.5 (0.5-4.4)	0.46	8.46	5.72	1.5 (0.5-4.4)	0.48	4.16	2.89	1.4 (0.5-4.2)	0.51
19F	1.75	1.02	1.7 (0.5-5.6)	0.37	8.30	3.60	2.3 (0.7-7.5)	0.17	3.53	1.98	1.8 (0.5-5.8)	0.34
23F	0.51	0.52	1.0 (0.2-3.9)	0.96	8.04	1.97	4.1 (1.0-16.5)	**0.049**	2.70	1.15	2.4 (0.6-9.5)	0.23

Within groups

	Change 8 weeks after revaccination vs. before revaccination						Change 12 months after revaccination vs. before revaccination					
	Group C		Group D		Group C vs. D		Group C		Group D		Group C vs. D	
Serotype	GMR (95% CI)	P	GMR (95% CI)	P	GMR (95% CI)	P	GMR (95% CI)	P	GMR (95% CI)	P	GMR (95% CI)	P
1	8.6 (4.3-17.0)	**<0.001**	4.6 (2.9-7.1)	**<0.001**	1.9 (0.8-4.2)	0.13	2.9 (1.4-5.7)	**0.002**	2.2 (1.4-3.5)	**<0.001**	1.3 (0.6-2.9)	0.55
3	2.9 (1.7-5.0)	**<0.001**	3.3 (2.3-4.7)	**<0.001**	0.9 (0.5-1.7)	0.71	1.3 (0.7-2.2)	0.36	1.5 (1.1-2.1)	**0.020**	0.8 (0.4-1.6)	0.63
4	35.0 (17.5-69.8)	**<0.001**	5.7 (3.6-8.8)	**<0.001**	6.2 (2.7-14.0)	**<0.001**	11.4 (5.7-22.8)	**<0.001**	2.8 (1.8-4.4)	**<0.001**	4.0 (1.8-9.1)	**<0.001**
5	8.3 (3.7-18.3)	**<0.001**	5.0 (3.0-8.4)	**<0.001**	1.6 (0.6-4.2)	0.30	2.5 (1.1-5.6)	**0.023**	2.5 (1.5-4.1)	**<0.001**	1.0 (0.4-2.6)	0.98
6B	10.6 (5.5-20.5)	**<0.001**	4.0 (2.6-6.1)	**<0.001**	2.6 (1.2-5.8)	**0.014**	4.3 (2.2-8.4)	**<0.001**	2.4 (1.6-3.6)	**<0.001**	1.8 (0.8-4.0)	0.13
7F	7.2 (3.6-14.7)	**<0.001**	4.4 (2.8-6.9)	**<0.001**	1.7 (0.7-3.9)	0.24	2.6 (1.2-5.2)	**0.010**	2.9 (1.8-4.5)	**<0.001**	0.9 (0.4-2.1)	0.78
9V	11.3 (5.9-21.8)	**<0.001**	4.7 (3.1-7.2)	**<0.001**	2.4 (1.1-5.2)	**0.029**	4.1 (2.1-8.0)	**<0.001**	2.5 (1.7-3.9)	**<0.001**	1.6 (0.7-3.6)	0.22
14	6.5 (3.4-12.3)	**<0.001**	2.5 (1.7-3.8)	**<0.001**	2.6 (1.2-5.5)	**0.014**	2.6 (1.3-4.9)	**0.004**	2.0 (1.3-3.1)	**<0.001**	1.3 (0.6-2.7)	0.54
18C	4.1 (2.1-8.0)	**<0.001**	3.2 (2.1-4.9)	**<0.001**	1.3 (0.6-2.8)	0.55	1.8 (0.9-3.4)	0.096	1.9 (1.2-2.9)	**0.004**	0.9 (0.4-2.1)	0.88
19A	4.0 (2.3-6.9)	**<0.001**	4.1 (2.9-5.8)	**<0.001**	1.0 (0.5-1.9)	0.96	2.0 (1.1-3.4)	**0.014**	2.1 (1.4-2.9)	**<0.001**	1.0 (0.5-1.8)	0.90
19F	4.7 (2.8-7.9)	**<0.001**	3.5 (2.6-4.9)	**<0.001**	1.3 (0.7-2.4)	0.34	2.0 (1.2-3.3)	**0.007**	1.9 (1.4-2.7)	**<0.001**	1.0 (0.6-1.9)	0.91
23F	15.8 (8.6-28.9)	**<0.001**	3.8 (2.5-5.5)	**<0.001**	4.2 (2.0-8.6)	**<0.001**	5.3 (2.9-9.7)	**<0.001**	2.2 (1.5-3.2)	**<0.001**	2.4 (1.2-5.0)	**0.015**

	Change 12 months after revaccination vs. 8 weeks after revaccination					
	Group C		Group D		Group C vs. D	
Serotype	GMR (95% CI)	P	GMR (95% CI)	P	GMR (95% CI)	P
1	0.3 (0.2-0.7)	**0.002**	0.5 (0.3-0.8)	**0.002**	0.7 (0.3-1.5)	0.36
3	0.4 (0.2-0.8)	**0.003**	0.5 (0.3-0.6)	**<0.001**	1.0 (0.5-1.8)	0.91
4	0.3 (0.2-0.7)	**0.002**	0.5 (0.3-0.8)	**0.002**	0.6 (0.3-1.5)	0.31
5	0.3 (0.1-0.7)	**0.003**	0.5 (0.3-0.8)	**0.006**	0.6 (0.2-1.6)	0.31
6B	0.4 (0.2-0.8)	**0.007**	0.6 (0.4-0.9)	**0.014**	0.7 (0.3-1.5)	0.35
7F	0.4 (0.2-0.7)	**0.004**	0.7 (0.4-1.0)	0.073	0.5 (0.2-1.2)	0.14
9V	0.4 (0.2-0.7)	**0.003**	0.5 (0.3-0.8)	**0.003**	0.7 (0.3-1.5)	0.34
14	0.4 (0.2-0.8)	**0.004**	0.8 (0.5-1.2)	0.31	0.5 (0.2-1.0)	0.065
18C	0.4 (0.2-0.8)	**0.012**	0.6 (0.4-0.9)	**0.012**	0.7 (0.3-1.6)	0.45
19A	0.5 (0.3-0.8)	**0.010**	0.5 (0.4-0.7)	**<0.001**	1.0 (0.5-1.9)	0.94
19F	0.4 (0.3-0.7)	**<0.001**	0.5 (0.4-0.8)	**<0.001**	0.8 (0.4-1.4)	0.41
23F	0.3 (0.2-0.6)	**<0.001**	0.6 (0.4-0.9)	**0.006**	0.6 (0.3-1.2)	0.13

Supplemental Table 5. Comparison of serotype specific IgG antibody concentrations (GMC; µg/ml) between patients with and without hypogammaglobulinemia (HG) among KLL patients (group A and B) with mixed model analysis.

[a] Adjusted for group (A or B); HG hypogammaglobulinemia; GMC Geometric mean concentration; GMR Geometric mean ratio; CI Confidence interval.

	Before revaccination				8 weeks after revaccination 1				8 weeks after revaccination 2				12 months after revaccination 1			
	HG (n=18)	no HG (n=55)	HG vs. no HG		HG (n=16)	no HG (n=47)	HG vs. no HG		HG (n=15)	no HG (n=45)	HG vs. no HG		HG (n=13)	no HG (n=44)	HG vs. no HG	
Serotype	GMC	GMC	GMR[a] (95% CI)	P[a]	GMC	GMC	GMR[a] (95% CI)	P[a]	GMC	GMC	GMR[a] (95% CI)	P[a]	GMC	GMC	GMR[a] (95% CI)	P[a]
1	0.05	0.13	0.4 (0.1-1.0)	0.051	0.08	0.58	0.1 (0.04-0.3)	**<0.001**	0.08	0.96	0.1 (0.04-0.3)	**<0.001**	0.06	0.48	0.1 (0.04-0.4)	**<0.001**
3	0.06	0.08	0.7 (0.3-1.6)	0.45	0.10	0.20	0.4 (0.2-0.9)	**0.037**	0.08	0.34	0.3 (0.1-0.6)	**<0.001**	0.08	0.17	0.4 (0.2-0.9)	**0.024**
4	0.02	0.08	0.2 (0.1-0.5)	**0.002**	0.05	0.46	0.1 (0.03-0.3)	**<0.001**	0.05	0.69	0.1 (0.02-0.2)	**<0.001**	0.04	0.37	0.1 (0.03-0.3)	**<0.001**
5	0.08	0.09	0.9 (0.3-2.5)	0.80	0.15	0.35	0.3 (0.1-0.9)	**0.030**	0.12	0.39	0.2 (0.1-0.7)	**0.009**	0.07	0.24	0.3 (0.1-0.9)	**0.036**
6B	0.08	0.13	0.6 (0.2-1.7)	0.32	0.08	0.46	0.2 (0.1-0.5)	**0.002**	0.08	0.62	0.1 (0.05-0.4)	**<0.001**	0.05	0.38	0.2 (0.1-0.5)	**0.002**
7F	0.11	0.54	0.2 (0.1-0.5)	**0.001**	0.22	1.20	0.1 (0.05-0.4)	**<0.001**	0.29	1.45	0.1 (0.05-0.3)	**<0.001**	0.23	1.01	0.1 (0.05-0.4)	**<0.001**
9V	0.06	0.22	0.3 (0.1-0.7)	**0.012**	0.11	0.81	0.1 (0.05-0.4)	**<0.001**	0.09	1.24	0.1 (0.03-0.3)	**<0.001**	0.07	0.61	0.1 (0.04-0.4)	**<0.001**
14	0.51	0.86	0.6 (0.2-1.8)	0.34	0.59	1.31	0.4 (0.1-1.1)	0.083	0.51	1.63	0.3 (0.1-0.9)	**0.044**	0.37	1.21	0.3 (0.1-1.0)	0.053
18C	0.31	0.77	0.4 (0.1-1.0)	0.058	0.55	2.30	0.2 (0.1-0.6)	**0.002**	0.58	2.76	0.2 (0.1-0.5)	**0.001**	0.38	1.76	0.2 (0.1-0.6)	**0.002**
19A	0.29	0.68	0.4 (0.1-1.2)	0.11	0.44	1.53	0.3 (0.1-0.8)	**0.021**	0.36	2.00	0.2 (0.1-0.6)	**0.005**	0.30	1.19	0.2 (0.1-0.8)	**0.013**
19F	0.11	0.38	0.3 (0.1-0.8)	**0.013**	0.22	1.34	0.2 (0.1-0.5)	**<0.001**	0.23	2.03	0.1 (0.04-0.3)	**<0.001**	0.20	1.34	0.1 (0.04-0.4)	**<0.001**
23F	0.13	0.29	0.4 (0.1-1.4)	0.15	0.16	1.27	0.1 (0.03-0.4)	**<0.001**	0.16	1.71	0.1 (0.03-0.3)	**<0.001**	0.11	0.88	0.1 (0.04-0.5)	**0.002**