antibodies. In vaccine trials involving infants and young children, determination of rotavirus-specific lymphoproliferative activity may be more accurate than determination of rotavirus-specific neutralizing antibody responses in discriminating between active and passively acquired immune responses and predicting protection against rotavirus disease.

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Changing Epidemiology of Measles in Hong Kong from 1961 to 1990—Impact of a Measles Vaccination Program

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With the use of measles vaccine since 1967, Hong Kong has experienced a low incidence of measles until a major outbreak in 1988. A shift in the distribution of susceptible children to older age groups was suddenly accelerated in the 1988 outbreak. The attack rate increased by 18.9-fold for children >10 years old, while that for those in the best-protected age group of 1–4 years was only 2.2-fold. Of the cases during that outbreak, 56.3% would have been considered preventable with the present vaccination regimen, and vaccine failures accounted for only 20.4% of the cases. Present control strategies aim at increasing the coverage rate rather than introducing a two-dose regimen, which may be necessary when vaccine failures account for a larger proportion of measles cases.

Measles remains a major cause of mortality and morbidity in developing countries and is responsible for 1.5 million deaths a year [1]. It is still a major cause of morbidity in developed countries, and measles outbreaks continue to occur despite the use of measles vaccine for more than two decades [2]. Hong Kong has experienced tremendous change from 1961 to 1990, with a decrease of the mortality rate for children <5 years old from 64 to 8 per 1000 live births [1]. Since the introduction of measles vaccine in 1967, measles incidence and case fatality rates have declined substantially; however, a major outbreak occurred in January–June 1988. Similar outbreaks after a period of low incidence in several developed countries have renewed interest in measles control strategies [2]. Here we examine the changing epidemiol-

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ogy of measles from 1961 to 1990 in Hong Kong and the nature of the 1988 outbreak to explore strategies for the future control and eventual eradication of measles.

Methods

Measles is a statutory notifiable disease in Hong Kong, and there is no legal requirement for immunization. Voluntary measles vaccination was introduced in December 1967 with a single dose of Schwarz vaccine given to children ≥6 months old. Vaccines were purchased from Smith Kline & French (Rimevax, Pluserix; Rixensart, Belgium) and Institute Merieux (Trimovax, Rouvax; Lyon, France). Vaccine virus titers were >1000 $TCID_{50}$ per dose. The age of vaccination was raised to 9 months in 1971 and to 12 months in 1979. Vaccine status was documented with a personal immunization record that was filled in by a health care worker and kept by parents. Immunization returns were sent back to the Statistical Unit, Department of Health. Measles cases were defined as cases reported by fully registered medical doctors.

The coverage rate among the target population was <70% before 1976, 70%–80% between 1976 and 1984, and ~80% since 1984. Data on measles notifications were collected and analyzed by the Statistical Unit. Every case of measles reported to the Department of Health was followed up by a review of the case record and an interview with the family by a trained community health nurse. Yearly population data were based on published figures from the Census and Statistics Department (Hong Kong government). The yearly raw epidemiologic data on measles from 1961 to 1990 were grouped into six periods and four age groups (table 1).

Results

During the prevaccine era, epidemics occurred biennially with an incidence rate of >100 per 100,000, a case-fatality rate of 4%–25% and a mortality rate of >100/million (figure 1). Since the introduction of measles vaccine, the average rates of incidence, case fatality, and mortality dropped from 85.9/100,000; 13%; and 102.3/million in 1961–1967 to 11.7/100,000; 0.24%; and 0.29/million in 1981–1987, respectively. Smaller outbreaks occurred less frequently from the late 1960s to the early 1980s. When the coverage rate was increased to ~80% in 1984, the incidence rate for the first time was <6 per 100,000 consecutively for 3 years before the January–June 1988 major outbreak.

Table 1 shows the age distribution expressed as percentage of total cases and age-specific attack rates for the four age groups from 1961 to 1990. Children 1–4 years old benefitted most, with the percentage of total cases decreasing by ~10% successively through the first four periods before the 1988 epidemic. The corresponding decrease in the age-specific attack rate was from 524 to 103/100,000. For children <1 year old, the age-specific attack rate was halved since the introduction of the vaccine; however, the percentage of total cases increased successively by 5% when the age of vaccination was increased from 6 to 9, and then to 12 months of age. The population of children <1 year old decreased from 106,700 to 72,100 from 1961 to 1990. The vulnerability of this group when not immunized was reflected by the continually high age-specific attack rates. For children >10 years of age, the attack rate and percentage of total cases increased from 1.4/100,000 and 1.3% in the prevaccine era to 20/100,000 and 31% in the 1988 outbreak.

Comparing the age-specific attack rates between the preepidemic phase (1980–1987) and the epidemic year (1988) for each age group, the increases were 18.9-fold (>10 years), 5.2-fold (5–9 years), 3.6-fold (<1 year), and 2.2-fold (1–4 years). The gradual shift in the age distribution of cases from children 1–4 years old to both younger and older age groups in the years before the outbreak suddenly accelerated in the epidemic year: The percentage of children 1–4 years old dropped further from 42.6% to 23% and that of children >10 years old increased from 8.5% to 31% (table 1).

Table 1. Age-specific attack rates and age distribution of measles cases in Hong Kong.

Years (vaccination or outbreak status)	Average vaccination coverage (%)	Rate (% cases by age* group)				
		<1	1–4	5–9	≥10	Total
1961–1967 (prevaccine)	0	444 (14.7)	524 (73.4)	63 (10.4)	1.4 (1.3)	87.0
1968–1970 (vaccine at 6 months)	50	202 (15)	179 (62.3)	39 (20.3)	0.7 (1.7)	27.0
1971–1979 (vaccine at 9 months)	55	250 (20)	181 (55.6)	45 (19)	1.1 (3.3)	23.0
1980–1987 (vaccine at 12 months)	75	231 (25.4)	103 (42.6)	38 (22.5)	1.06 (8.5)	14.0
1988 (epidemic)	80	831 (19)	228 (23)	196 (27)	20 (31)	55.0
1989–1990 (after epidemic)	89	22 (17.6)	12 (42.8)	6 (25.7)	0.3 (13.9)	1.6

NOTE. Age-specific attack rate expressed as cases per 100,000. Percentage of each age group of total number of cases; a small percentage was not included due to missing data on age.

* Age in years.

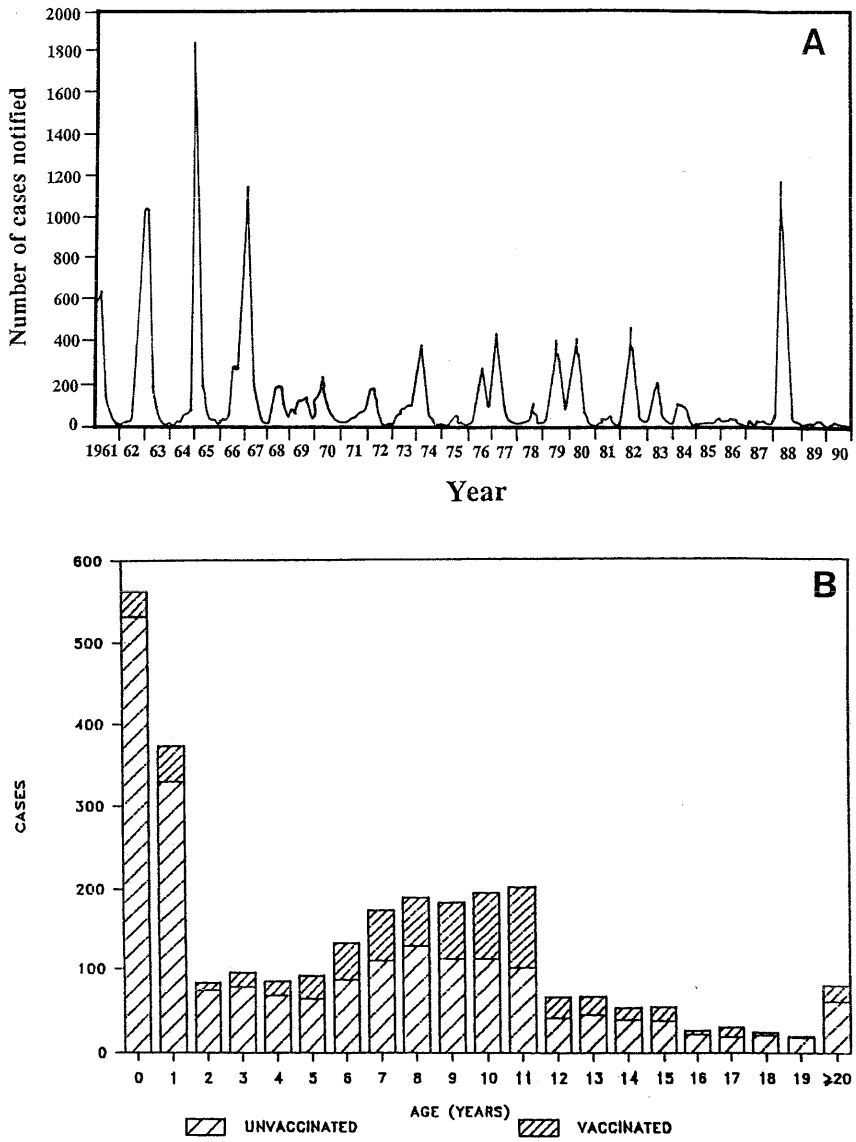

Figure 1. **A,** Monthly measles notifications, Hong Kong, 1961–1990. **B,** Age distribution of measles cases, by immunization status, Hong Kong, 1988.

Figure 1 shows the age distribution of measles cases in 1988 and vaccination status. Most cases occurred in children <1 year old and those in primary school. Only 657 (23.6%) of the 2788 cases in January–June 1988 included a history of measles immunization. Of these, 568 cases (20.4%) had been immunized on or after their first birthday. Vaccine efficacy was estimated to be 90%–95% based on the data from this outbreak [3]. Measles occurred among 561 infants, who were less than the recommended age for immunization. Therefore, the remaining 1570 cases (56.3%) represent those "potentially preventable." There was a male predominance in the measles cases with male-to-female ratios for age groups of 1.70 (<1 year), 1.27 (1–4 years), 1.21 (5–9 years), and 1.18 (10–14 years).

Control measures for the outbreak included (1) temporarily lowering the minimum age for immunization to 6 months in April 1988; (2) special immunization teams visiting nurseries, child health centers, and primary schools; (3) strengthening surveillance with active case finding and vaccinating unvaccinated close contacts; (4) disseminating health education information and publicity through television, radio, and newspapers; and (5) establishing immunization centers in strategic sites throughout the territory. More than 70,000 doses of measles vaccine were administered between 23 April and 28 July. Of these, >40% were given to children <1 year old. Children immunized at <1 year were reimmunized at 18 months. Notification of measles reached a peak in April 1988 and returned to the usual level in July 1988. There were <150 measles cases per year for the following 2 years, with the incidence rate reaching an all-time low of 1.6 per 100,000 (table 1).

Discussion

The changing epidemiology of measles since the introduction of vaccination in Hong Kong represents a shift in the age distribution of susceptible children. Despite only moderate coverage levels during the late 1960s and early 1970s, the overall incidence rates have declined dramatically. The consequence was that the unvaccinated individuals were less likely to contact infected persons and acquire natural immunity. This would lead to gradual entry of more and more unvaccinated susceptible children into older age groups, as reflected by the changing age distribution of the measles cases through the first four periods before the 1988 outbreak (table 1).

The increase of the interepidemic durations from 2 to 3–6 years was due to the increased time required for the accumulation of enough susceptible children to sustain an outbreak. This changing pattern of age distribution of measles cases and lengthening of the interepidemic duration were predicted and observed in many countries [4–5] but not in some [6]. It was estimated in the United Kingdom that the measles vaccination programs increased the proportion of immune children aged 3 years old (from 26% in 1958 to 61% in 1975), roughly maintained the proportion of immune children among 7 year olds (at 80%), but reduced the proportion of immune children among 11 year olds (from 91% in 1966 to 74% in 1975) [4]. This continuing shift of distribution of susceptible children into older age groups could lead to sizeable outbreaks among teenagers and young adults and has been documented in countries such as the United States [2] and Israel [7].

Another interesting shift in age distribution in Hong Kong was the gradual increase in the proportion of measles cases in children <1 year old, which was mainly due to a decrease in the incidence rate among children 1–4 years old (table 1). Another reason may be the two-phase immunization policy adopted in Hong Kong, that is, initially immunizing at 6 months, then at 9 months, and now at 12 months. This policy was adopted on the assumption that achieving high coverage at ages 6–9 months would reduce measles transmission in young children and allow a subsequent change in the age at immunization to ≥12 months, when all children have lost maternal antibodies and vaccine efficacy is higher [8]. However, when the age at vaccination was increased, the number of unvaccinated infants who were susceptible quickly increased, and outbreaks occurred among them. Hence, an unchanging one-stage strategy may result in lower morbidity and mortality than a strategy with the same level of coverage that switches to immunizing older children [5].

The measles incidence rates were low (<6/100,000) for 3 consecutive years, with gradual accumulation of susceptible children before a major outbreak from January to June 1988. The two peaks in the age distribution of the measles patients, that is, those <1 year old and those in primary school, are due to different reasons and therefore require different strategies for control (figure 1).

Children <1 year old were younger than the recommended age for immunization and their illnesses were therefore considered "unpreventable." The strategy required to decrease measles in children <1 year old may be to introduce a measles vaccine that is immunogenic, such as the Edmonston-Zagreb strain [9]. For children in primary school, a sizeable proportion were immunized against measles and (figure 1) therefore considered unpreventable. These would represent either primary or secondary vaccine failures [10]. Secondary vaccine failure occurs when immunity is lost after initial seroconversion and appears to be rare in recipients of live-measles vaccine [10]. Nevertheless, secondary vaccine failures in a measles outbreak have been documented; 5% of children who seroconverted in one study later contracted measles [10]. Primary vaccine failure may be a more serious problem. Measles vaccine may have a 1.7%–10% failure rate [11, 12].

In Hong Kong a seroconversion rate of 98.4% by neutralization test and 96.2% by hemagglutination inhibition test has been documented for children aged 9–24 months who received intramuscular Schwarz vaccine in the 1960s [13]. Boys predominated among the nonseroconverters, particularly at ages 12–20 months [14]. Of interest, boys predominated in the 1988 epidemic. However, the reason for this male predominance is unclear and may be due to an increased complication rate in boys compared with girls [15], leading to more boys presenting to physicians.

Despite the intense interest in the role of vaccine failures in measles outbreaks in the West, it must be emphasized that vaccine failures accounted for only 20.4% of the 2788 measles cases in the 1988 outbreak in Hong Kong; measles vaccine failures in the United States from 1985 to 1986 were 40% [2]. Most cases (56.3%) in Hong Kong were children >1 year old who had not been vaccinated against measles; by the present vaccination program these cases would be considered preventable.

Future strategies for control should aim at increasing the coverage rate. For preschool children (1–4 years), there is a high proportion of unvaccinated children (figure 1). Every time they interact with the health care delivery system should be viewed as an opportunity to immunize. For school-aged children, "mop-up" immunization for those not immunized was adopted for primary 1 children, as primary school education is compulsory in Hong Kong [16]. In 1989 immunization coverage was increased from 85% to 97.4% among primary 1 children by mop-up immunization [16]. This strategy will not, however, address the problem of vaccine failures, which may be controlled by a two-dose regimen [7]. This was achieved in Sweden [17].

The cost-benefit ratio of mop-up immunization compared with a two-dose regimen will depend on the changing proportion of vaccine failures among the measles cases. When

mop-up immunization becomes more successful, the proportion of preventable unvaccinated cases will decrease while that of vaccine failures will increase. There may come a time in Hong Kong when a two-dose regimen is necessary to control and eradicate measles.

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