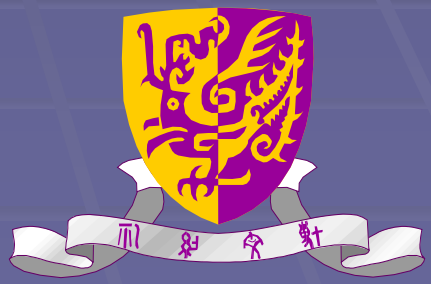
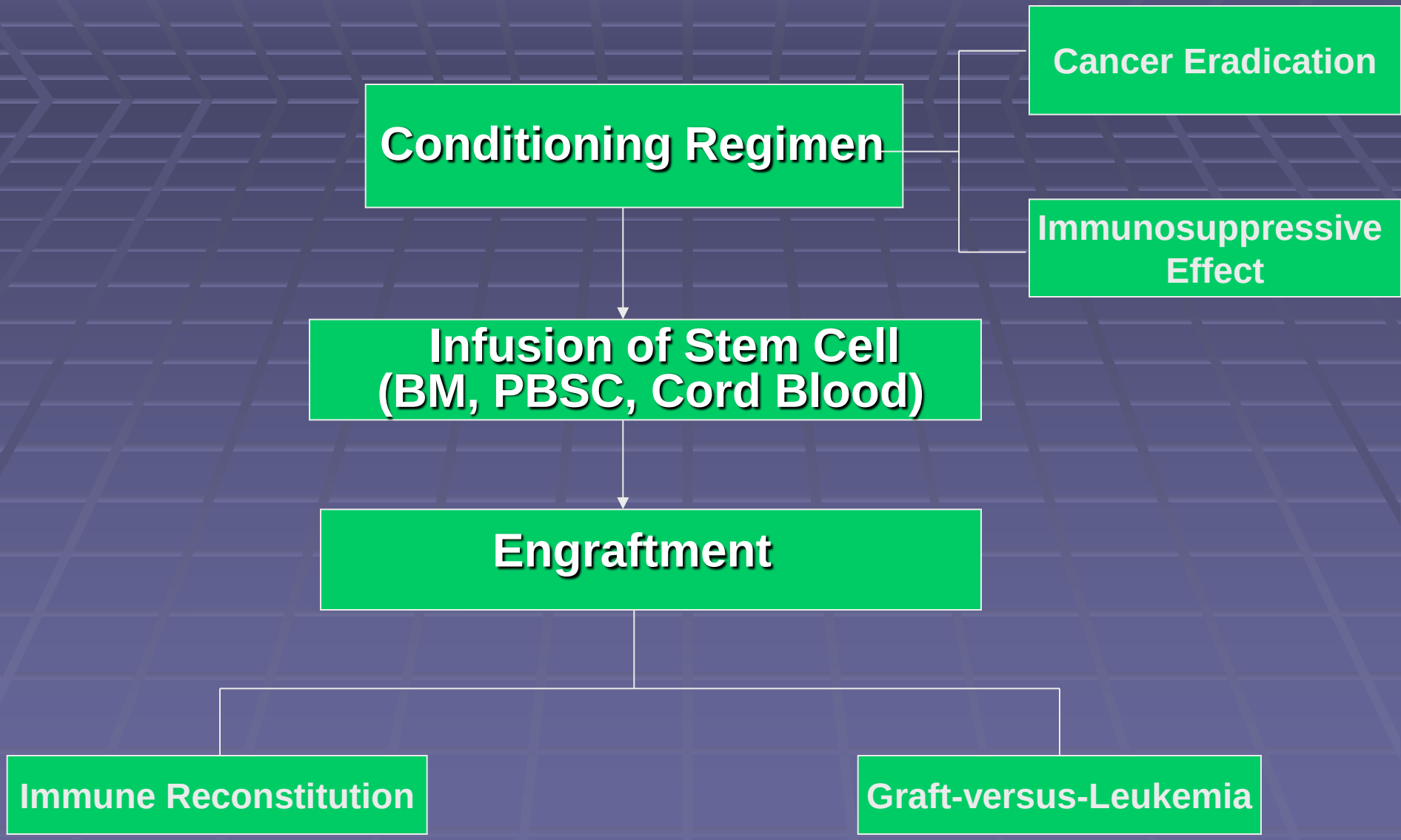
Workshop On Infections in Transplant Recipients: Prevention, Control and Management

Vaccination for Paediatric HSCT Recipients

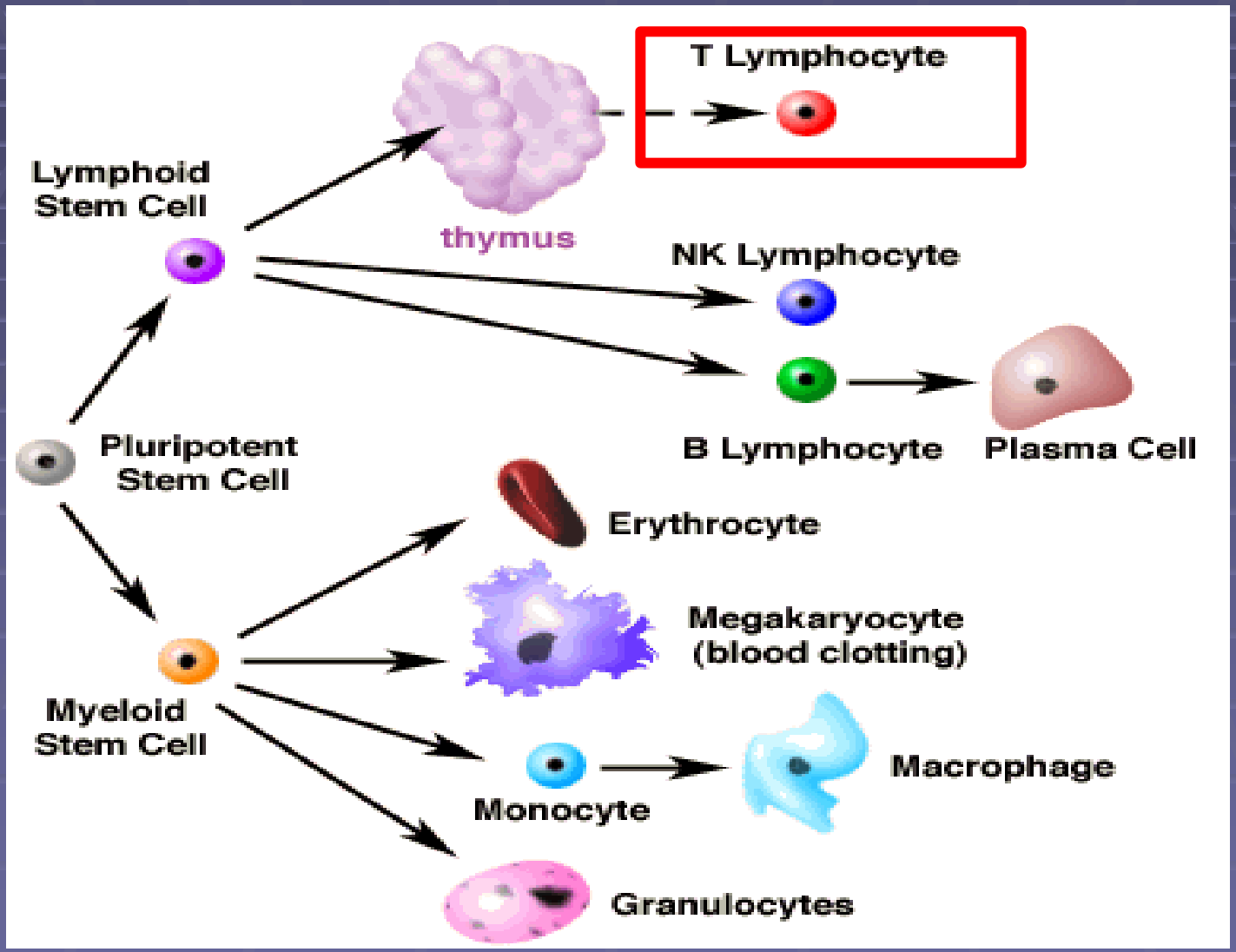
Dr Frankie WT Cheng, MD
Associate Consultant
Clinical Associate Professor (Honorary)
Lady Pao's Children's Cancer Centre
Department of Paediatrics, PWH,
The Chinese University of Hong Kong



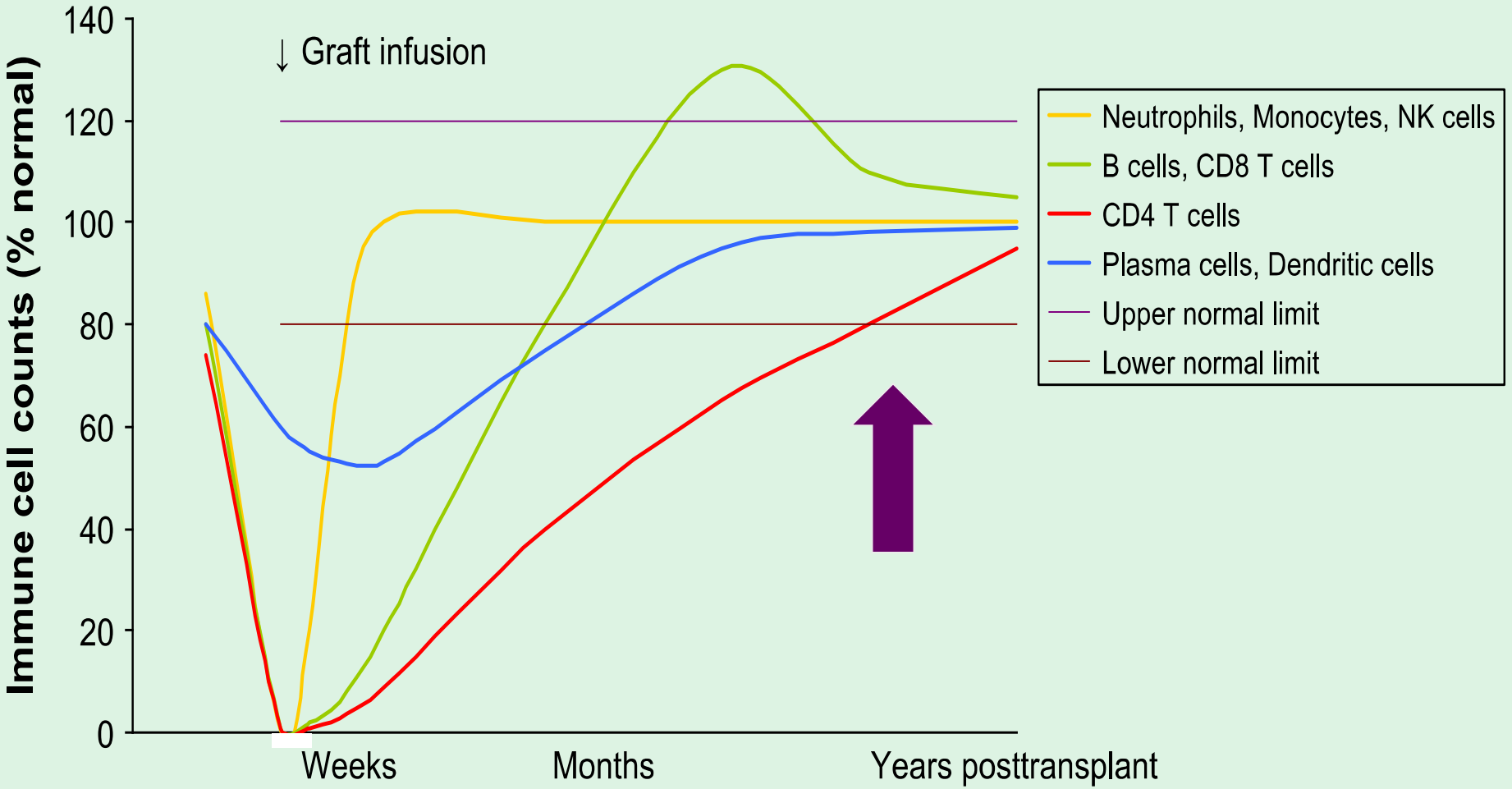
Outline of HSCT



Recovery of Immune System after HSCT



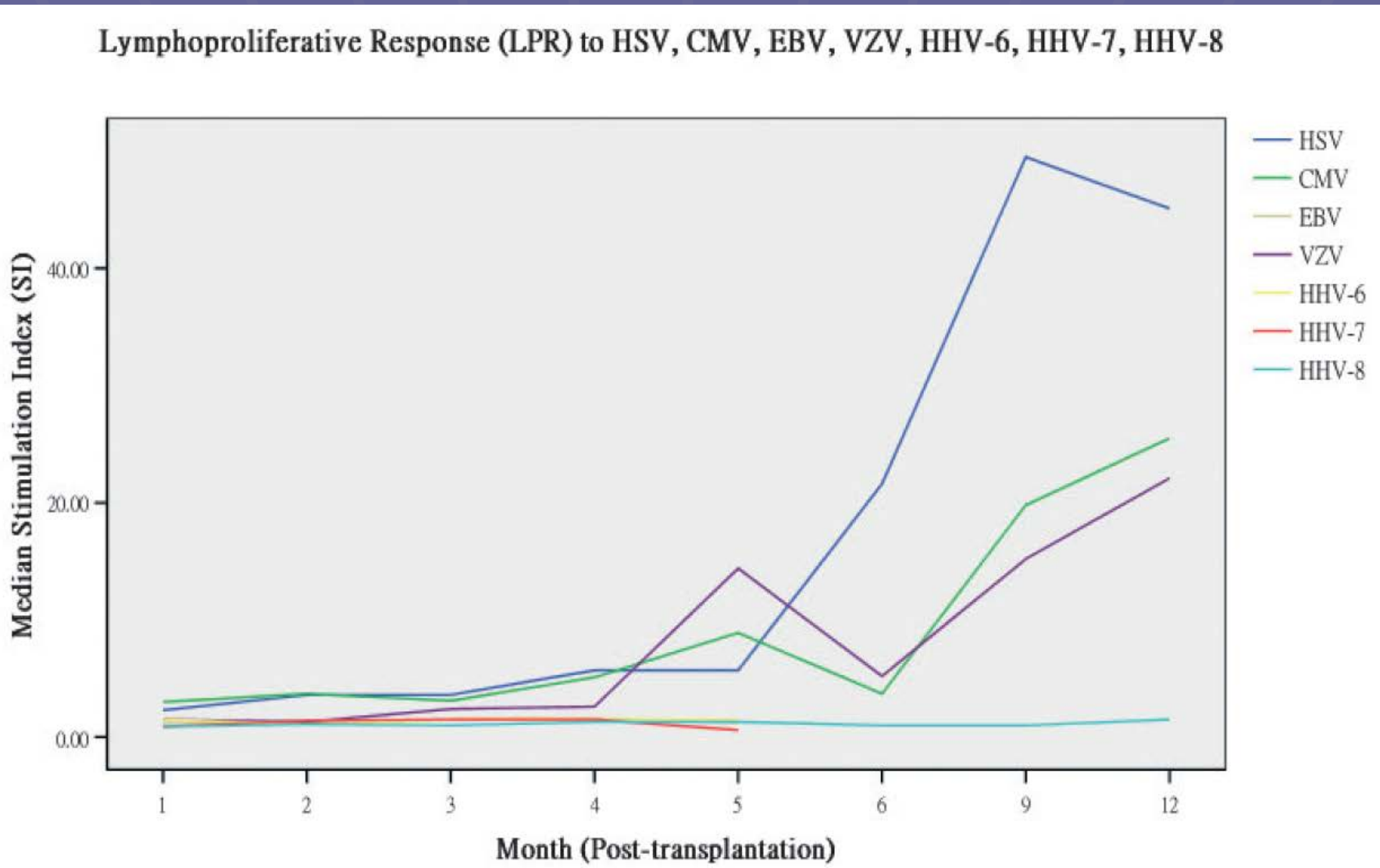
http://www.ismaaustralia.com/wp-content/uploads/2010/10/immune.bmp



Tomblyn et al. Biol Blood Marrow Transplant 2009 15:1143-1238

Recovery of Cellular Immunity

- In 1990s, Alanko S et al
  - Total T lymphocyte count normalized at 1-3 months after stopping chemotherapy
  - Naïve CD4 seemed to recover faster in younger children than older children
  - Regeneration of memory lymphocyte were more effective in adults than children
- In 2000s, Kosmidis et al
  - CD4 dropped significantly at 6 months after stopping intensive chemotherapy and persisted up to 12 months
  - Memory T cell deficit up to 18 months after stopping intensive chemotherapy
- T-cell reconstitution was delayed even in the phase of maintenance chemotherapy (in case of ALL)



Lymphoproliferative responses to HSV, CMV, EBV, VZV, HHV-6, -7, and -8.

Cheng et al. Pediatr Transplant 2010;14:761-769.

Goggle Image

Questions from Patients/Parents

So early?

Why need vaccination again?

???

Will it be harmful?

How many doses ?

Vaccinations for HSCT Recipients

- Guidelines for Preventing Opportunistic Infections Among Hematopoietic Stem Cell Transplant Recipients
  - Recommendations of CDC, the Infectious Disease Society of America, and the American Society of Blood and Marrow Transplantation

    -MMWR 2000 / 49(RR10)

Biol Blood Marrow Transplant. 2009 October ; 15(10): 1143–1238. doi:10.1016/j.bbmt.2009.06.019.

Guidelines for Preventing Infectious Complications among Hematopoietic Cell Transplant Recipients: A Global Perspective

Recommendations of the Center for International Blood and Marrow Transplant Research (CIBMTR®), the National Marrow Donor Program (NMDP), the European Blood and Marrow Transplant Group (EBMT), the American Society of Blood and Marrow Transplantation (ASBMT), the Canadian Blood and Marrow Transplant Group (CBMTG), the Infectious Disease Society of America (IDSA), the Society for Healthcare Epidemiology of America (SHEA), the Association of Medical Microbiology and Infectious Diseases Canada (AMMI), and the Centers for Disease Control and Prevention (CDC), **Marcie Tomblyn**, **Tom Chiller**, **Hermann Einsele**, **Ronald Gress**, **Kent Sepkowitz**, **Jan Storek**, **John R Wingard**, **Jo-Anne H Young**, and **Michael A Boeckh**

2013 IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised Host

Lorry G. Rubin,[1] Myron J. Levin,[2] Per Ljungman,[3,4] E. Graham Davies,[5] Robin Avery,[6] Marcie Tomblyn,[7] Athos Bousvaros,[8] Shireesha Dhanireddy,[9] Lillian Sung,[10] Harry Keyserling,[11] and Insoo Kang[12]

[1]Division of Pediatric Infectious Diseases, Steven and Alexandra Cohen Children's Medical Center of New York of the North Shore-LIJ Health System, New Hyde Park; [2]Section of Pediatric Infectious Diseases, University of Colorado Denver Anschutz Medical Campus, Aurora; [3]Department of Hematology, Karolinska University Hospital; [4]Division of Hematology, Department of Medicine Huddinge, Karolinska Institutet, Stockholm, Sweden; [5]Department of Immunology, Great Ormond Street Hospital & Institute of Child Health, London, United Kingdom; [6]Division of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, Maryland; [7]Department of Blood and Marrow Transplant, H. Lee Moffitt Cancer Center and Research Institute, University of South Florida, Tampa; [8]Department of Gastroenterology and Nutrition, Children's Hospital Boston, Massachusetts; [9]Department of Allergy and Infectious Diseases, University of Washington, Seattle; [10]Division of Hematology-Oncology, Hospital for Sick Children, Toronto, Ontario, Canada; [11]Division of Pediatric Infectious Diseases, Emory University of School of Medicine, Atlanta, Georgia [12]Section of Rheumatology, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut

An international panel of experts prepared an evidenced-based guideline for vaccination of immunocompromised adults and children. These guidelines are intended for use by primary care and subspecialty providers who care for immunocompromised patients. Evidence was often limited. Areas that warrant future investigation are highlighted.

Vaccination

Vaccination for HSCT Donors

- Donors
  - Should we vaccinate them solely due to patient's concern / benefit?
    - Can we give them the "scheduled" inactivated vaccines before donation?
    - Can we vaccinate them with "scheduled" live attenuated vaccines before donation?

Vaccination for HSCT Recipients

- In general, post-HSCT patients should be viewed as “never vaccinated” patients regardless of the pre-transplant status

- Antigen-specific antibody titres will progressively decrease with time after HSCT

TABLE 2. Seropositivity of diphtheria, tetanus, pertussis, hepatitis B, measles, mumps, and rubella in pediatric oncology patients

Vaccine-preventable infectious diseases	Visit 1	Visit 2	Visit 3	Visit 4
Diphtheria (total)	82.1%	78.6%	75.0%	89.3%
Diphtheria (hematology)	78.6%	71.4%	71.4%	78.6%
Diphtheria (solid tumor)	85.7%	85.7%	78.6%	100%
Tetanus (total)	96.4%	96.4%	92.9%	85.2%
Tetanus (hematology)	92.3%	96.4%	92.9%	78.6%
Tetanus (solid tumor)	100%	96.4%	92.9%	92.3%
Pertussis (total)	96.5%	96.2%	100%	100%
Pertussis (hematology)	92.9%	100%	100%	100%
Pertussis (solid tumor)	100%	92.3%	100%	100%
Hepatitis B (total)	29.6%	25.9%	32.1%	40.7%
Hepatitis b (hematology)	15.4%	14.3%	35.7%	42.9%
Hepatitis b (solid tumor)	42.9%	38.5%	28.6%	38.5%
Measles (total)	70.4%	—	71.4%	70.4%
Measles (hematology)	76.9%	—	71.4%	71.4%
Measles (solid tumor)	54.3%	—	71.4%	69.2%
Mumps (total)	55.6%	—	60.7%	51.9%
Mumps (hematology)	53.9%	—	57.1%	42.9%
Mumps (solid tumor)	57.1%	—	64.3%	61.5%
Rubella (total)	70.4%	—	64.3%	70.4%
Rubella (hematology)	69.2%	—	64.3%	69.2%
Rubella (solid tumor)	71.4%	—	64.3%	71.4%

Cheng et al. Pediatr Hematol Oncol 2010;27:195-204.

Vaccination for HSCT Patients

- In general, can be started 6 months after post-transplant for inactivated vaccines
  - Too early: difficult to mount sufficient immune response
  - Too late: a balance between acquiring infectious diseases
  - ….

Vaccination for HSCT Patients

- For influenza vaccine and pneumococcal conjugated vaccines
  - Can consider starting 3-4 months after HSCT if there is community outbreak

Vaccination for HSCT Patients

- For Live Attenuated Vaccines
  - At least 24 months after transplantation
  - No active GVHD
  - Not on immunosuppressive therapy and 8-11 months after last dose of IVIG
  - 2-dose regimen for MMR and Varicella vaccines

Vaccination Recommendation for Post HSCT Paediatric Recipients

Vaccines	1st dose	2nd dose	3rd dose
Diphtheria, Tetanus, Acellular Pertussis + HBV + HiB + IPV	12 months post-transplant:	2 months after 1st dose	2 months after 2nd dose*
13-valent conjugated pneumococcal vaccine (PCV-13)	6 months post-transplant	2 months after 1st dose	2 months after 2nd dose
23-valent polysaccharide pneumococcal vaccine (Pneumovax)	2 months after **3rd dose** of PCV-13**		
Inactivated influenza vaccine (IM)	At least 6 months post-transplant and follow CHP's recommendation on that year	1 month after 1st dose in children < 9 years old	
Measles, mumps, rubella (SC)	> 24 months post-transplant in the patient with no evidence of chronic GVHD or on immunosuppressants	At least 6 month from 1st dose	

Goggle Image

Vaccination after Chemotherapy?

- Efficacy vs harmful effect
- Inactivated vaccines vs live-attenuated vaccines
- Protection of high risk group

Humoral Immune Response after Post-chemotherapy Booster DTP Vaccine in Pediatric Patients With Hematological Malignancies

Cheng et al. Pediatr Blood Cancer 2009;52:248-253.

Patients' Characteristics

Parameters	Vaccine group (n=15)	Control group (n=14)	p-value
Mean age	8.39 ± 3.67	8.41 ± 3.82	0.99
Male, n (%)	9 (60.0%)	10 (71%)	0.76
ALL	12	12	
AML	3	2	
Mean duration of chemotherapy, months	20.5 ± 8.79	22.4 ± 7.74	0.53

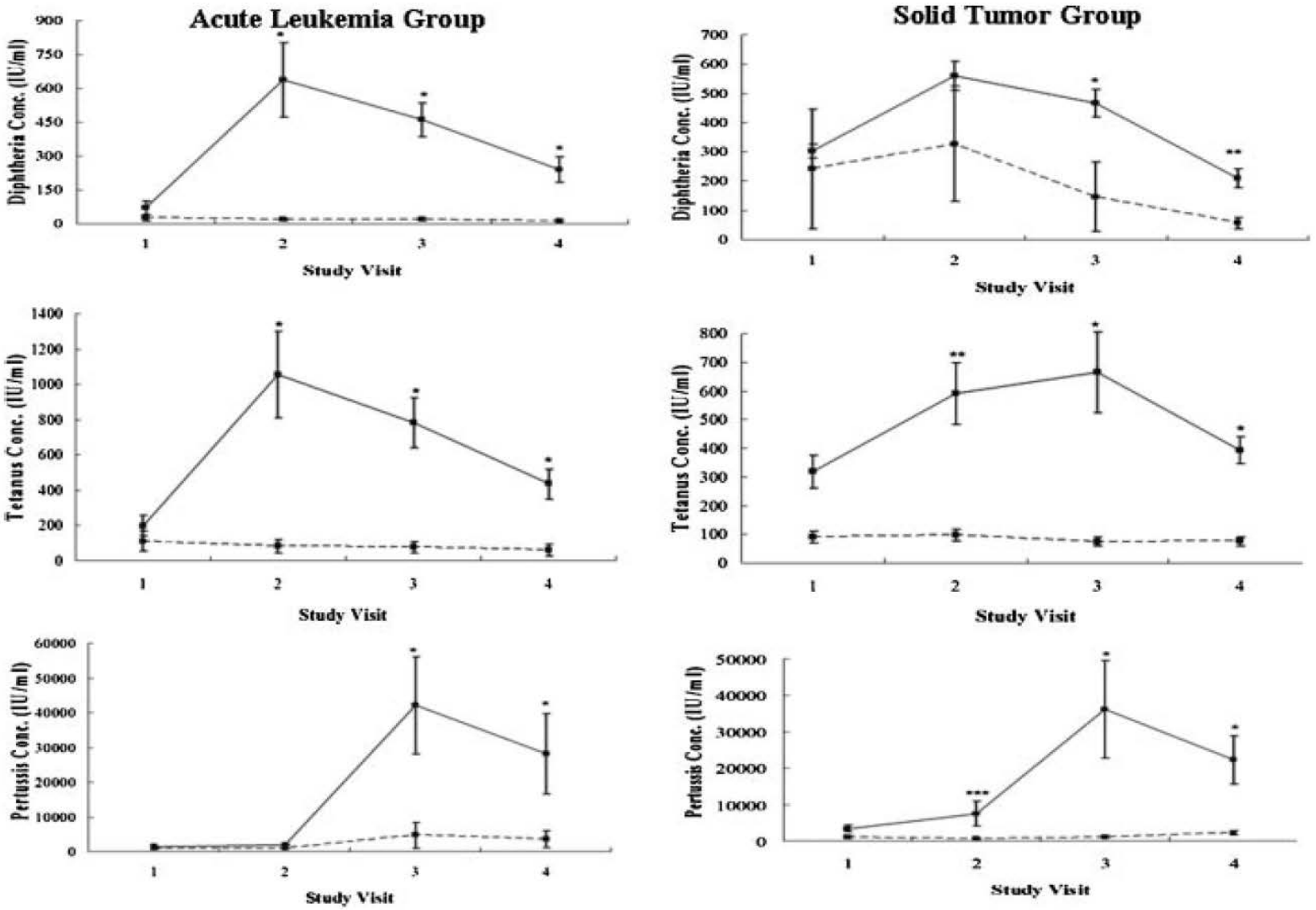
Cheng et al. Pediatr Blood Cancer 2009;52:248-253.

Study Time Points

TABLE I. Study Flowchart

	Time Following Completion of Chemotherapy				
	6 months (baseline, visit 1)	8 months (visit 2)	10 months (visit 3)	12 months (visit 4)	18 months (visit 5)
Immunological surveillance					
Complete blood count with differential's	+	+	−	+	+
Lymphocyte subsets by flow cytometry	+	−	−	+/−	+/−
Serum IgG, IgM and IgA levels	+	−	−	+	+
Antibodies to diphtheria, tetanus, and pertussis	+	+	−	+	+
Antibody to hepatitis B virus surface antigen	+	+	−	+	+
Antibodies to mumps, measles, rubella	+	−	−	+	+
Booster vaccination					
DTP vaccine	+	+	+	−	−

Cheng et al. Pediatr Blood Cancer 2009;52:248-253.



Longitudinal changes in serum concentrations of diphtheria, tetanus, and pertussis antibodies in patients with acute leukemia and solid from the vaccine (solid lines) and control (dashed lines) groups. Error bars represent standard errors of mean. Asterisks are significant s for comparisons between vaccine and control groups at respective study visits: $*P < 0.001$; $**P < 0.005$; $***P < 0.01$.

Cheng et al. Pediatr Blood Cancer 2009;52:248-253.

Pandemic (H1N1) 2009 vaccine in paediatric oncology patients: one dose or two doses?

Table I. Clinical characteristics and immune response to two doses of pandemic (2009) H1N1 vaccine.

Patient	Primary diagnosis	Sex	Age at vaccination (years)	Absolute neutrophil count at vaccination ($\times 10^9$/l)	Absolute lymphocyte count at vaccination ($\times 10^9$/l)	TP0*	TP1*	TP2*
1	Germ cell tumour	Male	2·9	4·8	4·8	<1:40	1:80	1:80
2	ALL‡	Male	3·3	2·3	0·9	<1:40	<1:40	1:320
3	ALL	Male	4·3	1·7	0·4	1:40	1:80	ND†
4	ALL	Female	4·8	1·9	0·9	1:40	<1:40	1:320
5	AML§	Female	5·1	2·6	3·7	<1:40	1:80	1:160
6	Osteosarcoma	Female	5·1	3·4	1·5	<1:40	1:80	1:160
7	ALL	Female	5·3	2·9	1·0	<1:40	<1:40	1:80
8	ALL	Female	5·4	1·7	1·1	<1:40	<1:40	1:80
9	ALL	Female	5·5	3·2	6·8	<1:40	1:80	1:320
10	Osteosarcoma	Male	6·3	2·4	2·8	<1:40	1:80	ND†
11	ALL	Female	9·2	1·5	0·6	<1:40	<1:40	1:80
12	AML	Male	9·4	3·7	3·6	1:160	1:160	1:320

Cheng et al. Br J Haematol 2010

Conjugate Pneumococcal Vaccine

- Forty-four patients (20 males; 24 females) with median age 9.5 years were studied.
- After two doses of PCV-7, 86–100% of patients had protective antibody titres against the seven vaccine serotypes.
- There was no documented invasive pneumococcal disease in our cohort during the study period

Cheng et al. Arch Dis Child 2010.

Potential Clinical Applications

- Influenza vaccine and pneumococcal vaccines should be seriously considered in paediatric oncology patients who are still on treatment
- Recheck Hepatitis B, measles, mumps and rubella antibodies at 6 months after completion of chemotherapy and revaccinate with booster vaccines for those seronegative patients is a reasonable approach
- Assessment of Diphtheria, Tetanus and Pertussis antibodies are not routine service in most of the laboratories in Hong Kong

Acknowledgements

Medical team

- Dr Li, Chi Kong
- Dr Lee, Vincent
- Dr Shing, Ming Kong
- Dr Leung, Wing Kwan

Laboratory, CUHK

- Prof Paul Chan
- Prof TF Leung
- Mr. Wong, Raymond
- Mr. Pong, Henry

Thank You !