

## Evaluation on the Effectiveness of the National Childhood Immunisation Programme in Singapore, 1982-2007

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### Abstract

**Introduction:** We undertook a study to evaluate the effectiveness of the National Childhood Immunisation Programme (NCIP) over the past 26 years by reviewing the epidemiological trends of the diseases protected, the immunisation coverage and the changing herd immunity of the population during the period of 1982 to 2007. **Materials and Methods:** The epidemiological data of all cases of diphtheria, pertussis, poliomyelitis, measles, mumps, rubella and acute hepatitis B notified to the Communicable Diseases Division, Ministry of Health (MOH) from 1982 to 2007 were collated and analysed. Data on tuberculosis (TB) cases were obtained from the TB Control Unit, Tan Tock Seng Hospital. Cases of neonatal tetanus and congenital rubella syndrome (CRS) among infants born in Singapore were identified from the Central Claims Processing System. The number of therapeutic abortions performed for rubella infections was retrieved from the national abortion registry. Coverage of the childhood immunisation programme was based on the immunisation data maintained by the National Immunisation Registry, Health Promotion Board. To assess the herd immunity of the population against the various vaccine-preventable diseases protected, the findings of several serological surveys conducted from 1982 to 2005 were reviewed. **Results:** The incidence of vaccine-preventable diseases covered under the NCIP had declined over the last 26 years with diphtheria, neonatal tetanus, poliomyelitis and congenital rubella virtually eliminated. The last case of childhood TB meningitis and the last case of acute hepatitis B in children below 15 years were reported in 2002 and 1996, respectively. **Conclusion:** The NCIP has been successfully implemented as evidenced by the disappearance of most childhood diseases, excellent immunisation coverage rate in infants, preschool and school children, and high level of herd immunity of the childhood population protected.

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**Key words:** Epidemiology, Herd immunity, Vaccine-preventable diseases

### Introduction

Singapore has a comprehensive National Childhood Immunisation Programme (NCIP) which first covered smallpox (1862), followed by diphtheria (1938), tuberculosis (TB) (1957), poliomyelitis (1958), pertussis and tetanus (1959) and measles and rubella (1976).<sup>1</sup> In October 1985, hepatitis B vaccination was introduced into the programme for babies born to hepatitis B carrier mothers, and subsequently extended to all newborns in September 1987.<sup>2</sup> The rubella immunisation programme first introduced into the NCIP for pre-adolescent female primary school leavers (11 to 12 years) in November 1976, was extended to male primary school leavers and national

service recruits in April 1982, and subsequently to all children 1 year of age when the monovalent measles and rubella vaccines were replaced by the trivalent measles, mumps and rubella (MMR) vaccine in 1990.<sup>3</sup> In the same year, mumps and rubella were made legally notifiable diseases. A 'catch-up' measles immunisation programme for secondary and pre-university students using the MMR vaccine was implemented from July to November 1997 to curb the resurgence of measles, and the second dose of MMR vaccine was added to the NCIP in the following year.<sup>4</sup> The monovalent rubella vaccine given to both male and female primary school leavers continued until it was replaced by the second dose of MMR vaccine in 1998. From 2001 to

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2004, 'catch-up' hepatitis B immunisation programmes were implemented, starting with students in secondary schools, junior colleges, centralised institutes, institutes of technical education, polytechnics and universities, followed by full-time national servicemen, and subsequently, students in 18 special schools.<sup>5</sup> BCG vaccine routinely administered to school children who were Mantoux non-reactors was discontinued in July 2001.<sup>6</sup> The immunisation schedules of the 9 diseases covered under the NCIP from birth to school leavers in 1982, and amendments made in 1985, 1990, 1998, 2001 and 2008 are shown in Table 1. Only diphtheria and measles immunisations are compulsory by law.

For basic vaccinations scheduled during the preschool years (birth until 6 years), they are provided free for citizens at the polyclinics, with the exception of the hepatitis B vaccine which is charged at cost and paid through Medisave. Permanent residents are subsidised 50% and foreigners pay full costs. Vaccinations scheduled during the school-going age (7 years until 12 years) are provided free by the School Health Services (SHS) of the Health Promotion Board (HPB) for all students, regardless of their nationalities.

We undertook a study to evaluate the effectiveness of the NCIP over the past 26 years by reviewing the epidemiological trends of the diseases protected, the immunisation coverage and the changing herd immunity of the population during the period 1982 to 2007.

## Materials and Methods

### *Case Surveillance*

The epidemiological data of all cases of diphtheria, pertussis, poliomyelitis, measles, mumps, rubella and acute hepatitis B notified to the Communicable Diseases Division, Ministry of Health (MOH) from 1982 to 2007 were collated and analysed. Data on TB were obtained from the TB Control Unit, Tan Tock Seng Hospital. Cases of neonatal tetanus and congenital rubella syndrome (CRS) among infants born in Singapore were identified from the Central Claims Processing System, a national inpatient discharge database which covered all hospitals in Singapore. The number of therapeutic abortions performed for rubella infections was retrieved from the national abortion registry. The clinical case definition was based on the guidelines produced by the MOH.<sup>7</sup> Imported cases were those who acquired the infection outside Singapore and included foreigners seeking medical treatment in Singapore.

### *Immunisation Coverage*

The annual immunisation coverage was obtained from the National Immunisation Registry (NIR) maintained by the HPB. It is responsible for collecting and maintaining accurate, complete and current vaccination records of all

children from birth to 18 years of age. Even though only the notifications of diphtheria and measles immunisation are mandated by the Infectious Disease Act, both public and private healthcare institutions routinely notified NIR of all immunisations that had been administered to preschool children. The SHS provided records of all immunisations carried out in schools and at the Immunisation Clinic in the Student Health Centre, HPB.

### *Herd Immunity*

To assess the changing herd immunity of the population against various vaccine-preventable childhood diseases, the findings of several seroepidemiological surveys conducted periodically in Singapore were collated and analysed. These included seroprevalence studies on diphtheria, pertussis, tetanus, hepatitis B, measles, mumps and rubella carried out from 1982 to 2005. The subjects of these surveys were apparently healthy children and adults aged between 6 months and over 45 years who voluntarily reported at the nearest designated polyclinics following publicity in the mass media. Blood samples were collected with informed consent. In addition, serological surveys on hepatitis B were conducted in school children aged 5 to 19 years in 1987 and in a primary school in 1994 after parental consent had been obtained. The laboratory methods used for the detection of antibodies or antitoxins of the various surveys had been described elsewhere.<sup>8-13</sup> Stored blood samples obtained during the 1998 and 2004 national health surveys for non-communicable diseases were also tested for hepatitis B virus markers in 1999 and 2005, respectively<sup>5,14</sup> and for rubella in 2005.<sup>15</sup> The subjects sampled in these 2 surveys were adults aged 18 to 74 years and representative of the general population. The survey methodology had been described.<sup>14,16</sup>

### *Statistical Analysis*

The denominators used for the calculation of annual age-specific incidence rates were the corresponding estimated mid-year populations compiled by the Department of Statistics, Singapore. For the calculation of the annual incidence rates of infants with CRS, the total number of live-births was obtained from the Registry of Births and Deaths. The target population of infants and preschool children for the calculation of immunisation coverage was based on notification of births obtained from the Registry of Births and Deaths while the target population for school-going children was based on student population data from the Ministry of Education. SPSS Software Version 15.0 (SPSS Chicago, IL) was used for statistical analysis. Differences in seropositivity rates were computed and tested for statistical significance using the Z-test for two independent proportions. Statistical significance was taken as  $P < 0.05$ .

Table 1. National Childhood Immunisation Schedule in Singapore in 1982 and Amendments in 1985, 1990, 1998, 2001 and 2008

Age	At birth	1 month	3 months	4 months	5 months	1-2 years	18 months	6-7 years (Primary 1)	11-12 years (Primary 6)	15-16 years (Secondary 4)
1982	BCG		DPT – 1 <sup>st</sup> dose Oral Sabin – 1 <sup>st</sup> dose	DPT – 2 <sup>nd</sup> dose Oral Sabin – 2 <sup>nd</sup> dose	DPT – 3 <sup>rd</sup> dose Oral Sabin – 3 <sup>rd</sup> dose	Measles (1 dose)	DPT – 1 <sup>st</sup> booster Oral Sabin – 1 <sup>st</sup> booster	BCG (Direct BCG if no previous vaccination) DT-containing vaccine – 2 <sup>nd</sup> booster Oral Sabin – 2 <sup>nd</sup> booster	BCG for Mantoux non-reactors if: 1) no previous vaccination or 2) only one vaccination given more than 10 years ago DT-containing vaccine – 3 <sup>rd</sup> booster Oral Sabin – 3 <sup>rd</sup> booster Rubella (1 dose for boys and girls)	BCG for Mantoux non-reactors if: 1) no previous vaccination or 2) only one vaccination given more than 10 years ago
			<b>Amendments</b>							
1985	Hepatitis B* – 1 <sup>st</sup> dose	Hepatitis B – 2 <sup>nd</sup> dose			Hepatitis B – 3 <sup>rd</sup> dose administered at 5-6 months <sup>*,**</sup>	0	0	0	0	
1990						MMR vaccine (1 <sup>st</sup> dose) replaced monovalent Measles vaccine		0	0	
1998									MMR vaccine (2 <sup>nd</sup> dose) replaced monovalent Rubella vaccine	
2001								Discontinued BCG booster. If no evidence of BCG vaccination, to refer to TBCU for further action.	Discontinued BCG for Mantoux non-reactors	Discontinued BCG for Mantoux non-reactors
2008								Discontinued DT-containing vaccine – 2 <sup>nd</sup> booster MMR vaccine (2 <sup>nd</sup> dose) brought forward from primary 6 to primary 1	Discontinued DT-containing vaccine – 3 <sup>rd</sup> booster DT-containing vaccine – 2 <sup>nd</sup> booster administered in primary 5 (10-11 years old) instead of primary 1 <sup>*,**</sup>	

\* Hepatitis B vaccine first given to babies of hepatitis B surface antigen carrier mothers in October 1985 and subsequently extended to all newborns in September 1987. \*\* 3<sup>rd</sup> dose of Hepatitis B vaccination can be given with the 3<sup>rd</sup> dose of DPT and Oral Sabin for the convenience of parents. \*\*\* In view of the short supply of childhood DT vaccine, the vaccine to be used can either be a Td (adult) vaccine or the combined tetanus, reduced diphtheria and acellular pertussis (Tdap) vaccine.

Table 2. Reported Diphtheria, Poliomyelitis, Neonatal Tetanus, Pertussis, Congenital Rubella and Childhood Tuberculous Meningitis in Singapore, 1982-2007

Year	Diphtheria	Poliomyelitis	Neonatal tetanus	Pertussis	Congenital rubella	Childhood Tuberculous meningitis*
1982	6 (2)	1 (1)	1	7	3	4
1983	4 (4)	2 (2)	3	7	10	1
1984	0	2 (2)	1	1	7	0
1985	0	0	0	0	3	1
1986	1	2 (2)	0	9	3	1
1987	1 (1)	0	0	9	2	1
1988	0	0	0	11	0	0
1989	1 (1)	0	0	1	2	0
1990	1	1 (1)	0	8	4	0
1991	1 (1)	0	0	5	1	0
1992	1	0	0	14	4	0
1993	0	0	0	1	4	0
1994	0	0	0	2	2	0
1995	0	0	0	1	2	2
1996	1 (1)	0	0	4 (1)	2	2
1997	0	0	0	2	0	2
1998	0	0	0	1	0	0
1999	0	0	0	1	2	1
2000	0	0	0	2 (1)	0	1
2001	0	0	0	1	2	0
2002	0	0	0	0	1	1
2003	0	0	0	1	0	0
2004	0	0	0	1	0	0
2005	0	0	0	2	1	0
2006	0	1 (1)	0	3	0	0
2007	0	0	0	38	0	0

\* &lt;10 years of age

( ) Imported case

## Results

### *Epidemiological Trends*

#### *Diphtheria, Pertussis and Tetanus*

From 1982 to 2007, there had been 17 cases of diphtheria reported in Singapore. Ten of these cases were imported (Table 2). The last indigenous case was reported in 1992. It involved a 41-year-old male local resident with multiple comorbidities. *Corynebacterium diphtheriae var gravis* was isolated from his blood. He subsequently died from septicaemia secondary to bacterial endocarditis.

An average of 4 sporadic cases of pertussis were reported annually among infants less than one year of age who were either unimmunised or incompletely immunised. Majority of

the infections were locally acquired. A sharp increase from 3 cases in 2006 to 38 cases in 2007 was noted (Table 2).

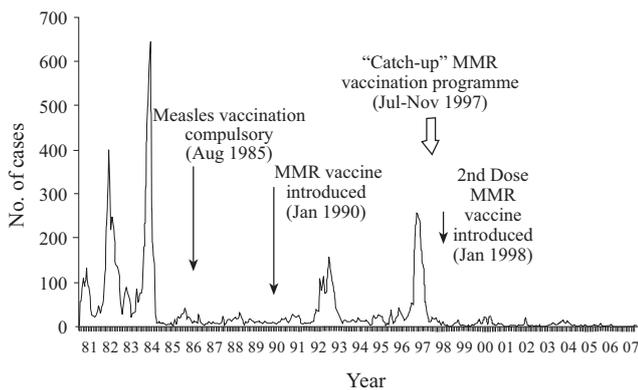
Neonatal tetanus has virtually disappeared. The last case was reported in 1984 (Table 2).

#### *Poliomyelitis*

No indigenous poliomyelitis case was reported during the period of review. All the cases reported up to 2006 were imported, involving foreigners seeking medical treatment in Singapore.

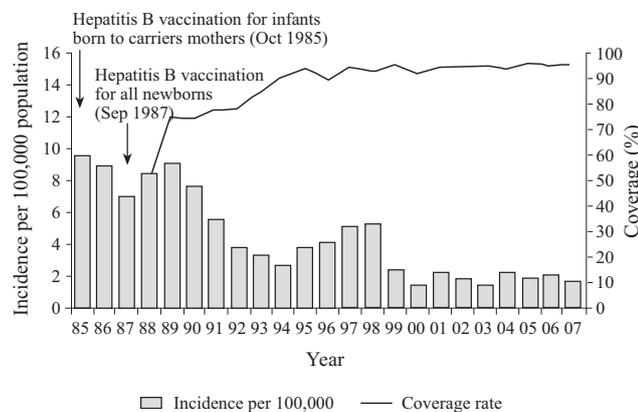
#### *Tuberculosis*

Childhood tuberculous meningitis was uncommon with the last case reported in 2002 (Table 2).



\* Laboratory confirmed cases were reported from June 2000 onwards.

Fig. 1. Impact of the mandatory measles vaccination, "catch-up" MMR vaccination programme and introduction of second dose of MMR vaccine on reported measles cases in Singapore, 1981-2007\*.



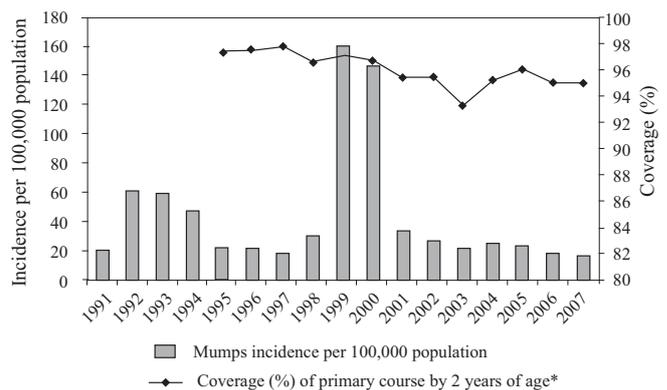
+ Indigenous cases.

Fig. 3. Incidence per 100,000 population from acute hepatitis B<sup>+</sup> and immunisation coverage rates in Singapore, 1985-2007.

**Measles, Mumps and Rubella**

Before measles immunisation was made compulsory under the Infectious Diseases Act in 1985, cyclical outbreaks occurred from 1982 to 1984. Thereafter, the incidence declined from 2417 cases in 1984 to between 123 and 218 cases during the period 1985 to 1991. A resurgence was noted in 1992 (606 cases), 1993 (665 cases) and 1997 (1414 cases). There was a corresponding shift in the peak age distribution of measles from preschool children less than 5 years of age to older children, youths and young adults.<sup>17</sup> Following implementation of the "catch-up" measles vaccination programme for school children aged 12 to 18 years in 1997 and incorporation of the second dose of MMR vaccine for all primary six school children aged 11 to 12 years in 1998, the incidence of measles decreased sharply from 141 cases in 2000 to 15 cases in 2007 (Fig.1).

There was a large resurgence of mumps in 1999 when its incidence rate per 100,000 population increased five-fold to 161.3 from 30.1 in the previous year (Fig. 2). This



\* The immunisation data from 1991-1994 were incomplete.

Fig. 2. Mumps incidence (per 100,000 population) and MMR immunisation coverage in Singapore, 1991-2007.

was caused by the highly attenuated Rubini mumps virus strain of the MMR vaccine which conferred no protection to vaccinated children.<sup>18</sup> Following de-registration of the implicated vaccine and its replacement by the MMR vaccine containing the Jeryl-Lynn strain in 1999, the incidence of mumps declined rapidly with an incidence rate of 17.0 per 100,000 population in 2007. The age-specific incidence rate was highest in children 5 to 14 years of age.

During the period 1991 to 1999, the incidence of rubella peaked in 1993 (12.8 per 100,000 population), 1996 (13.3 per 100,000 population) and 1999 (10.9 per 100,000 population). These cyclical patterns disappeared with the declining trend in subsequent years. In 2007, the incidence was 1.8 per 100,000 population. Preschool children generally had the highest incidence rate with the majority being infants below 1 year of age as they were not eligible for MMR vaccination. In 1999 and 2000, older children and adults were observed to have higher incidence rates because of several institutional outbreaks which affected mainly unvaccinated foreigners.<sup>15</sup> CRS had almost disappeared with the incidence rate declining from 0.08 per 1000 live-births in 1992/1993 to 0.03 per 1000 live-births in 2004. No cases of CRS were reported in 1997, 1998, 2000, 2003, 2004, 2006 and 2007. Therapeutic abortions performed on account of rubella infection had also dropped significantly from 30 cases in 1991 to 1 case in 2007.

**Hepatitis B**

The incidence rate of indigenous cases of acute hepatitis B decreased from 9.5 per 100,000 population in 1985 to 1.7 per 100,000 population in 2007 (Fig. 3). The number of reported cases in children less than 15 years of age also declined correspondingly from 10 in 1983 to 0 since 1997.

**Immunisation Coverage for the Period 2003-2007**

*Diphtheria, Pertussis and Tetanus*

The coverage for infants below one year of age completing

Table 3. Diphtheria Immunisation, 2003-2007

Year	Coverage* for children at 2 years of age				School children#					
	Completed primary course		Boosters given		Boosters given			Boosters given		
	No.	Coverage (%)	No.	Coverage (%)	School entrants	No.	Coverage (%)	Primary school leavers	No.	Coverage (%)
2003	38,064	96.0	33,389	84.0	49,788	46,747	94.0	52,177	49,482	95.0
2004	36,587	95.0	34,740	90.0	47,918	45,040	94.0	51,694	49,169	95.0
2005	34,030	96.0	32,205	91.0	44,110	41,437	94.0	51,908	49,725	96.0
2006	31,948	95.0	30,138	90.0	44,572	41,371	93.0	50,382	49,302	98.0
2007	31,778	97.0	29,050	88.0	48,122	44,533	93.0	49,383	48,534	98.0

\* Data refers to immunisation given to all Singaporean and Singapore PR children

# Coverage by School Health Service may not include all booster immunisation done by private practitioners

the primary course of diphtheria (D), pertussis (P) and tetanus (T) immunisation given as triple DPT antigen was consistently maintained at between 95% and 97%, while 84% to 91% completed the first DT booster doses at 2 years of age. For school children, 93% to 94% of the primary 1 entrants and 95% to 98% of the primary 6 leavers received DT boosters (Table 3).

#### *Poliomyelitis*

In the case of poliomyelitis vaccination, 95% to 97% of infants below one year of age completed the primary course of trivalent Sabin oral vaccine and the first boosters were administered to between 83% and 91% of 2-year-old children. Of the primary school entrants and leavers, 92% to 94% and 95% to 98%, respectively, completed the booster doses.

#### *Tuberculosis*

BCG vaccination coverage of preschool children from birth to 2 years of age was between 98% and 99.3%.

#### *Measles, Mumps and Rubella*

Between 93% and 95% of preschool children were vaccinated with the first dose of MMR vaccine at 2 years of age while 94% to 96% of primary school leavers received the second dose.

#### *Hepatitis B*

The coverage of the primary course of 3 doses of hepatitis B vaccine completed by 2 years of age ranged from 94% to 96%.

### **Changing Herd Immunity**

#### *Diphtheria, Pertussis and Tetanus*

A serological survey was conducted between 1982 and 1984 to evaluate the herd immunity of the population against diphtheria.<sup>8</sup> Of the subjects between 6 months and

over 40 years of age tested, 94.6% possessed protective diphtheria neutralising antitoxin (titre >0.01 IU/mL). The geometric mean titres (GMT) were generally high with sharp anamnestic response elicited by periodic boosters administered. About 14% of adults above 40 years of age had no protective immunity against diphtheria toxin. Another study carried out in 1993 showed that solid immunity was maintained with almost 98% of the subjects who had an immunisation history possessing protective antitoxic immunity. Virtually all those who were non-immune were adults above 20 years of age.<sup>9</sup>

The seroepidemiological survey conducted in 1993<sup>10</sup> found that 70.3% of the population 6 months to over 40 years of age had protective pertussis antitoxin (titre >1:16). The immunity declined from between 76.9% and 92.2% in children aged less than 5 years to 63.5% in the 5 to 9-year age group, 51.2% in the 10 to 14-year age group and 50% in the 15 to 19-year age group. It was maintained at between 60.3% and 64.7% in adults above 20 years of age.

Blood samples obtained during the 1982 to 1984 survey were also tested for tetanus antitoxin.<sup>11</sup> Overall, 19.3% of the population had no immunity to tetanus (antitoxin titre <1:10). Among adults above 30 years of age, 38% to 47.9% were not immune. In the seroepidemiological survey conducted in 1993, 95.5% to 99.6% of the population aged between 6 months and 30 years were found to possess immunity (particle agglutination antitoxin titre >1:16).<sup>12</sup> Virtually all the children (99.6%) below 5 years of age were immune. The immunity level decreased progressively with age from 98.6% in children aged 5 to 9 years to 97% in those aged 10 to 19 years, 95.6% in those aged 20 to 29 years, 79.2% in those aged 30 to 39 years and 50% in those aged 40 years and above.

#### *Poliomyelitis*

In the 1982 to 1984 survey, blood samples were further tested to assess the immune status of the population

against the three serotypes of poliovirus. It was found that 93.9% of the population had neutralising antibodies (>1:4) to poliovirus 1, 96.5% to poliovirus 2 and 96.7% to poliovirus 3. Adults above 30 years of age had a relatively high level of susceptibility to poliovirus infection: 10.2% to 12% above 30 years of age had no immunity against poliovirus 1; 14.3% above 40 years had no immunity against poliovirus 2 and 14% in the 30 to 39-year age group had no immunity against poliovirus 3. There was a general decline in the GMT among the older age groups. The survey also showed that all those who had a history of having completed the primary course of immunisation against poliomyelitis were seropositive against all three types of poliovirus.<sup>19</sup> In the 1993 survey, 99.5% of the population were immune to poliovirus 1, 99.0% to poliovirus 2 and 97.8% to poliovirus 3. Even adults above 30 years of age had a relatively low level of susceptibility to poliovirus, with 93.6% possessing neutralising antibodies to all the three serotypes of poliovirus.<sup>20</sup>

#### *Measles, Mumps and Rubella*

The overall seroprevalence for measles in the 1989/1990, 1993 and 1998 surveys<sup>13,21</sup> were 91.4%, 91.5% and 77.9%, respectively. The last survey was conducted after the "catch-up" measles immunisation programme using the MMR vaccine in 1997 and the introduction of the second dose of MMR vaccine to those aged 11 to 12 years in 1998. The seroprevalence in those aged 10 to 14 years was noted to increase significantly 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. The lower overall level of immunity in 1998 was largely due to a significantly lower seroprevalence in those aged 2 to 4 years (86.8% in 1993 versus 52.4% in 1998,  $P < 0.001$ ) and 5 to 9 years (81.6% in 1993 versus 70.1% in 1998,  $P = 0.04$ ).<sup>22</sup>

In the 1989/1990 survey which was conducted just before and at the introduction of the MMR vaccine in 1990, the overall seroprevalence of antibody to mumps was 72%.<sup>13</sup> The seroprevalence in children below 5 years old was 22%. It increased to 72.4% in 1993, but decreased significantly to 25.6% in 1998 after the Jeryl-Lyn mumps strain of the MMR vaccine in the NCIP was replaced by the Rubini mumps strain.<sup>23</sup>

The overall seroprevalence of rubella in the 1989/1990 survey was 47.6%. It was low in children below 10 years of age (7% to 11%) but increased two-fold from 42% in those aged 10 to 14 years to 90% in those aged 15 to 19 years.<sup>13</sup> In the 1993 survey,<sup>24</sup> the seroprevalence was found to have increased from 69.9% in 1 year-old infants to 97.9% in children aged 2 to 3 years. It then decreased to 70.8% in the 4-year-olds and 27.5% in children aged 5 to 9 years. The seroprevalence was 62.5% in children aged 10 to 14

years and 94.4% in adolescents aged 15 to 19 years. In the 1998 survey,<sup>25</sup> the seroprevalence was found to range from 87.4% to 96.6% among those aged 15 to 34 years. The overall seroprevalence of rubella among children and adults aged between 6 months and over 45 years increased significantly from 47.6% in 1989/1990 to 71.7% in 1993, and 80.2% in 1998 ( $P < 0.05$ ,  $\chi^2$  test for trend). In adults aged 18 to 24 years and 25 to 29 years tested for antibodies against rubella in 2005, 14.3% and 14.1%, respectively were seronegative.

#### *Hepatitis B*

Prior to the implementation of the national hepatitis B childhood immunisation programme in 1985, the prevalence of hepatitis B virus (HBV) infection (any HBV markers positive) was 9.3% in children below 5 years of age, 10.9% in the 5 to 14-year age group, 22.7% in the 15 to 24-year age group, 24.6% in the 25 to 34-year age group and 40.5% to 54.6% in those above 35 years of age.<sup>26</sup> In the 1993 survey, it was found that the age-specific prevalence of HBV infection had increased to 63.1% in children below 5 years of age, 57.6% in those aged 5 to 14 years and 43.4% in those aged 15 to 24 years.<sup>27</sup> Among vaccinated children, the prevalence of antibody against hepatitis B surface antigen (anti-HBs) was 79.4% in those below 5 years of age, 77.3% in those aged 5 to 14 years and 70.3% in those aged 15 to 24 years. The anti-HBs prevalence was only 6.1% in unvaccinated children aged 5 to 14 years.

In a study of 625 students aged between 5 and 19 years of age in 1987, the prevalence of hepatitis B surface antigen (HBsAg) positivity and HBV infection was 3.3% and 12.6%, respectively.<sup>26</sup> A 1994 survey in primary 1 students revealed that 76.5% had a history of hepatitis B immunisation. None of the children was found to be HBsAg positive. The anti-HBs positivity rate of vaccinated children (91.3%) was significantly higher than that of unvaccinated children (2.5%). When the same cohort of students was followed-up one year later, all the students remained negative for HBsAg. The prevalence of anti-HBs of the vaccinated students showed a slight decline to 88.6% in 1995.<sup>28</sup>

In the 1998/1999 serological survey,<sup>29</sup> the age-specific prevalence of HBV infection was observed to have increased from 63.1% in 1993 to 90% in children below 5 years of age, and from 57.6% to 68.5% in those aged 5 to 14 years. The anti-HBs prevalence of vaccinated children below 5 years of age increased to 89.9% from 79.4% in 1993. Of 991 children and adults sampled in this survey, HBsAg and antibody against hepatitis B core antigen (anti-HBc) (a marker of past infection) was detected in 4.6% and 27.1%, respectively of the unvaccinated group compared to 0% and 5.3%, respectively of the vaccinated group. These differences were highly statistically significant ( $P < 0.0005$ ).

Following the catch-up hepatitis immunisation programme for older children and young adults from secondary school to university levels between 2001 and 2004, and based on blood samples obtained during the national health surveys conducted in 1998 and 2004, the anti-HBs prevalence in the 18 to 29-year age group had increased significantly from 27.9% in 1998 to 41.7% in 2004 ( $P < 0.001$ ).<sup>5</sup>

## Discussion

The NCIP has been successfully implemented as evidenced by the declining disease incidence, excellent immunisation coverage rate and high level of herd immunity of the childhood population protected. Dreadful childhood diseases such as poliomyelitis, neonatal tetanus, diphtheria, childhood TB meningitis and congenital rubella have been virtually eliminated with the last indigenous case reported in 1978, 1984, 1992, 2002 and 2005, respectively. Singapore was among the countries in the WHO Western Pacific Region which was certified polio-free on 29 October 2000.<sup>30</sup> The high level of herd immunity of the childhood population to diphtheria, pertussis and poliomyelitis induced by the immunisation programme ensures that these diseases could not establish a foothold in Singapore despite their continuous introduction from outside the country.

However, the sudden increase in the incidence of pertussis among unimmunised or incompletely immunised infants from an annual average of 4 cases to 38 cases in 2007 should not be of major concern as it is likely to be artefactual. One of the reasons for the increase could be due to the introduction of polymerase chain reaction (PCR) diagnostic test for the detection of *Bordetella pertussis*. Pertussis was made a notifiable disease under the Infectious Diseases Act in 2008 and its incidence in adults should be closely monitored as they have been shown to be the reservoir of infection for unimmunised neonates and infants in other developed countries.<sup>31</sup>

The incidence of measles decreased significantly as a result of increased immunisation coverage from 58.8% in 1981<sup>4</sup> to between 93% and 95% after measles vaccination was made compulsory by law. However, administration of a single dose of measles vaccine in the NCIP is inadequate for the interruption of measles transmission as experienced in several well-vaccinated countries<sup>32-34</sup> and as shown by the resurgences in 1992/1993 and 1997 in Singapore. These resurgences were triggered off when a pool of susceptibles has accumulated to a critical threshold level and were not due to vaccine failure as the measles has been consistently demonstrated to have an efficacy of above 92%.<sup>22</sup> With the implementation of the 'catch-up' measles immunisation programme in 1997 and the introduction of the two-dose measles immunisation schedule using the MMR vaccine in 1998, the incidence among local residents has dropped

to 0.2 per 100,000 population in 2007. By achieving an immunisation coverage of at least 95% at an average age of 2 years for each cohort of preschool children, measles transmission can be interrupted.

Unlike measles, the huge resurgence of mumps in 1999 to 2000 was due to the absence of protection conferred by the Rubini mumps virus strain of the MMR vaccine used in the NCIP. Based on epidemiological investigations of several institutional outbreaks, the vaccine efficacy of the Jeryl-Lyn strain, Urabe strain and Rubini strain mumps vaccine were 80.7%, 54.4% and -55.3%, respectively.<sup>35</sup> The lack of protection conferred by the Rubini strain of the MMR vaccine was confirmed by serological findings which showed that the seroprevalence for mumps in children below 5 years of age had decreased significantly from 72.4% in 1993 to 25.6% in 1998. There was also a corresponding decline in measles seropositivity which dropped from 86.8% in 1993 to 52.4% in 1998 in children 2 to 4 years of age and from 81.6% to 70.1%, respectively, in those 5 to 9 years of age. This could be due to the lowered measles antibody response elicited by the implicated MMR vaccine.

The successful implementation of the rubella vaccination programme has resulted in the virtual elimination of congenital rubella. The periodic serological surveys conducted showed increasing rubella antibody prevalence among preschool and primary school leavers covered in the NCIP. Moreover, the high seroprevalence of 93.4% in the 15 to 24 year age group in 1993 confirmed the immunogenicity of the monovalent rubella vaccine. The level of susceptibility to rubella among women in the reproductive age group had gradually declined from 44% in 1975 to 28% in 1985 and maintained at between 10% and 20% from 1987 to 1998. The last survey conducted in 2005 showed that a considerable proportion (15.8%) of women 18 to 44 years of age remained susceptible to rubella infection.<sup>15</sup> This is of concern as the susceptibility level is higher than that in some European countries and Australia (2.2% to 6.2%).<sup>36</sup> Therefore, there should be more public awareness and health education activities to highlight this concern and every opportunity taken to identify all susceptible women and to ensure that they are vaccinated against rubella.

The hepatitis B immunisation programme is highly successful in reducing both the incidence of acute hepatitis B and the prevalence of chronic hepatitis B carriage. The incidence of acute hepatitis B in children less than 15 years of age declined from 10 cases in 1983 to 0 since 1997. The herd immunity (anti-HBs >10mIU/mL) induced by the immunisation programme was 90% in children below 5 years of age in 1999. The 'catch-up' hepatitis B immunisation programme implemented from 2001 to 2004 has significantly raised the herd immunity of young adults aged 18 to 29 years, and representative of the general population, from 27.9%

in 1998 to 41.7% in 2004 ( $P < 0.001$ ). The prevalence of hepatitis B surface antigen (HBsAg) carrier rate in children 5 to 9 years of age was 3.4% in 1987,<sup>37</sup> but no carrier was detected among primary school students in 1994/1995.

While the overall immunisation coverage has been maintained at a high level of above 90%, there is no room for complacency. The high level of herd immunity of the population so arduously acquired over the years through the NCIP must be maintained. Outbreaks should be thoroughly investigated to ensure that they are not due to vaccine failure as in the case of MMR vaccine containing the Rubini mumps strain which was deregistered in 1999. Moreover, with the large influx of immigrants from countries without comprehensive immunisation programmes and coverage, the risk of localised outbreaks such as rubella is high, especially in settings where these susceptibles congregate. These immigrants and non-residents in schools and work places should be closely monitored and foreign students without valid immunisation records should be identified and vaccinated. Health education to prevent non-compliance to vaccination due to myths and misconceptions of the public regarding immunisations must be appropriately addressed. Otherwise, public concern such as the unfounded link between autism and the MMR vaccine or the harmful effects of the mercury-containing vaccine preservative, thimerosal, might decrease the uptake of the MMR vaccine, which had resulted in measles outbreaks and deaths in the UK.<sup>38,39</sup> Public health messaging and addressing public concerns are therefore of paramount importance.<sup>40</sup>

Unimmunised children and adults not covered by the NCIP remain highly susceptible to vaccine-preventable diseases, especially when travelling to countries which are endemic for these diseases or where outbreaks are occurring. Serological surveys showed relatively low herd immunity of the adult population against tetanus, pertussis, diphtheria and poliomyelitis. More than half in the 18 to 19-year age group did not have immunity to hepatitis B and are at risk of acquiring the disease through sexual exposure.<sup>41</sup> Therefore, the immunisation records of adults should be routinely elicited and appropriate vaccines administered to protect them from the risk of infection.<sup>42</sup>

One limitation of this review is that the population sampled in the various serological surveys, except for the 1998 and 2004 national health surveys, are not representative of the general population and that the laboratory tests used for the detection of antibodies/antitoxins were not the same throughout. However, the findings, for example for pertussis, were similar to studies conducted by other investigators.<sup>43,44</sup> It should also be noted that not all the reported clinical cases of rubella and mumps were confirmed by specific laboratory tests.

Several revisions to the NCIP have been made over the

years. The factors that impact on immunisation policy include disease epidemiology, vaccine availability, development of new vaccines, costs, safety and efficacy, as well as public acceptance. In view of the shortage of supply of childhood DT vaccine, the NCIP was further revised in 2008. The third booster dose for primary school leavers was omitted and the second booster is now given at primary 5 instead of primary 1. The vaccine to be used can either be a Td (adult) vaccine or the combined tetanus, reduced diphtheria and acellular pertussis (Tdap) vaccine. In shifting the second booster dose from primary 1 to primary 5, consideration was taken into the findings of a serological study which showed that there is sufficient immunity against diphtheria and tetanus conferred by the earlier preschool immunisations.<sup>45</sup> Based on the practices of other developed countries such as the US, UK and Australia, the second dose of MMR vaccine was also brought forward from primary 6 to primary 1 to shorten the interval between the 2 doses in 2007. The rationale is to prevent a build-up of a population susceptible to measles, especially those who did not respond to the primary dose. This would not affect clinical protection against rubella due to the anamnestic response to natural infection.

The NCIP will continue to be reviewed periodically based on the experience of other healthcare systems with regards to the inclusion of new vaccines,<sup>46,47</sup> epidemiological and economic impact as well as socio-cultural issues. For example, pneumococcal vaccination has just been added to the NCIP. However, although WHO has recently recommended that oral rotavirus vaccines be included in all national immunisation programmes, this recommendation was not implemented because of the low likelihood of complications arising from rotavirus-related infections in Singapore.<sup>48</sup> Vaccines against Haemophilus influenza B, varicella zoster virus, and human papilloma virus infections have also not been incorporated although they have been registered in Singapore and are available on an individual basis.

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