Cost-Benefit Analysis of a Regional System for Vaccination against Pneumonia, Meningitis Type B, and Typhoid Fever

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In early 1989 PAHO began examining a proposal for a regional program that would develop and disseminate vaccines of particular interest to its Member Countries. As part of that examination, a cost-benefit analysis was performed. That general analysis, presented here, sought to point up key factors that would strongly influence whether or not the program's benefits outweighed its costs.

The program's two fundamental components, vaccine development and vaccine administration, were evaluated separately. Using a discount rate (r) of 10%, 10-year vaccine development costs were estimated at US$80.3 million in constant dollars. It was felt that enough people (at least 19.5 million a year) would be vaccinated so that the program would benefit from economies of scale. The total discounted number of vaccinations administered over a 20-year period was expected to be in the range of 400 to 506 million.

Using these figures, estimates were made of the maximum that could be spent on vaccine administration without exceeding anticipated benefits. Considering only treatment costs saved through vaccination, assuming all sick people were treated, the ceiling cost for vaccinating one person against one target disease would be in the range of US$0.52–0.58. Even if not all the sick were treated, however, the Regional Vaccine System (SIREVA) would still appear justified if the benefits per disease case prevented were found to average between US$1,000 and US$2,000. Even so, it should be noted that these estimates are subject to a good deal of additional variation because of uncertainties regarding the worth of many elements evaluated—including the costs of lost work time, disability, and mortality—and because some of the elements involved—such as pain, suffering, and death—fall outside the purely economic realm.

Although mass vaccination of vulnerable populations has been quite successful at reducing communicable disease morbidity and mortality, we still confront serious public health problems arising from diseases for which no adequate vaccines exist (*1, 2*). Either a vaccine has not been developed, there having been only partial progress to date; or the existing vaccines are of limited effectiveness; or they are restricted to certain pathogenic serotypes and therefore would not protect the populations exposed to other serotypes; or they are too costly for mass application. In view of this situation, the governments participating in the World Children's Conference held in September 1990 proposed various measures including development of an "infant vaccine" for safe early protection against a variety of diseases (*3*).

Independently, in early 1989 the Pan American Health Organization began examining the prospects for undertaking a regional effort to perfect and disseminate certain vaccines. These vaccines would be directed against a limited number of diseases of particular interest to PAHO's

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Member Countries because of the high morbidity and mortality they caused or because of large expenditures needed to treat their victims. This initiative, named the Regional Vaccine System (Sistema Regional de Vacunas—SIREVA), was seen as including the phases of epidemiologic research in the participating countries, basic research to develop the new vaccines, clinical and field trials, and construction and operation of a pilot production plant to support these other phases.

Once a vaccine had been found effective, safe, and affordable, production on a commercial scale would begin, possibly under arrangements with state or private laboratories; and mass vaccination of children would commence, perhaps through an extension of the Expanded Program on Immunization (EPI). The three diseases of bacterial origin considered targets of the effort are pneumococcal pneumonia, meningococcal meningitis caused by Group B *Neisseria meningitidis*, and typhoid fever.

SIREVA's original design included three options designated "A," "B," and "C." Option A dealt only with meningitis and typhoid fever, while options B and C included development of vaccines against all three target diseases. However, option B included only 10 participating countries with 10 collaborating national laboratories, while option C included 17 countries—thus envisioning vaccination of a larger population and implying greater development costs for SIREVA directed at identifying serotypes and testing vaccines in all 17 countries. All three options called for two principal laboratories or vaccine centers to be involved in the project, one associated with the National Institute of Public Health of Mexico and the other with the Oswaldo Cruz Foundation in Brazil, these being the centers with the greatest experience and technical sophistication in the Region.

On analyzing the costs and benefits of the three options, it was concluded that the pneumonia vaccine should definitely be included in the system and that all three vaccines could be applied in the 17 countries of the Region where the selected diseases are now of major importance. However, it was also decided that the system would be developed in 10 countries, since a network of 10 national laboratories would be sufficient for the epidemiologic work and the clinical and field trials. This option became the final version of the proposal (*4*).

The only variation still being considered deals with the number of people who would be vaccinated against meningitis, the cost-benefit calculations being repeated for two possible scales of operation that differ by a factor of two. It should be noted that the limit placed on the number of countries initially involved would not limit later administration of the vaccines in other countries of the Americas, or even in other regions, where the cost of vaccination might be justified by the benefits.

The purpose of the present analysis is to estimate and compare SIREVA's costs and benefits, and to establish under what circumstances the benefits would justify the costs, and thus justify establishment of the system.

With respect to costs, it is necessary to distinguish between two elements: expenditures for vaccine *development* (including field trials and adaptation to different epidemiologic conditions) and expenditures for vaccine *administration* (that is, for vaccinating the population). Beyond that, however, it is not the purpose of this presentation to distinguish between different kinds of costs. Therefore, the account that follows makes no attempt to discuss the composition of the costs attributable to SIREVA (that is, their distribution among basic research, clinical trials, field trials, pilot production, etc.);

only their distribution over time will be considered. Similarly, we will not consider the biologic, chemical, and epidemiologic aspects of the target diseases and prospective vaccines. Rather, the information used in this analysis deals only with the numbers of people that would be vaccinated and the numbers that would become sick or die if unvaccinated; the costs of implementing SIREVA, vaccinating the population, and treating patients; and possible additional benefits attributable to vaccination. The last part of the analysis estimates the sensitivity of the results to changes in the parameters utilized, this type of estimate being especially crucial when neither the costs nor the benefits are known but must be estimated with varying degrees of precision.

The costs attributable to SIREVA as such (the vaccine development costs cited above) have been estimated for a period of 10 years under the assumption that, although the system could continue to function for many more years, the expenditures in the eleventh and following years would be dedicated to the development of new vaccines not contemplated in the initial plans. Therefore, it would not be correct to attribute or charge expenses of those future years to the first three diseases, and vaccination against them would have to justify only the expenses of SIREVA's first decade. These expenses, presented by year in Table 1, have been estimated at US$115.3 million in constant dollars.

Table 1. Cost of SIREVA, by year, in constant US$.[a]

Year	Cost of SIREVA (CS), in millions of US$
1	5.41
2	26.36
3	11.23
4	10.33
5	10.53
6	10.48
7	10.43
8	10.43
9	10.06
10	10.06
Total (CS, not discounted)	115.32
Total (CS*, discounted)	80.31

[a]The analysis only attributes the costs of the first 10 years of SIREVA to the development of vaccines against meningitis, typhoid fever, and pneumonia because it is expected that initiation of vaccination with all three vaccines will occur in the first decade.

Any cost-benefit analysis is based on what are called *present values* of cost and benefit flows over time, these flows being discounted according to how far in the future they occur. This procedure requires the selection of a *discount rate* (r), which is conceptually equivalent to an interest rate. A cost t years in the future is then estimated by dividing the present cost (C) by (1 + r) for each of t − 1 years (5), the discounted cost being

$$C/(1 + r)(1 + r)(1 + r) \ldots n = C/(1 + r)^{(t-1)} = C \times (1 + r)^{(-t+1)}.$$

For example, if an item's present cost (C) were $1,000 and the discount rate were 10% (0.10), then its discounted cost five years in the future (t = 5) would be $683, calculated as follows:

$$\begin{aligned}\text{Year 5 discounted cost} &= C \times (1 + r)^{(-t+1)} \\ &= \$1{,}000 \times (1 + 0.10)^{(-5+1)} \\ &= \$1{,}000 \times (1.10)^{(-4)} \\ &= \$1{,}000/1.1^{(4)} \\ &= \$683\end{aligned}$$

Of course, the total discounted cost (C*) over t years would be the sum of the costs in each of the years considered (from here on we shall use an asterisk [*] to designate a discounted sum). And so, if we let the letters CS stand for the SIREVA costs (for vaccine development), the total SIREVA costs appearing in Table 1, dis-

counted over the decade, can be expressed by the formula

$$CS^* = \text{SUM } CS(t) \times (1 + r)^{(-t+1)}$$

where CS(t) is the undiscounted cost in year t, $(1 + r)^{(-t+1)}$ is the discount factor, and SUM indicates the sum of the costs of all the years in question. The same method can be used to calculate discounted benefits.

Annex 1 lists the multiplicative discount factors in the form $(1 + r)^{(-t+1)}$ for a discount rate of 10% per year ($r = 0.10$) from Year 1 of SIREVA (when the factor is equal to 1.0) to Year 30, which is the furthest horizon considered in this analysis and for which the factor decreases to only 0.063. This means that one dollar of cost or benefit that only occurs in Year 30 would have a present value of $0.063; and conversely, $0.063 invested today at a rate of interest of 10% per year would have a value of $1.00 after 30 years. The last line of Table 1 illustrates the effect of discounting the future costs of SIREVA at 10% per year over the course of a decade, which reduces the undiscounted figure (US$115.3 million) to a discounted cost of US$80.3 million.

The use of other discount rates would obviously give other totals. However, it has been judged that any reasonable rate would fall between 8% and 15% per year, and that changes introduced by using such rates as extreme values would be a good deal smaller than possible changes introduced by uncertainties regarding the value of other variables. For example, the cost of vaccinating one individual is not yet known, but it is conceivable that it could vary by a factor of 10, while a discount rate of 8% would not differ from one of 15% by as much as a factor of two. Moreover, changes in the discount rate only affect the relative weights of one year versus another; they do not affect the relative weights of costs and benefits occurring in the same year. Therefore, the question of whether the benefits justify the costs is not as sensitive to variations in the discount rate as it is to variations in the costs or benefits taken separately.

ANTICIPATED EFFECTS OF SIREVA

According to the projections for SIREVA, it will be possible to begin vaccination against typhoid fever in Year 7 of the system's operation. Vaccination against meningitis would begin in Year 9, and vaccination against pneumonia in Year 10. In all three cases it is anticipated that vaccination will commence at a high rate, so as to reduce the number of susceptible individuals in the existing population. Later, the number of vaccinations carried out would be reduced to focus on newborns at relatively higher risk, though possible fluctuations could be occasioned by future outbreaks.

In the case of pneumonia, only one year of high coverage is foreseen. This high coverage phase would extend over five years for the other two diseases, and in the case of typhoid fever there would be a period of intermediate coverage followed by a second reduction in the coverage rate after another four years.

Table 2 shows estimates of the numbers of people who would be vaccinated against each of the three target diseases in any given year. However, the number of individuals vaccinated does not correspond to the number immunized, because development of vaccines that are 100% effective is not anticipated; rather, the estimates of disease cases and deaths prevented (see Table 3) are based on the assumption that the vaccines will be 90% effective. It should also be noted that the Table 2 data refer to individuals rather than to vaccine doses, since a series of two or more doses per person may be

Table 2. The projected numbers of individuals to be vaccinated, by target disease and year.

Year	No. vaccinated (NUM), in millions, against: Meningitis	Typhoid fever	Pneumonia	Total
7		65		65.0
8		65		65.0
9	39.0–78	65		104.0–143.0
10	39.0–78	65	39.0	143.0–182.0
11	39.0–78	65	19.5	123.5–162.5
12	39.0–78	39	19.5	97.5–136.5
13	39.0–78	39	19.5	97.5–136.5
14	19.5–39	39	19.5	78.0–97.5
15	19.5–39	39	19.5	78.0–97.5
16	19.5–39	26	19.5	65.0–84.5
17	19.5–39	26	19.5	65.0–84.5
—	—	—	—	—
—	—	—	—	—
30	19.5–39	26	19.5	65.0–84.5
Discounted total no. vaccinated (NUM), in millions:*				
20-year horizon	106–212	227	67	400–506
30-year horizon	126–251	253	87	466–591

Table 3. Total discounted numbers of disease cases prevented, deaths prevented with treatment of all cases, and deaths prevented without treatment of any cases, over 20-year and 30-year horizons.

	20-year horizon	30-year horizon
Cases prevented (PREC*):		
Meningitis	9,547–19,094	11,313–22,626
Typhoid fever	305,897	341,075
Pneumonia	16,835	21,700
Deaths prevented, with treatment of all cases (PREDT*):		
Meningitis	477–955	565–1,130
Typhoid fever	3,059	4,411
Pneumonia	1,684	2,170
Total	5,220–5,698	7,146–7,711
Deaths prevented, without treatment of any cases (PRED*):		
Meningitis	4,774–9,547	5,657–11,314
Typhoid fever	30,590	34,108
Pneumonia	5,051	6,511
Total	40,415–45,188	46,276–51,933

needed to complete the vaccination and achieve 90% immunization.

The cost-benefit analysis also assumes that the cost of vaccinating one individual will be independent of the number of people vaccinated. The latter number will always be large enough (at least 19.5 million per year) to benefit from possible economies of scale. Similarly, it is assumed that the benefit obtained per individual vaccinated will be constant and independent of how many others receive the vaccine. Among other things, this implies that the chance of one unvaccinated individual becoming ill does not depend on the number of individuals immunized; that is, a possible "collective immunity" effect is not taken into account (*6*).

As a consequence of these assumptions, the total discounted costs and benefits can be found by totaling and discounting the number of people vaccinated and later applying to that discounted sum the costs and benefits per person. More explicitly, if the cost of vaccinating someone against disease "i" is designated VAC(i), then by definition the total cost (CST) of vaccinating some number (NUM) of people against disease i in some future year t is as follows:

$$CST(i,t) = VAC(i) \times NUM(i,t),$$

and discounting and totaling both sides of the equation yields

$$\begin{aligned} CST^*(i) &= SUM\, CST(i,t) \times (1 + r)^{(-t+1)} \\ &= SUM\, VAC(i) \times NUM(i,t) \\ &\quad \times (1 + r)^{(-t+1)} \\ &= VAC(i) \times SUM\, NUM(i,t) \\ &\quad \times (1 + r)^{(-t+1)} \\ &= VAC(i) \times NUM^*(i) \end{aligned}$$

The same type of calculation can be applied to the number of disease cases prevented (applying as a multiplicative factor the probability that a vaccinated individual would have acquired the disease if he or she had not been vaccinated); to the number of deaths prevented (successively applying the probability that an individual with the disease died of it, whether or not the effects of curative treatment on the probability of survival are considered); and to the total benefit obtained from vaccination (using the individual or unit benefit as the multiplicative factor).

In relating all these calculations to a discounted sum of individuals, one is not saying that an individual vaccinated 15 years from now is worth less than one vaccinated before that, but only that the economic value of the cost and the associated benefit are less today because they occur further in the future. This discounting and totaling of individuals instead of monetary sums is nothing more than a valuable mathematical simplification. Variables employed in making relevant calculations and the formulas used to discount and total them are summarized in Annex 2, which also contains a glossary of all of the terms utilized in the analysis.

The discounted and totaled numbers of individuals vaccinated, designated NUM*, are shown at the bottom of Table 2 by disease for two different horizons—20 years and 30 years. In contrast to the SIREVA costs for vaccine development (CS), which end in 10 years, the costs of administering the vaccines (CST) never end, so long as the disease is controlled but the pathogens are not eradicated. Therefore, for the purposes of this analysis, it is necessary to choose a final year. It seems reasonable to think that if SIREVA could be justified, this justification would probably occur within 20 years, a period that would include more than a decade of application of each vaccine.

Beyond 20 years, any protection becomes very speculative; in particular, it is not known what might happen to the risks of acquiring a disease or the benefits

of being protected. Solely to illustrate a longer horizon, the calculations have been repeated for a 30-year period. As will be seen, this extension of the period does not significantly affect the system's net estimated worth.

As the Table 2 projection shows, during the 20 years following SIREVA's initiation the equivalent, in terms of present value, of between 106 million and 212 million people would be vaccinated against meningitis, some 227 million would be vaccinated against typhoid fever, and some 67 million would be vaccinated against pneumonia. Overall, in discounted terms, between 400 million and 506 million people would be vaccinated during the period, the actual figure depending on the extent of vaccination against meningitis. This total could refer to the discounted equivalent of 400–506 million individuals; or it could involve fewer individuals, some of them being vaccinated against two or even three of the target diseases.

On extending the horizon to 30 years these values increase, but much less than proportionately to the number of additional years of vaccination because the discount factors (see Annex 1) give little weight to the years furthest away. In terms of present values, the entire third decade has the same value as only the last five years of the second decade, which in turn are only worth the same as the first year by itself.

To go from the number of people vaccinated to the number of disease cases prevented it is necessary to multiply by the effectiveness of the vaccine (which determines whether the person is really immunized) and then by the chance that the person would become sick if not immunized. The effectiveness of all three vaccines is estimated at 90%, while the incidences of the three diseases (per 100,000 population at risk) are estimated at 10 (with a maximum of up to 50) for meningitis, 150 for typhoid fever, and 28 for pneumonia. These figures give the likelihood of preventing a disease case by vaccinating one person a probability of 9, 135, and 25 chances per 100,000, respectively. (Only the lower estimated incidence is used for meningitis, because this reduces the benefits without affecting the costs; and if SIREVA is justified under these circumstances, it would be even more justified if the disease incidence were higher.)

The probabilities of preventing a case are shown in Table 4, which will be discussed later, while Table 3 indicates the estimated numbers of cases that would

Table 4. The estimated cost of treatment (in constant US$), probability of preventing one case, and implied maximum cost of vaccination,[a] by disease, independent of the number of vaccinations.

	Meningitis	Typhoid fever	Pneumonia
Probability of preventing one case, SUF(i) × EFV(i)	9.0×10^{-5}	1.35×10^{-3}	2.5×10^{-4}
Unit cost of treatment, BTR(i)	$3,000	$584	$6,306
Implied maximum cost of one vaccination, SUF(i) × EFV(i) × BTR(i)	$0.27	$0.79	$1.58

[a]The implied maximum cost of vaccination is the value such that the cost of vaccinating one person compensates exactly for the probable cost of having to treat that individual for the disease. It is calculated by multiplying the unit cost of treatment by the probability of preventing one case. For this calculation the fixed cost of developing vaccines against the target diseases is not considered.

be prevented, by disease, for horizons of 20 and 30 years. By far the greatest disease prevention occurs with regard to typhoid fever, because of its high incidence, the discounted number of cases to be prevented totaling over 300,000. For meningitis and pneumonia the estimated figures are lower by an order of magnitude, ranging from 10,000 to 23,000 for meningitis and from 17,000 to 22,000 for pneumonia.

In some cases a person who acquires the disease will die. The likelihood of this varies greatly, depending on the disease and whether the victim does or does not receive adequate and timely treatment. With such treatment almost no one dies of typhoid fever, since the death rate is estimated at no more than 1%; and even without treatment that rate rises to only 10%. Regarding pneumonia, it is estimated that the lethality is 3% with treatment and 10% without treatment, while for meningitis the corresponding rates are estimated at 5% and 50% (4). Therefore, the numbers of deaths prevented are not proportional to the numbers of cases prevented—the risk of death depending on the particular disease involved and also varying by a factor as great as 10, depending on whether one assumes that each patient does or does not receive appropriate treatment.

Table 3 shows the estimated numbers of deaths that vaccination would prevent, by type of disease, and also shows the total numbers of deaths preventable by SIREVA. Showing these latter totals is appropriate; for although it would be incorrect to total the numbers of cases of diseases that are very different with respect to severity and danger, it is legitimate to total the resulting deaths. Depending on the horizon selected, the totals range from 40,000 to 52,000 deaths prevented if no treatment is assumed, and from 5,000 to 8,000 if it is assumed that every victim receives appropriate care.

ECONOMIC BENEFIT: TREATMENT COST SAVED

The benefits obtained by preventing one case of a disease include some that are difficult to quantify or evaluate economically, such as reduction of the patient's pain and suffering. Other benefits, although possibly less important, are easier to evaluate in economic terms; among these is the treatment cost saved as a result of not having to care for the patient. Clearly, attributing this monetary benefit to vaccination depends on an assumption that the victim would receive the treatment if he were to contract the disease. This benefit is received by the person or institution that otherwise would have to pay the treatment cost, whether the paying party is the patient or not.

Thus, one way to compare costs with benefits is to relate the cost of vaccinating one person with the expected cost of treating that individual, considering these procedures as alternatives. Obviously, this last assumption is more reasonable when the treatment results in a complete cure, without permanent injury to the patient. When the patient dies despite the treatment (which is possible with all diseases and occurs in up to 10% of pneumonia cases) or is left with significant sequelae (as can easily occur with meningitis), treatment is a very incomplete substitute for prevention.

Of course, one must compare the cost of vaccination with the *expected* or *probable* cost of care, because not all vaccinated individuals would become sick if unvaccinated. The comparison depends, therefore, on the likelihood that the vaccine would prevent a case of the disease. This likelihood, as already noted, is shown on the first line of Table 4; it is calculated by multiplying the effectiveness of the vaccine (EFV) against disease (i) by the probability of suffering the disease, SUF(i). This is the same logic that has been used

to justify eradication of poliomyelitis, through the savings in treatment costs that would result from vaccinating virtually the entire population at risk (7).

The second line in Table 4 shows the average cost of providing a patient with correct and timely care, designated BTR(i). This is estimated to range from less than $600 in the case of typhoid fever to more than $6,000 in the case of pneumonia. Taken together, the likelihood of preventing a case and the cost of treating that case determine a hypothetical cost of prevention where the prevention and treatment costs would equal one another, and so the *net* saving from vaccination would be zero. This cost can be viewed as the *implied maximum cost* of vaccination in the sense that at any lower cost the vaccination would be less costly than the treatment.

As can be seen on the third line of the table, this latter cost, SUF(i) × EFV(i) × BTR(i), is calculated by multiplying the probability of preventing one case by the cost of treating one case. And the *cost* of preventing one case is the cost of one vaccination, VAC(i), divided by the probability of preventing one case with one vaccination or

$$VAC(i) / [SUF(i) \times EFV(i)].$$

On relating this expression to the cost of treatment, BTR(i), one sees that where

$$VAC(i) = SUF(i) \times EFV(i) \times BTR(i)$$

there is exact equality between vaccination and treatment costs; and likewise, where

$$VAC(i) < SUF(i) \times EFV(i) \times BTR(i)$$

vaccination offers a net economic benefit. In monetary terms (see Table 4), the corresponding values range from $0.27 per vaccination in the case of meningitis to $1.58 in the case of pneumonia. Regarding typhoid fever, it should be noted that the low cost of treating one case of this disease is partially balanced by its high incidence in the population, so that the implied maximum cost of vaccination against typhoid fever is $0.79, or almost three times the implied maximum cost in the case of meningitis.

As has been said, until the vaccines are developed and administered on a mass scale, there can be no exact picture of vaccination cost. The interpretation of the calculations in Table 4 is that vaccination will be justified—through savings in treatment costs, without considering other benefits—as long as it costs no more than $0.27 per vaccination against meningitis, etc. If, for example, it were feasible to vaccinate at a unit cost of $0.10—which would cover not only the cost of the vaccine but also the cost of distributing and administering it to the population, then clearly vaccination would be highly worthwhile. In contrast, if the unit cost were $1.00, only vaccination against pneumonia would appear to be justified, assuming no other benefits were considered.

Even if one compares only vaccination and treatment, however, the calculation presented in Table 4 is still incomplete because the vaccines involved do not yet exist and have to be developed. This implies that the benefits, in the form of saved medical costs, would have to cover not only the costs of vaccination (costs "outside SIREVA" or CST), but also the vaccine development costs "within" SIREVA (CS). In addition, SIREVA is attempting to develop three vaccines, without the total cost of the program being attributed to one or another of these products.

The first of these conditions implies that the maximum cost allowed for vaccination is going to be less than that shown in Table 4, since the benefits must also cover SIREVA's vaccine development

costs. The second condition (of coproduction or inseparability) implies that judging the worth of each vaccine individually makes no sense, because it will be necessary to judge the entire system with respect to the *average* cost of vaccination against the three target diseases.

This matter can be summarized as follows: For there to be a net benefit after considering *both* types of costs, it is necessary that

$$BENT^* > CS^* + CST^*,$$

where BENT is the total benefit in saved treatment costs—the cost of treating one individual times the number of cases prevented. (Table 3 indicates the number of cases prevented, and Table 4 shows the unit costs of treatment.) As noted above,

$$CST^* = VAC \times NUM^*,$$

where VAC denotes the average cost of vaccination within the time interval involved. Both BENT* and CST* must be summed for all the target diseases, and both must also be discounted and summed over time. Then, in order for the net benefit condition to be met, it is necessary that

$$BENT^* - CS^* > VAC \times NUM^*,$$

which results in the implied maximum value of VAC being the total benefit less the cost of SIREVA (the expression on the left of the inequality sign) divided by the total number vaccinated, or

$$VAC < [BENT^* - CS^*] / NUM^*.$$

Table 5 presents the corresponding calculations. Starting with the values of CS* and NUM* from Tables 1 and 2, respectively, Table 5 proceeds to list values for the three ingredients of BENT*, these being the saved costs of treating each disease, and the BENT* totals for 20-year and 30-year horizons. The last entries

Table 5. The average implied maximum cost of vaccination (in constant US$) derived from the number of individuals vaccinated, treatment costs, and the cost of SIREVA, for 20-year and 30-year horizons.

	20-year horizon	30-year horizon
Costs of SIREVA (CS*), in US$ millions	80.3	80.3
Total number of vaccinations (NUM*), in millions	400–506	465–591
Saving on treatment costs (BENT*), by disease, in US$ millions:		
Meningitis	29–57	35–68
Typhoid fever	179	199
Pneumonia	106	137
Total, three diseases	313–342	370–404
Net saving, after deducting SIREVA's cost (BENT* − CS*), in US$ millions	233–262	290–324
Average implied maximum cost of one vaccination—VAC (net savings divided by the number of vaccinations), in US$	0.52–0.58	0.55–0.62

show the 20-year and 30-year values of BENT* − CS* and of VAC.

The figures shown indicate that over a period of 20 years some US$80.3 million, at present value, would be spent developing the three vaccines, which would be administered to the discounted equivalent of 400–506 million individuals. The disease cases prevented would represent an estimated saving of $29–$57 million for meningitis, $179 million for typhoid fever, and $106 million for pneumonia. The total benefit would amount to $313–$342 million before subtracting the costs of SIREVA itself, yielding a net benefit of $233–$262 million. After dividing this amount by the total number to be vaccinated, it can be concluded that SIREVA is justified with respect to the treatment costs saved as long as the population could be vaccinated for no more than $0.52–$0.58 each. If one individual were to receive all three vaccines, the permitted cost would rise to $1.56–$1.74. Applying these same calculations to the 30-year horizon yields an average permitted cost that is greater by a few cents because the costs of SIREVA would be distributed over more years of vaccination, and so their relative weight in the total costs would be less.

OVERALL BENEFITS FROM SIREVA AND VACCINATION COSTS

The exercise in the previous section fixes a value on the benefit derived from SIREVA, equating it to saved medical treatment costs, and on this basis estimates the maximum cost of vaccination that would be compatible with a net positive benefit. This procedure can be reversed by first fixing a value on the cost of vaccination and then deriving from it an estimate of the *minimum* benefits providing justification for SIREVA. In this case, the benefits could be of any type, without being limited to the treatment costs saved. The worth of preventing a death, the value of economic production saved by preventing death or illness, the reduction of physical and emotional suffering, and other benefits could be included. In this regard, since the disease cases and deaths prevented are the most quantifiable results of vaccinating the population, it seems natural to estimate minimum benefits in terms of these concepts.

The condition that must be satisfied is

$$BEN^* > CS^* + CST^* = C^*,$$

where C* is the total costs and BEN* is the discounted sum of *all* the benefits (including BENT*, the benefit of not having to treat those who would become ill). If we then designate the benefit or "utility" per case prevented as UTU, and the number of cases prevented as PREC*, we see that for case prevention alone to satisfy the condition it will be necessary for

$$UTU \times PREC^* > C^*,$$

or equivalently,

$$UTU > C^* / PREC^*.$$

Similarly, if we designate the benefit per death prevented as UTUD, we see that for mortality prevention alone to satisfy the condition it will be necessary for

$$UTUD > C^* / PRED^*,$$

where PRED* is the number of deaths that would occur in the absence of vaccination and treatment.

The corresponding calculations appear in Table 6. They are limited to the 20-year horizon, since it was determined (in Table 5) that extension of the horizon to 30 years does not significantly affect the results. Starting with the cost of SIREVA (CS*), numbers of cases prevented

Table 6. Implied minimum benefit per case prevented and per death prevented as a function of the cost of vaccination, without considering patient treatment (20-year horizon).

	Cost of vaccination (VAC)	
	US$1.00	US$10.00
Total number of cases prevented (PREC*), in thousands	332–342	332–342
Total number of deaths prevented (PRED*), in thousands	40–45	40–45
Cost of SIREVA (CS*), in US$ millions	80.3	80.3
Cost of vaccination (CST*), in US$ millions	400–506	4,000–5,060
Total cost (C*), in US$ millions	480–586	4,080–5,140
Minimum benefit per case prevented (C*/PREC*), in US$ thousands[a]	1.4–1.7	12.3–15.0
Minimum benefit per death prevented (C*/PRED*), in US$ thousands[b]	12.0–13.0	102.0–114.2

[a]The values for the minimum benefit do not change significantly on extending the horizon to 30 years.
[b]The minimum benefit per death prevented does not attribute any benefit to preventing nonfatal disease cases.

(PREC*), and numbers of deaths prevented (PRED*) that appear in Tables 1 and 3, Table 6 derives the other component of the total cost—the cost of vaccination—from the total number vaccinated (see Table 2), using a unit cost (VAC) first of $1 and then of $10.

The resulting total cost (C*) is then used to calculate the benefits per case prevented (UTU). It turns out that the first VAC cost ($1) yields values quite close to those that would permit justification of SIREVA solely on the basis of medical treatment costs saved, while the second VAC cost ($10) yields values so high that the benefits per case prevented would have to be substantially greater.

The results of attributing the entire benefit to the prevention of death (UTUD) are shown in the last line of the table. Naturally, the benefit involved would have to be much greater. Given that, on the average, approximately 10% of the untreated cases would terminate in death, the minimum benefit per death prevented would have to be some 10 times greater than the minimum benefit per disease case prevented.

For example, at a cost of vaccinating one person for $1.00, SIREVA is justified so long as an average benefit per case prevented of between $1,400 and $1,700 is obtained. This is based on the estimate that a total of $480 to $586 million at present value will be spent in order to prevent a total of some 332,000–342,000 cases of the three diseases.

The minimum necessary benefit per case rises to $12,000 if the cost of vaccination is fixed at $10; it does not rise in the same proportion as the unit cost of vaccination because the actual expenditures of SIREVA are not affected. It should be noted, however, that when the cost per vaccination is $1.00 or greater, these fixed costs of developing the vaccines are of relatively

little importance compared to what would have to be spent applying them. Therefore, justifying the vaccination is almost equivalent to justifying SIREVA, if there is no other way to develop the vaccines that is less costly than the system proposed.

The final calculations (on the last line of Table 6) are somewhat artificial, since they attribute benefits only to the prevention of death. This establishes a kind of "maximum of the minimum" for the necessary benefit justifying SIREVA—at levels on the order of $12,000 in the first instance and $100,000 in the second.

It should be noted, however, that benefits from cases prevented and deaths prevented can be combined. That is, it is appropriate to compensate for the costs of SIREVA through any combination of benefits per death prevented and benefits per nonmortal case prevented that satisfies the relationship

$$[UTU \times (PREC^* - PRED^*)] + (UTUD \times PRED^*) > C^*,$$

where UTU, the benefit per case prevented, would be substantially less than UTUD, the benefit per death prevented. The expression ($PREC^* - PRED^*$) refers to the number of individuals who would become sick but not die if they were not vaccinated.

Both the calculations in Table 5 and those in Table 6 implicitly assume that the benefit associated with vaccination occurs immediately, simultaneously with vaccination. This assumption is justified if the target disease would probably attack an individual within a short time or never, as is typically true of the diseases targeted by the Expanded Program on Immunization, which affect primarily children (although those diseases can appear several years later than the normal age of immunization). If, on the other hand, a large proportion of those affected will typically become ill many years after vaccination—and if the vaccine retains its effectiveness for many years, so that it is not necessary to repeat the vaccination frequently—the calculations that were just presented can prove optimistic or overly favorable because they do not consider the interval between the moment of vaccination and the probable moment of becoming ill.

The greater this interval, the longer the benefits are delayed relative to the costs, and the greater they have to be to compensate for this delay. The way to adjust for the possible optimistic bias is to estimate the average interval between vaccination and illness in years (D) and then to discount the benefits with respect to the costs by the factor $(1 + r)^{-D}$, utilizing the same discount rate (r) applied elsewhere.

By way of example, Table 7 shows the sizes of adjustments associated with several different intervals of delay. Thus, if the benefits were delayed an average of 10 years, they would have only 38.55% of the value they would have if they appeared immediately. The rest of the table shows the impact of these adjustments on parameters calculated in Table 5 (the implied maximum cost of vaccination) and Table 6 (the implied minimum benefit per case prevented). As can be seen, a relatively short delay such as five years does not greatly affect the results; but longer delays such as 15 years produce much stronger effects—resulting in multiplication or division of the benefits or costs by a factor of four or more.

CONDITIONS JUSTIFYING SIREVA AND SENSITIVITY OF THE RESULTS

It has not been possible to carry out a closed and precise cost-benefit analysis for the proposed system at this time because its exact costs are not known and

Table 7. The effects of adjusting for the delay between vaccination and disease onset upon the implied maximum cost of vaccination and upon the implied minimum benefits of preventing a disease case, in constant US$.

	Delay (D), in years				
	0	5	7	10	15
Adjustment factor (AJUD)	1.000	0.7513	0.5132	0.3855	0.2394
Effects on the implied maximum cost of vaccination (original value multiplied by the adjustment factor), in US$:					
By disease, without counting the cost of SIREVA:					
Meningitis	0.27	0.20	0.14	0.10	0.06
Typhoid fever	0.79	0.59	0.41	0.30	0.19
Pneumonia	1.58	1.19	0.81	0.61	0.38
Average for SIREVA (all costs for three diseases):					
Minimum	0.52	0.39	0.27	0.20	0.12
Maximum	0.58	0.44	0.30	0.22	0.14
Effects on the implied minimum benefit per case or death prevented (original value divided by the adjustment factor) in US$ thousands:					
Per case prevented; vaccination cost = US$1.00:					
Minimum	1.4	1.9	2.7	3.6	5.8
Maximum	1.7	2.3	3.3	4.4	7.1
Per death prevented; vaccination cost = US$1.00:					
Minimum	12.0	16.0	23.4	31.1	50.1
Maximum	13.0	17.3	25.8	33.7	54.3

there is no consensus on how to evaluate its benefits. Therefore, the analysis presented in the above sections is based on the relationships between these unknown elements, rather than upon definitive values assigned to them. For every level of benefit per disease case prevented, there is a corresponding maximum value for vaccination cost that still leaves a positive net benefit. And conversely, each unit cost of vaccination establishes a minimum for the total benefit of preventing one case (or one death) compatible with net benefit from the system. The corresponding calculation of these two ways of presenting the relationship, shown in Tables 5 and 6, can be considered the essence of the present analysis.

In general terms, the calculations allow one to conclude that SIREVA would be justified by its benefits if it were possible to develop the vaccines at the costs estimated for the different options and later to administer them to the population at a unit cost of half a dollar or less. At this level of expense, the system could generate sufficient treatment cost savings to compensate for the entire cost of developing and administering the vaccines. Even if it were assumed that in the absence of SIREVA not all the disease victims would receive adequate and timely treatment, the system would still be jus-

tified if benefits per disease case prevented were found to have a minimum average value between $1,000 and $2,000. Part of these benefits would derive from prevention of deaths; and if it were estimated that it would be worth spending somewhat more than $10,000 on the average to avoid one death, this benefit alone would justify the proposed expenditures.

How sensitive are these results to variations in the different parameters considered in the analysis? If a small change in one of them causes the system to stop appearing viable, then the proposal would be risky, given the great uncertainty in the estimated values. The analysis has taken into account all of the following factors: the cost of SIREVA itself (development of the vaccines), the cost of vaccinating one individual against one disease, the cost of treating one case of a disease, the number of individuals vaccinated, the effectiveness of the vaccine, the incidence of the target diseases, their lethality with and without treatment, the discount rate, and the possible delay between a person's age at vaccination and age at disease onset. For some of these factors, where less is known or it is possible to anticipate a large variation, an explicit sensitivity analysis has been made. For other elements the probable variation in the factor and the consequences for the results have been discussed briefly. To terminate this analysis, the sensitivity of the conclusions to the elements mentioned are discussed below. In general, there is no reason for hesitation in exploring the possibilities of changes on the order of 10% or 20%; the concern is whether one ought to anticipate variations of an order of magnitude or so in the system's estimated yield.

Actual costs of SIREVA. The importance of these costs depends on whether they are large or small relative to the total vaccination cost. If they are small, they can vary considerably without greatly affecting the total cost. For example, at the maximum cost calculated for which vaccination is justified in terms of medical costs saved, the costs of SIREVA itself are one-third or less of the total cost, so that they could be underestimated by 50% and still not have a great effect upon the system's yield.

Aside from an increase in SIREVA's cost, the relative importance of this element would be greater if the unit cost of vaccination were less than estimated. In that case, however, the reduced cost of administering the vaccines would compensate for a large increase in the cost of developing them. For example, consider the calculation in Table 5 and assume that the element CS* (the cost of SIREVA) were doubled. Then CS* would be $160.6 million, but the system would still be justified for any vaccination cost VAC less than $0.36.

Vaccination cost. As has been seen, this element is crucial; and if one calculates benefits only in terms of medical expense saved, this imposes a clear maximum value upon vaccination cost that is at the level of $0.50. Increasing the unit vaccination cost to $1.00 requires greater total benefits; and if the vaccination cost were as high as $10.00, the saving in treatment cost by itself would be far too small to justify the system. Hence, everything depends on whether vaccination is achieved at a reasonable cost, and the proposal assumes that result. To achieve such a result, it may be necessary to incorporate the new vaccines into the EPI; that way the logistic costs would be minimal, and little more would have to be spent beyond that needed to cover the costs of manufacturing the vaccines.

Treatment cost. It is assumed that this element is relatively well known, so that its possible variations need not be taken into account. In any case, if the scheme of analysis utilized in Table 6 is adopted to consider the *total* value of the benefits

per case prevented, this treatment cost variable becomes less important—because it then constitutes only one component of the benefits, and perhaps not the greatest of them.

Number of individuals vaccinated. This factor is crucial for the simple reason that the costs of developing the vaccines must be offset by administering them to a large enough number of people. If it were not for this fixed development cost, the calculations in Table 4 could be applied directly; SIREVA's justification would be independent of the scale of operation; and the average cost of vaccination could be as high as $0.78. Comparing these calculations with the values listed in Table 5 shows how the need to compensate for the system's fixed costs affects the results. Both the maximum cost of vaccination and the implied minimum benefit vary directly with changes in the number of individuals covered by SIREVA. It is assumed, however, that the estimates of this latter number would not be in error by more than a small percentage.

Vaccine effectiveness. This factor cannot vary much because a vaccine would not be administered if it were not at least 70% or 80% effective. Therefore, vaccine effectiveness cannot affect the results very much. It would only be important if after expending millions of dollars on SIREVA, the effort failed and effective vaccines were not obtained; the entire proposal is based upon confidence that this will not occur.

Disease incidences. The estimates of these parameters are very low, the maximum value used being 150 cases per 100,000 inhabitants for typhoid fever. Any increase would only make the system more viable; and so the only consideration should be whether the incidences of the target diseases have been overestimated. Changes in the probability of getting sick affect the benefits the same way that changes in the number of people vaccinated do, but without affecting the cost—unless one could, at lower risk, vaccinate fewer people. The epidemiologic studies constituting part of the system's development will help to define these risks better and so to adjust, if necessary, the projected extent of mass vaccination.

Disease lethality. This factor cannot vary much, even admitting that it is not known exactly. In any case, it is important only if one desires to attribute a specific benefit to the prevention of death; for there would clearly be great benefit in preventing each of the target diseases even if no one died of them.

Discount rate. As has already been discussed, this element cannot vary by more than a factor of two, and its influence affects the distribution of costs and benefits over time without affecting their comparison in a given year. Therefore, the results of the analysis are not considered very sensitive to the rate selected.

Delay between vaccination and prevented illness. As Table 7 shows, this factor becomes a matter of concern if it is necessary to assume a delay of more than about half a decade. If the disease presents risks over the entire human lifespan, part of the benefit is left unperceived in terms of present value. Even though the probable impact of such a delay would only divide the benefits in half, this circumstance would require an average benefit twice as large, or a cost of vaccination half as large, as those projected.

It is clear that the justification, or lack thereof, of a project such as the one being analyzed depends upon how all of these elements are evaluated, and upon the values assigned to prevention of disease and death—values outside the purely economic realm. The present analysis only attempts to trace a dividing line between the possible combinations of factors, known or estimated, that show whether

or not SIREVA would be viable in the sense of producing benefits that more than compensate for its costs of development and application, within a reasonable span of time.

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REFERENCES

1. Institute of Medicine, National Academy of Sciences. *New vaccine development: establishing priorities (vols 1 and 2).* Washington, DC: National Academy Press; 1986.
2. World Health Organization. Research and development in the field of vaccines: progress report by the Director General. Executive Board, 87th Session. Geneva: 21 November 1990. (Document EB87/6).
3. World Health Organization, UNICEF, and UNDP. *Declaration of New York: the children's vaccine initiative.* New York: 10 September 1990.
4. Organización Panamericana de la Salud. SIREVA: estudio de factibilidad, sistema regional de vacunas para los países de América Latina y el Caribe. Unpublished document. Washington, DC: 1990.
5. Drummond MF, Stoddart GL, Torrance GW. *Methods for the economic evaluation of health care programs.* Oxford: Oxford University Press; 1986.
6. May RM. Ecology and population biology. In: Warren KS, Mahmoud A, eds. *Tropical and geographic medicine.* 2nd ed. New York: McGraw-Hill; 1990. (Chapter 19).
7. Musgrove P. Is polio eradication in the Americas economically justified? *Bull Pan Am Health Org.* 1988; 22(1):1–16.

Annex 1. Discount factors, by year, for a rate (r) of 10% per year.

Year	Factor	Comments
1	1.0000	Initiation of SIREVA
2	0.9091	
3	0.8264	
4	0.7513	
5	0.6830	
6	0.6209	
7	0.5645	Start of vaccination against typhoid fever
8	0.5132	
9	0.4665	Start of vaccination against meningitis
10	0.4241	Start of vaccination against pneumonia
11	0.3855	
12	0.3505	
13	0.3186	
14	0.2897	
15	0.2633	
16	0.2394	From Year 16 on the numbers of vaccinations do not vary.
17	0.2176	
18	0.1978	
19	0.1798	
20	0.1635	Sum for years 16 to 20 = 0.9981 Sum for years 1 to 20 = 9.3647
21	0.1486	
22	0.1351	
23	0.1228	
24	0.1117	
25	0.1015	
26	0.0923	
27	0.0839	
28	0.0763	
29	0.0693	
30	0.0630	Sum for years 21 to 30 = 1.0045 Sum for years 1 to 30 = 10.3692

Annex 2. Glossary of symbols, variables, and their relationships—in their approximate order of appearance in the text.

Symbol or variable	Definition
t = 1, 2, 3 . . .	Years since initiation of SIREVA
i = 1, 2, or 3	Disease
NUM	Number of vaccinations administered; equal to the number of individuals vaccinated if every individual is vaccinated against only one disease. NUM refers to the number of complete vaccinations, not to the number of doses, if vaccination requires the application of two or more doses.
PREC	Number of cases of a disease prevented by the vaccination program
BEN	Total benefit obtained by prevention of disease cases
C	Total cost
CS	Cost of SIREVA (for vaccine development)
CST	Cost other than for SIREVA (vaccine manufacture, distribution, and administration)

Note: The variables C, CST, NUM, PREC, and BEN are classified by disease (i) and year (t). The variable CS is classified solely by year; CS(i) does not exist. By definition, C(t) = CS(t) + CST(t).

Annex 2. Continued

Symbol or variable	Definition
SUM	Indicates the summation of a variable over a series of years t (up to 20 or 30 years in the calculations)
r	Discount rate for future years (0.1 or 10% in the calculations)
*	Indicates the discounted sum of a variable; for example, $C^* = \text{SUM } C(t) \times (1 + r)^{(-t+1)}$ and $BEN^* = \text{SUM } BEN(t) \times (1 + r)^{(-t+1)}$

Note: The variables C, CS, CST, NUM, PREC, and BEN are all transformed into C*, CS*, . . . , by discounted summation. For all except CS, the sum can be obtained for a single disease (i) or for all three diseases taken together.

VAC(i)	Unit cost of vaccinating one individual against one disease (i). Thus CST(i,t) = VAC(i) × NUM(i,t), and CST*(i) = VAC(i) × NUM*(i)
VAC	Summing for all three diseases gives the average implied maximum cost of vaccination. It is calculated as follows: VAC = (BENT* − CS*) / NUM*
EFV(i)	Effectiveness of the vaccine (i). (In the calculations it is always assumed that EFV equals 0.9 or 90%.)
SUF(i)	The probability of a person not vaccinated against target disease (i) acquiring that disease. Thus PREC(i,t) = SUF(i) × EFV(i) x NUM(i,t), which gives PREC*(i) = SUF(i) × EFV(i) × NUM*(i)
MOR(i)	The probability that an individual with disease (i) will die if not treated.
MORT(i)	The probability that an individual with disease (i) will die if treated.
PRED(i,t)	The number of deaths prevented by vaccination, assuming those ill would receive no treatment. PRED(i,t) = MOR(i) × PREC(i,t), and thus PRED*(i) = MOR(i) × PREC*(i). The corresponding totals for all of the target diseases taken together are PRED(t) and PRED*.
PREDT(i,t)	The number of deaths prevented by vaccination, assuming those ill would receive treatment. PREDT(i,t) = MORT(i) × PREC(i,t), and thus PREDT*(i) = MORT(i) × PREC*(i). The corresponding totals for all of the target diseases taken together are PREDT(t) and PREDT*.
UTU(i)	Unit benefit or utility of prevention—the benefit derived from preventing one case of disease (i). Thus the benefit of vaccinating one individual is UTU(i) × SUF(i) × EFV(i).
BEN(i,t)	The benefit derived from vaccinating NUM(i,t) individuals, so that BEN(i,t) = UTU(i) × SUF(i) × EFV(i) × NUM(i,t) = UTU(i) × PREC(i,t); and hence BEN*(i) = UTU(i) × PREC*(i). The corresponding totals for all of the target diseases taken together are BEN(t) and BEN*.

Note: The net unit benefit (benefit minus cost) of vaccinating one individual is UTU(i) × SUF(i) × EFV(i) − VAC(i), and the net total benefit is [UTU(i) × SUF(i) × EFV(i) − VAC(i)] × NUM(i,t) = BEN(i,t) − CST(i,t). The same relationship is valid for NUM*(i), BEN*(i), and CST*(i).

BTR(i)	Unit cost of treatment—the cost of adequately treating one case of disease (i).
BENT	The benefit derived solely from not having to treat disease cases. Note that BENT < BEN because the former does not include all of the benefits; hence BENT(i,t) = BTR(i) × PREC(i,t), and BENT*(i) = BTR(i) × PREC*(i). The corresponding totals for all of the target diseases taken together are BENT(t) and BENT*.
D	Delay (in years) between vaccination and the hypothetical onset of disease had the vaccinated individual not been vaccinated. The correct adjustment to the benefit derived from the prevention of one case can be calculated as follows: ADJD = $(1 + r)^{-D}$