Innholdsfortegnelse:

Innledning:

Temaet i hovedoppgaveprosjektet er revaksinering av barn som har gjennomgått cellegiftbehandling gjennom kvalitetssikring av retningslinjene som finnes for revaksinering av barn og ungdom som er ferdigbehandlet for kreft på St.Olavs Hospital og evaluering av hvordan immunglobuliner og rubella-antistoff blir påvirket av kreftbehandling hos disse pasientene. Veileder for prosjektet har vært Bendik Lund, barneonkolog og avdelingsleder ved Barnekreftavdelingen på St.Olavs Hospital. Svein Arne Nordbø, førsteamanuensis ved Mikrobiologen på St.Olavs Hospital, har vært samarbeidspartner.

Prosjektet skulle være gjennomførbart i løpet av IIIA-semesteret, januar 2017 til juni 2017, men diverse søknader ble påbegynt i forkant av terminen. NTNU sitt mål for hovedoppgaven er å videreutvikle studentens vitenskapelig og problemorienterte tenkemåte som vil fremme studentens evne til livslang læring. For å illustrere hvordan prosjektet har gitt meg en smakebit på hvor omfattende forskning kan være og hva som kreves for å velge en vitenskapelig retning presenteres arbeidet jeg har gjort for hovedoppgaveprosjektet punktvis i innledningen:

- Skrevet og fått godkjent søknad til REK og FOU/Barne- og Ungdomsklinikken på St.Olavs Hospital. Dette innebar å lage aldersavhengige infoskriv og samtykkeskjema samt spørreskjema til deltakerne i studien (eksempler vedlagt) som ble sendt ut til alle deltakere.
- Lagd søknad for uthenting av data fra SYSVAK, Folkehelseinstituttet.
- Opprettet et sikkert filområde hos HEMIT for lagring av pasientsensitiv informasjon og gjennomgått pasientjournaler i DocuLive for innhenting av data til studien.
- Tegne avtale med to ulike laboratorier (AMK og AMM) på St.Olavs Hospital for oppstart av blodprøvetaking av inkluderte pasienter i studien.
- Inkludere og informere bioingeniører, sykepleiere, sekretær og leger på Barnelaben/Barnekreftavdelingen om prosjektet for å optimalisere datainnhentings-prosessen. Jeg holdt et innlegg/presentasjon på 3 ulike kompetansedager for sykepleiere på Barnekreftavdelingen om prosjektet og om hvordan prosedyren for blodprøvetaking skulle foregå. Hospitert på Barn4 for å forstå hverdagen til barnekreftpasienter og barneonkologer.
- Skrevet abstrakt og manuskript i vitenskapelig artikkel-form (vedlagt)
- Lagd poster(vedlagt) som ble godkjent og presentert på konferansen; «NOPHO 35th Annual meeting 2017, 19 - 23 May, Stockholm, Sweden». NOPHO står for Nordic Society of Paediatric Haematology and Oncology og prosjektet var ett av 104 abstrakt som ble akseptert og presentert av Bendik Lund på konferansen.
- Lagd et utkast til informasjonsskriv og revaksineringsskjema(vedlagt) som skal implementeres i oppfølgingsrutinene av barn som er ferdigbehandlet for kreft på Barnekreftavdelingen, St.Olavs Hospital.

Abstract:

Background: Chemotherapy treatment for childhood cancer impair the cellular and humoral immune system in various degrees and affects the previous protection of childhood vaccination. Studies have shown protective antibody levels after revaccination of children treated with chemotherapy and this has led to different national revaccination guidelines, including Norwegian guidelines. In a study by Crawford et al [1] on Australian childhood cancer survivors, compliance to revaccination guidelines was poor. It was uncertain to what degree revaccination recommendations have been implemented at the Children's Department of St.Olavs University Hospital as well as compliance to these recommendations. We therefore investigated implementation of these guidelines at the Childrens Cancer Unit, St. Olavs Hospital.

It is difficult to investigate whether revaccination of childhood cancer survivors protects against the actual diseases because of a limited patient population combined with rare diseases, thus an indirectly measure of the effect of revaccination is quantification of vaccine-specific antibodies titres and immunoglobulin concentrations. Results from studies varies in antibody titres and immunoglobulin concentrations and we wanted to get an impression of the role of different chemotherapy regimens, single drugs or the role of time on revaccination. Hoping to raise new questions about humoral reconstitution post-chemotherapy and the actual need for revaccination we did a pilot study measuring rubella-specific antibody titres and immunoglobulins before and after chemotherapy treatment in childhood cancer survivors.

Methods: Children aged 0-18 years at time of diagnosis who finished chemotherapy treatment for cancer between 01.01.2010 to 31.12.2016 at St.Olavs University Hospital, Trondheim, Norway were included. Excluded were patients who had relapsed or died, or patients who had moved to another geographical region. In 2010 a guideline for revaccination after chemotherapy for children (RvG) was proposed for Norwegian paediatric oncologists (Flægstad and Knudsen) and has partly been used at the childhood cancer unit at St.Olavs University Hospital. The compliance of the RVG was evaluated through three sources: i) review of patient files, ii) through a questionnaire sent to the families, and iii) from data obtained through the national vaccine-register of Norway (SYSVAK). Recommendations given from the responsible clinician should have included an individually based revaccination schedule of DTP-IPV-Hib, MMR and pneumococcal vaccine, and been given within one year after cessation of therapy to be classified as appropriate. Revaccination had to include a first dose of DTP-IPV-Hib and pneumococcal vaccine(s) given within a year after cessation of chemotherapy and MMR given within a year after the recommended time in the RvG or a restart of the childhood vaccination program for patients <15 months at time of diagnosis to be adequate. Rubella antibody titres were analysed both from frozen samples taken at start of treatment and after finishing treatment. Immunoglobulin-levels were analysed after finishing treatment.

Results: 70 patients with a median age at diagnosis of 8,0 years were included. Of these, 34 were girls (48,6%), 26 patients had leukaemia (37,1%) and 44 patients had solid tumours, including CNS-tumours (62,9%). Review of patient journals showed that 67,1% (47/70) had gotten an acceptable revaccination recommendation of DTP-IPV-Hib and MMR, but only 25,7%(18/70) received a complete recommendation when including the requirement of pneumococcal vaccine. Of the questionnaires sent to the participants 81,3%(26/32) said that they had received a recommendation at our centre on revaccination after cessation of therapy. Current revaccination guidelines had partly been followed for the majority of patients. However, barely 1/5 of childhood cancer survivors had completed an adequate revaccination schedule. Participants given recommendations on revaccinations were more likely to receive booster vaccination post-chemotherapy. Because of the short time-span of this study, only 12 patients were included for biological studies. For eight of these patients serum was available from start of therapy. Of the four patients who had not received a boost of rubella vaccine, all had a decrease in rubella antibody titre during treatment, of which two had fallen from protective to un-protective antibody levels. 11 patients had normal IgG-, IgA- and IgM-concentration at various time after cessation of therapy, while one patient had low IgM-concentrations.

Conclusion: We have shown that there has been insufficient compliance with current guidelines for revaccination at our centre. Quality assurance of compliance with current guidelines for revaccination of childhood cancer survivors is important. A vaccination chart following the patient as a communication-tool towards the community nurse responsible for revaccination, might be a solution. A system for revaccination confirmation in the hospital file should be established. Chemotherapy seems to reduce protective antibody titre levels towards diseases included in the national vaccination program, but larger studies are needed to confirm this and to evaluate which drugs or drug regimens that has highest impact on antibody titre levels.

MANUSKRIPT:

Humoral immunity and revaccination in childhood cancer survivors

Mathias Tangenes (1), Svein Arne Nordbø (1,2), Bendik Lund (1,3)
1) Dept. of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology, Trondheim, Norway
2) Dept. of Medical Microbiology
3) Dept. of Pediatrics, St. Olav's University Hospital, Trondheim, Norway

Background:

Chemotherapy treatment for childhood cancer impair the cellular and humoral immune system in various degrees both during and after therapy, and might affect long-term protection of vaccines administered before the child started cancer chemotherapy. In the Western world, 5-year survival rates of childhood cancer have increased during the last four decades, and is now about 80% [1, 2]. Furthermore, for some subgroups of acute lymphoblastic leukaemia (ALL) survival is about 90% [3]. The increased prevalence of childhood cancer survivors requires better knowledge about how to reduce the therapy-induced long-term side effects and how we can avoid the long-term complications of standard chemotherapy, such as reduced immunity against vaccine-preventable diseases (VPDs).

Childhood cancer survivors have a temporarily immunosuppression after cessation of chemotherapy, with quantitative reduction of B-lymphocytes, T-lymphocytes, NK-cells and antibody responses [4, 5]. Studies differ in detail about immune reconstitution for children treated with chemotherapy, and some of the experience are from a time when treatment intensity was lower than today. The recovery rate of lymphocyte counts varies from 3-12 months, NK-cells in ALL patients normalizes within 6 months while the immune reconstitution of total B-cells take 1-6 months after cessation of chemotherapy [5-10]. In the reconstitution of CD4+ T-cells post-chemotherapy, earlier studies show that the recovery is age-dependent and differs between leukaemia and solid tumours [7, 11]. Recent studies claim that CD4+ T-cell counts are reduced for all types of cancer treated with chemotherapy and that the recovery is age-independent, that some subgroups of CD4+ T-cells recover within 3-6 months while other subgroups remained significantly reduced years after cessation of chemotherapy [5-7, 11, 12]. CD8+ T-cell counts are less affected by chemotherapy than CD4+ T-cells and they recover within 6 months' post-chemotherapy. Subgroups differ in recovery time and Ek et al. identified treatment intensity as a risk factor for reduced recovery rate. IgM and IgA are decreased after cessation of chemotherapy and return to normal within 6 months [6, 8, 12]. Some data conclude that IgG is not decreased at completion of chemotherapy [6, 12], but Van Tilburg, et al. showed that IgG, IgM and

IgA were reduced only during the first week post-treatment [5] and Perkins, J.L., A. Harris, and T.C. Pozos saw that 25% of the patients had low IgG levels 6 months after therapy [4]. Most of the research on immune reconstitution in childhood cancer survivors are based on children with leukemias, especially ALL, and focus on reduction of specific antibody levels and the need for revaccination after treatment for childhood cancer. There is a need for more studies that include both patients with leukemias and patients with solid tumors treated with today's treatment protocolls to clearify the details around immune reconstitution after childhood cancer.

Immune deficiency following chemotherapy might affect the previous protection of childhood vaccination [3] and studies have shown protective antibody levels after revaccination of children treated with chemotherapy [3, 13-18]. This has led to different national guidelines for revaccination of these patients [19, 20]. In 2010 a guideline for revaccination after chemotherapy for children (RvG) was proposed for Norwegian paediatric oncologists (Flægstad and Knudsen) and has partly been used at the childhood cancer unit at St.Olavs University Hospital, Trondheim, Norway. The guideline is based on a Swedish report on vaccination of childhood cancer by Ek and Nilsson [21], and on vaccination recommendations for stem cell transplant recipients by Ljungman, et al., [22]. and others [13, 23-26]. The RvG is shown in table 1(with permission from T. Flægstad), and compared to the Australian and Canadian guideline the recommendation for each vaccine with regard to number and timing of doses differs between the different levels of treatment intensity. Hence, the Norwegian guideline has a more individual approach than the Australian and Canadian guidelines. The RvG's recommendations are different in bone marrow transplant (BMT) patients (table 2).

Childhood vaccination prevents diseases that can cause serious morbidity and mortality. Surviving childhood cancer is a risk factor for infectious-related morbidity and mortality, most significantly for pneumonia [27], and immunisation for common infectious agents like pneumococci, haemophilus influenzae type b(Hib), influenza virus and varicella zoster virus(VZV) must therefore be highlighted. Increased "globalization" has led to people traveling and crossing country borders to a greater extent today, and childhood cancer survivors traveling to countries with high prevalence of VPDs might be at increased risk of rare infections, such as measles and rubella. Children that get their cancer diagnosis before finishing their childhood vaccination program are at risk of not completing their immunization program without adequate follow-up on vaccinations post-chemotherapy. In case of a relapse, the VZV vaccine may be particularly important for seronegative patients that will require new immunosuppressive chemotherapy because VZV-infections in immunosuppressive patients can cause serious complications like pneumonia, hepatitis, and death. In addition, varicella is a common occurring disease especially among small children, and the risk of being infected is high.

These examples, and the high survival rates of childhood cancer, illustrate the importance of sufficient revaccination of children treated with chemotherapy. In Norway, the primary health care nurse most

often administers the vaccines, but it is the paediatric oncology department that is responsible to recommend which booster vaccines to be given after cessation of chemotherapy. An incomplete recommendation could lead to reduced immunity against VPDs. At present, we identified only one study (Crawford, Heath et al. (2010)) in which compliance with current national guidelines on revaccination of children treated with chemotherapy [23] has been investigated.

In this study, we will investigate compliance with current guidelines for revaccination of childhood cancer survivors at our centre, both from the treating physicians' perspective and from the patients' perspective. A goal is also to identify patients that haven't received the recommended revaccinations. For these patients, a new recommendation will be given. In a small sample from the same patient cohort, we will also pilot whether it is feasible to measure vaccine-specific antibody titre-levels before and after treatment partly based on old frozen samples taken at start of therapy, and see if chemotherapy treatment affects antibody-titre levels. Specific rubella antibody titre is chosen because the analysis is easy accessible at our lab. Immunoglobulin-levels after therapy are also included in the evaluation of immune reconstitution.

TABLE 1: Revaccination schedule from the guideline for revaccination after chemotherapy for children (RvG) from 2010 by Flægstad and Knudsen.

Table 1

Month after finished treatment	DTP-IPV-Hib	VZV*	MMR	Pneumococcal vaccine†
ALL Standard/Intermediary risk, nonB-NHL stadium I-II	3	8+10	12	
AML,B-NHL	6	8+10	12	
ALL High risk, nonB-NHL stadium III-IV	6+8	10+12	24	
Solid tumours. Short/Low intensity treatment (ex. low risk-sarcoma, Hodgkin stadium I-II, Wilms' tumor low risk)	3	8+10	12	
Solid tumours. Long/High intensity treatment (ex. High risk-sarcoma, Hodgkin stadium III-IV, PNET)	6	10+12	24	

* VZV vaccination only given to VZV IgG-seronegative children.
† Can be given 3-6 months after finished treatment. To children between 12-23 months it's recommended with 2 doses of 7-valent conjugated pneumococcal vaccine(KPV-7) with at least 2 months interval between the doses. To children between 2-5 years there is only need of 1 dose of KPV-7 and thereafter 1 dose of 23-valent polysaccharide vaccine after an interval of at least 2 months. To children >5 years you only give the 23-valent polysaccharide vaccine.

TABLE 2: Recommendation from the RvG for revaccination of patients that have received bone marrow transplantation.

Table 2

Months after transplantation	12 months	14 months	24 months
DTP	X	X	X
Hib	X	X	X
IPV	X	X	X
Pneumococcal conjugated vaccine	X	-	-
MMR	-	-	X*

* MMR vaccine is only given to patients without chronic GVHD and without immunosuppressive treatment.

Ethics:

The study has been approved by the Regional Committee for Medical and Health Research Ethics in Norway (REK) (2016/1375) and by the research committee at the Department of Paediatrics, St. Olavs Hospital. Written informed consent were obtained from the included patients or his/her parents.

Methods:

70 children aged 0-18 at time of diagnosis who finished chemotherapy treatment for cancer between 01.01.2010 to 31.12.2016 at St.Olavs University Hospital were included. Excluded were patients who had relapsed or died, patients who had moved to another geographical region, and patients with active disease. Through review of patient files the participants were classified after diagnosis, treatment intensity and the different groups for revaccination highlighted in the RvG.

To evaluate compliance with revaccination guidelines, three levels were identified: i) recommendations documented in the patient hospital files, ii) the patients/parents perception or understanding of a recommendation, and iii) the documented actual vaccine status for each patient. A retrospective review of revaccination recommendations was obtained through review of patient files. To evaluate patient/parents perception of a recommendation, a questionnaire was sent to the patients and his/her parents. The recommendations from the hospital should have included an individually based revaccination schedule of diphtheria-tetanus-pertussis (DTP), inactivated poliomyelitis vaccine (IPV), Haemophilus influenza type b(Hib), measles-mumps-rubella (MMR) and pneumococcal vaccine (PKV), and recommendations should have been given within one year after cessation of

therapy to be classified as appropriate. The present actual vaccine status of each patient was identified through SYSVAK as of 29.03.2017. SYSVAK is the national, electronic immunisation registry that records an individual's vaccination status and vaccination coverage in Norway [28].

The revaccination had to fulfil some criteria: i) first dose of DTP-IPV-Hib and pneumococcal vaccine(s) given within a year after cessation of chemotherapy, ii) MMR given within a year after the recommended time in the RvG or iii) a restart of the childhood vaccination program for patients <15 months at time of diagnosis to be adequate, and iv) excluded patients who, in theory, still had time to complete their lacking revaccinations (Fig.1). We also categorised participants in 3 groups independently of the time limit we had chosen for an adequate revaccination; no vaccine-boosters post-chemotherapy, some of the boosters post-chemotherapy and a booster of each vaccine post-chemotherapy.

Among immunological parameters, serum titre of specific antibodies against rubella was measured within the period 01.02.2017 to 26.05.2017 and compared with serum levels of rubella antibodies from frozen serum taken at the time of the patient's cancer diagnosis. Serum concentrations of IgG, IgM and IgA were measured in the same period and concentrations were determined to be abnormal if they fell outside the age-specific reference value.

For detection of rubella antibodies, a chemiluminescent microparticle immunoassay with purified rubella virus was used as explained elsewhere [29, 30]. The analyse was done by Architect i2000, Abbott with ARCHITECT Rubella IgG Reagent Kit and ARCHITECT Rubella IgG Calibrators. The cut-off value was ≥10,0 IU/mL for protective antibody levels. Serum concentrations of IgG, IgA and IgM were measured by immunoturbidimetry (Siemens Advia Chemistry XPT). The age-specific reference values are based on a population of Canadian children [31] and converted to the in-house analytical method.

Data was analysed with IBM SPSS Statistics version 24. For comparing proportions Chi-square test were used. When data in columns were too small and violated the contingency table analysis assumptions, Fisher's exact test was used. A "p-value" of <0.05 was considered statistically significant.

FIGURE 1: Shows the process of including and excluding participants to the study and the final cohorts used.

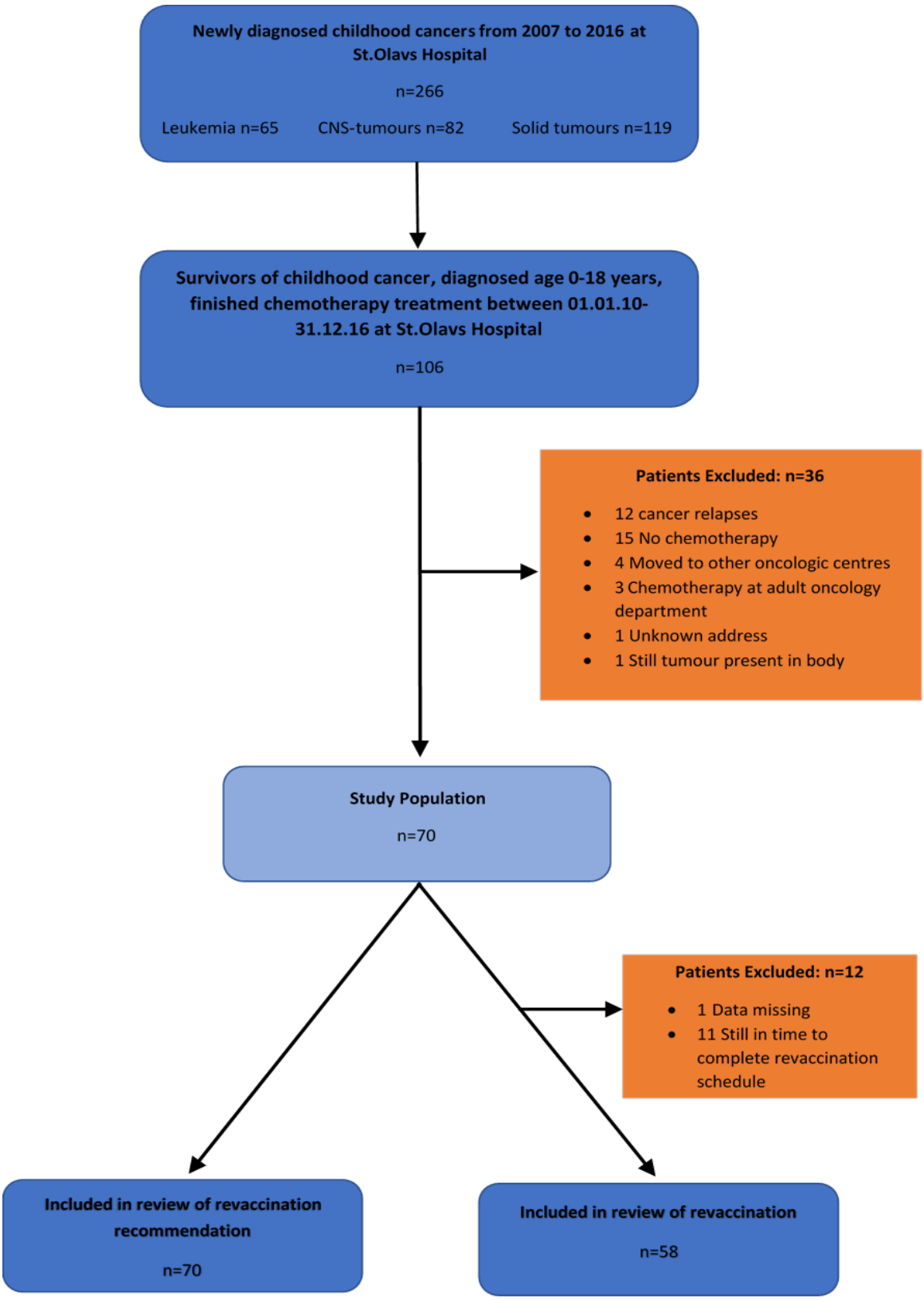


TABLE 3: An overview of patient's characteristics.

Table 3

Patient's characteristics	
Age at diagnosis, median years (range)	**8,0 (0-17)**
Sex (female/male)	34/36
Leukaemia, *n* (%)	26 (37,1)
- ALL, *n* (%)	22(31,4)
- AML, *n* (%)	4 (5,7)
Solid tumours including CNS- tumours, *n* (%)	44 (62,9)
- Hodgkin lymphoma, *n* (%)	12 (17,1)
- NHL, *n* (%)	3 (4,3)
- Burkitt's lymphoma, *n* (%)	1 (1,4)
- Hepatoblastoma, *n* (%)	4 (5,7)
- Wilms tumour, *n* (%)	5 (7,1)
- Neuroblastoma, *n* (%)	3 (4,3)
- Ewing sarcoma, *n* (%)	3 (4,3)
- Infantile fibrosarcoma, *n* (%)	1 (1,4)
- Rhabdomyosarcoma, *n* (%)	1 (1,4)
- Synovial sarcoma, *n* (%)	1 (1,4)
- Medulloblastoma, *n* (%)	2 (2,9)
- Retinoblastoma, *n* (%)	1 (1,4)
- Peripheral PNET, *n* (%)	1 (1,4)
- Germ cell tumour, *n* (%)	2 (2,9)
- Langerhans cell histiocytosis, *n* (%)	1 (1,4)
- Nasopharyngeal carcinoma, *n* (%)	1 (1,4)
- Epithelioid hemangioendothelioma, *n* (%)	1 (1,4)
- Pleuropulmonary blastoma, *n* (%)	1 (1,4)
Treatment intensity	
- Bone marrow transplantation, *n* (%)	2 (2,9)
- High, *n* (%)	25 (35,7)
- Low, *n* (%)	43 (61,4)

Results:

70 patients with a median age at diagnosis of 8,0 years were included (for details see table 3). Of these, 34 were girls (48,6%), 26 patients had leukaemia (37,1%) and 44 patients had solid tumours, including CNS-tumours (62,9%). Two patients had received BMT, while 43 had undergone low intensity chemotherapy treatment and 25 had received high intensity treatment. Seven patients had their childhood vaccination program interrupted by cancer diagnosis and were given a recommendation to restart the immunization program at the respective vaccination timings in the RvG. Included in the evaluation of vaccination were 58 patients that had SYSVAK-data and were not under revaccination after 29.03.17 (fig.1), both BMT-patients where in the exclusion group.

45,7% (32/70) of the questionnaires sent to the participants were sent back to us. Of these, 81,3%(26/32) answered that they had received a recommendation at our centre on revaccination after cessation of therapy. Review of patient journals showed that 67,1% (47/70) had gotten an acceptable revaccination recommendation of DTP-IPV-Hib and MMR, but only 25,7%(18/70) received a complete recommendation when including the requirement of pneumococcal vaccine (table 4).

19,0% (11/58) of the evaluated patients had completed an adequate revaccination schedule during the time limit chosen for this study and there was a slightly increase to 24,1% (14/58) who had received DTP-IPV-Hib, MMR and at least one of the pneumococcal booster vaccines independently of the time limit post-chemotherapy (table 4). Only 10,3 % (6/58) of childhood cancers didn't receive any vaccine boosters after cessation of therapy (table 4). Table 5 shows the frequencies of the given booster vaccines within and after the time limits. 25,8% (15/58) got at least one of the pneumococcal booster vaccines within the time limit. 20 of the 58 patients in the vaccination evaluation lacked recommendation on any booster vaccines at all, of these 70,0% (14/20) had still received a booster dose of DTP-IPV and 50% (10/20) had received a booster of MMR.

The patients who had received recommendations on DTP-IPV were more likely to have received DTP-IPV boosters after cessation of therapy (p=0,005). This association was also significant to recommendation of MMR and receival of MMR booster post-chemotherapy (p=0,002). If given an adequate recommendation participants were more likely to have completed an adequate revaccination schedule (p=0,017). From the responses in the questionnaires, there was no difference in having a vaccination plan or not in regard of receiving vaccination post-chemotherapy.

For results of the blood samples, see table 6. All 12 patients had normal concentrations of IgG and IgA. One patient had IgM-concentration below reference value and seven had IgM-concentrations in the lower end of the age-specific reference value. All participants who had received MMR-boost had protective levels of rubella antibody levels. Of the patients not revaccinated three had unprotective levels of rubella IgG, one has a concentration barely over 10 IU/ml (which was regarded as protective level) and one had a clear protective level of antibody titre. The two patients with an unprotective level of rubella antibody level pre-therapy had received MMR-vaccine before cancer diagnosis. Comparing the pre- and post-therapy concentrations in the three non-revaccinated patients showed a reduction of rubella-antibody titre post-chemotherapy.

‘

TABLE 4: Overview of recommendation given and boosters received.

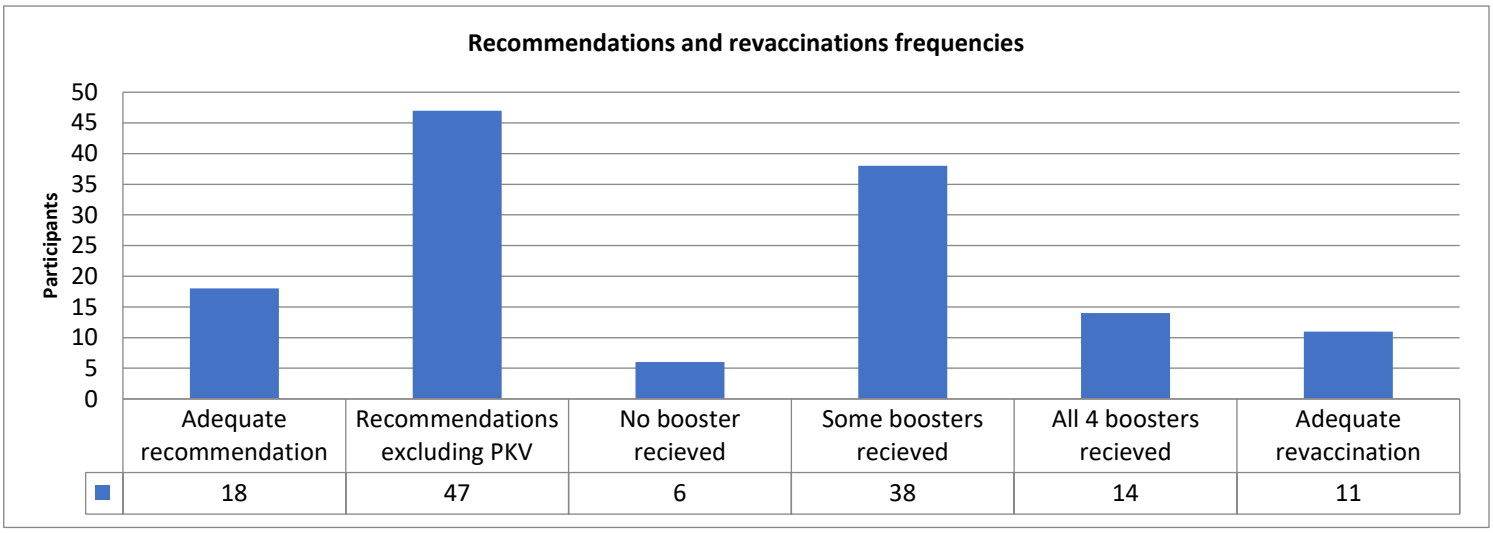


TABLE 5: Frequencies of vaccine boosters given within and after the time limits chosen in the study.

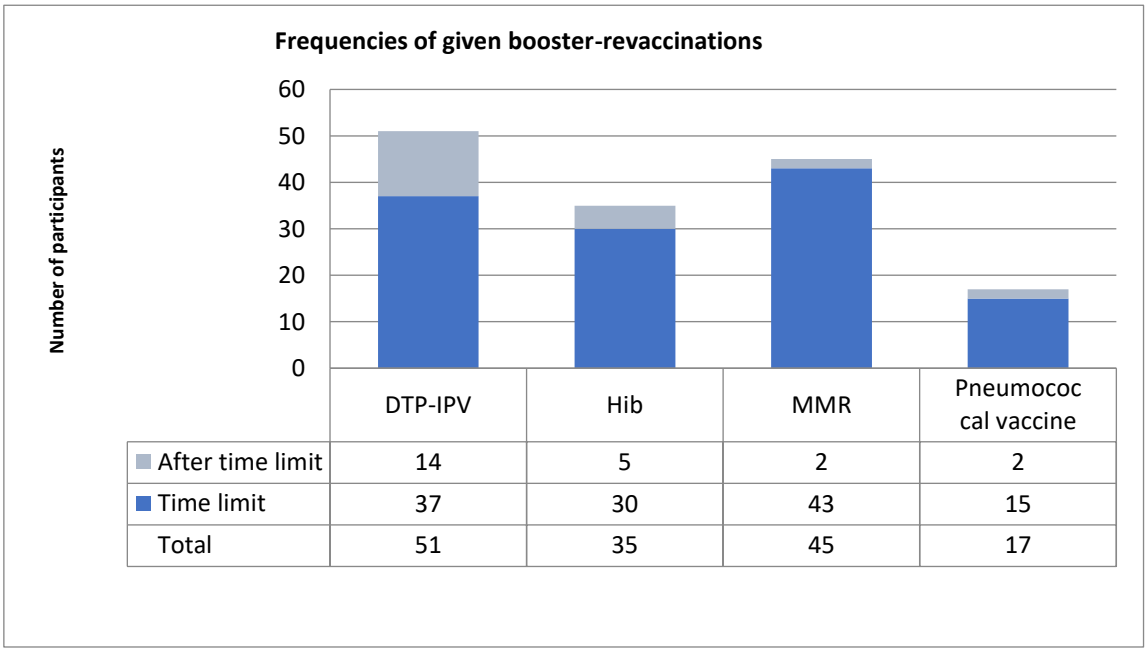


TABLE 6: Results of rubella antibody levels pre- and post-chemotherapy and the immunoglobulins concentrations post-chemotherapy.

ID	Rubella Before* (IU/ml)	Rubella After (IU/ml)	Disease	Treatment time (months)	Time from end of treatment to blood sample (months)	IgG (age specific reference value (g/L))	IgM (age specific reference value (g/L))	IgA (age specific reference value (g/L))
1	71,9	48,9	Hodgkin's lymphoma	3	6	7,1 (6,5-14,3)	1,0 (0,5-1,9)	0,7 (0,6-3,3)
2	No data	37,0	ALL (received boost)	30	52	11,3 (5,5-12,7)	0,6 (0,4-1,5)	0,8 (0,6-2,5)
3	25,8	50,4	NHL (recieved boost)	24	26	11,4 (6,5-14,3)	0,6 (0,5-1,9)	1,5 (0,6-3,3)
4	No data	10,2	Pleuropulmonal blastoma	8	17	9,5 (5,5-12,7)	0,5 (0,5-1,9)	1,7 (0,6-2,5)
5	No data	36,5	ALL	30	5	8,6 (5,5-12,7)	0,5 (0,5-1,9)	0,8 (0,6-2,5)
6	52,6	2,2	ALL	30	27	10,6 (6,9-15,7)	1,1 (0,6-2,3)	2,9 (1,1-3,7)
7	11,0	3,0	Synovial sarcoma	5	54	8,7 (6,5-14,3)	0,6 (0,4-1,5)	1,9 (1,1-3,7)
8	No data	53,6	Hepatoblastoma (received boost)	3	51	8,0 (5,5-12,7)	0,8 (0,4-1,5)	1,3 (0,6-2,5)
9	0,4	0,0	Hepatoblastoma	6	55	7,3 (5,5-12,7)	1,0 (0,5-1,9)	1,0 (0,6-2,5)
10	0,1	58,4	ALL (received boost)	30	14	10,3 (6,5-14,3)	0,7 (0,5-1,9)	0,8 (0,6-3,3)
11	82,5	59,9	ALL (received boost)	30	27	10,7 (5,5-12,7)	0,5 (0,4-1,5)	1,0 (0,6-2,5)
12	23.8	22,0	ALL (received boost)	30	34	10,0 (6,5-14,3)	0,4 (0,5-1,9)	1,0 (0,6-3,3)

* Reference values for rubella IgG concentrations: Negative: 0.0-4.9 IU / mL Grayzone (Equivocal): 5.0-9.9 IU / mL Positive: ≥10.0 IU / mL

Discussion:

Our study showed that for about two thirds of the patients some revaccination recommendations had been given, and about 90% of the patients had received a vaccine boost. Only 19,0% of childhood cancer survivors had completed an adequate revaccination schedule and participants given recommendations on revaccinations were more likely to receive booster vaccination post-chemotherapy.

In the study by Crawford, et al. [23] data on only 73% of the patients from the Australian Childhood Immunization Register (ACIR) were available, and vaccine information was also received from participants/parents in a telephone survey of documented immunisations and requesting their immunisation records form primary health care. Because of the risk of the participants/parents' recall bias and lack of ACIR-data for children >7 years old they stated that data in their study might be under-reported. In our study, we only received 45,7% of the questionnaires sent out to the 70 participants illustrating the difficulty of data collection through this method. In addition, 81,3% of the questionnaires stated that they had gotten a revaccination schedule post-chemotherapy, but this result was much higher than the results from reviewing patient journals. A reason implicating under-estimation of the patient journals-data could be that many recommendations were given without being recorded in the patient files and that the criteria for an adequate recommendation was too strict in our study. As stated in the Australian audit both the questionnaire and retrospective review of patient's journal are methods with many uncertainties. Other sources of error are that recommendations of pneumococcal vaccination in the RVG was not stated in a table such as for DTP-IPV-HIB and MMR making paediatric oncologist in a busy out-patient clinic forget to include it in a recommendation. For many families, there had gone several years since the recommendation was given and most of them probably lacked the knowledge of which vaccines to be included in a revaccination schedule, and therefore giving answers with uncertainties. In addition, due to the low number of questionnaires returned, one should be careful when interpreting these results. However, when excluding recommendation about pneumococcal vaccination the results from the questionnaires and patient journals were more similar. This may implicate that the reason for the low compliance to current guidelines could be in the quality of the recommendation given from the hospital and not because of patients/parents' lack of perception, especially when our results showed that it is more likely to receive an adequate revaccination status when given a complete recommendation.

The "loose" criteria for an accepted recommendation in our study, that it had to be given within a year after cessation of therapy, highlights the reduced compliance to current guidelines since all patients except BMTs should have had their first revaccination 3 or 6 months post-chemotherapy. The same can be said about the criteria of revaccination to be given within the first year, since most of the patients should have been given DTP-IPV-Hib and pneumococcal vaccines 3 or 6 months after

cessation of therapy. We excluded patients who still had time to receive a complete revaccination schedule and therefore only the patients who had past the time limit in this study could have gotten vaccines after SYSVAK-data was extracted. Because of this, the frequencies of vaccine boosters received without the time limit could be under-estimated, but it would not influence the results based on the time limit chosen for this study.

Compared to the Australian audit we based our revaccination status solely on SYSVAK-records, which had complete data on 69 of the 70 patients in the study. There is no data on the accuracy of SYSVAK's coverage, but from its start in 1995 it has been mandatory to register vaccines from the children immunization program and 65 of the participants are born in 1995 or later. The comprehensive vaccine database found in SYSVAK [32] makes it less likely to have under-reported vaccine status in our study and as well as in Australia there is a high vaccination coverage in the Norwegian population; in 2016 94% of 9 year olds born in 2007 were fully vaccinated for DTP and 96% for MMR [33]. Crawford et al. pointed out reduced compliance to national revaccination guidelines almost a decade ago and our results are much alike, raising an important question on how to improve revaccination of childhood cancer survivors. We also found that it was more likely to be revaccinated with a leukemic diagnosis than with a diagnosis of a solid tumour (p=0,006; data not shown). This was also found in the Australian audit, and a reason for our results might be the higher proportion of solid tumours in our study. The homogeneity of the leukemic group compared to the solid tumour group combined with more evidence-based data on revaccination of this group are factors that might influence the better results on revaccination of leukemic patients. In addition, 20 of the 58 patients in the vaccination evaluation lacked a recommendation on any booster vaccines at all, and of these 70,0% (14/20) had still received a booster dose of DTP-IPV and 50% (10/20) had received a booster of MMR, illustrating the impact of the Childhood Immunisation Program independently of any recommendation from the hospital. In the Childhood Immunisation Program in Norway every child receives a booster dose of DTP-IPV at 7 and 15 years of age and a booster of MMR at 11 years of age and this could also influence our results.

The results are based on guidelines from 2010 and since then it has been updated and it differs in details from the previous recommendations, particularly for pneumococcal vaccine and Hepatitis B recommendations [34]. To improve compliance of the revaccination process a revaccination chart given to each patient at end of treatment with a copy to the community nurse and family doctor might be a solution. Coordination with The Childhood Immunisation Program should also be taken into consideration on an individual basis. If the participant's vaccine status deviated from the RvG in this study they were given a written recommendation to complete their revaccination according to the present, updated guidelines used at our centre. Vaccination is voluntary and it is not to be avoided that some of the participants, or the parents, choose to not be revaccinated.

Within the short time span for this study, only 12 patients were included for biological studies of which only eight had stored serum from start of therapy. Of the four patients who had not received a boost of rubella vaccine, all had a decrease in rubella antibody titre during treatment, of which two had fallen from protective to un-protective antibody levels. This illustrates that chemotherapy possibly influences the protective levels of specific antibodies, but the role of different chemotherapy regimens, single drugs or the role of time remains unclear.

An important aspect to strengthen the study would be to include a control group of age-matched children measuring time from two different rubella antibody concentrations and the potentially reduction of specific antibody levels, especially when there has been a long time since the first and second measurement. A suggested design for a prospective study is to take the blood samples before diagnosis, at cessation of therapy, 1 year after end of treatment, 6 months after revaccination and at 5 years post-chemotherapy. Our sample size is too small to make any conclusions about the effect of diagnosis and treatment regimens on the level of rubella antibody titres and immunoglobulins, but the pilot raises interesting issues as if the changes in titre are related to treatment regimen, type of drugs, intensity, and treatment duration.

All the included participants had normal immunoglobulin concentrations at different times, ranging from 5 months to 55 months, post-chemotherapy. This observation supports the results shown by others. that immunoglobulin concentrations in childhood cancer survivors are not particularly affected by chemotherapy treatment or that the immunoglobulins recover during a short time-period post-chemotherapy [5, 6, 12]. However, another study has shown that around 25% had abnormal IgG concentrations 6 months post-chemotherapy and it is difficult to compare our results with this because of the various time of the blood samples taken in our study [4]. Most of the results are based on leukaemia-population while our data include both leukaemia and solid tumours.

A major issue with the Norwegian guidelines and other international guidelines is that they vary in detail and are based on limited evidence. As stated in most of the studies on vaccination of childhood cancer more data is needed to draw up evidence-based recommendations that differs between cancers, intensity of treatment and timing of revaccination. Even though Perkins, J.L., et al have shown that surviving childhood cancer treatment is a risk factor for infections and infection-related mortality their results was based on patients treated from 1970-1986 with less intensive chemotherapy protocols than today's and included patients treated without chemotherapy [27].

In conclusion, compliance to revaccination guidelines in childhood cancer survivors seems to be poor and effort should be done to implement such guidelines. Chemotherapy seems to influence protecting antibody levels of vaccine preventable diseases, but the underlying mechanisms of this seems unclear. Larger prospective studies on humoral immunity during chemotherapy in childhood cancer are needed.

ACKNOWLEDGEMENTS

We would like to thank the staff at the Children Oncology department, the staff at Women and Children Laboratory for collecting blood samples and to Marianne Vigstad, head of bioengineering research, and the rest of the staff at the Department of Medical Microbiology and the Department of Medical Biochemistry at St.Olavs Hospital for analysing the blood samples. This study would not be possible without the data received from SYSVAK, Folkehelseinstituttet.

References:

1. Hudson, M.M., M.P. Link, and J.V. Simone, *Milestones in the curability of pediatric cancers.* J Clin Oncol, 2014. **32**(23): p. 2391-7.
2. Pritchard-Jones, K., et al., *Sustaining innovation and improvement in the treatment of childhood cancer: lessons from high-income countries.* Lancet Oncol, 2013. **14**(3): p. e95-e103.
3. van Tilburg, C.M., et al., *Loss of antibodies and response to (re-)vaccination in children after treatment for acute lymphocytic leukemia: a systematic review.* Leukemia, 2006. **20**(10): p. 1717-22.
4. Perkins, J.L., A. Harris, and T.C. Pozos, *Immune Dysfunction After Completion of Childhood Leukemia Therapy.* Journal of pediatric hematology/oncology, 2016.
5. Van Tilburg, C.M., et al., *Immune reconstitution in children following chemotherapy for haematological malignancies: A long-term follow-up.* British Journal of Haematology, 2011. **152**(2): p. 201-210.
6. Ek, T., et al., *Immune reconstitution after childhood acute lymphoblastic leukemia is most severely affected in the high risk group.* Pediatr Blood Cancer, 2005. **44**(5): p. 461-8.
7. Alanko, S., T.T. Salmi, and T.T. Pelliniemi, *Recovery of blood T-cell subsets after chemotherapy for childhood acute lymphoblastic leukemia.* Pediatr Hematol Oncol, 1994. **11**(3): p. 281-92.
8. Alanko, S., T.T. Pelliniemi, and T.T. Salmi, *Recovery of blood B-lymphocytes and serum immunoglobulins after chemotherapy for childhood acute lymphoblastic leukemia.* Cancer, 1992. **69**(6): p. 1481-6.
9. Alanko, S., T.T. Salmi, and T.T. Pelliniemi, *Recovery of natural killer cells after chemotherapy for childhood acute lymphoblastic leukemia and solid tumors.* Med Pediatr Oncol, 1995. **24**(6): p. 373-8.
10. Ek, T., et al., *Intensive treatment for childhood acute lymphoblastic leukemia reduces immune responses to diphtheria, tetanus, and Haemophilus influenzae type b.* Journal of Pediatric Hematology/Oncology, 2004. **26**(11): p. 727-734.
11. Mackall, C.L., et al., *Age, thymopoiesis, and CD4+ T-lymphocyte regeneration after intensive chemotherapy.* N Engl J Med, 1995. **332**(3): p. 143-9.
12. Kantar, M., et al., *Immune Deficiencies following Cancer Treatment in Children.* Journal of Tropical Pediatrics, 2003. **49**(5): p. 286-290.
13. Esposito, S., et al., *Vaccinations in children with cancer.* Vaccine, 2010. **28**(19): p. 3278-3284.
14. Cesaro, S., et al., *Guidelines on Vaccinations in Paediatric Haematology and Oncology Patients.* BioMed Research International, 2014. **2014**: p. 707691.

15. Lehrnbecher, T., et al., *Revaccination of children after completion of standard chemotherapy for acute lymphoblastic leukaemia: a pilot study comparing different schedules.(Clinical report).* British Journal of Haematology, 2011. **152**(6): p. 754.
16. Allen, U.D., *Immunizations for children with cancer.* Pediatr Blood Cancer, 2007. **49**(7 Suppl): p. 1102-8.
17. Reinhardt, D., et al., *Impact of Conventional Chemotherapy on Levels of Antibodies Against Vaccine-Preventable Diseases in Children Treated for Cancer.* Scandinavian Journal of Infectious Diseases, 2003, Vol.35(11-12), p.851-857, 2003. **35**(11-12): p. 851-857.
18. Crawford, N.W., et al., *Optimizing immunization in pediatric special risk groups.* Expert Review of Vaccines, 2011. **10**(2): p. 175-86.
19. NHMRC. *The Australian Immunisation Handbook 10th edition*. 2016 [cited 2017 22.02]; Available from: http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home~handbook10part3~handbook10-3-3#114.
20. Immunization, T.N.A.C.o. *The Canadian Immunization Guide* 2016 [cited 2017 22.02].
21. Ek, T. and A. Nilsson. *VACCINATIONER VID BARNCANCER*. 2003 [cited 2017 23.02]; Available from: http://www.blf.net/onko/page16/files/Vaccinationsprogram%20v%201.pdf.
22. Ljungman, P., et al., *Vaccination of stem cell transplant recipients: recommendations of the Infectious Diseases Working Party of the EBMT.* Bone Marrow Transplantation, 2005. **35**(8): p. 737.
23. Crawford, N.W., et al., *Survivors of childhood cancer: An Australian audit of vaccination status after treatment.* Pediatric Blood & Cancer, 2010. **54**(1): p. 128-133.
24. Abzug, M., *Vaccination in the Immunocompromised Child A Probe of Immune Reconstitution*, in *Pediatr. Infect. Dis. J.* 2009. p. 233-236.
25. Skinner, R., et al., *Royal College of Paediatrics and Child Health (RCPCH) best practice statement on immunisation in the immunocompromised child*. 2002. p. S58-S59.
26. Nøkleby, H., *Vaccination of immunocompromised patients.* Tidsskrift for den Norske lægeforening : tidsskrift for praktisk medicin, ny række, 2002. **122**(28): p. 2711.
27. Perkins, J.L., et al., *Infections among long-term survivors of childhood and adolescent cancer: a report from the Childhood Cancer Survivor Study.* Cancer, 2014. **120**(16): p. 2514-21.
28. Norwegian Institute of Public Health. *Norwegian Immunisation Registry SYSVAK*. [cited 2017 23.02]; Available from: https://www.fhi.no/en/hn/health-registries/norwegian-immunisation-registry-sysvak/.
29. Eichler, R., et al., *Evaluation of the new ARCHITECT Rubella IgM assay.* Journal of Clinical Virology, 2007. **39**(3): p. 182-187.
30. Nilsson, A., et al., *Current chemotherapy protocols for childhood acute lymphoblastic leukemia induce loss of humoral immunity to viral vaccination antigens.* Pediatrics, 2002. **109**(6): p. e91.
31. Colantonio, D.A., et al., *Closing the gaps in pediatric laboratory reference intervals: a CALIPER database of 40 biochemical markers in a healthy and multiethnic population of children.* Clin Chem, 2012. **58**(5): p. 854-68.
32. Trogstad, L., et al., *The Norwegian immunisation register--SYSVAK.* Euro Surveill, 2012. **17**(16).
33. Nasjonalt folkehelseinstitutt. *Vaksinasjonsdekning i prosent (fullvaksinerte) per 31.12.2016 9-åringer (født 2007) - fylker*. 2017 [cited 2017 21.04]; Available from: https://www.fhi.no/globalassets/fylker_9_ar_2016.pdf.
34. Nasjonalt folkehelseinstitutt, *Anbefalinger for bruk av pneumokokkvaksine utenfor barnevaksinasjonsprogram i Norge*. 2015: Oslo.

Til foresatte til deltakere som er yngre enn 16 år Trondheim, 01.11.2016

Informasjon om *REVAK*-studien

Hei!

Dere som mottar dette brevet er blitt identifisert som foresatte til mulig deltager i vår undersøkelse om revaksinering etter cellegiftbehandling ved Barne- og ungdomsklinikken, Barn4, St. Olavs Hospital. Vedlagt dette brevet er følgende:

1) Informasjonsskriv
2) Samtykkeskjema
3) Spørreskjema

Først må dere lese informasjonsskrivet. Hvis dere bestemmer dere for at barnet deres skal delta må dere skrive under samtykkeskjema. For deltakere som er mindre enn 16 år skal disse bare lese gjennom informasjonsskrivet til seg selv (et for barn under 12 år og et for ungdom 12-16 år) og foresatte skal underskrive på samtykkeskjema som er stilet til foresatte.

Deretter må dere fylle ut spørreskjema og underskrive dette.
Vi er også interessert i deltagers dokumenterte vaksinestatus i forhold til relevante vaksiner. Informasjon om dette vil bli innhentet gjennom **SYSVAK** (hjemmeside: https://www.fhi.no/hn/helseregistre-og-biobanker/sysvak/) som er Folkehelseinstituttets (FHI) vaksineregister i Norge. Tilbakemelding på evt behov for ytterligere vaksiner vil bli gitt uavhengig av deltagelse i studien eller ikke.

Det er på forhånd innhentet tillatelse fra FHI for innhenting av disse opplysningene.

Hvis dere har bestemt dere for at barnet deres skal delta ber vi dere fylle ut samtykkeerklæringen og spørreskjema og putte begge deler i den vedlagte ferdigfrankerte konvolutten og poste brevet. Dere vil få tilbakemelding når prosjektet er ferdig.

Ved spørsmål bare ta kontakt med:
Bendik Lund, Barne- og ungdomsklinikken, St. Olavs Hospital
Pb 3250 Sluppen, 7006, Trondheim, Tlf: 72574059, mail: Bendik.Lund@stolav.no

Vennlig hilsen

Bendik Lund
Barnelege, St. Olavs Hospital
Førsteamanuensis, NTNU

Navn på tidligere pasient:

Fødselsdato:

Deltagernummer i studien:

Spørreskjema *REVAK*-studien

Hei!

Hvis du/dere sier ja til å bli med på REVAK-studien vil vi gjerne stille deg/dere noen få spørsmål.

1. Når (omtrent) startet du/barnet ditt behandling med cellegift for kreft? (mnd/år)
    a. Svar: ……

2. Når (omtrent) avsluttet du/barnet ditt cellegiftbehandlingen? (mnd/år)
    a. Svar: ……

3. Har du fått informasjon av sykehuslege om at du/barnet ditt bør ta vaksiner etter at du/barnet ditt ble ferdig med cellegiftbehandling?
    a. Svar: …… (ja/nei/vet ikke)

4. Hvis du/barnet ditt har fått en plan for vaksinering, har du/barnet ditt startet med dette?
    a. Skal begynne snart: ……..(ja/nei. Angi omtrent når)

    b. Har begynt med vaksiner, men er ikke helt ferdig: …….. (ja/nei)
    c. Er ferdig vaksinert: ……

Sted/dato: …… Signatur: ……

Skjemaet puttes i vedlagte svarkonvolutt sammen med samtykkeskjema.

FORESPØRSEL OM DELTAKELSE I FORSKNINGSPROSJEKT:

REVAKSINERING ETTER GJENNOMGÅTT CELLEGIFTBEHANDLING HOS BARN OG UNGDOM MED KREFT. *REVAK*-studien.

Dette er et spørsmål til deg om å delta i et forskningsprosjekt hvor vi skal undersøke om du har fått tilstrekkelig vaksinering (eller revaksinering) etter gjennomgått cellegiftbehandling. Vi vil også undersøke mekanismer for hvordan cellegiftbehandling påvirker immunforsvaret i forhold til effekt av tidligere vaksinering i barnevaksinasjonsprogrammet i Norge. Dette er viktig for å hindre eller redusere risikoen for smittsomme sykdommer som potensielt kan unngås gjennom vaksinering. Vi spør deg om deltakelse fordi du har gjennomgått cellegiftbehandling ved St. Olavs hospital (Barn4) og var ferdigbehandlet i perioden 2010-2016. Det er Barne- og Ungdomsklinikken på St.Olavs Hospital som er ansvarlig for forskningsprosjektet.

HVA INNEBÆRER PROSJEKTET?

Prosjektet innebærer at vi vil gjennomgå pasientjournalen din og se om du har blitt gitt anbefaling om revaksinering etter at du ble ferdigbehandlet og om anbefalingen er i tråd med de nasjonale anbefalingene for revaksinering etter cellegiftbehandling for barn og ungdom. Deretter vil vi undersøke om anbefalingene fra sykehuset har blitt fulgt opp gjennom et spørreskjema sendt til deg og din familie. Vi vil også be om en utskrift fra det nasjonale vaksinasjonsregisteret SYSVAK hvor all vaksinering registreres og sjekke om din vaksinestatus er tilfredsstillende. Hvis vi gjennom prosjektet finner at vaksinasjonsstatus ikke er optimal vil vi komme med en anbefaling om ytterligere vaksinering i samråd med ansvarlig barnekreftlege. Alle vil få tilbakemelding om resultatet av undersøkelsen og evt ny anbefaling om vaksinering. Denne tilbakemeldingen er uavhengig av om man deltar i prosjektet eller ikke.

Prosjektet innebærer også undersøkelse av mekanismer for vaksinestatus før og etter gjennomgått cellegiftbehandling. Dette innebærer analyse av noen ekstra blodprøver. Til dette vil det bli benyttet blodprøver som allerede tatt i forbindelse med den tidligere sykdommen din og blodprøver som tas ved kontroll på poliklinikken. Det vil bli tatt ekstra blodprøver i prosjektet, men ingen ekstra «stikk» pga prosjektet. Ved kontroll på sykehuset vil det bli tatt ca 20-40 ekstra bloddråper i forbindelse med vanlige blodprøver.

Tidsforbruket ved deltagelse i prosjektet vil være å fylle ut et kort spørreskjema, lese gjennom dette skrivet om studien, underskrive samtykke og postlegge samtykkeskjema og spørreskjema. Deltagelse i prosjektet vil ikke påvirke behandlingen eller oppfølgingen du får for din tidligere kreftsykdom.

I prosjektet vil vi innhente og registrere opplysninger om deltagerne fra pasientjournalen på St. Olavs Hospital. Det vil være opplysninger om alder, kjønn, diagnose, type cellegiftbehandling, blodverdier (hvite blodceller/immunglobuliner/virusantistoffer) før og etter behandling, evt informasjon om gjennomgått beinmargstransplantasjon/høydose-behandling, vaksinasjonsstatus, dato for diagnose og dato for når deltagerne var ferdigbehandlet. Vi vil også benytte nedfrosset serum (blodprøver) tatt ved sykdomsdebut som er lagret rutinemessig ved Avdeling for Mikrobiologi, St. Olavs Hospital og de nye blodprøvene som blir tatt ved kontroll på sykehuset.

I spørreskjemaet vil vi spørre om det er blitt gitt revaksinering eller ikke etter ferdigbehandling.

Som en tilleggsundersøkelse vil vi for leukemipasientene innhente informasjon om plasmacellenivåer i beinmargen før og etter cellegiftbehandlingen fra tidligere utførte analyser.

MULIGE FORDELER OG ULEMPER

Fordelen med studien er at din vaksinestatus vil bli undersøkt og om dette er tilfredsstillende etter gjennomgått cellegiftbehandling. Hvis undersøkelsen viser at ytterligere vaksiner bør gis vil det bli gitt beskjed.

Det er ingen umiddelbare ulemper ved undersøkelsen. Blodprøver som benyttes i undersøkelsen analyseres enten fra tidligere avgitte prøver eller i forbindelse med prøver som likevel tas ved sykehuset. Det blir ingen ekstra «stikk» ved deltagelse i undersøkelsen.

FRIVILLIG DELTAKELSE OG MULIGHET FOR Å TREKKE SITT SAMTYKKE

Det er frivillig å delta i prosjektet. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Du kan når som helst og uten å oppgi noen grunn trekke samtykke. Dette vil ikke få konsekvenser for den videre behandlingen eller oppfølgingen. Dersom du trekker deg fra prosjektet kan du kreve å få slettet all informasjon om deg i prosjektet med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner. Dersom du senere ønsker å trekke deg eller har spørsmål til prosjektet kan du kontakte overlege Bendik Lund, tlf: 72574059/92248978, mail: Bendik.Lund@stolav.no, eller Mathias Tangenes (medisinstudent), tlf: 48244943, mail: mathiata@stud.ntnu.no.

HVA SKJER MED INFORMASJONEN OM DEG?

Informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Du har rett til innsyn i hvilke opplysninger som er registrert om deg og rett til å få korrigert eventuelle feil i de opplysningene som er registrert.

Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger gjennom en navneliste. Alle data i prosjektet vil bli lagret elektronisk på et sikkert område på en server ved St. Olavs Hospital i prosjektperioden.

Prosjektleder har ansvar for den daglige driften av forskningsprosjektet og at opplysninger om deg blir behandlet på en sikker måte. Informasjon om deg vil bli anonymisert eller slettet senest fem år etter prosjektslutt.

HVA SKJER MED PRØVER SOM BLIR TATT AV DEG?

Prøvene som tas av deg vil bli analysert som en del av rutineanalysene ved St. Olavs Hospital. Det vil ikke bli opprettet noen prosjektspesifikk biobank.

GODKJENNING

Prosjektet er godkjent av Regional komite for medisinsk og helsefaglig forskningsetikk, saksnr. hos REK (2016/1375).

SAMTYKKE TIL DELTAKELSE I PROSJEKTET

JEG ER VILLIG TIL Å DELTA I PROSJEKTET **«REVAKSINERING ETTER GJENNOMGÅTT CELLEGIFTBEHANDLING HOS BARN OG UNGDOM MED KREFT. *REVAK*-STUDIEN.»**

Sted og dato

Deltakers signatur

Deltakers navn med trykte bokstaver

Som foresatte til_ (Fullt navn) samtykker vi til at hun/han kan delta i prosjektet

Sted og dato

Foresattes signatur

Foresattes navn med trykte bokstaver

Sted og dato

Foresattes signatur

Foresattes navn med trykte bokstaver

Anbefalt vaksinasjonsprogram etter gjennomgått cellegiftbehandling ved Barne- og ungdomsklinikken, St.Olavs Hospital

Cellegiftbehandling påvirker immunforsvaret og etter at man er ferdigbehandlet for barnekreft kan beskyttelsen fra tidligere vaksinasjoner ha forsvunnet. Sykdommene det vaksineres mot i barnevaksinasjonsprogrammet varierer fra vanlige infeksjoner som for eksempel influensa og lungebetennelse til sjeldne og alvorlige infeksjoner som meslinger og polio. For å redusere sjansen for å få disse infeksjonene finnes det anbefalinger for revaksinasjon av barn som har gjennomgått cellegiftbehandling. Disse gjelder for barn som har fulgt normalt vaksinasjonsprogram til 15 måneders alder og vaksinene det skal vaksineres mot er:

- Pentavalente vaksiner: Difteri, stivkrampe, kikhoste, poliomyelitt og haemophilus influenzae type b
- MMR-vaksine: Meslinger, kusma og røde hunder
- Pneumokokk-vaksine
- Varicella-vaksine: Bare for barn som ikke har hatt vannkopper; seronegative for Varicella Zoster Virus- IgG

Som hovedregel anbefales boosterdoser, «påfyllsdoser», til ulike tidspunkter etter ferdigbehandling. Tidspunktet for når vaksinene skal gis er påvirket av behandlingsintensitet barnet har vært utsatt for.

Det skal ikke gis levende vaksiner under pågående behandling eller ved residivmistanke! Ikke levende vaksine hvis < 3mnd siden det ble tilført immunglobuliner eller blodprodukter

For barn som har **påbegynt cellegiftbehandling før 15 måneders alder** og dermed ikke har fullført basisvaksinering(3 doser DTP-pol-Hib, 3 doser PKV13 og 1 dose MMR, i tillegg til 2 doser Rotavirusvaksine) bør man starte basisvaksineringen på nytt **for den aktuelle vaksinen**. *Eks: Det er gitt 2 doser DTP-pol-Hib og PKV13 før kreftdiagnose, deretter får barnet cellegiftbehandling. Da skal barnet få 3 nye doser med DTP-pol-Hib og 3 nye doser PKV13 etter barnet er ferdigbehandlet i tillegg til 1 dose MMR.* **Rotavirusvaksine** er aldri aktuell etter 6 måneders alder og skal ikke gis på nytt når barnet er eldre enn 6 måneder.

Ta med dette skrivet til helsestasjonen når du oppsøker lege eller helsesøster for vaksinasjon. Vi ber også om at du tar med vedlegget til lege/helsesøster, **som så returnerer det til oss når hele vaksinasjonsprogrammet er gjennomført.**

Vaksiner som er gitt til barn og unge skal også registreres i nasjonalt vaksinasjonsregister (SYSVAK).

Vennlig hilsen

Barn- og Ungdomsklinikken

St.Olavs Hospital

Anbefalinger om revaksinasjoner etter barnekreft:

Måneder etter avsluttet behandling:	**DTP-IPV-Hib** *Kombinasjonsvaksine: Infanrix-polio-Hib*		**MMR**	**Pneumokokk*** *Prevenar13* og/eller *Pneumovax*		**Varicella Zoster** Gis **kun** til VZV-seronegative	
For ALL Standard/Intermediær, nonB-NHL st I-II. For solide svulster med kort/lavintensiv behandling; Lavrisk sarckom, Hodgkin st I-II, Wilms tumor lavrisk	3		12	3	5	8	10
For AML, B-NHL	6		12	6	8	8	10
For ALL Høyrisk, nonB-NHL st III-IV.	6	8	24	6	8	10	12
For solide svulster med lang/høyintensiv behandling; Høyrisk sarkom, Hodgkin st III-IV, PNET	6		24	6	8	10	12

*Pneumokokkvaksine: Til barn mellom **12-23 mnd** anbefales 2 doser *Prevenar 13(PKV13)* med 2 måneders mellomrom. Til barn **>2 år** anbefales 1 dose *Prevenar 13* og så 1 dose *Pneumovax* med 2 måneders mellomrom[1].

Sendes, **etter at hele vaksinasjonsprogrammet er gjennomført,** til

Adresse

Navn: Personnr:

Vaksinasjonskategori:	ALL Standard/Intermediær, nonB-NHL st I-II. Solide svulster med kort/lavintensiv behandling; Lavrisk sarckom, Hodgkin st I-II, Wilms tumor lavrisk	AML, B-NHL	ALL Høyrisk, nonB-NHL st III-IV	Solide svulster med lang/høyintensiv behandling; Høyrisk sarkom, Hodgkin st III-IV, PNET
Kryss av for riktig vaksinasjonskategori				

Oversikt over vaksiner som er gitt etter ferdig behandling for barnekreft:

Anbefalte vaksiner:	**Dato**	**Dato**
DTP-IPV-Hib *Kombinasjonsvaksine: Infanrix-polio-Hib*		
MMR		
Pneumokokkvaksine For barn mellom 12-23 mnd		
Pneumokokkvaksine For barn >2 år		
Varicella Zoster Gis **kun** til VZV-seronegative		

Ønsker ikke vaksinasjon ☐

Dato: …….

Lege/Helsesøster

Vedlegg:

Utdypende informasjon:

Cellegiftbehandling påvirker immunforsvaret også etter man er ferdigbehandlet og pasienter som er ferdigbehandlet for kreft har større risiko for infeksjoner enn den generelle befolkningen[2]. Beskyttelsen fra tidligere vaksiner er redusert og en del infeksjoner kan forebygges gjennom en ny runde med aktiv immunisering. Effekten av revaksinering varierer med behandlingsintensiteten og tid etter behandlingsslutt. Derfor skal vaksinene gis til forskjellige tidspunkt avhengig av hvilken krefttype pasienten har blitt behandlet for. Anbefalingene i dokumentet er upubliserte retningslinjer av *Trond Flægstad* og *Per Kristian Knudsen* som i stor grad har basert skrivet på den svenske utredningen *Vaccinationer vid Barnecancer* av Torben Ek og Anna Nilsson, men også på flere andre internasjonale studier[3-8].

Det finnes flere publiserte studier som viser at vaksineantistoff-titer hos barn som har gjennomgått cellegiftbehandling er under protektivt nivå flere måneder etter de er ferdigbehandlet. På grunn av den gode responsen på revaksinering, der de aller fleste pasientene får antistoff-titer over protektivt nivå, har det kommet mange internasjonale anbefalinger om revaksinering av disse pasientene. Selv om det finnes lite informasjon om den kliniske betydningen og varigheten av redusert antistofftiter hos disse pasientene er vaksinasjon et enkelt tiltak for å beskytte den utsatte pasientgruppen mot unødige infeksjoner. I motsetning til flere internasjonale anbefalinger er de norske retningslinjene tilpasset behandlingsintensiteten pasientene har blitt utsatt for. Revaksinering gir dårligere beskyttelse kort tid etter man er ferdigbehandlet med høyintensiv kjemoterapi sammenliknet med lavintensiv kjemoterapibehandling. Derfor må revaksineringen skje ved et seinere tidspunkt for pasienter som har blitt behandlet med høyintensiv cellegift enn de som har blitt behandlet med lavintensiv cellegift. Ved uklarhet om hvilken behandlingsintensitet pasienten har fått skal man henvende seg til den behandlende enheten for nærmere avklaring. Det skal ikke gis levende vaksiner(MMR og Varicella) under pågående behandling eller ved residiv mistanke. Unngå å gi vaksiner i 3 måneder etter tilførsel av immunglobulin.

Praktisk gjennomføring:

Alle pasienter som har fått kjemoterapi og som er ferdigbehandlet for barnekreft skal få anbefalinger om revaksinasjon. Ved utskrivelse skal pasientene få informasjonsskriv med vaksinasjonsanbefalingene og utdypende informasjon om de enkelte vaksinene. Selve vaksinasjonen utføres på helsestasjon eller av fastlege og når alle anbefalte vaksinene er gitt skal oversikten over hvilke vaksiner som er gitt sendes tilbake til Barne- og Ungdomsklinikken på St.Olavs Hospital. Dokumentet med oppdatert vaksinasjonsstatus scannes inn i pasientens elektroniske journal. Generelt skal alle vaksiner som gis til barn og unge registreres i nasjonalt vaksinasjonsregister (SYSVAK).

Vaksinasjon hos barn med påbegynt cellegiftbehandling før 15 måneders alder:

Den generelle anbefalingen for barn som ikke har fullført basisvaksinasjonen(3 doser DTP-pol-Hib, 3 doser PKV13 og 1 dose MMR, i tillegg til 2 doser Rotavirusvaksine) er å komplettere den under pågående behandling(kun ikke-levende vaksiner). Effekten av vaksinasjonen vil ikke bli fullverdig hos disse pasientene, men en delvis beskyttelse er bedre enn ingen beskyttelse. Vaksinasjon av ikke-levende vaksiner kan gis i perioder med lav behandlingsintensitet(f.eks vedlikeholdsfasen, behandlingsopphold).

Ved behandlingsslutt skal barn som ikke har fullført basisvaksinasjonen vaksineres på nytt for den aktuelle vaksinen. *Eks: Det er gitt 2 doser DTP-pol-Hib og PKV13 før kreftdiagnose, deretter får barnet cellegiftbehandling. Da skal barnet få 3 nye doser med DTP-pol-Hib og 3 nye doser PKV13 etter barnet er ferdigbehandlet i tillegg til 1 dose MMR.* Rotavirusvaksine er aldri aktuell etter 6 måneders alder og skal ikke gis på nytt når barnet er eldre enn 6 måneder. Det finnes lite litteratur som individualiserer tidspunktet for revaksinering av barn som ikke har fulgt normalt vaksinasjonsprogram. Derfor anbefaler vi samme starttidspunkt for de ulike vaksinene som oppgitt i retningslinjene for revaksinering etter barnekreft.

Utdypende informasjon om de ulike vaksinene: Supplement til vaksinasjonsskjema

- DTP(difteri-tetanus-pertussis/kikhoste)-polio-Hib:

Kombinasjonsvaksine med kun inaktiverte komponenter. Anbefalinger er å gi 1 boosterdose 3-6 måneder etter avsluttet behandling, hvis du har hatt høyrisiko ALL, non-B Non-hodgkin lymfom stadium III-IV gir man 2 boosterdoser henholdsvis 6 og 8 måneder etter behandlingsslutt.

- MMR(Meslinger, mumps/kusma, rubella):

En kombinasjonsvaksine med levende, svekket virus. Skal ikke gis ved pågående behandling eller ved mistanke om residiv. Skal gis 1 dose 12 eller 24 måneder etter avsluttet behandling avhengig av behandlingsintensitet. Man tar ikke antistoffmåling for å vurdere respons. Deretter følger man vanlig barnevaksinasjonsprogram og med 2.dose MMR i 6.klasse, for den aldersgruppen det er aktuelt.

- ***Pneumokokkvaksine(PKV13 og/eller PPV23):***

2 vaksiner der begge inneholder kun inaktiverte komponenter. *Prevenar 13(PKV13)* er en pneumokokk-konjugatvaksine og gir immunologisk minne enn *Pneumovax(PPV23)*. Den beskytter mot færre pneumokokkserotyper enn PPV23, men gir derimot sterkere beskyttelse mot de pneumokokkserotypene den dekker. Pneumokokkvaksinen kan gis 3-6 måneder etter avsluttet behandling avhengig av behandlingsintensitet. Til barn mellom 12-23 mnd anbefales 2 doser *PKV13* med 2 måneders mellomrom og til barn over 2 år anbefales 1 dose med *PKV13* og så 1 dose med *PPV23* etter et intervall på minst 2 måneder.

- Varicella-vaksine:

Vaksinen inneholder levende, svekket virus. Skal ikke gis ved pågående behandling eller ved mistanke om residiv. Anbefalingen om varicella-vaksinasjon er forbeholdt seronegative pasienter; barn som ikke har hatt vannkopper før. Vannkopper hos immunsupprimerte pasienter gir et mer alvorlig forløp. Varicella-vaksinering hos seronegative ferdigbehandlede pasienter kan være spesielt viktig ved et eventuelt senere residiv av kreftsykdommen hvor det kreves ny immunsupprimerende cytostatikabehandling. Anbefalingen innebærer 2 doser med 2 måneders intervall og starttidspunkt er avhengig av lav/høy-intensiv behandling. For lavintensiv kjemoterapi anbefales den 8 + 10 måneder etter ferdigbehandling og for høyintensivbehandling 10+12 måneder etter avsluttet behandling. Primært antistoffpositive behøver ikke å vaksineres selv om de har lave antistofftiter etter avsluttet behandling. Cellulært immunforsvar bevares ofte.

Referanser:

1. Nasjonalt folkehelseinstitutt, *Anbefalinger for bruk av pneumokokkvaksine utenfor barnevaksinasjonsprogram i Norge*. 2015: Oslo.
2. Perkins, J.L., et al., *Infections among long-term survivors of childhood and adolescent cancer: a report from the Childhood Cancer Survivor Study.* Cancer, 2014. **120**(16): p. 2514-21.
3. Esposito, S., et al., *Vaccinations in children with cancer.* Vaccine, 2010. **28**(19): p. 3278-3284.
4. Crawford, N.W., et al., *Survivors of childhood cancer: An Australian audit of vaccination status after treatment.* Pediatric Blood & Cancer, 2010. **54**(1): p. 128-133.
5. Abzug, M., *Vaccination in the Immunocompromised Child A Probe of Immune Reconstitution*, in *Pediatr. Infect. Dis. J.* 2009. p. 233-236.
6. Ek, T. and A. Nilsson. *VACCINATIONER VID BARNCANCER*. 2003 [cited 2017 23.02]; Available from: http://www.blf.net/onko/page16/files/Vaccinationsprogram%20v%201.pdf.
7. Skinner, R., et al., *Royal College of Paediatrics and Child Health (RCPCH) best practice statement on immunisation in the immunocompromised child*. 2002. p. S58-S59.
8. Nøkleby, H., *Vaccination of immunocompromised patients.* Tidsskrift for den Norske lægeforening : tidsskrift for praktisk medicin, ny række, 2002. **122**(28): p. 2711.

NTNU
Norwegian University of Science and Technology

ST. OLAVS HOSPITAL
TRONDHEIM UNIVERSITY HOSPITAL

IMMUNE RECONSTITUTION AND FOLLOW-UP ON REVACCINATION GUIDELINES IN CHILDHOOD CANCER SURVIVORS

Mathias Tangenes[1] Svein Arne Nordbø[1,2] Bendik Lund[1,3]
[1]Dept. of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology, Trondheim, Norway;
[2]Dept. of Medical Microbiology, [2]Dept. of Pediatrics, St. Olav's University Hospital, Trondheim, Norway

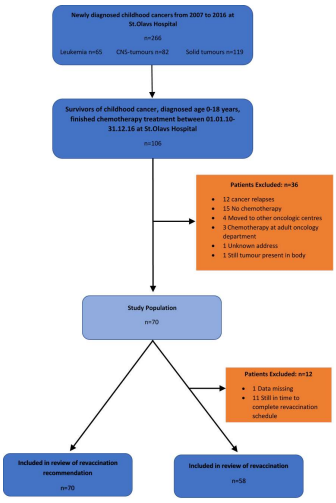
NOPHO
35th Annual meeting,
Stockholm, Sweden

BACKGROUND

Chemotherapy in childhood cancer impair the cellular and humoral immune response in various degrees and might affect the long term protection of vaccines administered before the child started chemotherapy. Studies have shown protective antibody levels after revaccination of children treated with chemotherapy and this has led to different national revaccination guidelines[1,2].

OBJECTIVE

Compliance of guidelines for revaccination after chemotherapy for children in a Norwegian childhood cancer unit has been reviewed as well as challenges in the revaccination process (Fig1). A pilot study of differences in rubella-antibody titers before and after treatment, and IgG-levels post-chemotherapy, were also evaluated for some of the participants.



METHODS

Study group and inclusion

70 patients with a median age at diagnosis of 8,0 years were included. Of these, 34 were girls, 26 patients had leukaemia and 44 patients had solid tumours, including CNS-tumours. 2 patients had received bone marrow transplantation, while 37 had undergone low intensity chemotherapy treatment and 21 had received high intensity treatment.

Compliance of guidelines for revaccination were evaluated through review of patient files, through a questionnaire sent to the families, and from data obtained through SYSVAK, the national vaccine-register of Norway, and compared to guidelines for revaccination after chemotherapy for children (RvG) proposed for Norwegian paediatric oncologists in 2010 (Flægstad and Knudsen).

Laboratory analysis

Rubella antibody titers were analyzed both from frozen samples taken at start of treatment and after finishing treatment. IgG levels were analyzed after finishing treatment.

Revaccination recommendations

Recommendations should have included an individually based revaccination schedule of DTP-IPV-Hib, MMR and pneumococcal vaccine, and been given within one year after cessation of therapy to be classified as appropriate.

Revaccination

Revaccination had to include a first dose of DTP-IPV-Hib and pneumococcal vaccine(s) given within a year after cessation of chemotherapy and MMR given within a year after the recommended time in the RvG or a restart of the childhood vaccination program for patients <15 months at time of diagnosis to be adequate.

Fig 1.

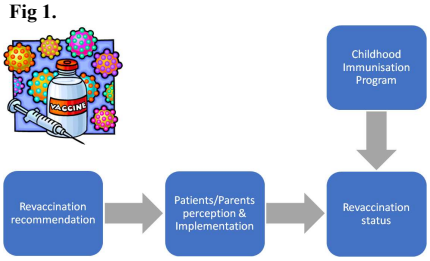


Fig 1. Stages in the revaccination process for childhood survivors after cessation of therapy in the Norwegian health care system. The Childhood Immunisation Program will inadvertently act as a security net for some vaccine-boosters.

RESULTS

25,7% (18/70) had gotten an acceptable revaccination recommendation (Tab.1), but increased to 67,1% (47/70) when excluding the requirement of pneumococcal vaccine.

19,0% (11/58) of the patients had completed an adequate revaccination schedule and there was a slightly increase to 24,1% (14/58) who had received DTP-IPV-Hib, MMR and at least one of the pneumococcal booster vaccines post-chemotherapy when excluding the time limit (Tab.1).

Recommendations, regardless of whether it was given for DTP-IPV, MMR or a complete, adequate one, gave significantly better revaccination results on the implied boosters of the recommendation given (p=0,005, p=0,002 and p=0,017).

Table 1

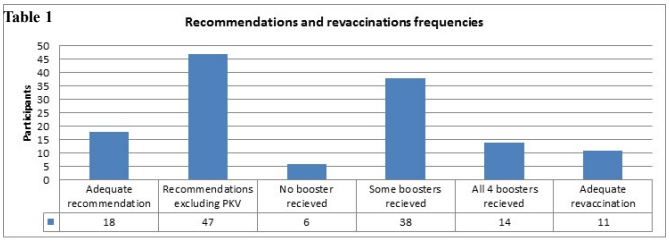


Table 1. shows an overview of recommendation given and boosters received.

Table 2

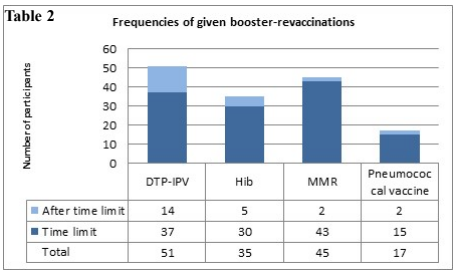


Table 2. shows the frequencies of vaccine boosters given within and after the time limits chosen in the study.

Before (IU/ml)	After (IU/ml)	Disease	Treatment time (months)
82,50	59,90	ALL	30
0,10	58,40	ALL (received boost)	30
25,80	50,40	NHL (received boost)	24
71,90	48,90	Hodgkins Lymfom	3
52,60	10,00	ALL	30

Table 3. shows rubella antibody titers before start and after finished treatment, disease, and treatment time. IgG-levels were within normal reference values for included patients (n=7; data not shown).

DISCUSSION

We showed that barely 1/5 of childhood cancer survivors had completed an adequate revaccination schedule. For the majority, current revaccination guidelines had partly been followed, and participants given recommendations on revaccinations were more likely to receive booster vaccination post-chemotherapy. Poor compliance to revaccination guidelines has also been shown by others [3]. Of participants lacking recommendations, 70% still had received a boost of DTP-IPV illustrating the influence of the Childhood Immunisation Program on the revaccination status. To improve compliance of the revaccination process a revaccination chart given to each patient at end of treatment with a copy to the community nurse and family doctor might be a solution. Coordination with The Childhood Immunisation Program should also be taken into consideration on an individual basis.

CONCLUSION

Quality assurance of compliance with current guidelines for revaccination of childhood cancer survivors is important. Chemotherapy might reduce specific antibody titer levels, but further studies are needed to evaluate which drugs that has highest impact on antibody titer levels.

Acknowledgements

Thanks to The Norwegian immunisation register, SYSVAK, for delivering vaccination data.

References

1.Lehrnbecher, T., et al., *Revaccination of children after completion of standard chemotherapy for acute lymphoblastic leukaemia: a pilot study comparing different schedules.(Clinical report).* British Journal of Haematology, 2011. **152**(6): p. 754.
2.van Tilburg, C.M., et al., *Loss of antibodies and response to (re-)vaccination in children after treatment for acute lymphocytic leukemia: a systematic review.* Leukemia, 2006. **20**(10): p. 1717-22.
3.Crawford, N.W., et al., *Survivors of childhood cancer: An Australian audit of vaccination status after treatment.* Pediatric Blood & Cancer, 2010. **54**(1): p. 128-133.

NTNU
Norwegian University of Science and Technology

ST. OLAVS HOSPITAL
TRONDHEIM UNIVERSITY HOSPITAL