Predictors related to the occurrence of a measles epidemic in the city of São Paulo in 1997

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ABSTRACT *A matched case-control study was performed to identify risk factors for measles during an epidemic that occurred in 1997 in the city of São Paulo, in the Brazilian state of the same name. Measles cases from the city of São Paulo from 1 January 1997 to 15 August 1997 were included in the study. The criteria for case definition were age below 30 years, having received no measles vaccine 5–21 days before the onset of rash, and laboratory confirmation by IgM antibodies detection.*

From a bank of confirmed measles cases, 130 cases for each of five age ranges (under 1 year, 1–5 years, 6–20 years, 21–24 years, and 25–29 years) were picked at random according to a systematic criterion proportional to the number of cases in seven areas of the city. Data were collected through a home survey, and for each measles case studied two controls matched by age and place of residence were selected. The matched conditional logistic regression analysis for the potential risk factors from the univariate analysis showed that the best predictors for acquiring measles during the epidemic were: lack of measles vaccination, previous contact with a measles-like disease at home or on the job, having been born either outside the state of São Paulo or in a rural area, being employed, and spending time in a semiclosed institution, such as a nursery, day care center, or school. The risk factors were not homogeneous for the different age groups. The data in the present survey suggest that, in addition to lack of vaccination, other risk factors should be considered when planning a measles vaccination strategy for a developing country.

Vaccination to protect against measles has been routine in Brazil since 1973. However, in the Brazilian state of São Paulo periodic outbreaks of measles continued to occur, mainly involving children under 5 years of age. Those outbreaks were likely due to the vaccination schedules adopted and the relatively low vaccination coverage achieved.

In 1986 an extensive measles epidemic occurred in Greater São Paulo, the largest urban center in Brazil. Greater São Paulo includes the city of São Paulo and 37 neighboring cities. There were approximately 2 800 hospitalized cases notified to the Center of Epidemiological Surveillance (CES) of the Department of Health of the state of São Paulo (30.7 cases / 100 000 inhabitants). A home survey that CES carried out in 1986 indicated that approximately 83 000 cases occurred among children younger than 15 years of age (unpublished data).

Based on the data from that home survey, in 1987 the CES made a decision to promote a mass vaccination campaign in the state of São Paulo, for

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the population aged 9 months to 14 years. The aim of this strategy was to rapidly interrupt measles transmission. Additionally, routine vaccination was improved by supplementing the first vaccine dose, done at the age of 9 months, with a second one, given at the age of 18 months. The CES set up a more efficient and effective system of epidemiological surveillance of measles in the state of São Paulo. The system included mandatory notification and serological confirmation of all cases fulfilling the clinical case definition for measles of the United States Centers for Disease Control and Prevention (1).

Between 1988 and 1992, the incidence of measles progressively decreased, with 3 395 cases in the state of São Paulo notified to the CES during this 5-year period. In 1992 a national measles mass immunization campaign was conducted by the Ministry of Health of Brazil. In the city of São Paulo the number of measles cases continued to decrease in the following years, dropping to 9 laboratory-confirmed cases in 1996 (2).

At the beginning of 1997 there was a rapid increase in the incidence of measles in the city of São Paulo. By the end of that year there were 20 186 confirmed cases reported from the state of São Paulo (3), with 18 933 of them occurring in persons residing in Greater São Paulo. Of the 17 458 cases for whom patient age was known, 12 099 occurred in persons older than 15 years and 3 904 were among those younger than 5 years. The highest age-specific incidence rate was reported for infants under 1 year of age (871 cases per 100 000 population) (2).

The objective of the present study was to identify predictors related to the occurrence of the 1997 epidemic of measles in the city of São Paulo, Brazil.

METHODOLOGY

An analysis of the risk factors for the incidence of measles in 1997 in the city of São Paulo was performed according to age range by a case-control study.

The city of São Paulo is part of Greater São Paulo, which is located in the southeastern Brazilian state of São Paulo. The city covers an area of 1 509 km^2 and in 1996 had an estimated population of 9.8 million inhabitants. The city is subdivided into 98 administrative districts, which the city's Health Secretariat groups into 10 regional administrations (RAs). Those 10 RAs have high socioeconomic heterogeneity.

Measles cases resident in the city of São Paulo from 1 January 1997 to 15 August 1997 were included in the present study. The measles cases were defined in terms of three criteria: 1) age below 30 years, 2) having received no measles vaccine 5 to 21 days before the onset of exanthema, and 3) laboratory confirmation by detection of IgM antibodies by a commercial indirect enzyme immunoassay (Dade Behring, Marburg, Germany) or by IgM capture enzyme immunoassay (4), done by the Adolfo Lutz Institute in São Paulo. That public institution is a reference center of the Pan American Health Organization (PAHO) for the strategy of measles elimination in the Americas. For each measles case that we studied we selected two controls who met three criteria: 1) belonging to the same age range as the case, 2) residing in the same neighborhood as the case at the time of the disease, and 3) presenting no rash, fever, cough, coryza, or conjunctivitis during 1997.

Based on the vaccination strategies adopted in the state of São Paulo, five age ranges were studied: younger than 1 year, 1 to 5 years, 6 to 20 years, 21 to 24 years, and 25 to 29 years. The cases and the controls in the first two age groups and in the oldest age group had not been targeted in the mass vaccination campaigns of 1987 and 1992.

The two middle age groupings were originally for 6–14 years and 15–24 years, but they were later regrouped as 6–20 years and 21–24 years, as a function of the number of cases in the sample. These age groups had been targeted in two mass vaccination campaigns: the one of persons 6–9 years old was focused on in the 1992 campaign, the one for those 10–14 in both the 1992 and 1987 campaigns, and the one for persons 15–24 in the 1987 campaign.

The sample size was calculated using Epi Info software, version 6.4a (U.S. Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America). The sample size was based on the following premises: 95% confidence limit, 80% test power, 10% exposure among controls, and 2.5 odds ratio.

The sample of 130 measles cases per age range was picked at random from the bank of confirmed measles cases notified to the CES. In the state of São Paulo there is compulsory notification of all suspected measles cases. It is the responsibility of the basic health units or of the regional health entities to conduct the investigation, fill out a measles investigation chart, and send that chart to the CES. The health units that provide patient care are responsible for collecting blood for diagnosis.

The sample lots were drawn in proportion to the number of measles cases that had occurred in seven clusters which were regroupings of the 10 regional health administrations (RAs) of the city of São Paulo. Six out of the 10 RAs had a lower incidence of measles cases, thus not allowing the inclusion of a sufficient number of measles cases in all age groups. The researchers used geographical criteria and regrouped these 6 RAs into three sets of two neighboring RAs.

The data collection field activities were performed from November 1997 through March 1998. Data were collected through a home survey using a form specifically prepared for our study. Questions related to the socioeconomic standing of the interviewees—including housing, occupation, educational level, per capita income, and socioeconomic status—were classified as control variables. Among the study variables were: sex; vaccination status; contact with measles-like disease; place of contact with measles-like disease; being employed; contact with the public on the job; use of public transport to go to work (bus, train, or subway); time spent on public transport to go to work; spending time in semiclosed institutions, such as nurseries, day care centers, and schools; going to places where large groups of

people gathered; and using health services (public and/or private). A number of other study variables had to do with migration, including: being born outside the city of São Paulo; being born outside the state of São Paulo; being born in a rural area; residing in the state of São Paulo in May 1987 and June 1992, when mass vaccination campaigns against measles were conducted; length of time the migrant had been residing in the city São Paulo when had measles; length of time the migrant had remained in birthplace outside the city or state of São Paulo; length of time the migrant remained in an urban birthplace outside the city of São Paulo; and length of time the migrant remained in a rural birthplace outside the city of São Paulo.

The study variables were first submitted to a univariate analysis by the chi-square (χ^2) test in order to calculate the odds ratio (OR) and 95% confidence interval (CI).

The variables having a significance of $P < 0.2$ were included in the multivariate analysis, applying matched conditional logistic regression using the Egret for Windows software program (Cytel Software Corporation, Cambridge, Massachusetts, United States). The variables were introduced into the multivariate model in order, beginning with the highest odds ratio and progressing to the lowest odds ratio.

RESULTS

Univariate analysis

The univariate analysis indicated that not having been vaccinated against measles was a potential risk factor for three age ranges: 1–5 years, 6–20 years, and 21–24 years (Table 1).

As for the variables concerning the source of infection, having had measles was related to a history of contact with similar diseases at home, for all the age ranges studied. Contact with measles in the workplace was a risk factor only for those in the 25–29 age range.

Spending time in such semiclosed institutions as nurseries, day care centers, and schools showed a correlation for three age ranges: younger than 1 year, from 1 to 5 years, and from 6 to 20 years.

For the variable of using health services, there was a significant difference between cases and controls for children younger than 1 year and for those 1–5 years old.

Univariate analysis showed that being employed was a risk factor for measles among the interviewees in the age groups of 6–20 years, 21–24 years, and 25–29 years.

The use of public transportation to go to and from work proved to be a predictor of acquiring measles only for the 25–29 age group. Analysis of the time spent in the public transportation system indicated that there was an association both when this time was less than 270 minutes per day and when it was more than 270 minutes per day. However, the relationship was much stronger for longer periods, with an odds ratio of 12.72 for periods of more than 270 minutes per day and an odds ratio of 2.21 for periods of less than 270 minutes per day.

For the different variables related to migration, practically all of them were positively related with measles risks in the age ranges of 6–20 years, 21–24 years, and 25–29 years. When we compared the length of time spent living in the birthplace and the time spent living in the city of São Paulo, we found a positive association with measles risk for more recent migration to the city of São Paulo. Not having been a resident of the state of São Paulo during the mass vaccination campaigns held in May 1987 and June 1992 was also a risk factor.

Among those 1–5 years old, fewer of the variables related to migration were risk factors, probably because those children's migration had been more recent. In this age group there was a positive relation between measles and: 1) not having been born in the city of São Paulo or in the state of São Paulo, 2) having lived in the city of São Paulo for less than 1 year when they had the measles, and 3) being a migrant born in an urban area outside the city of São Paulo and having lived in that birthplace for more than 1 year.

Matched conditional logistic regression analysis

When the matched conditional logistic regression analysis was done for the group younger than 1 year, a positive relation with measles remained for three variables: spending time in semiclosed institutions, no vaccination, and previous contact with a measles-like disease (Table 2).

For the cases and controls in the age group of 1–5 years, the variables that remained as risk factors after the matched conditional logistic regression analysis were: no vaccination, previous contact with a measles-like disease at home, and being a migrant not born in the state of São Paulo.

For those 6–20 years old, the risk factors identified by multivariate analysis were: no vaccination against measles, previous contact with a measles-like disease at home, and the fact that a migrant had remained in the birthplace for 3 years or more.

The logistic regression analysis identified four variables as remaining risk factors for the age group of 21–24 years: no vaccination, being employed, having been born in a rural area, and not living in the state of São Paulo in 1987.

In the last age range analyzed, 25 to 29 years, contact with a measles-like disease on the job and being a male proved to be risk factors after matched conditional logistic regression analysis.

DISCUSSION

The number of susceptible individuals in the population and the rate of contact between susceptible and ill subjects are considered important factors for the occurrence of measles epidemics (5).

The most constant risk factor detected in this survey was the lack of vaccination against measles. The highest odds ratios for this nonvaccination risk factor were observed in infants younger than 1 year and in the age group of 1–5 years. Those two age groups together accounted for 22% (3 904/17 458) of the confirmed measles

TABLE 1. Odds ratios (95% confidence interval) for different age ranges of significant risk factors for measles during the epidemic in the city of São Paulo, Brazil, in 1997, as determined by univariate analysis[a]

Risk factor (Reference odds ratio)	< 1 year	1 to 5 years	6 to 20 years	21 to 24 years	25 to 29 years
Vaccination status (Vaccinated = 1.0)					
Not vaccinated at 9 months of age or later, documented	NS[b]	15.57 (6.38–37.98)	8.17 (13.44–19.43)	24.38 (2.92–203.58)	NS
Not vaccinated at 12 months of age or later, documented	NS	21.41 (8.29–55.90)	8.54 (3.56–20.53)	6.42 (2.20–18.75)	NS
Not vaccinated at 9 months of age or later, verbal and documented	7.19 (2.17–23.80)	14.78 (6.09–35.87)	6.91 (3.01–15.88)	6.25 (2.58–15.15)	NS
Not vaccinated at 12 months of age or later, verbal and documented	NS	19.54 (7.62–50.13)	6.95 (3.01–16.02)	5.78 (2.37–14.08)	NS
Sex (Female = 1.0)					
Male	NS	NS	1.63 (1.01–2.61)	1.60 (1.05–2.46)	5.20 (3.14–8.60)
Previous contact with a measles-like disease (No contact = 1.0)	3.15 (1.84–5.39)	NS	NS	NS	NS
At home	4.78 (1.52–15.05)	6.98 (2.17–22.41)	3.07 (1.24–7.61)	4.24 (1.59–11.31)	4.78 (1.52–15.05)
On the job	NE[c]	NE	NE	NE	14.29 (3.66–55.88)
Spending time in a semiclosed institution (No time there = 1.0)	8.09 (2.72–24.03)	2.12 (1.03–4.38)	0.39 (0.22–0.72)	NS	NS
Using health services (Not using = 1.0)	1.81 (1.05–3.11)	1.48 (1.03–2.12)	NS	NS	NS
Being employed (Not employed = 1.0)	NE	NE	2.37 (1.27–4.45)	2.92 (1.68–5.08)	2.56 (1.52–4.30)
Use of public transportation to go to work (Own transport = 1.0)	NE	NE	NS	NS	1.97 (1.13–3.44)
Time spent in public transportation < 270 min	NE	NE	NS	NS	2.21 (1.31–3.78)
Time spent in public transportation ≥ 270 min	NE	NE	NS	NS	12.72 (3.40–47.56)
Migration (Born in city or state of SP = 1.0)					
Not born in city of SP	NS	3.15 (1.44–6.89)	6.07 (3.11–11.84)	3.51 (2.15–5.74)	2.77 (1.53–5.02)
Not born in state of SP	NS	5.45 (1.96–15.12)	6.26 (3.21–12.21)	4.93 (2.81–8.66)	3.91 (2.18–7.20)
Born in a rural area	NS	NS	NS	3.20 (1.79–5.73)	2.85 (1.55–5.26)
Not living in state of SP in May 1987	NE	NE	5.04 (2.70–9.49)	2.55 (1.64–3.95)	4.31 (2.39–7.76)
Not living in state of SP in June 1992	NE	NE	3.88 (2.09–7.18)	1.58 (1.03–2.42)	2.09 (1.17–3.72)
When had measles, had been residing in city of SP for a period of:	NE	Less than 1 year 10.33 (2.21–48.21)	Less than 4 years 9.39 (4.02–21.96) 4 to 11 years 4.73 (1.98–11.28)	Less than 8 years 4.39 (2.61–7.37)	Less than 12 years 5.56 (2.73–11.31)
Remained in birthplace (outside city of SP) for a period of:	NE	Less than 2 years 2 years 3 to 5 years all NS	3 to 15 years 6.40 (2.65–15.49) 16 years or more 28.50 (7.57–107.31)	4 years or more 4.05 (2.44–6.72)	14 years or more 5.40 (2.66–10.94)
Remained in birthplace (urban area outside city of SP) for a period of:	NE	1 year or more 22.32 (2.83–175.73)	3 to 13 years 6.65 (2.10–21.05) 14 years or more 10.02 (3.35–29.97)	4 years or more NS	14 years or more NS

TABLE 1. (Continued)

Risk factor (Reference odds ratio)	< 1 year	1 to 5 years	6 to 20 years	21 to 24 years	25 to 29 years
Remained in birthplace (rural area outside city of SP) for a period of:	NE	NE	1 to 15 years 7.77 (2.27–26.59) 16 years or more 24.58 (4.96–121.79)	14 years or less NS 15 years or more NS	4 years or less 5 to 11 years 11 years or more All NS
Remained in birthplace (outside state of SP) for a period of:	NE	NE	3 to 15 years 5.24 (2.27–12.06) 16 years or more 25.53 (7.00–93.09)	14 years or less NS 15 years or more NS	10 to 16 years 4.80 (1.99–11.60) 17 years or more 7.08 (3.34–15.06)

[a] Significant at the $P < 0.05$ level.
[b] NS = not significant.
[c] NE = not evaluated.

cases reported from Greater São Paulo whose age was known.

The children in these two younger age ranges were not targeted either in the mass vaccination campaign promoted by the Department of Health of the state of São Paulo in 1987 or in the national campaign of 1992. This finding emphasizes the importance of mass vaccination campaigns for developing countries.

Furthermore, administrative data available from the CES indicate a reduction of routine vaccination coverage against measles among infants younger than 1 year in the period of 1990–1996 in the state of São Paulo. Vaccination coverage, which was 107.6% in 1990, dropped to 95.3% in 1996. (The figure of 107.6% is due to registration errors and/or underestimation of the target population.) The same decline in vaccination coverage must have occurred with respect to the coverage of vaccination at 15 months, since at this age the vaccination coverage is usually lower than that observed at 9 months. These CES data agree with the results of our study, which found that 60% of the children aged 1 to 5 years who had measles in 1997 had not been vaccinated at 12 months of age or later.

Taken together, these data suggest that when adequate vaccination coverage is not achieved with routine measures, periodic mass vaccination campaigns must be considered, especially as part of wider programs of measles elimination in developing countries (6).

The lack of vaccination was an important risk factor even for those age groups targeted by the mass vaccination campaigns of 1987 and 1992. This may have been a consequence of a significant number of São Paulo residents not participating in the campaigns or of the fact that they were persons who were not living in São Paulo at the

TABLE 2. Predictors of the measles epidemic in the city of São Paulo, Brazil, in 1997, determined by matched conditional logistic regression analysis

Age range	Predictor	Case (%)	Control (%)	Odds ratio	95% CI
Younger than 1 year	Not vaccinated at 9 months of age or later (verbal and/or documented information)	97.7	85.3	14.58	3.63–58.53
	Previous contact with a measles-like disease	36.7	18.2	3.73	2.03–6.86
	Spending time in a semiclosed institution	13.7	3.2	14.68	3.37–63.91
1 to 5 years	Not vaccinated at 9 months of age or later (verbal and/or documented information)	47.0	4.7	14.45	5.30–39.38
	Previous contact with a measles-like disease at home	16.8	4.0	4.93	1.21–20.04
	Not born in state of SP	4.0	3.5	19.69	1.10–353.54
6 to 20 years	Not vaccinated at 9 months of age or later (verbal and/or documented information)	36.9	8.4	4.72	1.66–13.41
	Previous contact with a measles-like disease at home	12.5	4.7	5.82	11.94–17.47
	Migrant to state of SP who had remained in birthplace for 3–15 years	19.2	10.2	4.01	1.18–13.54
	Migrant to state of SP who had remained in birthplace for ≥16 years	15.8	3.8	17.65	2.84–109.72
21 to 24 years	Not vaccinated at 9 months or later (verbal and/or documented information)	65.1	56.3	5.73	1.72–19.11
	Employed	82.6	64.2	3.64	1.72–7.72
	Migrant to city of SP born in a rural area	52.3	22.0	3.88	1.84–8.16
	Not living in state of SP in May 1987	71.1	38.3	4.63	1.89–11.35
25 to 29 years	Previous contact with a measles-like disease on the job	13.6	1.6	69.90	10.72–455.78
	Male	71.2	31.9	6.45	3.05–13.64

time of the campaigns, as can be observed in the results for those in the age group of 21–24 years.

Our survey indicated the great importance of migration in the increased incidence of measles in a large urban center. For all the age ranges above 1 year of age, individuals born outside the city of São Paulo or the state of São Paulo showed a greater risk of contracting measles. Additionally, for those in the age group of 21–24 years migration to the state of São Paulo after May 1987 and migration from a rural area to the city of São Paulo proved to be important risk factors for measles.

In comparison to persons living in densely populated cities, unvaccinated individuals residing outside the large urban centers, especially in rural areas, continue to be susceptible to measles when they are older (7, 8). In a study of measles in Senegal, Boue (9) showed that while 100% of the children living in urban areas had antibodies against measles at the age of 18 to 24 months, in rural areas this percentage was reached only at 10 years of age. Transmission of the measles virus usually is low in rural areas during interepidemic periods due to the less frequent contact between susceptible and infected individuals when compared to populations living in large urban areas (7). The less frequent contact in rural areas is due to the dispersion of the population among small communities. Given that, in rural areas measles will occur later in life, frequently during adulthood (8).

When persons who have not been exposed to the measles virus migrate to large urban centers, it increases the pool of susceptible individuals in those cities (7). Additionally, there is a greater likelihood for migrants to be exposed to the etiological agent, especially if we consider the greater concentration and higher occurrence of the disease in urban centers (10). It is also known that the residences of migrants are usually not distributed randomly throughout large cities, but instead tend to be clustered. In the case of measles, some studies indicate that herd immunity is not effective in preventing epidemics since an antibody prevalence against this disease close to 100% does not function as a protective mechanism (11, 12). It is believed that this protection would only be offered if susceptible individuals were distributed at random, something that rarely occurs (12).

Also with respect to adult migrants, an additional question is the high mobility existing in an urban center, with the large number of social contacts that occur increasing the likelihood of measles virus dissemination (13).

The data in our survey suggest that, when planning mass vaccinations, the definition of the age range to be reached should take local conditions into account. Thus, in rural regions the age group targeted by the campaigns should be expanded in order to avoid the creation of large populations of susceptible individuals. In urban areas where mass vaccination campaigns have already been conducted, the identification and vaccination of migrants from rural areas could also help prevent the accumulations of susceptible groups.

The higher measles risk for males aged 25 to 29 years was unexpected. We think that this phenomenon was probably linked to some differential exposure by sex that was not detected by the variables we analyzed.

Another noteworthy finding in our study was that only 27% of the interviewees who had measles reported contact with a similar disease. This percentage is indicative of the difficulty in determining the probable source of contagion of measles, especially in large urban centers.

The data in our survey suggest that, in addition to lack of vaccination, other risk factors should be considered when planning a measles vaccination strategy for a developing country.

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Factores predictivos de la ocurrencia de una epidemia de sarampión en la ciudad de São Paulo en 1997

RESUMEN

Se realizó un estudio de casos y controles apareados para identificar los factores de riesgo de sarampión durante una epidemia que tuvo lugar en 1997 en la ciudad de São Paulo, en el estado brasileño del mismo nombre. Se incluyeron los casos de sarampión ocurridos en esa ciudad entre el 1 de enero y el 15 de agosto de 1997. Los criterios para definir los casos fueron: edad inferior a 30 años, no haber sido vacunado contra el sarampión en los 5–21 días anteriores al inicio del exantema y confirmación mediante la detección de anticuerpos IgM. A partir de un banco de datos de casos confirmados de sarampión, se seleccionaron aleatoriamente 130 casos de cada uno de los siguientes grupos de edad: menores de 1 año, 1 a 5 años, 6 a 20 años, 21 a 24 años y 25 a 29 años; la selección se hizo de acuerdo con un criterio sistemático proporcional al número de casos en siete zonas de la ciudad. Los datos fueron recolectados mediante una encuesta domiciliaria y por cada caso de sarampión se estudiaron dos controles emparejados según la edad y el lugar de residencia. El análisis de regresión logística condicional de los posibles factores de riesgo identificados en el análisis univariado reveló que los factores que mejor predecían la adquisición de la enfermedad durante la epidemia eran: 1) la ausencia de vacunación contra el sarampión; 2) el contacto previo, en casa o en el trabajo, con un caso de enfermedad similar al sarampión; 3) el haber nacido fuera de São Paulo o en una zona rural; 4) el estar empleado, y 5) el pasar parte del día en una institución semicerrada, como una guardería, un centro infantil o una escuela. Los factores de riesgo no fueron homogéneos para los diferentes grupos de edad. Los datos de este estudio indican que, además de la falta de vacunación, habría que considerar otros factores de riesgo a la hora de planificar una estrategia de vacunación contra el sarampión en países en desarrollo.