Ⅳ. 研究成果の刊行物・別刷

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総　説

基礎疾患をもつ小児に対する同時接種によるワクチン接種

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要　旨

インフルエンザ菌b型（ヒブ）ワクチン，肺炎球菌ワクチンは，小児の重症細菌性感染症を予防するための重要なワクチンである．当センターでは，基礎疾患をもつ小児に対して，これらのワクチンを含む同時接種による予防接種を推奨し，2007年12月より2011年2月の間に計104名，のべ170回の同時接種を実施してきた．年齢の中央値は13か月(2か月～17歳)，1人当たりの接種時のワクチン接種数の中央値は3接種（範囲：2～7接種）であった．患者の基礎疾患としては，胆道閉鎖症などの消化器疾患，肝移植後，神経疾患，循環器疾患などが全体の約3/4を占めた．接種後28日までに報告された有害事象は1件，副反応は3件であった．基礎疾患をもつ小児は，ヒブ，肺炎球菌などの細菌感染症に感染すると重症化する危険性が高い．したがって，これらの小児をワクチンで予防できる疾患から守るためには，混合ワクチンの少ない現在の日本においては，同時接種による効率のよい，かつ早期の接種が重要である．

キーワード：小児，予防接種，同時接種，安全性，基礎疾患

はじめに

基礎疾患を持つ乳幼児は，生直後からその時間の大半を診断，治療などに費やすことが多く，予防接種可能な時期に限界がある．一方で，心臓疾患や，薬剤による免疫抑制状態におかれた基礎疾患のある乳幼児が，インフルエンザ菌b型(ヒブ)，肺炎球菌などの細菌感染症に罹患すると，一般健常児に比べ，重症化し，予後と死亡率に大きな影響を与える可能性がある．

WHOが世界の乳幼児に接種を推奨しているワクチンの中で，ヒブワクチン，結合型肺炎球菌ワクチンは，国内でそれぞれ2008年12月，2010年2月に販売された．海外においては，これらのワクチンは既に普及しており，ヒブ感染症[1]，肺炎球菌感染症[2]は減少，その疾患の疫学を大きく変えるまでに至った．一方で，これらのワクチンは，乳幼児期早期に接種を完了することで，その最大限の効果をもたらすことが出来る．早期接種するためには，他の必要なワクチンとの同時接種が必要である[3]．しかしながら，本邦においては，予防接種は，原則1回に1ワクチン，ただし，あらかじめ混合されていない2種以上のワクチンについて，医師が必要と認めた場合には，同時に接種を行うことができるとされている[4]．国内において健常児におけるヒブワクチンを含むワクチンの同時接種の安全性はデータが存在するが[5]，基礎疾患を持つ乳幼児に対して，両ワクチンを含めた同時接種の際の安全性に関しての情報は存在しない．

当センターでは，特にヒブワクチン，肺炎球菌ワクチン販売後，基礎疾患を持つ小児に対して，積極的に同時接種による効率的な予防接種を推奨してきた．

方　法

2007年12月より2011年2月までに国立成育医療研究センターにおいて，同時接種を実施した基礎疾患をもつ小児，計104名の接種年齢，接種ワクチン，接種後28日までの有害事象，副反応などの以上情報を電子カルテをもとに抽出した．実際の接種は，当センター外来看護師によって，両上腕の外伸側下1/3，両上腕三角筋上部に接種が実施され，接種本数が4本以上の場合は，担当の医師が実際に接種を行った．

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結　果

1）同時接種患者の背景

同時接種は，計104名に対して，のべ170回の接種が実施された．性別は，男性42名（40%），女性62名（60%）であり，年齢の中央値は13か月（2か月～17歳），1人当たりの1回接種の中央値は3接種（範囲：2～7接種）であった．患者の基礎疾患は，胆道閉鎖症などの消化器疾患，肝移植後，神経疾患，循環器疾患などが全体の約3/4を占めた（図1）．

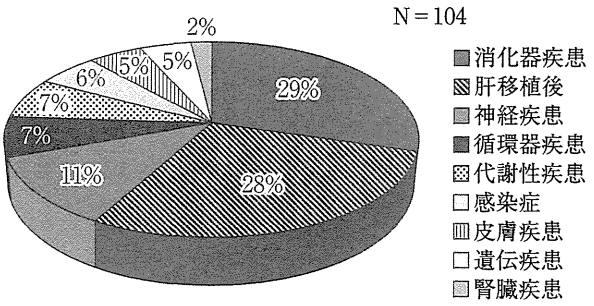

図1　全患者の基礎疾患の内訳

2）接種の状況（表1）

i）三種混合（DPT）ワクチン，ヒブワクチン，肺炎球菌ワクチンの同時接種

3つのワクチンの同時接種は，肺炎球菌ワクチン発売後の2010年2月から実施され，計36接種(29症例)に実施された．年齢の中央値は5か月（範囲：3～40か月），性別は，男性16名(55%)，女性13名(45%)であり，更にその中の5接種においては，他のワクチンとの同時接種を実施した．その内訳は，上記3つのワクチンに加えて，B型肝炎ワクチン(2接種)，BCGワクチン(1接種)，インフルエンザワクチン(1接種)，MRワクチン＋水痘ワクチン＋B型肝炎ワクチン（1接種）であった．

ii）ヒブワクチンを含む同時接種（31接種，29人）

ヒブワクチンを含む同時接種(ただし，DPTワクチン，ヒブワクチン，肺炎球菌ワクチンの3つのワクチンの同時接種を除く)は，計18接種(17症例)に実施され，2008年12月のヒブワクチン発売後から開始された．年齢の中央値は24か月(範囲：2～43か月)，性別：男性9名（31%），女性20名（69%）であった．ヒブワクチンとDPTワクチンの同時接種は，5接種，4名に実施され，その中の3接種では，更に上記2つのワクチンに加えて，B型肝炎（1接種），B型肝炎＋インフルエンザ(2接種)の同時接種が実施された．一方で，ヒブワクチンと肺炎球菌の同時接種は，18接種(17人）に行われ，更なるワクチンの同時接種を11接種で行った．その内訳は，上記2つのワクチンに加えてMRワクチン(3接種)，インフルエンザワクチン(3接種)，B型肝炎ワクチン(3接種)，インフルエンザワクチン＋B型肝炎ワクチン（1接種），インフルエンザワクチン＋ムンプスワクチン＋水痘ワクチン（1接種）であった．ヒブワクチンとその他のワクチンとの同時接種は8接種（8人）に行われた．

iii）肺炎球菌ワクチンを含む同時接種34接種（30人）

肺炎球菌ワクチンを含む同時接種（ただし，DPTワクチン，ヒブワクチン，肺炎球菌ワクチンの3つのワクチンの同時接種，並びに，ヒブワクチンと肺炎球菌ワクチンの同時接種を除く)は，男性10名(33%)，女性20名（64%）に実施され，年齢の中央値は，31か月(2～94か月)であった．肺炎球菌ワクチンとDPTワクチンの同時接種は，15接種（13人）に実施され，更なるワクチンの同時接種を6接種で行った．その内訳は，上記2ワクチンに加えて，B型肝炎ワクチン(3接種)，MRワクチン(2接種)，MRワクチン＋ムンプスワクチン＋水痘ワクチン(1接種)であった．また，肺炎球菌とその他のワクチンとの同時接種は19接種(17人）に実施された．

3）ワクチン接種後の有害事象，副反応

i）有害事象

報告された有害事象は1件（1/170, 0.5%）で，2歳3か月女児，肝移植後で，ヒブ，肺炎球菌，B型肝炎ワクチンを接種，接種後4時間後に頻回の嘔吐があり，救急室を受診したが，経過観察で改善した．ワクチン接種との直接の因果関係はないものと考えられた．

ii）副反応

報告されたワクチン接種後の副反応は，計3件（3/170, 1.7%）であった．それぞれの具体例を記載する．

症例1）4歳9か月女児，壊血病（栄養不良）を持つ児で，MR，水痘，ムンプスワクチンを同時接種後25日目に水痘を発症した．分離されたウイルスは，ワクチン株であることが判明し，症状は，自然経過で改善した．ワクチン株のウイルスが同定されたことにより，ワクチンとの因果関係ありと判断された．

症例2）1歳1か月女児，気管支喘息，アトピー性皮膚炎を持つ児で，MR，ヒブ，肺炎球菌ワクチン接種翌日に局所の発赤があったが，自然に軽快した．

症例3）9か月女児，胆道閉鎖症術後，肝移植前の接種で，MR，水痘，ムンプス，B型肝炎，日本脳炎，ヒブ，BCGワクチンの計7つのワクチン接種6時間後に発熱，2日後に解熱した．因果関係は明らかではなかったが，他の発熱の誘因，症状が同定されなかった．

表1　ヒブワクチン，肺炎球菌ワクチンを含んだ同時接種後28日までの副反応と有害事象

同時接種に含まれたワクチン			接種総数	接種患者数	副反応	有害事象
DPT	ヒブ	肺炎球菌				
○	○	○	36（ 49%）	29（ 46%）	0	0
○	○		5（ 7%）	4（ 6%）	0	0
○		○	15（ 20%）	13（ 21%）	0	0
	○	○	18（ 24%）	17（ 27%）	2例（発熱，局所の発赤）	1（嘔吐）
合計			74（100%）	63（100%）	2	1

考　察

今回，我々は，国立成育医療研究センターにおいて，基礎疾患をもつ小児に対するヒブワクチン，肺炎球菌ワクチンを含む同時接種を，計104名，のべ170回の接種を実施し，安全に実施できることを確認した．

同時接種については，海外では，既に幅広く実施されている医療行為であり[6][7]，複数のワクチン（生ワクチンを含む）を同時接種して，それぞれのワクチンに対する有効性について，お互いのワクチンによる干渉はないこと，複数のワクチン（生ワクチンを含む）を同時に接種して，それぞれのワクチンの有害事象，副反応の頻度が上がることはないことが確認されている[8]．一方で，同時接種において，接種できるワクチン(生ワクチンを含む)の本数に原則制限はないことも知られている[8]．同時接種の利点としては，特に基礎疾患のある児において，各ワクチンの接種率が向上し，ワクチンで予防される疾患から早期に守られること，保護者の経済的，時間的負担が減少すること，更には，医療者の時間的負担が減少することがあげられる．一方で，その短所としては，一回に多くの接種を実施するため，最終的な痛みの回数は同じであるものの，被接種者の一時的な複数の疼痛があげられる．

基礎疾患を持つ小児に対する予防接種は，予防接種を実施できる時期が限られていることから，出来るだけ効率よく予防接種を進めなくてはいけない．米国小児科学会は，基礎疾患を持つ児への予防接種は，特に禁忌がない限り，健常児と同様に接種されるべきであるとしている[9]．日本小児科学会は，同時接種は，予防接種を効率的に行うために重要かつ必要な医療行為であるという考え方を2011年1月に発表した[10]．また，2011年5月には，同時接種を基本とした予防接種スケジュールを発表し，同時接種によって，日本の子どもたちがより早期からワクチンで予防できる病気から守られるように提言をしている[10]．この考え方は，健康な小児のみならず，特に基礎疾患を持つ小児において，重要な概念であると考える．

2011年3月に，ヒブ，肺炎球菌ワクチンを含む同時接種1～7日後に7名の乳幼児の死亡例が報告され，2011年3月4日から3月31日まで，2つのワクチンの一時接種見合わせが行われた[11]．その間に，計3回の専門家による委員会が開催され，2つのワクチンと死亡例との間には，直接の因果関係がないこと，また，同時接種の安全性にも問題がないことが確認された．しかしながら，実際の医療現場においては，この一時見合わせのインパクトは極めて大きかったことは事実である．

一方で，乳児期早期のワクチンスケジュールはより過密になってきている．前述の一時見合わせの後にはヒブ，肺炎球ワクチンの添付文書には，基礎疾患のある小児には単回接種も考慮することとの一文が加わった．2011年11月には1価のロタウイルスワクチンが導入され，2012年には，5価のロタウイルスワクチン，更には，不活化ポリオワクチン，並びに三種混合ワクチン＋不活化ポリオワクチンの混合ワクチンも国内に導入される予定である．継続的にワクチンによる有害事象，副反応のモニタリングを行わないと前回と同様の事象が起った場合，予防接種の差し止めが起こる可能性がある．また，疾患そのもののサーベイランス，ワクチンによる有害事象，副反応のサーベイランスに加えて，この様な差し止めの是非や，新しいワクチンの導入．既に導入されたワクチンの効果，安全性の検証を行う米国ACIP（Advisory Committee on Immunization Practices）に代表されるような国のワクチン諮問機関（NITAG：National Immunization Technical Advisory Group）[12]の早期設立が望まれる[13]．

今回の後方視的研究の限界は，患者の有害事象，副反応を電子カルテから抽出したことによって，患者に有害事象，副反応が発生した場合でも，それが両親，本人の注意を引かない場合，あるいは軽症の場合，報告されていない可能性がある．したがって，有害事象，副反応の頻度が低く報告されている可能性がある．また，今回検討した104例，170接種では，頻度の少ない

有害事象，副反応の現状をとらえることは不可能であり，上述したような，有害事象，副反応の継続的サーベイランスが必要である．

日本において，同時接種という医療行為が普及するためには，その医療行為に対する啓発活動がまず重要である．また，予防接種を適切な時期に，いかに効率的に接種するかを啓発する活動も，重要な課題である．基礎疾患のある小児を含めて，日本の子どもたちがワクチンで予防できる疾患から守られるためには，混合ワクチンの少ない現在の日本においては，ワクチンを乳幼児早期に確実に，適切な時期に接種しなくてはならず，そのためには同時接種は必要な医療行為であり，その理解と普及が望まれる．

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Safety of Simultaneous Vaccination in Children with Underlining Diseases

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Vaccines for *Haemophilus influenzae* type b and *Streptococcus pneumoniae* for children are important to prevent invasive bacterial infections by these organisms. At the Center for Child Health and Development, Tokyo, Japan, we have recommended providing simultaneous vaccination for children with underlying diseases. We performed 104 children, in a total of 170 opportunities for children with underlying diseases between December, 2007 and February, 2011. The median age was 13 months (range: 2 months—17 years), the median numbers of vaccination per visit was 3 (range: 2—7). Approximately 75% of baseline diseases are gastrointestinal diseases including biliary atresia, status post liver transplantation, neurologic diseases, and cardiac diseases. Only one adverse event and three side effects were observed within 28 days after the simultaneous vaccination. Simultaneous vaccination is a common medical practice around the world. The risks for invasive infections by *Haemophilus influenzae* type b and *Streptococcus pneumoniae* are high in children with underlying diseases. To prevent the infections for high risk individuals, it is necessary to perform simultaneous vaccination to provide effective and appropriate protection against vaccine preventable diseases.

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Review

Current issues with the immunization program in Japan: Can we fill the "vaccine gap"?

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Vaccine gap

ABSTRACT

The "vaccine gap" is a term which has been used in Japan to indicate that the current immunization program is behind compared to the programs in other developed countries. The current national immunization program (NIP) which was established under the Japanese Immunization Law includes only six vaccines (eight targeted diseases), and the rest of available vaccines have been categorized as voluntary vaccines, which require out-of-pocket expense in order for the patients to receive them. This has led the vaccination rates for the voluntary vaccines remaining low, and the incidence of the target diseases remaining high. In addition, there are a few domestic rules that exist for immunizations including (1) subcutaneous injection is the standard method of vaccination, (2) the thigh is not considered to be the common site of vaccination in infants, and (3) the intervals of administration of inactivated and live vaccines are strictly determined by law. Along with the "vaccine gap" and the domestic rules, some movements to improve our current NIP are underway; including increased calls to change the NIP from civilians and professionals, the establishment of a group by the representatives from 13 medical professional societies asking the government to consider the immunization policy a "national policy" and seeking the establishment of a new and reorganized national immunization technical advisory group (NITAG). In addition, the Vaccination Subcommittee of Health Sciences Council was formed in the government to reform the current Immunization Law and NIP, which established a new national program for three voluntary vaccines funded by a temporary budget. We hope these new movements will fill the "vaccine gap" and that the NITAG will help ensure that vaccine policy becomes a national policy, and will provide necessary vaccinations without out-of-pocket expense to protect children in Japan from vaccine preventable diseases.

Contents

Abbreviations: Hib, *Haemophilus influenzae* type b; VZV, varicella zoster virus; NIP, national immunization program; HPV, human papillomavirus vaccine; PCV7, seven-valent conjugate pneumococcal vaccine; HBV, hepatitis B virus; VPD, vaccine-preventable diseases; NITAG, National immunization technical advisory group; DTaP, diphtheria, tetanus-toxoid, and acellular pertussis; DTwP, diphtheria, tetanus-toxoid, and whole cell pertussis; MMR, mumps, measles, rubella; JPS, Japan Pediatric Society; IPV, inactivated polio vaccine; BCG, Bacille de Calmette et Guérin; OPV, oral polio vaccine; ACIP, Advisory Committee on Immunization Practices; VAPP, vaccine-associated poliomyelitis paralysis.

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1. Introduction

The "vaccine gap" is a term which has been used for the last decade to indicate that the immunization program in Japan has been behind compared to the programs in other developed countries [1]. The best example is that the *Haemophilus influenzae* type b (Hib) vaccine, which has been known to be safe and the most effective vaccine for preventing invasive Hib infections [2], was introduced in Japan in 2008, which was more than 20 years later than other countries. In addition, some important vaccines, including the mumps vaccine, and varicella zoster virus (VZV) vaccine, have been available in Japan for the last two decades; however, they have not been in the national immunization program (NIP). Furthermore, the Hib vaccine, human papillomavirus vaccine (HPV), seven-valent conjugate pneumococcal vaccine (PCV7), and rotavirus vaccine have only recently been introduced in Japan since 2008; however, none of them is part of the NIP. Lastly, the hepatitis B virus (HBV) vaccine has so far only been used as a selective vaccination; and the universal HBV vaccination has not yet been included in the NIP. All these vaccines not in the NIP have been categorized as voluntary vaccines, as opposed to vaccines under the Japanese Immunization Law. To receive the voluntary vaccines, individuals must pay out-of-pocket expense, which has been a major obstacle to increasing the vaccination rates for each voluntary vaccine and decreasing the incidence of vaccine-preventable diseases (VPD).

The reasons why the "vaccine gap" exists are multi-factorial; a long history of fear about vaccinations, the existence of the Immunization Law imposing strict rules for immunization practice, the ineffectiveness of a systematic national surveillance system for VPD, insufficient resources of vaccine education for both medical personnel and civilians, and the lack of an effective national immunization technical advisory group (NITAG). In this review, we summarize these factors contributing to the "vaccine gap" and discuss a few current issues related to immunization in Japan.

2. The history of vaccine fears in Japan

The initial Immunization Law was launched in 1948, with the goal of decreasing the incidence of endemic diseases, such as smallpox, diphtheria, polio, tetanus, pertussis, tuberculosis, etc. After the significant improvement of the sanitary status and the distribution of available vaccines under the revised immunization law, the incidence of the endemic diseases in Japan decreased significantly. During the subsequent period, the vaccination rates for the targeted diseases were high, because receiving vaccines was considered a duty, and there was a penalty if citizens did not receive the required vaccines. Furthermore, Japanese scientists contributed to develop some novel vaccines to the world, including the VZV vaccine in 1974 [3] and the DTaP (diphtheria, tetanus-toxoid, and acellular pertussis) vaccine in 1981 [4].

There were two major events that impacted the immunization program in Japan. First, two fatalities after DTwP (diphtheria, tetanus-toxoid, and whole cell pertussis) vaccination were reported in 1975, and the vaccine was withheld for six years until a new acellular pertussis combination vaccine was available [4]. After that event, civilians started to have doubts about receiving the immunization because the risks of vaccination were emphasized by the mass media. As expected, the temporary discontinuation of the DTwP vaccine led to the resurgence of 13,000 pertussis cases and 20 deaths reported in 1979 [4]. The second event was in 1989 when the mumps, measles, rubella (MMR) vaccine caused vaccine-related aseptic meningitis due to the mumps component of the vaccine. The incidence of meningitis was estimated to be one case in every 500–900 vaccinations [5]. The vaccine was withdrawn from the market in 1993 based on the Japanese government's decision, and monovalent measles and rubella vaccines were recommended for children >1 year of age. Twelve years were required for the marketing of a new combination vaccine of measles and rubella, without the mumps component, and the lack of a combination vaccine with the mumps component is the reason why the disease is still endemic in Japan and many children have been suffering from its complications [6]. The delay of introducing the mumps strain causing less aseptic meningitis, which was carried out in order to protect domestic Japanese vaccine manufacturers, was criticized by the vaccine authorities [7]. The Japanese government was also sued several times for being responsible for vaccine adverse effects in the 1980s and 90s, including severe adverse events after small pox immunization. In addition, there were negative campaigns against the influenza vaccine by both citizens and medical professionals doubting its effectiveness and believing it to cause serious adverse effects. After these multiple events, the government has had difficulty in defending their vaccination policy, because they hesitate to be responsible for their decisions related to immunization. In 1994, the Immunization Law was revised, and the immunization was changed from a civic "duty" to an "effort duty", and mass immunization in schools was thus discontinued and changed to immunization on an individual basis. These movements decreased the vaccination rates in general and led to a failure to introduce new vaccines between 1991 and 2007, which led to the creation of the "vaccine gap". Only two new vaccines were licensed in Japan between 1990 and 2007 (hepatitis A virus, and measles and rubella combination vaccine) compared to 17 vaccines (including combination vaccines) introduced in the US during the same period.

3. Factors contributing to the "vaccine gap"

3.1. Vaccines under the law and voluntary vaccines

There is a unique classification of vaccines in Japan; vaccines defined by the immunization law, and voluntary vaccine not regulated by Japanese law (Table 1). Several important vaccines, including the mumps vaccine, VZV vaccine, and HBV vaccine have remained categorized as voluntary vaccines which require individuals to pay out-of-pocket, and considers them to be less important vaccines compared to the vaccines under the law. This led to low vaccination rates for these voluntary vaccines, and the incidence of the target diseases has remained high [8]. In contrast, the use of the HBV vaccine has been limited to children whose mothers are positive for the HBV surface antigen and individuals at high risk for HBV. Although the HBV carrier rate used to be high in Japan and the rate has decreased significantly due to selective immunization, we nevertheless hope to reduce the rate even further

Table 1
A comparison of vaccines under the immunization law and voluntary vaccines for children in Japan.

	Vaccines under the immunization law	Voluntary vaccines
Regulated by the immunization law	Yes	No
Vaccination fee	Almost free of charge (provided by the government and the local sector)	Out-of-pocket expense
Compensation for adverse effects	By the immunization law	By the PMDA law
Vaccines	Diphtheria, pertussis, tetanus vaccine (DTaP, DT) BCG Oral polio vaccine Measles rubella vaccine (MR, M, R) Japanese encephalitis vaccine Diphtheria tetanus vaccine	*Haemophilus influenzae* type b vaccine[a] 7 valent pneumococcal conjugate vaccine[a] Hepatitis B virus vaccine[b] Mumps vaccine Varicella zoster virus vaccine Human papillomavirus vaccine[a] Influenza vaccine Hepatitis A virus vaccine Rotavirus vaccine

PMDA: Pharmaceutical and medical devices agency.
[a] Supported by the temporary budget for fiscal years 2010–2011 and 2011–2012.
[b] Selective immunization is covered by the national health insurance system.

in order to reduce the drop out of selective immunization and to prevent horizontal transmission through intra-familial, intra-institutional, or sexual routes. Japan is surrounded by countries with a high incidence of HBV infection [9]. In addition, genotype A, which tends to shift to chronic hepatitis, is the predominant genotype accounting for up to 60% of acute HBV infections in Japan [10]. Furthermore, it is estimated that one third of pediatric HBV carriers were transmitted the disease by non-vertical transmission [11]. These facts strongly emphasize the importance of universal HBV vaccination. The new vaccines introduced after 2008, including the Hib vaccine, HPV vaccine, PCV7, and rotavirus vaccine, have also been categorized as voluntary vaccines as of March, 2012. The fee for receiving these vaccines for parents has been high, and the economic burden associated with these VPD has been also high.

3.2. Subcutaneous vs. intramuscular vaccination

Currently, subcutaneous vaccination is the standard method of vaccination in Japan. Intramuscular injection is limited to specific vaccines, including the HPV vaccine, the adjuvanted 2009 A/H1N1 vaccine, and the HBV vaccine for subjects older than 10 years of age. The reason why intramuscular injection has been restricted is that there was a report with an accumulation of approximately 3700 cases with contracture of the gluteal quadriceps muscle in the 1970s due to the frequent intramuscular injection of antibiotics or antipyretics for the treatment of common respiratory infections [12]. Although no case of muscle contracture has been reported due to the injection of vaccines, the Japanese Pediatric Society (JPS) made a statement that there is no safe place for intramuscular injection in children in 1972 to reduce unnecessary injections for common respiratory infections [12]. Since then, intramuscular injections to children have remarkably decreased, but the majority of vaccines have been administered subcutaneously.

Intramuscular injection is known to have benefits compared subcutaneous injection [13]; it causes fewer local reactions such as pain, redness, and swelling, and results in equal or greater immunogenicity in children immunized with the diphtheria, tetanus-toxoid vaccine [14]. In infants that received a tetravalent combination vaccine (diphtheria, pertussis, Hib and IPV), intramuscular injection also showed fewer local reactions and equal immunogenicity compared to subcutaneous injection [15]. Because intramuscular injection is the standard method of vaccination for the majority of vaccines (except for some live vaccines) in other countries, intramuscular injection should be reconsidered as a method of vaccination for Japanese children.

3.3. Anatomical site of vaccinations

The most common location used for the vaccination of children in Japan is the lateral side of the upper arms. The anterior frontal aspects of the thighs have not been used as the site of injection due to the fear of muscle contracture. When simultaneous vaccination is required to provide appropriate vaccines for children, especially in early infancy, Japanese physicians have started to raise questions about where to inject multiple vaccines in the small area of the upper arms in infants. In addition, it has been reported that it is best to separate the injection sites by at least one inch if the same anatomical site is used for intramuscular injection [16], but there have been no such studies regarding subcutaneous injection at the same anatomical site. To provide a sufficient location for vaccination, the anterior frontal aspects of the thighs should be included as a location of vaccination for Japanese children.

3.4. Obstacles impacting simultaneous vaccination

Simultaneous vaccination is a common and safe practice used to vaccinate children [17], and it is known to be efficacious to provide vaccines in a timely manner in order to appropriately protect children from VPD, to save time for caregivers and medical care personnel, and also to decrease the medical costs [18]. However, this practice has not been well distributed and understood in Japan, because there had been no need to perform simultaneous vaccination due to the lack of necessary vaccines, especially during early infancy. Following the introduction of the Hib vaccine and PCV7, there has been a need for simultaneous vaccination. Currently, there are doubts about the safety and efficacy of simultaneous vaccination voiced by both medical professionals and civilians.

To reduce the number of shots for young infants and children, it is necessary to develop and introduce combination vaccines. The usefulness of combinations vaccines has been confirmed by several studies to decrease the numbers of vaccinations and increase the vaccination rates [19–21]; however, there are currently only three combination vaccines available in Japan; the DTaP, DT, and MR vaccines produced by the domestic vaccine companies. Moreover, there is currently no combination vaccine containing components of HBV, Hib, or an inactivated polio vaccine (IPV). At this moment, the numbers of shots that should be completed with the current JPS recommended immunization program during early infancy is high. To date, due to the limited use of combination vaccines in Japan, simultaneous vaccination is a necessary practice to protect children from VPD. This message was clearly noted by the JPS in 2011. However, there has been a gap between the statement and actual practice. To widely distribute simultaneous

vaccination to protect children from VPD beginning from early infancy in Japan, both medical professionals and civilians need to understand the importance and safety of simultaneous vaccination. Furthermore, the introduction of combination vaccines to reduce the number of shots and increase the vaccination rates is urgently needed.

3.5. Rules about the vaccination intervals

Under the immunization law, the intervals at which different inactivated vaccines and live vaccines are given are strictly set to be greater than six days and greater than 27 days, respectively. These numbers were established by the Immunization Law to ensure that the responsible vaccine could be identified if an adverse event occurred after vaccination. These intervals prevent the general public from getting their vaccinations in a timely manner, especially after receiving lives vaccines [Bacille de Calmette et Guérin (BCG) and oral polio vaccine (OPV)] during early infancy. In general, the intervals of different vaccines are only set when parenteral live vaccines are given (28 days) [22]; therefore, these rules should be reconsidered to increase the vaccination rates and increase the opportunities for the vaccination of Japanese children.

3.6. The lack of an effective national immunization technical advisory group (NITAG)

The NITAG is important because it makes decisions that determine the national policy of vaccination; however, such a group does not exist in the current Japanese system. There have been a few committees organized by separate departments of the Ministry of Labor, Welfare, and Health to discuss issues related to immunization; however, there was little discussion regarding the long-term vision of national vaccination strategies and such committees have not been held either regularly or continuously. Because current infectious disease epidemiology clearly indicates that several VPD are still endemic in Japan and affect Japanese children, it is necessary to consider developing a vaccine policy setting system in Japan [23].

4. Current issues

4.1. Refusal of the oral polio vaccine due to fear of vaccine-associated poliomyelitis paralysis (VAPP)

Although the development of IPV using Sabin strain-derived vaccine was initiated in the 1990s in Japan, there has been delay of in the process for its production and authorization, which has therefore led to the current problematic situation, namely that Japan is the only developed country still routinely using the OPV as of March, 2012. There have been many programs on television and articles in newspapers describing the fears of vaccine-associated poliomyelitis paralysis (VAPP), which estimated the incidence of VAPP as 1.4 cases per one million vaccinations in Japan for the last 15 years based on the number of cases that have been reported as VAPP [24]. This led to a decrease in the OPV vaccination. Although a combination vaccine including Sabin strain-derived, inactivated polio and DTaP is expected to be licensed in Japan by the end of 2012 at the latest and the Director of the Ministry of Health, Labor, and Welfare has been trying to facilitate the process, there are caregivers who have had their children receive an imported and unlicensed IPV in Japan by paying for the vaccine out-of-pocket, and more than 20,000 children have been vaccinated this way. If adverse effects occur due to the vaccine, the government cannot be held responsible; the patients will have to be compensated by the insurance system of the importing company, with strict limitations for compensation. Some parents have been waiting for the IPV + DTaP combination vaccine, and have not had their children receive the OPV, which leads to the risk of developing a wild polio infection if the disease moves into Japan. The JPS warned the public about this situation and that everyone should avoid an unvaccinated status, because there are still some outbreak cases of wild polio that have occurred in various countries, including cases in China in August 2011 [25]. This issue will continue until the new Sabin strain-derived IPV + DTaP vaccine is licensed.

4.2. Temporary withholding of the Hib and PCV7 vaccines after a report of seven fatalities

On March 8, 2011, the Hib vaccine and PCV7 were temporarily withheld due to a report of accumulation of seven fatalities that occurred one to seven days after simultaneous vaccinations with the Hib vaccine and/or PCV7 and/or the DTaP vaccine or BCG. Detailed case analyses demonstrated that there was no causative relationship between these deaths and the vaccines according to an expert committee organized by the Ministry of Health, Labor, and Welfare. Two of the cases had severe congenital heart diseases; three patients had risk factors for sudden infant death syndrome; and one case was reported to have a human metapneumovirus infection. The accumulated fatality rates (including adverse events) were 0.13 and 0.15 per one million vaccinations for Hib and PCV7 in Japan between 2005 and 2010, respectively, which have been reported to range between 0.04–1.0 and 0.1–0.6, respectively, in other countries. No specific lots were identified to be responsible for causing the events. Additionally, no deviation in the process of vaccine certification was found. Therefore, the Scientific Committee assembled by the government concluded that there was no relationship between the vaccines and the fatal events, and vaccinations with both vaccines were resumed on April 1, 2011, 22 days after the interruption. Although no causal relationship between the vaccines and fatalities were identified, the following sentences were added to the package inserts for Hib and PCV7; Physicians need to notify their patients or the patients' guardians that there is an option for single vaccination, and single vaccination should thus be considered, especially for children with underlying diseases. These specific notes in the package inserts, which were added without the authorization of vaccine specialists, led to physician confusion regarding whether simultaneous vaccination is safe for Japanese children.

5. New movements to improve the immunization system in Japan

Although these critical issues have been discussed for decades [26], some important movements to improve our current NIP are underway. First, both the general public and medical professionals have voiced a desire to change the NIP, and these voices have become stronger every year. Approximately 2.7 million signatures from civilians and medical professionals led by the Japanese Medical Association were collected and presented to the government asking them to improve the NIP [27]. Second, representatives from 13 medical professional societies gathered to ask the government to consider immunization policy as a "national policy" and seeking the establishment of a new NITAG system to provide expert opinions for the government [23]. Finally, along with these movements, the government launched the Vaccination Subcommittee of Health Sciences Council to discuss the reform of the current Immunization Law and NIP in Japan [28]. All of these new movements led to the government's decision to establish a new national program for the Hib vaccine, PCV7, and HPV vaccines funded by a temporary budget. The government is further considering continuing this budget and

including these vaccines into the NIP, along with other important vaccines currently categorized as voluntary vaccines, such as the universal HBV vaccine, VZV vaccine, and mumps vaccine. Furthermore, the JPS launched a new immunization schedule which put the vaccines in an order of requirement and does not distinguish between the vaccines under the law and voluntary vaccines [29]. It is hoped that these new movements will reform the immunization law and improve the NIP in Japan, and that this will lead to the government providing necessary vaccines for all children without out-of-pocket expenses for the guardians in order to make sure that all children are protected from VPD.

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We dedicated this manuscript to Dr. Hitoshi Kamiya (1943–2011) who devoted his life to improving the immunization systems in Japan.

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Perinatal immunization education improves immunization rates and knowledge: A randomized controlled trial☆,☆☆

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ABSTRACT

Objectives: To determine if providing perinatal immunization education positively changes the immunization status of infants, influences the infant immunization knowledge, attitudes and beliefs of mothers and affects the intent to vaccinate children in Japan where immunization education is limited.

Methods: Pregnant women were recruited from three sites in Tokyo, Japan and were assigned to two intervention (pre- or postnatal education) groups and a control group. The immunization status of infants was assessed and a written survey was performed before and after the intervention.

Results: Among 119 study participants, 106 subjects replied to the post-survey. The intervention groups (34.3%) had higher immunization rates in infants at three months of age than the control group (8.3%) ($P = 0.005$); however, no differences were observed between the prenatal (29.4%) and postnatal groups (38.9%) ($P = 0.40$). The percentage of women intended to vaccinate their infants was higher in the intervention groups (61.4%) compared to the control group (33.3%) ($P = 0.01$). The improvement in score for basic knowledge was higher in the intervention groups, particularly in the prenatal group (mean ± S.D.: 3.4 ±1.8) compared to the control (1.9 ± 1.9) ($P = 0.003$).

Conclusions: Perinatal immunization education improved the immunization status of infants, increased the women's knowledge on immunization and intention to vaccinate their infants.

Introduction

The "vaccine gap" is a term that has been used to emphasize the delayed national immunization program in Japan (Saitoh and Okabe, 2012). In Japan, some vaccines are under the national immunization law and other vaccines are considered voluntary vaccines. The determination for which vaccines are categorized as covered under the law or voluntary vaccines has been determined by the government. The decision about which voluntary vaccines are received depends on the parents and they are required to pay an out-of-pocket fee. This financial burden is the major hurdle to increasing the vaccination coverage rates of the voluntary vaccines in Japan. For example, the penetration rate of seven-valent pneumococcal conjugate vaccine (PCV7) was <10% before the introduction of national temporary budget and the rate of hepatitis B virus (HBV) vaccine is <1%. The national temporary budget started in 2011 to help provide PCV7, *Haemophilus influenzae* type b (Hib), and human papilloma virus (HPV) vaccines without out-of-pocket fee and has contributed to increase vaccination rates of three vaccines; however, this budget still being categorized as temporary and the government has not revealed a specific future plan.

The other important issue is that immunization education programs regarding the voluntary vaccines for parents have not been

Abbreviations: VPD, Vaccine preventable diseases; PCV7, seven-valent pneumococcal conjugate vaccine; Hib, *Haemophilus influenzae* type b; HBV, hepatitis B virus; HPV, human papilloma virus; HBM, the Health Belief Model; IBM, the Integrated Behavioral Model.

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sufficiently implemented compared to the programs explaining the vaccines under the law. Information on the vaccines has been available to educate caregivers, including maternal booklets created by local governments. However, this information has been sparse and not standardized or widely distributed for the voluntary vaccines. As a result, most parents consider voluntary vaccines to be less important than the vaccines under the law (Murashige et al., 2011). These current situations have led to a failure to control diseases prevented by voluntary vaccines, such as HBV, varicella zoster virus, mumps, Hib, *Streptococcus pneumoniae*, and rotavirus. Providing more information about the importance of these vaccines may overcome the cost barriers and lead to increases in the vaccination rates.

It is important to know when education programs should be implemented and what information should be provided to parents (Fielding et al., 1994; Waterman et al., 1996). In the United States (U.S.), infant immunization education is systematically and routinely provided (Davis et al., 2004); however, the lack of time dedicated to education has been considered the greatest barrier to communication about the risks and benefits of vaccines (Davis et al., 2002, 2004). Mothers have indicated that they do not have sufficient information regarding immunization (Gust et al., 2005, 2008; Kennedy and Gust, 2005). The effectiveness of perinatal educational intervention has recently been demonstrated to improve maternal knowledge, attitudes, and beliefs regarding vaccination in the U.S. (El-Mnohandes et al., 2003; Vannice et al., 2011; Zuniga de Nuncio et al., 2003). These studies demonstrated that early intervention programs have been considered as useful educational information. In contrast, there are no data available that demonstrate the effectiveness of perinatal educational intervention programs on the vaccination rate in infants and improving the general vaccination knowledge base in Japan.

The purpose of this study was (i) to verify the effect of early educational intervention in a perinatal setting and (ii) to investigate the most effective perinatal period of time for initial immunization education in Japan, where the vaccination system has been behind compared to those in other developed countries.

Methods

Study setting

This randomized controlled trial study investigated the effectiveness of an infant immunization education program for pregnant and postpartum women during the perinatal period. Study subjects were recruited at three obstetrics hospitals in a metropolitan region in Tokyo from June 1, 2011 to July 31, 2011. The hospitals included a national hospital in Tokyo, a private hospital in Tokyo, and a maternity home in Kanagawa. The annual number of deliveries at each hospital was approximately 2000, 1000, and 250, respectively.

Eligibility and enrollment

Pregnant women ages 18 years or older were recruited by the investigators during gestational weeks 32–33 at antenatal classes at the national hospital and the private hospital in Tokyo and by the head midwife at the maternity home in Kanagawa. Demographic information was collected, including maternal age, employment status, date of birth of the infant, education, number of children, family structure, and annual income.

The participants completed a baseline survey after signing a consent form, and the data were collected using self-administered paper and pencil surveys on site. Completion of the survey took approximately 10 min. The instruction not to review any material during the baseline survey was given. All of the surveys were pilot tested by 20 pregnant women and mothers with infants and toddlers prior to initiation of the study, and the questionnaires were revised to improve clarity. The baseline surveys were completed from June 2, 2011 to August 30, 2011.

Each participant received a study identification number and was randomly assigned to one of three groups (two intervention groups and one control group) using a computer generated randomization list that was provided and stratified based on the three enrollment sites upon obtaining consent. Participants were blinded to their group assignment at recruitment and during completion of the baseline questionnaire. Because the intervention was an educational program, blinding the study staff and participants was not possible after the groups were assigned.

Sample size was calculated assuming a completion rate of three vaccines of 10% in the control group, 37 subjects in each study group would be sufficient to detect a completion rate of 40% in the intervention groups with an 80% power and an adjusted type 1 error of 5%.

This study was approved by the Institutional Review Board of the University of Tokyo and the National Center for Child Health and Development.

Intervention

Immunization education was provided for each intervention group during the prenatal or postpartum period. The interventions were conducted in an outpatient setting at the hospital for the prenatal intervention group during weeks 34–36 of gestation and in the hospital wards for the postnatal group 3–6 days after delivery, and the control group did not receive any educational instructions aside from routine check-up visits, which provide instruction only for vaccines under the law. The intervention session consisted of one-on-one interactive educational information on immunization. A single investigator played the role of the educator and covered a wide range of subjects related to immunization. The education session included information on vaccine types, the concept of vaccine-preventable diseases (VPDs), the effectiveness and side effects of vaccines, and the procedure for scheduling infant immunizations in conjunction with the use of an immunization booklet, which outlined all the relevant information, as determined by Japanese immunization specialists, and included an infant immunization schedule issued by the Japan Pediatric Society (2012). The scenario and hypothetical question–answer session were developed in advance. The sessions lasted approximately 10 min.

The post-survey was mailed to all of the participants approximately 100 days after delivery with a 500 yen (approximately 6 U.S. dollar) gift card as an incentive. The control group also received the educational materials when they completed the post-survey and was asked not to review the materials before completing the post-survey.

Outcomes

The primary outcome measure was self-reported up-to-date immunization status for the Hib and HBV vaccines and PCV7 among infants, at age 3 months. The 92-day assessment was used as the standard measure to time the initiation of immunization (Center for Disease Control and Prevention, 1995). The immunization status of each infant was evaluated between the ages of 62 and 92 days because infant immunization begins at two months of age, as determined by the Japanese Immunization Law (Ministry of Health, Labor and Welfare, Japan, 2012). The secondary outcome was the changes in maternal knowledge, attitudes and beliefs and the intent to immunize as measured by the pre- and post-study questionnaires. All participants were evaluated at the beginning of the study and when the infants were three months of age by self-report. Knowledge about VPDs was measured based on correct selection of 13 VPDs out of 21 communicable diseases that can be acquired by the age of two, with scores ranging from 1 to 13. Basic knowledge related to vaccination was measured using multiple choice items (Supplement Table 1). The number of questions answered correctly were added together to obtain a total knowledge score (maximum of 10). Self-reported knowledge related to an individual understanding of childhood vaccination was evaluated using six items using the Likert scale with scores of 1 ("I don't know"), 2 ("I know a little"), or 3 ("I know") (Supplement Table 2).

The Health Belief Model (HBM) (Becker, 1974) and the Integrated Behavioral Model (IBM) (Glanz et al., 2008) were used to assess psychosocial factors using a questionnaire (Painter et al., 2010) that has been used in previous studies (Daley et al., 2007; Glanz et al., 2008; Montano, 1986). Attitudes and beliefs about VPDs and vaccination based on the HBM (Becker, 1974) and the IBM (Glanz et al., 2008) included the perceived severity, perceived susceptibility, perceived benefits, perceived barriers, perceived self-efficacy, injunctive social norms, descriptive social norms, and perceived behavioral controls. All of the items were based on five-point Likert scales ranging from 1 (strongly disagree) to 5 (strongly agree) (Supplement Table 3). The original version was translated from English to Japanese by the investigator and accuracy was confirmed using reverse translation by three individuals who are skilled in the English language. The questionnaires were tested in a pilot study prior to being used.

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The question of intent to immunize was measured on a four-point scale with scores of 1 ("no"), 2 ("undecided"), 3 ("yes, for a specific vaccine"), and 4 ("yes").

Data analysis

Statistical analyses were performed using SPSS version 19.0 (Chicago, IL). All tests were two-tailed with a significance level of 0.05. Descriptive statistics were used to assess the distribution of the background and outcome variables among the survey respondents. We used the Fisher's exact test to perform bivariate analyses to examine data distributions and associations between variables. The Wilcoxon rank-sum test was used to compare mean scores for Likert scores to measure the secondary outcomes in each study group. The Kruskal–Wallis test was used to compare the mean change in pre- and post-survey scores between the three groups. A logistic regression analysis was used to investigate the influence of independent variables (changes in scores of knowledge, attitude, and belief before and after the intervention) upon HBV vaccination status. Univariable and multivariable analyses were performed. The multivariable analysis included variables that were significant at the 0.10 level in the univariate analysis; the final model was chosen using backwards model selection, with a 0.10 significance threshold for inclusion in the model.

Table 1
Characteristics of study participants.

	Prenatal (n = 34)	Postpartum (n = 36)	Control (n = 36)	P-value
Age (mean SD)	35.5 ± 5.2	35.9 ± 4.6	34.7 ± 3.8	0.52[a]
School level				
Middle/high school	3 (8.8)	6 (16.7)	4 (11.1)	0.68[c]
Junior college	12 (35.3)	8 (22.2)	13 (36.1)	
University	19 (55.9)	22 (61.1)	19 (52.8)	
Numbers of children				
0	30 (88.2)	35 (97.2)	28 (77.8)	0.07[c]
1	4 (11.8)	1 (2.8)	5 (13.9)	
≥2	0 (0.0)	0 (0.0)	3 (8.3)	
Maternal employment status				
Unemployed	20 (58.8)	13 (36.1)	13 (36.1)	0.15[c]
Employed	14 (41.2)	23 (63.9)	23 (63.9)	
Household annual income (thousand yen)				
2000–3999	6 (17.6)	4 (11.1)	2 (5.6)	0.50[b]
4000–5999	4 (11.8)	6 (16.7)	5 (13.9)	
6000–7999	2 (5.9)	5 (13.9)	6 (16.7)	
8000–9000	8 (23.5)	11 (30.6)	6 (16.7)	
≥10,000	13 (38.2)	10 (27.8)	14 (38.9)	

Numbers in parenthesis shows percentages in each group.
[a] ANOVA.
[b] Kruskal–Wallis test.
[c] Fisher's exact test.

Results

Study participants

Recruitment took two months. We approached 193 pregnant women and 119 (61%) agreed to participate in the study (Fig. 1), with 74 (62.2%) from the national hospital, 28 (24.1%) from a private hospital, and 17 (12.0%) from the maternal hospital. The number of participants in the prenatal, postnatal, and control groups were 37 (31%), 37 (31%), and 45 (38%), respectively. There were no statistically significant differences in the demographics between the three groups (Table 1). Because three participants in the control group did not return the baseline survey, the final number of participants was 116. A total of 106 post-survey questionnaires were returned (response rate: 92%). A detailed flow chart depicting the participants in each group is shown in Fig. 1.

Immunization rates at three months of age

The overall infant immunization rates for the three vaccines during the 92-day follow-up period were higher in the prenatal group (29.4%) and the postnatal group (38.9%) compared to the control group (8.3%) (P = 0.007) (Table 2). The two intervention groups combined had a higher rate of vaccination compared to the control

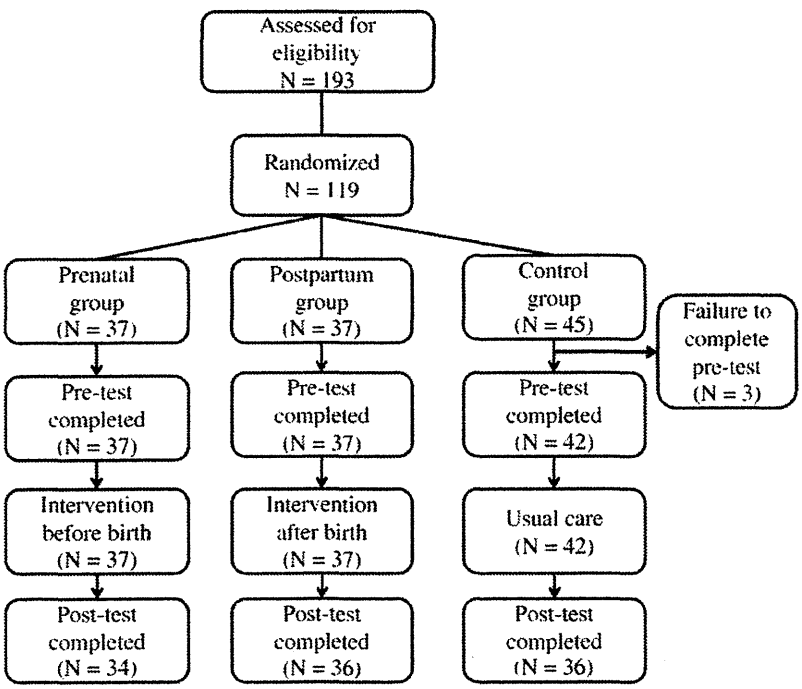

Fig. 1. Flow chart of the study participants.

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Table 2
Immunization status after intervention among three groups.

	Prenatal (n = 34)	Postpartum (n = 36)	Control (n = 36)	P-value[a]	Intervention[b] (n = 70)	Control (n = 36)	P-value[c]
Immunization status							
Completed three vaccines	10 (29.4)	14 (38.9)	3 (8.3)	0.007[e]	24 (34.3)	3 (8.3)	0.005[e]
Number of completed vaccination (range: 0–3)	2.2 ± 0.6	2.3 ± 0.7	1.9 ± 0.7	0.02[d]	2.2 ± 0.6	1.9 ± 0.7	0.01[f]
Types of vaccination							
Haemophilus influenzae type b (Hib)	32 (94.1)	35 (97.2)	32 (88.9)	0.44[e]	67 (95.7)	32 (88.9)	0.22[e]
Conjugated seven-valent pneumococcal (PCV7)	32 (94.1)	34 (94.4)	32 (88.9)	0.73[e]	66 (94.3)	32 (88.9)	0.44[e]
Hepatitis B virus (HBV)	10 (29.4)	14 (38.9)	4 (11.1)	0.02[e]	24 (34.3)	4 (11.1)	0.02[e]

Numbers: n (%) or mean ± S.D.
[a] Comparison between the three groups.
[b] Combination of prenatal and postpartum.
[c] Comparison between the intervention group and control group.
[d] Kruskal–Wallis test.
[e] Fisher's exact test.
[f] One-sample Wilcoxon rank-sum test.

group (34.3% vs. 8.3%, P = 0.005); however, no differences in immunization rates observed between the intervention groups (P = 0.40). When we compared each vaccine, the immunization rate of the HBV vaccine was higher in the intervention groups (34.3%) compared to the control group (11.1%) (P = 0.02); however, no significant differences in the vaccination rates of the Hib vaccine (P = 0.22) and PCV7 (P = 0.44) were observed between the two groups.

Intent to immunize

There was a significant difference in the responses regarding the intent to immunize infants between the intervention and the control group (P = 0.01) (Table 3). The percent of participants who answered 'yes' in the questionnaire was higher in the intervention groups (61.4%) compared to the control group (33.3%). This difference was not observed in the pre-test survey (data not shown).

Knowledge

There were significant improvements in all of the knowledge components between the pre- and post-intervention in all three groups (P = 0.001) (Table 4). A significant improvement in the basic knowledge regarding immunizations was observed between the three groups. The prenatal group showed the highest gain in scores (3.4 ± 1.8), followed by the postnatal group (2.6 ± 1.5) and the control group (1.9 ± 1.9) (P = 0.008) (Table 5). The VPD (P = 0.97) and self-knowledge scores (P = 0.44) did not change between the three groups. Changes in self-knowledge score was significantly associated with HBV vaccination status (P = 0.01) by univariate logistic regression analysis and this remained significant (P = 0.02) after controlling for other significant variables (Supplement Table 4).

Attitudes and beliefs

There were several significant improvements in the scores regarding the attitudes and beliefs toward immunization between the pre- and post-interventions. The perceived severity score improved in the prenatal and control groups (P = 0.01 and P = 0.002, respectively), but not in the postnatal group (P = 0.18). The perceived barrier score in the postpartum group increased after the intervention (P = 0.01), but not in the prenatal and control groups (P = 0.79 and P = 0.43, respectively) (Table 4). All of the groups showed higher scores for the injunctive social norm and the descriptive social norm following the intervention (P < 0.006). Changes in the scores between the pre- and post-test for each of the attitude and belief components did not change significantly between the three groups (P ≥ 0.05) (Table 5).

Perceived behavioral control affected HBV vaccination status (P = 0.03) by univariate logistic regression analysis; however, it did not remain significant after controlling for other significant variables (Supplement Table 4).

Discussion

This is the first randomized controlled study to demonstrate the effectiveness of pre- and postnatal immunization education to improve the vaccination status of infants and the knowledge, attitudes, and beliefs of mothers toward immunization. This study indicates that there is an advantage to providing information about immunization during the perinatal period to protect children from VPDs in Japan, where information regarding the immunization schedule during early infancy is limited and financial barriers to recipients exist.

The results of the current study support the importance of immunization education during the perinatal period. A previous study reported that the importance of parenting education program because education in perinatal period improved to complete the scheduled

Table 3
Intention to receive vaccines after intervention among three groups.

	Prenatal (n = 34)	Postpartum (n = 36)	Control (n = 36)	P-value[a]	Intervention[b] (n = 70)	Control (n = 36)	P-value[c]
Intention to receive vaccines							
No/undecided	0	0	0		0	0	
Yes, for sure	18 (52.9)	25 (69.4)	12 (33.3)	0.03[d]	43 (61.4)	12 (33.3)	0.01[d]
Yes, for specific vaccine	9 (26.5)	7 (19.4)	18 (50.0)		16 (22.9)	18 (50.0)	
No answer	7 (20.6)	4 (11.2)	6 (16.7)		11 (15.7)	6 (16.7)	

Numbers: n (%) or mean ± S.D.
[a] Comparison between the three groups.
[b] Combination of prenatal and postpartum.
[c] Comparison between the intervention group and control group.
[d] Fisher's exact test.

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Table 4
Scores of knowledge, attitudes and beliefs between pre-test and post-test among three groups.

	Range	Prenatal (n = 34)		P-value[a]	Postpartum (n = 36)		P-value[a]	Control (n = 36)		P-value[a]
		Pre-test	Post-test		Pre-test	Post-test		pre-test	post-test	
Knowledge										
VPD score	1–13	6.7 ± 2.9	11.2 ± 1.8	0.001*	6.0 ± 2.7	10.6 ± 2.4	0.001*	5.6 ± 3.2	10.1 ± 2.4	0.001*
Self-knowledge	1–12	4.0 ± 3.9	9.9 ± 2.1	0.001*	2.7 ± 2.5	9.7 ± 2.2	0.001*	3.6 ± 3.0	9.7 ± 1.9	0.001*
Basic knowledge	1–10	6.2 ± 1.7	9.5 ± 0.9	0.001*	6.7 ± 1.4	9.3 ± 1.0	0.001*	6.9 ± 1.6	8.8 ± 1.4	0.001*
Attitudes and beliefs										
Perceived severity (HBM)	2–10	7.9 ± 1.3	8.6 ± 1.3	0.01*	7.6 ± 1.4	7.9 ± 2.0	0.18	7.0 ± 2.1	8.2 ± 1.5	0.002*
Perceived susceptibility (HBM)	1–5	1.9 ± 1.1	1.9 ± 1.1	0.84	1.9 ± 1.0	1.8 ± 1.0	0.79	2.0 ± 1.0	2.1 ± 1.1	0.36
Perceived benefit (HBM)	4–20	11.5 ± 3.5	11.5 ± 6.6	0.22	10.3 ± 4.0	10.4 ± 4.6	0.82	10.1 ± 3.9	11.4 ± 8.6	0.46
Perceived barriers (HBM)	5–25	13.4 ± 3.4	13.2 ± 4.1	0.79	12.3 ± 3.1	13.2 ± 4.0	0.01*	11.7 ± 3.2	13.1 ± 8.4	0.43
Self-efficacy (HBM)	2–10	7.2 ± 1.2	7.5 ± 1.3	0.16	7.2 ± 1.7	7.5 ± 1.5	0.19	7.9 ± 0.9	7.5 ± 1.8	0.16
Perceived behavioral control (IBM)	1–5	3.4 ± 1.0	3.9 ± 1.7	0.06	3.4 ± 1.2	3.7 ± 1.2	0.26	3.7 ± 1.0	3.6 ± 1.5	0.57
Social norm (injunctive)	4–20	16.0 ± 2.5	17.5 ± 2.7	0.003*	15.9 ± 3.2	17.5 ± 2.3	0.001*	16.4 ± 2.4	18.4 ± 2.1	0.001*
Social norm (descriptive)	2–10	7.9 ± 1.6	9.4 ± 1.0	0.001*	8.1 ± 2.0	9.2 ± 1.5	0.005*	8.1 ± 2.5	9.2 ± 1.5	0.006*

Numbers: mean ± S.D.
VPD: Vaccine Preventable Diseases, HBM: Health Belief Model, IBM: Integrated Behavioral Model.
[a] One-sample Wilcoxon rank-sum test.
* p<.01.

immunization (El-Mnohandes et al., 2003). To improve parental knowledge, several studies have indicated the effects of early intervention in a prenatal care setting (Bjornson et al., 1997; Zuniga de Nuncio et al., 2003). Our study demonstrated that providing general information of infant immunization may have given positive impact on immunization status, knowledge and intent to immunize. As other data suggested (Vannice et al., 2011; Vora et al., 2009), our data also supported the fact that postpartum period is an important period to implement infant immunization education. These previous studies reported that perinatal education had positive effects on immunization status, knowledge, attitudes, and intent to vaccinate, when these variables were considered separately; however, our study showed that perinatal education had a simultaneous positive impact on all the above factors.

In this study, the intervention groups had higher immunization rates of the HBV vaccine compared to the control group. This is probably due to the fact that current HBV vaccination rate is low, estimated <1%. However, no significant differences in the immunization status of the Hib vaccine and PCV7 were observed. A possible explanation is that the government decided to provide a temporary budget for newly introduced vaccines, including the Hib, and HPV vaccines and PCV7, beginning in 2011, which was approximately two months before the participants were enrolled in the study. More than 90% of local governments offered support for all three of these vaccination fees and provided information to parents on the necessity of these vaccines. As a result, infants could readily receive Hib vaccine and PCV7 during this period, and the distribution rates of both vaccines improved from <10% to 60–70% at 6 months after implementation of the budget, which may explain why there were no differences in vaccination rates with respect to intervention status. Socioeconomic barriers have a significant impact on vaccination rates, and removing these barriers to vaccination is the first step to improving coverage (Diekema, 2012). Our results suggested that financial issue needs to be improved and all childhood vaccinations need to be included in vaccines under the law.

Another factor that may have impacted the results of this study is the dispersion of misleading information by influential individuals, vaccine safety advocates, and some clinicians. For example, the importance of the universal HBV vaccine has not been well communicated in Japan (Komatsu et al., 2009). HBV vaccine has typically been given only to infants of HBsAg-positive mothers. Our encouraging results regarding HBV vaccination suggest that maternal education improves immunization rates, particularly in areas where information is limited.

The knowledge score increased in the pre- and post-surveys between the three groups. It is possible that the participants obtained immunization information from different resources, such as home visits from medical personnel or at the one-month infant check-up by physician. The basic knowledge score significantly differed based on the type of intervention and changes in self-knowledge score

Table 5
Changing in scores of knowledge, attitudes and beliefs from pre-test to post-test among three groups.

	Range	Prenatal (n = 34)	Postpartum (n = 36)	Control (n = 36)	P-value[a]
Knowledge					
VPD score	1–13	4.5 ± 2.8	4.5 ± 2.9	4.6 ± 3.8	0.97
Self-knowledge	1–12	5.9 ± 2.8	6.9 ± 2.7	6.2 ± 2.8	0.44
Basic knowledge	1–10	3.4 ± 1.8	2.6 ± 1.5	1.9 ± 1.9	0.008*
Attitudes and beliefs					
Perceived severity (HBM)	2–10	0.8 ± 1.5	0.3 ± 1.9	1.3 ± 2.2	0.37
Perceived susceptibility (HBM)	1–5	0.03 ± 1.3	−0.03 ± 0.8	0.2 ± 0.9	0.39
Perceived benefit (HBM)	4–20	−0.2 ± 6.6	0.2 ± 4.2	1.4 ± 7.6	0.33
Perceived barriers (HBM)	5–25	−0.2 ± 3.6	0.8 ± 3.4	1.5 ± 7.6	0.40
Self-efficacy (HBM)	2–10	−0.2 ± 1.6	0.3 ± 1.3	−0.4 ± 1.3	0.05
Perceived behavioral control (IBM)	1–5	0.4 ± 1.3	0.3 ± 1.6	−0.1 ± 1.3	0.32
Social norm (injunctive)	4–20	1.5 ± 2.4	1.7 ± 2.7	1.8 ± 2.5	0.86
Social norm (descriptive)	2–10	1.5 ± 1.9	1.1 ± 2.3	1.2 ± 2.4	0.39

Numbers: mean ± S.D.
HBM: Health Belief Model, IBM: Integrated Behavioral Model.
[a] Kruskal–Wallis test.
* p<.01.

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were significantly associated with HBV vaccination status. The importance of education during the perinatal period has been confirmed in other studies in which pregnant women who received prenatal educational sessions on immunization demonstrated an improved knowledge regarding various aspects of vaccination (Zuniga de Nuncio et al., 2003). Another study showed that incorporating immunization education into routine prenatal care increased maternal knowledge regarding infant vaccines and reduced delayed immunization (Navar et al., 2007). Additional studies are necessary to clarify the improvement in knowledge regarding immunization as it relates to improved vaccination rates.

Several factors need to be considered when analyzing the data in this study. First, the sample size was small, which decreased the likelihood of detecting potential differences. Second, the introduction of temporary budget during this study period increased the vaccination rates of the Hib vaccine and PCV7, which can confound the study results. Additionally, a television commercial for the PCV7 was aired during the study period in Japan, which emphasized the necessity of the PCV7 and may have reduced the impact of the intervention. Third, the study participants were well-educated and had a high socioeconomic status and had the ability to obtain information related to immunization on their own through a variety of resources, which might have affected the outcome of our intervention. Although we compared the resources about infant immunization, no difference was identified. Furthermore, since not only educational background and remuneration differs, but also immunization policy and practice vary between countries, the results of this study may not be generalizable. Fourth, attendance at antenatal classes was voluntary, and enrollment in the study was solely at the discretion of the participants. In addition, a few participants from the control group withdrew from the study. As such, it is possible that pregnant women who were uninterested in immunization, or less active in child health, did not enroll in the study. This group may be a more important target population for this study. Fifth, we need to consider the self-report bias (Adams et al., 1999), which can result in an inflation of behavioral intention. Sixth, during this study period, the media reported on an oral polio vaccine that can cause vaccine-associated polio paralysis, which led to increase the attention of parents toward the safety rather than the importance of immunization, which may have played a role indifferences in the attitudes and beliefs toward immunization. Lastly, the follow-up period of the study was only three months. A longer observation period may highlight differences in the immunization completion rates.

Conclusions

Pre- and postnatal immunization education in pregnant women in Japan improved the immunization rates of infants and increased the intent to vaccinate infants and the maternal knowledge regarding immunization. Future research is necessary to investigate the optimal timing and content of immunization education and develop a standard education program with related materials to encourage the immunization of infants in Japan.

Conflict of interest statement

All authors have no conflict of interest.

Acknowledgments

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Appendix A

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, menthods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	none
Participants	4a	Eligibility criteria for particaipants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8-9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	none
Sample size	7a	How sample size was determined	7
	7b	When applicable, explanation of any interim analyses and stopping guidelines	none
Randomisation:			
Sequence	8a	Method used to generate the random allocation sequence	6
Generation	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Concealment Mechanism			
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	7

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	none
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	none
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	11
	13b	For each group, losses and exclusions after randomisation, together with reasons	11
Recruitment	14a	Dates defining the periods of recruitment and follow-up	6
	14b	Why the trial ended or was stopped	none
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	11, Figure 1
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	11-13
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	none
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	none
Harms	19	All importand harms of uninteded effects in each group (for specific quidance see CONSORT for harms)	none
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and if relevent, multiplicity of analyses	16-17
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	16
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	14-16
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	none
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	18

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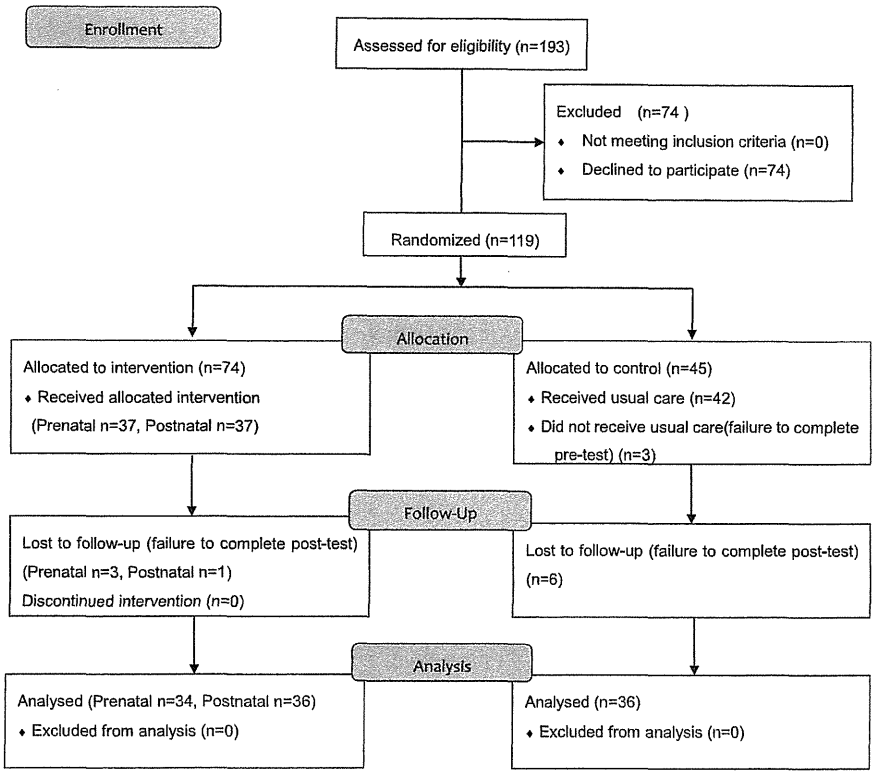

Appendix B. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ypmed.2013.03.003.

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Effective control of Epstein–Barr virus infection following pediatric liver transplantation by monitoring of viral DNA load and lymphocyte surface markers

Imadome K-I, Fukuda A, Kawano F, Imai Y, Ichikawa S, Mochizuki M, Shigeta T, Kakiuchi T, Sakamoto S, Kasahara M, Fujiwara S. Effective control of Epstein–Barr virus infection following pediatric liver transplantation by monitoring of viral DNA load and lymphocyte surface markers.

Abstract: EBV-associated PTLD is a serious complication of liver transplantation. We performed periodical molecular EBV monitoring in 140 consecutive pediatric patients who had living-related liver transplantation in the National Center for Child Health and Development, Tokyo. Sixty-three of the 140 patients showed elevation of EBV DNA level to $>10^2$ copies/μg DNA and were further examined immunologically by flow cytometry, and the dose of tacrolimus and/or cyclosporine A was adjusted according to the results. The decrease in CD4/CD8 ratio and the increase in the number of HLA-DR$^+$CD8$^+$ cells were observed in parallel with the decrease in EBV DNA load and in the number of CD19$^+$CD23$^+$ cells following the reduction in immunosuppressive drugs. Analysis with HLA tetramers in a patient demonstrated a dramatic increase in the number of CD8$^+$ T cells specific to the EBV latent protein LMP2 accompanying the decline of EBV DNA load, suggesting that T cells of this specificity were actually involved in the control of EBV infection. No clinically apparent PTLD has developed in the 140 recipients, suggesting that our program of EBV control by molecular EBV monitoring coupled with lymphocyte phenotype analyses is effective in controlling EBV infection in pediatric liver transplant recipients.

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Key words: Epstein–Barr virus – lymphoproliferative disorder – liver transplantation – real-time PCR – tetramer – flow cytometry – LMP2

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EBV is a ubiquitous γ-herpesvirus infecting more than 90% of the adult population in the world (1). Primary EBV infection, occurring usually in childhood, is asymptomatic in most cases and results in life-long latent infection. B lymphocytes are the major target of EBV infection and can be transformed by the virus into LCLs with a capacity for autonomous proliferation. In immunologically competent hosts, EBV-transformed lymphoblastoid cells are efficiently removed by the virus-specific cytotoxic T cells that recognize epitopes derived from a limited number of EBV proteins expressed in LCLs (2). EBV-transformed LCLs express six nuclear proteins (EBNAs 1, 2, 3A, 3B, 3C, and LP) and three membrane proteins (LMPs 1, 2A, and 2B).

Abbreviations: CMV, cytomegalovirus; CNIs, calcineurin inhibitors; EBNA, EBV nuclear antigen; EBV, Epstein–Barr virus; ECD, phycoerythrin Texas red; FITC, fluorescein isothiocyanate; LCL, lymphoblastoid cell line; LDLT, living donor liver transplantation; LMP, latent membrane protein; LT, liver transplantation; PBMC, peripheral blood mononuclear cells; PE, phycoerythrin; POD, postoperative days; PTLD, post-transplant lymphoproliferative disorder; RT-PCR, reverse transcription PCR.

Among the nine viral proteins, EBNAs 3A, 3B, and 3C are the most immunodominant proteins that elicit T-cell responses in the majority of hosts (2). Significant but lower levels of T-cell responses are also induced against other latent EBV proteins (2). In transplant recipients under treatment with immunosuppressive drugs, these LCLs are not effectively removed mainly because of T-cell immunodeficiency and may continue to proliferate causing the PTLD (3, 4). Analysis of immunoglobulin heavy chain genes showed that PTLD often arises from post-germinal-center B cells with non-functional immunoglobulin gene rearrangement. As B cells with such non-functional immunoglobulin genes are normally eliminated in germinal centers, it is speculated that EBV has rescued these cells via its anti-apoptotic proteins (5). The incidence of PTLD in liver transplant recipients has been reported to be 2–3% in adults and 8–10% in children (6–8). The higher rate in pediatric cases is explained by the higher frequency of EBV-seronegative recipients as compared with adult cases. EBV-seronegative recipients were reported to have a higher risk of PTLD because the virus is transmitted via the liver transplant and causes primary infection (9, 10), although contradictory results were also reported (11). PTLD occurs in the first two yr following transplantation in 80% of cases, although some additional occurrence is observed in later period (12). The mortality rate of EBV-associated PTLD was estimated to be around 20% (13).

To prevent or enable preemptive treatment of EBV-related PTLD, it has become a routine practice to monitor EBV DNA load in the peripheral blood of transplant recipients. This approach has brought a significant improvement in the results of not only liver transplantation but also other solid organ and hematopoietic stem cell transplantations (14–17). The aim of this study was to evaluate the efficacy of monitoring EBV DNA loads with lymphocyte phenotype analyses in the peripheral blood of recipients for preemptive controlling of EBV infection in pediatric LDLT.

Patients and methods

Patients

The study subjects comprised of 140 children who received LDLT at the National Center for Child Health and Development in Tokyo, the largest pediatric liver transplantation center in Japan, between November 2005 and October 2010. This study was a retrospective evaluation of the standard protocol, which has been performed at our institution. The following information was extracted from the medical record database: age, gender, and EBV serostatus of the donors and recipients; primary diseases, reasons for LT, the first postoperative date positive for EBV-PCR, and its duration; EBV-related disease, clinical outcome, and mortality. The indication for liver transplantation included biliary atresia (59 cases), fulminant liver failure (24 cases), methylmalonemia (10 cases), glycogen storage disease 1b (six cases), anomalies of the portal venous system (six cases), ornithine transcarbamylase deficiency (five cases), carbamyl synthase 1 deficiency (four cases), and others (26 cases). The recipients were mostly children, and their age distribution is as follows: < 1 yr, 61 cases; one yr, 18 cases; 2–5 yr, 24 cases; 6–9 yr, 19 cases; 10–15 yr, 14 cases; and 16 or older, four cases. The EBV serological status of both the recipient and the donor was determined in 123 of the 140 cases, and the age at LDLT and the number of patients who had elevation of EBV DNA load are shown in Table 1. Seventy-one recipients were EBV seropositive, and the remaining 52 recipients were seronegative. Recipients received liver grafts from fathers (n = 62), mothers (n = 75), grandfather (n = 1), brother (n = 1), and aunt (n = 1), and 120 of the 123 donors were EBV seropositive.

After LDLT, standard immunosuppression consisted of corticosteroids and tacrolimus. The corticosteroid was started intraoperatively (10 mg/kg/dose) and continued with tapering for the first three months after LDLT (1.0 mg/kg/day IV [days 1–3], 0.5 mg/kg/day IV [days 4–6], 0.3 mg/kg/day IV [day 7], 0.3 mg/kg/day orally [p.o.] [days 8–28], and 0.1 mg/kg/day p.o. [days 29–90]). Tacrolimus was also started one day after surgery, and the dose was adjusted to maintain a trough level of 10–15 mg/L for the first two wk, followed by 8–10 mg/L (days 15–28 after LDLT), 6–8 mg/L (days 29–90), and 4–6 mg/L (after day 91). Primary immunosuppressant was converted from tacrolimus to cyclosporine A when the patients suffered from tacrolimus-related adverse events. Most of the 140 patients were given acyclovir during the three months following transplantation for prophylaxis of herpes simplex virus diseases. Forty patients received ganciclovir because of positive CMV antigenemia. This research was approved by the Institutional Review Boards of the National Center for Child Health and Development (approval number 410), and written informed consent was obtained from all patients or guardians.

Molecular Epstein–Barr virus monitoring

Measurement of EBV DNA load was made every week while the patients remained in the hospital (usually for two months following transplantation), and thereafter every 1–3 months until one yr after transplantation. After that, EBV DNA was measured when physicians thought it necessary. Quantification of EBV DNA was carried out by a real-time quantitative PCR assay based on the TaqMan

Table 1. The number of recipients with elevation of EBV DNA load based on the donor and recipient pretransplant EBV serologic status

Donor/recipient EBV serologic status	N (%)	Age at LDLT, median months (range)	Number of recipients with elevation of EBV DNA load to $>10^2$ copies/μg DNA (%)
D+/R+	69 (56.1)	16 (1–257)	28 (41)
D+/R−	51 (41.5)	11 (5–119)	34 (67)
D−/R+	2 (1.6)	9 (4–26)	1 (50)
D−/R−	1 (0.8)	9 (9)	0 (0)
Total	123 (100)	16 (1–257)	63 (51)