Journal of Food and Drug Analysis
1999. 7(3) : 233-242

藥物食品分析
第七卷　第三期

The Relationship between the Cold Chain System and Vaccine Potency in Taiwan: (I) Live Measles Vaccine and MMR Vaccine

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ABSTRACT

Taiwan has a long history of using vaccines in order to protect people against certain infectious diseases. Several types of vaccines have been used successfully for protecting children from poliomyelitis, measles, and other acute infectious diseases. However, for the monovalent measles vaccine (MV), and the trivalent measles-mumps-rubella combined vaccine (MMR vaccine) which are made from live attenuated viruses, they are unstable unless stored at a proper low temperature, at a certain pH level, in darkness, and combined with some specific stabilizers. Maintaining these live virus vaccines at the recommended temperatures of +2 to +8°C is one of the most important limiting factors in this respect, particularly in a subtropical climate such as in Taiwan. This study investigated and evaluated the vaccine cold chain system at different storage levels, and selected several health stations and local hospitals/pediatric offices in each County/City of Taiwan to take samples of the MV and MMR vaccines and test their potency during the autumn of 1997. Our results show that all of the MV samples meet the requirements for the potency test, showing titers higher than the criteria of the WHO and the ROC (Taiwan) national standard. The MMR vaccine also maintained its potency, with the exception of a few mumps vaccines. This study found that the shorter the remaining term of validity (RTV) of MMR vaccines is, the more inactivation of the mumps virus could occur. The reason why the mumps vaccine of MMR vaccine seems unstable in Taiwan needs further investigation. Nevertheless, the results of this study reveal that the cold chain system used in Taiwan is satisfactory for vaccine storage.

Key words: **cold chain, MV, MMR vaccine, potency test, remaining term of validity.**

INTRODUCTION

Since the time of Edward Jenner 200 years ago, vaccination has been used to control several major infectious diseases such as smallpox, diphtheria, tetanus, pertussis, poliomyelitis, measles, mumps, and rubella[1].

Viral vaccines are highly sensitive biological

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Accepted for Publication: Aug. 19, 1999

products[2, 3], and the storage temperature, specific pH, light, adding stabilizers such as magnesium chloride, sorbitol, or gelatin, and other factors influence their protective titers[4,5]. The immunogenicity of live virus vaccines, unlike the inactivated ones, depends on the retention of a sufficient amount of live viruses to establish an infection in the susceptible recipient[6]. The live viruses of these vaccines, even when they were dried, show loss of infectivity by storage, and the rate for such loss increases as the temperature is elevated. Dried live virus vaccines should be stored continuously in a more stable cold chain system including the transport mechanism and the controlled refrigeration up to the time of delivery to the recipient[7,8]. Therefore, it is important to provide maximum stability for live virus vaccines during storage. The measles vaccine (MV) and the combined measles-mumps-rubella vaccine (MMR vaccine) investigated here are dried live attenuated virus vaccines and should be transported and stored under +2 to +8°C conditions to maintain their titers[9,10]. Maintaining the MV and MMR vaccine at the recommended temperatures between +2 to +8°C is one of the most important limiting factors in Taiwan which has a semi-tropical climate.[11]

Vaccines have been used for many years to protect people against certain communicable diseases in Taiwan. The MV and MMR vaccines have long been used to protect children from measles, mumps and rubella. The reported incidence of measles decreased steadily after the wide use of live measles vaccine in 1978 in the Taiwan area. However, island-wide outbreaks of measles still occur every 2-3 years. Most of the infected had not been vaccinated. After rubella vaccine was licensed in 1969, vaccination programs in the U.S. resulted in a great reduction in the reported cases of rubella and congenital rubella syndrome (CRS)[12]. Since 1984, the live rubella virus vaccine has been widely given to junior high school girls in the Taiwan area. As a result, only a few reported cases of rubella and CRS occurred during the period 1988 to 1993. In addition, the reported incidence of mumps in the Taiwan area decreased after the introduction of MMR vaccine in 1992. To improve living standards and make universal the practice of immunization, the Department of Health of the Executive Yuan initiated a plan for the elimination of poliomyelitis, CRS, measles, and neonatal tetanus in January 1991. An important part of the plan was to strengthen measures to safeguard the potency of vaccines. For example, through rigorous testings of each vaccine batch and the strict control of temperature, etc, the potency of vaccines could be maintained at a satisfactory level. However, it is still unknown whether there is a close relationship between the cold chain system and vaccine potency in Taiwan.

The cold chain system in transportation and storage of vaccines in the Taiwan area is a three-level storage/transport system (Fig. 1). Level I is composed of the health bureaus of Taipei City, Kaohsiung City and 21 Counties/Cities of Taiwan province; level II is composed of the health stations of each County/City; and level III is composed of local hospitals/pediatric offices and the health rooms of the City/County health station. The vaccines are transported to level I storage areas and stored in large-scale freezers after they have been qualified by testing at the National Laboratories of Foods and Drugs. At the request of health workers from level II, the vaccine is then transported and stored in the refrigerators of level II, for inoculation of children and adults in those areas. Finally, part of the vaccine is transported to level III when needed.

Several investigations have demonstrated that the MV and MMR vaccines have good efficacy[13-17]. Pabst *et al*. reported that both cellular and humoral immune responses were induced by MMR vaccination[14]. However, it was still unknown whether hot climate, the failure of a refrigerator mechanical system, a breakdown in the transport system, and other limiting factors in the cold chain system might affect the vaccine storage conditions and lower their potency[18]. In this study, we attempted to find a correlation between the vaccine potency and the cold chain system in Taiwan, and identify the possible factors affecting vaccine potency. The MV and MMR

vaccines were randomly sampled from the level II and III areas in our epidemic prevention system and tested for their potency. Our results demonstrated that the MV samples met the requirements in the potency test. Their titers showed no significant difference between the level II and III storage areas. All the results demonstrated that the MV was stable enough and not influenced by the vari-

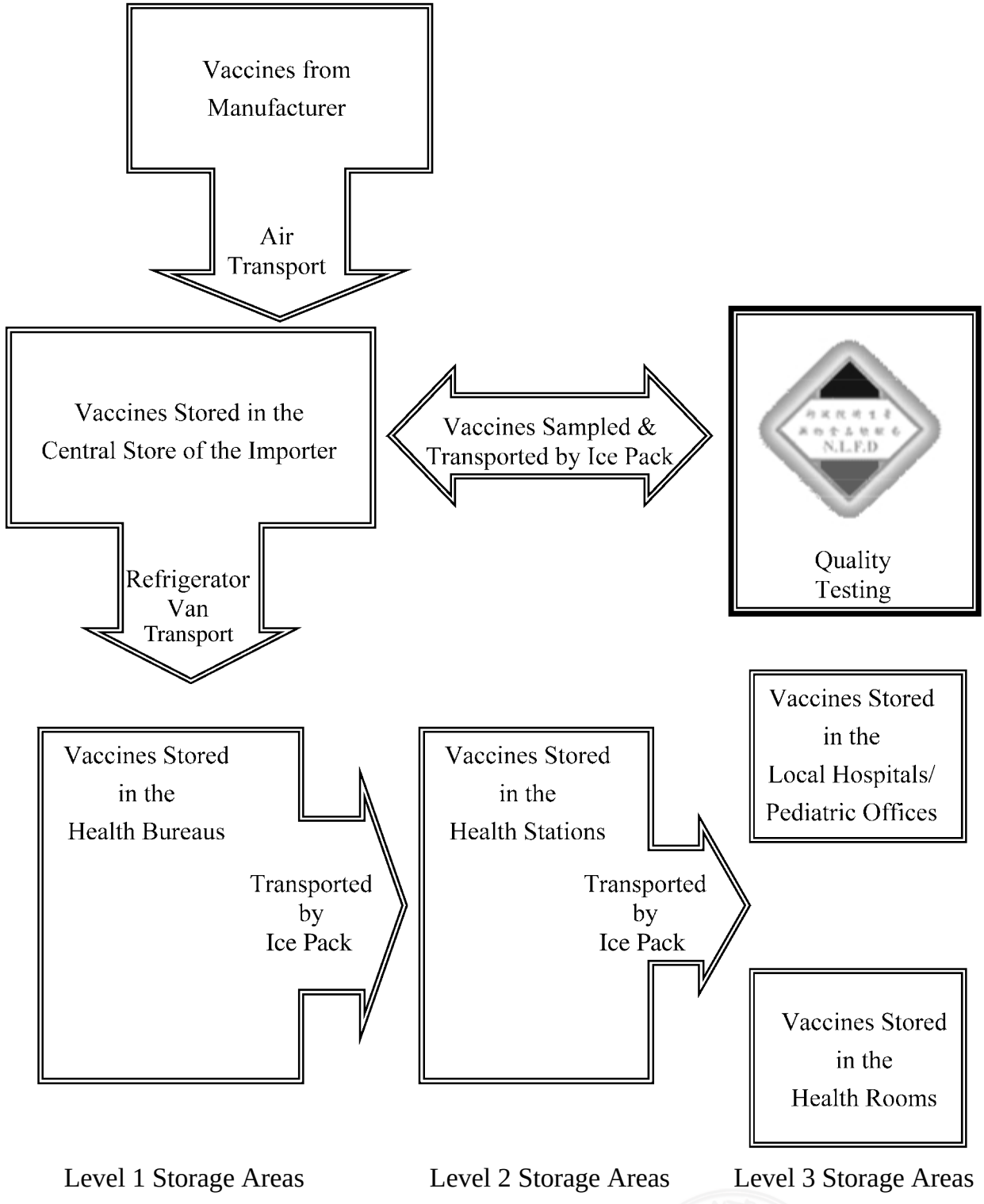


Figure 1. The flow chart of vaccine transport and storage in Taiwan's cold chain system.

able temperature conditions. The MMR vaccine maintained potency except for some dissatisfactory cases with lower titers in the mumps vaccine. We found that the short length of RTV was the major factor for the degradation of mumps potency in the MMR vaccine.

MATERIALS AND METHODS

I. *Materials*

Minimum essential medium (MEM) containing Earle's salts, L-glutamine, and sodium bicarbonate, heat-inactivated and qualified fetal bovine serum (FBS) , antibiotics (100x, lyophilized) and trypsin/EDTA solution were all purchased from Gibco BRL (Grand Island, NY). The neutralizing antisera of measles, mumps, and rubella viruses as well as the house standards of measles vaccine, mumps vaccine, and rubella vaccine were from Merck Sharp and Dohme (RAHWAY, NJ). The microtiter plates, tissue culture flasks, and other plastic accessories were from Corning/Costar (Nagog Park Action, MA).

II. *Vaccine Samples*

The freeze-dried measles vaccine and combined MMR vaccine were sampled from the health stations and health rooms/local hospitals/ pediatric offices at 23 Counties/Cities in the Taiwan area. All vaccine samples were coded and shipped with dry ice, and stored at -20°C before testing.

III. *Cell and Cell Culture*

All cells purchased from American Tissue Culture Collection (ATCC) were established into the master cell bank (MCB) and working cell bank (WCB) in our laboratory. Vero cells (ATCC CCL-81) were used for the potency tests of measles vaccine and mumps vaccine, while RK-13 cells (ATCC CCL-37) were used for rubella vaccine assay. All stock cultures were prepared from WBC. They were maintained in MEM supplemented with 10% FBS in a humidified incubator at 37°C under 5% CO_2 condition and passed at 5 to 12 generations.

IV. *Potency Test*

The potency test was conducted according to the methods for potency testing of vaccines used in the World Health Organization's (WHO) expanded program on immunization[19].

(I) *Measles/Mumps Vaccine Potency Test*

The potency of measles/mumps vaccine samples was tested by an *in vitro* microtitration assay. Serial dilutions of these samples and the reference standards preparation were inoculated in rows of 10 wells of microtiter plates, together with trypsinized Vero cell suspension. To avoid interference, mumps and rubella vaccine viruses (for measles titration) or measles and rubella vaccine viruses (for mumps titration) were neutralized by the addition of appropriate antisera. The plates were incubated at 35°C/5% CO_2 for 10~12 days. At the end of the incubation period, the numbers of the specific viral cytopathic effect (CPE) were counted and recorded. The $CCID_{50}$ (or $TCID_{50}$) per human dose was calculated using the Reed and Muench calculation method[20].

(II) *Rubella Vaccine Potency Test*

The potency of rubella vaccine samples was also tested by the *in vitro* microtitration assay. Serial dilutions of the samples and the reference standard preparation were inoculated in rows of 10 wells of microtiter plates, together with trypsinized RK-13 cell suspension. The measles and mumps vaccine viruses were neutralized by the addition of appropriate antisera to avoid interference. The plates were incubated at 33°C/5% CO_2 for 10~14 days. At the end of the incubation period, the CPE numbers were counted and recorded. The $CCID_{50}$ (or $TCID_{50}$) per human dose was calculated using the Reed and Muench calculation method[20].

V. *Statistical Analysis*

The SPSS statistic software was used to analyze experimental results. The student's T test and the Fisher's protected LSD (FPLSD) multiple

comparisons were used for analyzing the results of the MV and MMR vaccine potency tests.

RESULTS AND DISCUSSION

During 1997 Nov to 1998 Feb, we randomly selected the health stations, health rooms, local hospitals, and pediatric offices from the level II and III storage areas in Taiwan as the sampling areas. In total, we tested the 94 samples of MV vaccine and 40 samples of MMR vaccine from the above selected districts. After the samples were collected, they were immediately transported to our laboratory for vaccine potency testing.

I. *Measles Vaccine Potency*

In our testing results, all of the MV samples are qualified in the potency test and their average titer is 3.490 ± 0.229 $Log_{10}TCID_{50}$/dose (Table 1). The titers are higher than the criteria of the WHO and the national standard of the Republic of China (ROC) on Taiwan (not less than 3.0 $Log_{10}TCID_{50}$/dose/0.5mL or 1,000 $TCID_{50}$/dose/0.5mL). According to the temperature records of the sampling areas, the average storage temperature in the level II area (4.75°C) is lower than in level III (6.64°C). The temperatures of both storage areas are still in the normal range (2~8°C). We used the student's T statistic analysis to compare the potency of the vaccines stored in levels II and III. Table 2 shows that the measles potency between these two storage areas has also no significant differences ($P > 0.05$). It is possible that the higher quantities of the measles virus are filled in the final products. Therefore, the monovalent measles vaccine we tested could be more heat-stable than the MMR vaccines. The cold chain system in Taiwan has the ability to maintain the potency of the measles vaccine during the remaining term of validity (RTV).

II. *MMR Vaccine Potency*

The MMR vaccine consists of the monovalent measles vaccine, the monovalent mumps vaccine, and the monovalent rubella vaccine. In this study, we used the neutralizing antisera of these viruses to test the monovalent virus potency.

(I) *Measles Vaccine Potency*

Like MV, our results show that the average measles potency of MMR vaccine is 3.256 ± 0.229 $Log_{10}TCID_{50}$/dose (Table 3). The measles potency of all MMR samples are higher than the criteria of the WHO and the ROC national standard (not less than 3.0 $Log_{10}TCID_{50}$/dose/0.5mL or 1,000 $TCID_{50}$/dose/0.5mL). Already aware that the average storage temperature in the level II area was lower than in the level III area, this study sought to find out if any difference of measles potency between the different storage areas exists. Table 4 shows that the measles potency of MMR samples stored in level II are higher than in level III. These differences are significant ($P < 0.05$). Although all the measles potency results are satisfactory, our findings still show that the measles virus in the MMR vaccine is more affected by heat than the monovalent MV. Furthermore, the other two viruses may influence the measles potency in MMR vaccines. This could explain why our results found the monovalent MV poten-

Table 1. The Average Potency of the Monovalent Measles Vaccines

	Average Potency ($Log_{10}TCID_{50}$/dose/0.5 mL)
Measles Vaccine Sample	3.490 ± 0.229[a]
Reference Measles Vaccine	3.388 ± 0.038

[a] The average potency of the monovalent measles vaccines was shown as mean ± standard deviation.

Table 2. The potency of the measles vaccine sampled from the level II and III storage areas

Storage Area	Vaccine Potency ($Log_{10}TCID_{50}$/dose/0.5 mL)
Level II	3.518 ± 0.238[a]
Level III	3.468 ± 0.234

[a] The statistical analysis was done by student's T test and there were no significant differences (P = 0.549).

cy to be higher than the measles potency in the MMR vaccine.

(II) *Mumps Vaccine Potency*

This study shows that the average mumps potency of MMR vaccine is 4.196 ± 0.303 $Log_{10}TCID_{50}$/dose (Table 3). This is lower than the criteria of the WHO and the ROC national standard (not less than 4.3 $Log_{10}TCID_{50}$/dose/0.5mL or 20,000 $TCID_{50}$/dose/0.5mL). According to the results of student's T test for statistical analysis, there is no significant difference between the vaccines sampled from level II and III (Table 4). The lower average mumps potency is caused by some dissatisfactory vaccines sampled from the individual storage unit. However, the temperatures recorded in these health stations, health rooms, and local hospitals/pediatric offices are normal.

In order to find the possible factors that affect the mumps potency of MMR vaccines, we analyzed other data including the personal error of temperature recording, transport conditions, the fluctuation of temperature changes in the refrigerator and the condition of the vaccine itself. It was found that only the RTV factor concerns the decreased potency of mumps vaccine. Table 5 shows that most of the disqualified MMR vaccines belong to two production lots, and these are relatively closer to the expiration date than are the qualified ones. The RTV of the MMR vaccines we sampled, were divided into three groups: 1~6 months, 7~12 months, and over 12 months. The ANOVA analysis shown in Table 6-1 indicates significant differences among the RTV of MMR vaccines. The FPLSD results (Table 6-2) demonstrate that the MMR vaccines are closer to the end of the vaccine lifetimes and the mumps potency is more degraded. The difference of mumps potency between the newest MMR vaccines and the oldest ones is at 1.3 $Log_{10}TCID_{50}$/dose/0.5 mL. However, Dr. W. J. McAleer and colleagues have demonstrated that the infective degradation rate of mumps virus in the MMR vaccine are at 0.2~0.3 $Log_{10}TCID_{50}$/0.1 mL when the vaccines are stored at 2~8°C[21]. In addition, it is known that the minimal infectious dose of virus required to immunize a susceptible human being has been measured in titrations in man and are 20 $TCID_{50}$ for the measles virus[22], 317 $TCID_{50}$ for the mumps virus[23], and 40 $TCID_{50}$ for the rubella virus[24, 25]. Our study shows that the mumps virus of the MMR vaccine are more unstable than the other two. We suggest that there are two possible explanations: (1) It is due to the stabilizer, sorbitol-gelatin complex used in the MMR vaccine[26, 27].

Table 3. The average monovalent vaccine potency of the MMR vaccines

	Vaccine Potency ($Log_{10}TCID_{50}$/dose/0.5 mL)		
	Measles	Mumps	Rubella
MMR Vaccine Sample	3.256 ± 0.155	4.196 ± 0.303	3.246 ± 0.157
Reference Vaccine	3.394 ± 0.213	4.530 ± 0.243	3.402 ± 0.119
House Standard[a]	3.667 ± 0.911	4.937 ± 0.970	3.730 ± 0.806

[a] The house standards were provided from Merck Sharp and Dohme (measles, Lot. 10; mumps, Lot. 8; rubella, Lot. 7).

Table 4. The monovalent vaccine potency of the MMR vaccines sampled from the level II and III storage area

	Vaccine Potency ($Log_{10}TCID_{50}$/dose/0.5 mL)		
	Measles	Mumps	Rubella
Level II	3.313 ± 0.135[a]	4.210 ± 0.150	3.264 ± 0.201
Level III	3.230 ± 0.261	4.190 ± 0.068	3.237 ± 0.132

[a] The potency difference between the level II and III storage areas was statistically significant (P = 0.029).

This stabilizer is not sufficient to stabilize the MMR vaccine in the hot climate of Taiwan. Therefore, the mumps virus can not maintain potency for 2 years. (2) The mumps virus in the MMR vaccine is highly heat-sensitive. Although the average storage temperature is at normal range, the temperature of the refrigerator, which stored dissatisfactory vaccines, may have gone through extreme temperature variations many times each day. This variation could lead to mumps virus degradation. Furthermore, it is not clear whether these dissatisfactory MMR vaccines still elicit enough immune protection against mumps disease. Further investigation is needed to elucidate these problems.

(III) *Rubella Vaccine Potency*

All the rubella potency of MMR vaccines is qualified for the criteria of the WHO and the ROC national standards (not less than 3.0 $Log_{10}TCID_{50}$/dose/0.5mL or 1,000 $TCID_{50}$/dose/0.5mL). The average rubella potency of MMR vaccines is 3.490 ± 0.229 $Log_{10}TCID_{50}$/dose (Table 5-1). There are no significant differences of rubella potency between the MMR vaccines sampled from the level II and III storage areas (Table 5-2). The rubella potency is still qualified even though their RTV was very short. It was found that the measles virus and rubella virus in the MMR vaccine are very stable in our cold chain system.

CONCLUSION

In this study, we found that the cold chain system used in Taiwan is suitable to maintaining the measles vaccine. There are no significantly different temperature conditions between levels II and III even though the difference reaches close to

Table 5. The remaining term of validity (RTV) of the MMR vaccines

	Qualified MMR Vaccines	Disqualified MMR Vaccines
Average RTV (months)	7.065[a]	4.926

[a] The RTV difference between the qualified MMR vaccines and disqualified ones was statistically significant (P = 0.003).

Table 6-1. The ANOVA analysis of the mumps vaccine potency in the MMR vaccines among the RTV groups

	Sum of Squares	df	Mean Squarm	F value
Total	7.730	2		
RTV Group	0.795	82	0.397	4.699[a]
Error	6.935	84	0.0846	

[a] The mumps potency difference among the RTV groups was statistically significant (P = 0.012).

Table 6-2. Grouping of ranked average mumps potency with FPLSD

	RTV Groups[b]		
	A (>12 months)	B (7~12 months)	C (1~6 months)
The Mumps Potency of MMR Vaccines[a]	4.378 [c]	4.367[d]	4.143[e]

[a] The mumps vaccine potency of the MMR vaccines was shown as $Log_{10}TCID_{50}$/dose.

[b] The RTVs of the MMR vaccines were grouped into three groups. The group A, B, and C were designed to the over 12 months, the 7~12 months, and the 1~6 months, respectively.

[c] The rank of average mumps potency between the RTV groups was A > B > C.

[d] The mumps potency difference between the group A and B was not significant (P = 0.937) and underlined by the same line.

[e] The mumps potency difference between the group B and group C was statistically significant (P = 0.010).

2°C. The cold chain system in Taiwan can provide a relatively stable condition for measles vaccine storage. In addition, the MMR vaccines are also stable in this cold chain system except for a few mumps vaccines. Our results indicate that the shorter the RTV of MMR vaccines is, the more inactivation of the mumps virus occurs. It seems that the mumps virus of the MMR vaccine is less stable in Taiwan. Whether this is caused by insufficiency of the stabilizer in the mumps vaccine, or the virus strain of mumps vaccine is too heat-sensitive or other factors needs more investigation to clarify.

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Journal of Food and Drug Analysis. 1999. 7(3)

台灣地區疫苗效價與Cold Chain系統間之關係(I) 減毒活病毒麻疹疫苗及麻疹、腮腺炎、德國麻疹混合疫苗

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摘　要

台灣地區使用疫苗來保護民眾免於受到某些特殊傳染病的侵害已有相當長的歷史，其中將疫苗用於保護兒童不受小兒麻痺症、麻疹等惡性傳染病的感染已有相當良好的成效。然而對於目前我國所使用的減毒活病毒麻疹疫苗及麻疹、腮腺炎、德國麻疹混合疫苗而言，其為相當不安定的生物製劑，需要維持特定酸鹼度、避免光照、添加安定劑並儲存在特定的低溫環境中。因此，特別是在處於熱帶/亞熱帶氣候的台灣地區，這些活病毒疫苗在運送儲存時將溫度維持在2到8°C之間是疫苗cold chain系統最重要的限制因子。本研究之目的即在評估台灣地區麻疹疫苗及麻疹、腮腺炎、德國麻疹混合疫苗在不同的儲存階層中cold chain系統與疫苗效價間的關係。我們自民國86年9月起在台灣各縣（含直轄市）市中隨機選擇衛生所、衛生室及合約醫院針對上述二種疫苗進行抽樣與效價試驗。我們從試驗結果中發現，所有麻疹疫苗檢體的效價都能符合我國衛生署及世界衛生組織的相關規定；麻疹、腮腺炎、德國麻疹混合疫苗檢體除了部份個案外，亦皆能符合我國衛生署及世界衛生組織的相關規定，而混合疫苗中腮腺炎疫苗效價的降低可能與其較短之剩餘效期有關。本研究的結果顯示台灣地區所使用的cold chain系統已提供麻疹疫苗及麻疹、腮腺炎、德國麻疹混合疫苗相當合適的儲存環境。

關鍵詞：cold chain系統，麻疹疫苗，麻疹，腮腺炎，德國麻疹混合疫苗，效價試驗，剩餘效期。