 International Journal of Epidemiology 1999;**28**:550–557

Fuzzy Logic and measles vaccination: designing a control strategy

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Background The State of São Paulo, the most populous in Brazil, was virtually free of measles from 1987 until the end of 1996 when the number of cases started to rise. It reached alarming numbers in the middle of 1997 and local health authorities decided to implement a mass vaccination campaign.

Methods Fuzzy Decision Making techniques are applied to the design of the vaccination campaign.

Results The mass vaccination strategy chosen changed the natural course of the epidemic. It had a significant impact on the epidemic in the metropolitan area of São Paulo city, but a second epidemic in the State's interior forced the public health authorities to implement a second mass vaccination campaign 2 months after the first.

Conclusions Fuzzy Logic techniques are a powerful tool for the design of control strategies against epidemics of infectious diseases.

Keywords Measles, vaccination, fuzzy decision making, control strategies

Accepted 10 November 1998

Since the end of the 1960s progress in immunology has resulted in effective vaccines against many directly transmitted infections like measles, rubella, mumps, pertussis, meningitis of some serotypes and, more recently, haemophilus.

In Brazil some of these vaccines are already part of the immunization calendar, in particular, the measles vaccine. Due to its morbidity and mortality, measles has always been considered one of the main public heath problems around the world: in particular in the State of São Paulo, which has the greatest density of population in Brazil, with urban centres, like São Paulo City metropolitan area, housing millions of inhabitants.

In spite of efforts to control measles infections in São Paulo since the introduction of the specific vaccine in 1973, up to 1986 recurrent epidemics still caused great concern. Difficulties in attaining high coverage levels, several changes in the immunization regime, problems with the cold chain and the difficulties of reaching specific subpopulations at risk lead the Health Secretary of the State of São Paulo to implement a new strategy: between May and June 1987 all children <15 years received a single shot of measles vaccine, regardless of previous vaccination or natural infection. This mass vaccination campaign, followed by a strengthening in the routine vaccination and surveillance system, resulted in a 90% reduction in measles incidence in the State of São Paulo shortly afterwards. Subsequently, however, a significant drop in routine coverage resulted in an accumulation of susceptibles which triggered an epidemic of almost 24 000 cases in 1997. In order to control this epidemic, the public health authorities in the State of São Paulo decided to carry out a mass vaccination campaign.

This paper describes the application (for the first time to the best of our knowledge) of Fuzzy Logic concepts in choosing the best vaccination strategy from eight possible ones. A detailed description of this measles epidemic will be presented in a separate work.

Essentials of Fuzzy Logic

Fuzzy Logic is a superset of conventional (Boolean) logic that has been developed to handle the concept of partial truth-truth values between 'completely true' and 'completely false'. It may be considered a powerful tool for dealing with imprecision, uncertainty and partial truth aiming at tractability, robustness and low-cost solutions for real-world problems.

Fuzzy Logic was formally established by Lotf Zadeh, in 1965, with the introduction of the concept of *membership degree*, according to which a set could have elements that belong partially to it. In this way, if one assumes that X is the Universe set, the Fuzzy subset A of the X has a characteristic function associated to it:

$$\mu_A : X \rightarrow [0,1] \qquad (1)$$

that is generally called membership function.[1] The idea is that, for each $x \in X$, $\mu_A(x)$ indicates the degree to which x belongs to the fuzzy subset A.

In this sense, Fuzzy Logic differs from Crisp Logic (i.e. classical binary logic) basically for allowing that its statements assume other values besides *false* and *true*. Therefore, Fuzzy Logic concerns

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a logical system which is much closer in spirit to human thinking and natural languages than the traditional logic system.

First, the original theory of fuzzy sets was formulated in terms of the following specific operators of sets: *union, intersection* and *complement*.[2–5] These set theoretic operations for fuzzy sets are defined via their membership functions and mathematical operations like *max* (maximum) and *min* (minimum). In accordance with this, if A and B are two fuzzy sets, the membership function $\mu_{A \cup B}$ of the *Union* $A \cup B$ is defined for all $u \in U$ by

$$\mu_{A \cup B}(u) = \max\{\mu_A(u), \mu_B(u)\} \tag{2}$$

The membership function $\mu_{A \cap B}$ of the *Intersection* $A \cap B$ is defined for all $u \in U$ by

$$\mu_{A \cap B}(u) = \min\{\mu_A(u), \mu_B(u)\} \tag{3}$$

Finally, the membership function $\mu_{\bar{A}}$ of the *Complement* of a fuzzy set A is defined for all $u \in U$ by

$$\mu_{\bar{A}}(u) = 1 - \mu_A(u) \tag{4}$$

Fuzzy Logic in medicine

Nowhere in the field of science is the need for tools to deal with uncertainty more critical than in medicine and biology. Disease diagnosis involves several levels of imprecision and uncertainty, particularly in epidemiological studies. A single disease may manifest itself quite differently in different patients and with different disease status. Further, a single symptom may be indicative of different diseases, and the presence of several diseases in a single patient may disrupt the expected symptom pattern of any of them. This may cause a tremendous amount of imprecision and uncertainty in the interpretation of effect measures in analysis. Also, the best and most helpful descriptions of disease entities often use linguistic terms that are inevitably vague.

In spite of its potential in dealing with uncertainties, very few works applying Fuzzy Logic concepts in epidemiological problems has been presented so far.[6, 7]

Fuzzy Decision Making

Making a decision is one of the most fundamental activities of human beings.[2,5,8] This is particularly true in public health where decisions usually have relevance for millions of people. In the field of vaccination strategy design, decision making concerning the target population for the immunization programme, the proportion of susceptibles to be vaccinated, the optimal age at which to immunize children and the nature of the strategy, e.g. selective or indiscriminate, are examples of the variables to be optimized, subject to a set of constraints.

The subject of decision making is the study of how decisions are actually made and how they can be made better or more successfully.[2] Models of human decision making generally include the aggregation criteria or criteria of constraints.[9] For the case that criteria and/or constraints cannot be modelled crisply but as fuzzy sets a decision has been defined by Bellman and Zadeh[10] as the intersection of fuzzy sets representing either objectives or constraints. The grade of membership of an object in the intersection of two fuzzy sets, that is, the 'fuzzy set decision' was determined by the use of both the *min* (minimum) operator or the *product* operator.[9]

While decision making under conditions of risk has been modelled by probabilistic decision theories and game theories, fuzzy decision theories attempt to deal with vagueness and monospecificity inherent in human formulation of preferences, constraints and goals.[2]

In their first paper on Fuzzy Decision Making, Bellman and Zadeh[10] suggest a fuzzy model of decision making in which relevant goals and constraints are expressed in terms of fuzzy sets, and a decision is determined by an appropriate aggregation of these fuzzy sets. The decision models have the following components.[2]

a set A of *possible actions*;

a set of *goals*, $G_i (i \in \mathbf{N})$, each of which is expressed in terms of a fuzzy set defined on A;

a set of *constraints*, $C_j (j \in \mathbf{M})$, each of which is also expressed in terms of a fuzzy set defined on A.

The fuzzy set of decision, D, is that which simultaneously satisfies the given goals G_i and constraints C_j, and is:

$$D(a) = \min\left[\inf_{i \in \mathbf{N}} G_i(a), \inf_{j \in \mathbf{M}} C_j(a),\right]$$

for all $a \in A$.

Designing the vaccination strategy

We assume the objective of a vaccination campaign to be the reduction in measles infection of children under 14 years; the age interval where the measles virus is most likely to be circulating. This assumption is based on previous works which demonstrated that the force of infection of the measles virus has a strong age-dependence, peaking around 2 years of age in the absence of vaccination.[11] Therefore, in spite of the high proportion of cases aged 20–39 years, the highest incidence rate (normalized per 100 000 inhabitants) observed during the epidemic occurred in children under 5 years. In addition, contact patterns suggest that adult cases are the product of infective contacts of susceptible individuals in that age group with children under 14 years[12] the target age interval of the vaccination campaign. All subsequent analysis in this work is based on these assumptions.

We begin by considering eight possible vaccination strategies, comprised of combinations of selective vaccinations, (S_i), meaning vaccinating only children without past vaccination records, and indiscriminate vaccination, (I_j), i.e. vaccinating children irrespective of previous immunization history (i and j stand for the age intervals). Besides, we considered the use of mobile units (*MU*), meaning those vaccination sites that are not part of the primary care network, as opposed to fixed units (*FU*), those belonging to the network. Table 1 shows the various vaccination strategies considered.

The number of children, as well as the estimated proportion and number of susceptible children (assuming the sero-epidemiological profile of 1994 and the drop in the routine measles vaccine coverage discussed above) in each age interval of São Paulo State are shown in Table 2.

The last column of Table 2 is the maximum theoretical number of children to be vaccinated in each age group in order to

Table 1 Possible vaccination strategies

1.	$S_{9m–6y}–I_{6y–14y,\ MU+FU}$
2.	$S_{9m–6y}–I_{6y–14y,\ FU}$
3.	$S_{9m–14y,\ MU+FU}$
4.	$S_{6y–14y}–I_{9m–6y,\ MU+FU}$
5.	$I_{9m–14y,\ MU+FU}$
6.	$S_{9m–6y,\ FU}$
7.	$S_{9m–6y,\ MU+FU}$
8.	$I_{9m–6y,\ MU+FU}$

Table 2 Number, proportion of susceptible and number of susceptible children in the target age interval

Age	No. children[a]	Proportion susceptibles[b]	No. susceptibles
9 months	49 500	0.65	32 175
10 months	49 500	0.50	24 750
11 months	49 500	0.50	24 750
12 months	49 500	0.50	24 750
1–2 years	640 609	0.10	64 061
3–5 years	2 515 711	0.05	125 786
6–14 years	5 920 000	0.05	296 000
Total	9 274 331	–	592 272

[a] Estimated from official data.

[b] Estimated by dynamic modelling.[12]

stop the progression of current epidemics. The optimal strategy, therefore, would be that which maximizes the number of susceptible children vaccinated in the target age group without wasting resources by over-vaccinating children in any specific age group.

The next step was to invite a number of experts in vaccination campaigns from the Health Secretariat in São Paulo to provide a scale of efficacy and/or constraints for each of the possible strategies considered. The variables chosen by this expert team were: (a) *compliance* by the population, i.e. the proportion of the target population expected to comply with each strategy; (b) *human resources*, a relative scale of the staff required (including training) for the implementation of each strategy; (c) *transportation*, a relative scale of the difficulties in transporting people and materials for each strategy; and (d) *communication*, a relative scale of the difficulties of explaining to the population each possible campaign.

The minimum value of each of the variables will be that which determines the success of the strategy. The results of this expert consultation are presented in Table 3.

Values provided by the experts can be considered either as a proportion of the expected success of each strategy or as degrees of membership of the fuzzy sets of successful strategies. In both views the *min* (minimum) operator is the one which determines the expected results of each strategy. In addition, the *max* operator could be applied at this stage of the analysis if we consider the variables presented in Table 3 as the only constraint of the strategies. According to this method, the strategy which maximizes the success of the campaign would be strategy number 6.

The *minimum* values of the variables presented in Table 3 allowed us to estimate the expected number of children in each age group that would be vaccinated in each of the possible strategies. So, for instance, strategy number one is limited by the transport of people and materials and would therefore cover only 20% of the target population. As that strategy proposed vaccinating children selectively from 9 months to 6 years old and indiscriminately from 6 to 14 years only 20% of the susceptibles <6 years and 20% of all children aged 6–14 years would receive the vaccine. The minimum square of the difference between the number of children required to receive the vaccine and the number of children that the strategy would actually vaccinate in each age group would determine the efficacy of each possible strategy, according to the definition of optimal strategy, as presented above.

A normalized scale of the efficacy of each strategy is shown in Table 4. This was obtained by assuming that the most efficacious strategy is the one with the minimum square difference assigned value 1. The others are obtained as a relative scale based on multiples of the minimum square difference. Table 4 also shows the result of the economic costs of each strategy. This was calculated assuming a unit cost of US\$0.25 for the single measles vaccine, US\$1.40 for the measles-mumps-rubella (MMR) vaccine (given only to children over one year) and a unit cost of US\$0.75 for the administration of the vaccines. So, the economic cost of each strategy is obtained by the sum of the vaccine and administration unit costs times the total number of doses of each vaccine used (measles and MMR).

The next step in the analysis is to compare the two constraints on the success of each strategy, namely, those relative to the technical constraints (compliance, human resources, transportation and communication) and those relative to costs. For this we took the minimum between the minimum of the variables presented by the experts (last column of Table 3) and

Table 3 Variables determinants of strategy success

Strategy	Compliance	Human resources	Transport	Communication	Min[a]
1.	0.30	0.30	0.20	0.30	0.20
2.	0.45	0.60	1.00	0.50	0.45
3.	0.70	0.50	0.30	0.40	0.30
4.	0.40	0.40	0.30	0.40	0.30
5.	0.80	0.20	0.20	0.80	0.20
6.	0.60	1.00	1.00	0.70	0.60
7.	0.50	0.60	0.60	0.60	0.50
8.	1.00	0.70	0.40	1.00	0.40

[a] Minimum.

Table 4 A comparative scale of relative efficacies and economic costs for each strategy

Strategy	No. vaccinated	Relative efficacy	Economic costs (US$)	Relative costs
1.	1 243 254	0.049	3 178 223[a]	0.533
2.	2 797 322	0.098	5 959 168[a]	1.000
3.	177 682	1.000	414 359	0.070
4.	1 095 099	0.127	2 743 384[a]	0.460
5.	1 854 866	0.045	4 730 907[a]	0.794
6.	177 763	0.770	308 758	0.052
7.	148 136	0.761	370 509[a]	0.062
8.	1 341 732	0.147	3 352 374	0.563

[a] Additional cost of 20% for mobile units.

Table 5 Degree of membership of technical and cost constraings for each strategy

Strategy	Technical constraints	Cost constraints[a]	Min[b]
1.	0.20	0.467	0.20
2.	0.45	0.000	0.00
3.	0.30	0.930	0.30
4.	0.30	0.540	0.30
5.	0.20	0.206	0.20
6.	0.60	0.948	0.60
7.	0.50	0.938	0.50
8.	0.40	0.437	0.40

[a] Complement of column 5 of Table 4.
[b] Minimum.

the complement to the relative costs scale so that both scales are in the same constraint direction, such that their minimum values represent the maximum constraint, as shown in Table 5:

Now we have all the components of the decision model:

a set A of *possible actions*: the eight possible strategies

a set of '*goals*'*, $G_i(i \in \mathbf{N})$ defined on A: the relative efficacy of each possible strategy (third column of Table 4);

a set of *constraints* $C_j(j \in \mathbf{M})$, defined on A: the minimum between the technical and costs constraints (last column of Table 5).

The fuzzy decision, D, that simultaneously satisfies the given goals G_i and constraints C_j, is then:

$$D(a) = \min\ [G_i(a), C_j(a),] \tag{6}$$

for all $a \in A$, that is as shown in Table 6.

Therefore, the strategy that has the maximum degree of membership in the set of decision is strategy number 6, which selectively vaccinates children aged 9 months to 6 years, using only fixed units of the heath system. This strategy was then recommended to São Paulo public health authorities.

* By 'goal' (this is the jargon in fuzzy optimal control theory) we mean the achievable efficacy of each possible strategy and not the major goal of controlling the epidemic.

Table 6 Fuzzy decision setting

Strategy	$G_i(a)$	$C_j(a)$	$D(a)$
1.	0.049	0.200	0.049
2.	0.098	0.000	0.000
3.	1.000	0.300	0.300
4.	0.127	0.300	0.127
5.	0.045	0.200	0.045
6.	0.770	0.600	0.600
7.	0.761	0.500	0.500
8.	0.147	0.400	0.147

Table 7 Age-related incidence rates per 100 000 inhabitants

Age (years)	São Paulo city	State countryside	Total
<1	871.50	94.17	482.84
1–4	115.99	15.32	65.65
5–9	61.21	13.13	37.17
10–14	36.17	5.93	21.05
15–19	67.27	11.34	39.31
20–29	314.30	29.85	172.08
30–44	56.52	7.54	32.03

The measles epidemic in São Paulo

In São Paulo State, routine measles vaccination started in 1973. In spite of this, recurrent epidemics continued to occur until 1987, when the first mass vaccination campaign against measles was carried out. This reduced the average incidence rate to around 0.1 per 100 000 inhabitants; a level which persisted until the end of September 1996, by which time the number of measles cases notified to São Paulo health authorities had started to rise. After March 1997, the number of new cases started an exponential trend, characterizing the beginning of a new epidemic, reaching a total of 23 195 confirmed cases after one year, with 23 deaths. Regarding the age profile of the epidemic, it is noteworthy that 47% of the cases occurred in young adults aged 20–29 years. The second age group most frequently involved (15%) was that of children under one year who also showed the highest incidence rate per 100 000 inhabitants (Table 7).

The second highest incidence rates occurred in young adults at a time which corresponds to the age at which adults have greatest contact with young children. Those adults probably represent the parents of the children with the highest attack rates.

Figure 1 shows the epidemic wave in São Paulo State (bold continuous line), in the interior of the State (broken line) and in the City of São Paulo (dashed line), during the year of 1997.

The impact of the vaccination campaign

On 21 June 1987 the proposed vaccination strategy was implemented in the State of São Paulo. A total of 213 084 doses were given to children aged 9 months to 6 years. This figure represents a coverage of 6.5% of the entire population of the

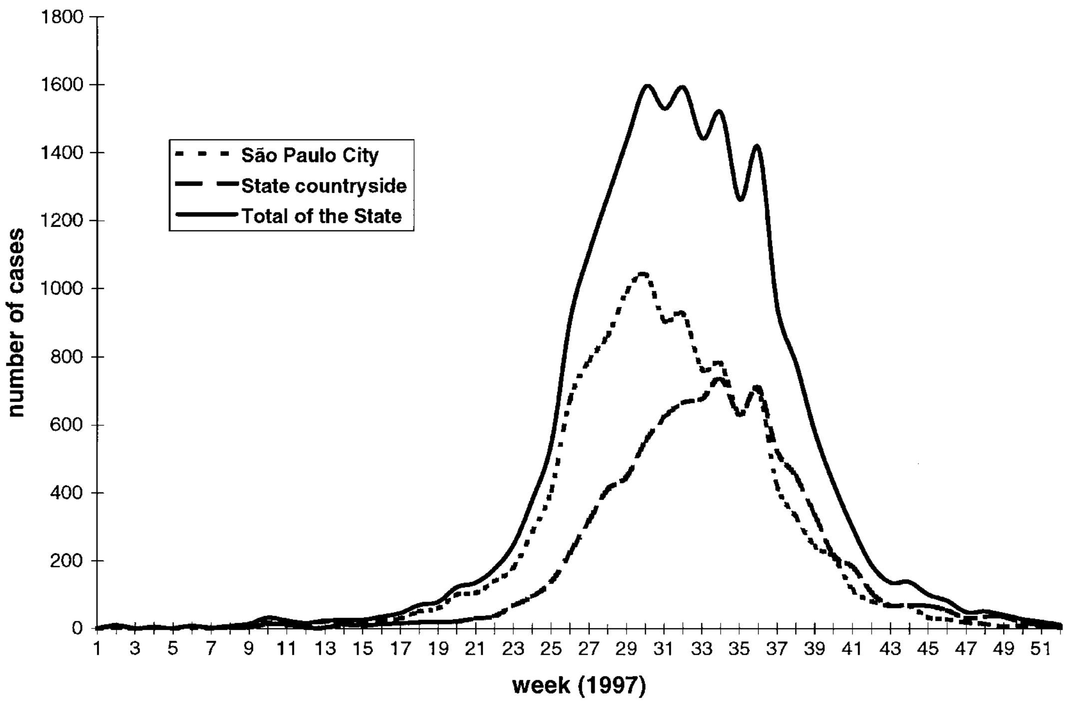

Figure 1 Number of measles cases, by administrative region of the State of São Paulo, by epidemiological week, 1997

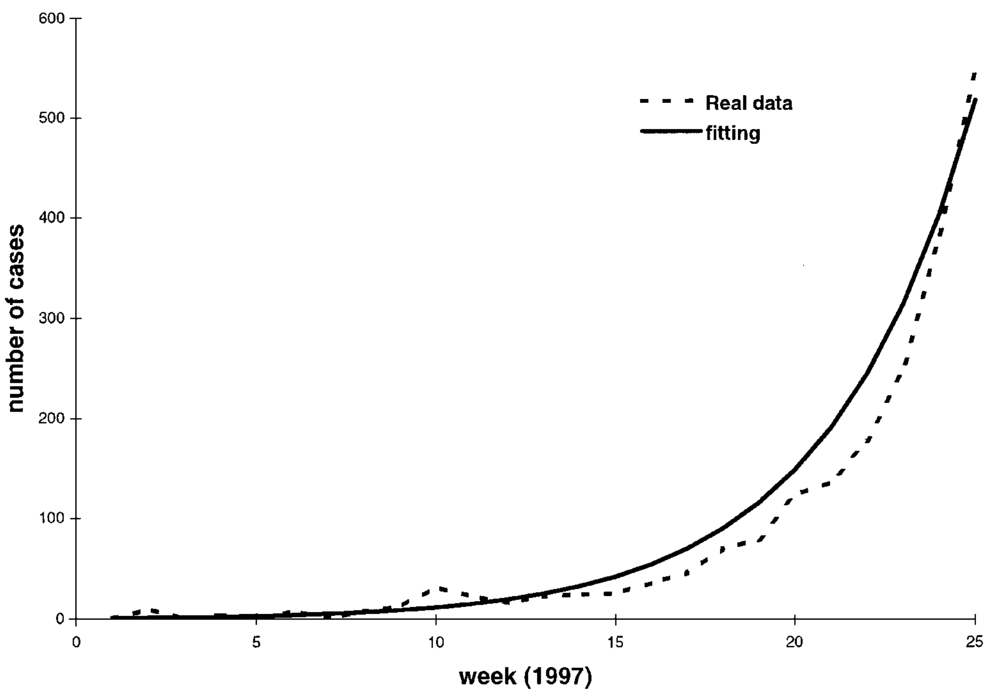

Figure 2 Fitting of the initial phase of the epidemic, up to the first vaccination (week 25)

State of São Paulo in the target age group (7.5% in the metropolitan region of São Paulo city, 5.1% in the interior of the State). There are no official data on the efficacy of the selection process, i.e. it is not known whether the small proportion of children vaccinated were those previously unvaccinated or not.

In order to estimate the natural course of the epidemic we first fitted a continuous function to the initial phase of the actual epidemic up to the week prior to the first intervention. As expected, it resulted in an exponential curve, with a positive growth rate of 0.25/week. Figure 2 shows the result of this fitting.

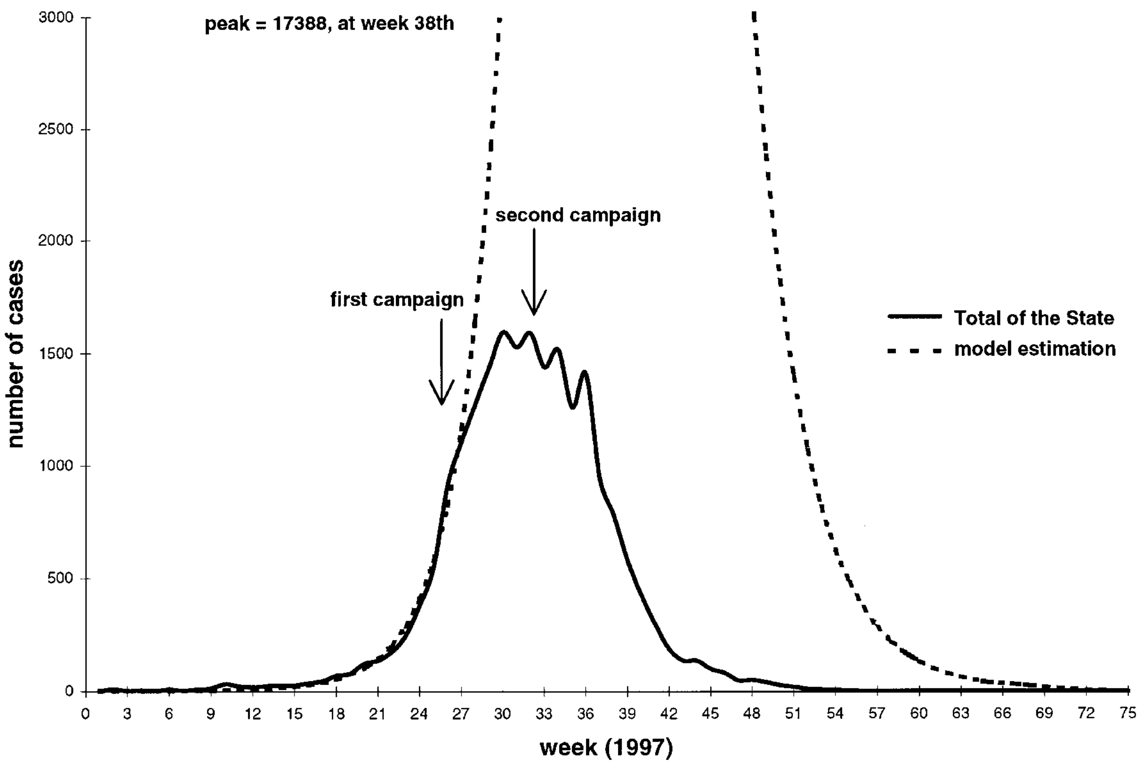

Figure 3 Actual epidemic curve compared to the estimation from the model

Next, we calculated the effective contact rate, β; a composite rate describing the probability of contact between susceptible and infected individuals and the probability that such a contact would result in a new case. This was done by assuming that the number of new infections, $y(t)$, increases exponentially (as seen in Figure 2) according to:

$$y(t) = y(0)\ \exp\{[\beta\bar{x} - (\mu + \gamma)]t\} \tag{7}$$

where $\bar{x}$ is the expected proportion of susceptibles, assumed to be equal to 10%; μ is the natural mortality rate of the population, assumed to be equal to 0.0003/week and γ is the inverse of the infectiousness period of measles, assumed to be equal to one week. The term between square brackets resulted in a value of β equal to 12.5/week.

Those parameters then fed a dynamic system of the classical SIR type, in order to retrieve the natural course of the epidemic in the absence of vaccination. The model had the form:

$$\begin{aligned} \frac{dx(t)}{dt} &= \mu[y(t) + z(t)] - \beta x(t)y(t) \\ \frac{dy(t)}{dt} &= \beta x(t)y(t) - (\mu + \gamma)y(t) \\ \frac{dz(t)}{dt} &= \gamma y(t) - \mu z(t) \end{aligned} \tag{8}$$

where $z(t)$ represents recovered (immune) individuals. The result of the simulation, with initial conditions $x(0) = 0.1$; $y(0) = 10^{-7}$ and $z(0) \cong 0.9$, with the actual epidemic underlying, can be seen in Figure 3.

As can be seen in Figure 3, the expected number of cases simulated by the model above would peak at around 17 500 cases at the 38th week, totalling almost 300 000 cases. This would represent an attack rate of around 8% of the susceptible population, a figure which is in the lower bound for other measles epidemics reported in the literature.[13–15] Also noteworthy in Figure 3 is the striking concordance between the simulated curve and the actual epidemic until week 25. At this point, there is a significant deflection of the exponential trend of the epidemic curve, which occurred just after the first intervention.

By comparing the expected (simulated) number of cases with that seen in the actual epidemic we may conclude that the proposed vaccination strategy (carried out at week 25) had a significant impact on the epidemic in the city of São Paulo. However, as can be seen from Figure 1, the number of cases in the interior of the State continued to rise after the first campaign, peaking around 10 weeks later. Possible causes for this will be discussed later. The health authorities then decided to carry out a second campaign which differed from the first one by the virtual absence of cost constraint considerations. Strategy number eight, therefore, was the best choice available, because it has the highest compliance, and it was implemented on 16 August (week 33). The total number of cases dropped significantly in all age groups and in the whole State soon after the second vaccination and the epidemic was then considered controlled.

Discussion

In spite of a 95% efficient vaccine which has been available for more than 25 years, measles still remains an important public health problem, killing more than one million children every year in developing regions[16] and with a *Disability-Adjusted Life-Years* (DALY) measure of 36.5×10^6, which is even higher than malaria (31.7×10^6) for the same regions.[16] As an easily transmissible infection with a Basic Reproduction Number[11] usually above 15, it demands very high levels of vaccine coverage (over 93%) in order to be eliminated. However, these levels of coverage are rarely maintained in routine schemes of immunization. Therefore, it is a usual control strategy, at least in developing countries, to carry out mass vaccination campaigns from time to time. In fact, this occurred in the State of São Paulo in 1987 and again in 1992, with a significant impact on measles incidence.

It is common to observe a severe drop in cases shortly after a mass vaccination campaign. As time passes, however, the residual fraction of non-responders to the vaccine and immigration of susceptible individuals from other areas of the country, start to accumulate in the population. This fact allied to the marked drop in coverage levels in the immunization routine observed in the last 2 years in the State of São Paulo, may explain the 1997 epidemic.

A subject of hot debate among public health authors, periodic mass vaccination has been considered an effective way to control measles epidemics.[17] The design of such a vaccination strategy is based on the rate of replenishment of susceptibles in the population following vaccination. When mass vaccination is intended to supplement an existing regime (as is the case in São Paulo State), the rationale is as follows:[17] the replenishment of susceptibles equals the birth rate, $1/L$ (as in other works, L denotes the population life expectancy), reduced by a fraction $(1 - p)$, where p is the proportion of newborn effectively vaccinated in the routine schedule. If we denote the proportion of children vaccinated in the campaign as p', then the interval, T_v, between two successive campaigns is given by

$$T_v = \frac{p'A}{(1 - p)}$$

where A is the average age of the first infection.

In very populous countries like Brazil and, in particular, in regions like the State of São Paulo, where mass vaccination campaigns aim to cover millions of individuals, any reasonable estimate of the minimum number to be vaccinated could represent savings of millions of dollars of public money.

When the São Paulo epidemic was detected and a vaccination campaign proposed, very few data were available which allowed the application of dynamic modelling (a more structured approach) to the design of the optimal vaccination schedule.[12] Moreover, the dynamics of a measles epidemic shortly after an intervention such as a mass vaccination campaign have been poorly documented in the literature. So, it would be very difficult to predict the impact of the intervention on the course of the epidemic. In addition, an important constraint was imposed—the total number of doses available was limited to only 300 000. This scenario encouraged us to attempt, for the first time (to the best of our knowledge), the use of Fuzzy Logic concepts to design the vaccination campaign.

The capacity of the Fuzzy Decision Model to predict the number of children that could be reached by the vaccination strategy can be evaluated by contrasting this number (177 763, which corresponds to 60% [Tables 3 and 4] of the susceptibles in the targeted population) with the actual number of children who received the vaccine (213 084, which corresponds to 72% of the susceptibles in the targeted population). Therefore, the fuzzy model prediction of the number of children that should be vaccinated has an accuracy of more than 80%. As a result the efficacy of the strategy was significant, at least for the metropolitan region of São Paulo city (Figure 1), notwithstanding the minor impact seen in the rest of the State. A possible explanation for this could be the inadequacy of the selectiveness criteria adopted (to vaccinate only previously unvaccinated children). As a matter of fact, another uncertainty, not forecasted by the initial model, was the decision of the public health authorities to extend the measles campaign to include other vaccines like diphtheria-pertussis-tetanus (DPT). However, shortly after midday on 21 June the DPT vaccine ran out, which probably demotivated the population. The latter argument is intended only as an example of how the unexpected can influence the final result of such a complex endeavour like a mass vaccination campaign.

In conclusion, we think that the Fuzzy Logic approach for designing the control strategy against the recent measles epidemic in São Paulo was very useful in the sense that it allowed the combination of intuitive information from public health experts and cost constraints into a coherent model. Moreover it proved to be very effective, in the sense that the strategy adopted resulted in significant control of the epidemic.

Our results, notwithstanding several intervening factors outside our control during the implementation of the proposed strategy, are very encouraging in demonstrating the potential of new techniques for the design of interventions in public health.

Acknowledgements

This work was partly supported by the grant PRONEX 4196093700. The authors are grateful to the experts who collaborate in the designing of the possible strategies.

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