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Practical revaccination guidelines for Bangladeshi children with cancer treated with cancer chemotherapy- A proposal

Abstract

Introduction: Childhood cancer may be immunocompromised as a result of the primary disease itself and the use of intensive chemotherapy (CT) with or without radiotherapy (RT). The damage to the immune system varies with the age of the patient, the type of cancer, and the type of CT used to treat it. Children with cancer need to be immunized against the common vaccine-preventable diseases after completion or during ongoing treatment of cancer. However, the immunization schedule for these children needs to be developed in our country. There are many guidelines from around the world to address this issue, however, there is no such comprehensive guideline from Bangladesh for the needs of our children with cancer.

The aims of this paper will be to address the rationale, methodology, relevant literature review, and process of development of updated guidelines for the vaccination of pediatric cancer patients. This document will help the pediatric oncologist and vaccine experts to prepare a contemporary revaccination guideline for the children of Bangladesh, which will help pediatricians to choose the best immunization program against vaccine-preventable diseases in children with cancer.

Objective: To review the current evidence on the revaccination of children and advice the best guidelines which are used in foreign countries for immunization of children with cancer. To inform the policy of immunization practices for contracts.

Methodology: Reviewing the available literature, especially those pieces of literature and guidelines from developing nations, a proposal has been drafted for Bangladeshi children. This proposal has mentioned guidelines used in developed and developing countries, which will help to generate a nationally relevant guideline for immunization of children with cancer. This proposal does not mention an immunization plan for children treated with targeted therapy, immunotherapy, or Bone Marrow Transplantation (BMT).

Proposal: Most of the available guidelines mentioned live vaccines are contraindicated during and up to 6 months after the chemotherapy. Non-live vaccines are also best given after 6 months. Annual inactivated influenza vaccine is recommended during chemotherapy whereas hepatitis B vaccine is recommended only for previously unimmunized children. Post-treatment re-immunization or catch-up schedule largely depends on the pre-chemotherapy immunization status. Sibling immunization should continue uninterrupted except for the oral polio vaccine which needs to be substituted by the injectable vaccine. Inactivated influenza vaccine is recommended and varicella vaccine is encouraged for all contacts including siblings.

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Introduction

Children with cancer are immunocompromised due to the disease itself, chemotherapy (CT), or radiotherapy (RT). Even after the end of CT and RT, they remain immunocompromised for months to years. This suggests that they should get the vaccination to prevent them from common childhood diseases which are called revaccination. The revaccination is very important for cancer-affected children to reduce pediatric non cancer related mortality and morbidity after the end of treatment. It has been found that infection rate of cancer survivors are more than siblings and after adjusting for age, sex and race, there are statistically significantly higher rate of infections among survivors. Survivors reported higher rates of all categories of infection, most notably pneumonia, hepatitis and sinusitis.

Pediatric cancer treatment Children have advanced faster in both poor and rich nations in the last two decades and in advanced countries, 85% of children with cancer now survive 5 years or more.[1] On the other hand, developing countries are also steadily improving outcomes of childhood cancer.[2] It is a new challenge for medical science to the prevention of infectious diseases in children who received chemotherapy or who are in follow-up. Bangladesh is far behind to address this proficiency and technology.

In Bangladesh, there are 13 to 15 lakh cancer patients with about 2 lakh newly diagnosed cases every year.[3] And expected near 13000 new pediatric cancer/year in Bangladesh .[4] All of those children did not have a chance to immunize during infancy due to the early start of cancer symptoms. A hospital-based study by Ghosh et al showed that fully immunized under five (U5) children with cancer were only 27.5%, whereas partially immunized and unimmunized U5 were 65% and 7.5% respectively.[5] This means the immunization percentage of children with cancer is much less than national coverage and survivors of those children have no chance of immunization/ re-immunization as we have no national policy and guidelines.

During CT and after CT+RT, infectious diseases are the main contributor to mortality and morbidity of children with cancer. So,

immunization for vaccine-preventable diseases is very important in children with cancer as it can lessen infection-related mortality/morbidity and bestow benefits to the comprehensive outcome of child health. Many developed countries have formulated guidelines for immunizing children with cancer[6,7] throughout chemotherapy as well as at the end of CT/RT, together with their national immunization schedules. But immunization of cancer-affected people is neglected in Low and Middle-Income countries (LMICs) due to the enormous caseload, the scarcity of trained personnel and funds as well as lack of awareness among treating oncologists and parents.[8] However, such recommendations from developing countries are scarce and hardly any guidance on childhood immunization strategies have come from Low and Middle-Income Countries.[9] In Bangladesh, any national body has not addressed the need for such immunization schedules. In the absence of any assigned recommendation in Bangladesh, the children who received chemotherapy are not getting reimmunization.

The present document will address the rationale for revaccination, the methodology of this proposal, relevant literature review in favor of revaccination, and the process of developing updated guidelines for the vaccination of pediatric cancer patients. This proposal will help the pediatric oncologist and vaccine experts of Bangladesh to prepare a contemporary vaccine guideline for children, which will help pediatricians of Bangladesh to select the best immunization program in case of infectious diseases of children who were treated for cancer and their siblings and parents/caregivers.

Objectives:

1. To review the current evidence on the revaccination of children.

2. To find out the internationally used best recommendations for vaccination of children receiving Chemotherapy and or Radiotherapy.

3. To inform the vaccination experts and Pediatric Oncologists of Bangladesh about the best Immunization program for children with cancer, their parents, siblings and caregivers.

Methodology

A Google and PubMed search has taken up to procure all recent publications on childhood immunization and the important publications on the revaccination of children with cancer were reviewed, including the immunization schedule of Bangladesh. A proposal has been generated based on the practice and evidence-based recommendations which have been published in journals in Bangladesh and foreign countries. This proposal has addressed the need for future research regarding the issue.

The proposed guidelines did not mention the needs of children treated with targeted therapy, BMT and immunotherapy. Other modalities of immunotherapy presently being augmented in the management of childhood cancers were not included in the proposal.

Process of development of guideline

This proposal will be circulated to departments of Pediatric Hematology and Oncology (PHO), respected pediatricians, immunization experts, and government bodies of Bangladesh. They will review the available literature again, especially those studied in developing nations, and by conducting essential research which is possible in our country, a guideline will be drafted. The draft guideline will be circulated among pediatric oncologists of Bangladesh and vaccine specialists of the Bangladesh Pediatric Association (BPA). After a discussion about the draft in a meeting subsequently, finalize the recommendation as a guideline.

Literature review

Significance of reimmunization in children with cancer

Immune suppression is a major problem for cancer patients. Due to the involvement of the T-cell/natural killer (NK) cells and B-lymphocytes both cellular and humoral immunity is affected.[10] The immune system develops compromise mostly because of cancer itself and because of treatment (CT /RT).[11,12] This immunosuppression may range from the slightest involvement of the immune system with localized solid tumors to huge immune suppression like acute leukemia. Some hematological cancers show specific immune defects e.g., Hodgkin lymphoma and Burkitt's lymphoma are related to lack of lymphocytic response to numerous antigens[13] and several levels of lymphocyte depletion, respectively.[14] In spite of these changes, the pediatric population rarely shows clinically significant immune deficiency prior to the start of chemotherapeutic agents.[15] The available statistics indicate that the damage to the immune system is related to the patient's age, the type of malignancy and the intensity of anticancer agents used to treat it.[16] Compared to the B-cells, the time to recovery seems to be longer in the case of T-cells[10,17] and some of the immune defects may persist even long after the end of chemotherapy.[18] Therefore, immunization during chemotherapy and for some time after the therapy may be unpredictable. Childhood acquired immunity through previous infections or vaccination also declines due to the cytotoxic therapy for cancer and needs boosting on recovery of immunity following the end of chemotherapy.[19]

Till now it is a critical question whether there is any real need for reimmunization after chemotherapy when the primary immunization has been completed previously in childhood? It is difficult to answer the question appropriately because the accessible data are conflicting and controversial. Though there is a lack of consensus, most scientists recommend immunization at the age of 6 months from the end of chemotherapy with the presumption that adequate immunity is gained around that time.[20–26] However, till now revaccination in children receiving cancer chemotherapy remains a conscious area for research to understand the need for it.

Optimal timing for vaccination following chemotherapy

Though children treated with CT and RT suffer from immunosuppression, booster doses of vaccines after the end of treatment can yield protective reactions in most cases. Among them some antigens (e.g., tetanus) seem to be more immunogenic than others antigens (e.g., measles, HBV, *S.pneumoniae*, *H.influenzae* type b).[24,27–30] Even cases of no sensitization to booster antigens have been described against measles.[17] General rules have been outlined as follows: live attenuated vaccines (poliovirus, yellow fever, typhus, measles, rubella, mumps and tuberculosis) should be avoided in immunosuppressive conditions, that is, when patients are receiving chemotherapy or within six months after the end of treatment. On the other hand, killed vaccines are also best given after 6 months from the termination of treatment. If any inactivated vaccine is given during anticancer therapy or before completion of 6 months following therapy, should not be taken into account as an effective dose. But an allocated annual inactivated influenza vaccine is recommended during chemotherapy. Vaccine for Hepatitis B virus is given for previously unvaccinated children as per the national schedule. Children with newly diagnosed cancer are to have pneumococcal vaccines (PCV23 and PCV13); if they fail to be administered earlier. Siblings of cancer patients should avoid the oral polio vaccine, while other immunization schedules can proceed without change. Contacts,

including siblings, should be encouraged for varicella and annual influenza vaccination.[31–33]

Strategy for vaccination

Re-immunization strategies for the pediatric population with cancer after CT/RT differ among research groups.[34] But mainly three feasible strategies have been described[29] i.e (a) A child associated with low protective antibody titers, she/he can get a booster shot (b) re-immunization without evaluating the remaining immunity, or (c) resume the meticulous national immunization schedule. Zignol, et al.[29] advocated the first plan. These researchers evaluated the serum antibodies titers of 192 pediatric cancer patients with solid tumors or leukemia and found low antibodies titers in 52% of patients, mostly Hepatitis B Virus (46%), followed by rubella virus, mumps virus, and measles. Evaluating the cost/effectiveness ratio and financial burden first strategy is not applicable in Bangladesh. Rather the second strategy is more suitable for Bangladesh.

Recommendation

Immunity and type of infection differ from country to country and the pattern of cancer and patient management is different in underdeveloped and developed nations. So, guidelines from the high-income countries (HICs) on immunization of children with cancer,[23–24,26] rarely reflect the problems of Low and Middle-Income Countries (LMICs) where most (90%) of the childhood cancers in the world are diagnosed. It is not wise to follow the guidelines of HICs in toto for the children of Bangladesh due to various reasons, including the cancer epidemiology, different national vaccination schedules, vaccine availability, price of vaccines, and national health infrastructure. Very few countries of LMICs like India developed immunization plans for their children with cancer.[9] We can review all those guidelines for preparing the contemporary vaccine guideline for children of Bangladesh. The present paperwork is a piece of sketch evidence and proposal for revaccination strategies of the developed and developing nations for children with cancer, which also dealt with the immunization of siblings and parents/caregivers. Immunization for children with BMT differs from children getting CT/RT and is far off the scope of this proposal.

The safe and efficacious use of vaccines has always been a vital challenge in children with immunodeficiency like cancer. These children with cancer are often at high risk of adverse consequences from vaccine-preventable diseases. Primary concerns are the safety of the vaccines used and the capability of the children to first mount and then a continuous protective immune response. Thus, special recommendations are required[35–37] for children under the age of one year with cancer, because the onset of iatrogenic immunosuppression by CT and RT occur before the completion of their primary immunizations.

Table 1 shows an overall synopsis of the various types of vaccines and the nature of the immune responses observed in the host.[38] Killed vaccines generally evoke a limited range of immune responses compared with live attenuated vaccines. In addition, long-lasting immunity with killed vaccines usually requires the use of boosters shot periodically.

Table 1 Example of Vaccination Strategies and the Nature of Protective Responses

Type of vaccine	Examples	Nature of protection
Live attenuated bacteria or inactivated bacteria/ bacterial components	BCG, cholera, pertussis	Antibody response
Live attenuated viruses	Oral polio	Antibody response; cell-mediated immune
response Killed viruses	Polio (IPV), influenza	Antibody response; cell-mediated immune
response Subunit (antigen) vaccines	Tetanus toxoid, diphtheria toxoid	Antibody response
Conjugate vaccines (protein-polysaccharide) influenzae,	Pneumococcus, H. meningococcus	Helper T-cell dependent antibody response
Synthetic vaccines	Hepatitis B (recombinant proteins)	Antibody response
Other: viral vectors; DNA vaccines	Research in progress in different settings (e.g., HIV)	Cell-mediated and humoral immune responses

Life Vaccines for children with cancer

When live vaccines are being considered in cancer patients, two things are taken into consideration i.e. efficacy and safety of vaccination. Most of the studies revealed that live vaccines should not be given within the first three months after the end of chemotherapy. The duration of withheld varies according to the type and duration of the immunosuppressive chemotherapeutic agent. Thus, it is impossible to make an absolute recommendation that encloses all sides. Other researchers considered that in vitro testing of immune function may provide a guide for safe timing in selected patients.[39] For most patients, in vitro testing is not a practical solution in many countries like Bangladesh as this test is not available here. Even many developed countries like Australia, Canada, United Kingdom, and USA do not practice in vitro testing. They recommended that live vaccines should be delayed for 6–12 months after immunosuppressive therapy.[39–42] Table 2 shows the recommendation for live vaccines by the Pediatric Hematology-Oncology Chapter, India; and the Indian Academy of Paediatrics.

Inactivated Vaccines for children with cancer

Like all other vaccines, the main aim of these inactivated vaccines is protective and continuous immune responses to pediatric cancer patients. The ability to develop protective immune responses in children with cancer depends on the gap between immunization and the administration of immunosuppressive therapy. After the end of chemotherapy, required immune responses can be yielded between 3 to 12 months after cessation of CT. Total lymphocyte counts exceeding 1×10^{-9} /L are required to elicit an adequate immune response by inactivated vaccines.[40] Re-immunization yields poor immune responses if vaccines are given during or immediately after the intensive phases of chemotherapy. Inactivated vaccination

is better to give at the maintenance phase of chemotherapy and booster dose is recommended more than three months after the end of chemotherapy. Table 3 summarizes the immunization schedules recommended for Indian cancer-affected children by the PHO chapter of India.[9]

Table 2 Recommendations for live vaccines[9]

Vaccine	During chemotherapy	After end of chemotherapy	
		Previously unimmunized children	Children with completed immunization
BCG	Not recommended, contact vaccination not discouraged	Single dose BCG at 6 mo after completion of chemotherapy.	Not recommended in previously immunised children with visible BCG scar
OPV	Not recommended, contact vaccination contraindicated	IPV preferred, when unavailable 3 doses of bOPV 1mo apart (maximum age 5 y)	IPV preferred, when unavailable 2 doses of bOPV 1mo apart (maximum age 5 y)
MMR	Not recommended, contact vaccination not discouraged.	Two doses of MMR (1 to 3 mo apart) should be given to all children after at least 6 mo of completion of chemotherapy.	Single dose of MMR should be given to all children after at least 6 mo of completion of chemotherapy
Varicella vaccine	Not recommended, contact vaccination encouraged.	2 doses of vaccine 1-3 mo apart. (after 6 mo of completing chemotherapy)	Single booster dose 6 mo after stopping chemotherapy
Live attenuated HAV	Not recommended	Single dose after 6 mo of completing chemotherapy	Single dose after 6 mo of completing chemotherapy
Rotavirus vaccine	Not recommended, contact vaccination not discouraged	Generally child outgrows the maximum permissible age, therefore not indicated.	Generally child outgrows the maximum permissible age, therefore not indicated.

BCG, bacillus calmette-guerin; OPV, oral polio vaccine; MMR, mumps measles rubella; HAV, hepatitis A vaccine

Table 3 Recommendations for Non-live vaccines

Vaccine	During chemotherapy	After end of chemotherapy	
		Previously unimmunized children	Children with completed immunization
DPT (age appropriate preparation- DwPT/ DaPT/ TdaP/Td)	Not recommended during ongoing chemotherapy.	3 doses at 0,1 and 6 mo (6 mo after stopping chemotherapy).	3 doses at 0,1 and 6 mo (6 mo after stopping chemotherapy).
Hib	Not recommended during ongoing chemotherapy.	Age >6 mo 2 doses 8 wk apart, followed by booster at 12 mo; 12-15 mo single dose followed by booster at 18 mo; 15-60 mo single dose (6 mo after stopping chemotherapy).	Single booster dose (6 mo after stopping chemotherapy).
IPV	Not recommended during ongoing chemotherapy.	2 doses of IPV 2 mo apart and 3rd dose after 6 mo (6 mo after stopping chemotherapy).	Single booster dose (6 mo after stopping chemotherapy). Two doses for children who received OPV as primary immunization.
HBV	4 doses of vaccine (0,1,2 and 12 mo) at double dosage is recommended for previously unimmunized children, no further doses for children who completed primary schedule prior to diagnosis.	3 doses at 0,1 and 6 mo (6 mo after stopping chemotherapy).	Single booster dose (6 mo after stopping chemotherapy).
HAV	Not recommended during ongoing chemotherapy.	2 doses 6 mo apart (6 mo after stopping chemotherapy).	Single booster dose (6 mo after stopping chemotherapy)
Inactivated Influenza Vaccine	Recommended single dose annually during chemotherapy.	Not recommended routinely beyond 1 y from the end of chemotherapy.	Not recommended routinely beyond 1 y from the end of chemotherapy

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Table Continued...

Vaccine	During chemotherapy	After end of chemotherapy	
		Previously unimmunized children	Children with completed immunization
Inactivated typhoid vaccine	Single booster dose (6 mo after stopping chemotherapy).	Single dose typhoid conjugate vaccine 6 mo after stopping chemotherapy.	Single dose typhoid conjugate vaccine 6 mo after stopping chemotherapy.
HPV	Not recommended during ongoing chemotherapy.	Age 9-14 y - 2 doses 6 mo apart in females, age >14 y - 3 doses at 0,1 and 6 mo (HPV2) or 0,2 and 6 mo (HPV4) in females (6 mo after stopping chemotherapy).	Insufficient data on booster dose but single booster dose may be considered in females.

DPT, diphtheria pertussis tetanus; wP, whole cell pertussis; aP, acellular pertussis; HiB, haemophilus influenza Type B; IPV, inactivated polio vaccine; HBV, hepatitis B vaccine; HAV, hepatitis A vaccine; HPV, human papilloma virus; HPV2, bivalent HPV, HPV4, quadrivalent HPV.

Some infants with cancer do not complete their primary immunization schedule. Younger children, especially those who had not finished their primary immunization schedule, are less protected against vaccine-preventable infection than the older ones[42] and these children suffer from several infections frequently. A hospital-based study in Bangladesh by Ghosh et al.[5] showed that 27.5% of under-five (U_5) children were unimmunized and 67.5% of children were partially immunized. These large numbers of children need different vaccine schedules. Table 4 describes briefly the immunization schedule of these unimmunized younger children.

Table 4 Schedule for the cancer patient <7 years not immunized during infancy[38]

	DTaP	IPV	HIB[a]	HBV	PV7[b]	Men[c]
First visit	X	X	X	X	X	X
2 Months later	X	X	X	X		
2 Months later	X	X				
6–12 Months later	X	X	X	X		
4–6 Years of age	X	X				
14–16 Years of age	Td[d] or Tdap[e]					

DTap, tetanus and diphtheria toxoids acellular pertussis; HiB, haemophilus influenza Type B; IPV, inactivated polio vaccine; HBV, hepatitis B vaccine; PV-7, seven-valent pneumococcal conjugate vaccine; Men- meningococcal conjugate vaccines; dTd tetanus.

Family members, health care providers, and caregivers

Immunization of siblings and family members is an important part of the prevention of vaccine-preventable diseases in cancer patients. Pediatric oncologists should be acutely aware of the vaccination of siblings and Health care workers.

Siblings: Siblings should get all non-live vaccines as per the national immunization program like inactivated influenza vaccine. They are recommended live vaccines like MMR, BCG, Rotavirus, Varicella, and Yellow fever vaccine as per schedule. The oral polio vaccine is not allowed for siblings including pulse polio but IPV is recommended for them. They can take the varicella vaccine if siblings are unimmunized and have not suffered from chickenpox before. When a child's sibling develops varicella vaccine-induced rash, then should not be in the contract of the index child till all lesions crust. Siblings can take rotavirus vaccine but child with cancer should refrain from changing the diapers of the vaccinated infant till 4 weeks from the day of vaccination.[21]

Parents: Varicella vaccine is recommended for parents if they are unimmunized and had not chickenpox before and if the parent develops varicella vaccine-induced rash, then they should stay away from the index child.[8] Inactivated Influenza vaccine is strongly recommended for them.

Health care workers: For proper care of immunocompromised children, Health care workers should be up to date on their immunizations. They should take all available vaccines but special attention should be given to hepatitis B vaccines, varicella, and influenza.

Conclusion

Re-immunization of cancer patients is not a known treatment option in our country. It is neglected in LMICs like Bangladesh. But it is very important for children with cancer to get protection against vaccine-preventable infection. To address this issue, we need to develop an updated guideline, which will incorporate our nation-specific concerns, integrate our national immunization schedule, and will be instrumental in achieving this important target.

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None

Conflicts of interest

The authors declare that they have no competing interests.

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