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Economic evaluation of options for measles vaccination strategy in a hypothetical Western European country

PH. BEUTELS[1]* AND N. J. GAY[2]

[1] *Centre for the Evaluation of Vaccination, Department of Epidemiology and Community Medicine, University of Antwerp, Universiteitsplein 1, 2610 Antwerp, Belgium*
[2] *Immunisation Division, Communicable Disease Surveillance Centre, Public Health Laboratory Service, London, UK*

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SUMMARY

In this study an analysis was made of economic costs and medical effects (by cost-effectiveness and cost–benefit analysis) associated with measles vaccination in a hypothetical Western European country. We analysed ten vaccination options in terms of past and future vaccination coverage. We show that several of the proposed strategies for improving measles vaccination coverage are preferable to maintaining the existing policies, regardless of past coverage and the viewpoint of the analysis. For society, very high coverage (95%) two-dose vaccination is most optimal, irrespective of past vaccination coverage. The addition of a one-time campaign (to reduce susceptibility in (pre-)adolescent age groups) to such a high coverage two-dose vaccination programme is cost-saving to the health-care payer and to society when coverage in the past was low ($\leqslant$70%). Even when coverage in the past was high (90%) for more than a decade, this 'maximum strategy' could be implemented at an acceptable cost to the health-care payer (incremental direct costs per discounted life-year gained $<$€30 000), and at net savings to society.

INTRODUCTION

This paper presents an economic evaluation of various vaccination strategies against measles infection in a hypothetical Western European country. The study was initiated by WHO EURO with the aim of investigating the relative effectiveness and efficiency of a range of measles vaccination strategies. Currently implemented strategies, although considered to be effective and efficient, may not necessarily be the most effective and the most efficient options available. We did not identify our analysis with any particular country, because we wanted it to be relevant to programme managers in as many European countries as possible. We have, however, limited the analysis to Western Europe in order to have sufficient homogeneity of input data related to such parameters as vaccine price, treatment costs and past and current vaccination practices. Nevertheless, the results should also be relevant to any other country with similar measles epidemiology, costs of disease and vaccination histories.

* Author for correspondence.

VACCINATION STRATEGIES

The present status of measles infection in any country will depend, in particular, on the history of its vaccination programme. We designed two scenarios for the past in our hypothetical country. Both are based on routine single-dose vaccination of 1-year-olds, assumed to have been in place for 15 years: in one scenario at 70% coverage; in the other at 90%

coverage. For either past policy, it was assumed that the decision-maker in the present had five options from which to choose (numbered from 0 to 4):

- Strategy 0: *status quo*, i.e. the continuation of single-dose vaccination at either 70 or 90% coverage.
- Strategy 1: a second dose is introduced at age 5 years and attains the same coverage as the already existing first dose (i.e. either 70 or 90%).
- Strategy 2: the coverage of the first dose is increased to 95%, without introducing a second dose.
- Strategy 3: first-dose coverage is increased to 95%, and additionally a second dose is introduced at age 5 years at 95% coverage.
- Strategy 4: the same as strategy 3, with the addition of a one-time campaign during the first year, targeted at age groups $\leqslant$15 years, of which $<$95% is immune to measles. We assumed that the campaign would reach 93% of the people in the targeted age groups.

The effect of the vaccination strategies was evaluated using a dynamic mathematical model of measles transmission [1]. For each of the ten situations, the model calculated the expected number of measles cases in each age group over time. The theoretical background and validity of the model have been described in previous publications [1, 2].

ECONOMIC EVALUATION

A separate spreadsheet application was developed for the economic evaluation (in MS Excel 97), comprising incremental cost-effectiveness and cost–benefit analyses. In the cost-effectiveness analysis we express in the first place the viewpoint of the health-care payer by including only direct health-care costs. In addition a broader societal perspective is adopted by including direct costs, as well as indirect time costs due to morbidity in the cost-effectiveness and due to morbidity and mortality in the cost–benefit analysis. We offer guidance for decisions on the basis of direct costs and total costs separately, because indirect cost estimations, especially of premature mortality, remain methodologically questionable and may lack credibility for some decision-makers [3–6]. We investigated each strategy in relation to a common strategy of reference (termed strategy 0), as well as to each of the other strategies. Thus it is hoped that many readers can identify at least one of the options with the situation in their country. Furthermore the strategy by strategy incremental analysis is necessary to allow for a correct assessment of the additional merits and costs of each strategy (a classic example illustrating the importance of investigating incremental cost-effectiveness can be found in Neuhauser and Lweicki [7]).

We assessed the strategies over a maximum time span of 50 years. In line with general recommendations, future monetary costs and benefits were discounted to their 1999 value using a 3% discount rate [8]. Non-monetary benefits (i.e. health effects) are presented both discounted (at the same rate as costs) and undiscounted. Influential parameters such as vaccination costs, disease costs and discount rates were varied in uni- and bivariate sensitivity analyses.

INPUT DATA

Modelled scenarios

The hypothetical country's population was set at 7·5 million, with an annual birth cohort of 100 000 newborns and life-expectancy at birth of 75 years. The size of the population and the birth cohort are irrelevant to the conclusions drawn from this analysis, because our main focus is on the relative efficiency of the various strategies and not on nominal outcomes. Indeed, cost-effectiveness ratios, net savings and benefit–cost ratios when calculated in an incremental analysis can be considered as measures of relative efficiency.

Vaccine efficacy was assumed to be 90% in the second year of life and 95% at older ages, offering life-long protection [9, 10]. The model indicated that measles remains endemic under strategies 0, 1 and 2. Under the past scenario of 70% coverage, strategy 1 yields more cases and has a narrower inter-epidemic period than strategy 2, whereas under the past scenario of 90% coverage the reverse is true. Strategy 3 is sufficient to eliminate measles infection after 10–15 years. Strategy 4 achieves this more rapidly, in less than 5 years. By elimination we mean that sustained transmission can no longer occur. Hence only imported cases can give rise to sporadic small outbreaks, which will die out naturally without intervention.

Increased vaccination coverage tends to shift the age distribution of cases towards older age groups. The change in the age distribution is most marked for the scenario with past vaccine coverage of 70% as much of the shift had already occurred in the scenario with past coverage of 90%. Under 70% past coverage, the percentage of cases older than 10 years increases from 19% prior to the intervention to 29–68% at time 50 years, with strategy 3 causing the greatest age shift.

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Table 1. *Baseline estimates by age at infection*

Parameter	Estimate per age group				
	0–4 years	5–9 years	10–14 years	15–19 years	⩾20 years
Case-fatality ratio (per 100 000)	18·0	9·6	32·0	87·2	92·6
Case-hospitalization ratio	5·8 %	1·7 %	1·7 %	1·6 %	5·3 %
Direct health care costs per case (€)	123	112	110	111	148
Work days lost per measles case*	0·4	0·4	0·3	0·2	2·0
Benchmark societal value per death (€)	190 859	221 258	256 499	297 353	178 400
Life-expectancy (years)	73	68	63	58	27

* Adjusted for unemployment.

Under 90 % past coverage, the increase is from 45 % to 64–70 %, with strategy 1 causing the largest shift. In view of the age-dependency of some of the other input parameters (see below), these differences will have an impact on the results, which is specific for each strategy.

Disease costs

All costs presented in this study have been valued at the 1999 price level, and converted to euros [€1 ≅ $US 1·07 (1999)]. Published English data were used to provide estimates of the age-specific complication [11, 12], and case-fatality ratios [13]. A search of the literature showed a wide range of estimated hospitalization probabilities between countries (the overall per case hospitalization probability varies between 1·4 and 19 %) [11, 14–17]. In general, European probabilities (1·4 % in England and Wales [11], 2·4 % in an outbreak in Indre et Loire, France [16], 2·4 % in Torino, Italy [18], 2·4 % in Northern Ireland [19] and 10·2 % in an outbreak in Catalonia, Spain [15]) were markedly lower than those estimated for other industrialized countries (18–19 % in the United States [14, 17], 14 % in New Zealand [20]). Aspects contributing to this variation may be related to differences in treatment practices (and health care organization), general socio-cultural differences and differences in the epidemiological situation (e.g. the average age at infection). Furthermore, it seems that the denominator for the calculation of these probabilities may have been overstated in some of the European studies by using all reported cases instead of only confirmed and probable cases. Nevertheless, the European probabilities are the most relevant basis of comparison for our analysis (if anything, the use of these probabilities may lead to conservative cost estimates). The hospitalization probabilities in this analysis were therefore based on a comprehensive set of French hospitalization data. According to these data, 2·5 % of all measles cases were hospitalized in France in 1997 (unpublished observation). The denominator in this study was corrected for misdiagnosis, by applying positive predictive values of diagnosis to the number of reported cases by age. The distribution according to age groups is given in Table 1. Average direct disease costs were estimated from previous and ongoing European analyses on the costs of measles. The previous studies included overall (non-age specific) direct cost estimates of €145 per case <10 years in Spain (dating from 1981 to 1982) [21] and €111 per case in Northern Ireland (dating from 1983) [19]. Neither of the published cost estimates from the past includes the costs of long-term care for sequelae [from neurological disorders like encephalitis and subacute sclerosing panencephalitis (SSPE)]. In a recent Belgian cost analysis direct costs including the costs for long-term sequelae were calculated at €227, 212, 210, 200 and 194 for the age groups of 0–4, 5–9, 10–14, 15–19 and ⩾20 years, respectively [22]. Without the inclusion of sequelae, these costs would be reduced to €136, 103, 112, 113, 151, respectively, which is similar to the (inflated) past estimates [22]. Preliminary direct cost estimates from France (excluding the costs of sequelae), are also of a similar order of magnitude (unpublished observation). In the baseline analysis, we chose to ignore the costs of long-term care

in order to provide a consistent European estimate (the level of long-term care provided by the health-care sector may vary between countries), meaning that from the Belgian study, we only considered the scenario without sequelae. In an attempt to include indirect costs of measles morbidity, we used the number of working days lost (usually by parents caring for ill children, and occasionally by the patients themselves when they acquire infection during adulthood). These estimates were derived from studies on measles in England and Wales and Spain [21], as well as from studies on varicella in Belgium [23], France [24], Germany [25] and Spain [26]. The varicella studies seem to provide conservative estimates (varicella being a generally milder disease than measles) and since these studies were recently made, they should better reflect current socio-economic and cultural behaviour *vis-à-vis* parental home care than the few older studies that were made for measles. In addition, an estimate was made of the indirect societal costs of mortality on the basis of the present value of future earnings (i.e. the human capital method). We consider this to be a conservative estimate, because with this method only employed man-years are taken into account, and these are valued in terms of gross earnings only. Anxiety, pain and suffering for the patient and his/her family and friends are thus ignored in this analysis. These estimates were based on average income and employment rates in the European Union (EU-15). The main baseline assumptions are summarized in Table 1. We consider each of these assumptions to be conservative (i.e. disfavouring vaccination).

Vaccination costs

Vaccination costs were estimated on the basis of ongoing cost analyses, expert opinion and on survey results from WHO EURO (C. Roure, personal communication, 1997). The average price of the vaccine was estimated as €6·3 per dose (these costs include the costs for adverse events, about €0·1 per dose). The marginal costs of administering the vaccine were assumed to increase with the coverage achieved. Up to 70% coverage the administration costs were estimated as €7·3 per dose. This was arbitrarily increased by 20% for every 5% increase in coverage above 70%. For the improvement of coverage from 90 to 95% – the final increase that would require the greatest effort – the administration costs per dose were estimated twice as high as those for the increase in coverage from 85 to 90%, and were thus €30·2 per dose. Apart from making vaccination costs dependent on coverage, we also assumed that the variable administration costs were one third greater for a vaccine dose at age 5 years than for a dose at age 15 months. Indeed, in some countries a measles dose at 5 to 6 years of age could be less compatible with the schedules for other vaccines.

For the campaign (as part of strategy 4), it was assumed that the vaccine price was identical to the price for the other strategies. The variable marginal administration costs were set equal to those of the second dose under strategy 3. The fixed marginal administration costs of the campaign were assumed to be €100 000. Based on these assumptions, the campaign would cost €17·9 per targeted child (and 19·4 per vaccinated child).

RESULTS

Cost-effectiveness analysis

In this section costs and effects are combined in a single measure: the Incremental Cost-Effectiveness Ratio (ICER). An ICER expresses the incremental costs needed to obtain one additional effect.

The cost-effectiveness planes depicted in Figure 1 gives a visual representation of the relationship between the different strategies. The horizontal axis indicates the additional number of life years gained by the different strategies. The corresponding net savings are indicated on the vertical axis. A strategy is considered more preferable the further to the right (the more additional life years it gains) and the higher (the more it saves or the less it costs) its position on the charts.

Scenario A – past coverage 70%

Given the past scenario of 70% coverage, all other strategies save more costs and life-years than strategy 1. This is the case for both viewpoints (that of the health-care payer and that of society). Strategy 2 saves the most direct costs of all strategies, while strategy 4 saves the most total costs of all strategies. Strategy 4 is by definition also the most effective strategy under consideration. From a societal point of view, strategy 4 therefore dominates the other 4 strategies.

For the health-care payer the attractiveness of the various strategies is not so obvious. Figure 2 summarizes the relationship between strategies 2, 3 and 4. The curves depict the additional costs and life-years of high coverage two-dose vaccination (strategies 3 and 4) *vs*. high coverage single-dose vaccination (strategy 2).

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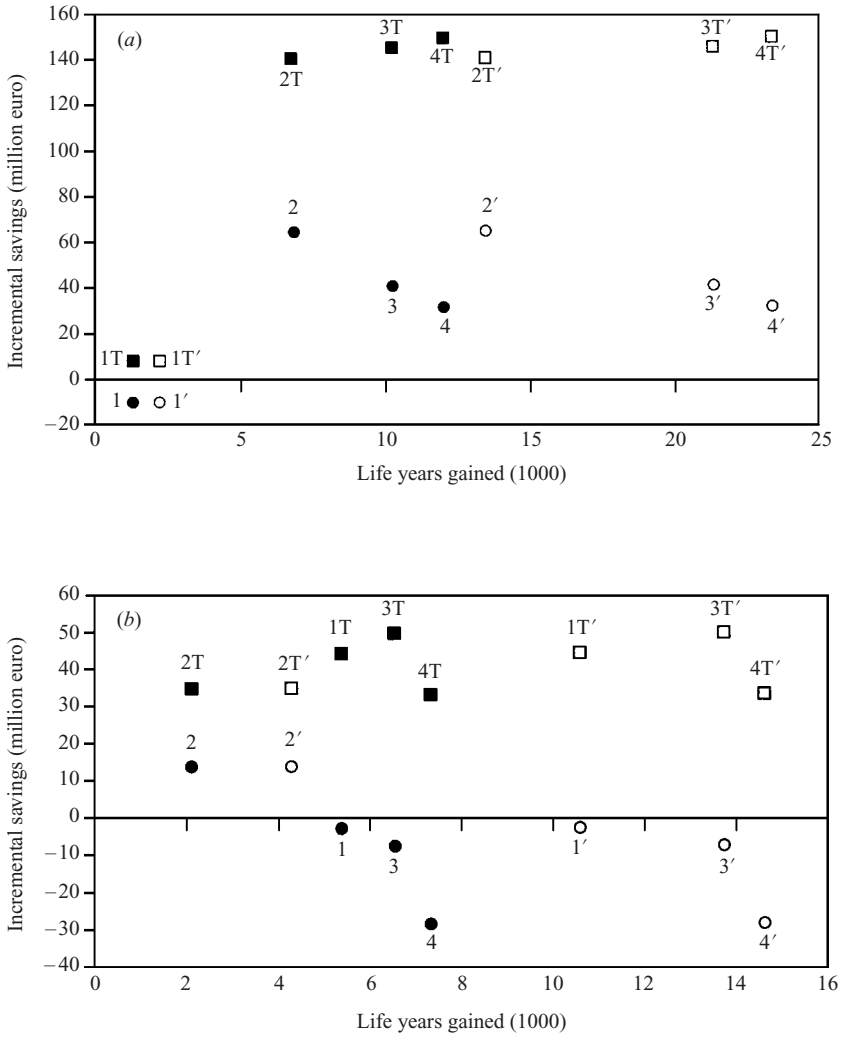

Fig. 1. Representation in a cost-effectiveness plane of incremental savings and life-years gained *vs.* strategy 0. The markers represent combined incremental savings (net costs if negative) and effect estimates for a given strategy *vs.* strategy 0. (*a*) Past scenario of 70% vaccine coverage. (*b*) Past scenario of 90% vaccine coverage. Circles: health-care payer's viewpoint (only direct health-care costs included). Squares: societal viewpoint [total costs (T): direct health-care costs and indirect time costs related to morbidity included]. Filled circles or squares: discounted life-years gained. Empty circles or squares: undiscounted life-years gained.

During the first 3 years, strategy 4 is less attractive than strategy 3, because the investment up-front is much greater due to the campaign. From then on the roles are reversed. The incremental cost-effectiveness of strategy 4 *vs.* 3 is in the order of €10 000 per discounted life-year gained after 3 years and stabilizes at about €5200 per discounted life-year gained after 10 years. If we adopt a criterion for cost-effectiveness of €40 000 per quality-adjusted life-year gained (based on Goldman et al. [27], as cited by Meltzer [28]), the addition of a mass campaign to a high coverage two-dose vaccination programme is good value for money [the use of life-years gained is conservative (an underestimation) in comparison to QALYs gained]. At €6313 and €6863 per discounted life-year gained, strategies 4 and 3, respectively, show acceptable ICERs *vs.* strategy 2 by the end of the time span. In sum, given past vaccination coverage of 70% or less, the most cost-effective option is to accompany the introduction of high coverage two-dose vaccination with a campaign targeted at susceptible youngsters. This applies to both viewpoints. The choice of health outcome (other than life-years gained) does not affect the prioritization of options (not shown).

In addition the order of the strategies does not change when effects are left undiscounted (see Fig. 1). The strategies with large effectiveness over a long period (strategies 3 and 4) are most sensitive to

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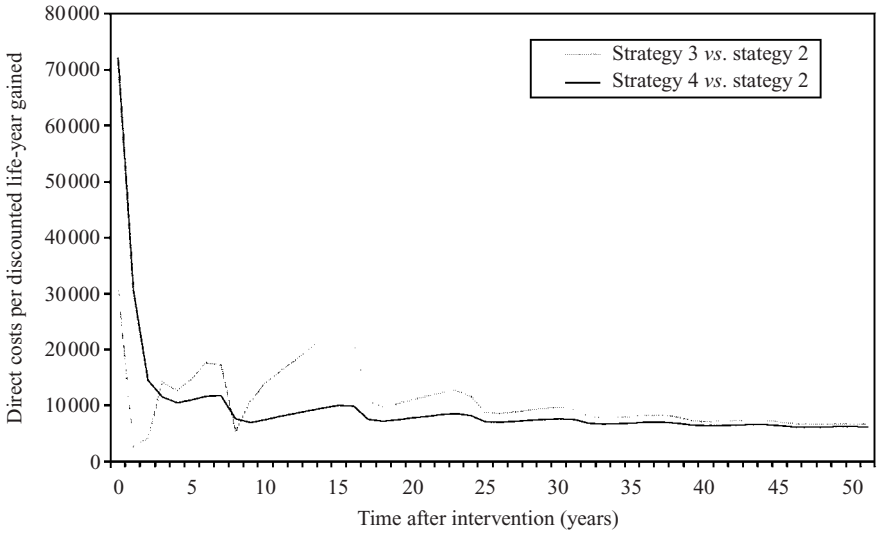

Fig. 2. Incremental direct costs per discounted life-year gained over the future, given single-dose vaccination at 70 % coverage for the last 15 years. Strategy 2, single-dose vaccination at 95 % coverage. Strategy 3, two-dose vaccination at 95 % coverage. Strategy 4, strategy 3 + a one time campaign targeted at age groups $\leqslant$15 years, with $<$95 % immune to measles.

discounting of effects (hence the large distance between the discounted and undiscounted estimates).

Scenario B – past coverage 90 %

Given the scenario with past coverage of 90 %, for the health-care payer there is no dominance of any strategy (Fig. 1). Increasing single-dose vaccination coverage by 5 % (strategy 2) is the only cost-saving alternative for the health-care payer, but it is also the least effective strategy. Relative to strategy 1, the direct ICER of the more effective option of two doses at 90 % (strategy 1) is acceptable at €5115 per discounted life-year gained.

In relation to two-dose vaccination at 90 % coverage (strategy 1), two-dose vaccination at 95 % has comparable cost-effectiveness with (strategy 4) or without (strategy 3) an additional campaign; €8000 and €5000 per discounted life-year gained, respectively. The direct ICER of strategy 4 *vs.* 3 levels off to about €26 200 per discounted life-year gained after a period of 5 years. Therefore, even with high vaccination coverage in the past, a one-time campaign to accompany a further sustained increase in coverage is relatively cost-effective by standard criteria (i.e. $<$€40 000 per discounted life-year gained).

Table 2 summarizes the ICERs for some of the relevant (non-dominated) options. Note again that the order of the strategies (here strategy 3 more cost-effective than strategy 4) does not change when effects are left undiscounted or when other health outcomes than life-years gained are used. For society all strategies are cost-saving, with strategy 3 yielding the greatest savings (see Fig. 1). The total ICER of strategy 4 *vs.* strategy 3 is €20 678 per discounted life-year gained.

Cost–benefit analysis

In cost–benefit analysis, the health gains are converted into monetary units. All effects are then expressed in a dollar value. In this analysis the conversion from effect to monetary benefit was achieved by assigning productivity losses to morbidity and mortality associated effects. Morbidity associated indirect time costs arise when ill persons or their family interrupt their normal activities in society to take care of the illness. Mortality related indirect costs are a consequence of time losses due to premature deaths.

Table 3 presents the results of the cost–benefit analysis. Numbers in bold are the best in their row. Under the scenario of 70 % coverage in the past, all incremental strategies result in net savings. The optimal choice for society would be to implement the most effective of these strategies, strategy 4. Under the scenario of 90 % coverage in the past, strategy 3 is the most effective strategy that still yields net savings for all incremental options. Nonetheless, strategy 4 also yields net savings *vs.* strategies 0 and 2, implying that from a societal point of view, a mass campaign can also be optimal if past coverage was limited to high level single-dose vaccination (90–95 %).

The benefit–cost ratios (BCRs) and net savings per extra vaccinee are indicators of the relative contribution of the various strategies to the potential savings

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Table 2. *Incremental cost-effectiveness ratios under the past scenario of 90% vaccination coverage (ratios with effects undiscounted in parentheses)*

Incremental direct health-care costs (€)	Strategy 3 *vs.* 0	Strategy 4 *vs.* 0	Strategy 3 *vs.* 1	Strategy 4 *vs.* 1	Strategy 3 *vs.* 2	Strategy 4 *vs.* 2	Strategy 4 *vs.* 3
Per case prevented	20 (10)	68 (34)	97 (36)	291 (147)	94 (45)	158 (82)	536 (491)
Per hospitalization prevented	713 (339)	2388 (1181)	2807 (1019)	9600 (4478)	3252 (1516)	5594 (2785)	21 252 (19 412)
Per death averted	60 550 (28 102)	199 465 (97 172)	182 523 (65 196)	641 743 (291 028)	236 974 (107 127)	405 611 (196 593)	1 492 483 (1 352 255)
Per life-year gained	1209 (576)	3933 (1974)	4089 (1508)	13 141 (6388)	4846 (2268)	8122 (4105)	26 363 (23 948)
Per work day gained	13 (6)	45 (22)	46 (16)	173 (74)	58 (26)	101 (48)	460 (419)

This incremental analysis allows for a health-care payer's interpretation of the relative efficiency between improved strategies (1, 2, 3, 4), instead of relative to the reference strategy (0) only.
Strategy 0: single-dose vaccination at 90% coverage.
Strategy 1: two-dose vaccination at 90% coverage.
Strategy 2: single-dose vaccination at 95% coverage.
Strategy 3: two-dose vaccination at 95% coverage.
Strategy 4: strategy 3 + a one-time campaign targeted at age groups $\leqslant$15 years, with $<$95% immune to measles.

of measles vaccination. They clearly show that the per-vaccinee effect is greatest for an increase in single-dose coverage. At a moderate investment (vaccinating an extra 5–25% of a cohort of 1-year-olds per year) it yields the highest return on investment for society. These indicators are attractive in the first place because the denominator is small (intervention costs or extra vaccinees), and only to a lesser extent because the numerator is high (benefits or net savings). Under past coverage of 70% it is clear that an increase of first dose coverage is more urgent and more beneficial than the introduction of a second dose at an equally moderate coverage level, because total net savings are much greater with strategy 2 than with strategy 1. Under past coverage of 90% this is not so clear. Although the BCRs are highest for strategy 2, strategy 1 yields greater net savings and would therefore be preferable to strategy 2. The difference between benefits and costs (i.e. net savings) offers more reliable guidance than the ratio of benefits to costs. For instance, a strategy with incremental costs of €1000 and benefits of €30 000 yields net savings of €29 000 and a BCR of 30, whereas a strategy with incremental costs of €1 million and benefits of €2 million yields net savings of €1 million and a BCR of 2. Therefore, society would clearly gain most from the latter strategy. However, the size of the investment is very country-specific. The greater the required investment and the longer it takes for the benefits to arise, the greater the opportunity costs (of other interventions foregone), implying that net savings *per se* are not the sole concern in decision-making.

Sensitivity analysis

We investigated the robustness of the findings in uni- and bivariate sensitivity analysis. We were unable to perform a complete probabilistic uncertainty analysis, because the complex dynamic simulation model runs separately from the economic model. As indicated above, we considered the base input parameters to be conservative. More favourable intervention assumptions will primarily improve the attractiveness of strategies that vaccinate more susceptible people (strategies 3 and 4). Therefore, setting the marginal variable vaccination costs equal for all strategies (at 14 per dose), does not change the relative order of the strategies, it only enforces the findings. The same applies when the costs of vaccine doses are all set equal to the costs of a dose at 15 months of age (in the base case other doses were 33% more expensive than a dose at 15 months). Applying a discount rate of 5% to both

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Table 3. *Incremental cost–benefit analysis (1999)*

	Strategy 1 *vs.* 0	Strategy 2 *vs.* 0	Strategy 3 *vs.* 0	Strategy 4 *vs.* 0	Strategy 3 *vs.* 1	Strategy 4 *vs.* 1	Strategy 3 *vs.* 2	Strategy 4 *vs.* 2	Strategy 4 *vs.* 3
Past scenario A (70% single-dose coverage)									
Net savings (€)	11 506 903	162 993 313	183 343 399	**194 775 591**	171 836 497	183 268 688	20 350 086	31 782 278	11 432 192
(per extra vaccinee)	(3)	**(128)**	(30)	(27)	(70)	(50)	(4)	(5)	(9)
Benefit–cost ratio	1·37	**12·01**	3·96	3·29	6·51	4·37	1·43	1·45	1·49
Past scenario B (90% single-dose coverage)									
Net savings (€)	67 804 536	43 420 940	**78 888 343**	65 851 997	11 083 807	−1 952 539	35 467 403	22 431 057	−13 036 346
(per extra vaccinee)	(15)	**(170)**	(15)	(10)	(23)	(−1)	(7)	(4)	(−10)
Benefit–cost ratio	2·59	**9·81**	2·47	1·83	2·02	0·95	1·73	1·30	0·49

This incremental analysis allows for a societal interpretation of the relative efficiency between improved strategies (1, 2, 3, 4), instead of relative to the reference strategy (0) only.
Strategy 0: no change in policy: single-dose vaccination at the existing coverage (70 or 90%).
Strategy 1: two-dose vaccination at the existing coverage (70 or 90% for both doses).
Strategy 2: single-dose vaccination at 95% coverage.
Strategy 3: two-dose vaccination at 95% coverage.
Strategy 4: strategy 3 + a one-time campaign targeted at age groups ⩽15 years, with <95% immune to measles.

costs and effects (instead of 3% in the base case) makes strategies 3 and 4 relatively less attractive, but it does not change the order, nor the fact that strategy 4 results in total net savings under both past scenarios (up until a discount rate of 8%). By applying Belgian health-care cost data (including the costs of long-term care, see above) all strategies under past scenario B will also yield direct net savings. The order of the strategies, however, remains the same (except that under past scenario A, strategy 4 dominates strategy 3 also for the health-care payer).

In general, sensitivity analysis of the economic parameters indicated that the results are most sensitive to treatment and vaccination costs (not shown). Nonetheless, the results are robust in that none of the variations would exceed the defined cost-effectiveness criterion, nor change the prioritization of strategies. Note that the evolution of cost-effectiveness over time is for all other incremental analyses much like strategy 4 *vs.* 2 in Figure 2. All the results are stable for time spans of 20 years or more, implying that the length of the time span beyond 20 years has limited impact on our results and conclusions.

Threshold analysis

One of the main findings in this study is that an improvement of single-dose coverage yields greater direct net savings than the addition of a second dose at the existing coverage level (i.e. strategy 2 results in greater direct net savings than strategy 1). In the baseline it was already assumed that vaccination costs increase disproportionately with coverage above a level of 70%. We performed a threshold analysis to determine the difference in vaccination costs that would make strategies 1 and 2 equivalent in direct net savings. Additionally, we performed threshold analyses on the societal value of death, to see which minimum value a decision maker would have to attach to mortality to choose the most effective of the options under consideration.

Past coverage 70%

With past coverage of 70% and baseline vaccination costs for strategy 1, direct net savings become equal for strategies 1 and 2 if the vaccination costs for strategy 2 average €45·5 per dose. Therefore vaccination costs to improve the coverage from 70 to 95% can become as high as €133 per dose before both strategies are equal in direct net savings (at that point strategy 2 is still preferable to strategy 1 from a societal perspective, in

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total net savings and BCR). This implies that the vaccination costs per dose of increasing single-dose vaccination coverage from 70 to 95% (i.e. the vaccination costs of the last 25% increase) can be more than eight times as high as the vaccination costs per dose of two-dose vaccination at 70% coverage, before both strategies are equivalent for the health-care payer's budget.

The choice between strategies 3 and 4 will depend greatly on the additional implementation costs of the campaign. The additional vaccination costs per vaccinated person in the campaign can amount to €74·7 before the ICER of strategy 4 *vs.* strategy 3 exceeds €40 000 in the long run. This implies that you can afford to spend almost four times as much on vaccination of susceptibles in the campaign than on vaccination with the second dose before the addition of a campaign to a high coverage two-dose strategy loses its attraction for the health-care payer.

In view of the fact that strategy 4 dominates strategy 3 when only morbidity related time costs are included, the societal decision maker would have to view the societal value of avoiding death as negative if s/he chooses not to implement strategy 4. If we exclude morbidity related time costs, the threshold societal value of an averted death would have to be at least 309 670 (irrespective of age at death) to prefer strategy 4 to strategy 3.

Past coverage 90%

With past coverage of 90% and baseline vaccination costs for strategy 1, direct net savings become equal for strategies 1 and 2 if the vaccination costs for strategy 2 average €22·7 per dose. This implies that the vaccination costs per dose of increasing single-dose vaccination coverage from 90 to 95% can be more than ten times higher (or €159) than the vaccination costs per dose of two-dose vaccination at 90% coverage, before both strategies are equally attractive to the decision maker. However, the relative attractiveness of strategy 2 *vs.* 1 depends highly on the baseline vaccination costs. The lower the vaccination costs per dose, the more strategies that use many doses of vaccine gain attractiveness (including strategy 1 relative to strategy 2). For instance, for vaccination costs per dose of €8·5 or lower, strategy 1 would save more than strategy 2. Therefore if past coverage was high (90%) and the vaccination costs per dose are rather low ($\leqslant$€8·5 per dose), the addition of a second dose seems more justified than a further increase of single-dose vaccination coverage. Note that strategy 1 is also more effective than strategy 2, and that the incremental direct costs per life-year gained are €5115.

The societal perspective shows clearly a preference for strategy 3. Indeed if only morbidity related time costs are included, strategy 3 dominates strategies 0, 1 and 2. So if a societal decision maker does not opt for a high coverage two-dose vaccination strategy, it means that s/he implicitly attaches a negative value to life. Or if we disregard morbidity-associated time costs, the threshold value of life above which savings arise to strategy 3 in relation to the next best option (strategy 1), would be €182 523. Furthermore in order to prefer strategy 4 to strategy 3, the decision maker would have to give a minimum value to life of €1 177 779. Note though that in this analysis, we did not account for future unrelated costs (i.e., costs which are not related to measles arising during the prolonged lifetime), which could be added to these threshold amounts to come to the overall value of life (which could explain a negative value of life to some decision makers). It is exceptional for any economic evaluation to include future unrelated costs. The impact of these costs in the context of vaccination is discussed elsewhere [29].

DISCUSSION

In this study an analysis was made of economic costs and medical effects associated with measles vaccination in Western Europe. We analysed ten vaccination options in terms of past and future vaccination coverage.

The analysis shows that additional efforts to increase the coverage of measles vaccination in view of elimination is an efficient way of using resources in the health-care sector. However, it is important to remember that we performed this analysis on the basis of several generalizations. The European Region is far more complex both in relation to measles vaccination history and present health-care sector facilities than we could incorporate in this general analysis. Due to these differences in epidemiological and economic parameters between different European countries, the accuracy of the analysis would be highest if it were carried out at the country level (until further notice the usual level at which health-care decisions are taken). Nevertheless we believe that, despite these generalizations, the general picture remains as it is drawn here: the relative (dis)advantage of the various vaccination strategies and their order of efficiency would be

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basically the same among different countries in Western Europe.

Based on the results of this analysis, the following conclusions can be made:

- There is ample evidence to show that several of the proposed strategies (1–4) for improving measles vaccination coverage are preferable to maintaining the existing strategy 0, regardless of past coverage and the viewpoint of the analysis (health-care payer or society).
- It is better to first increase the coverage of single-dose vaccination up to 90% (up to 95% if past coverage was less than 90% for most of the time) than it is to start two-dose vaccination at inferior vaccination coverage. Threshold analysis indicated that 8–10 times more could be spent per vaccination on the last part of the increase of single-dose coverage before single-dose vaccination loses its advantage over two-dose vaccination from a purely budgetary viewpoint.
- For society, very high coverage (95%) two-dose vaccination is the most optimal option, irrespective of past vaccination coverage. The economic value of a one-time campaign to supplement such a high coverage two-dose vaccination programme depends on the historical vaccination coverage. With a history of low coverage (i.e. 70% or less) the addition of such a campaign to eliminate susceptibility in (pre-)adolescent age groups is cost-saving to the health-care payer and to society. Given a history of high coverage (i.e. 90% or more), sustained for a long period, the addition of a campaign is no longer cost-saving to the health-care payer, but the ICER is of an acceptable magnitude. For society, this depends on the societal value of an averted death. If life is valued higher than 1·17 million a campaign is warranted. The desirability of implementing a campaign depends also on the magnitude of the investment (and the associated opportunity costs) it requires. This is country-specific. Therefore, given sustained 90% coverage in the past, the desirability of implementing a one-time campaign cannot be assessed conclusively by our analysis.

In sum, the incremental cost-effectiveness and cost-benefit of moving on to the final stages (strategy 3 or 4) are attractive, even if past coverage was high, but under the condition that high coverage can effectively be maintained. Indeed, we assumed that a continuing effort of vaccination would be necessary and that eradication would not be achieved within the (long) time horizon of the analysis. We have shown that measles vaccination strategies with very high levels of coverage maintained for a long period can be economically and epidemiologically superior to current existing strategies, even if coverage has already been high for more than a decade. Therefore it seems that it is in the interest of Western European countries to develop these elimination strategies, even if eradication will never be achieved. Improving measles vaccination strategies requires a long-term vision, demanding to heed the false sense of security that arises as we head towards a measles free world. Still, even if global measles eradication fails, sustained high coverage two-dose vaccination (which interrupts endemic transmission) seems more efficient (and less costly) to the health-care payer and society in Western Europe than strategies currently employed in a number of Western European countries.

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REFERENCES

1. Gay NJ, Pelletier L, Duclos P. Modelling the incidence of measles in Canada: an assessment of the options for vaccination policy. Vaccine 1998; **16**: 794–801.
2. Babad HR, Nokes DJ, Gay NJ, Miller E, Morgan-Capner P, Anderson RM. Predicting the impact of measles vaccination in England and Wales: model validation and analysis of policy options. Epidemiol Infect 1995; **114**: 319–44.
3. Koopmanschap MA, Rutten FFH. Indirect costs in economic studies: confronting the confusion. PharmacoEconomics 1993; **4**: 446–54.
4. Brouwer WBF, Koopmanschap MA. How to calculate indirect costs in economic evaluations: correspondence. PharmacoEconomics 1998; **13**: 563–9.
5. Liljas B. How to calculate indirect costs in economic evaluations: the author's reply. PharmacoEconomics 1998; **13**: 566–96.

6. Olsen JA, Smith RD. Theory versus practice: a review of 'willingness to pay' in health and health care. Health Econ 2001; **10**: 39–52.
7. Neuhauser D, Lweicki AM. What do we gain from the sixth stool guaiac? N Engl J Med 1975; **293**: 226–8.
8. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russel LB for the panel on Cost-Effectiveness in Health and Medicine. Recommendations of the panel on Cost-Effectiveness in Health and Medicine. JAMA 1996; **276**: 1253–8.
9. De Serres G, Boulianne N, Meyer F, Ward BJ. Measles vaccine efficacy during an outbreak in a highly vaccinated population: incremental increase in protection with age at vaccination up to 18 months. Epidemiol Infect 1995; **115**: 315–23.
10. Fine PE, Zell ER. Outbreaks in highly vaccinated populations: implications for studies of vaccine performance. Am J Epidemiol 1994; **139**: 77–90.
11. Miller CL. Severity of notified measles. BMJ 1978; **1**: 1253–5.
12. Miller C, Farrington CP, Harbert K. The epidemiology of subacute sclerosing panencephalitis in England and Wales 1970–1989. Int J Epidemiol 1992; **21**: 998–1006.
13. Ramsay M, Gay N, Miller E, Rush M. White J, Morgan-Capner P, Brown D. The epidemiology of measles in England and Wales: rationale for the 1994 national vaccination campaign. CDR Rev 1994; **4**: R141–6.
14. Gindler JS, Atkinson WL, Markowitz LE, Hutchins SS. Epidemiology of measles in the United States in 1989 and 1990. Pediatr Infect Dis J 1992; **11**: 841–6.
15. Godoy P, Dominguez A, Alvarez J, et al. Measles epidemiology in Catalonia (Spain): implications for a regional vaccination programme. Int J Epidemiol 1999; **28**: 558–62.
16. Baron S, Pulvenis D, Turco E. Investigation d'une épidemie de rougeole en Indre et Loire (mars 1995). Rev d'Epidemiol Santé Publique 1996; **44**: S19.
17. Atkinson WL, Kaplan JM, Clover R. Measles: virology, epidemiology, disease, and prevention. Am J Prev Med 1994; **10** (Suppl): 22–30.
18. Ruggenini AM, Zotti C, Pedronetto A, Milano R, Garella D, Sacchetti C. I Ricoveri ospedalieri in Torino per morbillo e relative complicanze, nel periodo 1973–1983: valutazioni sanitarie ed economiche, in rapporto alla opportunità dell'intervento vaccinale. Boll Ist Sieroter Milan 1986; **65**: 502–11.
19. McConnell WW, Tohani VK. Measles in the Southern Health Board – implications for resources. BMJ (Clin Res Ed) 1984; **289**: 293–6.
20. Mansoor O, Blakely T, Baker M, Tobias M, Bloomfield A. A measles epidemic controlled by immunisation. N Z Med J 1998; **111**: 467–71.
21. Taracena del Pinal B, Monton JL, Cristobal P, Gonzalez F, Casas J. Contribución al estudio de costos del sarampión en España. An Esp Pediatr 1983; **19**: 383–8.
22. Beutels P, Van Damme P, Van Casteren V, Gay NJ, De Schrijver K, Meheus A. The difficult quest for data on 'vanishing' vaccine-preventable infections in Europe: the case of measles in Flanders (Belgium). Vaccine 2002; **20**: 3551–9.
23. Beutels P, Van Damme P, Van Doorslaer E. Program evaluation of universal varicella vaccination in Belgium: preliminary results. ESOC 2000, Report No. 36.
24. Coudeville L, Paree F, Lebrun T, Sailly J. The value of varicella vaccination in healthy children: cost-benefit analysis of the situation in France. Vaccine 1999; **17**: 142–51.
25. Beutels P, Clara R, Tormans G, Van Doorslaer E, Van Damme P. Costs and benefits of routine varicella vaccination in German children. J Infect Dis 1996; **174** (Suppl 3): S335–41.
26. Diez Domingo J, Ridao M, Latour J, Ballester A, Morant A. A cost benefit analysis of routine varicella vaccination in Spain. Vaccine 1999; **17**: 1306–11.
27. Goldman L, Gordon D, Rifkind B, et al. Cost and health implications of cholesterol lowering. Circulation 1992; **85**: 1960–8.
28. Meltzer D. Accounting for future costs in medical cost-effectiveness analysis. J Health Econ 1997; **16**: 33–64.
29. Beutels P. Economic evaluation of vaccination programmes in humans: a methodological exploration with applications to hepatitis B, varicella-zoster, measles, pertussis, hepatitis A and pneumococcal vaccination. University of Antwerp, 2002.