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CONTENTS

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Measles Vaccine / Rubella Vaccine

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Abstract: In Japan, routine measles vaccination was introduced in 1978 and routine rubella vaccination in 1977. The measles vaccination rate is approximately 70% and this percentage has been on the increase in recent years. Although the number of patients with measles and the number of deaths from measles have decreased, measles has not been completely controlled because of the continuation of its sporadic or epidemic outbreaks. Routine rubella vaccination was initially administered to junior high school girls with a vaccination rate of approximately 70%. According to the revision of the Preventive Vaccination Law in 1994, routine rubella vaccination is to be administered to children. Junior high school students are to undergo rubella vaccination until 2003. The rate of rubella vaccination among junior high school students decreased to the 50% range, which resulted in an immunity gap among the population. The rate of rubella vaccination among children was in the 40% range. Since the epidemics during the period from 1992 to 1993, no epidemics of rubella have been reported although its sporadic outbreaks continue. The selective rubella vaccination to junior high school girls has failed to control the outbreak of congenital rubella syndrome. Although a strategy to promote the vaccination against measles and rubella has been adopted in Japan, the current vaccination rates are too low to eradicate the diseases. It is necessary to encourage people to undergo vaccinations against these infections. The introduction of combined measles-mumps-rubella (MMR) vaccine or measles-rubella (MR) vaccine is considered to be useful to increase the vaccination rates.

Key words: Measles; Rubella; Vaccine; Vaccination rate

Introduction

Measles and rubella are contagious diseases that can be prevented by vaccinations. In Japan, routine measles vaccination was introduced 22 years ago in 1978 and routine rubella vaccination has been administered for 23 years since 1977. During this period, combined measles-mumps-rubella (MMR) vaccine was introduced and held in abeyance (1989–1993), and the Preventive Vaccination Law was revised in 1994. Although vaccinations against measles and rubella have contributed to the prevention of these diseases to some extent, their occurrence

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has been continuously reported. Because several patients die of measles each year and the outbreak of congenital rubella syndrome (CRS) continues, the eradication of these diseases has been delayed in Japan. In industrialized countries such as Europe and the United States, people are recommended to receive two doses of MMR vaccine and the adoption of this vaccination system has contributed to the control of these diseases.[1,2)]

In Japan the revision of the Preventive Vaccination Law had few effects on the measles vaccination. After the revision, those who were recommended to receive rubella vaccination and the rate of rubella vaccination were definitely changed. The current conditions of vaccinations against measles and rubella and the outbreaks of these diseases suggest the necessity of encouraging people to receive these vaccinations. The present paper discusses the problems relating to the countermeasures to improve current conditions.

Clinical and Epidemiological Characteristics of Measles and Rubella

Measles is an extremely contagious disease and the incidence of subclinical infection is very low. During the prevaccine era epidemics usually occurred at intervals of one to three years and most children suffered from the clinical measles. In patients with measles, in addition to a high fever, maculopapular rash and respiratory symptoms, serious complications involving pneumonia, encephalitis (1/1,000) and subacute sclerosing panencephalitis (1/100,000) occur. Therefore, measles is regarded as a life-threatening disease.

Rubella is a relatively mild disease which frequently outbreaks among kindergarten and primary school children and is characterized by exanthema, lymphadenopathy and mild fever. Patients with subclinical infection account for 20 to 40%. Women in the first trimester of pregnancy who contract rubella, regardless of clinical or subclinical infection, may give birth to infants with congenital rubella syndrome (CRS) including cataracts, congenital heart disease, and deafness. The risk of CRS from rubella during the first trimester is approximately 20%.

A rubella epidemic causes major anxiety in society. For example, 20,000 babies with CRS were born in the United States in 1964 and 400 in Okinawa in 1965.[2,3)] Before the 1975–1977 nationwide rubella epidemic in Japan, rubella epidemics had occurred there in 10-year cycles. That is, an epidemic developed and continued for 4–5 years, followed by an interval of 4–5 years with no reported rubella cases. However, this pattern changed to one that is similar to those in the United States and Europe, i.e., rubella occurred endemically, with periodic epidemics. According to the results obtained from a seroepidemiologic survey conducted on the residents of Fukuoka prior to the introduction of routine rubella vaccination, rubella epidemics ceased when 40 to 60% of primary school children acquired immunity. In those days, the adults who acquired the antibodies to rubella accounted for 80 to 90%.[4)]

Vaccinations for Measles and Rubella and the Occurrence of the Diseases

1. Measles vaccination rate and outbreak of measles (Table 1)

Since the introduction of routine measles vaccination in Japan in 1978, the vaccination rate has ranged from 54 to 77% (approximately 70%). The revision of the Preventive Vaccination Law has had minimal effects. The preventive vaccination study group of the Ministry of Health and Welfare reported that no significant changes can be observed in the measles vaccination rate before and after the revision of the Preventive Vaccination Law. Accordingly the rate has been maintained at a constant level ranging from 71 to 75%.[5)]

According to the National Epidemiological Surveillance of Infectious Diseases in Japan (NESID), three peaks of measles outbreak

Table 1 Incidence of Measles and Rubella, Number of Related Deaths, Incidence of Congenital Rubella Syndrome, and Vaccination Rates

Year	Measles				Rubella				
	Number of patients per sentinel clinic and hospitals*[1]	Number of deaths*[2]	Vaccination rates		Number of patients per sentinel clinic and hospitals*[1]	Number of patients with CRS*[5]	Vaccination rates		
			(%)*[3]	[%]*[4]			Junior high school students (%)*[3]	Infants (%)*[3]	[%]*[4]
1977		138				106	27.3		
1978		181	72.6			19	72.4		
1979		80	59.1			11	63.7		
1980		50	54.2			5	65.1		
1981		52	63.9			24	64.8		
1982	24.10	24	65.5		163.55	45	72.2		
1983	30.18	47	69.5		40.46	8	74.0		
1984	57.77	90	72.9		23.21	3	72.6		
1985	11.40	36	65.8		18.02	8	70.1		
1986	19.22	88	70.4		41.57	8	72.1		
1987	22.66	96	77.3		172.94	134	70.6		
1988	16.10	78	75.3		67.42	33	68.2		
1989	11.72	34	76.5		32.87	9	69.6	50.8*[6]	
1990	17.14	53	65.5	[64.3]	20.63	—	68.8	28.3*[6]	
1991	28.68	39	71.4	[71.0]	27.29	—	69.0	29.2*[6]	
1992	13.20	14	69.2	[66.2]	92.67	—	70.6	25.9*[6]	
1993	14.25	14	67.5	[71.9]	60.97	—	67.2	7.1*[6]	
1994*[7]	8.89	11	74.5	—	14.79	—	66.8	—	
1995	7.32	7	68.3	[74.3]	6.67	—	53.1	98.1	[44.4]
1996	9.44	15	93.9	[74.6]	10.98	—	47.2	113.9	[47.5]
1997	6.50	18	94.0	[74.4]	19.61	—	50.3	114.7	[46.1]
1998	4.07	25	91.7	[71.1]	9.18	—	55.9	104.4	[49.0]

*[1]Number of patients per sentinel clinic and hospitals: The National Epidemiological Surveillance of Infectious Diseases, the Ministry of Health and Welfare.

*[2]Number of Deaths: Vital statistics reported by the Ministry of Health and Welfare.

*[3]The vaccination rate is calculated according to the number of measles vaccines based on the public health center report and the population to be vaccinated according to the data on the population reported by the Statistics Bureau, Ministry of Public Management.

*[4]The data from the Report of the Preventive Vaccination Study Group, the Ministry of Health and Welfare.

*[5]Congenital rubella syndrome (CRS): Number of births with CRS based on the results of the nationwide survey conducted in special schools for the deaf in Japan[10)]

*[6]MMR vaccination rate: (Kimura, M., *et al.*: *Handbook of Vaccinations*, 8th edition, Kindai Publishing Co. Ltd., 2000.)

*[7]Year of the revision of Preventive Vaccination Law

observed in 1983–1984, 1986–1987, and 1990–1991, and the number of patients with measles per sentinel clinic and hospitals during these periods was 30–57, 19–22, and 17–28, respectively. The figure has gradually decreased to between 4 and 9 since the last peak.

According to the vital statistics reported by the Ministry of Health and Welfare, the number of deaths from measles reported in 1978, the year when routine vaccination was introduced, was 181 and the numbers reported during the three peak periods mentioned above were 47–90, 88–96, and 53–39, respectively. Although a decreasing tendency in the number of deaths has been apparent thereafter, an increase was recognized in 1998. A total of 34 cases of subacute sclerosing panencephalitis was reported for the 9 year period from 1990 to 1998.[6)] In 1998, in addition to the outbreak of measles in Okinawa, epidemics prevailed in Osaka and Chiba Prefectures (Infection Diseases Weekly Report, 11th, 2000).

The incidence of measles is high especially among one-year-old infants. Researchers have recently been focusing on various trends such as severe measles among adults, premature or still births to maternal measles, newborn measles, measles among school children, and measles vaccine failure. In such circumstances, the incidence of adult measles was included as a new item in the 4 category in sentinel surveillance system in order to clarify the actual conditions surrounding the disease.[7] According to the results obtained from the seroepidemiologic investigation conducted as part of National Epidemiological Surveillance of Vaccine-Preventable Diseases in Japan (NESVPD), the measles vaccination rate has been maintained at the level of 70% and the antibody positive rate among children, ranging in age from 3 to 4, has reached a level exceeding 95% and that among population over five years of age has been maintained at a level ranging from 90 to 100%. These data suggest that about 20 to 30% children may be infected to a wild measles virus.[8]

2. Rubella vaccination rate and congenital rubella syndrome (Table 1)

According to a public health center report, the rate of rubella vaccination among junior high school girls in Japan ranged from 63 to 74% (approximately 70%) for the period from 1978, the year following the introduction of routine rubella vaccination, to 1994, the year of the revision of the Preventive Vaccination Law. This revision stipulated the adoption of an interim measure ensuring that junior high school students including boys and girls receive rubella vaccination until 2003. Due to the transition from rubella vaccination on a mass basis in their schools to that on an individual basis in their home doctors, the rate of vaccination has decreased to the 50% range (47–55%). This downward trend was more definitely recognized in local communities which accepted the alterations to the vaccination system.[9] The author and his colleagues conducted birth cohort analysis in Kitakyushu City in which the rubella vaccination rate was calculated by collecting the rubella vaccination interview charts. The results indicated that the rate, which ranged from 69 to 80% during the period of mass vaccination, decreased significantly to 6 to 14% after the introduction of individual vaccination.[5]

The rate of MMR vaccine among children ranged from 25 to 50% during the period between 1989 and 1992. The preventive vaccination study group of the Ministry of Health and Welfare reported that the rate of rubella vaccination among children has been maintained in the 40% range and pointed out a gradually increasing tendency.[5] According to the results obtained from the above mentioned birth cohort analysis in Kitakyushu City, the rate of rubella vaccination was around 60%.[5]

According to NESID rubella epidemics broke out at intervals about 5 years, i.e. in 1982, 1987–1988, and 1992–1993. The effects of the introduction of routine MMR vaccine and the revision of the Preventive Vaccination Law, which stipulated the administration of routine rubella vaccination during early childhood were recognized thereafter. No rubella epidemics have been reported in recent years although endemic outbreaks have been observed. The authors conducted a nationwide survey of the incidence of CRS in schools for the deaf for the period from 1965 until 1989. The birth of CRS occurred annually and 45 and 167 CRS babies were born respectively in rubella epidemic years, 1982 and 1987–1988. This survey evaluated the actual conditions for 12 years after the introduction of routine rubella vaccination of junior high school girls. The women could be divided into two groups: Those who were junior high school students at the time of the introduction of routine rubella vaccination and received the vaccination, and those who were high school students or who had graduated from high school at that time and did not receive rubella vaccination. The incidence of CRS among the newborns of the former group

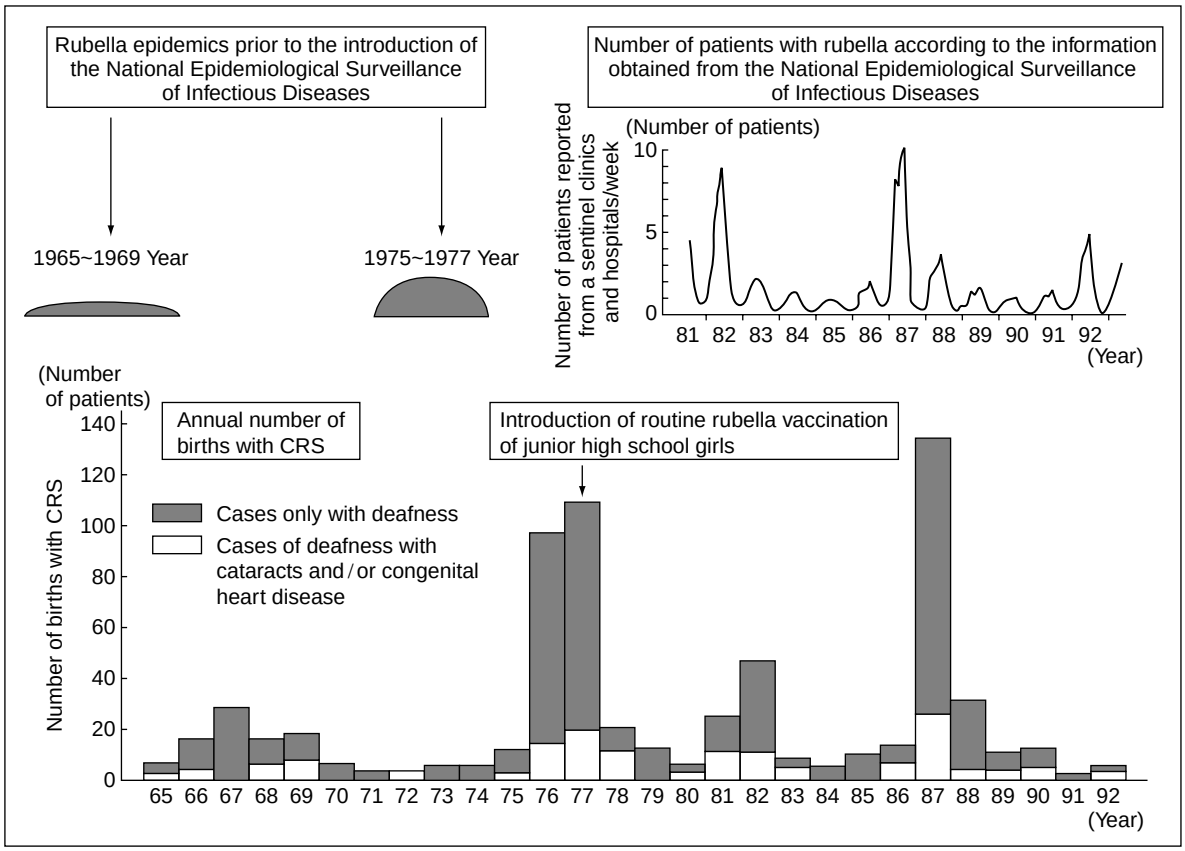

Fig.1 Rubella epidemics and the number of births with hearing impairment associated with CRS by year [Modification of the data reported by Kadoya, R., Ueda, K., Miyazaki, C. *et al.*[10)]]

was found to be significantly decreased, while that of the latter group was significantly increased. Therefore no decreasing tendency has been observed in the nationwide incidence of CRS (Fig. 1).[10)]

According to the results obtained from the seroepidemiologic survey of rubella (NESID, 1997), the antibody positive rates among males and females, ranging from 17 to 32 years in age, were approximately 70%, and more than 90% respectively. This phenomenon reflects the effect of the introduction of routine rubella vaccination of junior high school girls since 1997. Two peaks can be observed in the antibody acquisition rates in both boys and girls under 10 years of age; one corresponding to the introduction of MMR vaccine (1989–1993) and the other corresponding to the introduction of routine vaccination of children following the revision of the Preventive Vaccination Law in 1994 and the subsequent acquisition of the antibody. The immunity gap recognized in the teenaged group appears to reflect the low vaccination rate among junior high school students to whom the interim measure was applied (Fig. 2).[9)]

Measles and Rubella Vaccination Strategy in Europe and the U.S.

The significant increase in the vaccination rate in the United States contributed to a remarkable decrease in the incidence of measles. However, the number of those who did not receive a measles vaccination and those who received vaccination and failed to acquire immunity has increased and an increasing tendency in the incidence of measles has been

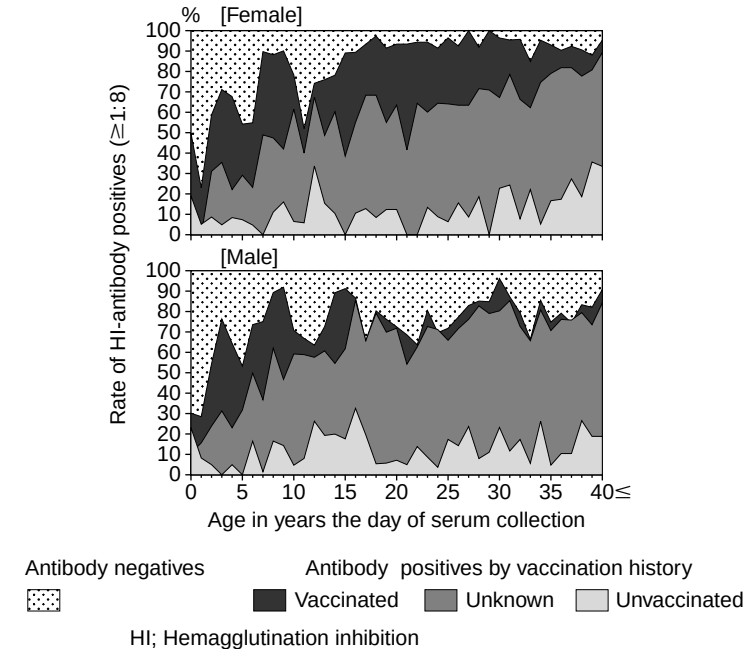

Fig. 2 Rubella antibody prevalence by age and sex, 1997, Japan (National Epidemiological Surveillance of Vaccine-Preventable Diseases 2000; 21: 1'–2')

observed among the older children. According to the estimated data, in order to eradicate measles by the introduction of single dose vaccination, the prevalence of measles antibody after vaccination should be more than 95% (measles vaccination rate 97–98%). During the period between 1988 and 1989, two doses of MMR vaccine was recommended in Europe and the United States to attain this high level of vaccination.[1)]

As in the case of measles, the introduction of rubella vaccinations of children (rubella vaccination rate 83%) succeeded in decreasing the incidence of rubella and CRS. The wider introduction of the vaccination was prompted by subsequent increases in the incidence of rubella among those in older age groups. Young women are recommended to receive vaccination. Following the transition from one dose of MMR vaccine to two doses against measles, two doses of MMR vaccine against rubella are recommended.[2)]

Several countries, which formerly adopted the English rubella vaccination policy under which only junior high school girls were immunized, have now adopted the new vaccination policy, which assigns two doses of MMR. Finland was the first country to adopt this system and has obtained satisfactory results.[1,2)]

Future Problems in Japan

The rates of measles and rubella vaccination are approximately 70% in Japan. A large epidemic is not expected although small epidemics, endemic or sporadic outbreaks appear to occur. Patients with measles and rubella are expected to be widely distributed across various generations. The incidence of measles and rubella among the older children and young adult will increase and more adults are expected to contract these diseases in the future. Inpatients with measles, deaths from measles and patients with CRS appear to occur continuously. Japan has fallen far behind in the introduction of an appropriate vaccination policy when compared with Europe and the United States.

Special attention should be directed to the low rates of vaccination against measles and rubella. Under the current Preventive Vaccination Law, the rates of routine vaccination against measles and rubella among infants and the rate of vaccination against rubella among junior high school students who are covered by the interim measure (including those in the age group where the vaccination rate has dropped significantly) are to be increased up to the level exceeding 85% at least. Promoting vaccination is a problematic issue and various measures to address this problem have been adopted in Europe and the United States. For example, campaigns to encourage the general public to receive vaccinations have been introduced in addition to the adoption of MMR vaccine. These measures have contributed toward increasing the rate of vaccinations.[1,2)]

Japan and Germany are two countries which are notorious for their low rates of measles vaccination and which are internationally regarded as being exporters of infections. A measles epidemic brought into Alaska by Japanese children has been reported.[11)] Japan and Germany are two highly industrialized countries in which measles transmission is still ongoing and, which have significantly contributed to its outbreak in the United States. Japan and Germany have less intensive measles control efforts than countries in the Western Hemisphere. Japan recommends one-dose measles vaccine and no longer requires vaccinations for school entry.[12)] The vaccination rate is regarded as being an index indicating the progress of public health, health education, internationalization, and the relationship between individuals and society.

It is necessary for us to conduct a survey of the incidence of infections including measles, rubella, adult measles, and CRS and to focus our attention on the incidences. On the basis of the results obtained, we need to consider formulating appropriate measures to improve the vaccination rates including the introduction of two-dose measles vaccination and MR or MMR vaccine. It is necessary to encourage people to undergo vaccinations against these infections.

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Problems with BCG Vaccination Program in Current Tuberculosis Control

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Abstract: The importance of BCG vaccination as a measure for tuberculosis control has traditionally been recognized in Japan. According to the current system, routine BCG vaccination is administered to infants of three and under, and to primary school and junior high school entrants. The overall BCG vaccination coverage rate among infants is estimated at approximately 97%, although the rates in certain prefectures are lower than 90%. This variation is attributable to differences in the policies of the local autonomies that are responsible for the BCG vaccination program, as well as to the technical level of tuberculin skin testing prior to BCG vaccination. The method of administering the BCG vaccination in Japan is the percutaneous method employing a multipuncture technique that has a drawback in its lack of technical uniformity. For example, the tuberculin positivity rate among primary school entrants who have been vaccinated in their infancy varies widely among prefectures, ranging from less than 30% to more than 70%. The speed of decline in the case rate of tuberculosis among Japanese infants is greater than that in Europe and the USA; Annual rates of decrease during 1976 through 1986 were 10% for 0–4 year olds in Japan, 11% for 5–9 year olds, and 4% for all ages, with the corresponding figures for the US being 5%, 4% and 6%, respectively. These figures may suggest the overall effectiveness of the BCG vaccination in Japan, however, the revaccination as currently practiced in Japan is considered to be of extremely limited effectiveness, if any. We therefore consider it necessary to maintain a higher coverage of the primary vaccination for the time being and higher quality standards in the vaccination technique.

Key words: BCG vaccination; Tuberculin test; Tuberculosis control program

The tuberculosis control program is a controversial issue in Japan because of the re-emergence of the disease in epidemics and in this situation, the necessity of reconsidering the tuberculosis control program has been indicated. Much attention has been focused on the policy of Directly Observed Treatment, Short course (DOTS) the core of which is intensive

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case management to ensure regular drug taking by patients. This policy has been adopted as a standard tuberculosis program strategy throughout the world, in both developing and developed nations. The remarkable progress in the treatment program in developing countries has even provoked enthusiastic discussion over the possibility of introducing individualized treatment for drug resistant tuberculosis based on the results of drug sensitivity testing (DOTS plus), which was effectively a dream for such nations until recently.

As is well known, a large-scale field trial on the efficacy of BCG vaccination conducted in South India during the late 1960s through the mid-70s produced negative results. This sent shock waves throughout the world in the 1980s, and gave rise to the subsequent controversy over BCG, however, in recent years, the controversy appears to have abated. When Indian researchers reported the results of the study in 1978, some TB experts were extremely satisfied with the results, whereas others were highly embarrassed, and heated debate continued between the two groups for many years thereafter. In the 1990s, a surge in the incidence of TB in the USA and other developed countries accompanied by increases in drug resistant TB and the nosocomial outbreak of TB again led to a discussion of the efficacy of the BCG vaccination. In 1996, Centers for Disease Control and Prevention (CDC), USA, concluded that the BCG vaccination was effective, although its necessity was limited given current circumstances in the USA.[1)] This conclusion was based on the results of meta-analysis, a mathematical methodology that was developed comparatively recently and which has gradually come to be accepted as a useful method of analysis.

On the other hand, tremendous efforts are being made to develop novel vaccines superior to BCG, exploiting new biomedical technologies. The author will review the problems with the BCG vaccination program as a measure of tuberculosis control in Japan in light of the current tuberculosis problem and its control together with a discussion of its related problems and prospects for the near future.

Current Conditions of Implementation of Mass Vaccination and Issues of Technical Assessment

Under the existing scheme, the BCG vaccination (the periodic vaccination) is administered to infants of three years and under (infants are advised to receive BCG vaccination as early as possible after the age of three months). BCG revaccination is to be administered to first-grade primary school and junior high school students (second-grade students who were vaccinated in the previous year may also be vaccinated again). Only those who have a negative reaction to a tuberculin test are eligible for BCG vaccination or revaccination.

In addition to the issues pertaining to the BCG vaccination technique, which is an unavoidable part of the percutaneous vaccination method, the tuberculin test also presents technical problems. Thus, the BCG vaccination program is unique in terms of the need for quality assurance and assessment. Accordingly, we need to be more careful in shifting from the mass vaccination system to the system of vaccination on an individual basis.

1. BCG vaccination coverage and area differences

The nationwide BCG vaccination coverage rate has been maintained at levels near 100%, and was 97.3% for 1997, according to a rough estimate based on the total number of infants who received BCG vaccination divided by the total number of births within a year. This high level of coverage may be maintained via the widespread adoption of the mass vaccination system, even after the introduction of the new vaccination program where a system for individual vaccination is being encouraged for other vaccines. However, prefectural variations in the coverage are apparent as shown in Fig. 1.

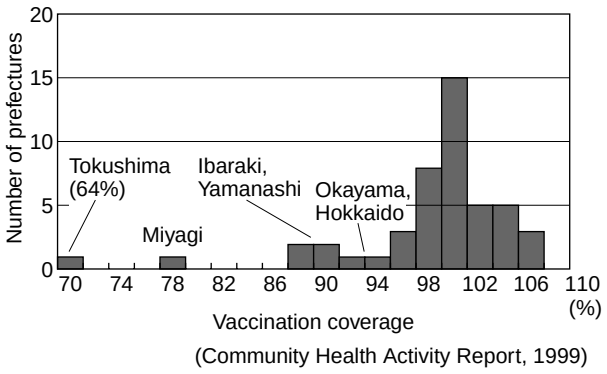

Fig. 1 Distribution of prefectures by BCG vaccination coverage among infants (1997)

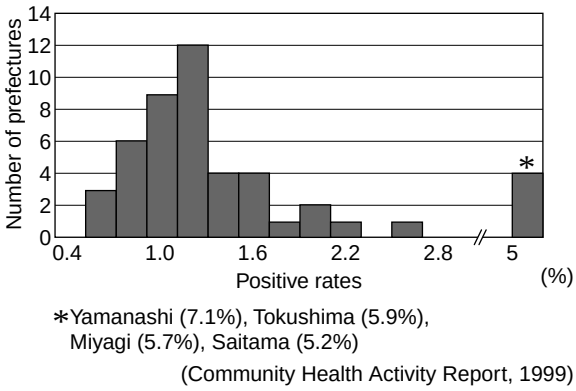

Fig. 2 Distribution of prefectures by tuberculin positive rate of unvaccinated children (1997)

In many prefectures the coverage rate is almost 100% (in some areas it exceeds 100% due to the estimation formula), whereas there are prefectures with rates of around 90%, or even with rates as low as 80% (Fig. 1). In view of the existence of prefectural disparities in BCG vaccination coverage, wider differences may be seen at the levels of public health centers, and municipalities (cities, towns and villages).

This gap in BCG vaccination coverage among areas is mainly attributable to differences in the policies adopted by municipalities including cities, towns, and villages, including methods of public relations, actions taken to address non-attenders, the number of opportunities for mass BCG vaccination in a year, and the accessibility of the sites for mass vaccination. Furthermore, attention needs to be directed to the tuberculin skin testing technique, which is conducted prior to BCG vaccination.

Figure 2 gives the distribution of prefectures according to the tuberculin positivity of the infants tested prior to the vaccination. The national positive rate is 1.4%, which is considered reasonable, whilst conceding that most of the positive tests are so-called false positive reactions. However, some prefectures report figures as high as 5% or more. There are two possible causes for this abnormally high positive rate. One is a technical problem in the testing, specifically, over-reading reactions, such as reading intra-dermal or subcutaneous bleeding due to injection as erythema. The other cause is that tested subjects are older in relative terms, i.e., including those aged two or three years of age. The tuberculin tests given to these "older" infants are more likely to produce "non-specific" reactions than those given to young infants, which may inflate the positive rate.

2. Variations in the technical level of tuberculin testing

According to the report of the tuberculin test results in infants by the Okinawa Branch of the Japan Anti-Tuberculosis Association, an association considered to have a very high technical level of testing, infants under one year who had erythema measuring 10 mm or more in diameter accounted for 1.0% of those tested, while the proportion for those aged one, two, and three years was 2.1%, 4.2%, and 7.1%, respectively. Since the prevalence of tuberculosis infection among these infants is estimated to be less than 0.1%, so-called "positive" tests in these age groups are considered to be mostly false positive reactions. Infants who have a "positive" reaction to the test are referred to a further examination that includes X-ray and tuberculin re-testing. As a result, some of them can be given chemoprophylaxis without any certain evidence of tuberculosis infection.

Because BCG works by conferring immunity

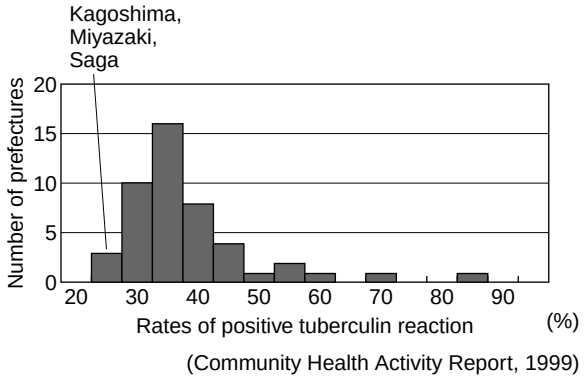

Fig. 3 Distribution of prefectures by tuberculin positive rate of primary school entrants (1997)

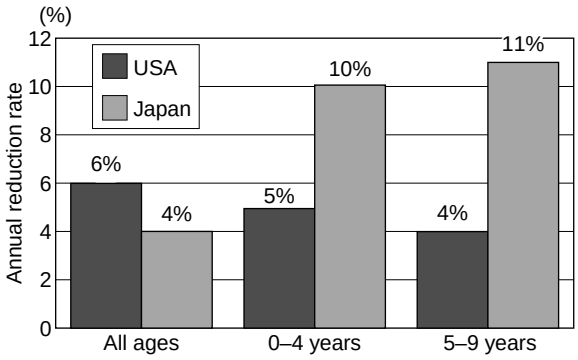

Fig. 4 Comparison of speed of decline in tuberculosis case rates, Japan and USA (All forms of tuberculosis, 1976–1986)

to those not previously infected, and because older infants have false positive reactions to the tuberculin test more frequently, earlier tuberculin testing followed by BCG vaccination is commonly recommended for infants, ideally before they reach the age of one. Regarding improvements to the tuberculin test technique the ultimate remedy would be for physicians to gain skill through experience under proper guidance and self-assessment. In some areas, only specific doctors with sufficient experience are assigned to tuberculin testing in order to secure a higher degree of technical skill.

3. Variations in BCG vaccination technique

Variations in BCG vaccination techniques is the next issue. The most serious problem with the current percutaneous vaccination method is the difficulty in securing technical uniformity, particularly uniformity in the pressure applied on the needled plunger piercing the skin. The most reliable method of technical assessment is to perform a post-vaccination tuberculin test, but for practical reasons it is also recommended to observe the local reaction at the site of vaccination. To this end, it is useful to count how many needle scars out of a total of 18 are left on the skin at 6 months after vaccination.

Within the scope of the current routine scheme, the technical level of the BCG vaccination for infants can also be assessed by observing the tuberculin reactions at the time of entry to primary school. Fig. 3 gives the distribution of prefectures by the tuberculin positive rates of first-grade elementary school students. The national positive rate was 39%. The rate was high in prefectures such as Okinawa (81%), Hokkaido (65%) and Miyagi (58%), while it was particularly low in Kagoshima (22%), Miyazaki (21%), and Saga (25%). These data demonstrate the existence of remarkable inequality in the technical level of vaccination across Japan. The reduction of such technical gap will have a significant impact on the future prospects for the BCG vaccination program, as discussed below.

Controversy Over the Effectiveness of the BCG Vaccination Program

As mentioned above, the controversy over the preventive efficacy of the BCG vaccination against tuberculosis appears to have diminished around the world. In Japan, a case-control study conducted by Takamatsu *et al.*[2] demonstrated the significant efficacy of the BCG vaccination. Moreover, a comparative study of the trends in age-specific tuberculosis case rates in Japan and the USA, where BCG vaccination is not practiced, also supports the BCG efficacy of Japan (Fig. 4). Before the reversal in tuberculosis case rates in both Japan and the USA, the rate of

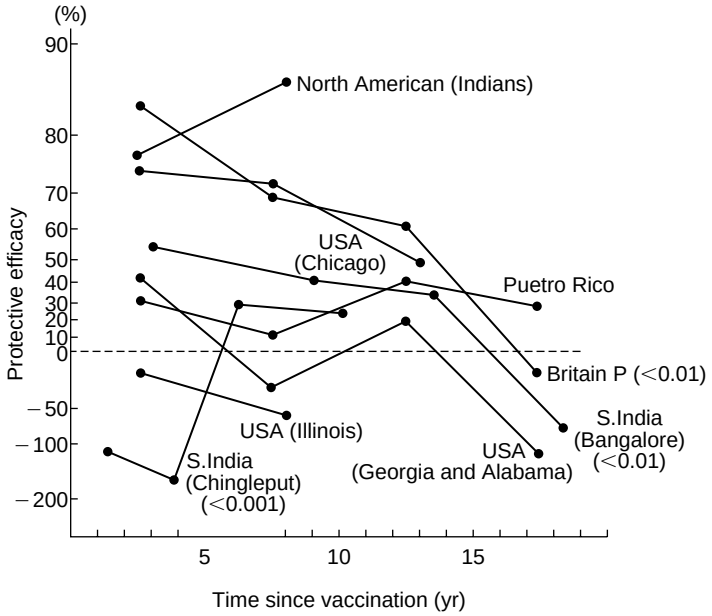

Fig. 5 Changes in protective efficacy of BCG against tuberculosis over time since vaccination, in randomized controlled trials. (p values refer to changes in efficacy over time in the years studied. No p value signifies no significant change.) (Smith PG)[3)]

decline for all ages was faster in the USA, however, it was clearly faster in Japan for infants and children. The Japanese infants' superiority can also be seen in the absolute value of the case rate. This comparison is more remarkable when it comes to comparing the rate for adults; that for Japan is several time higher than that in the USA. It should be borne in mind that this BCG efficacy is limited to the infancy and childhood, as is demonstrated in the findings from overseas studies and from the work of Takamatsu *et al.* as well. According to a famous field trial conducted in the UK, BCG vaccination efficacy lasts for 10 to 15 years after the vaccination, which fact has been confirmed by other observations (Fig. 5).

The efficacy of revaccination with BCG presents another issue. This argument is highly relevant to the issue of the revaccination scheme for primary school and junior high school entrants discussed in Section 3, and also to the vaccination for health care providers in the nosocomial tuberculosis prevention program.

The latter case has a unique problem in that it concerns the vaccination of a population the majority of whom previously received vaccination more than 10 years ago, and the protective efficacy of the former vaccination is supposed to have already waned. The efficacy of the BCG vaccination for adults, young adults or adolescents in particular, has been well established by a BMRC trial in which BCG given at around the age of 14 years was shown to be potent for a period of 15 years. The problem originates from the possibility that the residual immunological effect of the previous vaccination may interfere with the subsequent vaccination, to result in a reduction in the expected efficacy. It is therefore suspected that the subsequent vaccination cannot induce the same degree of efficacy as that due to the primary vaccination. These doubts can only be dispelled by the implementation of clinical trials. This type of randomized controlled trial on the efficacy of BCG revaccination among nurses is in progress at the National Kinki Central Hospi-

tal and others. Once the results of these trials are reported, or in the event that any other strong epidemiological evidence becomes available, we will have to deal with the tuberculosis risk among young nurses which is more than double that of the general female population, using BCG vaccination as one of the emergency options. This is the recommendation of the recently published guidelines "Guidelines for Preventing Nosocomial Transmission of Tuberculosis.[4)]

Future Prospects

The future prospects for the BCG vaccination policy, including the possibility of its total abolition, have been the subject of much debate recently. The decision as to whether to abolish the BCG vaccination is dependent on what levels of infantile tuberculosis victims will be acceptable, in exchange for the pay off in costs and adverse reactions. To date, there has been no argument for discontinuation based on such considerations. At the same time, the introduction of an alternative means of complimenting the policy should also be considered.

Aside from the issue of primary BCG vaccination for infants, the revaccination of primary school pupils was recently discussed by the Tuberculosis Control Panel of the Public Health Council; There were two pressing reasons for this discussion. First, it was suspected that the benefits of revaccination under the current scheme would be very limited, even admitting the efficacy of revaccination itself. Second, the need to do more to address the problem of the strong local reaction due to Koch's phenomenon, which sometimes causes keloid formation, following revaccination. There has been a marked increase in the incidence of this adverse reaction after the revision of the scheme in 1995 to expand the target population for revaccination so that individuals with erythema measuring 5–9 mm in diameter were included in addition to those with erythema measuring 0–4 mm.

The Panel reached the following conclusion: Besides its prophylactic role, the current revaccination system is considered to play an important role in providing opportunities for those who have failed to acquire sufficient immunity to TB due to poor vaccination technique or who missed the vaccination. Therefore, the argument for discontinuation of BCG revaccination should be made having given sufficient consideration to this factor. Based on this conclusion, the establishment of a system of technical assessment of the infantile primary vaccination was recommended.

As mentioned in Section 1, the actions to be taken by the government are clear. They should include the implementation of technical training for the physicians responsible for tuberculin skin testing and BCG vaccination, appropriate technical assessment with feed back, and appropriate action for those individuals who were insufficiently vaccinated. All these actions should be incorporated into a new BCG vaccination program. This concept was not clearly recognized in the former program. One exception was the program for BCG assessment of the Yamagata prefectural government that was implemented with the cooperation of both the local medical association and the local school health authority during the 1980s.[5)] This important local experience should become a model for the establishment of a country-wide technical assessment system for BCG vaccination.

The issue of the recent incidence of straight forward technical errors in tuberculin testing and BCG vaccination requires serious attention. For example, there are still cases of incorrect vaccination with only one percutaneous shot instead of the required two shots. Unnecessarily strong action is taken for those who have a false positive reaction to tuberculin tests. Also, inappropriate treatment procedures are often used for the local reactions and the axillary lymph node swelling following BCG vaccination. Recently, the Japan Anti-Tuberculosis Association produced an educational video to be used for training in the BCG vaccination

technique and the proper treatment of these reactions.[6)]

In 1998, a total of 275 children aged from zero to 14 years developed tuberculosis, including three cases of meningitis. This apparently low figure is credited to the BCG vaccination however, there have been steady increase in the number of infection sources to which children are being exposed. Japan uses the BCG vaccination as one of the measures for protecting children from tuberculosis. There is still room for further efforts to increase the effectiveness of this measure, and to develop other preventive measures as well.

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Vaccines for International Travelers
—Vaccinations, Destinations, Clinics for Vaccinations—

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Abstract: The types, frequency and methods of vaccination are occasionally different in different countries. The World Health Organization (WHO) promotes the Expanded Program of Immunization (EPI), which recommends that children receive the poliomyelitis vaccine, BCG, diphtheria, pertussis and tetanus (DPT) vaccine and the measles vaccine. As a rule, children who go abroad with their parents should receive these six vaccines in advance of travel or in the destination country. Unvaccinated adult international travelers are also advised to receive essential vaccinations in advance. Thereafter, vaccinations against diseases that are known to be prevalent in the destination country, and against the diseases that are known to infect visitors are suggested, and appropriate vaccinations selected. Needless to say, the types and priority of vaccines to be administered will depend on the traveler's intended life style during his/her stay and the length of the trip. More expert advice on international travel/vaccination is being sought recently. The author hopes that this paper will serve as a useful resource for the better understanding of vaccinations.

Key words: Vaccine; International travel; Traveler's vaccine

Introduction

Physicians are expected to play an important role in providing international travelers with appropriate medical advice so that they can be protected from being carelessly exposed to generally preventable infection. The importance of providing expert advice on the prevention of infection by vaccination has been increasing.

Each country requires specific types, frequency and methods of vaccination according to its health care system. World authorities including WHO are promoting the Expanded Program of Immunization (EPI) which recommends children to receive vaccination against the following six diseases: Poliomyelitis, BCG, diphtheria, pertussis and tetanus (DPT), and

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measles.

If parents take their children abroad, such children should receive the above six vaccines in advance or in the destination country. Unvaccinated adult travelers are also recommended to receive essential vaccines ahead of time. The diseases which appear to be prevalent in the destination country and those which appear to infect visitors should also be considered and appropriate vaccinations selected for the traveler.

Basic Rules of Vaccination for Travelers

1. Planning a flexible schedule of vaccination

If a traveler requires several vaccinations within a certain period of time, he/she is recommended to plan a flexible schedule of vaccinations. Generally, two or three months are necessary and if possible, six months are recommended for these vaccinations before departure.

2. Avoid receiving vaccination immediately prior to departure

The possibility that expected adverse reactions (e.g. fever and rash, which may manifest 10 days after vaccination with live vaccines) and unexpected serious adverse reactions may develop immediately after arrival or during the sojourn in the foreign country should be considered. In order to prevent the occurrence of these events, which may induce anxiety, vaccination immediately prior to departure should be avoided. Travelers are advised not to receive live vaccines within two to three weeks before departure and inactivated vaccines within three to four days before departure.

3. Simultaneous vaccinations and intervals for vaccinations

With the exception of cholera and yellow fever vaccines, many immunobiologics can be given simultaneously (on the same day). The physician should explain the following to the individual who requires vaccination or his/her guardian to obtain their consent: The simultaneous administration of vaccines is mentioned as an approved technique in the Japanese Guidelines of Preventive Vaccinations and has been generally regarded as a medically effective method. The increased incidence of adverse reactions and the diminished immune response to some vaccines following simultaneous vaccination are not expected.

4. Priority of vaccinations

As in the case of the vaccine against yellow fever, if the vaccination against a certain disease is required according to the sanitary conditions of the destination country, a traveler should receive the vaccination (a traveler is obliged to undergo the vaccination). For children, top priority should be given to the administration of the above-mentioned six vaccinations (EPI vaccines). Unvaccinated adult travelers are also recommended to receive these essential vaccines in advance, except BCG.

The diseases which appear to be prevalent in the destination country and those which appear to infect visitors should also be considered and appropriate vaccinations selected for the traveler. Needless to say, the types and priority of vaccines to be administered will depend on the traveler's life style during his/her stay and the length of his/her stay.

It is not always necessary for travelers to receive multiple vaccines within a short period of time if the length of their stay in the destination country is approximately one to two weeks. However, if travelers are accompanied by children, such children are advised to at least receive routine vaccinations in Japan in advance. Travel agencies are also responsible for recommending travelers to receive routine vaccinations. Parents should be aware that taking unvaccinated children to a foreign country because of insufficient preparation may expose them to infectious diseases.

Quality of Vaccines Administered in Foreign Countries

Travelers occasionally receive vaccinations while staying in a foreign country. Although the vaccines provided in developed countries are of high quality, the pharmaceutical manufacturers in developing countries may produce vaccines which rarely meet WHO quality specifications. Therefore travelers are generally recommended to select clinics which frequently provide vaccination to foreigners.

In view of the fact that vaccines are preserved in refrigerators, power failure and voltage related problems may cause the quality of vaccines to deteriorate. It is necessary to consider storage conditions in selecting reliable clinics in certain regions. Disposable syringes and needles are available in most regions although the condition of these devices should be confirmed in certain regions in advance.

Types of Travel and Recommended Vaccinations

Children are advised to receive routine vaccinations according to their age. Unvaccinated adult travelers are also recommended to receive essential vaccines in advance. The types of vaccines to be administered to travelers according to the purpose of travel are as listed below.

1. Short-term business travel

If an individual is planning to stay in a developed country, vaccination is not generally required. If an individual is planning to stay in countries other than Europe or North America, the administration of hepatitis A vaccine and oral typhoid vaccine, if available, is recommended. If an individual is planning to stay in Africa or South America, he/she requires vaccination for yellow fever.

2. General group sightseeing tours

Specific preventive vaccination is unnecessary although appropriate hygiene should be practiced by paying special attention to meals, drinking water, and hand washing. If an individual is planning to stay in Africa or South America, he/she requires vaccination for yellow fever.

3. General individual tours

Generally, specific preventive vaccination is unnecessary. However, young travelers who economize on traveling expenses by staying in unsanitary hotels and eating food at unhygienic restaurants should exercise sufficient care because the contaminated environment may cause contagious diseases. In addition to the routine vaccinations to be indicated for business travelers, vaccinations for hepatitis B and rabies should occasionally be considered.

4. Adventure tours

Adventure tours include visits to places which lack medical care facilities. Therefore travelers should acquire knowledge of primary care to cope with diseases, obtain information on infections prevailing in the destination country, and receive routine vaccinations. Furthermore, they are expected to receive as many types of preventive vaccinations as possible, such as those against tetanus, Japanese encephalitis, hepatitis A, hepatitis B, rabies, plague, typhoid, meningococcal meningitis, and tick-borne encephalitis depending on the conditions of prevalence in the destination country.

5. Volunteer activities, etc. in developing countries

As in the case of adventure tourists, volunteers should be careful about the diseases prevailing in the destination country they plan to visit.

6. Long stay

If an individual is planning to stay in a developed country for a long period of time, he/she will need to receive the vaccinations which are

Table 1 Recommended Vaccines for Adults by Destination (General Recommendations)

Vaccines \ Destinations	North America	Middle and South America	East Asia	South Asia	Middle and Near East	Africa	Western Europe	Eastern Europe
Poliomyelitis	×	×	△	○	△	△	×	×
Diphtheria	×	×	×	×	×	×	×	△
Tetanus	○	○	○	○	○	○	○	○
Japanese encephalitis	×	×	○	○	×	×	×	×
Hepatitis A	×	△	○	○	○	△	×	×
Hepatitis B	×	×	○	○	△	△	×	×
Rabies	△	△	△	△	△	△	△	△
Yellow fever	×	○	×	×	×	○	×	×
Cholera	×	×	×	×	×	×	×	×
Typhoid*	×	×	○	○	△	△	×	×
Meningococcic meningitis*	×	×	×	×	△	△	×	×
Plague	×	×	×	×	×	×	×	×

○: Immunization is necessary. △: Immunization is occasionally necessary. ×: Immunization is unnecessary.

* : Immunization is to be administered in the destination country because the vaccine is not available in Japan.

Partial modification was made to the table listed in "Vaccinations for Parents and Their Children Traveling Overseas" by Y. Nakamura [Modification was made to the tables listed in "International Travel and Health (WHO, Geneva, 1994, p.80–81) and "1997 Red Book" (American Academy of Pediatrics, p.5).]

Table 2 Recommended Vaccines for Infants by Destination (General Recommendations)

Vaccines \ Destinations	North America	Middle and South America	East Asia	South Asia	Middle and Near East	Africa	Western Europe	Eastern Europe
BCG	△	○	○	○	○	○	△	○
Poliomyelitis	○	○	○	○	○	○	○	○
DPT	○	○	○	○	○	○	○	○
Measles	○	○	○	○	○	○	○	○
Japanese encephalitis	×	×	○	○	×	×	×	×
Hepatitis B	×	×	△	△	△	△	×	×
Yellow fever	×	○	×	×	×	○	×	×

○: Immunization is necessary. △: Immunization is occasionally necessary. ×: Immunization is unnecessary.

Partial modification was made to the table listed in "Vaccinations for Parents and Their Children Traveling Overseas" by Y. Nakamura [Modification was made to the tables listed in "International Travel and Health (WHO, Geneva, 1994, p.80–81) and "1997 Red Book" (American Academy of Pediatrics, p.5).]

routinely required in Japan. Special attention, however, should be directed to country-based differences in routine vaccinations. Therefore travelers who are planning to stay in a foreign country for a long period of time should receive the vaccinations that are required in that country. In this case, as mentioned previously, the quality of vaccines and methods of vaccinations should be confirmed in advance.

Types of Vaccinations Recommended According to the Destination Country

Recommended immunizing agents indicated for adults and infants according to the destination country are summarized in Table 1 (adults) and Table 2 (infants). Those listed in the tables should be regarded as standard immunobiologics with the prerequisite that routine vac-

Table 3 Information on Vaccinations for International Travelers

- **Books and Publications**
  1. Conditions of Vaccinations for Children-International Conditions
     Compiled under the supervision of Hirayama, M., Okabe, N. and Fukushima, S.
     Technical adviser: Nakamura, A.
     Published by Association of Maternal and Child Healthcare (2000) (in Japanese)
  2. Information on Foreign Maternal and Child Health; Access Guide
     Edit. Okabe, N.
     Association of Maternal and Child Healthcare (1998) (in Japanese)
  3. Information on Foreign Health Care
     The Ministry of Health and Welfare/Narita Airport Quarantine Station (2000) (in Japanese)
  4. Vaccinations for Parents and Their Children Traveling Overseas
     Edit. Nakamura, Y., Okabe N, and Onozaki, I.
     Association of Maternal and Child Health (1999) (in Japanese)
- **Internet Website**
  1. Child Care Information
     http://www.mcfh.or.jp/
     Association of Maternal and Child Healthcare
  2. JICA-Information on Visiting Foreign Countries
     http://www.jica.go.jp/
     Japan International Cooperation Agency
  3. Health Management Center for Individuals Working Overseas-Local Information for Individuals Working Overseas
     http://www.johac.rofuku.go.jp/
     Labor and Welfare Organization
- **Telephone Service**
  1. Health Management Center for Individuals Working Overseas (Labor and Welfare Organization)
     Information is available to individuals.
     Phone: 045-474-6001
  2. Medical Foundation for Japanese Staying Abroad
     Information is available to corporations.
     Phone: 03-3593-1001
  3. Division of Quarantine, Narita Airport Quarantine Station
     Information is available to individuals.
     Phone: 0476-34-2310

cinations have been completed at specified ages. Individuals should make further inquiries for details regarding the vaccinations to be performed in each region. In addition to medical professionals, the materials, websites and centers listed in Table 3 are available to the public and may serve as useful sources of information. The details of vaccines are not mentioned in this paper because of space limitations. Necessary information can be obtained by making inquiries at the centers listed in Table 3 or from the materials listed in the Reference section at the end of this paper.

Clinics for Vaccinations or Centers Which Provide Information on Vaccinations

Although there are a number of clinics that provide vaccination services in Japan, some clinics do not offer these services. Preventive vaccinations for international travelers differ from routine vaccinations and the clinics that provide vaccination services are not designated according to their scale. Considering the difficulty of finding appropriate clinics, the author recommends those who are planning to travel overseas to make inquiries at the centers listed

in Table 3 and to obtain necessary information by accessing relevant websites and reading reference materials. Furthermore, the author gives them the following advice.

1. Family doctors

Asking for the frank opinion of the family doctor is one of the best ways to obtain necessary information. Family doctors may administer vaccines at their clinics or may suggest appropriate medical care facilities.

2. Local public health centers, ward offices, city offices, etc.

Although local public health centers were in charge of preventive vaccinations, recently it is more common for the public health and welfare divisions of local administrative bodies to handle the affairs related to vaccinations. Local administrative bodies do not usually provide clinical vaccination services but an increasing number of divisions of local administrative bodies offer appropriate advice on vaccination including how to receive vaccinations, the names of medical care facility providing vaccination services, and where to go to collect necessary information.

3. Local medical associations

The members of local medical associations may offer appropriate advice on vaccinations and suggest reliable clinics that provide vaccination services. In some regions, medical associations have established vaccination centers in cooperation with clinics.

4. Pediatric departments at general hospitals

Generally, pediatric departments are responsible for vaccinations at general hospitals. It is necessary to inquire about whether they accept outpatients requiring vaccinations and whether they administer vaccinations to international travelers.

5. Quarantine stations

Currently, quarantine stations provide special vaccinations including vaccination for yellow fever, and such facilities accepting inquiries from international travelers are increasing. Quarantine stations are not established in all the prefectures of Japan, therefore inquiring about vaccinations at the nearest station is recommended as one of the methods to collect necessary information.

6. Vaccination centers

Recently, the Ministry of Health and Welfare promotes the designation of one medical facility per prefecture to act as a vaccination center. Such medical facilities may provide information on vaccinations for international travelers. Therefore inquiring at the division in charge (division of public health, welfare or infectious diseases) in each prefecture is recommended.

Conclusion

The author has summarized the essential information on vaccines for international travelers (traveller's vaccines) in this paper. The basic rules of vaccinations for international travelers, the quality of vaccines provided at clinics in foreign countries, the types of vaccinations recommended according to the purpose of international travel, the types of vaccinations recommended according to the destinations (Tables 1, 2) and materials, websites and centers which provide relevant information (Table 3) are also explained. Mention is also made of the clinics and facilities offering advice to the general public who have questions about vaccinations. More expert advice on vaccination is being sought in recent years, in line with the increase in the number of international travelers. The author hopes that this paper will serve as a useful material for understanding vaccinations.

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The Economic Benefit of Vaccination

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Abstract: To evaluate the economic benefit of vaccination in Japan, five index diseases, i.e., measles, mumps, rubella, chickenpox, and influenza, for which data on related medical care costs and the protection rate and adverse reactions associated with vaccination are available, were chosen from among infectious diseases currently targeted by vaccination in this country. The economic benefit was calculated according to the method proposed by Wiedermann *et al.* The economic benefit in terms of the benefit cost ratio was highest for the measles vaccine (5.8:1), followed by mumps (2.8:1), rubella (2.0:1), chickenpox (2.6:1), and influenza (1.5:1) vaccines. When the measles vaccination rate is 90%, the economic benefit of this vaccine alone in Japan exceeds 30 billion yen, reflecting the enormous benefit which can be reaped by vaccination overall. Thus, we should be mindful of the tremendous economic benefit of vaccination, as well as its contribution to health.

Key words: Economic benefit; Health care costs; Vaccination costs; Technology assessment

Introduction

Since the enactment of the Preventive Vaccination Law in 1948, the vaccination system in Japan has been effective in preventing the development and spread of infectious diseases and contributing to improvement and progress in the area of public health. The role of vaccination in the prevention of infectious diseases is critical, and many think that the ultimate goal of vaccination, the total eradication of the targeted infectious diseases, might soon be reached.

However, even though these infectious diseases are generally no longer life threatening due to the widespread use of vaccinations, the treatment of infectious diseases still accounts for a large portion of medical care costs in Japan.

According to statistics released by the Ministry of Health, Labour and Welfare, even measles, which can be almost completely prevented if scheduled immunizations are properly executed, affects more than 30,000 people in Japan every year, out of which some will die. These figures reflect the complacency with regard to infectious diseases due to the successful widespread use of vaccination. We should however be ever aware of the threat of infectious diseases and appreciate the importance of vaccination.

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Table 1 Equation for Calculation of Economic Benefit

$$Q_C = \frac{C_{TH}}{C_V + (1-P)C_{TH}}$$

Q_C : Benefit cost ratio
C_{TH} : Health care cost/person
C_V : Vaccination cost/person
P : Protection rate

(Wiederman, G. *et al.*: *Dev Biol Standard* 1979; 43: 273–277)

Table 2 Equation for Calculation of Health Care Cost

$$C_{TH} = C_{OUT} + P_{IN} \times C_{IN}$$

C_{TH} : Health care cost/person
C_{OUT} : Outpatient care cost/person
P_{IN} : Hospitalization rate
C_{IN} : Inpatient care cost/person

This paper discusses the benefits of vaccination from the economic viewpoint,[1] to provide a deeper understanding of vaccination.

Method of Calculation and Results

The index diseases used to evaluate the economic benefit of vaccination in Japan, i.e., measles, mumps, rubella, chickenpox, and influenza, were chosen from among infectious diseases currently targeted by vaccination in this country. Data on related medical care costs and the protection rate and adverse reactions of vaccination are available for measles, mumps, rubella, and chickenpox, while it is possible to determine the effective prevention rate for influenza within a short period of time.

1. Measles, mumps, rubella, and chickenpox

The economic benefit of vaccination was calculated in the same manner as Kamiya *et al.*,[2] according to the method proposed by Wiedermann *et al.*,[3] as shown in Table 1. The health care cost per person (as of June 1, 2000) was calculated by separating direct cost and indirect cost (home care cost), as shown in Table 2.[4] The hospitalization rate was determined as 5% for measles, 0.5% for mumps, 0.05% for rubella, and 1% for chickenpox, based on available data.

The vaccination cost is calculated from the necessary expenditure for vaccination and the cost of treatment for predicted adverse reactions. Specifically, the protection rate of the measles vaccine is estimated to be 97.7%, and the incidence of adverse reactions mainly in the form of fever is estimated to be 20%, which results in at least one visit of the vaccinee to an outpatient clinic. The protection rate of the mumps vaccine is calculated to be 96.2%. Meningitis as an adverse reaction is projected to occur in one out of 10,000 vaccinees. The protection rate of the rubella vaccine is estimated to be 97%, and no adverse reactions requiring treatment are projected. Since about 12% of vaccinees catch chickenpox within 2 years after the chickenpox vaccination, the protection rate of this vaccine is estimated to be 86.7%.

The outpatient care cost calculated from actual cases is ¥58,802 for measles, ¥19,644 for mumps, ¥17,224 for rubella, and ¥29,572 for chickenpox. Thus, the cost is highest for measles, which requires many days of treatment and longer nursing. The inpatient care cost, also calculated from actual cases, is ¥287,687 for measles, ¥319,775 for mumps, ¥177,688 for rubella, and ¥397,858 for chickenpox. The high figure for chickenpox is attributable to the high cost of subsequent drug treat.

The above data were introduced into the equation shown in Table 2. The health care cost per person thus calculated is ¥73,186 for measles, ¥21,243 for mumps, ¥17,313 for rubella, and ¥33,551 for chickenpox; the cost is highest for measles, being 4.2-fold higher than that for rubella.

The necessary cost for vaccination (C_V) was calculated from the equation shown in Table 3. For vaccines which are covered by scheduled immunizations, the necessary cost was calculated based on the individual vaccination fees. The cost of vaccination for vaccines given on a voluntary basis was calculated based on the

Table 3 Equation for Calculation of Cost of Vaccination

$$C_V = M_V + P_V \times C_{TH\text{-}V}$$

C_V : Vaccination cost / person
M_V : Vaccination fee
P_V : Rate of adverse reactions to vaccination
$C_{TH\text{-}V}$: Cost for treatment of adverse reactions

Table 4 Economic Benefit of Each Vaccine

Vaccines	Benefit cost ratio
Measles	5.8:1
Mumps	2.8:1
Rubella	2.0:1
Chickenpox	2.6:1
Influenza	1.5:1

average-rank vaccination fees among pediatric clinics in Tokyo.

The vaccination cost which includes the costs incurred in the treatment of adverse reactions caused by the vaccine, is ¥10,903 for measles, ¥6,710 for mumps ¥7,970 for rubella, and ¥8,500 for chickenpox. Introducing these figures into the equation shown in Table 1, the economic benefit was calculated for each vaccine in terms of the benefit cost ratio (Table 4). The benefit cost ratio is highest for the measles vaccine (5.8:1), followed by the mumps (2.8:1), chickenpox (2.6:1), and rubella (2.0:1) vaccines.

2. Influenza

Unlike the aforementioned four diseases, some reports still raise doubts as to the benefit of the influenza vaccine. These doubts are based on the specific characteristics of the influenza virus. Many researchers do not agree on the economic benefit of influenza vaccine, considering the low protection rate associated with influenza vaccination.

A total of 126 patients were inoculated against influenza at the author's clinic during the winter of 2000 and they were followed together with a control group of 76 non-vaccinees. During the observation period, 28 (22.2%) of the 126 vaccinees came down with influenza compared to 28 (36.8%) of the 76 non-vaccinees. The incidence of influenza was significantly lower among vaccinees, with a Fisher's straight line probability of $P = 0.010247$. The effective prevention rate for influenza vaccine was 39.7%, which was higher than the impression obtained from our clinical experience. This gap between perception and observed results arose because vaccinations are apt to be felt ineffective at the scene of clinical practice if effective prevention rates are lower than 50%.[5)]

The mean health care cost per patient with influenza, including indirect cost, was ¥76,800, assuming that two days of ambulatory treatment and five days of absence from work are necessary for adult patients. When this figure was introduced into the equation shown in Table 1, the benefit cost ratio of influenza vaccination was 1.5:1, based on the calculation that two inoculations cost ¥6,000. The economic benefit of the influenza vaccine was lower than that of vaccinations for other diseases; this low benefit was attributable to the low protection rate of the influenza vaccine.

Technology Assessment

On June 20, 2000, the World Health Organization (WHO) announced the results of their assessment of health system performance based on the level of medical service and the general health of people in various countries around the world. Japan ranked first in the world in terms of attainment of health reflected by average life expectancy and the length of a healthy life. However, Japan came in much lower at tenth place in the area of the efficiency of the health system, which reflects the absence of an established health care policy for the efficient use of effective medical technology.[6)]

The assessment of medical technology is important in the development of such a policy. This assessment involves determining whether

the benefit of using medical technology is worth the amount of social resources spent to do so. However, health care policy based on such a technological assessment should include the improvement of the quality of health care as part of its goals, rather than merely keeping down the cost of health care.

The recent Medicaid reform in Oregon in the United States was based on prioritizing health care services, using a cost-benefit analysis technique. The most effective and efficient health care service under this plan is vaccination to children, whereas terminal care and treatment of minor diseases are given a lower priority, casting a new light on the importance of preventive medicine.[7)]

Conclusion

It is difficult to accurately estimate the benefit of vaccination to society, taking into consideration various factors including the cost of vaccination, adverse reactions to the vaccine, age at disease onset, disease complications, and family structure.

However, an outline of the economic benefit of vaccination could be obtained by calculating the health care cost for spontaneously caught diseases seen in daily clinical practice taking into consideration the protection rate of vaccination. It was thus found that the benefit cost ratio of measles vaccine is the highest (5.8:1), while that of influenza vaccine is the lowest (1.5:1). If the cost for nursing provided by parents and days of absence from work, nurseries / kindergartens, or schools is estimated in a more generous manner in the calculation of the health care cost per person, the economic benefit of vaccination would be even higher.

Kamiya *et al.* have previously estimated the economic benefit of measles vaccination based on the assumption that the vaccination rate is 90%. They reported that the economic benefit would exceed 30 billion yen. It is certain that the corresponding benefit greatly exceeds this figure now. Considering this, currently implemented vaccination is providing a huge wealth to our country.[8)] We should take another look at the tremendous economic benefit of vaccination, in addition to its contribution to the health care of the people.

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Social Welfare and Music Therapy
—Music Therapy Activities at Social Welfare Institutions—

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Abstract: Although music therapy has not been fully recognized in Japan, activities that can be broadly defined as a form of music therapy have been conducted at social welfare institutions. However, with the advent of a certification system for music therapists, a survey was conducted on the type of music therapy activities that are currently practiced in Japan. The survey covered 514 institutions for the mentally handicapped nationwide (response ratio of 62.7 percent) and information was collected on the type of music activities that were conducted, the content and benefits derived from these activities, the problems related to implementing these activities, and the technical knowledge of facility staff members about music therapy. The findings have shown that several impeding factors had to be resolved before music therapy activities could be implemented, despite the expectations of many of the institutions regarding the introduction of music therapy and the acknowledged significance of music therapy activities.

Key words: Social welfare institutions;
Institutions for the mentally handicapped;
Music therapy; Music activities

Introduction

Research on the implementation of music therapy in Japan has hitherto focused mainly on facilities where music therapy activities have been conducted by music therapists or practitioners, but only minimal research has been carried out at facilities where such practitioners were extant, i.e., on facilities where music therapy had yet to be introduced.

Therefore, this paper has surveyed institutions for the mentally handicapped throughout Japan in order to study the conditions that may or may not be conducive to introducing music therapy activities, the content of music activities, the benefits that are derived, and the prob-

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Table 1 Music Activities Conducted by Facilities
(Total percentage includes other facilities)

	Adult Facilities (%)	Children's Facilities (%)	Total (%)
1. As music therapy	18.7	15.9	18.5
2. Recreation	62.7	43.2	59.9
3. Occasional activity	53.6	64.8	55.6
4. Part of the daily curriculum	28.9	46.6	32.1
5. Group activity	23.0	4.5	20.6
6. Not conducted	12.7	1.1	10.5
7. Others	3.8	11.4	5.1

lems that prevail in implementing music therapy, the conditions that are faced by facilities, and the technical knowledge of facility personnel about music therapy. The information that has been collected will serve as a source of reference in promoting music therapy in the future.

Research Approach

Questionnaires were posted to 820 randomly selected institutions for the mentally handicapped throughout Japan. The survey was carried out from February 17 to March 10, 1999 and 514 institutions or 62.7 percent of the facilities that were targeted responded (418 institutions for adults, 88 institutions for children, 8 shelters and other type of facilities).

Findings and Examination

1. Prevailing conditions in music therapy

The ratio of institutions which responded that they had incorporated some form of music therapy in their curriculum was 89.5 percent of the total number of respondents, of which the majority or 59.9 percent stated that music was a recreational activity, followed by 55.6 percent that indicated that music was used occasionally, and 32.1 percent which reported using music as part of their daily curriculum (see Table 1).

Although 18.5 percent of the respondents stated that they had incorporated music therapy in their activities, the degree or extent to which "music therapy" is defined or practiced is not clear. This has made it difficult to accept the numerical figures at face value.

Of the facilities that had not incorporated music therapy in their curriculum (10.5 percent), the ratio for adult facilities (12.7 percent/number of adult facilities) was higher than the ratio for children's facilities. This is attributed to the fact that adult facilities are focused mainly on productive activities related to learning and employment. Additionally, the large differences in perception among the facility personnel regarding music activities has tended to diminish the facility's need to introduce music activities. There may also be impeding circumstances that has made the introduction of music activities difficult.

2. Music activities

The most popular form of music activity that was conducted was karaoke or singing (82.1 percent), followed by the playing of musical instruments (56.6 percent), physical movements to music (46.7 percent), and group-oriented music appreciation (25.9 percent), excluding individual listening activities (see Table 2).

Music activities were conducted once a week by the majority of the institutions (19.8 percent) to two to three times a month (19.2 percent). For many of the facilities, one music session lasted 51 to 90 minutes (30.7 percent) or 31

Table 2 Music Activity Content
(Total percentage includes other facilities)

	Adult Facilities (%)	Children's Facilities (%)	Total (%)
1. Singing (including karaoke)	84.2	70.5	82.1
2. Playing musical instruments (including ensemble, improvisation activities)	55.7	59.1	56.6
3. Physical movements to music	44.5	56.8	46.7
4. Music appreciation	27.0	20.5	25.9
5. Mixed activities	20.8	38.6	23.9
6. Others	10.5	9.1	10.1

Table 3 Music Activity Supervisors
(Total percentage includes other facilities)

	Adult Facilities (%)	Children's Facilities (%)	Total (%)
1. In-house music therapist	0.5	0.0	0.4
2. In-house music supervisor	4.3	3.4	4.1
3. Facility staff member	86.4	87.5	86.8
4. Temporary music therapist	4.5	4.5	4.7
5. Outside volunteer	22.2	12.5	20.4
6. Others	4.8	10.2	5.6
7. None	1.9	1.1	1.8

to 50 minutes (28.0 percent).

3. Music activity directors

In response to the question about music activity supervisors, only 0.4 percent and 4.5 percent of the facilities stated that an in-house music therapist and music director, respectively, were in charge of music activities. In contrast, an overwhelming majority (86.8 percent) responded that music activities were conducted by a facility staff member. Hence it was found that music activities conducted at welfare facilities in Japan were mainly supervised by facility staff members (see Table 3).

Only 2.3 percent of the institutions stated that they paid fees or transportation expenses for outside directors (temporary or volunteer workers) and 17.9 percent indicated that expenses or fees were not paid at all (see Table 4).

4. Recognizing the benefits derived from music activities

In categorizing the survey findings according to the benefits that were derived from music activities, it was found that they were, in descending order, stabilizing emotional effects (34.6 percent), increased social skills (32.1 percent), increased work aspirations or for life in general (30.0 percent), stress relief (27.6 percent), and functional training benefits in the area of physical exercise, speech training, an improved use of tools, and cooperation and adaptation (25.5 percent) (see Table 5).

As can be seen from the above, many of the benefits are in synchronization with the goals of music therapy and the boundary between music activities, that are carried out at the institutions, and music therapy is blurred.

Table 4 Payments Made to Non-staff Supervisors
(Total percentage includes other facilities)

	Adult Facilities (%)	Children's Facilities (%)	Total (%)
1. Remuneration, transportation expenses	2.2	3.4	2.3
2. Remuneration only	12.9	9.1	12.5
3. Transportation expenses only	1.7	0.0	1.4
4. No payments made	18.4	15.9	17.9
5. Others	3.1	4.5	3.3

Table 5 Benefits Derived from Music Activities
(Total percentage includes other facilities)

	Adult Facilities (%)	Children's Facilities (%)	Total (%)
1. Stabilizing emotional effects	34.4	34.0	34.6
2. Increased social skills	31.3	35.2	32.1
3. Increased work or life aspirations	30.1	26.1	30.0
4. Stress relief	30.6	13.6	27.6
5. Functional training benefits	19.4	52.2	25.5
6. Improvements in self-expression	23.9	20.5	23.0
7. Promoted leisure activity skills	13.9	2.3	11.9
8. Others	10.5	11.4	10.7

5. Problems in implementing music activities

The most common problems faced by the institutions were the lack of specialists and specialized knowledge, inadequate technical knowledge of staff members, and insufficient understanding by facility personnel (30.7 percent), followed by environment-related reasons such as location, equipment, noise, and funding (18.3 percent), problems that are inherent to group activities (unable to meet individual needs, various handicapped related problems, age disparities, degree of disease severity) (18.3 percent), time constraints (11.3 percent), and the shortage of staff members (8.4 percent).

A few of the institutions stated that activities other than vocational or work-related activities were not implemented or commented that they felt that supervised music activities did not have to be conducted at a facility for adults. Other constraints that were described by institutions included the difficulty of introducing the practice of paying fees to music therapists and supervisors or allocating staff personnel to supervise music activities under the present system of available measures and in view of Japanese society's perception of music therapy, the difficulty of sustaining music activities due to the work shifts of staff personnel, and the lack of time needed to gain technical expertise in music therapy.

Conclusion

In order for music therapy activities to be widely incorporated in the curriculum of many institutions, the music therapist must gain the cooperation of the facility staff members, coordinate the music therapy program with the

other activities of the institution, and gain an overall understanding of the conditions faced by each facility. In turn, the institution must endeavor to gain accurate knowledge and understanding of music therapy and to recognize music therapy as a specialized vocation. Additionally, administrative measures to employ a music director or music therapist at the institution are also required.

In the case of institutions where staff members play a focal role in carrying out music activities, training opportunities to help acquire and improve the specialized knowledge and skills in music therapy (music activities) should be made available.

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Music Therapy in Terminal Care

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Abstract: Voice, sound, and music have been the vehicle of emotional expression for mankind from time immemorial and music, in particular, has had the power to open the human mind to enable human beings to express their inner emotions. The use of music in terminal care, the focal form of treatment for patients suffering from terminal diseases, has clearly shown that music mitigates the pain and suffering, provides temporary relief, and assists memory recall of past events. The author has addressed these issues in this paper based on personal study and experience.

Key words: Music therapy; Reduction of pain or suffering; Ventilation; Memory assistance of past events

Introduction

Prayer, accompanied by music, has been the means of mitigating the pain and suffering of disease since time immemorial and it is one of the major reasons why music has been applied in medical and health care. It is surmised that human beings, like all the other creatures of this planet, communicated through a variety of vocal utterances at the beginning of creation before the advent of language. The voice was a form of music orchestration that expressed the human mind and a gamut of emotions from joy to anger. Hence music has been a means of human communication.

Based on this view, the author would like to regard music as significant not only as artistic compositions but as an expression of the human soul. It is said that the foundations of modern music therapy evolved in ancient Greece and ancient writings of that time have described music "as that which permeates the depths of the soul, allows the innate and introspective to come forth, and uplifts the emotions". During the era of Hippocrates, the venerated ancient Greek physician, the use of music by the majority of the populace in ancient Greece as a source of healing is easily conceivable. The author's long-term experience in conducting music therapy corroborates Hippocrates' doctrine propounding the importance of applying music to treat and cure human diseases. This is particularly substantiated in the area of terminal care; and this paper summarizes the role that music therapy has fulfilled in this area.

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Fundamentals of Terminal Care

A complete or radical cure does not exist for any disease in its terminal stages. Therefore, the objective of terminal care is to assist the patient to achieve some form of substantiality, fullness or quality of life (QOL) in the time that is left by mitigating or alleviating the successive onslaught of physical pain and suffering and the accompanying emotional turmoil, apprehensions, disquiet, depression, the fear of approaching death, and the emotional and psychological struggle to accept death.

The benefits stemming from music therapy, when it is applied to substantiate terminal care, is compelling. However, due to the inherent difficulty of corroborating the physiological and biochemical benefits that is derived from music therapy, in most cases, physicians are relegated to observing the beneficial changes described by patients. But the benefits, in terms of QOL, can be measured by studying the patient records prior to and after the use of music therapy and time-lapse observation records.

Specific Music Therapy Techniques

1. Group sessions

Patients, who are ambulatory or who are able to move about in wheelchairs, as well as their family members are assembled to listen to music or to participate in singing activities. Although individual dialogues are not possible in such group sessions, it provides an opportunity for many patients to weep and release pent-up emotions and to gain a sense of comfort and relief at the end of the session. Women patients, in particular, are uninhibited about releasing their emotions in front of others, but many male patients are customarily embarrassed to openly show emotion or tears. Some refuse to enter the assembly room and discreetly remain either outside or in their private rooms.

2. Individual sessions

Individual sessions are conducted for male patients and bedridden patients in their private rooms. Patients are able to listen to their favorite music and are able to openly express their thoughts and emotions. In many cases, the act of listening intensively to music also mitigates the physical and mental pain and suffering, enables the patient to articulate the introspective, and provides an opportunity to indulge in humor and pathos to their hearts' content. The music therapist will bring various portable musical instruments and will play and sing for the patient. Musical instruments such as the small harp, drum, or maracas are placed near the patient's bedside to encourage the patient to touch and play the instrument.

Objectives of Music Therapy

The objectives of QOL or activity of daily life (ADL) are: 1) mitigate physical pain and suffering, 2) release inner thoughts and emotions, 3) help the recollection of past memories, and 4) promote group work. These objectives are explained in detail below.

1. Mitigating physical pain and suffering

Many cases have been observed where physical pain and suffering have been mitigated during the time that is spent by patients listening intently to their favorite music. Respiratory conditions have also been seen to improve temporarily.

Patients utilizing oxygen inhalers who are brought to the assembly room in wheelchairs have been observed to extract their inhalation tubes and to begin talking or singing loudly while listening to the music. Although this appears to be a one-time phenomenon, it signifies a temporary improvement of the respiratory function. Unfortunately, due to the difficulty of measuring respiratory function in a hospice, this cannot be corroborated by data, but there are plans to implement a simple means of measuring the respiratory function in the future. However, when music therapy was collectively implemented for bronchial asthma patients, an

improved peak flow was reported,[1)] an indication that music improves respiratory function.

2. Releasing inner thoughts and emotions

Patients are able to express their inner thoughts and emotions naturally while listening to their favorite music and to immerse themselves in the humor and pathos of the moment. This is often followed by an uplifting sense of well being. This is the strength of music, but its impact and effects on the human brain is as yet unknown; and it is a subject for future research.

3. Recollecting past memories

The task faced by terminally ill patients is to find closure of past regrets and events and to recollect and immerse themselves in happy memories. These painful or happy memories are always remembered in conjunction with the music that was popular at the time these events occurred. Therefore, when music or songs are played or sung to the patients by the music therapist, past events are remembered with great clarity, and they are able to immerse themselves in their recollections. The work is very inspiring.

4. Promoting grief work

As explained above in section 2, Releasing Inner Thoughts and Emotions, much of the inner turmoil of the patient, i.e., the acceptance of death and the parting with family members and friends, can be resolved. However, the work of the music therapist is also to provide grief care for the family members of terminally ill patients.

This involves the vital task of explaining the symptoms of the illness to family members at the initial start of the patient's hospitalization, of providing frequent explanations of the symptomatic changes that occur with the progression of the disease, and conducting comforting, compassionate dialogues with family members. Music is therapeutically applied for music-loving family members to help them release their inner emotions, to come to terms with the patient's approaching death, and to assist them to accept the death of a beloved family member in a stable frame of mind.

When attending family members begin to show signs of emotional instability, the therapist will encourage them to listen to their favorite music in a separate room to help them ease their inner emotions and tensions and they are allowed to return to the patient's bedside when they have regained their composure. Additionally, music is therapeutically applied to help family members regain their mental and emotional composure following the patient's death if it is requested.

The favorite music of the patient is also performed at the request of the family when the patient is discharged from the facility after their death, as a kind of funerary tribute.

Music Applied by the Therapist

As explained earlier, the therapist applies the favorite music of the patient and the music genre is diverse. Many terminal patients request songs from their hometowns, children's folk songs, lullabies, folk songs and some request the *enka* songs about mothers and of their hometowns. There are not many Japanese patients who request classical music, but terminal patients who were raised as Christians tend to request hymns and classical music pieces.

Interestingly, many terminal patients, who were fond of classical music in their youth or when they were healthy, seem to lose the desire or capacity to listen to classical music. To many Europeans and Americans, classical music reflects the familiar melodies of the composer's country, but this common heritage is not shared by the Japanese and classical music appears to fulfill a different role. Additionally, music sung in the baritone and alto or slow tempo music is very effective for terminal patients and the aged.

In Europe and the United States

The number of hospices in Europe and the United States vastly outnumber the facilities in Japan and the number of hospices that practice music therapy is also greater. Academic conferences centered on music therapy for terminal and pain care are held annually. The author, who gave a presentation two years ago at such a conference, has found that the content of music therapy that is practiced in Japan and other countries is similar. The papers that are presented from Europe and the United States are mainly written by music therapists; therefore, they are not published in medical journals. However, there is constant cooperation from physicians.

Recently, it has been reported that the adverse symptoms stemming from chemotherapy were greatly reduced in many cases when cancer patients listened to their favorite music during the treatment.[2)] Although this is not directly related to terminal care, it is one area of study which the author would like to explore.

Conclusion

The music therapy techniques that have been described in this paper have been applied by the author in his work at the Peace House Hospice (Hatano City, Kanagawa Prefecture) and the pain care ward at St. Luke's International Hospital. There is a total of approximately 40 hospital wards and hospices that are dedicated to pain care in Japan, of which nine facilities apply music therapy. The spread of music therapy in the treatment of the elderly and its effectiveness in helping terminal patients in hospices have been clearly proven. It will continue to be an essential component in the treatment of the elderly and terminal patients in future.

The content of the music therapy that is conducted for patients in the hospices and the pain care hospital wards does not differ.

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Randomized Controlled Trials on Hypertension

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Abstract: Numerous randomized controlled trials on hypertension have been conducted since the Veterans Administration (VA) Study on severe hypertension more than 30 years ago. The consensus derived from these trials comprises the following: (1) Lowering of systolic pressure by 10–20 mgHg and of diastolic pressure by 5–10 mgHg reduces cerebrovascular disease by 35–40% and coronary heart disease by 10–15%; (2) A similar degree of beneficial effects is observed in the hypertensive elderly; (3) In primary prevention of cerebrovascular disease, diuretics, β-blockers, Ca-antagonists, and ACE-inhibitors are effective; (4) In secondary prevention of coronary heart disease, β-blockers and ACE-inhibitors are effective; of heart failure, ACE-inhibitors and AII-receptor antagonists are effective; and of nephropathy ACE-inhibitors and Ca-antagonists appear to be effective. The results of randomized controlled trials of new drugs such as AII-receptor antagonists and conventional drugs are expected to be published soon.

Key words: Hypertension; Randomized controlled trials; Evidence based medicine; Target organ damage

Introduction

Many randomized controlled studies on hypertension have been conducted since the VA Study on severe hypertension was performed more than 30 years ago. The consensus derived from these studies is summarized as follows:

(1) Lowering of systolic pressure by 10–20 mgHg and of diastolic pressure by 5–10 mgHg reduces cerebrovascular disease by 35–40% and coronary heart disease by 10–15%;
(2) A similar degree of beneficial effects is observed in the hypertensive elderly;
(3) The higher the diastolic pressure and the older the patients (but among those younger than 80) are, the higher is the benefits of the blood pressure lowering effect;
(4) Diuretics, β-blockers and Ca-antagonists have been demonstrated as effective in pri-

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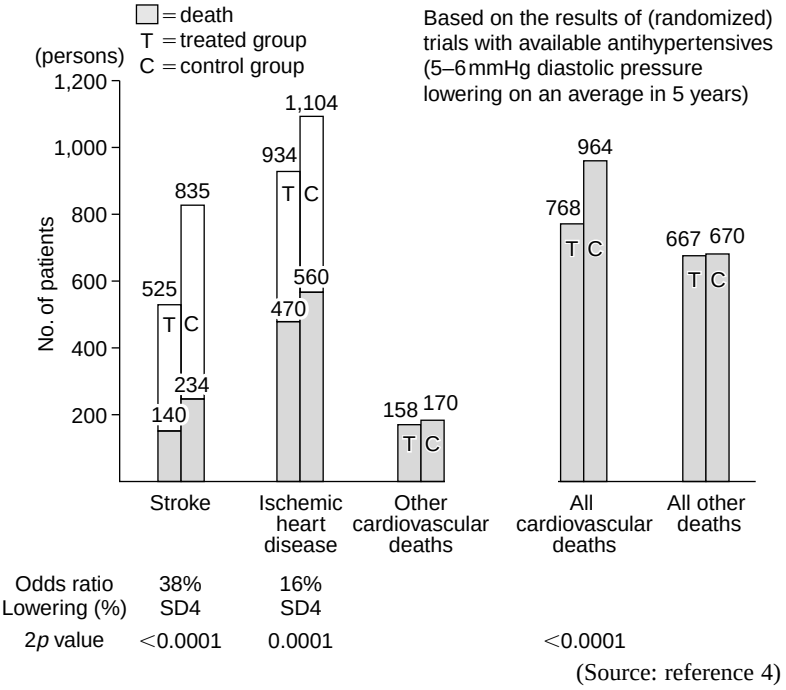

Fig. 1 Effect of antihypertensive treatments on mortality and morbidity from cardiovascular diseases
Total: 47,667
Mean diastolic pressure difference: 5–6 mmHg
Onset of complication: mean 2–3 years

mary prevention of cerebrovascular disease. According to STOP-Hypertension 2[1] published at the end of 1999, ACE-inhibitors and Ca-antagonists have shown substantially similar effects as conventional diuretics and β-blockers;

(5) β-blockers and ACE-inhibitors have been demonstrated as effective in secondary prevention of ischemic heart disease, ACE-inhibitors and β-blockers of heart failure, and ACE-inhibitors and Ca-antagonists of renal dysfunction. As regards heart failure, it is now clear that AII-receptor antagonists show similar benefits as ACE-inhibitors (ELITE II).[2]

The results of comparative studies on new drugs such as AII-receptor antagonists and conventional drugs are expected to be published successively. The outline of the results of these studies is discussed below.

Summary of Randomized Controlled Studies on Hypertension

The result of analysis[3] of 17 clinical trials (47,653 patients, mean age, 56; the follow-up period, 4–5 years) in the west such as the study on diuretics and β-blockers by Whelton *et al.* discussed in the 2000 edition of "Guideline for Treatment of Hypertension" published by the Japanese Society of Hypertension reveals the following.

(1) In the group treated with antihypertensives, the risk of developing stroke decreased by 38% and that of ischemic heart disease (IHD) by 16%.

(2) The higher the diastolic blood pressure (DBP) was, the higher the benefits of antihypertensive treatments became. In the groups of lower than 110 mmHg DBP, 110–114 mmHg, and above 115 mgHg, the numbers of patients per 1000 in each group for

whom stroke was prevented were 9, 19, and 35, respectively, and those for whom ischemic heart disease was prevented were 5, 12, and 15, respectively.

(3) The older the patients were, the higher was the efficacy of antihypertensive treatments. The numbers of subjects per 1000 for whom stroke was prevented in the groups of younger than 60 and older than 60 was 9 and 23, respectively, and those for whom IHD was prevented were 5 and 13, respectively.

These results coincide with that of meta-analysis of studies on diuretics and β-blockers published by Collins *et al.* in 1994 in which stroke decreased by 38% and IHD by 16%, respectively in the treated groups compared to the control groups (Fig. 1).

Historically speaking,

(1) the preventive effect of antihypertensive treatments on mortality and morbidity from cardiovascular risk in the severe and the moderate hypertensions (DBP≥105 mmHg) was demonstrated by the VA Study reported in 1970;

(2) the beneficial effect of antihypertensive treatments to reduce cardiovascular risk in mild hypertension (DBP≥90 mmHg) was also demonstrated in many studies such as Australian National Study (1980) and MRC Study (1985);

(3) clinical trials on the hypertensive elderly have advanced in the 1990s and established the efficacy of antihypertensive treatments (Table 1);

(4) in recent years, randomized controlled studies comparing conventional diuretics and β-blockers with new Ca-antagonists, ACE-inhibitors and α_1-blockers are being conducted and their results published.

Comparison of Conventional Antihypertensives (diuretics, β-blockers) and New Antihypertensive Drugs (ACE-inhibitors, Ca-antagonists, α_1-blockers) (Table 2)

The results of comparative studies on drugs such as diuretics and β-blockers that were used in large scale clinical tests in the past and comparatively new drugs such as ACE-inhibitors, Ca-antagonists, and α_1-blockers are now being published. Basically, there are observed no differences in the mortality and morbidity of cardiovascular disease according to the new and the old drugs. Characteristics of these results are discussed below.

(1) In CAPPP,[5] because the blood pressure level at the start was higher in the ACE-inhibitor group than the group of diuretics or β-blocker, the incidence of stroke was higher in the ACE-inhibitor group. However, compared to the groups administered diuretic or β-blocker, ACE-inhibitor restrained development of diabetes mellitus (DM) and decreased the incidences of stroke, myocardial infarct, and cardiovascular death in DM.

(2) In STOP-Hypertension 2,[1] no difference in the morbidity and mortality of cardiovascular disease was observed between the conventional drug group and the new drug group. On the other hand, there were a fewer incidences of myocardial infarction and congestive heart failure in the group dosed ACE-inhibitor than in the Ca-antagonist group.

(3) In INSIGHT[6] and NORDIL,[7] no difference in the morbidity and mortality of cardiovascular disease was observed between the Ca-antagonist group (sustained release nifedipin and sustained release diltiazem) and the diuretic and β-blocker groups. On the other hand, heart failure increased in the nifedipin group compared to the diuretic group. In the diltiazem group, the incidence of stroke significantly decreased compared to the groups dosed diuretics or β-blockers.

(4) According to the intermediate analysis of ALLHAT study[8] of the United States, α_1-blockers and diuretic in the high risk hypertensive group showed similar results regarding the mortality of coronary heart disease

Table 1 Major Clinical Trials on the Hypertensive Elderly

Name of trial	EWPHE	HEP	SHEP	STOP	MRC II	STONE	Syst-Eur	Syst-China
Age of subjects	≥60	60–79	≥60	70–84	65–74	60–79	≥60	≥60
No of subjects	840	884	4,736	1,627	4,396	1,632	4,695	2,394
Entered BP(mmHg)								
systolic	160–239 &	170–280 &	160–219 &	180–230 &	160–209 &	160–209 &/or	160–219 &	160–219 &
diastolic	90–119	105–120	<90	≥90 or 105–120	<115	296	<95	<95
Pre-treatment BP	180/101	187/100	177/77	195/102	185/91	168/98	174/86	170/86
Antihypertensive	diuretic	β-blocker	diuretic	1. β-blocker	1. β-blocker	Ca-antagonist	Ca-antagonist	Ca-antagonist
(†:used secondarily)	†methyldopa	†diuretics †methyldopa	†β-blocker	2. diuretics	2. diuretic	†ACE-inhibitor †diuretics	†ACE-inhibitor †diuretics	†ACE-inhibitor †diuretics
Trial method	dbl. blind	open	dbl. blind	dbl. blind	sgl. blind	sgl. blind	dbl. blind	sgl. blind
Follow-up (yr)	4.7	4.4	4.5	2.1	5.8	3.0	2.0	4.0
Post-treatment BP(mmHg)								
Treated group	150/85	162/77	144/68	167/87	152/77	146/85	151/79	150/81
Control group	171/95	180/88	155/71	186/99	166/83	155/90	161/84	159/84
Effectiveness (relative risk)								
Cerebrovascular	0.64	0.58*	0.67*	0.53*	0.75*	0.43*	0.58*	0.62*
Coronary heart	0.82	1.03	0.73*	0.87#	0.81		0.70#	1.06#
Heart failure	0.78	0.68	0.45*	0.49*		0.32	0.71	0.42
All cardiovascular	0.71*	0.76*	0.68*	0.60*	0.83*	0.40*	0.69*	0.63*

*: significantly different,
#: only for myocardial infarction
: BP for HEP and MRC II are estimated values.

(Source: Japanese Society of Hypertension: Guideline for Treatment of Hypertension, 2000 (JSH 2000))

Table 2 Major Randomized Controlled Trials Comparing Conventional Drugs (Diuretics, β-blockers) and New Drugs (ACE-inhibitors, Ca-antagonists, α_1-blockers)

Name of trial Published in	CAPPP 1999, *LANCET*	STOP-Hypertension 2 1999, *LANCET*	INSIGHT 2000, *LANCET*	NORDIL 2000, *LANCET*	ALLHAT targeted for 2002
Subjects	Essential hypertension	Elderly hypertension	Hypertension	Hypertension	Hypertension
Age	25–66	70–84	55–80	50–74	≥55
No. of subjects	10,985	6,614	6,321	10,881	ca. 40,000 (24,335)
Drugs	ACE–inhibitor (captopril) vs. diuretics / β-blockers	β-blockers or diuretics vs. Ca-antagonists (felodipine, isladipine) vs. ACE-inhibitors (enalapril, lisinopril)	Ca-antagonists (sustained release nifedipine) vs. diuretics	Ca-antagonists (sustained release diltiazem) vs. diuretics / β-blockers	Ca-antagonists (amlodipine) or ACE inhibitors (lisinopril) or α_1-blocker (doxazosin) vs. diuretics (chroltalidone)
Period of trial	Six years	Four years	Four years	Four & half years	Six (3.3) years
Method of trial	PROBE*	PROBE*	Double blind	PROBE*	Double blind
Results Onset of cardiovascular disease	Onset / death by cardiovascular disease were equal	Results of conventional and new (Ca-antagonist / ACE inhibitor) antihypertensive were equal	Equal to diuretics	Equal to diuretics / β-blockers	Intermediate analysis (Mar 2000) revealed no difference between the groups in the onset of lethal coronary heart diseases and non-lethal myocardial infarction, but α_1-blocker was found to have elevated the risk of heart failure by two times compared to diuretics, and the test on α_1-blocker was suspended
Mortality of cardiovascular disease			Equal to diuretics	Equal to diuretics / β-blockers	
Other results	Development of stroke ACE inhibitor> conventional drug Development of DM ACE inhibitor< conventional drug	ACE inhibitors significantly restrained development of myocardial infarction and congestive heart failures compared to Ca antagonists	Heart failure increased in nifedipine group	Stroke decreased in diltiazem group	

*Prospective Randomized Open Blinded End-point Study

ABCD: Appropriate Blood Pressure Control in Diabetes Trial
ALLHAT: Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial
CAPPP: The Captopril Prevention Project
CIBIS II: Cardiac Insufficiency Bisoprolol Study II
ELITE II: Evaluation of Losartan in the Elderly Study II
EWPHE: European Working Party on High Blood Pressure in the Elderly Trial
FACET: Fosinopril versus Amlodipine Cardiovascular Events Randomized Trial
HEP: Hypertension in Elderly in Primary Care
HOT: Hypertension Optimal Treatment Study
HYVET: The Hypertension in the Very Elderly Trial
INSIGHT: International Nifedipine GITS Intervention as a Goal for Hypertension Treatment
MDRD: Modification of Diet in Renal Disease Study
MERIT-HF: Metoprolol CR/XL Randomized Intervention Trial in Heart Failure
MICRO-HOPE: Microalbuminuria, Cardiovascular, and Renal Outcome-Heart Outcome Prevention Evaluation
MRC: Medical Research Council Study
MRC II: Medical Research Council Trial II
NICS-EH: National Intervention Cooperative Study in Elderly Hypertensives
NORDIL: The Nordic Diltiazem Study
SHEP: Systolic Hypertension in the Elderly Program
STONE: Shanghai Trial of Nifedipine in the Elderly
STOP-Hypertension 2: Swedish Trial in Old Patients with Hypertension 2
Syst-China: Systolic Hypertension in China Trial
Syst-Eur: Systolic Hypertension in Europe Trial
UKPDS: UK Prospective Diabetes Study

and development of non-fatal myocardial infarction. On the other hand, the α_1-blocker group showed a high incidence of cardiovascular disease, particularly of heart failure.

Results of Studies on Special Populations and Co-existing Diseases

1. Stroke

As mentioned above, antihypertensive treatments are clearly effective in primary prevention, and very recently PROGRESS study showed the secondary prevention by ACE inhibitors. For primary prevention, lowering of blood pressure is basically important and similar results are achieved with any type of antihypertensive drugs (STOP-hypertension 2: diuretics, β-blockers vs. Ca-antagonists · ACE-inhibitors, INSIGHT: nifedipine, GITS vs. diuretic, etc.)

According to the NORDIL study published in 2000, the incidence of stroke decreased significantly in the sustained release diltiazem group compared to the groups of diuretics or β-blockers.

2. Ischemic heart disease (IHD)

Regarding primary prevention, there may be observed a significant decrease in a single study, but meta analysis reveals, as mentioned above, that treatment with antihypertensives such as diuretics and β-blockers can control the onset of IHD by more than 10% and less than 20%.

The effect of β-blocker (without endogenous sympathomimetic stimulating action) has been established for the secondary prevention. There is a report that diltiazem is effective in preventing recurrence in non-Q infarct patients without heart failure.

ACE-inhibitors have been established to inhibit onset of sudden death or heart failure by the remodeling after myocardial infarction.

The J-curve phenomenon (excessive blood pressure lowering may manifest the contrary effect of exacerbating prognosis in IHD) was not observable up to DBP of 80 mmHg according to the result of HOT.[9]

3. The hypertensive elderly

(1) As shown in the meta analysis of the hypertensive patients aged 60 and over (Table 1), the antihypertensive treatments basically controls stroke and IHD as in the case of those aged younger than 60. This is similar to the case of systolic blood pressure (SHEP, Syst-Eur, Syst-China).
(2) As for the types of antihypertensives, efficacy of diuretics has been established (EWPHE, STOP-Hypertension, MRC II, SHEP). Efficacy of Ca-antagonists, particularly of long acting dihydropyridine, has been demonstrated (Syst-Eur, Syst-China, STONE, NICS-EH).
(3) In the very elderly subjects (aged 80 and over), benefits of antihypertensive has not yet been established. The result of ongoing HYVET study is awaited.

4. Chronic heart failure

In treating hypertension accompanying chronic heart failure, efficacy of ACE-inhibitors has been established.[10] As for β-blockers, beneficial effects of carvedilol (US Carvedilol trial), bisoprolol (CIBIS II), and metoprolol (MERIT-HF) are being established.

Diuretics are also useful, and spironolactone has been demonstrated recently as effective for improving prognosis of severe heart failure.[11]

AII-receptor antagonists show a similar degree of improvement for prognosis of heart failure as ACE-inhibitors, with their merit of fewer side effects (ELITE II).[2]

5. Nephropathy

Hypertension adversely affects prognosis of renal insufficiency, requiring intense blood pressure lowering. If urinary protein is more than 1 g/day, 125/75 mmHg or lower is the target value (MDRD). WHO/ISH guideline as well as JSH 2000 guideline base its target on this value.

ACE-inhibitors restrain urinary protein in diabetic nephropathy and non-diabetic nephropathy as well as progression of nephropathy.[12]

6. Diabetes mellitus

In HOT using Ca-antagonists, there was evidence that lowering blood pressure to the lowest target level (DBP$<$80 mmHg) in diabetic hypertensive patients resulted in lowering risks of cardiovascular events. This is also confirmed in UKPDS using β-blockers and ACE-inhibitors.[13]

ACE-inhibitors were confirmed to restrain lowering of renal functions in diabetic nephropathy.

ACE-inhibitors (CAPPP,[5] MICRO-HOPE[14]), and Ca-antagonists (HOT, Syst-Eur) were effective for the prevention of cardiovascular disease in diabetic patients. Although not randomized controlled studies, there are reports that ACE-inhibitors have more favourable effects on IHD events compared with Ca-antagonists in diabetic patients.

Conclusion

Mega trials on hypertension were discussed. These results or evidences cannot necessarily be applied directly to one's patients. True evidence-based-medicine (EBM) in daily clinical scene should consider blood pressure levels, severity of disease in individual patients, type and degree of complications and compliances while taking into consideration the result of these randomized controlled studies.

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