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Cost–benefit analysis of tetanus prophylaxis by a mathematical model

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SUMMARY

A mathematical model has been developed which allows estimation of the epidemiological and economic effects of different tetanus vaccination strategies. The model was used to simulate the epidemiology of tetanus in Italy from 1955 to 1982, and then applied to a district of Tuscany by utilizing data obtained from a seroepidemiological survey carried out in the same area. For this district we simulated vaccination programmes designed to reach, within 1 or 10 years, coverages of 60 or 90% of the population aged over 10 years who had not been exposed to the neonatal vaccination programme. The most effective strategy, from both the epidemiological and economic point of view, seems to be 90% coverage reached in 1 year's time. Benefits would be increased by improving the reliability of vaccinal anamnesis.

INTRODUCTION

Tetanus in Italy does not represent a major cause of death as in developing countries, but is nevertheless the cause of significant mortality. As the disease can be prevented by vaccination, it is unacceptable that 200 reported cases (with 150 deaths) per year should still occur (Ribero, Tagger & Fara, 1983). Undoubtedly, the compulsory vaccination programme of newborns begun in 1968 has greatly reduced tetanus incidence, but older people, and especially the women who have not been vaccinated during military service, remain at risk. It is urgent, therefore, to vaccinate the whole population. This measure would also be economically advantageous because it would curb the use of passive immunoprophylaxis, which is far more expensive and confers only short-lasting protection.

Mathematical models can be employed to assess the potential impact of preventive measures (Bailey, 1975; Anderson, 1982). Cvjetanovic, Grab & Uemura (1978) constructed a mathematical model to simulate tetanus epidemiology in developing countries: in such model, however, great importance was given to neonatal tetanus, the incidence of which is high in such countries, and the weight of serum prophylaxis was not considered. In Italy, on the contrary, neonatal tetanus is extremely rare and immunoglobulin prophylaxis largely used. The model we have developed takes these important differences into account (Carducci *et al.* 1986).

METHODS

Mathematical formulation

In the technique of modelling used by Cvjetanovic, Grab & Uemura (1978), the population was grouped into five classes on the basis of tetanus epidemiology characteristics, namely susceptibility, sickness, death from tetanus, active immunity and passive immunity. In addition, since tetanus incidence in Italy varies considerably in different age groups (Ribero, Tagger & Fara, 1983), we considered eight 10-year age classes. The possible flows from an epidemiological class to another are presented in Fig. 1. In the model it is also necessary to consider the entry of newborns, the exit of people dying from other causes and the transfer from a given age class to the following one. In order to reduce the complexity of the model we have neglected neonatal tetanus which is almost absent in Italy and children were considered to enter into the population at 3 months of age, that is at the time compulsory vaccination is initiated. Such flows are regulated by several parameters (Table 1) which express the probability that an individual moves from one class to another and are calculated using available information on the natural history of the disease (Gottlieb *et al.* 1964; Germanier, 1984; Smith, 1985) or health statistics (ISTAT 1955–82; Covarelli & Marconi, 1980); unfortunately, these data are quite often imprecise. The parameter that indicates the probability of passage from the susceptibility class to the sickness class (called 'force of infection') is particularly difficult to calculate: it depends on climatic, environmental, economic, social, sanitary and individual factors, which are often difficult to quantitate. In the case of tetanus, which is not transmitted from man to man, the force of infection is directly related to the incidence of the disease in the absence of artificial immunization.

The flows among the epidemiological classes are mathematically represented by a system of differential equations (Table 2), which express the time-related changes of the classes. For solving the equations, the time differentials were transformed into finite differences, choosing a relatively short time unit (a month) as compared with the time needed to detect variations in the epidemiological dynamics of tetanus.

The equations are solved by the iterative method and, since our model is deterministic, it tends to stabilize after a certain number of iterations, reaching a stationary situation of stable endemicity in which the variations of every epidemiological class are null. Initially, the age-specific forces of infection were roughly estimated on the basis of the tetanus age-specific incidences and used to solve the equations. Calculated age-specific incidences were compared with real ones and the results of such comparison were used to correct the age-specific forces of infection to reach a new stable endemicity more similar to the real situation. This trial-and-error procedure was repeated until the stable endemicity corresponding as closely as possible to the real situation was reached. Starting from this, it was possible to predict the effects of various immunization programmes for different coverages. Knowing the costs of treating patients and of active and passive immunoprophylaxis procedures, it was also possible to evaluate the cost/benefit balance.

An appropriate computer program was written in Basic for the Olivetti personal computer M24, to proceed to the iterative solution of the equations.

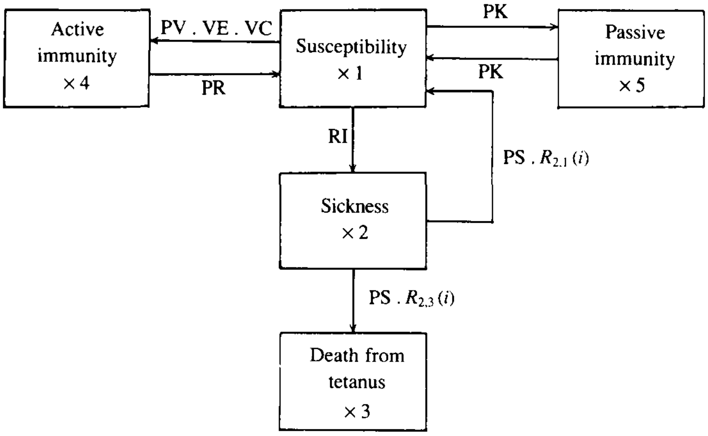

Fig. 1. Flow-chart of the epidemiology of tetanus in developed countries.

Table 1. *Symbols used in the mathematical model*

Symbol	Meaning	Calculated from	Reference
xT(*i*)	Population in the age class *i*	—	ISTAT (1955–82)
PB	Monthly birth-rate	Annual birth-rate	ISTAT (1955–82)
PD(*i*)	Monthly age-specific death-rates	Annual age-specific death rate	ISTAT (1955–82)
PA(*i*)	Month flow-rates from each age class the following one	PB, PD(*i*) and population at the age *i*	ISTAT (1955–82)
PR	Monthly probability of exit from the class of active immunity	Duration of active immunity (10 years)	Gottlieb (1964) Germanier (1984) Smith (1985)
PI	Monthly probability of exit from the class of passive immunity	Duration of passive immunity (2 months)	Smith (1985)
PS	Monthly probability of exit from the sickness class	Duration of illness (1 month)	Hospital data
$R_{2.3}(i)$	Tetanus age-specific fatality rates	Average of the years 1955–78	ISTAT (1955–78)
$R_{2.1}(i)$	Age-specific recovery rates	$1-R_{2.3}(i)$	ISTAT (1955–78)
PK	Monthly probability of immunoglobulins administration	Annual rates of Ig administration: 5% for Italy 7% for the considered district	Covarelli (1980) Carducci (1987)
RI(*i*)	Age-specific forces of infection	Age-specific incidences	ISTAT (1955–82)
VE	Vaccine effectiveness	99·9%	Smith (1985)
VC(*i*)	Age-specific vaccination coverages	98% for newborns simulated for the others	Bistoni (1978), Pellegrini (1985)
PV	Monthly probability of vaccination	Simulated	
$R_{4.1}(i)$	Age-specific fractions of vaccinated subjects that do not have ten years boosters	Simulated	

Table 2. *Equations of the mathematical model*

Terms of the equations	Meaning
Class of susceptibility	Exit
$\Delta x_1(i) = -x_1(i).\mathrm{RI}(i)$	Infection
$-x_1(i).\mathrm{VE}.\mathrm{VC}(i)\mathrm{PV}$	Vaccination
$-x_1(i).\mathrm{PK}$	Immunoglobulin prophylaxis
$-x_1(i).[\mathrm{PD}(i)-\Delta x_3(i)/x\mathrm{T}(i)+\mathrm{PA}(i)]$	* Death from other cases or exit towards the following age class
	Entry
$\Delta x_1(i) = +x_4(i).\mathrm{PR}.R_{4,1}(i)$	Loss of active immunity
$+x_5(i).\mathrm{PI}$	Loss of passive immunity
$+x_2(i).\mathrm{PS}.R_{2,1}(i)$	Recovery
$+x_1(i-1).\mathrm{PA}(i-1)$	† Entry from the previous age class
Class of sickness	Exit
$\Delta x_2(i) = -x_2(i).\mathrm{PS}$	Recovery or death from tetanus
$-x_2(i).[\mathrm{PD}(i)-\Delta x_3(i)/x\mathrm{T}(i)+\mathrm{PA}(i)$	Idem*
	Entry
$+x_1(i).\mathrm{RI}(i)$	Infection
$+x_2(i-1).\mathrm{PA}(i-1)$	Idem†
Class of death from tetanus	Entry
$\Delta x_3(i) = +x_2(i).\mathrm{PS}.R_{2,3}(i)$	Death from tetanus
Class of active immunity	Exit
$\Delta x_4(i) = -x_4(i).\mathrm{PR}.R_{4,1}(i)$	Loss of active immunity
$-x_4(i).[\mathrm{PD}(i)-\Delta x_3(i)/xT(i)+\mathrm{PA}(i)]$	Idem*
	Entry
$+x_1(i).\mathrm{VE}.\mathrm{VC}(i).\mathrm{PV}$	Vaccination
$+x_4(i-1).\mathrm{PA}(i-1)$	Idem†
Class of passive immunity	Exit
$\Delta x_5(i) = -x_5(i).\mathrm{PI}$	Loss of passive immunity
$-x_5(i).[\mathrm{PD}(i)-\Delta x_3(i)/x\mathrm{T}(i)+\mathrm{PA}(i)]$	Idem*
	Entry
$+x_1(i).\mathrm{PK}$	Immunoglobulin prophylaxis
$+x_5(i-1).\mathrm{PA}(i-1)$	Idem†

RESULTS

Validation of the model

The model was used to simulate the evolution of tetanus incidence in Italy from 1955 to 1982. We considered a population with the same age structure and mean birth rate and age-specific mortality rates of the Italian population during such period (ISTAT, 1955–82). Initially, the model was adapted to a stable endemicity situation corresponding to the one present in Italy in the 1950s, as obtained from ISTAT (1955–82) and other published data (Ribero, Tagger & Fara, 1983).

Using such data, the development of tetanus incidence in Italy from 1955–82 was simulated taking into account the immunization measures started in 1963 (compulsory vaccination of high-risk workers) and 1968 (vaccination of all newborns). Reported and simulated incidences are shown in Fig. 2; there is an excellent agreement between the two curves (Wilcoxon test). Fig. 3 presents both

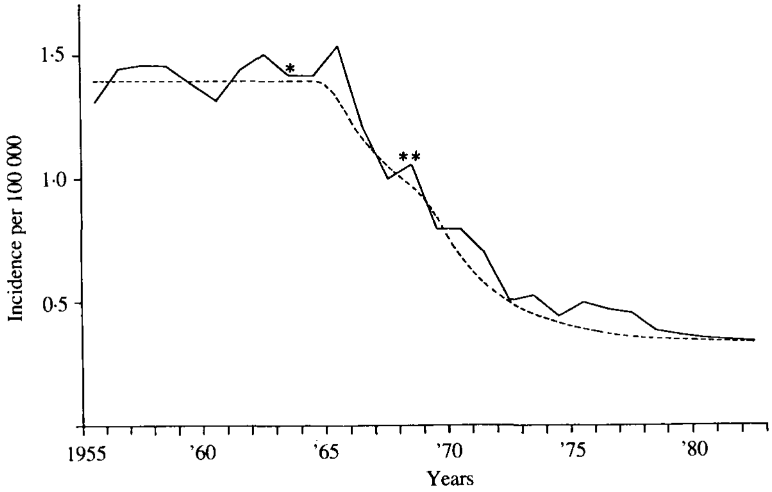

Fig. 2. Changes of tetanus incidence in Italy from 1955–82. Reported (——) and simulated (- - -) values. *Compulsory vaccination of high-risk workers introduced. **Compulsory vaccination of all newborns introduced.

simulated and reported age-specific incidences during two different periods: from 1958 to 1960 and from 1978 to 1980. Again the Wilcoxon test indicates a good fitness.

In a given situation, the model is validated if the simulated age distribution of resistant individuals corresponds to that of seropositive individuals found in a serological survey. We have utilized the data obtained from a serological survey of antitetanus immunity recently carried out in a district of Tuscany (Carducci *et al.* 1987). This district includes industrial and agricultural areas, has a population of 93000 inhabitants and birth rate and mortality rates respectively of 10·3 and 10·8 per 1000 inhabitants. The tetanus incidence in this area (5·4 per 100000 inhabitants), significantly exceeds the Italian average (0·3 per 100000 inhabitants). This difference can be explained by the fact that the Tuscany data were based on hospital registers while the Italian average was based on reported cases which are known to be affected by under-reporting everywhere. The Tuscany situation was simulated by using the 1980 age structure, birth and age-specific death rates (O.E.R. of Tuscany, 1981). Age-specific forces of infection were estimated on the basis of tetanus incidence in Tuscany while the probability of Ig administration was derived from our previous data. The parameters describing the natural history of the disease – namely, incubation period, duration of active and passive immunity, duration of illness, fatality rates, vaccine effectiveness – and coverage of the newborns, were left unchanged. As shown by Fig. 4, the age-specific incidence and distribution of resistant individuals calculated by our mathematical model coincided with that observed in the serological study (Wilcoxon test).

Simulation of vaccination strategies

The epidemiological situation in the area of Tuscany considered, indicates the necessity not only of prolonging anti-tetanic immunity duration by boosting the

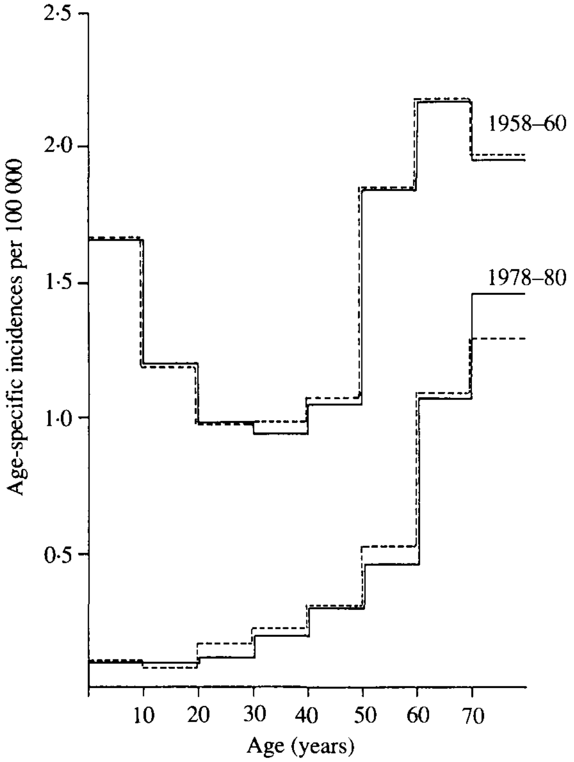

Fig. 3. Reported (——) and simulated (– – –) age-specific incidences of tetanus in Italy during the periods 1958–60 and 1978–80.

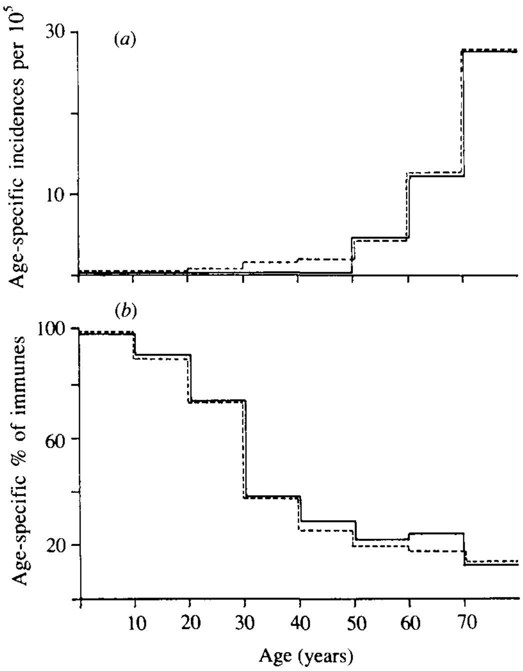

Fig. 4. Reported (——) and simulated (– – –) age-specific incidences of tetanus (*a*) and percent of immunes (*b*) in the considered district of Tuscany.

vaccinated subjects, but also of extending the vaccination to the age groups for whom it is at present not compulsory.

The model was used to simulate the effects of a number of vaccination schedules and coverage levels. It was assumed that the vaccine used had 99·9% effectiveness (Smith, 1985) and that primary vaccination (two doses) was followed by a booster shot a year later.

Vaccination coverage was taken as 60 or 90% for the population over 10 years of age (in children the coverage of compulsory vaccination is already 98%) (Bistoni *et al.* 1978; Pellegrini *et al.* 1985). For both coverages the following strategies were simulated:

(1) Mass immunization performed over a period of 1 year, followed by boosters every tenth year.

(2) Continuous immunization of susceptible persons to reach the desired coverage after a 10-year interval.

Fig. 5 shows the calculated effects of these strategies on tetanus incidence: at a 60% level of coverage reached in 1 year, the model predicts a substantive initial reduction in tetanus incidence, while if the same coverage is obtained in 10 years the incidence slightly decreases. At the highest level of coverage (90%) reached in 1 year, the model predicts a very marked reduction in the incidence even in the second year, while with a gradual immunization program the incidence decreases more slowly.

Cost–benefit analysis

Cost–benefit analysis is based on a comparison of the cost of the vaccination campaigns with the benefits resulting from saving in medical treatment of disease cases and immunoglobulin administration (Grab & Cvjetanovic, 1971). Total cost of treating a case of tetanus was estimated at 6·6 million Italian lire. The cost for public health services were calculated as 950 lire for a dose of tetanus toxoid and respectively as 8000 and 15000 lire for 250 and 500 IU immunoglobulin. To this, the cost of manpower, transportation, syringes, disinfectants and registration must be added. On the basis of estimates done for other vaccinations (Porro de'Somenzi, 1979; Bergamini *et al.* 1983), such cost was considered to be 2000 lire for a complete vaccination course and 700 lire for administering a booster dose of vaccine or immunoglobulins. The cost of immunoglobulin and toxoid doses administered by family doctors should be added; this is not easily evaluated. The cost of information and sanitary education campaigns required to educate the population before and during the immunization programmes is also difficult to calculate, owing to the different ways in which they can be done, We did not, therefore, consider these costs.

In the district of Tuscany considered, from 1982 to 1985 an average of 4·5 cases of tetanus per year was reported with an expense of about 30 million lire/year; during the year 1985 first aid stations administered 1000 doses of 250 IU and 3500 doses of 500 IU immunoglobulins, with a total expense of 55 million lire. In the same year, the doses of tetanus toxoid bought by public health bodies were about 5000 at a cost of 8·25 million lire. Thus, on the whole, tetanus prophylaxis and treatment cost more than 80 million lire/year.

Fig. 6 shows the economic effects of the four simulated strategies. With the 1-year mass immunization campaigns the balance between benefits and costs is

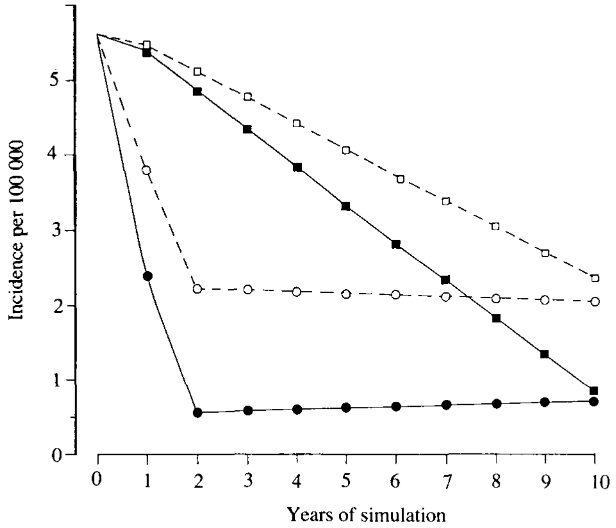

Fig. 5. Simulated effects of four vaccination strategies on tetanus incidence in the considered district of Tuscany. ●——●, Coverage 90% reached in 1 year; ■——■, coverage 90% reached in 10 years; ○--○, coverage 60% reached in 1 year; □--□, coverage 60% reached in 10 years.

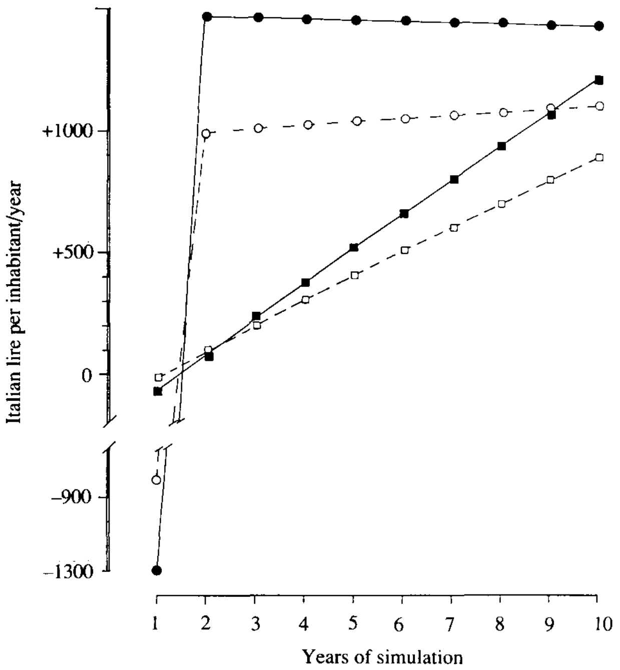

Fig. 6. Differences between benefits and costs for the four strategies simulated. ●——●, Coverage 90% reached in 1 year; ■——■, coverage 90% reached in 10 years; ○--○, coverage 60% reached in 1 year; □--□, coverage 60% reached in 10 years.

Table 3. *Economic effects of improving anamnesis reliability: cumulated benefit–cost differences in 10 years (lire × 1000/inhabitant)*

	Anamnesis reliability		
	70 %	90 %	
Strategy		Personal cards	Antitoxin titration
Coverage 60 % in 1 year	8·5	9·6	7·4
Coverage 60 % in 10 years	4·5	6·3	2·6
Coverage 90 % in 1 year	11·7	12·0	11·3
Coverage 90 % in 10 years	5·8	7·2	4·3

negative in the first year due to the large initial expense, but becomes rapidly positive reaching maximum levels by the second year. The balance of gradual vaccination strategies is always positive, but, from the second year onwards, less favourable than that of mass campaigns: it is only after the tenth year that the balance of gradual vaccination with 90 % coverage slightly exceeds that of the 1-year campaign with 60 % coverage.

In addition, we must consider that immune subjects are often given immunoglobulins because their immune status is unknown. Our serological survey has revealed that the predictive value of negative or doubtful anamnesis is 69 % (Carducci *et al.* 1987). We can therefore infer that at present about 30 % of the immunoglobulin doses used are given to resistant individuals. Such waste can be avoided either by the use of personal health cards (with an additional cost of about 200 lire for every vaccinated individual) or by determining the antitoxin titre (with an additional cost of about 8000 lire for every wounded patient). Table 3 shows the economic consequences of the two solutions expressed as cumulated benefit–cost difference in 10 years. Improving the predictive value of negative anamnesis from 69 to 90 % would lead to a consistent reduction in immunoglobulin consumption. However, the balance between benefits and costs greatly depends on the means by which such improvement is achieved: the use of personal cards would increase this balance while the antitoxin titration would decrease it.

DISCUSSION

Mathematical models aimed at predicting the epidemiological and economic effects of preventive programmes may help deciding health strategies. To obtain reliable predictions, it is however essential that the mathematical formulation of the model is correct, as well as the values of the different parameters and variables considered. It is always difficult, often impossible, to collect the right data to be applied to the model. Here, we were forced to use approximated values in regard to duration of illness and of active and passive immunity, age-specific fatality rates and frequency of booster administration in various age groups. Concerning the entire Italian population, we also lacked precise data on age-specific incidences, due to under-reporting, and on seropositivity frequencies as the available serological surveys were too scattered. For this reason, in order to simulate vaccination strategies and perform cost–benefit analysis, we have focused on Tuscany population for which we had more precise information.

Our study has clearly demonstrated that a vaccination campaign that would reach a high coverage in a short time would be the most efficacious in both epidemiological and economic terms. The study has also shown that the economic advantages of mass vaccination should be substantially increased by improving the reliability of vaccinal anamnesis thus further reducing the use of passive immunoprophylaxis. Such improvement should be obtained by personal cards documenting the vaccinal status, since determining the antibody titre would be more expensive and often impracticable. The success of the procedure is, however, strictly dependent on a proper education of the general population and of physicians in particular.

Although we cannot be sure that the results of cost–benefit analysis for Tuscany can be extended to the entire Italian population, it seems reasonable to think that the conclusions on vaccination strategies can.

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