

# Post Mass-Immunization Measles Outbreak in Taoyuan County, Taiwan: Dynamics of Transmission, Vaccine Effectiveness, and Herd Immunity

Min-Shi Lee, MPH;\*† Li-Li Lee, MSc;\* Hour-Young Chen, PhD;\* Ying-Chang Wu, MSc;\* and Chi-Byi Horng, PhD\*

## ABSTRACT

**Objectives:** Analysis of national surveillance data and a sero-epidemiologic investigation were conducted to elucidate the causes and epidemiologic characteristics of a measles outbreak in Taoyuan, Taiwan, 1994.

**Methods:** Measles cases were identified through a national surveillance system. Reported cases and their physician or school nurses were interviewed to trace additional suspect cases and were sampled for serologic diagnosis. Measles-specific IgG and IgM were assayed. A confirmed case was defined as being positive for measles IgM test but not having received measles vaccination within the previous 3 months.

**Results:** The outbreak began in Taoyuan City in December 1993 and continued to spread in primary schools and kindergartens, but caused only sporadic cases in neighboring towns. Among 42 confirmed cases, 15 (38%) were primary school children and 16 (38%) were kindergarten children. Among 24 confirmed cases with a vaccination record, 7 had one dose of vaccination, 4 had two doses of vaccination, and 13 (54%) were unvaccinated. The overall measles susceptible proportion at a kindergarten before the outbreak was 8.1% (17/209) and the overall measles cumulative incidence among susceptibles was 0.65 (11/17).

**Conclusions:** A measles vaccination coverage of 82% with the first dose at 9 months of age and 63% with the second dose (measles, mumps, and rubella) at 15 months was inadequate to block measles virus circulation in Taoyuan City in 1994. The

city center, with a growing population, represents a high risk as an epicenter for measles outbreaks. Measles outbreaks may occur in a school population with 92% herd immunity.

**Key Words:** herd immunity, measles outbreak, seroepidemiology, vaccine efficacy

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Measles is an acute and highly contagious viral disease. It remains a major killer of infants in developing countries with low vaccination coverage, and continues to cause outbreaks in countries with over 90% vaccination coverage, despite the fact that an effective live-attenuated measles vaccine has been licensed since the 1960s.<sup>1–3</sup> Epidemiologic and theoretic studies suggest that measles can be eradicated for the following reasons: (1) humans are its only natural host, (2) persistent infection is rare and cannot serve as source of transmission, and (3) effective vaccines are available, and (4) the virus has a high degree of antigenic stability.<sup>1–2</sup> Moreover, because measles vaccination is highly cost-effective, the World Health Organization (WHO) has proposed establishing a goal of eradicating measles virus globally by the year 2005 to 2010.<sup>4</sup>

Historically, measles infection in Taiwan has been widespread, with epidemics occurring every 2 years before the introduction of mass immunization in 1978. Since then, measles mortality rates had decreased significantly, but reports of measles cases continued with periodic large-scale, island-wide outbreaks in 1984–85 and 1988–89. In an effort to adjust to the transitional nature of the epidemiologic characteristics of the measles infection in Taiwan, researchers changed the recommended measles vaccination schedule several times during this period: one dose at 9 months of age established in 1978, two doses at 9 and 15 months of age beginning at 1984, returning to one dose at 12 months of age in January 1988, and again to two doses in May 1988. Since 1991, measles, mumps, and rubella (MMR) vaccine has been introduced to replace the second dose of measles vaccine in 15-month-old children.<sup>5–6</sup> In addition, a mass campaign

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National Institute of Preventive Medicine, Taipei, Taiwan.

\*Present affiliation: Wellcome Trust Centre for the Epidemiology of Infectious Disease, Department of Zoology, University of Oxford, Oxford, United Kingdom.

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Address correspondence to Min-Shi Lee, Department of Biological Sciences, University of Warwick, Coventry CV4 7AL, UK.

of MMR vaccination among primary and secondary school children was conducted in 1991-93. The coverage rate achieved in the target population during the campaign was approximately 90%.<sup>7</sup> Following a 1-year-period of near zero incidence, a measles outbreak erupted in Taoyuan County in the spring of 1994. To investigate and elucidate the epidemiologic characteristics of measles transmission against a background of a moderately high level of measles vaccine coverage, the authors analyzed surveillance data and conducted an active hospital, community, and school investigation as well as a seroepidemiologic study in a kindergarten where measles was erupting.

## MATERIALS AND METHODS

### Background

Taoyuan County consists of 13 cities or towns and its administrative and economic center, Taoyuan City is only 30 km from the capital, Taipei City. The population and population density in Taoyuan City in 1990 were 241,263 persons (6932 persons/km<sup>2</sup>), which increased to 260,680 persons (7490 persons/km<sup>2</sup>) in 1994.<sup>8</sup> Based on the health statistics of Taoyuan City, the vaccination coverage of measles vaccine at 9-month-old and MMR vaccine at 15-month-old in 1993 were 82% and 63%, respectively.

### Surveillance Data

Measles is a reportable disease in Taiwan. Physicians routinely report suspect cases (fever, rash, and one of cough, coryza, and conjunctivitis) to the appropriate County Health Department, which assumes the responsibility of collecting blood samples for case verification (serology done at National Institute of Preventive Medicine [NIPM]), as well as interviewing the physicians and contacts of the cases, to identify the source and the size of the outbreak.

After 11 months without any reported measles cases, the Taoyuan County Health Bureau noted an apparent increase in the reported cases of measles at the beginning of 1994; however, their attempt to identify the geographic or demographic linkage between these reported cases was unsuccessful. On May 10, based on the preliminary reporting data, which identified the high risk group of the outbreak as kindergarten and primary school children, national health authorities at the Department of Health (DOH) alerted local physicians to report any further suspect cases and advised the Taoyuan County Health Bureau to accelerate the MMR campaign among primary school children who were not immunized as originally scheduled in 1993, owing to a shortage of MMR vaccine.

### Seroepidemiologic Investigation and Outbreak Control

On May 18, the NIPM joined the local health authority in the efforts to interview the reported cases, local physi-

cians, and school nurses and noted that the outbreak was spreading from a primary school to a kindergarten in Taoyuan City. Consequently, a seroepidemiologic investigation was initiated in the affected kindergarten. A self-administered questionnaire (including demographic, clinical, and vaccination information) was sent to parents of the kindergarten children, and serum samples were collected from the kindergarten children, with parents' consent, before an emergency immunization with one dose of MMR on June 9, 1994. Also in June, the Taoyuan County Health Bureau initiated a check of the vaccination records of all kindergarten children in Taoyuan County and subsequently immunized, with one dose of MMR vaccine, those children who had never received MMR vaccination.

### Measles Antibody Tests

Measles IgG and IgM were assayed in all serum samples, using a commercial enzyme-linked immunosorbent assay (ELISA) kit (Biowhittaker Inc., Maryland, USA). Measles IgG-negative specimens were retested for measles IgG by means of another commercial ELISA kit (Enzygnost Measles, Behring, Marburg, Germany), which offered greater sensitivity than the former kit.<sup>9</sup> A confirmed case of measles infection was defined as one having tested positive for measles IgM in an individual who received no measles vaccination within the previous 3 months.<sup>10</sup>

### Vaccine Effectiveness and Vaccine Failure Rate

The vaccination status of all reported cases and kindergarten children was determined according to their vaccination record. Kindergarten children who did not participate in the serosurvey were excluded from analysis. Each immunized child with a positive assay for measles IgM or a negative assay for measles IgG was classified as a case of vaccine failure. Vaccine effectiveness was estimated according to the method of Orenstein et al.<sup>11</sup>

### Statistical Analysis

The statistical association between two nominal or ordinal variables was tested by the chi-square, Fisher's exact or Mantel-Haenszel chi-square test for trend. The 95% confidence intervals (CI) of vaccine effectiveness also were calculated.<sup>12</sup> All the statistical analyses were conducted by Epi Info, Version 6.<sup>13</sup>

## RESULTS

### Descriptive Epidemiology

Forty-two laboratory-confirmed cases and seven clinically suspect cases without blood specimens were identified. Among 42 confirmed cases, 22 (52%) were identified through physician reporting and 20 (48%) were found

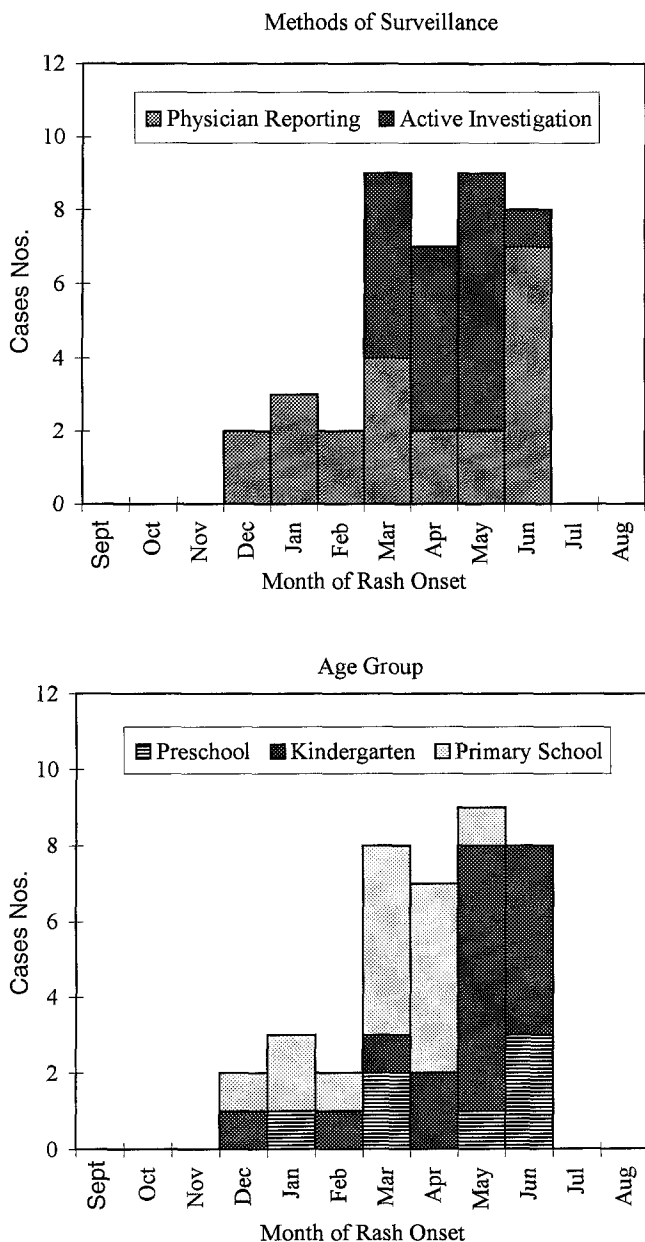


Figure 1. Epicurve of measles outbreak in Taoyuan County, Taiwan, September 1993 to August 1994, categorized by the methods of surveillance (top) and by age group (bottom). Two of 42 confirmed cases were lost to follow-up.

through active investigation, such that the proportion of cases found through physician reporting was 32% (8/25) between March and May, which increased to 87.5% (7/8) in June ( $P < 0.05$ , Fisher's exact test) (Figure 1, top). The age distribution of the 42 confirmed cases was as follows: 15 (38%) primary school children (7-12 y), 16 (38%) kindergarten children (4-6 y), 7 (17%) preschool children (1-3 y), and 3 (7%) infants (< 1 y) (Table 1). Of the 24 confirmed cases who had a vaccination record, 7 (29%) had received one dose of vaccination, 4 (17%) had

Table 1. Age Distribution and Vaccination History of Measles Cases in Taoyuan, Taiwan, December 1993-June 1994

Characteristics	Laboratory-Confirmed Cases (n=42) n (%)	Clinically Suspect Cases (n=7) n (%)
Age (y)		
≤8 months	1 (2)	1 (14)
9-11 months	2 (5)	2 (29)
1-3	7 (17)	0
4-6	16 (38)	0
7-12	15 (36)	3 (43)
≥13	1 (2)	1 (14)
Doses and age at vaccination		
One dose	7 (29)	1 (20)
<12 months	5	0
≥12 months	2	1
Two doses	4 (17)	0
Unvaccinated	13 (54)	4 (80)
No record	18	2

received two doses of vaccination, and 13 (54%) were unvaccinated (see Table 1). The outbreak erupted from Taoyuan City in December 1993 and continued to spread in primary schools and kindergartens (Figure 1, bottom) but caused only sporadic cases in neighboring towns (data not shown). Since July 1994, Taoyuan County Health Bureau has not observed any confirmed cases of measles.

### Seroepidemiologic Investigation

Among 312 kindergarten children, 209 (67%) children participated in the serosurvey. Those children who participated in the serosurvey were similar to total children with respect to age (61%, 69%, and 68%,  $P = 0.56$ , chi-square test, Table 2) and vaccination history (83% vs 79%,  $P = 0.27$ , chi-square test, Table 3). The overall measles IgM seropositive proportion was 5.3% (11/209) and varied from 0% in grade 2 to 5.7% in grade 1 and 11.8% in grade 3 ( $P < 0.05$ , Fisher's exact test). The overall measles IgG seronegative proportion was 2.9% (6/209) and varied from 0% in grade 3 to 8.6% in grade 1 and 3.1% in grade 2 ( $P < 0.05$ , Fisher's exact test). The susceptible proportion and cumulative incidence among susceptibles were 14.3% and 0.4 in grade 1, 3.1% and 0 in grade 2, and 11.8% and 1.0 in grade 3, respectively ( $P < 0.05$ , Fisher's exact test) (see Table 2).

Among 312 kindergarten children, 249 (79%) children had received measles vaccination, 14 (5%) children were unvaccinated, and 51 (16%) children had no vaccination record. The attack rates significantly decreased from 28.6% in unvaccinated children to 6.0% in one-dose vaccinees, 3.3% in two-dose vaccinees, and 0% in three-dose vaccinees ( $P = 0.02$ , chi-square test for trend) (see Table 3). The overall vaccine effectiveness was 86% (95% CI = 44-96) and increased from 79% (95% CI = 6-95) for one dose to 88% (95% CI = 41-98) for two doses and 100% for three doses (see Table 3). The overall vaccine

Table 2. Susceptible Proportion and Cumulative Incidence by Grade during Measles Outbreak in a Kindergarten in Taoyuan, Taiwan, May–June 1994

Grade	Age (y)	Children <i>n</i>	Serum <i>n</i> (%)	Measles		Susceptible* <i>n</i> (%)	Cumulative Incidence <sup>†</sup>
				IgM (+) <i>n</i> (%)	IgG (-) <i>n</i> (%)		
1	3–4	57	35 (61)	2 (5.7)	3 (8.6)	5 (14.3)	0.40
2	4–5	143	98 (69)	0 <sup>‡</sup>	3 (3.1)	3 (3.1)	0 <sup>‡</sup>
3	5–6	112	76 (68)	9 (11.8)	0 <sup>‡</sup>	9 (11.8)	1.00
Total	3–6	312	209 (67)	11 (5.3)	6 (2.9)	17 (8.1)	0.65

\*Includes measles IgG-negative and IgM-positive children; <sup>†</sup>number IgM+/number susceptible; <sup>‡</sup>P < 0.05, Fisher's exact test.

failure rate was 6.4% (95% CI = 3.2–11.1) and decreased from 10.4% (95% CI = 4.3–20.3) for one dose to 4.4% (95% CI = 1.2–11.0) for two doses and 0% for three doses (P = 0.06, chi-square test for trend) (see Table 3). Ten children receiving one dose of measles vaccine before 12 months of age had the lowest vaccine effectiveness (30%, 95% CI = 0–87) and the highest vaccine failure rates (20%, 95% CI = 2.5–55.6). However, attack rates (P = 0.12, chi-square test for trend), vaccine effectiveness, and vaccine failure rates (P = 0.48, chi-square test for trend) were not associated with age at vaccination, probably because of small sample size (see Table 3).

## DISCUSSION

The high proportion (54%) of confirmed measles cases in the surveillance data that were unvaccinated, in conjunction with the well-monitored vaccine coverage of approximately 79% (32% with 1 dose and 47% with ≥2 doses) among the kindergarten children, are highly suggestive that the cause of this outbreak may be attributed to lack of vaccination. In addition, based on the local health statistics, the measles vaccine coverage of first dose at 9 months of age and MMR vaccine at 15 months in 1993 were 82% and 63%, respectively. Consequently, the Department of Health in Taiwan has recommended that all kindergarten and primary school children should

receive two doses of measles-containing vaccine and has implemented this policy by checking vaccination records and undertaking "catch-up" immunization, since June 1994.

The overall measles susceptible proportion before the outbreak at the kindergarten in this study was 8.1% but varied from 3.1% in grade 2 to 14.3% in grade 1. This showed that a measles outbreak can erupt in a school population characterized by 92% herd immunity. Gustafson et al also found that a measles outbreak occurred in a secondary school with 95% herd immunity as measured by a measles IgG ELISA.<sup>14</sup> Mathematic modelling research has predicted that measles is eradicable if vaccine-induced immunity lasts lifelong and herd immunity homogeneously reaches 90 to 95%.<sup>15</sup> However, in reality neither vaccine uptake nor contact patterns are randomly distributed, which has an important implication for the design of immunization programs, which must recognize the distribution of susceptibles and reduce their concentration.<sup>16–18</sup> In addition, other contributing factors for a measles outbreak in a highly vaccinated population are primary and secondary vaccine failures.<sup>19–21</sup>

Primary vaccine failure is strongly associated with the age at vaccination. Among children over 15 months of age, measles vaccines are highly efficacious with seroconversion over 95% in a hospital-based short-term evaluation.<sup>1–3</sup> However, the efficacy and seroresponse of measles vaccine decreased to 85 to 95% in the setting of

Table 3. Measles Vaccine Effectiveness (VE) and Vaccine Failure Rates (VFR) Among Kindergarten Children in Taoyuan County, Taiwan, June 1994

Vaccination History (Doses & Age)	Children <i>n</i> (%)	Serum <i>n</i> (%)	Measles IgM (+) <i>n</i>	Attack Rate* %	VE <sup>†</sup> % (95% CI) <sup>‡</sup>	Measles IgG (-) <i>n</i>	VFR <sup>‡</sup> % (95% CI) <sup>‡</sup>
Vaccinated	247 (79)	173 (83)	7	4.0	86 (44–96)	4	6.4 (3.2–11.1)
One dose	99 (32)	67 (32)	4	6.0	79 (6–95)	3	10.4 (4.3–20.3)
<12 months	12	10	2	20.0	30 (0–87)	0	20.0 (2.5–55.6)
12–14 months	33	25	2	8.0	72 (0–95)	0	8.0 (1.0–26.0)
>14 months	14	10	0	0	100	1	10.0 (0.3–44.5)
Unknown	40	22	0	0	100	2	9.1 (1.1–29.2)
Two doses	126 (40)	90 (43)	3	3.3	88 (41–98)	1	4.4 (1.2–11.0)
Three doses	22 (7)	16 (8)	0	0	100	0	0
Unvaccinated	14 (5)	7 (3)	2	28.6	Reference	0	
No record	51 (16)	29 (14)	2	6.9		2	
Total	312	209	11	5.3		6	

\* Attack rate = No. of Measles IgM(+) / No. of Serum; <sup>†</sup>VE = [(ARU-ARV)/ARU], where ARU=attack rate of unvaccinated, ARV=attack rate of vaccinees; <sup>‡</sup>VFR = [No. of IgM(+) plus No. of IgG(-)] / No. of Vaccinees; <sup>‡</sup>95%CI=95% confidence interval.

community health stations and clinics, because of the problems of cold chain, work load, and injection technique.<sup>1-3,22,23</sup> Although the immunity of current live-attenuated measles vaccine is believed to be durable,<sup>1,19</sup> additional evidence has shown that secondary vaccine failure is not rare, especially in a highly vaccinated population with low possibility of natural booster from wild virus.<sup>24-29</sup> Two longitudinal studies detected 5% (9/175) and 1.2% (4/333) secondary vaccine failure rates during a follow-up of 10 years in Canada and 12 years in China, respectively.<sup>24,25</sup> In addition, Chen et al in the United States and Hirose et al in Japan also serologically documented seven and five clinical cases of secondary vaccine failure, respectively.<sup>26,27</sup> Moreover, two other studies also proposed the existence of secondary vaccine failure based on the observation of an IgM response in only 77.4% and 84.3% of vaccinated measles cases, respectively.<sup>28,29</sup> Although secondary vaccine failure may cause mild symptoms and not appear to be a major impediment to measles control at the moment, it needs to be continuously monitored until the success of global measles eradication.<sup>4,29,30</sup>

This study cannot differentiate primary from secondary vaccine failure because of the shortage of paired sera. The overall vaccine failure rate in this study was 6.4%, which varied from 20% for one dose under 12 months of age to 8% for one dose at 12 to 14 months, and 4.4% for two doses of measles vaccination, figures that are similar to those reported in a hospital-based seroconversion study among infants and young children in 1988 in Taipei.<sup>31</sup> The strategy of two doses of measles vaccination at 9 and 15 months, implemented since 1988, should have reduced the susceptibles among children under 6 years of age, but high vaccine failure rate (20%) for the first dose at 9 months of age and low coverage (63%) for the second dose may have been responsible for the increased overall risk of measles infection among this birth cohort. The health authority in Taiwan should consider changing the recommended age of the first dose from 9 months to 12 months when measles activity is so low that infants have a low probability of exposure to measles cases.

The policy of a single booster of measles vaccine (or MMR) among kindergarten or school children, to improve both individual protection and herd immunity by reducing the primary and secondary vaccine failure, is widely applied in many countries.<sup>3,4,32,33</sup> The optimal ages and strategy (e.g., "catch-up" in unimmunized individuals or universal immunization) should be determined by vaccine coverage and seroepidemiologic data, particularly considering the waning of vaccine-induced immunity and long-term effect of revaccination.<sup>34-38</sup> In addition, the requirement of mandatory measles immunization should be extended to nurseries, to further reduce the risk of a measles outbreak.

The city center, with a high population density often acts as the epicenter of respiratory infectious diseases, such as measles and influenza.<sup>2,6,39,40</sup> During an island-wide measles epidemic in 1988-89 in Taiwan, Lee et al found that the measles outbreak started in the capital (Taipei City), persisted for 15 months, and gradually spread to neighboring counties.<sup>6</sup> Therefore, measles surveillance must strengthen its timeliness in urban areas, to constrain the extent of any outbreak through the implementation of timely control actions.

The goal of measles elimination in Taiwan by 2000 has been established.<sup>7</sup> Although no confirmed case was detected in 1995-96, five sporadic confirmed cases occurred in 1997, and a small outbreak, with nine confirmed cases, erupted in 1998.<sup>41</sup> Based on the findings of this study, the future direction for measles elimination in Taiwan may focus on (1) increasing the two-dose coverage of measles vaccination to over 90% in preschool children; (2) sustaining the two-dose coverage to over 95% in nursery, kindergarten, and primary schools, by checking immunization records and immunizing unvaccinated individuals; (3) strengthening the efficiency of the surveillance system; and (4) combining seroepidemiologic data and mathematic modelling to design the optimal immunization policy.

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