A 24-YEAR REVIEW ON THE EPIDEMIOLOGY AND CONTROL OF MEASLES IN SINGAPORE, 1981-2004

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Abstract. The objective of our paper is to review the epidemiology of measles in Singapore and the impact of the measles vaccination program on the control of measles. Our review will form the basis for a critical appraisal of our future measles control program. We analyzed the trend of reported measles cases in relationship to measles vaccination coverage from 1981 to 2004 using routine measles notifications and measles vaccination data submitted to the Ministry of Health and the National Immunization Registry, respectively. We determined the measles vaccine efficacy using data from epidemiological investigations of reported institutional measles outbreaks. The herd immunity of the population against measles was accessed through three seroepidemiological surveys that we conducted in 1989/1990, 1993 and 1998. In addition, we collected blood specimens from every clinically diagnosed case of measles notified to the Ministry in 1998/1999 to for measles-specific IgM antibodies in order to evaluate the proportion of clinically diagnosed cases of measles that were laboratory confirmed. The incidence of measles has decreased significantly since 1981 as a result of increased vaccination coverage of 89-93% following implementation of compulsory measles vaccination in 1985. However, resurgences still occurred in 1992/1993 and 1997. With the implementation of the two-dose measles vaccination schedule, the annual number of laboratory confirmed cases of measles to date has been less than 150. Vaccine efficacy of the trivalent MMR vaccine based on institutional outbreak investigations was consistently above 92%. We also found that the overall seroprevalence of the population to measles has decreased from approximately 91.5% in 1989/1990 to 1993 to 77.9% in 1998 (mainly in children < 4 years old) and that only 7% of clinically notified cases of measles were serologically confirmed to be positive for measles. Achieving a vaccination coverage of more than 95%, tightening our MMR vaccine delivery system and strengthening surveillance of measles are essential components which must be addressed in order to interrupt measles transmission in Singapore.

INTRODUCTION

In the 1960s and 1970s, records of the Middleton (Infectious Disease) Hospital showed that measles epidemics occurred every one to three years and that most children in Singapore developed measles after one year of age (Goh, 1983). Following a cost-benefit analysis on the use of monovalent measles vaccine in the childhood population, measles vaccination was introduced to the Singapore immunization program for preschool children aged 12 - 24 months in October 1976 (Committee on Epidemic Diseases, 2003). The initial vaccination acceptance rate was poor, with only 24.6% of the target population vaccinated in 1977, due to the cultural belief that measles infection was a natural and inevitable part of childhood (WHO, 1979; Committee on Epidemic Diseases, 2003). Intensive health education programs were launched from 1977 to 1979 to correct this cultural belief and to publicize the benefits and safety of measles vaccination. At the same time, measles was made a notifiable infectious disease under the Infectious Disease Act on 1 October 1980 and the clinical criteria for diagnosis were disseminated to all medical practitioners.

In view of the high disease incidence in preschool and primary school children, all pre-primary and primary one school registrants were routinely checked for certificates of measles im-

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munization or natural measles infection issued by medical practitioners from 1981 onwards. This led to the vaccine rate increasing to 58.8% in that year. However, cyclical epidemics continued to occur and the highest incidence of 2,417 cases (including 7 deaths) occurred in 1984 (Committee on Epidemic Diseases, 2003).

Subsequently, measles vaccination was made compulsory by law for children aged 12-24 months in August 1985; the intention was to interrupt measles transmission by achieving a vaccination coverage of at least 95% at an average of 2 years for each cohort (Committee on Epidemic Diseases, 1997). Following a review of the national childhood immunization program by the Expert Committee on Immunization, the monovalent vaccine was substituted by the trivalent Mumps, Measles and Rubella (MMR) vaccine in January 1990.

A sharp rise in the incidence of measles cases in 1997 led to the implementation of a "catch-up vaccination" from July-November 1997 when children aged 12-18 years were immunized for measles regardless of their measles vaccination status or past history of measles. Subsequently, a second dose of measles vaccine as a component of the MMR vaccination was introduced into the childhood immunization program in January 1998 for all primary school children aged 11-12 years.

The objective of this paper is to review the epidemiology of measles and the impact of the measles vaccination program by analyzing a) the trend of reported measles cases in relationship to measles vaccination coverage from 1981 to 2004; b) the measles vaccine efficacy determined during epidemiological investigation of reported institutional outbreaks; c) the herd immunity of the population against measles through periodic seroepidemiological surveys; and d) the proportion of clinically diagnosed cases of measles that are laboratory confirmed. The review will form the basis for a critical appraisal of our future measles control program.

MATERIALS AND METHODS

Data on the incidence of measles was obtained from the routine mandatory measles notifications submitted to the Communicable Diseases Division, Ministry of Health by clinicians and clinical laboratories.

The clinical case definition of measles was based on established World Health Organization (WHO) criteria (WHO, 2001). Cases are defined as persons with fever, maculopapular rash, together with cough, coryza or conjunctivitis. Laboratory confirmed cases were defined as those with positive measles-specific IgM antibodies, at least a four fold rise in antibody titer or positive virus isolation. Epidemiological information on age, gender, illness onset, vaccination history and residential address and place of work/school were furnished by the notifying doctor in the official notification form.

When a cluster of two or more epidemiologically related cases in a home, school or workplace setting was identified, epidemiological investigations were conducted by trained public health officers to identify other unreported cases. The data on the vaccination status (date of vaccination, type of vaccine administered) were obtained from the health booklet issued to each child. We then calculated the attack rates in unvaccinated children (ARU) and vaccinated children (ARV). Vaccine efficacy (VE) in outbreak investigations was calculated using the following formula: VE (%) = [(ARU-ARV) ÷ ARU] x 100 % (Orenstein *et al*, 1985). Preschool and schoolchildren without a history of measles immunization were subsequently referred to the nearest government polyclinic and school health clinic, respectively, for vaccination.

The annual measles immunization coverage of each cohort aged 24 months was obtained from the National Immunization Registry (NIR). All registered medical practitioners are required by law to notify the NIR when an immunization against measles is given. Parents/guardians whose children have missed the vaccination at 12-15 months are routinely reminded to bring them to their family doctors or government polyclinics for vaccination.

In order to assess the level of immunity of the population against measles, seroepidemiological surveys were conducted in 1989-1990, 1993 and 1998 (Committee on Epidemic Diseases, 1991, 1995; Ministry of the Environment,

1999). Blood samples were collected from healthy children and adult volunteers aged 6 months to over 45 years of age at designated government polyclinics after consent was obtained. Information gathered at the time of blood collection included basic demographic data and history of previous measles vaccination. The blood samples were analyzed for measles IgG antibodies using measles enzyme immunoassay (Whampole Laboratory, USA) at the Department of Pathology, Singapore General Hospital.

A survey was also conducted in 1998/1999 to evaluate the reliability of a clinical diagnosis of measles. An attempt was made to collect a blood specimen from every clinically diagnosed case of measles notified to the Ministry one to six weeks after the onset of illness to test for measles-specific IgM antibody, rubella-specific IgM antibody and dengue-specific IgM antibody.

Data analysis was carried out using the Microsoft Excel 96 and Epistat Statistical Package. The χ^2 test was used to compare differences in proportions. The level of significance was set at 5% unless otherwise stated.

RESULTS

Epidemiology

Prior to the implementation of compulsory measles vaccination in 1985, cyclical outbreaks of measles occurred between 1981 and 1984. Thereafter, the number of cases of measles decreased from 2,417 cases in 1984 to 123-218 cases in 1985-1991. However, a resurgence of measles was observed in 1992 (606 cases), 1993 (665 cases) and 1997 (1,414 cases) (Fig 1). At the same time, the peak age distribution of measles was noted to have shifted from preschoolchildren less than five years of age (from 66.7% in 1981-1983 to 33% in 1997) to older children, youths and adults (from 5.3% in those over 10 years of age in 1981-1983 to 54.7% in 1997) (Oh *et al*, 1995; Committee on Epidemic Diseases, 1997).

Since the implementation of a two-dose measles vaccination to all primary school leavers (aged ≥ 11 years) in January 1998, the proportion of reported cases of measles in children under the age of one year increased from 16.5% in 1999-2001 to 42.5% in 2003, but decreased to 15.6% in 2004 (Table 1). Despite the implementation of a two-dose MMR policy in 1998, indigenous cases of measles continued to occur in Singapore. The number of laboratory confirmed cases of measles in Singapore was 65 cases in 1999 and 141 cases in 2000. Thereafter, it decreased to 61 cases in 2001, 57 cases in 2002 and 33 cases in 2003, but increased to 96 cases in 2004.

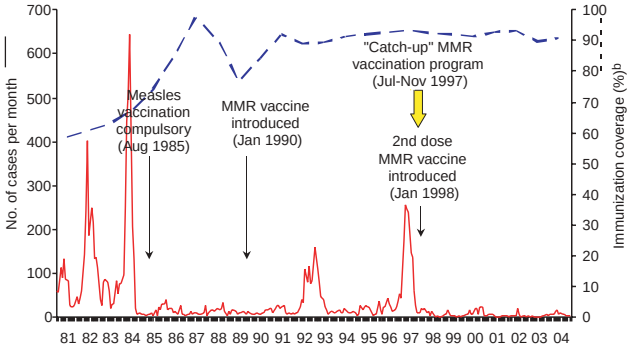
Vaccination coverage

The MMR vaccination coverage rate at two years of age achieved the target of 95% in 1987. From 1992 to 2004, vaccination coverage was around 89-93% (Fig 1). The preliminary MMR vaccine coverage rate at two years of age for 2004 was 91%. The coverage for primary school leavers aged 11-12 years remained consistently high at close to 100%.

Vaccine efficacy

Based on outbreak investigations conducted in preschools and primary schools, the vaccine efficacy of the monovalent measles vaccine was found to be high at more than 98% (Committee on Epidemic Diseases, 2003). In the case of the trivalent MMR vaccine, the efficacy was consistently above 92% (Committee on Epidemic Diseases, 1997).

An institutional outbreak of measles (all serologically confirmed) occurred in a primary school from 16 April 2004 to 6 May 2004, affecting a total of 9 students (aged 8 to 14 years)



[a]Only laboratory confirmed cases were reported from June 2000; [b]for children <2 years

Fig 1–Incidence of reported measles and immunization coverage rate, Singapore, 1981-2004[a].

Table 1
Age distribution and annual incidence rates of reported measles in Singapore, 1993-2004.

Age group (yrs)	1993-1995			1996-1998			1999-2001[a]			2002			2003			2004		
	No. of cases	%	Mean annual rate[b]	No. of cases	%	Mean annual rate[b]	No. of cases	%	Mean annual rate[b]	No. of cases	%	Incidence rate[b]	No. of cases	%	Incidence rate[b]	No. of cases	%	Incidence rate[b]
< 1	115	11.4	76.7	263	14.3	181.1	44	16.5	36.5	18	31.6	47.7	14	42.5	37.5	15	15.6	42.6
1-4	304	30.1	52	378	20.6	64.7	86	32.2	16.9	20	35.1	10.8	7	21.2	3.9	20	20.8	11.4
5-9	162	16.1	24.2	162	8.8	21.4	27	10.1	3.6	8	14.0	3.1	1	3.0	0.4	11	11.5	4.3
10-14	140	13.9	22.6	240	13.1	38.4	11	4.1	1.6	2	3.5	0.7	1	3.0	0.4	16	16.7	5.8
>15	288	28.5	4.4	792	43.2	11	99	37.1	1.3	9	15.8	0.3	10	30.3	0.7	34	35.4	1.1
Total	1,009	100	11.5	1,835	100	19.7	267	100	2.7	57	100	1.4	33	100	0.8	96	100	2.3

[a] Only laboratory confirmed cases of measles were reported with effect from June 2000
[b] per 100,000 population based on the estimated mid-year total population of the corresponding period (Source: Department of Statistics, Singapore)

from five classes. The population of the affected classes was 184. Approximately 93.0% of these students had documented evidence of prior measles vaccination. None of the students had received the second dose MMR vaccine yet. The attack rate was 2 (1.2%) of 171 students in the vaccinated group and 7 (53.8%) of 13 students in the unvaccinated group. The calculated vaccine efficacy for the first dose of MMR vaccine was 97.8%.

Seroepidemiology

A total of 500, 600 and 926 blood samples were collected in the 1989/1990, 1993 and 1998 surveys, respectively. The overall seroprevalences in the population were 91.4, 91.5 and 77.9%, respectively. The decline in 1998 was mainly due to a significantly lower seroprevalence in those aged 2-4 years (86.8% in 1993 as compared to 52.4% in 1998; $p < 0.001$) and 5-9 years (81.6% in 1993 *vs* 70.1% in 1998; $p = 0.04$) (Fig 2). As a result of the "catch-up vaccination" in 1997 and the introduction of the second dose of measles vaccination to those aged 11-12 years in 1998, the seroprevalence in those aged 10-14 years increased from 71.7% in 1993 to 89.1% in 1998 ($p = 0.02$). The seroprevalence remained high at 94.1% to 98.9% in those ≥ 15 years. There was no significant difference in seroprevalence by gender or ethnic group in all three seroepidemiological surveys.

Cross-sectional validation of clinical definition for measles

Of 246 measles cases reported in 1998/1999, only 50 (20.3%) were laboratory confirmed. Convalescent blood samples were successfully obtained from 114 (58.2%) of the remaining 196 clinically diagnosed cases. Only 7% (8 cases) were positive for measles, with the remainder being positive for rubella (42.1%), dengue (5.3%) or negative for all three diseases (45.6%) (Committee on Epidemic Diseases, 2003).

DISCUSSION

With increasing vaccination coverage resulting from compulsory measles vaccination in 1985, the disease incidence dropped sharply, but resurgences occurred in 1992/1993 and

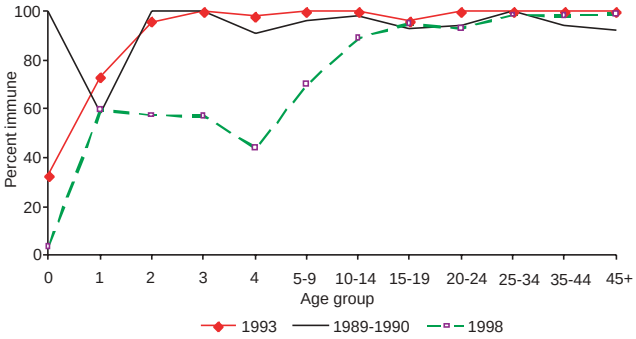


Fig 2–Age-specific prevalence of antibody to measles in Singapore, 1989-1990, 1993 and 1998-1999.

again in 1997. These resurgences were due to an accumulation of susceptibles (non-immune persons) to a critical threshold level and were not due to vaccine failure as demonstrated by the high vaccine efficacy of >90%. This highlighted that strategies that rely on administration of a single dose of measles vaccine are inadequate for the interruption of measles transmission (Duclos *et al*, 1995, 1999; Pelletier *et al*, 1998). As such, the two-dose regimen was subsequently introduced into the childhood immunization program. No outbreak has since occurred among those vaccinated with two doses of vaccine.

The increased proportion of reported cases of measles occurring in children under the age of one year from 1999 to 2003 is not unexpected as the bulk of the susceptible population following the 1997 "catch-up vaccination" would now be within this category of persons who have yet to be immunized. The subsequent decrease in the proportion of reported measles in children under the age of 1 year in 2004 could be attributed to the accumulation of susceptible individuals in the older age groups over time. A similar pattern was seen in Hong Kong following their 1997 "catch-up vaccination" program whereby the proportion of measles cases in children under the age of one year increased from 19.3% in 1996 to 46.4% in 1998, but decreased to 37.5% and 31.1% in 2000 and 2001, respectively (Chuang *et al*, 2002).

The herd immunity of the population against measles was found to be maintained at above 90% in the 1989/1990 and 1993 surveys. However, it declined to 77.9% in 1998; the decline was mainly noted in children below 4 years of age. It is not known whether the use of a less efficacious MMR vaccine from one manufacturer which was responsible for the massive resurgence of mumps in 1999-2000 was related to the observed diminished seropositivity in 1998. (Goh, 1999; Ong *et al*, 2005). Another serological survey will be conducted this year to assess the immune status of the population vaccinated with a different MMR vaccine since May 1999.

The WHO Western Pacific Regional Plan of Action for Measles Elimination, which was endorsed in September 2003, has set the year 2012 as the earliest reasonable target date for measles elimination in the region (WHO, 2003, 2004). As Singapore moves towards achieving the regional goal of measles elimination, several aspects of the current measles vaccination program need to be addressed.

The coverage for the first dose of measles vaccination is still below the target of 95% set by the WHO (WHO/UNICEF, 2001). Mathematical modelling shows that this level of coverage is required for the effective interruption of measles transmission. This was amply demonstrated in the above mentioned measles outbreak in the primary school in April 2004 whereby a single dose of MMR vaccine at a relatively high coverage of 93% was inadequate in preventing an outbreak. Furthermore, it is known that the average seroconversion rate following a single dose of measles vaccination at 15 months of age is approximately 87-99%, leaving a small proportion of children in each cohort still susceptible to measles infection. Investigations showed that virtually all the reported measles cases in Singapore have not been vaccinated against the virus (Goh *et al*, 1999). To increase coverage and raise the herd immunity level of the childhood population, the current practice of MMR immunization required for new entrants (local and foreigners) into kindergartens, preschools and primary schools should be strictly adhered to. At the same time, children who have not completed their primary series of MMR vaccination should continue to be tracked and followed up. Community outreach health education messages on the benefits of MMR vaccination should also be

further intensified.

Our study showed that only approximately seven percent of the clinically diagnosed cases of measles reported locally turned out to be measles by laboratory testing. This is consistent with other studies which have demonstrated the low positive predictive value of clinical case definitions when the incidence of measles is low in a community (Hutchins *et al*, 2004). It also highlights the growing necessity for laboratory confirmation of measles to avoid misidentification of cases and improve disease surveillance.

In conclusion, our experiences in the control of measles in terms of the unique nature of Singapore being a small city state can be extended to other city states and smaller countries, especially those within the Western Pacific region. Achieving vaccination coverage of more than 95%, tightening of the MMR vaccine delivery system and strengthening surveillance of measles are essential components which must be addressed in order to interrupt measles transmission in Singapore. These would be the first two areas for improvement as we embark towards measles elimination.

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