Impact of Supplementary Immunization Activities in Measles-Endemic Areas: A Case Study From Guangxi, China

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Because of limited resources, each year during the period from 1999 through 2007, only about one-quarter of the 111 counties in Guangxi province were selected by means of risk assessment to participate in Supplementary Immunization Activities (SIAs), targeting children aged 8 months to 14 years during 1999–2003 and 8 months to 10 years during 2004–2007. Approximately 2 million doses of measles vaccines were administrated each year during SIAs. Estimated from the National Notifiable Diseases Surveillance System, with a reliable internal consistency over years, the average annual incidences of measles before SIAs (1993–1998), during the first phase (1999–2003), and during the second phase (2004–2007) were 16.05, 9.10, and 2.46 cases per 100,000, respectively. The overall provincewide annual incidence decreased by 84.67%, from 12.12 cases per 100,000 in 2000 to 2.10 cases per 100,000 in 2007. The percentage of counties with annual incidence ≥10 cases per 100,000 decreased from 55% in 1993 to <1% in 2007. Compared with the pre-SIA period, the greatest decrease in annual incidence was 83.93% for the 10–14.9-year-old group and the smallest decrease was 46.16% for children <1 year old. The multiple-year SIAs targeting children in selected high-risk counties were effective in controlling measles in mountainous, impoverished, and multiethnic measles-endemic areas.

After having successfully eradicated wild-type poliomyelitis, China has moved toward the ambitious goal of eliminating measles by 2012 [1]. While many developed provinces have progressed rapidly from a strategy of epidemic prevention to a goal of measles elimination, several sparsely populated poorer provinces, which were also measles-endemic areas, made little or no progress during the 1990s [2]. There is a consensus that the feasibility of measles elimination in China would depend greatly on improving measles control in these impoverished provinces [3].

Guangxi (full name is Guangxi Zhuang Autonomous Region) is one of China's 5 minority autonomous provincial-level administrative divisions. Here, we simply refer to it as Guangxi. It is located on the southern frontier area, bordered by Vietnam to the south (Figure 1). The region covers more than 236,000 km^2 (approximately the same size as the Lao People's Democratic Republic) and has a population of 50 million (similar to South Africa, the 25th most populous country) [4]. As indicated by the region's full name, Guangxi Zhuang Autonomous Region, approximately one-third of the population is of the Zhuang ethnic group. Much of the territory is mountainous with a subtropical climate characterized by high humidity, monsoons, and long hot summers [5]. During recent years, Guangxi's economy has been growing rapidly; however, it languishes behind many other parts of the

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Figure 1. Location of Guangxi Province in China.

country and is ranked 20th of 31 administrative divisions in mainland China in terms of gross domestic product (GDP) per capita [6]. The underdeveloped economy, multiethnic population, subtropical climate, and mountainous terrain pose great challenges for public health services, including measles control.

Between 1960 and 1969, prior to the widespread availability of measles vaccine, the annual incidence of measles in Guangxi was, on average, 800 cases per 100,000 population, with approximately 150,000 cases and 1500 deaths reported each year [7]. The establishment of the Expanded Program of Immunization, in early 1980, with improved integrated cold-chaining and increased coverage of Expanded Program of Immunization vaccines, had resulted in remarkable declines in the morbidity and mortality of measles. The interepidemic interval, although increased, nevertheless remained, indicating that the immunization coverage was not sufficient to interrupt the transmission of the measles virus [8, 9]. The national polio immunization days conducted in 1993–1995 provided the critical momentum to enhance overall immunization services nationally, and measles incidence in Guangxi reached a historic low in 1995 [10, 11]. However, there was a resurgence, with 5908 cases of measles reported in 1998 as a result of the fundamentally insufficient Expanded Program of Immunization service network [11]. Because of an average annual incidence of measles of >15 cases per 100,000 in 1990–1998, the National Plan for Accelerated Measles Control, issued by the Ministry of Health in 1998, categorized Guangxi as "group C," a category for which the goal was outbreak control [2, 3].

To accelerate the measles control program locally and to achieve the national goal of measles elimination by the end of 2012, Guangxi has conducted 2-phase multiple-year Supplementary Immunization Activities (SIAs) since 1999. Because of limited health budgets, Guangxi's SIAs were conducted in selected high-risk counties only over a period of several consecutive years. The procedure thus differed from the approach recommended by the World Health Organization, which generally requires the entire administrative unit to conduct the campaign simultaneously over a short period of time in order to interrupt the circulation of indigenous measles virus by eliminating the reservoirs [12, 13]. Using an observational study design, the current study investigated changes in annual incidence of measles cases before, during, and after the SIAs in Guangxi to assess the effectiveness of the intervention.

The study provides additional data for fine-tuning current measles elimination strategies and helping to assess the feasibility of measles elimination in impoverished areas with limited resources.

METHODS

Study Population

By the end of 2005, the total population of Guangxi had reached 49.25 million. The population density is about 208 per square kilometer. Approximately one-third of the population is of the Zhuang ethnic minority, the biggest minority group in China. There are also a substantial number of residents of the Dong and Miao minorities. Other ethnic groups include Yao, Hui, Yi, Shui, and Gin. Guangxi is known for its ethnolinguistic diversity, with 4 dialect languages spoken in the capital of Nanning alone. In 2005, the birth and death rates were 14.26% and 6.09%, respectively. The number of children aged 0–14 years was 12 million, accounting for 23.76% of the total population. More than 66% of the population lives in rural areas [5]. Measles vaccine is provided mostly through vaccination rounds, which are conducted every 2 months in rural areas and at least once a month in urban areas. In some developed urban areas, measles vaccine is delivered weekly or even daily. The current immunization schedule in Guangxi, which started in 2004, recommends the first measles dose to be administered to children at the age 8 of months and the second dose at the nationally recommended age of 7 years, around the time of entry to elementary school. The 1999 national coverage survey using probability proportional to size sampling indicated that the coverage with 1 dose of measles vaccine by 12 months of age was >95%. However, the actual coverage was considerably lower because of unregistered births [3].

Data Sources

Measles has been a class B reportable disease in China since 1950. It is a legal requirement for the name, age, sex, address, date of onset, and vaccination status of all suspected measles cases to be reported to the National Notifiable Diseases Reporting System (NNDRS) within 24 hours of detection [14]. Before 2000, this information was collected by mail or telephone, but it is now reported online. The clinical signs used to diagnose measles are the presence of a fever and maculopapular rash, together with at least 1 of the following: cough, coryza, or conjunctivitis. The numbers and descriptive information regarding measles cases used in the current report are based on data submitted to the NNDRS. Population denominators for calculation of incidence were determined on the basis of data provided by the Guangxi Bureau of Statistics. In Guangxi, a group C area, improving the timeliness of reporting and serologic confirmation of measles outbreaks is the priority; whereas suspected measles cases in outbreak settings were subjected to laboratory confirmation, sporadic cases were only confirmed clinically, using the above mentioned case definition. Therefore, we do not present laboratory confirmation data because they are incomplete.

Selection of High-Risk Counties

The key feature of Guangxi's SIA strategy was that the target areas were selected after critical review of the epidemiological situation. Although it is desirable to use seroprevalence as a criterion, in Guangxi, as in other parts of China, reliable seroprevalence data are not readily available. Reliably estimating immunization coverage in China has always been problematic, largely as a result of the "floating population" (seasonal economic migrants) and unplanned or unregistered births [10, 15]. Therefore, trends of reported clinical measles cases by county were used to identify the high-risk areas [16]. We simplified a standard susceptible-infective-recovered model [17] by placing more emphasis on the interval between measles epidemics to make the methodology more straightforward and applicable to local health professionals. Specifically, 3 groups of high-risk counties were identified:

1. Those with a measles incidence of ≥ 10 cases per 100,000 population during the previous year.
2. Those with a measles incidence during the peak year of the last epidemic cycle of ≥ 10 cases per 100,000, and in which the average interepidemic interval was longer than 4–5 years after the last peak year.
3. Those with a measles incidence of ≤ 5 cases per 100,000 during the past 5 years and no outbreaks for at least 8 years.

Execution of Supplementary Immunization Activities

For the selected high-risk counties, estimates of the number of eligible children in each county and in neighboring counties were made to determine the number of doses of vaccines needed. The final list of counties selected for the following year's SIAs was made by the provincial public health department on the basis of availability of resources, including personnel, vaccines, and funding. To boost herd immunity in a geographically wider area, the list could include counties sharing a border with high-risk counties. The final list of counties selected for the upcoming SIAs was finalized and announced in early January of each year. The SIAs were then processed according to a standardized protocol, which required all immunization activities to be completed no later than the end of February, the typical measles epidemic season in Guangxi. It was required that static immunization from mobile brigades, schools, and public parks be offered for well-documented populations during early SIA days and mobile immunization or door-to-door canvassing be performed in marginal communities or populations in later SIA days.

Study Design of the Current Analyses

The current study used a typical observational study design to examine changes in the incidence of measles before and after the SIAs. The pre-SIA period was defined as the period from 1993 through 1998. The first phase of the SIAs was 1999–2003, when 8-month-old to 14-year-old children were targeted for measles vaccination. The second phase was 2004–2007, when the target age range changed to 8 months to 10 years and all urban areas were covered regardless of whether they had already been subject to SIA previously. No statistical tests were performed because of the practical nature of the current study, and the entire population of Guangxi used as the denominator. Nor did we examine changes in measles mortality. By 1995, China as a whole had already met the goal endorsed by the 42nd World Health Assembly in 1989 and the World Summit for Children in 1990 of reducing the incidence of measles by 90% and mortality by 95% of prevaccination levels by 1995 [18, 19]. Case management of measles has improved dramatically over the last 2 decades in China, and currently, there are virtually no deaths from measles in Guangxi (the total number of measles deaths reported to NNDRS from the period 2003–2008 was 16, with 8 cases reported in 2007 alone) [11]. The effect of the SIAs on mortality was too small to be detected, and the decline in the mortality of measles might, by and large, be a function of better case management rather immunization per se [20, 21].

RESULTS

Starting from 1999, around 20–30 counties in Guangxi have been selected each year as high-risk counties for SIAs (Table 1). Approximately 2 million children were immunized annually during SIAs, representing about one-quarter of children under 15 years of age in the province. More children were vaccinated annually during the second phase, which targeted a narrower age range (8 months– to 10 years), than during the first phase, which targeted children aged 8 months to 14 years. However, the second phase covered more counties than the first. Because only limited geographic areas were covered by each round of SIAs, the effect of the first 2 rounds of SIAs on the provincewide annual incidence of measles was relatively small; in fact, instead of decreasing, the number of cases reported during the first 2 years of SIAs increased (Figure 2). Starting from the third year of SIAs, the provincewide annual incidences declined continuously until 2007, the cutoff year of the data collection for the current study.

The effect of the SIAs was also assessed by examining the average annual incidence of measles before the SIAs (1993–1998), during the first phase (1999–2003), and during the second phase (2004–2007). The incidence of measles during these periods was 16.05, 9.10, and 2.46 cases per 100,000, respectively. The average annual decrease in incidence between the second phase of SIAs and the pre-SIA period was 84.67%. Overall, the annual provincewide incidence decreased dramatically, from 12.12 cases per 100,000 in 2000 to 2.10 cases per 100,000 in 2008. In contrast, China as a whole reported a nationwide resurgence of measles in 2007 and 2008, the biggest increase since 1992 (Figure 2). The national incidence was as high as 8.4 cases per 100,000 in 2007 and 10.04 cases per 100,000 in 2008.

In Guangxi, the cycle of measles epidemics has been interrupted and transmission of indigenous virus brought under control. The incidence of measles has decreased gradually and smoothly, without peaking, since 2000. The proportion of counties with an annual incidence of $\geq$10 cases per 100,000 has been reduced from 0.55 (49 of 80 counties) in 1993 to $<$0.01 (1 of 111 counties) in 2007. During the period from 1989 through 2001, on average, 25 counties had an annual incidence of $>$20 cases per 100,000, and this number decreased dramatically to $<$4 counties, on average, during the period from 2002 through 2007 (Figure 3).

Table 1. Numbers of Total Population, Children Eligible for Vaccination in High-Risk Counties, and Vaccine Doses Delivered, 1999–2007, Guangxi, China

	First phase					Second phase			
Parameter	1999	2000	2001	2002	2003	2004	2005	2006	2007
Number of high-risk counties[a,b]	23	21	20	22	24	26	34	27	30
Total population, millions	8.64	7.59	7.87	10.41	8.96	12.66	16.50	20.29	15.87
No. of eligible children, millions	2.16	1.90	1.97	2.60	2.24	2.11	2.00	2.29	1.74
Doses of vaccine, [c]millions	1.80	1.18	1.64	2.27	1.82	2.61	2.12	2.43	1.86
Incidence of measles, cases per 100,000 population	7.94	12.12	13.32	7.96	5.24	2.91	3.23	1.87	2.10

NOTE. [a] The number of counties in Guangxi increased from 89 in 1989 to 111 in 2007, because some big counties split into 2 or more smaller ones. Increases in population and administrative considerations were the reasons for this reorganization.

[b] If the upcoming year was predicted as an epidemic year by time-series analysis of annual incidence, the county would be identified as high risk. Counties with an incidence of measles of $\geq$10 cases per 100,000 population for the previous year were automatically categorized as high risk.

[c] During the first phase of the measles immunization campaign, there was an insufficient supply of measles vaccine because of financial and logistical constraints; this situation improved dramatically after the central government provided political commitment and logistical support.

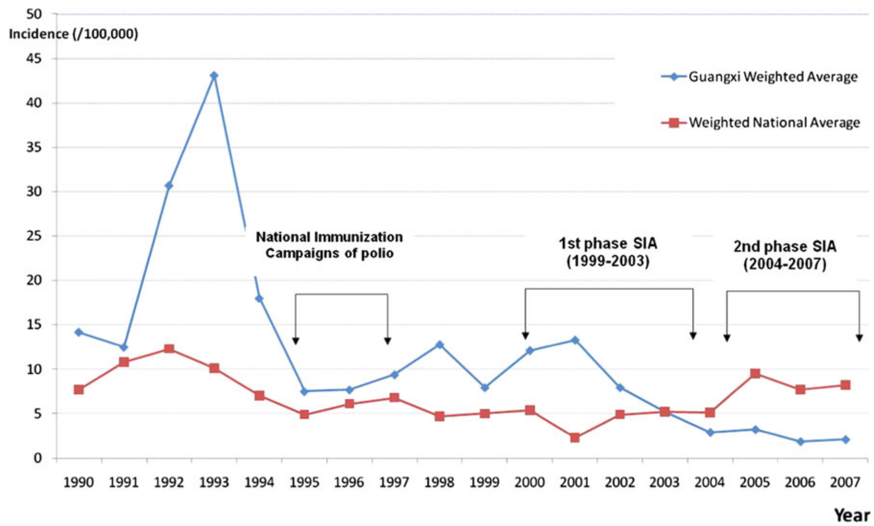

Figure 2. Comparison of the annual incidence of measles between Guangxi and China as a whole, 1990–2007, National Notifiable Diseases Reporting System.

Compared with the period prior to the SIAs, the maximum decrease in the incidence of measles after 2 phases of immunization was observed in the 10–14.9-year-old group, which had a weighted mean incidence during 2004–2007 of 2.54 cases per 100,000. This is 90% lower than during the pre-SIA period, when the incidence was 25.69 cases per 100,000. The smallest decrease was observed among children <1 year old, for whom the weighted mean incidence during 2004–2007 was 46% lower than during the pre-SIA period (Figure 4).

DISCUSSION

One of the key strategies for successful elimination of measles has been SIAs, including catch-up and follow-up vaccination programs [22–25]. However, China had yet conducted nationwide SIAs until the year 2011. mainly as a result of sharp variations in measles epidemiology, access to immunization services, and resources among and within provinces [26]. The central government stipulated that measles control and elimination programs be carried out in accordance with the specific circumstances of each province. Using the general guidelines from the central government and taking into consideration the pattern of measles epidemiology and availability of resources, Guangxi has developed and implemented an SIA strategy with risk assessment as its critical strategic planning tool.

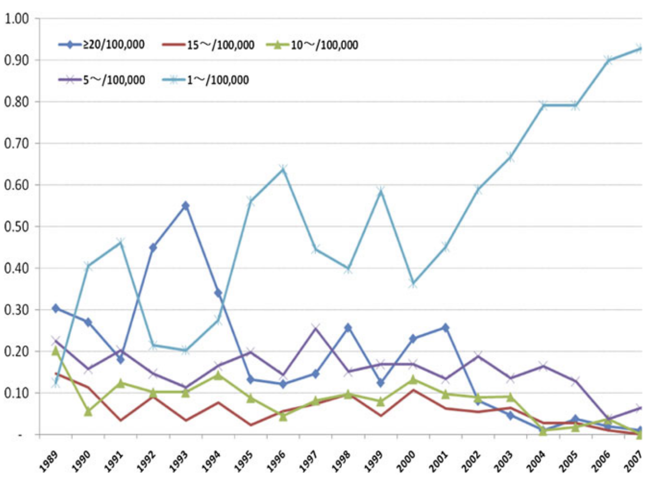

Figure 3. Proportion of counties with different categories of measles incidence, 1989–2007, Guangxi, China.

As the province ranked 20th of the 31 administrative divisions in mainland China in terms of GDP per capita, Guangxi has a severe shortage of funds to support immunization services [27]. The block grant from the provincial government for SIAs (including polio, hepatitis B, measles, and others) was about 10 million Chinese yuan (≈1.3 million US$) between 2000 and 2007, far less than adequate for a provincewide SIA [27]. Using a selective approach to implement SIAs to focus limited resources on the highest risk areas might be the most effective and timely way to reduce the accumulation of susceptible populations and prevent epidemics. In Guangxi, as in many parts of the world, immunization coverage among minority populations lags behind that of the majority population for various reasons, including cultural or religious resistance to immunization, language barriers, and reluctance of public health services to impinge on minority autonomy. In addition, to support the unique cultures and heritages of ethnic minorities, China's "one child" policy does not apply to ethnic minority families. Higher birth rates increase the vulnerability of minority-inhabited areas to measles outbreaks. For example, Rongshui, a remote, mountainous, and minority-inhabited county of Guangxi, experienced persistent measles epidemics, with an interepidemic interval of 3–5 years. The incidence in 2001, the peak year of the

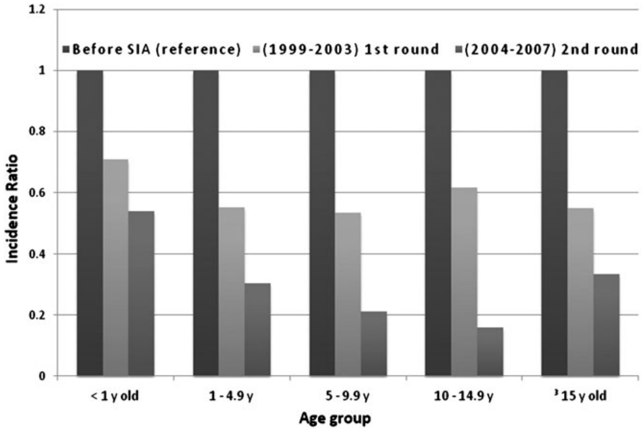

Figure 4. Incidence ratios between measles immunization campaign (MIC/SIA) phases by age group, 1999–2007, Guangxi, China. The pre-MIC period was defined as the period from 1993 through 1998.

recent epidemic cycle, remained as high as 53 cases per 100,000, substantially higher than the provincial average in the same year [11]. In addition to the sociodemographic challenges, the mountainous terrain and subtropical climate create conditions unfavorable to measles control programs in Guangxi. Although studies have documented a high rate of seroconversion following receipt of domestically manufactured measles vaccine in optimal settings [28], our survey of 9818 children, aged 8 months to 4 years, conducted in the year 2000 showed that the positive rate was 82.8% and the protective rate was just 49.4% [29]. The challenges posed by such factors as an underdeveloped economy, ethnic minority populations with high birth rates, a subtropical climate, and mountainous terrain require that SIAs be customized to local conditions under the principle set out by central government [7, 9, 30, 31].

The SIAs in Guangxi produced an outcome similar to that achieved in Africa, as described by Otten et al [32], and that in The Pan American Health Organization, as described by de Quadros et al [23]. Otten et al concluded that, to maintain measles deaths at near zero, a 3-pronged strategy was needed in areas with low rates of routine immunization: a catch-up campaign for children from 8–9 months to 15 years of age; routine measles vaccination coverage of $\geq$80%; and regular follow-up campaigns every 3–4 years, targeting children from age 8–9 months to 4–5 years [32]. Because measles is cyclical and the interepidemic interval is the key parameter for selecting high-risk counties in Guangxi, nearly every county in Guangxi was selected once in the first and once in the second phase. Because the goal of the control program in Guangxi was to further reduce the incidence of measles rather than to maintain a near-zero mortality rate, the follow-up campaigns targeted a wider age range than that recommended by Otten et al [32], ie, 8 months to 14 years, compared with 8 months to 5 years. Children $\geq$5 years old who are infected with the measles virus act as a reservoir and source of infection for younger children. The relatively large effect of the SIAs on children aged 5–14.9 years indicates that reducing the reservoir of virus and, hence, the source of infection might be the mechanism that leads to successful reduction in the incidence of measles by means of SIAs. Although there may be a major programmatic challenge to achieve, SIAs have been highly effective, because they are able to reach children that had previously been missed by routine immunization [10, 15, 33–36].

In the current study, using clinical cases reported from NNDRS without laboratory confirmation means that there is a degree of uncertainty about whether all the reported cases are actually measles cases. No studies have been conducted to evaluate the sensitivity of NNDRS on measles surveillance, and the completeness of measles reporting in China is unknown. The consistency of the underreporting over the years, however, makes NNDRS a valid source to examine the trend of measles [37]. There is a possibility that underestimates may occur as a result of China's effort to improve surveillance for severe acute respiratory syndrome (SARS). After the SARS outbreak in 2004, surveillance for all communicable diseases, including measles, has been substantially strengthened, which has resulted in an increase in the number of cases reported, compared with the years before 2004, and therefore underestimation rather than overestimation of the effectiveness of SIAs [38]. No data on seroconversion rates following SIAs were available, which greatly limited our ability to assess the effect of SIAs on the dynamics of infection and immunity. Perhaps the greatest limitation of the current study was that it was an observational study. Nevertheless, it is ethically unacceptable to conduct an experimental study in public health to assess the effectiveness of an intervention with an already well-established benefit [10, 15, 35]. It is also beyond the scope of the current study to evaluate the cost-effectiveness of SIAs. However, because Guangxi's approach was discriminative and risk based, the likelihood of substantially exceeding the herd immunity threshold, if it occurred, was small. The marginal effect might be much greater than that from SIAs if conducted provincewide without taking account of the local epidemic situation. With these limitations in mind, we believe, to the best of our knowledge, that the current study is the first to document an immunization campaign conducted in China with a fairly large population using a rotating risk assessment procedure. The majority of previous studies were conducted among relatively small populations [39–46].

In summary, Guangxi's experience has shown that SIA with risk assessment as the essential component is effective in controlling epidemics in measles-endemic areas within a reasonable timescale. SIA will be operationally less challenging in other Chinese regions with more favorable socioeconomic and environmental conditions. Despite all the challenges, including language barriers, and difficulties in transporting vaccine because of mountainous terrain and in maintaining the quality of vaccine in a subtropical climate, SIA has been successfully conducted in Guangxi. Nevertheless, we do not want to overemphasize the impact of the SIAs without acknowledging the crucial role played by the routine immunization service. This has been strengthened by the momentum built by the SIAs and is as important as catch-up programs for previously unvaccinated children. Indeed, both might be key factors to success in Guangxi [9, 10, 15, 29, 30, 31, 35, 47].

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